Supporting Information

for

Open Source Drug Discovery - Highly Potent Antimalarial Compounds Derived from the Tres Cantos Arylpyrroles

Alice E. Williamson[1], Paul M. Ylioja[1], Murray N. Robertson[1], Yevgeniya Antonova-Koch[2],Vicky Avery[3], Jonathan Baell[4], Harikrishna Batchu[5], Sanjay Batra[5], Jeremy N. Burrows[6], Soumya Bhattacharyya[5], Felix Calderon[7], Susan A. Charman[4], Julie Clark[8], Benigno Crespo[7], Matin Dean[1], Stefan L. Debbert[9], Michael Delves[10], Adelaide S. M. Dennis[11], Frederik Deroose[12], Sandra Duffy[3], Sabine Fletcher[3], Guri Giaever[13], Irene Hallyburton[14], Francisco-Javier Gamo[6], Marinella Gebbia[13], R. Kiplin Guy[7], Zoe Hungerford[1], Kiaran Kirk[11], Maria J. Lafuente-Monasterio[7], Anna Lee[13], Stephan Meister[2], Corey Nislow[13], John P. Overington[15], George Papadatos[15], Luc Patiny[16], James Pham[17], Stuart A. Ralph[17], Andrea Ruecker[10], Eileen Ryan[4], Christopher Southan[18], Kumkum Srivastava[5], Chris Swain[19], Matthew J. Tarnowski[1], Patrick Thomson[20], Peter Turner[1], Iain M Wallace[15,#], Timothy N. C. Wells[6], Karen White[4], Laura White[1], Paul Willis[6], Elizabeth A. Winzeler[2], Sergio Wittlin[21] and Matthew H. Todd[1*‡]

1 *School of Chemistry, The University of Sydney, NSW 2006, Australia*
2 *University of California San Diego, Dept. Pediatrics, Pharmacology & Drug Development, CNCB-128, 9500 Gilman Drive, La Jolla, CA-92093, USA*
3 *Discovery Biology, Eskitis Institute for Drug Discovery, Griffith University, Nathan, QLD 4111, Australia*
4 *Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, VIC 3052, Australia*
5 *CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow, 226 031, India*
6 *Medicines for Malaria Venture, PO Box 1826, 20 rte de Pre-Bois, 1215 Geneva 15, Switzerland*
7 *Tres Cantos Medicines Development Campus, Diseases of the Developing World, GlaxoSmithKline, Severo Ochoa 2, 28760 Tres Cantos, Spain*
8 *Department of Chemical Biology & Therapeutics, MS 1000, Room E9050, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN, 38105-3678, USA*
9 *Department of Chemistry, 233 Steitz Science Hall, 711 E. Boldt Way, Lawrence University, Appleton, WI 54911, USA*
10 *Department of Life Sciences, Imperial College London, South Kensington, London SW7 2AZ, UK*
11 *Research School of Biology, The Australian National University, Canberra, ACT 2601, Australia*
12 *Asclepia Outsourcing Solutions, Damvalleistraat 49, B-9070 Destelbergen, Belgium*
13 *Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, 160 College Street, Toronto, Ontario M5S 3E1, Canada*
14 *Drug Discovery Unit, Division of Biological Chemistry and Drug Discovery, University of Dundee, Dundee, DD1 5EH, UK*
15 *European Molecular Biology Laboratory – European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SD, UK*
16 *Ecole Polytechnique Fédérale de Lausanne (EPFL), Institute of Chemical Sciences and Engineering (ISIC), Lausanne, 1015, Switzerland*
17 *Department of Biochemistry & Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Victoria, 3010, Australia*
18 *IUPHAR/BPS Guide to PHARMACOLOGY, Centre for Integrative Physiology, School of Biomedical Sciences, University of Edinburgh, Edinburgh, EH8 9XD, UK*
19 *Cambridge MedChem Consulting, 8 Mangers Lane, Duxford, Cambridge CB22 4RN, UK*
20 *School of Chemistry, The University of Edinburgh, Joseph Black Building, West Mains Road, Edinburgh, Scotland EH9 3JJ, UK*
21 *Swiss Tropical and Public Health Institute, Socinstr. 57, 4051 Basel, Switzerland*
#Current address: Novartis Institutes for BioMedical Research, 250 Massachusetts Avenue, Cambridge, MA 02144, USA
‡The authorship list for this paper is alphabetical aside from the bookenders: the corresponding author is shown last and the first three authors performed the majority of the experimental work.
* To whom correspondence should be addressed: matthew.todd@sydney.edu.au, @mattoddchem

SI Index

SI Datasets (listed below) have been uploaded to the journal separately.
Complete Electronic Laboratory Notebooks, images of NMR Spectra for novel compounds, and archived snapshots of OSM wiki pages are available from The University of Sydney eScholarship Repository at http://hdl.handle.net/2123/14132, http://hdl.handle.net/2123/14123 and http://hdl.handle.net/2123/15389 respectively.

Chemical Protocols (includes Figures with prefix "SC")

I. General experimental details S6
II. Experimental procedures and characterization data S7
1. General Experimental S7
2. Original hits and their putative prodrug fragments S9
Fig SC1. Resynthesis of the GSK Aryl Pyrrole Esters. S9
3. Amide Analogs S19
Fig SC2. The Full Set of Amide Analogs Evaluated. S19
3.2 Commercial amides S31
4. The "Near Neighbour" 2-Iminothiazolidinones S33
Fig SC3. Synthesis of Near Neighbours S33
Fig SC4. X-Ray Crystallographic Structural Assignments of OSM-S-35, OSM-S-42, OSM-S-54 and OSM-S-9 S34
Fig SC5. Assessment of Reactivity of exo Double Bond in Near Neighbor Compounds S34
5. Synthetic Attempts Towards the Ether Analog (OSM-S-236) S72
Fig SC6. Attempted syntheses of ether analog OSM-S-236 and suggested pathway of decomposition S72
6. Amines S73
Fig SC7. Synthesis of Amine Analogs S73
6.1 Commercial amines S77
7. Modified esters S79
Fig SC8. Synthesis of Modified Esters S79
7.1 Commercial esters S83
8. Ketones S84
Fig SC9. Ketone analogs via Friedel-Crafts acylation S84
9. Sulfonamides S87
Fig SC10. Synthesis of Sulfonamides S87
10. Pyrazoles S93
Fig SC11. Synthesis of Pyrazole Analogs S93
11. Oxazoles S98
Fig SC12. Synthesis of Oxazole Analogs S98
12. Triazoles S106
Fig SC13. Synthesis of Triazole Analogs S106
13. Commercial oxadiazole S109
References for Chemical Protocols S110

Biological Protocols for All Assays and Selected Biological Results (Includes Tables with Prefix "SB")

Table SB1. Evaluation of Resynthesized Hits and Potential Prodrug Fragments S113
Table SB2. Evaluation of Synthetic and Commercial Amide Analogs S113
Table SB3. Evaluation of Near Neighbour Series S114
Evaluation of Amine Analogs S115
Table SB4. Evaluation of Modified Ester Analogs S115
Evaluation of Ketone Analogs S116
Evaluation of Sulfonamides S116
Evaluation of Pyrazoles S116
Evaluation of Oxazoles S116
Evaluation of Triazoles S116
Potency Evaluation, Ralph Data, Round 1 S116
Potency Evaluation, Ralph Data, Round 2 S116
Potency Evaluation, GSK Data, Round 1 S116
Potency Evaluation, GSK Data, Round 2 S116
Potency Evaluation, Avery Data, Round 1 S117
Potency Evaluation, Avery Data, Round 2 S117
Potency Evaluation, Avery Data, Round 3a S117
Potency Evaluation, Avery Data, Round 3b S117
Potency Evaluation, Avery Data, Round 3c S117
Potency Evaluation, Avery Data, Round 4 S117

Potency Evaluation, Avery Data, Round 5 S117
Potency Evaluation, Batra Data S117
Potency Evaluation, Dundee Data, Round 1 S117
Potency Evaluation, Dundee Data, Round 2 S117
Potency Evaluation, Guy Data 1 S118
Table SB5. Solubility and Metabolic Stability of Selected Compounds S118
Charman Data Round 1 S119
Charman Data Round 2 S119
Metabolic Stability Assay S119
hERG Assay S119
Avery Late Stage Gametocyte Assay 1 S120
Avery Late Stage Gametocyte Assay 2 S122
Imperial DGFA Assay S122
In Vivo P. berghei Assay S122
P. berghei Pharmacokinetics Measurements S122
Charman Plasma Stability Studies S122
Charman Glutathione Trapping Experiments S123
Liver Stage Assay S123
Nislow Mode of Action Studies S124
Parasite Rate of Reduction (PRR, "Rate of Killing") Assay S125
In Silico Prediction of Target S126
DHODH Assay S126
Kirk Ion Regulation Assay S126
Similarity Mapping S126
References for Biological Protocols S127

Other Text-based Files

Text S1. Protocol and Results for PRR Assay for Compounds OSM-S-5, -10, -35, -37, -39 and -51. S128
Text S2. Methods Employed in Commercial Acquisition of Compounds. S137
Text S3. Methods and Results Arising from Second Assay from Ralph Laboratory. S138
Text S4. Results from Assay Performed by Batra Laboratory. S142
Text S5. Protocol Employed for Testing by Batra Laboratory. S143
Text S6. Synthetic Planning by Asclepia for Ether Compound (OSM-S-236). S145
Text S7. Synthetic Planning by Asclepia for Miscellaneous Compounds. S146
Text S8. Description of Procedures Used in Bioisostere Analysis. S149
Text S9. Potency Curves Derived from hERG Assay. S150
Text S10. Data and Method for the Dual Gamete Formation Assay. S152
Text S11. Target Prediction Analysis for OSM-S-39. S155
Text S12. Data and Methods Employed in DHODH Assay. S157

Figures

Fig S1. Screengrab of Synaptic Leap Node 343 (http://www.thesynapticleap.org/node/343), Open Source Drug Discovery for Malaria, Matthew Todd, 2011. Description of Laws Governing Project. S161

Fig S2. Screengrab of Synaptic Leap Node 349 (http://www.thesynapticleap.org/node/349), Known Near Neighbours of Initial Tres Cantos Leads, Matthew Todd, 2011. S164

Fig S3. Screengrab of Synaptic Leap Node 344 (http://www.thesynapticleap.org/node/344), Proposed Resynthesis Strategy for TCMDC-123812 and TCMDC-123794, Paul Ylioja, 2011. S166

Fig S4. Screengrab of MacinChem (http://macinchem.org/reviews/vortex/tut26/scripting_vortex26.php), Importing Open Source Malaria Project Data, Chris Swain 2015. S168

Fig S5. Screengrab of MacinChem (http://www.macinchem.org/reviews/osm/osmipython.php), Accessing Open Source Malaria Data using an iPython Notebook, Chris Swain, 2015. S172

Fig S6. Screengrab of Open Source Malaria Google+ discussion (https://plus.google.com/114702323662314783325/posts/Pma1Ddk2XCy), Discussion of Potential Assay Bias, 2012. S175

Fig S7. Similarity Network Map to identify Purchasable Compounds Around the GSK Lead Series (Related to Text S2) S182

Fig S8. Similarity Map of Purchaseable Compounds around OSM-S-35. (Related to Text S2) S183

Fig S9. Screengrab of Synaptic Leap Node 399 (http://www.thesynapticleap.org/node/399), Purchasable Compound Similarity Maps, Iain Wallace, 2012. (Related to Text S2) S184

Fig S10. Screengrab of Synaptic Leap Node 404 (http://www.thesynapticleap.org/node/404), Shop Till You Hit, Chris Southan, 2012. (Related to Text S2) S189

Fig S11. Screengrab of Blog Post (http://cdsouthan.blogspot.se/2012/05/shop-till-you-hit-chemical-suppliers.html), Shop Till You Hit: Chemical Suppliers and Malaria OSDD, Chris Southan, 2012. (Related to Text S2) S191

Fig S12. Potency Curves for OSM-S-72 to OSM-S-95 S201

Fig S13. Potency Curves for OSM-S-35, OSM-S-106, OSM-S-108 to OSM-S-116 S203

Fig S14. Screengrab of Biological Evaluation of Compounds ELN (http://malaria.ourexperiment.org/biological_data/2982), First Set of Biological Data from Sanjay Batra's Lab, CDRI, Lucknow, Matthew Todd, 2012. S206

Fig S15. LogP Calculations for Representative Near Neighbour Compounds, ChemBioDraw Ultra v14.0.0.117. S208

Fig S16. Correlation between LogP and Potency for Representative Near Neighbour Compounds S209

Fig S17. Screengrab of Synaptic Leap Node 367 (http://www.thesynapticleap.org/node/367), Biological Results for First Set of Compounds, Matthew Todd, 2012. S210

Fig S18. Screengrab of Blog Post, In the Pipeline (http://blogs.sciencemag.org/pipeline/archives/2010/02/08/polluting_the_literature_with_pains), Polluting the Literature with PAINS, Derek Lowe, 2010. S216

Fig S19. Screengrab of Blog Post, In the Pipeline (http://blogs.sciencemag.org/pipeline/archives/2014/09/26/pains_go_mainstream), PAINS Go Mainstream, Derek Lowe, 2014. S222

Fig S20. Screengrab of Near Neighbours ELN (http://malaria.ourexperiment.org/near_neighbours/2237), Reduction of 4-Fluoro Near-Neighbour Michael-Acceptor (PMY 36-2), Paul Ylioja, 2012. S234

Fig S21. Screengrab of Near Neighbours ELN (http://malaria.ourexperiment.org/near_neighbours/2259), Reduction of 4-Fluoro Near-Neighbour (N-H) Michael-Acceptor (PMY 39-1), Paul Ylioja, 2012. S236

Fig S22. Screengrab of Near Neighbours ELN (http://malaria.ourexperiment.org/near_neighbours/2181), Reduction of 4-Fluoro Near-Neighbour Michael-Acceptor (PMY 36-1), Paul Ylioja, 2012. S238

Fig S23. Screengrab of Near Neighbours ELN (http://malaria.ourexperiment.org/near_neighbours/2523), Testing Reactivity of Michael-Acceptor of ZYH 6-2 (PMY 41-1), Paul Ylioja, 2012. S240

Fig S24. Screengrab of Synaptic Leap Node 412 (http://www.thesynapticleap.org/node/412), Desired Compounds Consultation Phase 2, Matthew Todd, 2012. S242

Fig S25. Screengrab of Synaptic Leap Node 416 (http://www.thesynapticleap.org/node/416), Consultation Outcome, Paul Ylioja, 2012. S248

Fig S26. Potency Curves for OSM-S-96 to OSM-S-105. S255

Fig S27. Targeted Bioisostere List for Pyrrole Phenyl Replacements. S256

Fig S28. Broader Bioisostere Database for Pyrrole Phenyl Replacements. S258

Fig S29. Bioisostere Map for OSM-S-35. S263

Fig S30. Screengrab of Synaptic Leap Node 400 (http://www.thesynapticleap.org/node/400), Bioisosteric Transformation Maps, Iain Wallace, 2012. S264

Fig S31. Liver Stage Potency Curve for OSM-S-106 and OSM-S-111. S266

Fig S32. Gene Set Enrichment Map for OSM-S-9 (500 μM) S267

Fig S33. Gene Set Enrichment Map for OSM-S-12 (1 mM) S268

Fig S34. Gene Set Enrichment Map for OSM-S-31 (1 mM) S269

Fig S35. Gene Set Enrichment Map for OSM-S-39 (500 μM) S270

Fig S36. Gene Set Enrichment Map for OSM-S-51 (125 μM) S271

Fig S37. Composite PRR Assay Results and Potencies for Compounds OSM-S-5, -10, -35, -37, -39 and -51. S272

Fig S38. Ion Regulation Assay for Compounds OSM-S-4, -5, -35, -51, -106, -111. S273

Fig S39. Similarity Map Surrounding OSM-S-39 from the ChEMBL Database (v13). S276

Fig S40. Screengrab of Blog Post, In the Pipeline (http://blogs.sciencemag.org/pipeline/archives/2016/07/21/company-time-for-your-own-ideas-or-not), Company Time for Your Own Ideas, Or Not? Derek Lowe, 2016. S277

Datasets (Uploaded Separately)

Dataset S1. All Molecules in Excel Format.
Dataset S2. All Molecules in SDF Format.
Dataset S3. Potency Data from Ralph Assay 1
Dataset S4. Potency Data from GSK Assay 1
Dataset S5. Potency Data from Avery Assay 1
Dataset S6. Similarity Network Data for Tres Cantos Series in Cytoscape Format (see Text S1)
Dataset S7. Map of Purchaseable Compounds Around OSM-S-35 in Cytoscape Format (see Text S1)
Dataset S8. Potency Data from Ralph Assay 2
Dataset S9. Potency Data from GSK Assay 2
Dataset S10. Potency Data from Avery Assay 2
Dataset S11. Potency Data from Avery Assay 3a
Dataset S12. Potency Data from Avery Assay 3b
Dataset S13. X-Ray Structural Information for OSM-S-35, -42, -54 and -9.
Dataset S14. Potency Data from Avery Assay 5
Dataset S15. Potency Data from Guy Assay
Dataset S16. Potency Data from Avery Assay 3c
Dataset S17. Potency Data from Dundee Assay 1
Dataset S18. Potency Data from Dundee Assay 2
Dataset S19. Bioisostere Analysis in Cytoscape Format
Dataset S20. Solubility and Microsomal Stability Data for OSM-S-5, -6, -9, -10, -37, -38, -39 and -54.
Dataset S21. Solubility and Microsomal Stability Data for OSM-S-111.
Dataset S22. Data from oral *in vivo P. berghei* mouse trial for compounds OSM-S-5, -6 and -35.
Dataset S23. Pharmacokinetic Data from oral *in vivo P. berghei* mouse trial.
Dataset S24. Human and Mouse Plasma Stability Data for OSM-S-5.
Dataset S25. Metabolite Identification Assay Data for OSM-S-35 in Human Liver Microsomes
Dataset S26. hERG Assay Data for Compounds OSM-S-5 and -35.
Dataset S27. Avery Late Stage Gametocyte Assay 1.
Dataset S28. Avery Late Stage Gametocyte Assay 2.
Dataset S29. UCSD Liver Stage Assay 1.
Dataset S30. UCSD Liver Stage Assay 2.
Dataset S31. UCSD Liver Stage Assay 3.
Dataset S32. Nislow Gene Set Enrichment Analysis Data, Excel Format.
Dataset S33. Nislow Gene Set Enrichment Analysis Data, Spotfire Format.
Dataset S34. Nislow Gene Set Enrichment Analysis Data, Powerpoint Format.
Dataset S35. Nislow Fitness Defect Scores for all Deletion Strains, Excel Format.
Dataset S36. Data from GSK DHODH Assay
Dataset S37. Data from Kirk Ion Regulation Assay
Dataset S38. Similarity Map Surrounding OSM-S-39 in Cytoscape Format

Chemical Protocols

I. General experimental details

All commercially available reagents and solvents were purchased and used as received from Sigma-Aldrich or Alfa-Aesar. Drying of glassware at 115 ˚C overnight and activation of molecular sieves in a microwave was performed when anhydrous conditions were required. Dichloromethane was distilled over calcium hydride. Reflux reactions were performed with a paraffin oil bath. Flash column chromatography was performed with Grace Silica Gel 60 (40 – 63 μm, 230 – 400 mesh), with solvent ratios as specified. All novel compounds listed below are italicised.

Melting points were obtained on an Optimelt Automated Melting Point System and reported in degrees Celsius. Optical rotation was recorded on a Perkin Elmer 341 polarimeter with Na lamp (589 nm).

^{1}H and ^{13}C nuclear magnetic resonance spectroscopy was conducted on a Bruker Avance III 500 (^{1}H at 500.1 MHz, ^{13}C at 125.8 MHz, ^{19}F at 470.6 MHz), a Bruker Avance III 400 (^{1}H at 400.1 MHz, ^{13}C at 100.6 MHz, ^{19}F at 376.5 MHz), a Bruker Avance 300 (^{1}H at 300.1 MHz, ^{13}C at 75.5 Hz, ^{19}F at 282.4 MHz) or a Bruker Avance 200 (^{1}H at 200.1 MHz) with deuterated solvents ($CDCl_3$, *d*-DMSO, MeOD) used without further purification. Signals are reported in the order chemical shift (ppm downfield with respect to the solvent residual), integration, multiplicity, coupling constants *J* (in Hertz) and assignments.

Low-resolution mass spectrometry was performed on a Finnigan LCQ mass spectrometer, with either electrospray ionisation (ESI) mode or atmospheric-pressure chemical ionisation (APCI) under positive mode. High-resonance mass spectrometry was performed on a Bruker 7T Fourier Transform Ion Cyclotron Resonance mass spectrometer, with either electrospray ionisation (ESI) mode or atmospheric-pressure chemical ionisation (APCI) under positive mode.

Infrared spectroscopy was performed on a Bruker Alpha FT-IR spectrometer under transmission mode, with absorbances reported as wave numbers.

Each experimental entry contains a publically accessible hyperlink to the representative example from the Open Source Malaria electronic lab notebook (ELN, http://malaria.ourexperiment.org) reported in this experimental section and also to a page where all attempts at the reaction are collated. Raw and processed data are available on the ELN, which have been archived for publication at The University of Sydney institutional repository at http://hdl.handle.net/2123/14132

II. Chemistry: Experimental procedures and characterization data

1. General Experimental

General Procedure A: Paal-Knorr synthesis of *N*-aryl pyrroles

Aniline (1.1 equiv.) and 2,5-hexanedione (1 equiv.) were heated to the stated temperature. After the stated time, the reaction was cooled to rt and purified to obtain the N-*aryl pyrrole* product.

General Procedure B: Vilsmeier-Haack formylation of pyrroles

DMF (6–12 equiv.) was stirred under a nitrogen atmosphere in an ice-bath. Phosphoryl chloride (1.0–1.3 equiv.) was added and the reaction stirred for 25 min. A solution of *pyrrole* (1.0 equiv.) in DMF (6–7 equiv.) was added dropwise over 5 min. The reaction was removed from the ice-bath and allowed to warm to rt. After 45–60 min the reaction was poured over ice and the pH adjusted to 6 (approx. 20% /NaOH (aq.)) and left stirring overnight. 20% NaOH(aq) added until pH 11 and left for a further 30 min. The solid was filtered and washed with water and then recrystallised to obtain the desired *aldehyde.*

General Procedure C: Hantzsch-type synthesis of *N*-aryl pyrroles

Ethyl acetoacetate (1.0 equiv.) and K_2CO_3 (1.3 equiv.) in MeCN (0.5 M) were cooled to 0 ˚C. NaI (1.0 equiv.) was added in a single portion and then chloroacetone (1.1 equiv.) was added dropwise and stirred for 15 min at 0 ˚C then allowed to warm to rt. After a further 15 min, sodium iodide (1.1 equiv.) was added and the reaction mixture was stirred for 1.5 h when a yellow suspension formed. The reaction mixture was heated at reflux for the stated time, cooled and then filtered. The filtrate was concentrated under reduced pressure and dissolved in EtOAc, washed with water, brine/water (1:1), brine, dried ($MgSO_4$), filtered and then concentrated under reduced pressure to yield ethyl 2-acetyl-4-oxopentanoate as a crude brown oil (NMR consistent with product),[1] which was combined with the *aniline* (1.2 equiv.) and the reaction heated to 80–90 ˚C for the stated time. The reaction was allowed to cool to rt and was dissolved in EtOAc. The solution was washed with citric acid (10% aqueous solution), water, brine and then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resultant crude substance was then purified to give the desired *ester* product.

General Procedure D: Hydrolysis of pyrrole-3-esters to their corresponding acids

Pyrrole-3-ester (1 equiv.) was dissolved in EtOH and NaOH (20% aqueous solution, ~17 equiv.). The reaction was heated to reflux for the stated time and then cooled in ice. HCl (15% aqueous solution) was added slowly until a precipitate formed (pH 1). The mixture was stirred for a further 15 min and then filtered, washed with water and dried *in vacuo*.

General Procedure E: EDCI mediated amide coupling

Acid (1.0 equiv.) was dissolved in CH_2Cl_2, EDCI (1.2 equiv.) and HOBt (0.1 equiv.) were added and the mixture stirred for 20 min. *Amine* (1.5 equiv.) was added and the reaction mixture stirred at rt for the stated time. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), filtered and evaporated to give the crude product which was purified by flash column chromatography over silica.

General Procedure F: Acid chloride mediated amide/ester formation

Acid (1 equiv.) was dissolved in dry PhMe (0.1 M) with sonication and cooled to 0 ˚C, DMF (cat ~ 1 drop) was added followed by thionyl chloride (2.9 equiv.). The reaction mixture was allowed to warm to rt and stirred for the stated time and then the reaction was concentrated to remove thionyl chloride. The *crude acid chloride* was taken up in PhMe (0.1 M) and then the solvent removed *in vacuo* followed by trituration from hexane (0.05 M). The *crude acid chloride* was then dissolved in the stated solvent and cooled to 0 ˚C. A solution of the stated *amine* (1.1 equiv.) and *base* (1.5 equiv.) was added to the *acid chloride* and the reaction mixture stirred for the stated time whilst warming to rt. The reaction was quenched by the addition of water and then extracted with CH_2Cl_2. Organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica (0–20% EtOAc/petrol).

General Procedure H: 2-Imidathiazoline synthesis

Thiazolidin-one (1.0 equiv.) was dissolved in EtOH (~0.1 M) and piperidine (1.5 equiv.) was added. *Aldehyde* (1 equiv.) was added and the resulting mixture stirred at the stated temperature for the stated time. The reaction mixture was cooled to rt and then the precipitate was filtered and washed with cold EtOH to provide the desired product, which was purified by the stated method.

General Procedure I: Reductive amination

Aldehyde (1.0 equiv.) was dissolved in acidic MeOH (0.1 M) and then *amine* (1.3 equiv.) was added. The reaction mixture was stirred for the stated time at rt and then sodium cyanoborohydride (1.1 equiv.) was added in two portions. The reaction was stirred at rt for the stated time and then volatiles removed under reduced pressure, treated with 1M NaOH and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated before purification to give the desired *secondary amine* product.

2. Original hits and their putative prodrug fragments

Synthetic Approach

Conversion of the acid OSM-S-4 to OSM-S-5 (TCMDC-123812), the first of the original GSK hits to be resynthesized, was achieved using a base and bromoacetamide; this was found to be superior to a number of attempted alternatives including coupling with glycolamide either *via* the pyrrole's acid chloride or directly through the use of coupling reagents (diisopropylcarbodiimide (DIC) or propylphosphonic anhydride (T3P)). OSM-S-6 (TCMDC-123794), was synthesised from the acid (OSM-S-4) *via* the coupling of the corresponding acid chloride with a functionalised antipyrene moiety OSM-S-192, itself made from commercially available 4-aminoantipyrene and glycolic acid, using the acetonide[2-3] of the latter (OSM-S-193).

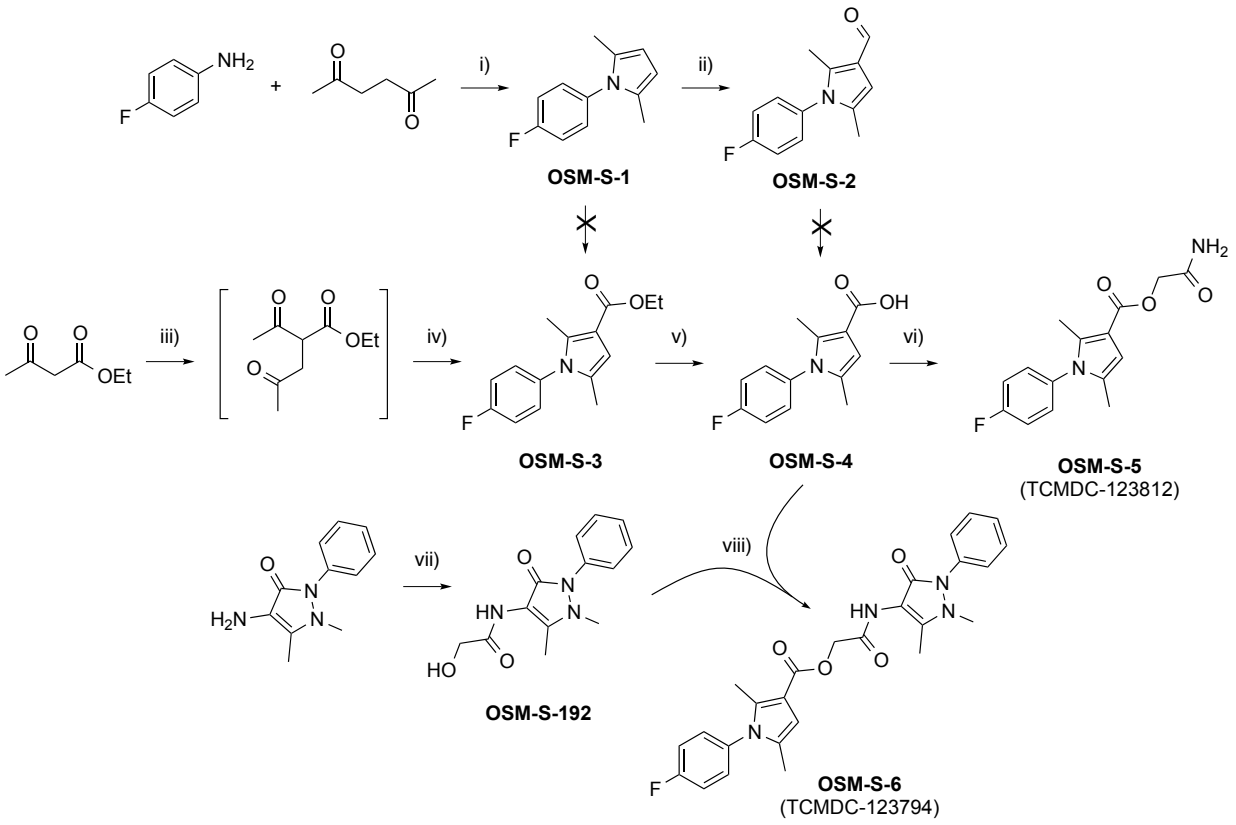
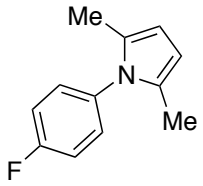


Fig SC1. Resynthesis of the GSK Aryl Pyrrole Esters. Reagents and Conditions: i) 110 ˚C, neat; ii) DMF, $POCl_3$, 10 ˚C to rt; iii) K_2CO_3, chloroacetone, NaI, K_2CO_3, 80 ˚C; iv) 4-fluoroaniline, 80 ˚C; v) 20% aqueous NaOH solution, EtOH, reflux; vi) 2-bromoacetamide, K_2CO_3, DMF, rt; vii) glycolic acid acetonide, toluene, reflux; viii) OSM-S-4, $SOCl_2$, toluene, cat. DMF, 2 h, then OSM-S-192, K_2CO_3, Et_3N.

1-(4-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrole, OSM-S-1



Representative Example: http://malaria.ourexperiment.org/uri/17

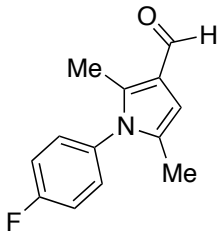
Prepared according to General Procedure **A** from: 4-fluoroaniline (10.4 mL, 110 mmol, 1.1 equiv.) and 2,5-hexanedione (11.7 mL, 100 mmol, 1.0 equiv.); 110 ˚C (oil bath temp.) for 15 h then the mixture was dissolved in hot EtOH (15 mL) and a mixture of EtOH (30 mL) and citric acid (10% aqueous solution, 15 mL). The solution was slowly cooled to approx. 10 ˚C with periodic shaking. The resulting crystals were filtered and washed with water (approx. 200 mL) to provide the product as pale tan crystals (16.9 g, 89%); **m.p.** 48–49 ˚C (EtOH/H_2O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.21–7.11 (4H, m), 5.89 (2H, s), 2.01 (6H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 161.9 (d, *J* 247.4), 135.0 (d, *J* 2.7), 129.9 (d, *J* 8.5), 128.9, 116.0 (d, *J* 22.6), 105.8, 12.9; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -114.1; **m/z** (APCI+) 190 $[M+H]^+$.

InChi=1S/C12H12FN/c1-9-3-4-10(2)14(9)12-7-5-11(13)6-8 -12/h3-8H,1-2H3.

All attempts: http://malaria.ourexperiment.org/uri/4b5

Data consistent with literature.[4]

1-(4-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrole-3-carbaldehyde, OSM-S-2



Representative example: http://malaria.ourexperiment.org/uri/1f

Prepared according to General Procedure **B** from DMF (5.0 mL), phosphoryl chloride (1.18 mL, 12.7 mmol, 1.2 equiv.) then OSM-S-1 (2.00 g, 10.5 mmol, 1.0 equiv.) in DMF (5 mL); recrystallised from (MeCN/water) to obtain a first crop of tan free-flowing powder (2.05 g, 89%); **m.p.** 117–118 ˚C (MeCN/water); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.87 (1H, s), 7.22–7.20 (4H, m), 6.38 (1H, s), 2.27 (3H, s), 1.98 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 185.3, 162.5 (d, *J* 249.7), 138.8, 132.8 (d, *J* 2.2), 131.0, 129.7 (d, *J* 8.7), 122.0, 116.6 (d, *J* 22.8), 106.0, 12.6, 11.2; **m/z** (APCI+) 218 $[M+H]^+$.

InChi=1S/C13H12FNO/c1-9-7-11(8-16)10(2)15(9)13-5-3-12(14)4-6-13/h3-8H,1-2H3.

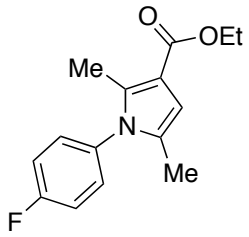
Improvement to preparative method received here:

http://www.thesynapticleap.org/node/344#comment-712.

All attempts: http://malaria.ourexperiment.org/uri/4b8

Data consistent with literature.[4,5]

Ethyl 1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, OSM-S-3



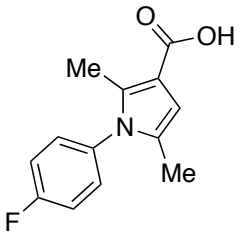
Representative Example: http://malaria.ourexperiment.org/uri/20

Prepared according to General Procedure **C** from: ethyl acetoacetate (2.00 mL, 15.7 mmol, 1.0 equiv.), K_2CO_3 (2.82 g, 20.4 mmol, 1.2 equiv), NaI (2.58 g, 17.2 mmol, 1.1 equiv.) and chloroacetone (1.39, 17.2 mmol, 1.1 equiv.) in MeCN (30 mL); reflux for 20 h. Then crude intermediate combined with 4-fluoroaniline (1.78 mL, 18.8 mmol); 90 ˚C for 2 h. Crude product dissolved in warm EtOH (4 mL) and cooled in ice until crystallisation initiated, then 40% EtOH (16 mL) was added slowly with stirring. Cooled in ice for 30 min then filtered, washed with 20% EtOH and dried under vacuum to provide the desired product as red/brown crystals (2.77 g, 61%); **m.p.** 63–66 ˚C (EtOH/H_2O); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.19–7.16 (4H, m), 6.37 (1H, s), 4.28 (2H, q, *J* 7.1), 2.28 (3H, s), 1.96 (3H, s), 1.34 (3H, d, *J* 7.1); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 165.6, 162.3 (d, *J* 248.8), 136.2, 133.7 (d, *J* 2.9), 129.9 (d, *J* 8.7), 128.8, 116.4 (d, *J* 22.8), 111.6, 107.6, 59.3, 14.5, 12.6, 12.3; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.5; **IR** ν_{max} (neat) /cm^{-1} 1697, 1512, 1218, 1079, 775; **HRMS** (ESI+) found 262.12378 $[M+H]^+$, $C_{15}H_{17}NO_2F$ requires 262.12374.

InChI=1S/C15H16FNO2/c1-4-19-15(18)14-9-10(2)17(11(14)3)13-7-5-12(16)6-8-13/h5-9H,4H2,1-3H3.

All attempts: http://malaria.ourexperiment.org/uri/2c5

1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid, OSM-S-4



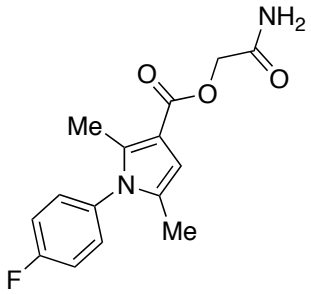
Representative Examples: http://malaria.ourexperiment.org/uri/81

Prepared according to General Procedure **D** from: **OSM-S-1** (2.16 g, 8.27 mmol) in EtOH (30 mL) and 20% NaOH(aq) (40 mL); reflux for 16 h; pale brown powder (1.73 g, 89%); **m.p.** 241–242 ˚C (acetone/H_2O) decomposition; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.19 (4H, app d, *J* 6.4), 6.42 (1H, br s), 2.30 (3H, s), 1.97 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 171.09, 162.4 (d, *J* 249.0), 137.8, 133.6 (d, *J* 2.7), 129.9 (d, *J* 8.6), 129.2, 116.5 (d, *J* 22.8), 110.8, 108.2, 12.6, 12.5; **IR** ν_{max} (neat) /cm^{-1} 2928, 1694, 1420, 1310, 1202, 921, 640.

InChI=1S/C13H12FNO2/c1-8-7-12(13(16)17)9(2)15(8)11-5-3-10(14)4-6-11/h3-7H,1-2H3,(H,16,17).

All attempts: http://malaria.ourexperiment.org/uri/2c6

2-Amino-2-oxoethyl 1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, TCMDC-123812, OSM-S-5



Representative example: http://malaria.ourexperiment.org/uri/163

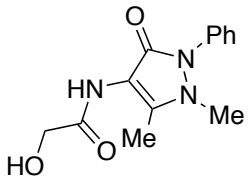
OSM-S-4 (200 mg, 0.857 mmol, 1.0 equiv.) was dissolved in DMF (4.5 mL) at rt and then solid potassium carbonate (237 mg, 1.71 mmol, 2.0 equiv.) was added in two portions. The reaction mixture was stirred at rt for 15 min and then 2-bromoacetamide (142 mg, 1.02 mmol, 1.2 equiv.) was added in a single portion. After 3 h, the reaction mixture was partitioned between EtOAc and water (12 mL, 1:1) and extracted with EtOAc (3 × 6 mL). The combined organic layers were washed with water, brine and dried ($MgSO_4$) to give an orange oil. The reaction mixture was dried *in vacuo* for 4 h to give a crystalline orange gum and then purified by flash column chromatography over silica (5:1 to 9:1, EtOAc/petrol) to provide the title compound as a white solid (196 mg, 79% yield); **m.p.** 176–177 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.21–7.17 (4H, m), 6.37 (1H, s), 6.03 (2H, app br

d, *J* 70.2), 4.74 (2H, s), 2.30 (3H, s), 1.98 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 171.1, 163.7, 162.5 (d, *J* 249.3), 137.8, 133.3 (d, *J* 3.4), 129.8 (d, *J* 8.7), 129.4, 116.6 (d, *J* 23.0), 109.9, 107.4, 61.8, 12.6, 12.4; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -111.92; **IR** ν_{max} (neat) /cm^{-1} 3430, 1686, 1512, 119, 1214, 1090, 773; **HRMS** (ESI+) found 313.09578 $[M+Na]^+$, $C_{15}H_{15}N_2O_3FNa$ requires 313.09589.

InChI=1S/C15H15FN2O3/c1-9-7-13(15(20)21-8-14(17)19)10(2)18(9)12-5-3-11(16)4-6-12/h3-7H,8H2,1-2H3,(H2,17,19).

All examples: http://malaria.ourexperiment.org/uri/2c7

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-hydroxyacetamide, OSM-S-192



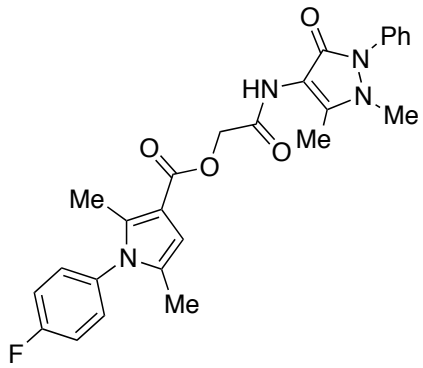
Representative example: http://malaria.ourexperiment.org/uri/25

Glycolic acid (2.1 g, 27 mmol, 1.00 equiv.) was stirred in acetone (40 mL) with a few crystals of *p*-TSA for 1 h. $NaHCO_3$ (~1 g) was added and dried ($MgSO_4$) before filtration and partial concentration to a colourless oil (^{1}H NMR consistent with acetonide/glycolic acid and acetone in~ 1:2.4:11.8).[6,2] The crude oil was stirred in toluene (40 mL), the material crystallised and was dissolved by heating. 4-Aminoantipyrine (5.73 g, 28.2 mmol, 1.05 equiv.) was added and the reaction heated to reflux. After 15.5 h, the reaction was cooled to yield an orange solid suspended in a near colourless solvent. The solid was dissolved by addition of EtOAc and CH_2Cl_2 and then concentrated to form a pale orange foam (7.67 g), which was then dissolved in water (~150 mL) and washed with EtOAc (3 × 50 mL). The aqueous layer was concentrated under reduced pressure to yield a tan foam which was purified by flash column chromatography over silica (0–10% MeOH in CH_2Cl_2) to yield the desired product (710 mg, 14% yield) along with 5.67 g of impure material; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.59 (1H, s), 7.51–7.46 (2H, m), 7.38–7.33 (3H, m), 4.37–3.98 (1H, bs) 4.16 (2H, s), 3.12 (3H, s), 2.22 (3H, s), **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 172.5, 161.7, 150.0, 133.8, 129.4, 127.8, 125.2, 106.5, 62.4, 35.3, 11.7.

InChI=1S/C13H15N3O3/c1-9-12(14-11(18)8-17)13(19)16(15(9)2)10-6-4-3-5-7-10/h3-7,17H,8H2,1-2H3,(H,14,18)

All attempts: http://malaria.ourexperiment.org/uri/5a5

2-((1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-2-oxoethyl 1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, TCMDC-123794, OSM-S-6



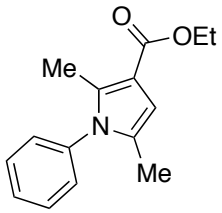
Representative example: http://malaria.ourexperiment.org/uri/2a

The required acid chloride was synthesised according to General Procedure **F** from **OSM-S-4** (104 mg, 0.446 mmol, 1.0 equiv.) and then the residue was dissolved in MeCN (5 mL) and then **OSM-S-192** (131 mg, 0.490 mmol, 1.1 equiv.) in MeCN (2 mL) and Et_3N (0.2 mL) was added and the reaction heated to 60 ˚C for 15 h. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was purified by flash chromatography over silica (0–3% MeOH/CH_2Cl_2) to obtain a glassy solid (17 mg, 8% yield); **m.p.** 196–198 ˚C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.66 (1H, br s), 7.47–7.44 (2H, m), 7.40–7.37 (2H, m), 7.32–7.28 (1H, m), 7.21–7.14 (4H, m), 6.44 (1H, d, *J* 0.9), 4.87 (2H, s), 3.09 (3H, s), 2.31 (6H, s), 1.95 (3H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 167.0, 163.7, 162.4 (d, *J* 249.2), 161.4, 149.4, 137.7, 134.6, 133.4 (d, *J* 3.1), 129.8 (d, *J* 8.7), 129.4, 129.2, 126.9, 124.1, 116.5 (d, *J* 23.1), 109.9, 107.7 (2C), 62.1, 36.2, 12.6, 12.5; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.14; **IR** ν_{max} (neat) /cm^{-1} 1701, 1511, 1209, 1095, 769; **m/z** (ESI+) 477 $[M+H]^+$; **HRMS** (ESI+) found 499.17513 $[M+Na]^+$, $C_{26}H_{25}N_4O_4FNa$ requires 499.17520.

InChI=1S/C26H25FN4O4/c1-16-14-22(17(2)30(16)20-12-10-19(27)11-13-20)26(34)35-15-23(32)28-24-18(3)29(4)31(25(24)33)21-8-6-5-7-9-21/h5-14H,15H2,1-4H3,(H,28,32).

All attempts: http://malaria.ourexperiment.org/uri/2c8

Ethyl 2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylate, OSM-S-31



Representative example: http://malaria.ourexperiment.org/uri/50

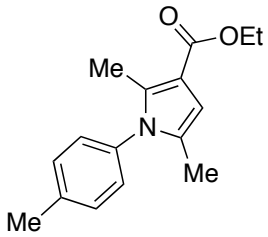
Prepared according to General Procedure **C** from: ethyl acetoacetate (6.0 mL, 47 mmol, 1.0 equiv.), K_2CO_3 (8.45 g, 61 mmol, 1.1 equiv.), NaI (7.1 g, 47 mmol, 1.0 equiv.) and chloroacetone (4.8 mL, 52 mmol, 1.1 equiv.); reflux for 2 h. Then crude intermediate combined with aniline (1.2 mL, 13 mmol); 80 ˚C for 75 min. Crude product was purified by flash column chromatography over silica (2–15% EtOAc/petrol) to yield the desire product as a yellow oil (952 mg, 37%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.50–7.41 (2H, m), 7.18–7.15 (2H, m), 6.38 (1H, s), 4.28 (2H, q, *J* 7.1,), 2.29 (3H, s), 1.97 (3H, s), 1.34 (3H, t, *J* 7.1); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 165.7, 137.8, 136.2, 129.4, 128.7, 128.5, 128.2, 111.5, 107.6, 59.2, 14.6, 12.6, 12.4; **IR** ν_{max} (neat) /cm^{-1} 2978, 1693, 1411, 121; **m/z** (APCI+) 244 $[M+H]^+$.

InChI=1S/C15H17NO2/c1-4-18-15(17)14-10-11(2)16(12(14)3)13-8-6-5-7-9-13/h5-10H,4H2,1-3H 3.

All attempts: http://malaria.ourexperiment.org/uri/2e1

Data consistent with literature.[7]

Ethyl 2,5-dimethyl-1-(p-tolyl)-1H-pyrrole-3-carboxylate, OSM-S-30



Representative example: http://malaria.ourexperiment.org/uri/4f

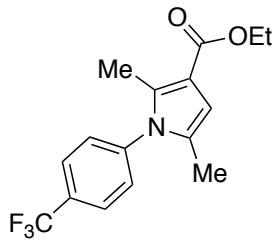
Prepared according to General Procedure **C** from: ethyl acetoacetate (2.00 mL, 15.7 mmol), K_2CO_3 (2.82 g, 20.4 mmol), NaI (2.7 g, 18 mmol) and chloroacetone (1.60 mL, 17.2 mmol) in MeCN (30 mL); 80 ˚C for 2.5 h. Then crude intermediate combined with *p*-toluidine (2.02 g, 18.8 mmol); 90 ˚C for 1.5 h. Crude product was purified by flash column chromatography over silica (2–10% EtOAc in petrol) to yield the title compound as a bright yellow crystalline solid (1.80 g, 46%); **m.p.** 60–63 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.27 (2H, d, *J* 7.6), 7.04 (2H, d, *J* 7.6), 6.36 (1H, s), 4.27 (2H, q, *J* 7.0), 2.42 (3H, s), 2.28 (3H, s), 1.96 (3H, s), 1.34 (3H, t, *J* 7.0); **^{13}C**

NMR (76 Hz, $CDCl_3$) δ: 165.6, 138.4, 136.2, 135.0, 129.9, 128.7, 127.8, 111.2, 107.3, 59.1, 21.0, 14.5, 12.5, 12.2; **IR** ν_{max} (neat) /cm^{-1} 2982, 1693, 1515, 1411, 1218, 1081, 767; **m/z** (APCI+) 258 $[M+H]^+$; **HRMS** found 280.13088 $[M+Na]^+$, $C_{16}H_{19}NO_2Na$ requires 280.13080.

InChI=1S/C16H19NO2/c1-5-19-16(18)15-10-12(3)17(13(15)4)14-8-6-11(2)7-9-14/h6-10H,5H2,1-4H3.

All attempts: http://malaria.ourexperiment.org/uri/2e0

Ethyl 2,5-dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrrole-3-carboxylate, OSM-S-32



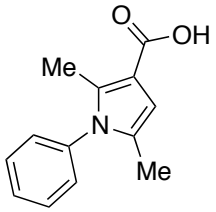
Representative example: http://malaria.ourexperiment.org/uri/35

Prepared according to General Procedure **C** from: ethyl acetoacetate (6 mL, 47 mmol), K_2CO_3 (8.45 g, 61.1 mmol) NaI (7.05 g, 47 mmol,) and chloroacetone (4.8 mL, 51.7 mmol); reflux for 2 h. Then crude intermediate combined with *p*-(trifluoromethyl)aniline (1.62 mL, 12.9 mmol); 80 ˚C for 75 min. Crude product was purified by flash column chromatography over silica (2–15% EtOAc/petrol) to yield the desire product as a pale yellow crystalline solid (1.85 g, 55%); **m.p.** 66–68 ˚C (EtOAc/petrol); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.78 (2H, d, *J* 8.0), 7.33 (2H, d, *J* 8.0), 6.41 (1H, s), 4.28 (2H, q, *J* 7.0), 2.30 (3H, s), 1.99 (3H, s), 1.35 (3H, t, *J* 7.0); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 165.4, 140.9, 135.7, 130.7 (q, *J* 32.9), 128.7, 128.4, 126.5 (bd, *J* 3.5), 123.6 (q, *J* 272.1), 112.2, 108.2, 59.3, 14.4, 12.5, 12.2; **^{19}F{^{1}H} NMR** -62.7; **IR** ν_{max} (neat) /cm^{-1} 2928, 1681, 1614, 1414, 1322, 1215, 1065, 541, 770; **m/z** (APCI+) 312 $[M+H]^+$; **HRMS** found 312.12052 $[M+H]^+$, $C_{16}H_{17}F_3NO_2$ requires 312.12059.

InChI=1S/C16H16F3NO2/c1-4-22-15(21)14-9-10(2)20(11(14)3)13-7-5-12(6-8-13)16(17,18)19/h5-9H,4H2,1-3H3

All attempts: http://malaria.ourexperiment.org/uri/2e2

2,5-Dimethyl-1-phenyl-1H-pyrrole-3-carboxylic acid, OSM-S-12



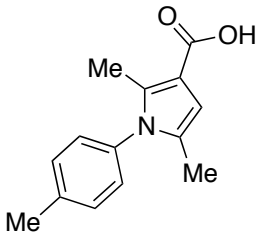
Representative example: http://malaria.ourexperiment.org/uri/42

Prepared according to General Procedure **D** from: **OSM-S-31** (487 mg, 2.00 mmol) in EtOH (10 mL) and 20% NaOH(aq) (13 mL); reflux for 4 h; brown powder (333 mg, 77%); **m.p.** 210–211 ˚C (H_2O) decomposition; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.56–7.47 (3H, m), 7.24–7.20 (2H, m), 6.47 (1H, bs), 2.34 (3H, s), 2.01 (3H, s); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 171.4, 137.6, 129.4, 129.1, 128.6, 128.1, 110.7, 108.1, 12.6, 12.5; **IR** ν_{max} (neat)/ cm^{-1} 2938, 1657, 1541, 1456, 1265; **m/z** (APCI+) 230 $[M+H]^+$; **HRMS** (ESI+) found 238.08376 $[M+Na]^+$, $C_{13}H_{13}NO_2Na$ requires 238.08385.

InChI=1S/C13H13NO2/c1-9-8-12(13(15)16)10(2)14(9)11-6-4-3-5-7-11/h3-8H,1-2H3,(H,15,16).

All attempts: http://malaria.ourexperiment.org/uri/2ce

2,5-Dimethyl-1-(p-tolyl)-1H-pyrrole-3-carboxylic acid, OSM-S-13



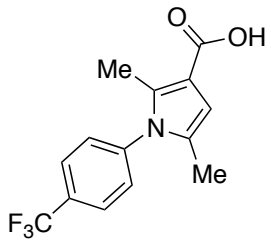
Representative example: http://malaria.ourexperiment.org/uri/43

Prepared according to General Procedure **D** from: **OSM-S-30** (522 mg, 2.03 mmol) in EtOH (10 mL) and 20% NaOH(aq) (13 mL); reflux for 16 h; pale pink solid (395 mg, 85%); **m.p.** 228–240 ˚C (H_2O) decomposition; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.32 (2H, bd, *J* 8.0 Hz), 7.09 (2H, bd, *J* 8.0 Hz), 6.44 (1H, s), 2.46 (3H, s), 2.33 (3H, s), 2.00 (3H, s); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 171.2, 138.6, 137.8, 135.0, 130.0, 129.2, 127.9, 110.5, 107.9, 21.1, 12.7, 12.5; **IR** ν_{max} (neat) /cm^{-1} 2820, 1656, 1516, 1428, 1269; **m/z** (ESI-) 228 $[M-H]^-$; **HRMS** (ESI+) found 252.09946 $[M+Na]^+$, $C_{14}H_{15}NO_2Na$ requires 252.09950.

InChI=1S/C14H15NO2/c1-9-4-6-12(7-5-9)15-10(2)8-13(11(15)3)14(16)17/h4-8H,1-3H3,(H,16,17)

All attempts: http://malaria.ourexperiment.org/uri/2e0

2,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrrole-3-carboxylic acid, OSM-S-14



Representative example: http://malaria.ourexperiment.org/uri/44

Prepared according to General Procedure **D** from: **OSM-S-32** (542 mg, 1.74 mmol) in EtOH (10 mL) and 20% NaOH(aq) (13 mL); reflux for 4 h; cream solid (402 mg, 82%); **m.p.** 241–242 ˚C (H_2O) decomposition; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.80 (2H, d, *J* 8.1), 7.35 (2H, d, *J* 8.1), 6.46 (1H, s), 2.32 (3H, s), 2.00 (3H, s); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ: -62.7; **m/z** (APCI+) 298 $[M+H]^+$; **HRMS** (ESI-) found 587.13991 $[M-2H+Na]^-$, $C_{14}H_{10}NO_2F_3Na$ requires 587.13869.

InChI=1S/C14H12F3NO2/c1-8-7-12(13(19)20)9(2)18(8)11-5-3-10(4-6-11)14(15,16)17/h3-7H,1-2H3,(H,19,20)

All attempts: http://malaria.ourexperiment.org/uri/2d0

3. Amide Analogs

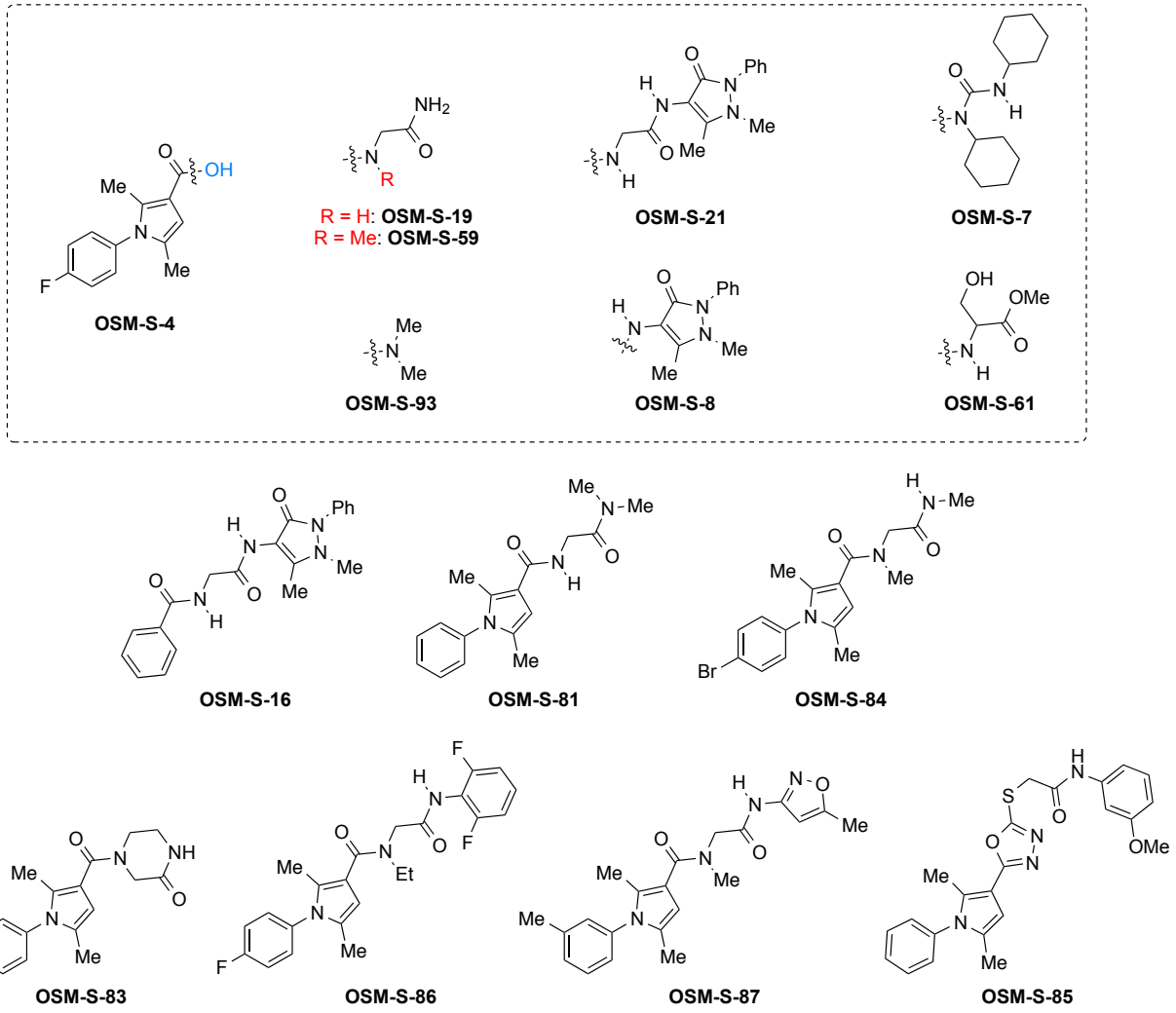
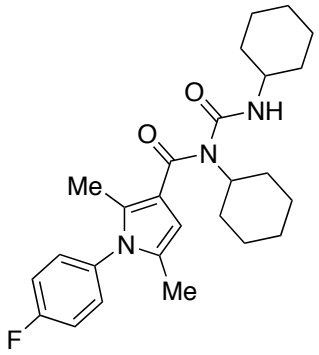


Fig SC2. The Full Set of Amide Analogs Evaluated. Compounds OSM-S-19, -21, -59, -61 were obtained by conversion of the acid to the acid chloride, while compounds OSM-S-8 and -16 were obtained with T3P couplings[8] and compound -93 through the use of EDCl as a coupling agent. Compounds OSM-S-81, -83, -84, -86, -87 and the oxadiazole analog OSM-S-85 were purchased.

N-Cyclohexyl-N-(cyclohexylcarbamoyl)-1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide, OSM-S-7



Representative example: http://malaria.ourexperiment.org/uri/30

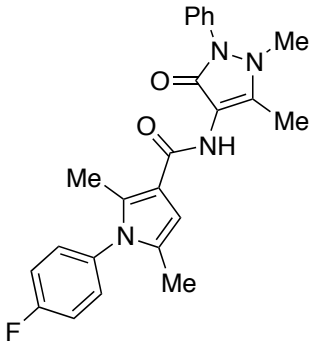
Note: Undesired by-product of reaction.

OSM-S-4 (50 mg, 0.21 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (7 mL) and cooled in ice. DCC (49 mg, 0.24 mmol, 1.1 equiv.) was added. After 5 min, 4-aminoantipyrine (48 mg, 0.24 mmol, 1.1 equiv.) was added as a solution in CH_2Cl_2 (1 mL). After 40 min, the reaction was allowed to warm to rt and stirred for 24 h, prior to the addition of 4-DMAP (~10 mg). The reaction mixture was concentrated under reduced pressure, diluted with EtOAc (3 mL) filtered and purified by flash column chromatography over silica (10–50% EtOAc, then 10% MeOH/ CH_2Cl_2) to obtain the title compound as a pale yellow solid (59 mg, 64% yield); **m.p.** 132 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.22–7.11 (4H, m), 6.54 (1H, br app d, *J* 7.3), 6.10 (1H, s), 4.26 (1H, br t, *J* 11.8), 3.69–3.61 (1H, m), 2.22–2.11 (5H, m), 1.95 (3H, br s), 1.83–1.79 (6H, m), 1.63–1.55 (4H, m), 1.37–1.08 (8H, m); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 169.5, 162.3 (d, *J* 248.9), 155.3 134.0, 133.7 (d, *J* 2.2), 129.8 (d, *J* 8.7), 128.7, 116.4 (d, *J* 23.2), 116.3, 106.1, 57.7, 49.3, 32.6, 31.1, 26.4, 25.6, 25.4, 24.5, 12.5, 12.2; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.41; **IR** ν_{max} (neat) /cm^{-1} 2927, 2854, 1685, 1636, 1512, 1222; **m/z** (ESI+) 462 $[M+Na]^+$; **HRMS** (ESI+) found 462.25251 $[M+Na]^+$, $C_{26}H_{34}N_3O_2FNa$ requires 462.25273.

InChI=1S/C26H34FN3O2/c1-18-17-24(19(2)29(18)23-15-13-20(27)14-16-23)25(31)30(22-11-7-4-8-12-22)26(32)28-21-9-5-3-6-10-21/h13-17,21-22H,3-12H2,1-2H3,(H,28,32)

All attempts: http://malaria.ourexperiment.org/uri/2c9

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide, OSM-S-8



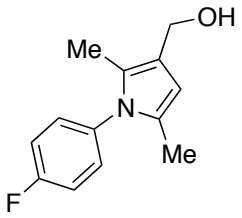
Representative example: http://malaria.ourexperiment.org/uri/65

OSM-S-4 (150 mg, 0.643 mmol, 1.0 equiv.) and 4-aminoantipyrine (144 mg, 0.707 mmol, 1.1 equiv.) were dissolved in EtOAc (approx. 3 mL) and pyridine (0.30 mL, 3.85 mmol, 6.0 equiv.) and placed in a water bath at rt. T3P 50% in EtOAc (0.780 mL, 0.129 mmol, 2.0 equiv.) was added and the reaction mixture stirred overnight. HCl (0.5 M, 20 mL) was added and the mixture extracted with EtOAC (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL), brine, dried ($MgSO_4$), filtered and evaporated to give a brown solid (170 mg). Purification by flash column chromatography over silica (3% MeOH in CH_2Cl_2) gave recovered starting material (101 mg, 69%) and the title product (30 mg, 11%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.50–7.39 (4H, m), 7.33–7.29 (1H, m), 7.19–7.15 (4H, m), 6.28 (1H, s), 2.86 (3H, s), 2.33 (3H, s), 2.30 (3H, s), 1.97 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 164.4, 163.4, 161.9, 148.7, 135.0, 134.8, 133.7, 129.9, 128.9, 126.5, 123.8, 116.5, 116.3, 111.0, 101.8, 105.3, 36.7, 12.9, 12.6, 12.2; **IR** ν_{max} (neat) /cm^{-1} 1654, 1508, 1220, 762, 704; **m/z** (ESI+) 419 $[M+H]^+$; **HRMS** (ESI+) found 441.16966 $[M+Na]^+$, $C_{24}H_{23}N_4O_2FNa$ requires 441.16973.

InChI=1S/C24H23FN4O2/c1-15-14-21(16(2)28(15)19-12-10-18(25)11-13-19)23(30)26-22-17(3)27(4)29(24(22)31)20-8-6-5-7-9-20/h5-14H,1-4H 3,(H,26,30).

All attempts: http://malaria.ourexperiment.org/uri/2ca

(1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methanol, OSM-S-11



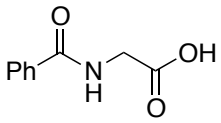
Representative example: http://malaria.ourexperiment.org/uri/14f

OSM-S-2 (1.00 g, 4.60 mmol, 1 equiv.) was dissolved in MeOH (75 mL). Sodium borohydride (174 mg, 4.69 mmol, 4 hydride equiv.) was added and the reaction mixture stirred for 4 h at rt. Sodium borohydride (44 mg, 1.17 mmol, 1 hydride equiv.) was added and the reaction mixture stirred for a further 30 min. Acetone (25 mL) was added to the reaction mixture, stirred for 10 min and then concentrated under reduced pressure. Water was added to the residue and extracted with CH_2Cl_2 (3 × 30 mL). The extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a pale brown solid (953 mg, ~94% yield) which was stored at –20 ˚C under nitrogen and used as crude in the next reaction; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.19–7.14 (4H, m), 6.02 (1H, s), 4.54 (2H, s), 2.05 (3H, s), 2.04 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 162.0 (d, *J* 247.4), 134.9 (d, *J* 2.9), 130.0 (d, *J* 8.6), 128.3, 126.7, 119.1, 116.1 (d, *J* 22.7), 106.8, 57.7, 12.7, 10.5; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -113.62.

InChI=1S/C13H14FNO/c1-9-7-11(8-16)10(2)15(9)13-5-3-12(14)4-6-13/h3-7,16H,8H2,1-2H3

All attempts: http://malaria.ourexperiment.org/uri/2cd

Hippuric acid, OSM-S-15



Representative example: http://malaria.ourexperiment.org/uri/5e

Glycine (12.5 g, 0.17 mol, 1.00 equiv.) was dissolved in NaOH(aq) (13.3 g in ~130 mL water, 0.33 mol, 2.00 equiv.). The flask was placed in a water bath at rt and benzoyl chloride (21 mL, 0.18 mol, 1.06 equiv.) was added portion-wise over 1 h whilst keeping the temperature below 30 ˚C. The reaction was stirred for 1 h and then cooled in ice. Conc. HCl(aq) (~20 mL) was added and the mixture stirred for 30 min. The copious white precipitate was filtered and washed with water. The crude product was triturated with hot CH_2Cl_2 (100 mL) for 10 min then filtered and washed with further CH_2Cl_2 (2 × 20 mL). After air drying (10 min), the product was dissolved in boiling water (~500 mL), hot filtered to remove some residual solid and allowed to crystallise

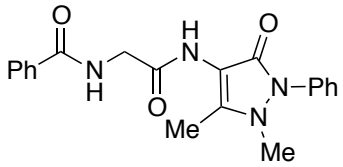
slowly overnight. The crystals were filtered out and washed with water to obtain the product hippuric acid as white needles (22.4 g, 75%); **m.p.** 189–190 ˚C (H_2O); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.96–7.92 (1H, m), 7.58–7.46 (1H, m), 4.15 (2H, s).

InChI=1S /C9H9NO3/c11-8(12)6-10-9(13)7-4-2-1-3-5-7/h1-5H,6H2,(H,10,13)(H,11,12).

All attempts: http://malaria.ourexperiment.org/uri/2d1

Data consistent with literature.[9]

_N_-(2-((1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1_H_-pyrazol-4-yl)amino)-2-oxoethyl)benzamide, OSM-S-16



Representative example: http://malaria.ourexperiment.org/uri/75

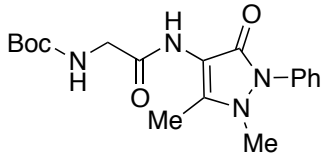
OSM-S-15 (500 mg, 2.79 mmol, 1.00 equiv.) and 4-aminoantipyrine (623 mg, 3.07 mmol, 1.10 equiv.) were dissolved in DMF (2.5 mL) and pyridine (1.30 mL, 16.1 mmol, 5.78 equiv.). The mixture was cooled in an ice/bath and T3P (50 wt.% in EtOAc, 3.1 mL, 4.9 mmol, 1.74 equiv.) was added. The mixture was allowed to warm to rt and the mixture stirred for 21 h. Water (10 mL) was added and a precipitate formed and the reaction solidified. The resultant solid was filtered and washed with water and a small amount of EtOAc then dried under vacuum, to yield a white powder (655 mg, 64%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.38 (1H, bs), 7.85 (2H, d, *J* 7.5), 7.73 (1H, t, *J* 5.5), 7.46–7.39 (3H, m), 7.37–7.26 (5H, m), 4.25 (2H, d, *J* 5.6), 3.08 (3H, s), 2.18 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 169.8, 167.6, 162.1, 150.7, 134.1, 133.7, 131.4, 129.4, 128.3, 127.6, 127.3, 125.1, 107.2, 43.4, 35.4, 11.7.

InChi=1S/C20H20N4O3/c1-14-18(20(27)24(23(14)2)16-11-7-4-8-12-16)22-17(25)13-21-19(26)15-9-5-3-6-10-15/h3-12H,13H2,1-2H3,(H,21,26)(H ,22,25).

All examples: http://malaria.ourexperiment.org/uri/2d2

Prepared according to literature method, data consistent with literature.[10]

***tert*-Butyl(2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino)-2-oxoethyl)carbamate OSM-S-17**



Representative example: http://malaria.ourexperiment.org/uri/76

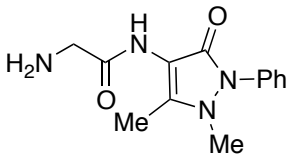
Boc-Gly-OH (500 mg, 2.85 mmol, 1.00 equiv.) and 4-aminoantipyrine (638 mg, 3.14 mmol, 1.10 equiv.) were dissolved in DMF (2.5 mL) and pyridine (1.30 mL, 16.14 mmol, 5.65 equiv.). The mixture was cooled in an ice/bath and T3P (50 wt.% in EtOAc, 3.10 mL, 4.85 mmol, 1.7 equiv.) was added. The mixture was allowed to warm to rt and stirred for 21 h. Water (30 mL) was added and the mixture stirred for 20 min. The pH 5 solution was modified to pH 8 by addition of a 10% aqueous solution of $NaHCO_3$ and then extracted with EtOAc (× 3). Combined organic extracts were washed with water (× 3), brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a yellow/white solid, (646 mg, 63%) which was used without purification in the next step; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.20–9.06 (1H, m), 7.48–7.43 (2H, m), 7.38–7.28 (3H, m), 5.62–5.56 (1H, m), 3.92 (2H, bd, *J* 4.6), 3.09 (3H, s), 2.20, (3H, s), 1.45 (9H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 207.0, 169.5, 162.0, 156.0, 150.4, 134.3, 129.3, 127.3, 124.8, 107.7, 79.6, 44.0, 35.7, 30.9, 28.4, 12.0.

InChI=1S/C18H24N4O4/c1-12-15(20-14(23)11-19-17(25)26-18(2,3)4)16(24)22(21(12)5)13-9-7-6-8-10-13/h6-10H,11H2,1-5H3,(H,19,25)(H,20,23).

All attempts: http://malaria.ourexperiment.org/uri/2d3

Data consistent with literature.[11]

***N*-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)glycinamide**, **OSM-S-18**



Representative example: http://malaria.ourexperiment.org/uri/8d

Crude **OSM-S-17** was dissolved in THF (5 mL) and TFA (0.5 mL) was added dropwise to the yellow solution, which turned red during addition. HCl (4M in dioxane, 0.5 mL, 2 mmol) was added and the reaction mixture stirred for 2.5 h at rt. Further HCl (4M in dioxane, 2.0 mL, 8 mmol) was added and the reaction was stirred

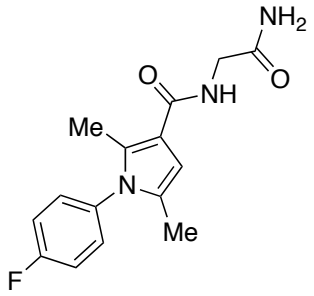
overnight. The crude reaction mixture was concentrated to give a yellow solid that was used as crude in the next experiment.

InChi=1S/C13H16N4O2/c1-9-12(15-11(18)8-14)13(19)17(16(9)2)10-6-4-3-5-7-10/h3-7H,8,14H2,1-2H3,(H,15,18)

All examples: http://malaria.ourexperiment.org/uri/2d4

Data consistent with literature.[10]

N-(2-Amino-2-oxoethyl)-1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide, OSM-S-19



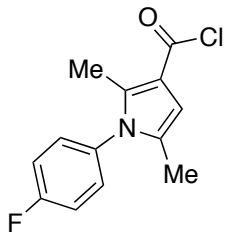
Representative example: http://malaria.ourexperiment.org/uri/8e

A suspension of glycinamide.HCl (51 mg, 0.51 mmol, 1.2 equiv.) and DIPEA (0.11 mL, 0.89 mmol, 2.3 equiv.) was stirred in anhydrous DMF (6 mL) and **OSM-S-4** (90 mg, 0.39 mmol, 1.0 equiv.) in anhydrous THF (4 mL) and added. The reaction mixture was heated to 80 ˚C overnight and then cooled to rt and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica (50–100% EtOAc/hexane then 0–20% MeOH/CH_2Cl_2) to obtain a clear yellow oil containing residual DIPEA and the expected product. The white powder was dissolved in 10% $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL), the organic phase was separated and washed with water (3 × 10 mL), brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to obtain the title compound as a white powder (44 mg, 39%); **m.p.** 193–195 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.25–7.12 (4H, m), 6.43–6.22 (2H, m), 6.13 (1H, s), 5.39 (1H, s), 4.09 (2H, d, *J* 5.5), 2.30 (3H, s), 1.98 (3H, s); **IR** ν_{max} (neat) /cm^{-1} 3322, 1630, 1510, 1223; **m/z** (ESI+) 312 $[M+H]^+$; **HRMS** (ESI+) found 312.11177 $[M+Na]^+$, $C_{15}H_{16}N_3O_2Na$ requires 312.11188.

InChI=1S/C15H16FN3O2/c1-9-7-13(15(21)18-8-14(17)20)10(2)19(9)12-5-3-11(16)4-6-12/h3-7H,8H2,1-2H3,(H2,17,20)(H,18,21).

All attempts: http://malaria.ourexperiment.org/uri/2d5

1-(4-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrole-3-carbonyl chloride, OSM-S-20



Representative example: http://malaria.ourexperiment.org/uri/bd

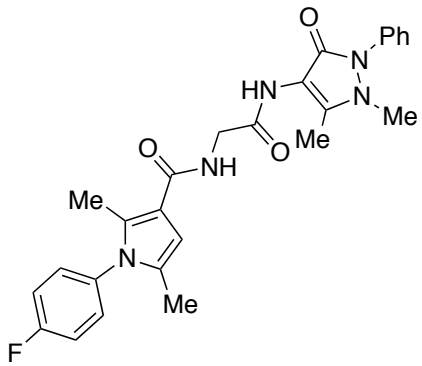
OSM-S-4 (500 mg, 2.14 mmol, 1.0 equiv.) was stirred in dry PhMe (3 mL) and cooled in ice. Thionyl chloride (0.310 mL, 4.29 mmol, 2.0 equiv.) was added at 0 ˚C and then the reaction was allowed to warm to rt. After 3 h, the reaction was concentrated under reduced pressure twice from PhMe (3 mL). The residue was triturated twice with hexane (10 mL) and the filtrate concentrated under reduced pressure to obtain the acid chloride as a yellow solid (298 mg, 55%). The product was used without further purification.

InChI=1S/C13H11ClFNO/c1-8-7-12(13(14)17)9(2)16(8)11-5-3-10 (15)4-6-11/h3-7H,1-2H3

All attempts: http://malaria.ourexperiment.org/uri/2d6

Prepared according to literature procedure.[12]

N-(2-((1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-2-oxoethyl)-1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide, OSM-S-21



Representative example: http://malaria.ourexperiment.org/uri/8f

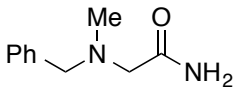
Crude **OSM-S-17** was stirred in anhydrous THF (4 mL) and DIPEA (1.00 mL, 7.63 mmol, 10 equiv.) was added. After stirring for 5 min, acid chloride prepared according to general procedure **F** from **OSM-S-4** (178 mg, 0.763 mmol, 1.0 equiv.) was added and the reaction heated to 80 ˚C for 20 h and then the reaction was cooled to rt and concentrated under reduced pressure. The crude orange oil was dissolved in CH_2Cl_2 (10 mL) and

washed with 10% $NaHCO_3$ (10 mL), water (3 × 10 mL), brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure prior to purification by flash column chromatography over silica (50-100% EtOAc/hexane, then 5% MeOH in CH_2Cl_2) afford a yellow solid (162 mg, 67% over 2 steps based on **OSM-S-17**); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.11 (1H, bs), 7.41–7.19 (5H, m), 7.13–7.06 (4H, m), 6.62 (1H, t, *J* 5.4), 6.11 (1H, s), 4.15 (2H, d, *J* 5.7), 3.01 (3H, s), 2.23 (3H, s), 2.18 (3H, s), 1.87 (3H, s); **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ: -112.8 **IR** ν_{max} (neat) /cm^{-1} 3852, 1650, 1510, 1221; **m/z** (ESI+) 498 $[M+Na]^+$; **HRMS** (ESI+) found 498.19109 $[M+Na]^+$, $C_{26}H_{26}N_5O_3FNa$ requires 498.19119.

InChI=1S/C26H26FN5O3/c1-16-14-22(17(2)31(16)20-12-10-19(27)11-13-20)25(34)28-15-23(33)29-24-18(3)30(4)32(26(24)35)21-8-6-5-7-9-21/h5-14H,15H2,1-4H3,(H,28,34)(H,29,33).

All attempts: http://malaria.ourexperiment.org/uri/2d7

2-(Benzyl(methyl)amino)acetamide, OSM-S-284



Representative example: http://malaria.ourexperiment.org/uri/107

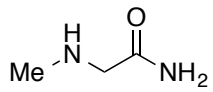
Glycinamide.HCl (500 mg, 4.52 mmol, 1.0 equiv.) was dissolved in minimum water and sodium hydroxide (0.180 mg, 4.5 mmol, 1.00 equiv.) was added. A precipitate formed and the mixture was concentrated under reduced pressure. Methanol (15 mL), AcOH (1.5 mL) and benzaldehyde (0.60 mL, 5.87 mmol, 1.3 equiv.) were added. Sodium cyanoborohydride (370 mg, 5.87 mmol, 1.3 equiv.) was added portion-wise to the hazy solution, allowing bubbling to cease between portions. The reaction was stirred at rt overnight and then concentrated under reduced pressure. The residues was basified using 2 M $NaOH_{(aq)}$, extracted using CH_2Cl_2 (6 × 20 mL), washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to a thick oil. A white solid (650 mg total) was obtained after drying *in vacuo*. The white solid was dissolved in MeOH (10 mL) and AcOH (0.25 mL) and then aqueous formaldehyde solution (37 wt. %, 0.7 mL, 9 mmol, 2.00 equiv.) was added and the mixture was stirred at rt for 5 min. Sodium cyanoborohydride (300 mg, 4.75 mmol, 1.05 equiv.) was added portion-wise over 10 min and the reaction stirred at rt overnight. The reaction mixture was concentrated under reduced pressure, 2 M NaOH (10 mL) was added with stirring for 10 min. The mixture was extracted into CH_2Cl_2 (3 × 15 mL) and then combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to a colourless translucent thick oil (640 mg) which was purified by flash column chromatography over silica (4% MeOH/CH_2Cl_2) to provide the title compound as an colourless viscous oil (containing other impurities) that solidified on standing (410 mg, 39%) and the *bis*-benzylated side product (190 mg, 17%). The desired product was used without further purification in the next step; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.39–7.24 (5H, m), 7.06 (1H, bs), 5.78 (1H, bs), 3.58 (2H, s), 3.04 (3H, s), 2.31 (3H, s).

InChI=1S/C10H14N2O/c1-12(8-10(11)13)7-9-5-3-2-4-6-9/h2-6H,7-8H2,1H3,(H2,11,13)

^{1}H NMR data consistent with literature precedent.[13]

Prepared according to literature procedure.[14]

2-(Methylamino)acetamide, OSM-S-285

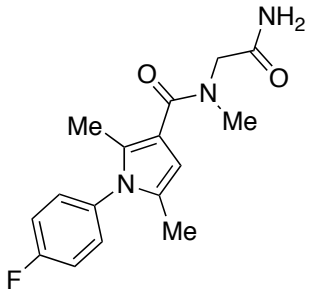


Representative example: http://malaria.ourexperiment.org/uri/114

10% Pd on charcoal (195 mg, 15 % wt.) was suspended in EtOH (50 mL) and then **OSM-S-284** (1.30 g, 7.29 mmol 1 equiv.) in EtOH (40 mL) was added to the catalyst suspension and the mixture hydrogenated in a Parr hydrogenator (stirred not shaken) overnight (118-110 psi). The reaction was vented but found to be incomplete. 10% Pd on charcoal (195 mg, 15 % wt.) was added and the reaction placed 200 psi hydrogen pressure, falling to 187 psi after 6 h. The reaction was vented, filtered (Celite^{TM}) and concentrated under reduced pressure to give a clear oil (0.65 g, 101% of theory yield) which was used as crude in the next reaction; **m/z** (ESI+) 88.9 $[M+H]^{+}$.

InChI=1S/C3H8N2O/c1-5-2-3(4)6/h5H,2H2,1H3,(H2,4,6)

N-(2-Amino-2-oxoethyl)-1-(4-fluorophenyl)-N,2,5-trimethyl-1H-pyrrole-3-carboxamide, OSM-S-59



Representative example: http://malaria.ourexperiment.org/uri/119

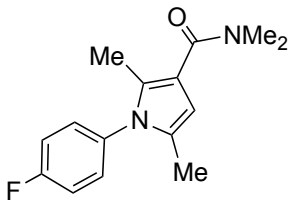
Acid chloride was prepared according to General Procedure **F** from: **OSM-S-4** (250 mg, 1.1 mmol, 1.0 equiv.) and thionyl chloride (0.16 mL, 2.1 mmol, 2.0 equiv.) in PhMe (2 mL). A solution of the crude acid chloride in THF (8 mL) was added dropwise to a stirred solution of **OSM-S-285** (142 mg), DIPEA (0.40 mL, 2.3 mmol, 2.1 equiv.) and 4-DMAP (a few crystals) in THF (2 mL) After 2.5 days, the crude product was purified by flash chromatography over silica (2–4% MeOH/CH_2Cl_2) to give the title compound as a white foam (44 mg, 14%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.17 (4H, d, *J* 6.47), 6.79 (1H, s), 6.09 (1H, bs), 6.02 (1H, s), 4.14 (2H, s), 3.21 (3H, s), 2.12 (3H, s), 1.96 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 172.3, 169.3, 162.2 (d *J* 248.3), 133.8 (d *J* 2.9), 129.8

(d *J* 8.7), 128.3, 116.4, 116.1, 113.5, 106.2, 12.5, 12.0; **$^{19}F\{^{1}H\}$ NMR** (282 MHz, $CDCl_3$) δ: -112.8; **HRMS** (ESI+) found 326.12838 [M+Na], $C_{16}H_{18}N_3O_2FNa$ requires 326.12753.

InChI=1S/C16H18FN3O2/c1-10-8-14(16(22)19(3)9-15(18)21)11(2)20(10)13-6-4-12(17)5-7-13/h4-8H,9H2,1-3H3,(H2,18,21)

All attempts: http://malaria.ourexperiment.org/uri/2ff

1-(4-Fluorophenyl)-N,N,2,5-tetramethyl-1H-pyrrole-3-carboxamide, OSM-S-93



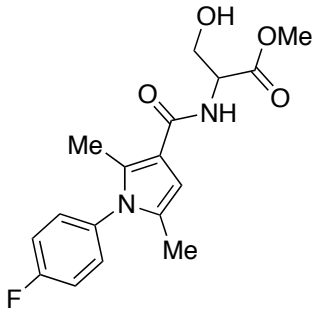
Representative example: http://malaria.ourexperiment.org/uri/1a2

Prepared according to General procedure **E** from: **OSM-S-4** (0.10 g, 0.43 mmol, 1.0 equiv.) was, EDCI (0.10 g, 0.52 mmol, 1.2 equiv.), HOBt (6 mg, 0.043 mmol, 0.10 equiv.) and dimethylamine (~5.6 M in absolute EtOH, 0.12 mL, 0.64 mmol, 1.5 equiv.) dissolved in CH_2Cl_2 (5.8 mL); rt 5 h. Crude oil purified by flash column chromatography over silica, (10–20% EtOAc in CH_2Cl_2) to afford a pale yellow semi-solid (53 mg, 47%); **m/z** (APCI+) 264 $[M+H]^+$; **HRMS** (APCI) found 261.13973 $[M+Na]^+$, $C_{16}H_{19}NO_2Na$ requires 261.13977.

InChI=1S/C15H17FN2O/c1-10-9-14(15(19)17(3)4)11(2)18(10)13-7-5-12(16)6-8-13/h5-9H,1-4H3

All attempts: http://malaria.ourexperiment.org/uri/321

Methyl 2-(1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxamido)-3-hydroxypropanoate, OSM-S-61



Representative example: http://malaria.ourexperiment.org/uri/11f

Acid chloride was prepared according to General Procedure **F** from**: OSM-S-4** (250 mg, 1.07 mmol, 1.0 equiv.) and thionyl chloride (0.160 mL, 2.14 mmol, 2.0 equiv.) in PhMe (2 mL) and then dissolved in THF (3 mL). In a

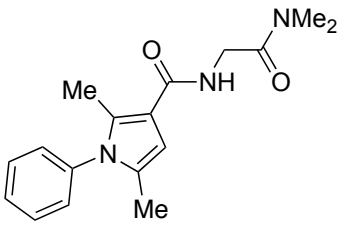
separate vessel, a suspension of DL-serine methyl ester hydrochloride (183 mg, 1.18 mmol, 1.1 equiv.) was stirred in THF (10 mL). DIPEA (0.623 mL, 3.54 mmol, 3.3 equiv.) was added, followed by the acid chloride solution. The reaction mixture was stirred at rt for 16 h and then concentrated under reduced pressure. A saturated aqueous solution of $NaHCO_3$ (aq) and water (1:1) were added to the residue and extracted with CH_2Cl_2 (3 × 15 mL). The extracts were then washed with brine, dried ($MgSO_4$), filtered and concentrated to a tan foam that was purified by flash column chromatography over silica (1–4% MeOH in CH_2Cl_2) gave the title compound as a white foam (166 mg, 46%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.21–7.12 (4H, m), 6.77 (1H, bd, *J* 6.6), 6.20 (1H, s), 4.83 (1H, dt, *J* 7.2 and 3.5), 4.01 (2H, d, *J* 3.9), 3.80 (3H, s), 3.55 (1H, bs), 2.28 (3H, s), 1.96 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 171.5, 166.2, 162.4 (d, *J* 248.8), 134.6, 133.6, 129.8 (d, *J* 8.7), 116.3 (d, *J* 23.1), 113.4, 105.0, 63.9, 54.7, 52.6, 12.5, 12.2; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.5; **HRMS** (ESI+) found 357.12285 [M+Na], $C_{17}H_{19}N_2O_4FNa$ requires 357.12211.

InChI=1S/C17H19FN2O4/c1-10-8-14(16(22)19-15(9-21)17(23)24-3)11(2)20(10)13-6-4-12(18)5-7-13/h4-8,15,21H,9H2,1-3H3,(H,19,22)

All attempts: http://malaria.ourexperiment.org/uri/301

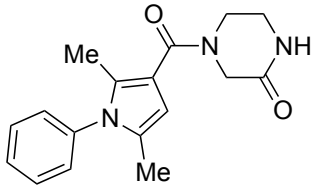
3.2 Commercial amides

N-(2-(Dimethylamino)-2-oxoethyl)-2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxamide, OSM-S-81



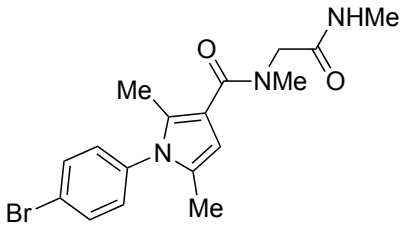
InChI=1S/C17H21N3O2/c1-12-10-15(17(22)18-11-16(21)19(3)4)13(2)20(12)14-8-6-5-7-9-14/h5-10H,11H2,1-4H3,(H,18,22)

4-(2,5-Dimethyl-1-phenyl-1H-pyrrole-3-carbonyl)piperazin-2-one, OSM-S-83



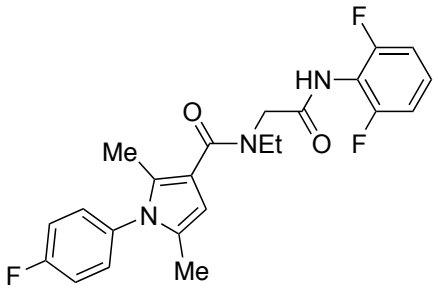
InChI=1S/C17H19N3O2/c1-12-10-15(17(22)19-9-8-18-16(21)11-19)13(2)20(12)14-6-4-3-5-7-14/h3-7,10H,8-9,11H2,1-2H3,(H,18,21)

1-(4-Bromophenyl)-N,2,5-trimethyl-N-(2-(methylamino)-2-oxoethyl)-1H-pyrrole-3-carboxamide, OSM-S-84



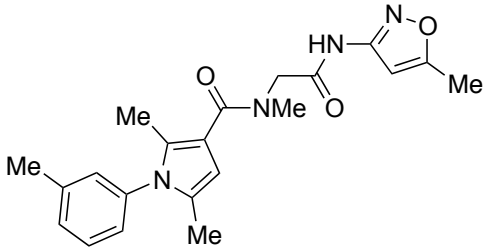
InChI=1S/C17H20BrN3O2/c1-11-9-15(17(23)20(4)10-16(22)19-3)12(2)21(11)14-7-5-13(18)6-8-14/h5-9H,10H2,1-4H3,(H,19,22)

N-(2-((2,6-Difluorophenyl)amino)-2-oxoethyl)-N-ethyl-1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide, OSM-S-86



InChI=1S/C23H22F3N3O2/c1-4-28(13-21(30)27-22-19(25)6-5-7-20(22)26)23(31)18-12-14(2)29(15(18)3)17-10-8-16(24)9-11-17/h5-12H,4,13H2,1-3H3,(H,27,30)

N,2,5-Trimethyl-N-(2-((5-methylisoxazol-3-yl)amino)-2-oxoethyl)-1-(m-tolyl)-1H-pyrrole-3-carboxamide, OSM-S-87



InChI=1S/C21H24N4O3/c1-13-7-6-8-17(9-13)25-14(2)10-18(16(25)4)21(27)24(5)12-20(26)22-19-11-15(3)28-23-19/h6-11H,12H2,1-5H3,(H,22,23,26)

4. The "Near Neighbor" (NN) 2-Iminothiazolidinones

The NN analogs were obtained from the relevant pyrrole obtained in multi-gram quantities *via* a Paal-Knorr cyclisation using 2,5-hexanedione and the relevant aniline (Fig SC3); this cyclisation for the OSM-A compounds was found to proceed well with catalytic sulfamic acid.[15] The pyrrole could be furnished with an aldehyde in good yield using Vilsmeier-Haack conditions.[16] The community suggestion mentioned in the main paper (Fig S2 Synaptic Leap Node 344, paper ref 63), to include an overnight hydrolysis step during the work-up, resulted in a significant improvement in yield on a gram scale. The aldehydes were condensed with 2-iminothiazolidin-4-ones.[17,18,19] Unsubstituted phenyl-2-iminothiazolidin-4-ones (*e.g.,* OSM-S-35) were converted to the acyl, cyclohexyl and methylenenitrile derivatives (*e.g.,* OSM-S-49, -54 and -43 respectively) by standard substitutions in the presence of base.

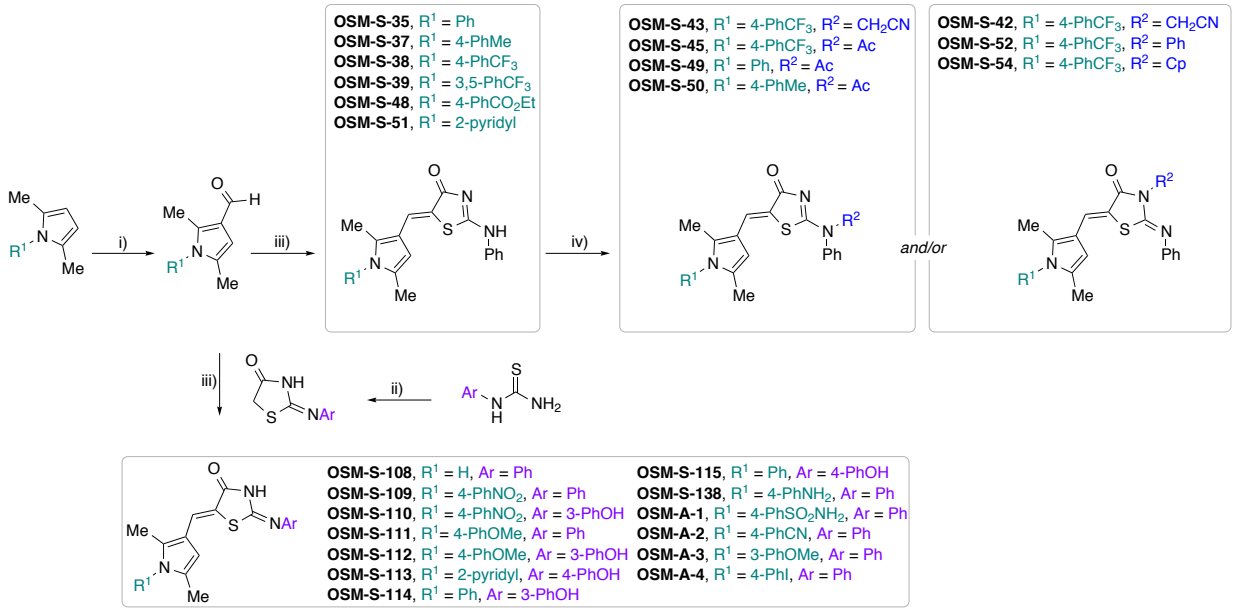


Fig SC3. Synthesis of Near Neighbours. Conditions: i) $POCl_3$/DMF, 45 min, 0 ˚C to rt; ii) *N*-(aryl)thiourea, ethyl bromoacetate, sodium acetate trihydrate, EtOH; iii) 2-aryliminothiazolidin-4-one, piperidine, EtOH, 60 ˚C; iv) acetic anhydride, pyridine, toluene, 80 ˚C; or cyclopentylbromide, NaH, DMF, 60 ˚C; or bromoacetonitrile, NaI, K_2CO_3, MeCN, 80 ˚C then rt.

The double bond geometry reported for the original hits was undefined. Analysis of OSM-S-35 by X-ray crystallography (Fig SC4A) revealed *Z*-geometry for the alkene of the only product, consistent with a previous assignment based on NMR spectroscopy;[Error! Bookmark not defined.] *Z*-geometry was seen in all other molecules in this series characterised by X-ray crystallography and was therefore assumed for the series generally. Alkylation of one precursor with bromoacetonitrile gave two separable isomers, one of which (OSM-S-42) gave X-ray quality

crystals, revealing that the methylenenitrile was attached to the iminothiazolidinone nitrogen (Fig SC4B). The other methylenenitrile-functionalised isomer (OSM-S-43) was therefore assigned to be the *N*-phenyl substituted isomer. On substitution with cyclopentyl bromide or acetyl chloride, however, only one isomer was observed and isolated. Both these samples gave X-ray quality crystals revealing that in the case of cyclopentyl bromide, the substituent had become attached to the iminothiazolidinone nitrogen (OSM-S-54, Fig SC4C), whereas with acetyl chloride the substituent was attached to the exocyclic nitrogen (OSM-S-9, Fig SC4D).

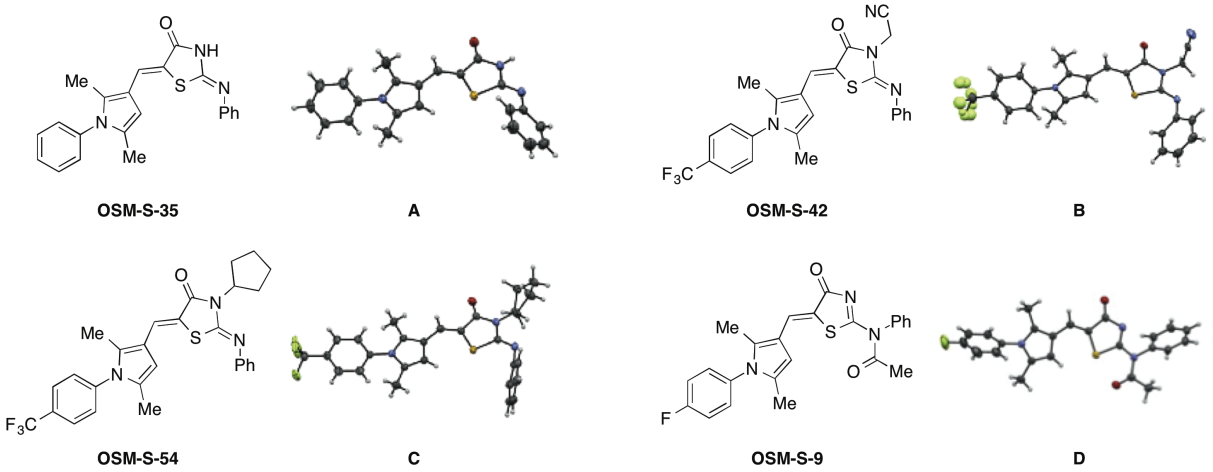


Fig SC4. X-Ray Crystallographic Structural Assignments of OSM-S-35 (A), OSM-S-42 (B), OSM-S-54 (C) and OSM-S-9 (D). (Raw data: Dataset S13 XRay)

Reactivity of NN Exocyclic Double Bond to External Nucleophiles

Treatment of OSM-S-9 (Fig S20)[20] or OSM-S-10 (Fig S21)[21] with sodium borohydride, attempted hydrogenation (Fig S22)[22] or addition of benzylthiol (Fig S23)[23] did not result in reaction at the double bond by ^{1}H NMR spectroscopic or mass spectrometric analysis. These conditions may not effectively mimic *in vivo* metabolic processes.

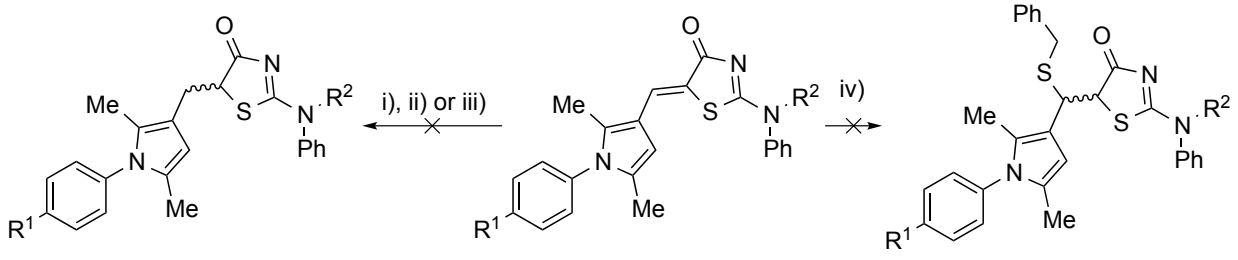
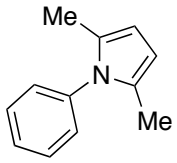


Fig SC5. **Assessment of Reactivity of *exo* Double Bond in Near Neighbour Compounds**. Reagents and Conditions: i) R^1 = F, R^2 = Ac (OSM-S-9), $NaBH_4$, MeCN, 18 h, rt gave deacylated product (OSM-S-10), quant.; ii) R^1 = F, R^2 = H (OSM-S-10), $NaBH_4$, MeCN, 60 ˚C; iii) R^1 = F, R^2 = Ac (OSM-S-9), 10% Pd/C (20% w/w), hydrogen (1 atm), EtOH, rt; iv) R^1 = CF_3, R^2 = H (OSM-S-38), benzylthiol, CH_2Cl_2, 40 ˚C then K_2CO_3, 20 h.

2,5-Dimethyl-1-phenyl-1*H*-pyrrole, OSM-S-25



Representative example: http://malaria.ourexperiment.org/uri/231

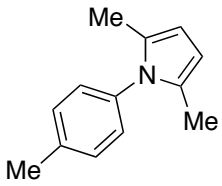
Prepared according to General Procedure **A** from aniline (1.97 g, 21.2 mmol, 1.1 equiv.) and 2,5-hexanedione (2.26 mL, 19.3 mmol, 1.0 equiv.); 110 ˚C (oil bath temp.) for 16 h. The crude brown oil was purified by flash column chromatography over silica (2% EtOAc in petroleum ether 40–60 ˚C) to give the desired product (3.19 g, 96% yield); **m.p.** 49–50 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.44–7.36 (3H, s), 7.21–7.17 (2H, t), 5.90 (2H, s), 2.02 (6H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 139.1, 129.1. 128.8, 128.3, 127.7, 105.8, 13.1; **IR** ν_{max} (neat) /cm^{-1}; 1597, 1520, 1494, 1401, 1318, 1037, 1006, 773, 747, 717, 695, 646; **m/z** (APCI) 173 $[M+H]^+$.

InChi=1S/C12H13N/c1-10-8-9-11(2)13(10)12-6-4-3-5-7- 12/h3-9H,1-2H3.

All attempts: http://malaria.ourexperiment.org/uri/2d

Data consistent with literature.[4]

2,5-Dimethyl-1-(*p*-tolyl)-1*H*-pyrrole, OSM-S-26



Representative example: http://malaria.ourexperiment.org/uri/4b

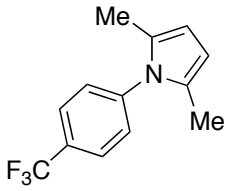
Prepared according to General Procedure **A** from: *p*-toluidine (7.03 g, 65.6 mmol) and 2,5-hexanedione (7.00 mL, 59.7 mmol); 80 ˚C for 4.5 h. The product was extracted with EtOAc (20 mL), washed with 10% citric acid (3 × 20mL), brine (20 mL), dried ($MgSO_4$), filtered and stirred with activated charcoal for 1 h to remove coloured impurities. The mixture was filtered, washed with EtOAc and then concentrated under reduced pressure. The resulting brown crystalline solid was dissolved in warm EtOH (20 mL) and then cooled to 0 ˚C. The resultant solid was filtered and dried *in vacuo* to yield the title compound as an ochre-coloured solid (8.30 g, 75 %); **m.p.** 45–46 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.23–7.20 (2H, m), 7.08–7.05 (2H, m), 5.88 (2H, s), 2.38 (3H, s), 2.01 (6H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 137.5, 136.6, 129.8, 128.9, 128.1, 105.7, 21.3, 13.2; **IR** ν_{max} (neat) /cm^{-1}1513, 1403, 1320, 826, 750; **m/z** (ESI^+) 187 $[M+H]^+$.

InChi=1S/C13H15N/c1-10-4-8-13(9-5-10)14-11(2)6-7-12(14)3/h4-9H,1-3H3.

All attempts: http://malaria.ourexperiment.org/uri/2dc

Procedure adapted from the literature.[24] Data consistent with literature.[4]

2,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole, OSM-S-27



Representative example: http://malaria.ourexperiment.org/uri/22

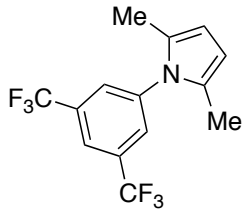
Prepared according to General Procedure **A** from: 4-(trifluoromethyl)aniline (6.0 mL, 47 mmol, 1.1 equiv.) and 2,5-hexanedione (5.0 mL, 43 mmol, 1.0 equiv.); 80 ˚C for 7 h. The resulting brown crystalline solid was dissolved in hot EtOH (25 mL). The solution was slowly cooled to ~10 ˚C with periodic shaking. The resulting crystals were filtered and washed with citric acid (3 × 10mL) and water (3 × 10 mL) and dried *in vacuo* to provide the title compound (6.08 g, 60%); **m.p.** 70–73 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* 8.2), 7.34 (2H, d, *J* 8.3), 5.93 (2H, s), 2.05 (6H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 142.3, 129.8 (q, *J* 32.7), 128.1, 128.6, 126.3 (m), 123.9 (q, *J* 272.1), 106.6, 13.0; **IR** ν_{max} (neat) /cm^{-1} 1615, 1402, 1325, 1128, 1064, 850, 759; **m/z** (ESI+) 241 $[M+H]^+$.

InChi=1S/C13H12F3N/c1-9-3-4-10(2)17(9)12-7-5-11(6-8-12)13(14,15)16/h3-8H,1-2H3.

All attempts: http://malaria.ourexperiment.org/uri/2dd

Data consistent with literature. [4]

1-(3,5-Bis(trifluoromethyl)phenyl)-2,5-dimethyl-1H-pyrrole, OSM-S-33



Representative example: http://malaria.ourexperiment.org/uri/52

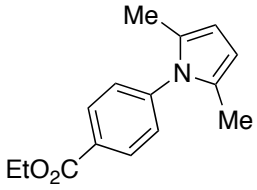
Prepared according to General Procedure **A** from 3,5-bis(trifluoromethyl)aniline (3.9 mL, 25 mmol) and and 2,5-hexanedione (2.9 mL, 25 mmol); 120 ˚C for 42 h. The crude brown oil was purified by flash column chromatography over silica (2% EtOAc in petroleum ether 40–60 ˚C) to provide the title compound as a pale yellow oil (2.7 g, 35%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72 (2H, d *J* 0.3Hz), 5.96 (2H, br d, *J* 1.7), 2.07 (6H, br d, rotamers 6H); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 140.9, 133.0 (q, *J* 33.9), 128.8, 128.6 (q, *J* 3.6), 123.1 (q, *J* 272.6), 121.5 (dq *J* 3.5 and 3.8), 107.6, 13.1; **IR** ν_{max} (neat) /cm^{-1} 1615, 1402, 1325, 1128, 1064, 850, 759; **HRMS** (APCI+) 308 $[M+H]^+$; **HRMS** (ESI+) found 308.08557 $[M+H]^+$, $C_{14}H_{12}F_6N$ requires 308.08685.

InChI=1S/C14H11F6N/c1-8-3-4-9(2)21(8)12-6-10(13(15,16)17)5-11(7-12)14(18,19)20/h3-7H,1-2H3.

All attempts: http://malaria.ourexperiment.org/uri/2e3

*The product is a known compound (CAS: 175205-51-3) but no experimental data was found.

Ethyl 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzoate, OSM-S-40



Representative example: http://malaria.ourexperiment.org/uri/5f

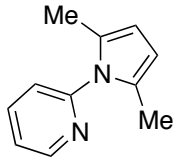
Prepared according to General Procedure **A** from: ethyl 4-aminobenzoate (15.1 g, 91.4 mmol) and 2,5-hexanedione (10.7 mL, 91.4 mmol); 80 ˚C for five days; crude product purified by flash column chromatography over silica (100% hexane) to give a pale yellow crystalline solid (5.8 g, 26% yield); **m.p.** 60–61 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ: 8.15 (2H, d, *J* 8.0), 7.28 (2H, d, *J* 8.0), 5.92 (2H, s), 4.41 (2H, q, *J* 7.0), 2.04 (6H, s), 1.41 (3H, t *J* 7.0); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 165.2, 143.1, 130.5, 129.7, 128.6, 128.1, 106.6, 61.2, 14.4, 13.1; **IR** ν_{max} (neat) /cm^{-1} 1712, 1606, 1508, 1400; **m/z** (APCI) 244 $[M+H]^+$.

InChI=1S/C15H17NO2/c1-4-18-15(17)13-7-9-14(10-8-13)16-11(2)5-6-12(16)3/h5-10H,4H2,1-3H3.

All attempts: http://malaria.ourexperiment.org/uri/2ea

The product is a known compound (CAS: 5159-70-6) and ^{1}H NMR, ^{13}C NMR and IR spectra are all consistent with spectra from Bio-Rad Laboratories.[25]

2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)pyridine, OSM-S-41



Representative example: http://malaria.ourexperiment.org/uri/60

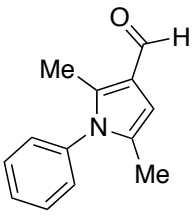
Prepared according to General Procedure **A** from: 2-aminopyridine (10.1 g, 108 mmol) and 2,5-hexanedione (12.7 mL, 108 mmol); 80 ˚C for five days; crude product purified by flash column chromatography over silica (10% EtOAc in hexane) to yield the title compound as a pale yellow oil (3.03 g, 17% yield); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.58 (1H, dd, *J* 4.7 and 1.1), 7.77 (1H, dt, *J* 7.8 and 1.9), 7.24 (1H, ddd, *J* 7.8, 4.7 and 0.7), 7.18 (1H, d, *J* 7.8) 5.91 (1H, s), 2.13 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 152.2, 149.4, 138.1, 128.5, 122.4, 122.0, 107.1, 13.3; **m/z** (APCI) 173 $[M+H]^+$.

InChi=1S/C11H12N2/c1-9-6-7-10(2)13(9)11-5-3-4-8-12-11/h3-8H,1-2 H3.

All attempts: http://malaria.ourexperiment.org/uri/2eb

Data consistent with literature.[26]

2,5-Dimethyl-1H-phenyl pyrrole-3-carboxaldehyde, OSM-S-28



Representative example: http://malaria.ourexperiment.org/uri/4d

Prepared according to General Procedure **B** from DMF (1.5 mL, 19 mmol), phosphoryl chloride (0.31 mL, 3.3 mmol), 2,5-dimethyl-1H-phenyl-pyrrole (0.51 g, 3.0 mmol) in DMF (2.0 mL); recrystallised from EtOH (3 mL), filtered and washed with water (3 × 10 mL) to give a grey free-flowing powder (0.41 g, 64%); **m.p.** 88–90 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.88 (1H, s), 7.55–7.50 (3H, s), 7.22–7.19 (2H, m), 6.39 (1H, s), 2.28 (3H, s), 1.99 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 185.3, 138.9, 137.0, 131.0, 129.6, 128.9, 128.0, 121.9, 105.8, 12.7,

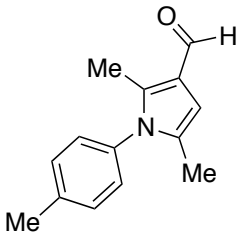
11.2; **IR** ν_{max} (neat) /cm^{-1} 1650, 1422, 801, 669; **m/z** (ESI+) 200 $[M+H]^+$.

InChi=1S/C13H13NO/c1-10-8-12(9-15)11(2)14(10)13-6-4-3-5-7-13/h3-9H,1-2 H3.

All attempts: http://malaria.ourexperiment.org/uri/2de

Data consistent with literature.[4]

2,5-Dimethyl-1H-(p-tolyl)-pyrrole-3-carboxaldehyde, OSM-S-29



Representative example: http://malaria.ourexperiment.org/uri/4e

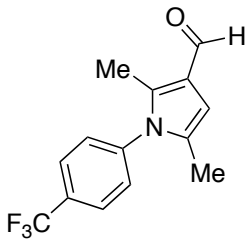
Prepared according to General Procedure **B** from DMF (1.5 mL, 19.4 mmol), phosphoryl chloride (308 µL, 3.3 mmol), **OSM-S-26** (556 mg, 3.0 mmol) in DMF (2.0 mL); recrystallised (MeCN/H_2O), filtered and washed with water (3 × 10 mL) to give a grey/brown powder (423 mg, 71%); **m.p.** 109–111 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.86 (1H, s), 7.31 (2H, d, *J* 7.9), 7.07 (2H, d, *J* 7.9), 6.37 (1H, s), 2.44 (3H, s), 2.27 (3H, s), 1.98 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 185.2, 139.0, 138.9, 134.3, 131.1, 130.2, 127.7, 121.8, 105.6, 21.2, 12.6, 11.2; **IR** ν_{max} (neat) /cm^{-1} 3935, 1651, 1515, 1422, 811; **m/z** (ESI+) 214 $[M+H]^+$.

InChI=1S/C14H15NO/c1-10-4-6-14(7-5-10)15-11(2)8-13(9-16)12(15)3/h4-9H,1-3H3.

All attempts: http://malaria.ourexperiment.org/uri/2df

Data consistent with literature.[4]

2,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrrole-3-carbaldehyde, OSM-S-34



Representative example: http://malaria.ourexperiment.org/uri/58

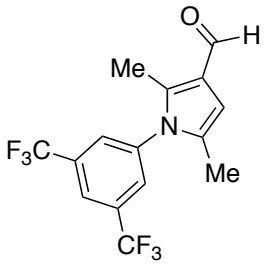
Prepared according to General Procedure **B** from DMF (8.0 mL, 104 mmol), phosphoryl chloride (0.86 mL, 9.2 mmol), **OSM-S-27** (2.0 g, 8.4 mmol) in DMF (6 mL); filtered and washed with water to give a pale brown

powder (2.0 g, 90%) used without further purification; **m.p.** 85–87 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.90 (1H, s), 7.81 (2H, d, *J* 8.4), 7.36 (2H, d, *J* 8.4,), 6.42 (1H, s), 2.30 (3H, s), 2.00 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 185.4, 140.3, 138.4, 131.3 (q, *J* 32.9), 130.8, 128.7 (2C), 126.9 (q, *J* 3.6), 123.7 (q, *J* 272.4), 122.5 (2C), 106.6, 12.8, 11.3; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -62.70; **IR** ν_{max} (neat) /cm^{-1} 1658, 1614, 1520, 1424, 1401, 1321; **m/z** (ESI+) 268 $[M+H]^+$; **HRMS** (ESI+) found 290.07619 $[M+Na]^+$, $C_{14}H_{12}NO_3F_3Na$ requires 290.07687. *InChI=1S/C14H12F3NO/c1-9-7-11(8-19)10(2)18(9)13-5-3-12(4-6-13)14(15,16)17/h3-8H,1-2H3.*

All attempts: http://malaria.ourexperiment.org/uri/2e4

*The product is a known compound (CAS: 256529-25-6) but no experimental data are available.

1-(3,5-Bis(trifluoromethyl)phenyl)-2,5-dimethyl-1H-pyrrole-3-carbaldehyde, OSM-S-36

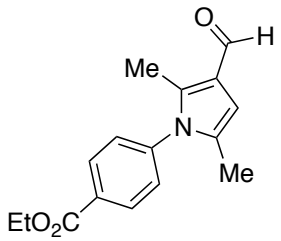


Representative example: http://malaria.ourexperiment.org/uri/55

Prepared according to General Procedure **B** from: DMF (2.0 mL, 26 mmol), phosphoryl chloride (0.20 mL, 2.1 mmol), **OSM-S-33** (0.51 g, ~1.6 mmol) in DMF (6 mL); filtered and washed with water to give a crude dark brown powder (496 mg, ~90%) which was used without further purification; **m.p.** 85–87 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.90 (1H, s), 8.04 (1H, s), 7.74 (2H, s), 6.44 (1H, app d, *J* 0.7), 2.33 (3H, s), 2.03 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 185.4, 138.8, 138.0, 133.6 (2C, q, *J* 34.3), 130.6, 128.7 (2C, q, *J* 3.4), 123.0 (2C, dq *J* 3.8 and 3.9), 122.9, 122.7 (2C, q, *J* 273.1), 107.4, 12.8, 11.4; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -62.94; **IR** ν_{max} (neat) /cm^{-1} 1659, 1473, 1407, **HRMS** (ESI^+) found 336.08190 $[M+H]^+$, $C_{15}H_{11}F_6NO$ requires 336.08176. *InChI=1S/C15H11F6NO/c1-8-3-10(7-23)9(2)22(8)13-5-11(14(16,17)18)4-12(6-13)15(19,20)21/h3-7H, 1-2H3.*

All attempts: http://malaria.ourexperiment.org/uri/2e6

Ethyl 4-(3-formyl-2,5-dimethyl-1*H*-pyrrol-1-yl)benzoate, OSM-S-46



Representative example: http://malaria.ourexperiment.org/uri/69

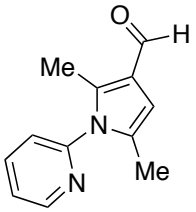
Prepared according to General Procedure **B** from: phosphoryl chloride (0.64 mL, 7.4 mmol) and **OSM-S-40** (1.5 g, 6.2 mmol) in DMF (20 mL); 0 ˚C to rt for 1 hour; product collected by filtration as a pale brown powder (1.6 g, 93%); **m.p.** 112–114 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.90 (1H, s), 8.21 (2H, d, *J* 8.4), 7.30 (2H, d, *J* 8.4), 6.40 (1H, s), 4.44 (2H, q, *J* 7.0), 2.30 (3H, s), 2.00 (3H, s), 1.43 (3H, t, 7.0); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 185.2, 165.5, 140.8, 138.3, 131.0, 130.9, 128.0, 122.2, 106.4, 61.4, 14.3, 12.6, 11.2; **m/z** (APCI+) 272 $[M+H]^+$.

InChI=1S/C16H17NO3/c1-4-20-16(19)13-5-7-15(8-6-13)17-11(2)9-14(10-18)12(17)3/h5-10H,4H2,1-3H3.

All attempts: http://malaria.ourexperiment.org/uri/2f0

Product is a known compound (CAS: 52034-37-4) and H NMR, C NMR and IR spectra are consistent with spectra from Bio-Rad Laboratories.[27]

2,5-Dimethyl-1-(pyridin-2-yl)-1H-pyrrole-3-carbaldehyde, OSM-S-44



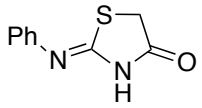
Representative example: http://malaria.ourexperiment.org/uri/67

Prepared according to General Procedure **B** from: phosphoryl chloride (0.90 mL, 9.7 mmol, 1.1 equiv.) and **OSM-S-45** (1.5 g, 8.7 mmol, 1.0 equiv.) in DMF (20 mL); 0 ˚C to rt overnight; product collected by filtration as a brown solid (1.5 g, 83%); **m.p.** 61–64 ˚C (MeCN/water); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.85 (1H, d, *J* 1.3), 8.64 (1H, d, *J* 4.7), 7.94–7.88 (1H, m), 7.44–7.39 (1H, m), 7.27–7.23 (1H, m), 6.35 (1H, s), 2.33 (3H, s), 2.04 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 185.2, 150.1, 149.7, 138.5 (× 2), 130.5, 123.7, 122.2, 122.1, 106.2, 12.5, 11.0; **IR** ν_{max} (neat) /cm^{-1} 1653, 1587, 1532, 1470, 1438; **m/z** (APCI) 201 $[M+H]^+$; **HRMS** (APCI) found 201.10165 [M+H], $C_{12}H_{13}N_2O$ requires 201.10279.

InChI=1S/C12H12N2O/c1-9-7-11(8-15)10(2)14(9)12-5-3-4-6-13-12/h3-8H,1-2H3

All attempts: http://malaria.ourexperiment.org/uri/2ee

(*Z*)-2-(Phenylimino)thiazolidin-4-one, OSM-S-286



Representative example: http://malaria.ourexperiment.org/uri/32

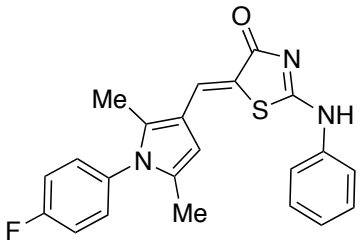
Prepared according to a literature procedure[28] from *N*-phenylthiourea (8.0 g, 53 mmol) and sodium acetate trihydrate (7.2 g, 53 mmol) were stirred in EtOH (25 mL). Ethyl bromoacetate (5.7 mL, 52 mmol) was added and the reaction heated to reflux. After 4 h, the reaction was poured over ice (130 mL). After the ice had melted the solid was filtered and recrystallised from hot EtOH (~150 mL) to obtain fine tan crystals (8.5 g, 84%); **^{1}H NMR** (200 MHz, DMSO-d_6) δ: 11.91–11.03 (1H, m), 7.71–7.67 (1H, m), 7.37 (2H, t, *J* 7.7), 7.20–7.09 (1H, m), 7.06–6.93 (1H, m), 3.98 (2H, s).

InChI=1S/C9H8N2OS/c12-8-6-13-9(11-8)10-7-4-2-1-3-5-7/h1-5H,6H2,(H,10,11,12)

Data in accordance with literature procedure.[29, 30]

All attempts: http://malaria.ourexperiment.org/uri/2f1

(*Z*)-5-((1-(4-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrol-3-yl)methylene)-2-(phenylamino)thiazol-4(5*H*)-one, OSM-S-10



Representative example: http://malaria.ourexperiment.org/uri/95

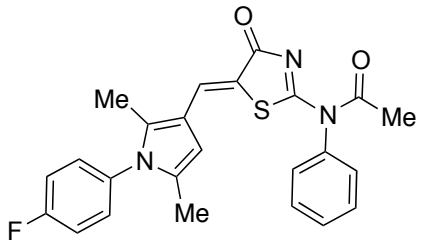
Prepared according to General Procedure **H** from: **OSM-S-286** (357 mg, 1.86 mmol) and **OSM-S-2** (404 mg, 1.86 mmol) in EtOH (30 mL) and piperidine (0.310 mL, 3.70 mmol; 60 ˚C, 4 h then rt overnight; canary yellow powder filtered and dried under reduced pressure to yield the desired product (572 mg, 79%); **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.79 (1H, s), 7.50–7.42 (2H, m), 7.22–7.17 (8H, m), 6.11 (1H, s), 2.17 (3H, s), 2.14 (3H, s).

InChI=1S/C22H18FN3OS/c1-14-12-16(15(2)26(14)19-10-8-17(23)9-11-19)13-20-21(27)25-22(28-20)24-18-6-4-3-5-7-18/h3-13H,1-2H3,(H,24,25,27)/b20-13-

All attempts: http://malaria.ourexperiment.org/uri/2cc

Prepared according to literature precedent.[31]

(Z)-N-(5-((1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)-N-phenylacetamide, OSM-S-9



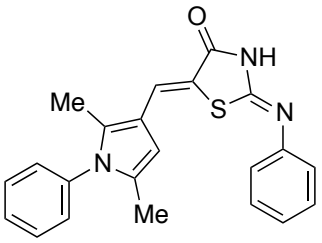
Representative example**:** http://malaria.ourexperiment.org/uri/98

OSM-S-10 (0.29 g, 0.73 mmol, 1.0 equiv.) was stirred in PhMe (10 mL) with pyridine (0.12 mL, 1.5 mmol, 2.0 equiv.). Acetic anhydride (0.30 mL, 2.9 mmol, 4.0 equiv.) was added and the yellow slurry heated to 100 ˚C for 21 h. The reaction mixture was allowed to cool to rt, hexane (10 mL) was added, briefly stirred and the reaction was filtered to obtain a yellow powder (0.23 g, 72%); **^{1}H NMR** (300 MHz, DMSO-d_6) δ: 7.76 (s, 1H), 7.61–7.55 (m, 5H), 7.51–7.42 (m, 4H), 6.32 (s, 1H), 2.17 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 178.5, 174.5, 172.8, 131.8 (d, *J* 245.9), 139.8, 137.1, 133.1 (d, *J* 2.6), 132.0, 130.1 (d, *J* 8.8), 129.9, 129.6, 129.2, 128.6, 119.4, 116.5 (d, *J* 22.6), 115.7, 105.4, 25.1, 12.4, 10.7; **^{19}F{^{1}H} NMR** (282 MHz, DMSO-d_6) δ: -112.7; **IR** ν_{max} (neat) /cm^{-1} 1707, 1584, 1512, 1368, 1313, 119, 1172; **m/z** (ESI+) 434 $[M+H]^+$; **HRMS** (ESI+) found 434.13315 $[M+Na]^+$, $C_{24}H_{21}N_3O_2FS$ requires 434.13330; **CCDC1045854**.

InChI=1S/C24H20FN3O2S/c1-15-13-18(16(2)27(15)21-11-9-19(25)10-12-21)14-22-23(30)26-24(31-22)28(17(3)29)20-7-5-4-6-8-20/h4-14H,1-3H3/b22-14-

All attempts: http://malaria.ourexperiment.org/uri/2cc

(2Z,5Z)-5-((2,5-Dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-35



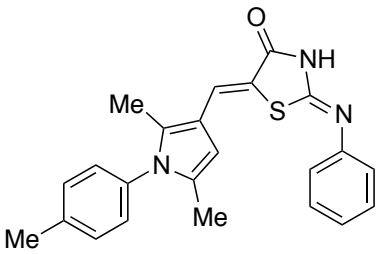
Representative example: http://malaria.ourexperiment.org/uri/256

Prepared according to General Procedure **H** from: **OSM-S-286** (77 mg, 0.39 mmol) and **OSM-S-28** (80 mg, 0.39 mmol) in EtOH (6 mL) and piperidine (60 μL, 0.58 mmol); 60 ˚C overnight; resulting precipitate filtered and washed with EtOH to give a mustard coloured solid (65 mg, 0.17 mmol, 43%); **m.p.** 273 ˚C (decomposes); **^{1}H NMR** (300 MHz, DMSO–d_6) δ: 12.11–11.13 (1H, m) 7.78 (1H, bs), 7.65–7.47 (4H, m), 7.41 (2H, t, *J* 7.9 Hz), 7.36–7.28 (2H, m), 7.17 (1H, t, *J* 7.4 Hz), 7.04 (1H, bs), 6.24–5.97 (1H, m), 2.09 (3H, s), 2.04–1.8 (3H, m); **^{13}C NMR** (101 MHz, DMSO–d_6) δ: 137.0, 134.5, 131.0, 129.5 (× 2), 129.4, 128.7, 127.9, 124.5, 123.8, 121.3, 121.0, 120.1, 114.8, 104.8, 12.6, 12.4, 10.7; **IR** ν_{max} (neat) /cm^{-1} 1703, 1637, 1591, 1495, 1300, 1173; **m/z** (ESI+) 374 $[M+H]^+$; **HRMS** (ESI+) 374.13105 $[M+H]^+$, $C_{22}H_{20}N_3OS$ requires 374.13271; **CCDC1045853**.

InChI=1S/C22H19N3OS/c1-15-13-17(16(2)25(15)19-11-7-4-8-12-19)14-20-21(26)24-22(27-20)23-18-9-5-3-6-10-18/h3-14H,1-2H3,(H,23,24,26)/b20-14-

All attempts: http://malaria.ourexperiment.org/uri/2e5

(2Z,5Z)-5-((2,5-Dimethyl-1-(p-tolyl)-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-37



Representative example: http://malaria.ourexperiment.org/uri/56

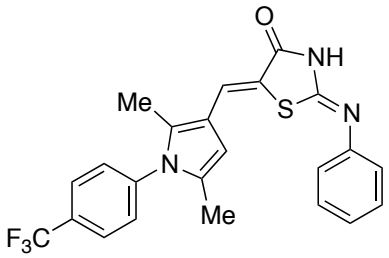
Prepared according to General Procedure **H** from: **OSM-S-286** (123 mg, 0.640 mmol) and **OSM-S-29** (145 mg, 0.627 mmol) in EtOH (15 mL) and piperidine (0.100 mL, 1.01 mmol); 60 ˚C, 4.5 h; resulting precipitate filtered and washed with EtOH to give a fine yellow powder (124 mg, 51%); **m.p.** 279 ˚C (decomposition); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.72 (1H, s), 7.44–7.37 (2H, m), 7.29–7.25 (3H, m), 7.23–7.13 (3H, m), 7.04 (2H, d, *J* 8.1), 6.11 (1, s), 2.43 (3H, s), 2.13 (3H, s), 1.97 (3H, s); **^{13}C NMR** (76 MHz, $CDCl_3$) δ: 169.2, 148.2, 138.7,

138.5, 135.9, 135.3, 135.1, 134.9, 131.6, 130.5 (× 2), 130.4, 129.9, 129.6, 129.2, 129.0, 128.5, 128.1 (x2), 127.6, 125.3, 125.0, 124.4, 121.8, 120.7, 115.7, 115.2, 109.6, 105.2, 21.2, 13.1, 12.8, 11.1, 11.0; **IR** ν_{max} (neat) /cm^{-1} 1737, 1599, 1590, 1516; **m/z** (ESI+) 388 $[M+H]^+$; **HRMS** found 388.14765 $[M+H]^+$, $C_{23}H_{22}N_3OS$ requires 388.14836.

InChI=1S/C23H21N3OS/c1-15-9-11-20(12-10-15)26-16(2)13-18(17(26)3)14-21-22(27)25-23(28-21)24-19-7-5-4-6-8-19/h4-14H,1-3H3,(H,24,25,27)/b21-14-

All attempts: http://malaria.ourexperiment.org/uri/2e7

(2Z,5Z)-5-((2,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-38



Representative example: http://malaria.ourexperiment.org/uri/59

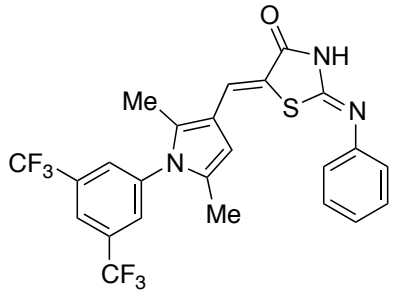
Prepared according to General Procedure **H** from: **OSM-S-286** (230 mg, 1.20 mmol) **OSM-S-34** (320 mg, 1.20 mmol) and piperidine (0.180 mL, 1.82 mmol) in EtOH (15 mL); 60 ˚C, 4 h; resulting precipitate filtered and washed with EtOH to give a yellow powder (365 mg, 69% yield); **m.p.** 308 ˚C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d^6) δ: 7.86 (2H, d *J* 7.1), 7.85 (1H, bs), 7.56–7.43 (3H, m), 7.34 (2H, t, *J* 7.4), 7.13–7.08 (1H, m), 6.97 (1H, bs), 6.18–5.96 (1H, m), 2.05 (3H, bs), 1.98–1.88 (3H, m); **^{13}C NMR** (101 MHz, DMSO-d^6) δ: 140.6, 134.4, 131.0, 129.5, 129.1, 128.8, 126.8, 125.3, 124.7, 122.6, 121.5, 120.3, 116.0, 105.4, 12.4, 10.8; **IR** ν_{max} (neat) /cm^{-1} 2779, 1698, 1650, 1610, 1521, 1391, 1317; **m/z** (ESI+) 442 $[M+H]^+$;

HRMS (ESI+) found 464.10145 $[M+Na]^+$, $C_{23}H_{18}F_3N_3OSNa$ requires 464.10149.

InChI=1S/C23H18F3N3OS/c1-14-12-16(15(2)29(14)19-10-8-17(9-11-19)23(24,25)26)13-20-21(30)28-22(31-20)27-18-6-4-3-5-7-18/h3-13H,1-2H3,(H,27,28,30)/b20-13-

All attempts: http://malaria.ourexperiment.org/uri/2e8

(2Z,5Z)-5-((1-(3,5-bis(Trifluoromethyl)phenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-39



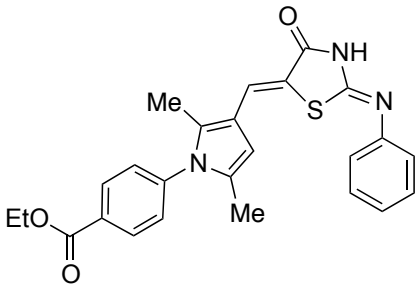
Representative example: http://malaria.ourexperiment.org/uri/64

Prepared according to General Procedure **H** from: **OSM-S-286** (58 mg, 0.30 mmol) and **OSM-S-36** (0.30 g, 0.90 mmol) in EtOH (15 mL) and piperidine (0.14 mL, 1.4 mmol); 60 ˚C, 1.5 h; resulting precipitate filtered and washed with EtOH to yield a mustard powder (0.20 g, 44% yield); **m.p.** 255 ˚C (decomposes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.99 (1H, s), 7.70–7.68 (3H, m), 7.43 (2H, t, *J* 7.9), 7.26–7.20 (3H, m), 6.19 (1H, s), 2.16 (3H, s), 2.02 (3H, s); **^{13}C NMR** (100 MHz, DMSO-d^6) δ: 139.8, 135.5, 132.5 (q, *J* 33.6), 132.1, 130.4, 130.0, 127.8, 125.2, 124.2, 123.5, 121.7, 121.1, 119.7, 117.1, 116.4, 106.5, 13.2, 11.6; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -62.9; **IR** ν_{max} (neat) /cm^{-1} 1623, 1597, 1498, 1472, 1445, 1461; **m/z** (ESI+) 510 $[M+H]^+$; **HRMS** (ESI+) found 510.10796 $[M+H]^+$, $C_{24}H_{18}F_6N_3OS$ requires 510.10693.

InChI=1S/C24H17F6N3OS/c1-13-8-15(9-20-21(34)32-22(35-20)31-18-6-4-3-5-7-18)14(2)33(13)19-11-16(23(25,26)27)10-17(12-19)24(28,29)30/h3-12H,1-2H3,(H,31,32,34)/b20-9-

All attempts: http://malaria.ourexperiment.org/uri/2e9

Ethyl 4-(2,5-dimethyl-3-((Z)-((Z)-4-oxo-2-(phenylimino)thiazolidin-5-ylidene)methyl)-1H-pyrrol-1-yl)benzoate, OSM-S-48



Representative example: http://malaria.ourexperiment.org/uri/71

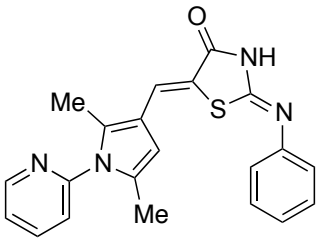
Prepared according to General Procedure **H** from: **OSM-S-286** (354 mg, 1.84 mmol) and **OSM-S-46** (500 mg, 1.84 mmol) in EtOH (10 mL) and piperidine (0.28 mL, 2.76 mmol); 60 ˚C, 20 h; resulting precipitate filtered and

washed with EtOH to yield a fine yellow powder (772 mg, 94% yield); **m.p.** 248 ˚C (decomposes); **^{1}H NMR** (300 MHz, DMSO–d_6) δ: 11.70 (1H, bs), 8.11 (2H, d, *J* 7.8), 7.79–7.47 (4H, m), 7.41 (2H, t, *J* 7.4), 7.18 (1H, t, *J* 7.5), 7.09–6.94 (1H, m), 6.31–6.04 (1H, m), 4.36 (2H, q, *J* 7.0), 2.13 (3H, bs), 2.06–1.93 (3H, m), 1.35 (3H, t, *J* 7.0); **^{13}C NMR** (76 Hz, DMSO–d_6) δ: 165.5, 141.5, 134.7, 134.6, 131.3, 130.8, 130.4, 129.9, 129.5, 128.8, 125.0, 123.9, 121.8, 120.7, 116.3, 116.2, 115.8, 105.8, 61.5, 14.6, 12.8, 11.2; **IR** ν_{max} (neat) /cm^{-1} 1710, 1644 1590, 1421, 1391, 1317; **m/z** (ESI+) 913 $[2M+H]^+$; **HRMS** (ESI+) 468.13527 $[M+Na]^+$, $C_{25}H_{23}N_3NaO_3S$ requires 468.13578.

InChI=1S/C25H23N3O3S/c1-4-31-24(30)18-10-12-21(13-11-18)28-16(2)14-19(17(28)3)15-22-23(29)27-25(32-22)26-20-8-6-5-7-9-20/h5-15H,4H2,1-3H3,(H,26,27,29)/b22-15-

All attempts: http://malaria.ourexperiment.org/uri/2f2

(2Z,5Z)-5-((2,5-Dimethyl-1-(pyridin-2-yl)-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-51



Representative example: http://malaria.ourexperiment.org/uri/79

Prepared according to General Procedure **H** from: **OSM-S-286** (480 mg, 2.50 mmol) and **OSM-S-44** (500 mg, 2.50 mmol) in EtOH (20 mL) and piperidine (370 μL, 3.75 mmol); 60 ˚C, 2.5 h; resulting precipitate filtered and washed with EtOH to give the product as a yellow-brown powder (635 mg, 68% yield); **m.p.** 276–278 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.65–8.63 (1H, m), 7.88 (1H, dt, *J* 7.6, 1.9), 7.74 (1H, bs), 7.45–7.37 (3H, m), 7.27–7.19 (4H, m), 6.15 (1H, bs), 2.22 (1H, bs), 2.22 (3H, s), 2.07 (3H, s); **IR** ν_{max} (neat) /cm^{-1} 1722, 1628, 1591, 1494, 1367, 1268; **m/z** (ESI+) 397 $[M+Na]^+$; **HRMS** (ESI+) found 375.12741 $[M+H]^+$, $C_{21}H_{19}N_4OS$ requires 375.12680.

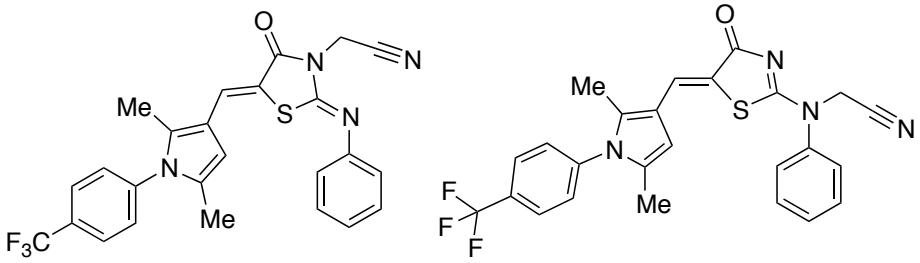
InChI=1S/C21H18N4OS/c1-14-12-16(15(2)25(14)19-10-6-7-11-22-19)13-18-20(26)24-21(27-18)23-17-8-4-3-5-9-17/h3-13H,1-2H3,(H,23,24,26)/b18-13-

All attempts: http://malaria.ourexperiment.org/uri/2f5

2-((2Z,5Z)-5-((2,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)acetonitrile, OSM-S-42

and

(Z)-5-((2,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-2-(phenyl(prop-2-yn-1-yl)amino)thiazol-4(5H)-one, OSM-S-43



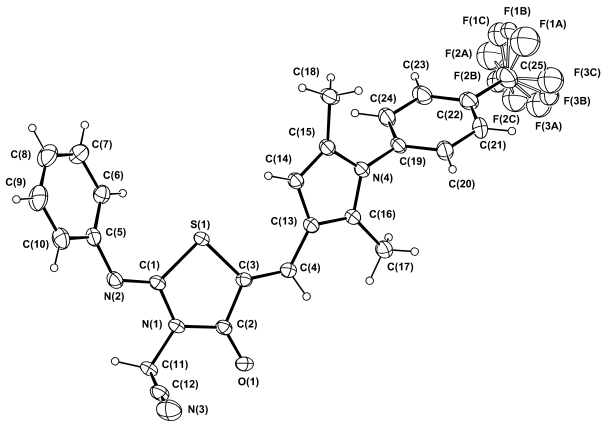
Representative example: http://malaria.ourexperiment.org/uri/8b

Potassium carbonate (313 mg, 2.26 mmol, 2.0 equiv.), sodium iodide (280 mg, 1.88 mmol, 1.7 equiv.) and **OSM-S-38** (496 mg, 1.12 mmol, 1.0 equiv.) were stirred in acetonitrile and bromoacetonitrile (95.7 µL, 1.36 mmol, 1.2 equiv) was added. The mixture was heated to 80 ˚C for 3 h. The mixture was extracted with ethyl acetate (40 mL) and washed with water (3 × 20 mL), brine (20 mL) and then concentrated under reduced pressure to give a brown gum which was purified by flash column chromatography over silica (20-50% ethyl acetate in hexane) to afford **OSM-S-42** as a greenish-brown solid (133 mg, 24%) along with the title compound **OSM-S-43** as a yellow-brown solid (243 mg, 45%).

OSM-S-42: **m.p.** 182–183 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.80–7.74 (3H, m), 7.41 (2H, t, *J* 7.5), 7.32 (2H, d, *J* 8.3), 7.23–7.19 (1H, m), 7.10–7.07 (2H, m), 6.15 (1H, s), 4.84 (2H, s). 2.16 (3H, s), 1.99 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 165.6, 149.1, 147.5, 140.7, 135.6, 131.7, 131.1 (2C, q, *J* 32.9), 129.5, 129.5, 128.6, 126.9 (2C, q, *J* 3.8), 125.2, 123.7 (2C, q, *J* 273), 121.4, 116.2, 114.1, 106.2, 112.7, 29.8, 12.8, 11.3; **^{19}F{H} NMR** (282 MHz, $CDCl_3$) δ: -62.6; **IR** ν_{max} (neat) / cm^{-1} 3391, 1706, 1633, 1519, 1377, 1322; **m/z** (ESI) 982 $[2M+Na]^+$; **HRMS** (ESI+) found 503.11264 $[M+H]^+$, $C_{25}H_{19}F_3N_4NaOS$ requires 503.11239; **CCDC1045851**.

InChI=1S/C25H19F3N4OS/c1-16-14-18(17(2)32(16)21-10-8-19(9-11-21)25(26,27)28)15-22-23(33)31(13-12-29)24(34-22)30-20-6-4-3-5-7-20/h3-11,14-15H,13H2,1-2H3/b22-15-,30-24+

All attempts: http://malaria.ourexperiment.org/uri/2ec

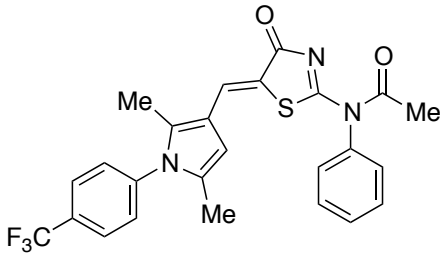


OSM-S-43: **m.p.** 72–74 ˚C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.84 (1H, s), 7.77 (2H, d, *J* 8.3), 7.62–7.61 (3H, m), 7.52–7.50 (2H, m), 7.31 (2H, d, *J* 8.3), 6.00 (1H, s), 5.03 (2H, s), 2.15 (3H, s), 1.96 (3H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 181.0, 177.8, 140.7 (2C, q, *J* 1.4), 139.4, 135.6, 131.4, 131.0 (2C, q, *J* 33.0), 130.8, 130.7, 128.5, 128.0, 127.9, 126.8 (2C, q, *J* 3.6), 123.7 (2C, q, *J* 273), 122.1, 116.4, 114.4, 105.8, 40.9, 12.8, 11.2; **^{19}F{H} NMR** (282 MHz, $CDCl_3$) δ: -62.6; **IR** ν_{max} (neat) / cm^{-1} 1599, 1519, 1374, 1325; **m/z** (ESI) 503 $[M+Na]^+$; **HRMS** (ESI+) found 503.11295 $[M+H]^+$, $C_{25}H_{19}F_3N_4NaOS$ requires 503.11239.

InChI=1S/C26H20F3N3OS/c1-4-14-31(21-8-6-5-7-9-21)25-30-24(33)23(34-25)16-19-15-17(2)32(18(19)3)22-12-10-20(11-13-22)26(27,28)29/h1,5-13,15-16H,14H2,2-3H3/b23-16-

All attempts: http://malaria.ourexperiment.org/uri/2ed

(Z)-N-(5-((2,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)-N-phenylacetamide, OSM-S-45



Representative example: http://malaria.ourexperiment.org/uri/74

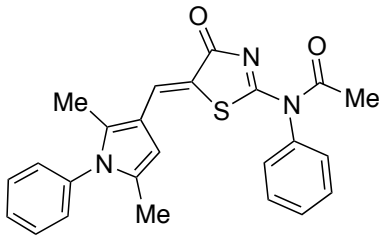
OSM-S-38 (0.10 g, 0.22 mmol, 1 equiv.) was dissolved in toluene (~20 mL) and stirred under a nitrogen atmosphere. Pyridine (~40 µL, 0.44 mmol, 2 equiv.) was added, followed by acetic anhydride (~80 µL, 0.88 mmol, 4 equiv.) and the mixture was refluxed under nitrogen at 80 ˚C for 7 h. The liquid was then evaporated off under reduced pressure to give a yellow powder which was purified by flash column chromatography over silica to provide the product as a yellow solid (98 mg, 92%); **m.p.** 309–311 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.87

(1H, s), 7.74–7.71 (2H, m), 7.49–7.40 (3H, m), 7.30–7.19 (4H, m), 6.36 (1H, bs), 2.10 (3H, s), 2.05 (3H, s), 1.99 (3H, s); **^{13}C NMR** (76 MHz, $CDCl_3$) δ: 180.2, 175.5, 172.8, 140.6, 139.5, 136.6, 131.8, 131.3, 131.0 (d, *J* 32.6), 130.2, 129.6, 128.5, 128.3, 126.7 (d, *J* 3.6), 120.6, 117.1, 106.9, 25.3, 12.8, 11.2; **^{19}F{H} NMR** (282 MHz, $CDCl_3$) δ: -62.6; **IR** ν_{max} (neat) / cm^{-1} 1705, 1581, 1519, 1479, 1425, 1391; **HRMS** (ESI+) 506.11167 $[M+Na]^+$, $C_{25}H_{20}F_3N_3NaO_2S$ requires 506.11260.

InChI=1S/C25H20F3N3O2S/c1-15-13-18(16(2)30(15)21-11-9-19(10-12-21)25(26,27)28)14-22-23(33)29-24(34-22)31(17(3)32)20-7-5-4-6-8-20/h4-14H,1-3H3/b22-14-

All attempts: http://malaria.ourexperiment.org/uri/2ef

(Z)-N-(5-((2,5-Dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)-N-phenylacetamide, OSM-S-49



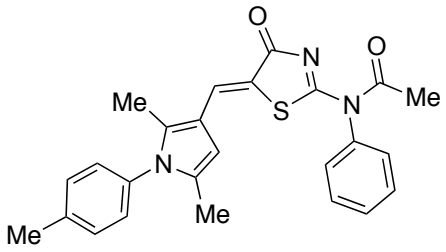
Representative example: http://malaria.ourexperiment.org/uri/77

OSM-S-35 (49 mg, 0.13 mmol, 1.0 equiv.) was partially dissolved in toluene (~5 mL) and stirred under a nitrogen atmosphere. Pyridine (~20 µL, 0.25 mmol, 1.9 equiv.) was added, followed by acetic anhydride (~40 µL, 0.4 mmol, 3.0 equiv.). The mixture was heated to 80 ˚C and stirred overnight. The liquid was then evaporated under reduced pressure to give a yellow powder (0.10 g, quant.); **m.p.** 237–238 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.88 (1H, bs), 7.45–7.35 (6H, m), 7.24–7.19 (2H, m), 7.12–7.07 (2H, m), 6.32 (1H, bs), 2.07 (3H, s), 2.03 (3H, s), 1.95 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 180.1, 175.3, 172.6, 139.4, 137.3, 132.0, 131.7, 130.0, 129.4 (x 2), 128.7, 128.2, 127.7, 120.0, 116.4, 106.1, 25.2, 12.6, 11.0; **IR** ν_{max} (neat) /cm^{-1} 1705, 1580, 1495, 1424, 1369; **HRMS** (ESI+) 416.14285 $[M+H]^+$, $C_{24}H_{22}N_3O_2S$ requires 416.14327.

InChI=1S/C24H21N3O2S/c1-16-14-19(17(2)26(16)20-10-6-4-7-11-20)15-22-23(29)25-24(30-22)27(18(3)28)21-12-8-5-9-13-21/h4-15H,1-3H3/b22-15-

All attempts: http://malaria.ourexperiment.org/uri/2f3

(Z)-N-(5-((2,5-Dimethyl-1-(p-tolyl)-1H-pyrrol-3-yl)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)-N-phenylacetamide, OSM-S-50



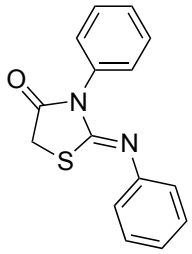
Representative example: http://malaria.ourexperiment.org/uri/78

OSM-S-37 (50 mg, 0.13 mmol, 1.0 equiv.) was partially dissolved in toluene (~5 mL) and stirred under a nitrogen atmosphere. Pyridine (~20 µL, 0.25 mmol, 1.9 equiv.) was added, followed by acetic anhydride (~40 µL, 0.4 mmol, 3.0 equiv.). The mixture was heated to 80 ˚C and stirred overnight. The mixture was evaporated under reduced pressure to give a yellow powder which was dissolved in ethyl acetate and adsorbed onto silica, washed with hexane (~150 mL) then washed off the silica with ethyl acetate and concentrated under reduced pressure to return a yellow powder (25 mg, 54%); **m.p.** 256–258 ˚C (decomposes); **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 8.23 (1H, s), 7.53–7.33 (3H, m), 7.29–7.16 (4H, m), 7.10–7.06 (2H, m), 6.41 (1H, s); 2.44 (3H, s), 2.16 (3H, s), 2.12 (3H, s), 2.00 (3H, s); **IR** ν_{max} (neat) /cm^{-1} 1712, 1635, 1605, 1520, 1493, 1364, 1322, 1267; **HRMS** (ESI+) 388.14793 $[M\text{-}C_2H_3O+H]^+$, $C_{23}H_{22}N_3OS$ requires 388.14836.

InChI=1S/C25H23N3O2S/c1-16-10-12-22(13-11-16)27-17(2)14-20(18(27)3)15-23-24(30)26-25(31-23)28(19(4)29)21-8-6-5-7-9-21/h5-15H,1-4H3/b23-15-

All attempts: http://malaria.ourexperiment.org/uri/2f4

(*Z*)-3-Phenyl-2-(phenylimino)thiazolidin-4-one, OSM-S-47



Representative example: http://malaria.ourexperiment.org/uri/70

N,N-Diphenylthiourea (8.0 g, 35 mmol, 1.0 equiv.) was mixed with sodium acetate trihydrate (4.8 g, 35 mmol, 1.0 equiv.) in EtOH (30 mL). Ethyl bromoacetate (3.8 mL, 35 mmol, 1.0 equiv.) was added in portions and the

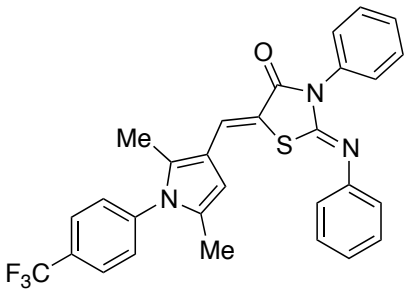
mixture heated to 60 ˚C under nitrogen overnight. The mixture was poured over ice and filtered to give a fine white crystalline solid (8.6 g, 92%); **m.p.** 175–176 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.52–7.46 (2H, m), 7.43–7.34 (3H, m), 7.33–7.27 (2H, m), 7.12–7.07 (1H, m), 6.92–6.89 (2H, m), 3.91 (2H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 171.3, 154.8, 148.0, 134.7, 129.2, 129.1, 128.9, 127.9, 124.5, 120.8, 32.8; **IR** ν_{max} (neat) /cm^{-1} 1722, 1628, 1591, 1494, 1367; **m/z** (APCI) 269 $[M+H]^+$.

InChI=1S/C15H12N2OS/c18-14-11-19-15(16-12-7-3-1-4-8-12)17(14)13-9-5-2-6-10-13/h1-10H,11H2/b16-15-

All attempts: http://malaria.ourexperiment.org/uri/2f1

*The product is a known compound (CAS: 790-04-5) and ^{13}C NMR and IR spectra are consistent with those found in the literature.

(2Z,5Z)-5-((2,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-3-phenyl-2-(phenylimino)thiazolidin-4-one, OSM-S-52



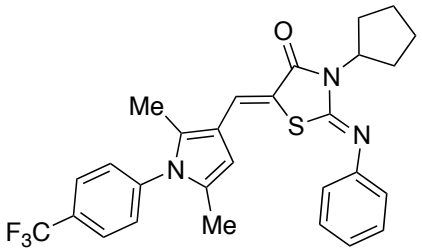
Representative example: http://malaria.ourexperiment.org/uri/7a

Prepared according to General Procedure **H** from: **OSM-S-47** (0.40 g, 1.5 mmol) and **OSM-S-34** (0.40 g, 1.5 mmol) in EtOH (20 mL) and piperidine (220 μL, 2.2 mmol); 60 ˚C, 1.5 h; resulting precipitate filtered and washed with EtOH to yield a grey solid (0.65 g, 84% yield); **m.p.** 226–227 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.57 (1H, s), 7.52 (2H, d, *J* 8.3), 7.31–7.24 (3H, m), 7.20–7.03 (6H, m), 6.90 (1H, t, *J* 7.4), 6.76 (2H, d *J* 7.4), 5.97 (1H, s), 1.91 (3H, s), 1.75 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 167.0, 151.9, 148.7, 140.8, 135.1, 134.5, 130.8 (d, *J* 36.7), 129.1, 128.6, 128.4, 128.1, 126.6 (d, *J*, 3.2), 125.2, 124.4, 121.1, 116.2, 114.2, 107.6, 106.1, 12.7, 11.1; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -62.3; **IR** ν_{max} (neat) /cm^{-1} 1712, 1635, 1605, 1520, 1493, 1364, 1322, 1267; **m/z** (ESI+) 540 $[M+Na]^+$; **HRMS** (ESI+) found 540.13279 $[M+Na]^+$, $C_{29}H_{22}F_3N_3NaOS$ requires 540.13240.

InChI=1S/C29H22F3N3OS/c1-19-17-21(20(2)34(19)25-15-13-22(14-16-25)29(30,31)32)18-26-27(36)35(24-11-7-4-8-12-24)28(37-26)33-23-9-5-3-6-10-23/h3-18H,1-2H3/b26-18-,33-28+

All attempts: http://malaria.ourexperiment.org/uri/2f6

(2Z,5Z)-3-Cyclopentyl-5-((2,5-dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-54



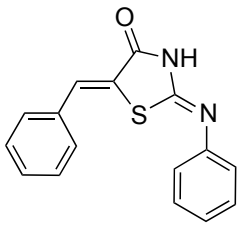
Representative example: http://malaria.ourexperiment.org/uri/83

Sodium hydride (27 mg, 0.68 mmol, 1.5 equiv.) was combined with DMF (2 mL) and stirred under a nitrogen atmosphere in an ice bath. **OSM-S-38** (200 mg, 0.45 mmol, 1 equiv.) was combined with DMF (8 mL) and added in portions over 3 min. The mixture stirred for 10 min and then cyclopentylbromide (60 µL, 0.56 mmol, 1.2 equiv.) was added drop-wise. The reaction mixture was stirred at 60 ˚C for 22 h and then quenched by drop-wise addition of water. A brownish-yellow precipitate was formed and then filtered, washed with water (~20 mL) and then dried under high vacuum. The crude solid was purified by flash column chromatography over silica (2–8% EtOAc in hexane) to afford the desired product as a brownish yellow solid (58 mg, 25%); **m.p.** 71–72 ˚C; **^{1}H NMR** (400 MHz, DMSO *d*-$_6$) δ: 7.92 (2H, d, *J* 8.4), 7.62–7.55 (3H, m), 7.43–7.39 (2H, m), 7.20–7.16 (1H, m), 7.03–7.00 (2H, m), 6.04 (1H, s), 5.05 (1H, q, *J* 8.4), 2.28–2.20 (2H, m), 2.12 (3H, s), 1.96 (3H, s), 1.93–1.84 (4H, m), 1.65–1.56 (2H, m); **^{13}C NMR** (101 MHz, DMSO *d*-$_6$) δ: 167.1, 151.1, 149.4, 141.5, 135.4, 132.0, 130.4, 127.6 (d, *J* 3.7), 126.2, 125.5, 125.0, 123.5, 122.0, 116.3, 114.3, 106.4, 55.6, 28.8, 26.1, 13.3, 11.7; **^{19}F{H} NMR** (376 MHz, DMSO *d*-$_6$) δ: -61.1; **IR** ν_{max} (neat) /cm^{-1} 2956, 1698, 1628, 1604, 1520, 1486, 1400, 1375, 1322; **HRMS** (ESI+) found 510.18203 $[M+H]^+$, $C_{28}H_{27}F_3N_3OS$ requires 510.18269; **CCDC1045852**.

InChI=1S/C28H26F3N3OS/c1-18-16-20(19(2)33(18)24-14-12-21(13-15-24)28(29,30)31)17-25-26(35)34(23-10-6-7-11-23)27(36-25)32-22-8-4-3-5-9-22/h3-5,8-9,12-17,23H,6-7,10-11H2,1-2H3/b25-17-,32-27-

All attempts: http://malaria.ourexperiment.org/uri/2f8

(2*Z*,5*Z*)-5-Benzylidene-2-(phenylimino)thiazolidin-4-one, OSM-S-55



Representative example: http://malaria.ourexperiment.org/uri/85

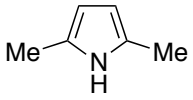
Prepared according to General Procedure **H** from: **OSM-S-286** (229 mg, 1.19 mmol, 1.0 equiv.) and benzaldehyde (126 mg, 1.19 mmol, 1.0 equiv.) in EtOH (15 mL) and piperidine (58.8 µL, 0.60 mmol, 0.5 equiv.); 60 ˚C, 4 h; resulting precipitate filtered and washed with EtOH to yield a fine, brownish yellow powder (170 mg, 51% yield); **m.p.** 260–261 ˚C; **^{1}H NMR** (500 MHz, DMSO–d_6) δ: 12.3 (1H, bs), 7.80–7.81 (1H, m), 7.63 (1H, m), 7.53–7.40 (6H, m), 7.22–7.19 (1H, m), 7.07–7.05 (1H, m); **IR** ν_{max} (neat) /cm^{-1} 2961, 2932, 2871, 2856, 1714, 1627, 1593, 1519, 1487; **m/z** (ESI+) 303 $[M+Na]^+$.

InChI=1S/C16H12N2OS/c19-15-14(11-12-7-3-1-4-8-12)20-16(18-15)17-13-9-5-2-6-10-13/h1-11H,(H,17,18,19)/b14-11-

All attempts: http://malaria.ourexperiment.org/uri/2f9

*A known compound (CAS: 38771-64-1 or 851429-54-4 or 1082659-12-8, depending on stereochemistry) with IR, mass and H NMR spectra available for the record - E/Z isomerism of the phenyl substitution uncharacterised.

2,5-Dimethyl-1*H*-pyrrole[32]



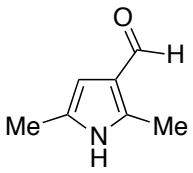
Representative example: http://malaria.ourexperiment.org/uri/20b

2,5-Hexanedione (5 g, 5.14 mL, 43 mmol) and ammonium carbonate (8.3 g, 86 mmol) was heated at 100 ˚C (melts at 86 ˚C) until effervescence stopped (90 min). Then heated to 115 ˚C for 30 min. Stirred overnight whilst cooling to room temp. Top layer of orange oil filtered off and bottom layer of orange liquid extracted with chloroform (2 mL). Combined organic layers were dried over $CaCl_2$ under nitrogen and then decanted into a 25 mL round-bottomed flask and purified by distillation *in vacuo*. Chloroform was removed at rt and the product was collected as a clear and colourless distillate (2.41 g, 59% yield) at 68–70 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.71 (1H, bs), 5.74 (2H, d, *J* 2.5), 2.21 (6H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 126.6, 106.2, 13.4.

InChI=1S/C6H9N/c1-5-3-4-6(2)7-5/h3-4,7H,1-2H3

Compound is a known commercial compound CAS: 625-84-3. Spectra match Sigma Aldrich website.[33]

2,5-Dimethyl-1*H*-pyrrole-3-carbaldehyde



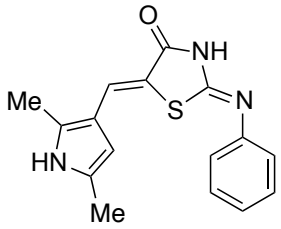
Representative example: http://malaria.ourexperiment.org/uri/20f

Prepared according to General Procedure **B** from: phosphoryl chloride (2.83 mL, 30.5 mmol) and **2,5-Dimethyl-1*H*-pyrrole** (2.4 g, 25.3 mmol) in DMF (24 mL); 0 ˚C to rt for 1.5 h; product collected by filtration as a beige powder (1.73 g, 55%) and used in the next step; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.76 (1H, s), 8.98 (1H, bs), 6.18 (1H, s), 2.48 (3H, s), 2.19 (3H, s); **^{13}C NMR** (76 MHz, $CDCl_3$) δ: 185.1, 138.0, 128.3, 122.1, 105.2, 12.5, 11.5.

InChI=1S/C7H9NO/c1-5-3-7(4-9)6(2)8-5/h3-4,8H,1-2H3

Compound is a known commercial compound CAS: 2199-63-5. Data in close agreement with the literature – NMR measured at lower field.[34]

(2Z,5Z)-5-((2,5-Dimethyl-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-108



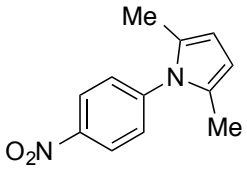
Representative example: http://malaria.ourexperiment.org/uri/213

Prepared according to General Procedure **H** from **OSM-S-286** (155 mg, 0.812 mmol) and **2,5-dimethyl-1*H*-pyrrole-3-carbaldehyde** (100 mg, 0.812 mmol) in EtOH (8.00 mL) and piperidine (0.120 mL, 1.22 mmol); 60 ˚C, 16 h; resulting precipitate filtered and washed with EtOH to yield a mustard powder (133 mg, 55%); **m.p.** 276 ˚C (decomposed); **HRMS** (ESI+) found 298.10083 $[M+H]^+$, $C_{16}H_{16}N_3OS$ requires 298.10086.

InChI=1S/C16H15N3OS/c1-10-8-12(11(2)17-10)9-14-15(20)19-16(21-14)18-13-6-4-3-5-7-13/h3-9,17H,1-2H3,(H,18,19,20)/b14-9-

All attempts: http://malaria.ourexperiment.org/uri/330

2,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrrole, OSM-S-287

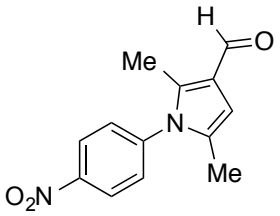


Representative example: http://malaria.ourexperiment.org/uri/216

4-Nitroaniline (1.0 g, 7.4 mmol, 1.1 equiv.) and 2,5-hexanedione (0.77 mL, 6.6 mmol, 1.0 equiv.) were heated to 110 ˚C (oil bath temp.) for 4 h. The reaction mixture was heterogeneous and no reaction was observed. Acetic acid (3 mL) was added and the reaction mixture stirred at 110 ˚C for 16 h. The reaction mixture was allowed to cool and then pH changed to 5 by addition of a saturated aqueous solution of sodium hydrogen carbonate. The aqueous mixture was extracted with EtOAc, washed with brine, dried ($MgSO_4$), filtered and evaporated to give an orange brown oil that was purified by flash column chromatography over silica (5–20% EtOAc in petroleum ether) to obtain the desired product (1.2 g, 83% yield) as a mustard coloured solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.34 (2H, d, *J* 8.7), 7.40 (2H, d, *J* 8.7), 6.00 (1H, s), 2.09 (6H, s); **^{13}C NMR** (76 MHz, $CDCl_3$) δ: 146.5, 144.6, 128.7, 128.4, 124.4, 107.3, 12.9.

InChI=1S/C12H12N2O2/c1-9-3-4-10(2)13(9)11-5-7-12(8-6-11)14(15)16/h3-8H,1-2H3

2,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrrole-3-carbaldehyde, OSM-S-288

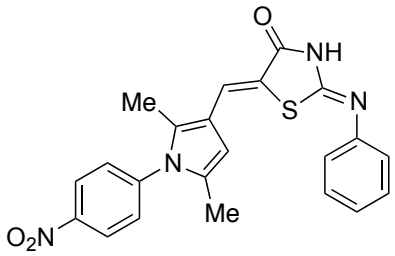


Representative example: http://malaria.ourexperiment.org/uri/232

Prepared according to General Procedure **B** from: phosphoryl chloride (0.610 mL, 6.55 mmol, 1.2 equiv.) and **AEW 35-1** (1.18 g, 5.46 mmol, 1 equiv.) in DMF (5 mL); 0 ˚ C to rt 1 h; slurry filtered to give a brown paste, triturated in EtOH to give a dark brown free-flowing powder that was dried *in vacuo* to give the desired product (453 mg, 34% yield); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.90 (1H, s), 8.42 (2H, d, *J* 8.5), 7.44 (2H, d, *J* 8.5), 6.44 (1H, s), 2.32 (3H, s), 2.03 (3H, s).

InChI=1S/C13H12N2O3/c1-9-7-11(8-16)10(2)14(9)12-3-5-13(6-4-12)15(17)18/h3-8H,1-2H3

(2Z,5Z)-5-((2,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-109



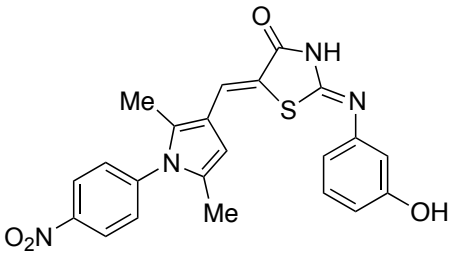
Representative example: http://malaria.ourexperiment.org/uri/244

Prepared according to General Procedure **H** from **OSM-S-286** (78 mg, 0.41 mmol) and **AEW 45-1** (100 mg, 0.41 mmol) in EtOH (6 mL) and piperidine (60 µL, 0.61 mmol); 60 ˚C, 5 h; resulting precipitate filtered and washed with EtOH to yield a dark orange solid (117 mg, 68%); **m.p.** 299–301 ˚C (decomposed); **HRMS** (ESI+) found 419.11717 $[M+H]^+$, $C_{22}H_{19}N_4O_3S$ requires 419.11724. *Product not soluble in $CDCl_3$, water, MeCN or mixture, sparingly soluble in DMSO, so no spectra obtained.

InChI=1S/C22H18N4O3S/c1-14-12-16(15(2)25(14)18-8-10-19(11-9-18)26(28)29)13-20-21(27)24-22(30-20)23-17-6-4-3-5-7-17/h3-13H,1-2H3,(H,23,24,27)/b20-13-

All attempts: http://malaria.ourexperiment.org/uri/331

(2Z,5Z)-5-((2,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrrol-3-yl)methylene)-2-((3-hydroxyphenyl)imino)thiazolidin-4-one, OSM-S-110



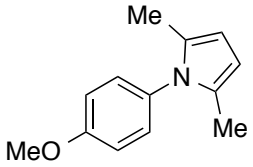
Representative example: http://malaria.ourexperiment.org/uri/245

Prepared according to General Procedure **H** from: (Z)-2-((3-hydroxyphenyl)imino)thiazolidin-4-one (85 mg, 0.41 mmol) and **AEW45-1** (100 mg, 0.41 mmol) in EtOH (6 mL) and piperidine (0.06 mL, 0.61 mmol); 60 ˚C, 5 h; resulting precipitate filtered and washed with EtOH to yield a mustard coloured solid (123 mg, 69%); **m.p.** not melted at 320 ˚C, (discoloured); **HRMS** (ESI+) found 435.11202 $[M+H]^+$, $C_{22}H_{19}N_4O_4S$ requires 435.11215. *Product not soluble so no spectra obtained.

InChI=1S/C22H18N4O4S/c1-13-10-15(14(2)25(13)17-6-8-18(9-7-17)26(29)30)11-20-21(28)24-22(31-20)23-16-4-3-5-19(27)12-16/h3-12,27H,1-2H3,(H,23,24,28)/b20-11-

All attempts: http://malaria.ourexperiment.org/uri/332

1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole, OSM-S-289

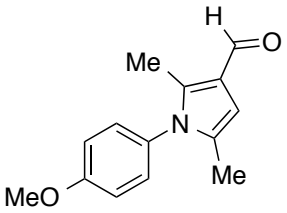


Representative example: http://malaria.ourexperiment.org/uri/217

Prepared according to General Procedure **A** from: anisidine (891 mg, 7.24 mmol, 1.1 equiv.) and 2,5-hexanedione (770 µL, 6.58 mmol, 1 equiv.); 110 ˚C (oil bath temp.), 20 h; crude black mixture was purified by flash column chromatography over silica (5–20% EtOAc in petroleum ether) to obtain the desired product (1.21 g, 6.01 mmol, 91% yield) as a pale yellow solid.

InChI=1S/C13H15NO/c1-10-4-5-11(2)14(10)12-6-8-13(15-3)9-7-12/h4-9H,1-3H3

1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carbaldehyde, OSM-S-290



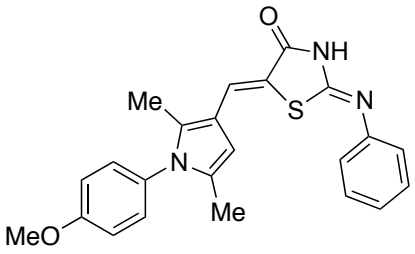
Representative example: http://malaria.ourexperiment.org/uri/233

DMF (2.5 mL) was stirred under a nitrogen atmosphere in an ice-bath. Phosphoryl chloride (0.658 mL, 7.03 mmol, 1.2 equiv.) was added and the reaction stirred for 25 min. A solution of pyrrole **AEW 36-1** (1.18 g, 5.86 mmol, 1 equiv.) in DMF (2.5 mL) was added dropwise over 5 min. The reaction was removed from the ice-bath and allowed to warm to rt whilst stirring for 1 h. The resulting brown reaction mixture was poured over ice (80 g) and pH modified to 6 (20% NaOH aq.) A brown precipitate formed and the mixture was stirred at rt for 3 h and pH decreased to 3, basified to pH 11 with (20% NaOH aq.) and left to stir for 1 h. The mixture reached pH 8 and was basified to pH 11 and left to stir for 30 min and then slurry filtered to give a brown paste. Triturated in EtOH to give a dark brown/black free-flowing powder that was dried *in vacuo to* give the desired product as a

dark brown powder (1.23 g, 5.34 mmol, 91% yield; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.86 (1H, s), 7.14–6.99 (4H, m), 6.37 (1H, s), 3.88 (3H, s), 2.27 (3H, s), 1.98 (3H, s).

InChI=1S/C14H15NO2/c1-10-8-12(9-16)11(2)15(10)13-4-6-14(17-3)7-5-13/h4-9H,1-3H3

(2Z,5Z)-5-((1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-111



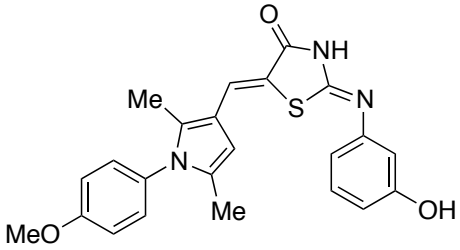
Representative example: http://malaria.ourexperiment.org/uri/246

Prepared according to General Procedure **H** from: **OSM-S-286** (83 mg, 0.44 mmol) and **AEW 46-1** (0.10 g, 0.44 mmol) in EtOH (6 mL) and piperidine (60 μL, 0.61 mmol); 60 ˚C, 5 h; resulting precipitate filtered and washed with EtOH to yield a yellow solid (98 mg, 55%); **m.p.** 266–268 ˚C (decomposed); **^{1}H NMR** (300 MHz, DMSO–d_6) δ: 11.7 (1H, bs), 7.81–7.08 (9H, m), 6.17–5.99 (1H, m), 3.85 (3H, s), 2.12–1.92 (6H, m); **^{13}C NMR** (76 Hz, DMSO–d_6): 159.6, 135.4, 131.8, 129.7, 129.5, 125.0, 124.3, 121.8, 120.7, 115.1, 105.0, 55.9, 13.0, 12.9, 12.9, 12.8, 11.2; **HRMS** (ESI+) found 404.14252 $[M+H]^+$, $C_{23}H_{22}N_3O_2S$ requires 404.14272.

All attempts: http://malaria.ourexperiment.org/uri/333

InChI=1S/C23H21N3O2S/c1-15-13-17(16(2)26(15)19-9-11-20(28-3)12-10-19)14-21-22(27)25-23(29-21)24-18-7-5-4-6-8-18/h4-14H,1-3H3,(H,24,25,27)/b21-14-

(2Z,5Z)-2-((3-Hydroxyphenyl)imino)-5-((1-(4-methoxyphenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)thiazolidin-4-one, OSM-S-112



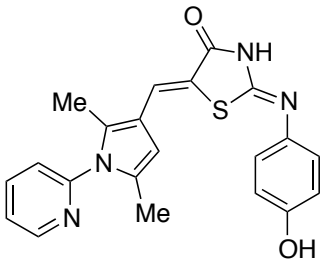
Representative example: http://malaria.ourexperiment.org/uri/247

Prepared according to General Procedure **H** from: (Z)-2-((3-hydroxyphenyl)imino)thiazolidin-4-one (90 mg, 0.44 mmol) and **AEW 46-1** (0.10 g, 0.44 mmol) in EtOH (6 mL) and piperidine (60 µL, 0.61 mmol); 60 ˚C, 5 h; resulting precipitate filtered and washed with EtOH to yield a yellow solid (143 mg, 78%); **m.p.** 282–286 ˚C; **^{1}H NMR** (400 MHz, DMSO–d_6) δ: 11.36 (1H, bs), 9.57 (1H, bs), 7.61–7.41 (1H, m), 7.18–7.05 (5H, m), 6.57 (1H, s), 6.43 (1H, bs), 6.15–6.00 (1H, m), 3.82 (3H, s), 2.09–1.91 (6H, m); **HRMS** (ESI+) found 442.11958 $[M+Na]^+$, $C_{23}H_{21}N_3O_3SNa$ requires 442.11958.

InChI=1S/C23H21N3O3S/c1-14-11-16(15(2)26(14)18-7-9-20(29-3)10-8-18)12-21-22(28)25-23(30-21)24-17-5-4-6-19(27)13-17/h4-13,27H,1-3H3,(H,24,25,28)/b21-12-

All attempts: http://malaria.ourexperiment.org/uri/334

(2Z,5Z)-5-((2,5-Dimethyl-1-(pyridin-2-yl)-1H-pyrrol-3-yl)methylene)-2-((4-hydroxyphenyl)imino)thiazolidin-4-one, OSM-S-113



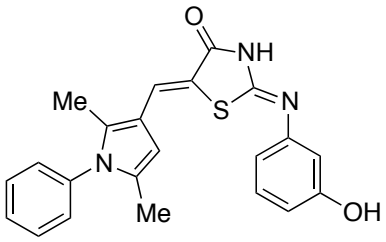
Representative example: http://malaria.ourexperiment.org/uri/253

Prepared according to General Procedure **H** from: (*Z*)-2-((4-hydroxyphenyl)imino)thiazolidin-4-one (72 mg, 0.4 mmol) and **OSM-S-44** (70 mg, 0.35 mmol) in EtOH (5 mL) and piperidine (50 µL, 0.52 mmol); 60 ˚C overnight; resulting precipitate filtered and washed with EtOH to give an orange/brown solid (55 mg, 40%); **m.p.** 310–315 ˚C (decomposed); **^{1}H NMR** (300 MHz, DMSO–d_6) δ: 11.45 (1H, bs), 9.49–9.45 (1H, m), 8.66 (1H, s), 8.08–8.06 (1H, m), 7.58–7.50 (3H, m), 6.95–6.93 (1H, m), 6.82–6.78 (2H, m), 6.17–6.05 (1H, m), 2.19–2.02 (6H, m); **HRMS** (ESI+) found 391.12266 $[M+H]^+$, $C_{21}H_{19}N_4O_2S$ requires 391.12232.

InChI=1S/C21H18N4O2S/c1-13-11-15(14(2)25(13)19-5-3-4-10-22-19)12-18-20(27)24-21(28-18)23-16-6-8-17(26)9-7-16/h3-12,26H,1-2H3,(H,23,24,27)/b18-12-

All attempts: http://malaria.ourexperiment.org/uri/335

(2Z,5Z)-5-((2,5-Dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene)-2-((3-hydroxyphenyl)imino)thiazolidin-4-one, OSM-S-114



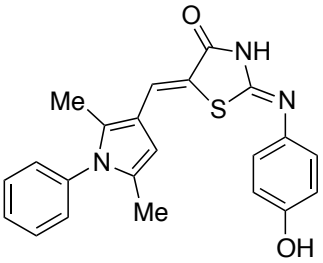
Representative example: http://malaria.ourexperiment.org/uri/257

Prepared according to General Procedure **H** from: (Z)-2-((3-hydroxyphenyl)imino)thiazolidin-4-one (80 mg, 0.41 mmol) and **OSM-S-28** (80 mg, 0.41 mmol) in EtOH (6 mL) and piperidine (60 µL, 0.62 mmol); 60 ˚C overnight; resulting precipitate filtered and washed with EtOH to give a dark yellow solid (124 mg, 79%); **m.p.** 294–300 ˚C; **^{1}H NMR** (300 MHz, DMSO–d_6) δ: 11.57 (1H, bs), 9.59 (1H, bs), 7.58–7.14 (8H, m), 6.58–6.44 (2H, m), 6.16–6.05 (1H, m) 2.11–1.96 (6H, m); **HRMS** (ESI+) found 412.10895 $[M+Na]^+$, $C_{22}H_{19}N_3O_2SNa$ requires 412.10902.

InChI=1S/C22H19N3O2S/c1-14-11-16(15(2)25(14)18-8-4-3-5-9-18)12-20-21(27)24-22(28-20)23-17-7-6-10-19(26)13-17/h3-13,26H,1-2H3,(H,23,24,27)/b20-12-

All attempts: http://malaria.ourexperiment.org/uri/336

(2Z,5Z)-5-((2,5-Dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene)-2-((4-hydroxyphenyl)imino)thiazolidin-4-one, OSM-S-115



Representative example: http://malaria.ourexperiment.org/uri/258

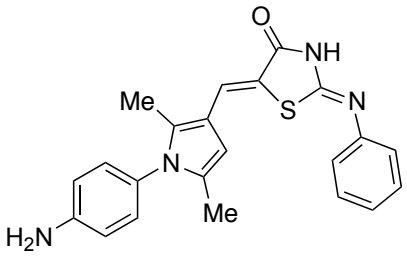
Prepared according to General Procedure **H** from: (Z)-2-((3-hydroxyphenyl)imino)thiazolidin-4-one (80 mg, 0.4q mmol) and **OSM-S-28** (80 mg, 0.41 mmol) in EtOH (6 mL) and piperidine (60 µL, 0.6 mmol); 60 ˚C overnight; resulting precipitate filtered and washed with EtOH to give an orange coloured solid (125 mg, 80%); **m.p.** not melted at 315 ˚C, (discoloured); **^{1}H NMR** (300 MHz, DMSO–d_6) δ: 11.23 (1H, bs), 9.48 (1H,

bs), 7.57–7.49 (5H, m), 7.33 (2H, t), 6.93 (1H, d, *J* 8.1), 6.81–6.78 (2H, m), 6.17–6.05 (1H, m), 2.13–1.94 (6H, m); **HRMS** (ESI+) found 412.10898 $[M+Na]^+$, $C_{22}H_{19}N_3O_2SNa$ requires 412.10902.

InChI=1S/C22H19N3O2S/c1-14-12-16(15(2)25(14)18-6-4-3-5-7-18)13-20-21(27)24-22(28-20)23-17-8-10-19(26)11-9-17/h3-13,26H,1-2H3,(H,23,24,27)/b20-13-

All attempts: http://malaria.ourexperiment.org/uri/337

(2Z,5Z)-5-((1-(4-Aminophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-S-138



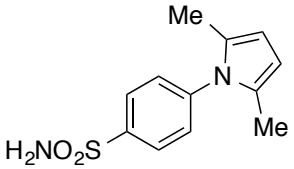
Representative example: http://malaria.ourexperiment.org/uri/36d

A catalytic amount of palladium on charcoal (10%) was added to a solution of **OSM-S-109** (40 mg, 0.16 mmol) in MeOH (2.4 mL) and DMF (0.6 mL) and the reaction was stirred under an atmosphere of hydrogen overnight. The reaction was then filtered through Celite™ and concentrated; **HRMS** (ESI+) found 389.14300 $[M+H]^+$, $C_{22}H_{21}N_4O_2S$ requires 389.14306.

All attempts: http://malaria.ourexperiment.org/uri/37b

InChI=1S/C22H20N4OS/c1-14-12-16(15(2)26(14)19-10-8-17(23)9-11-19)13-20-21(27)25-22(28-20)24-18-6-4-3-5-7-18/h3-13H,23H2,1-2H3,(H,24,25,27)/b20-13-

4-(2,5-Dimethyl-1H-pyrrol-1-yl)benzenesulfonamide, OSM-A-5

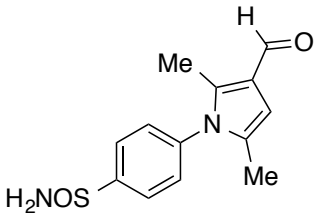


Representative Example: http://malaria.ourexperiment.org/uri/462

Prepared according to General Procedure **A** from: sulfanilamide (1.7 g, 10 mmol), 2,5-hexanedione (1.4 mL, 12 mmol) and sulfamic acid (50 mg, 0.50 mmol, 5 mol%); capped tube, 130 ˚C overnight. Solid recrystallized from

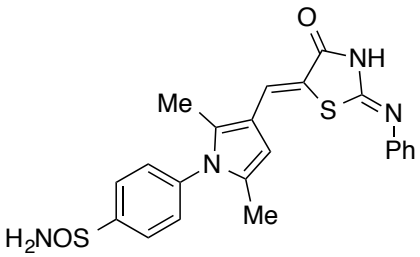
hot EtOH to give a beige powder; **^{1}H NMR** (400 MHz, $CDCl_3$): 8.04 (d, 2H), 7.37 (d, 2H), 5.93 (s, 2H), 5.25 (br s, 2H), 2.05 (s, 6H); **^{13}C NMR** (101 MHz, DMSO–d_6) δ: 143.0, 141.1, 128.4, 127.6, 126.7, 106.6, 12.8.
InChI=1S/C12H14N2O2S/c1-9-3-4-10(2)14(9)11-5-7-12(8-6-11)17(13,15)16/h3-8H,1-2H3,(H2,13,15,16)

4-(3-Formyl-2,5-dimethyl-1H-pyrrol-1-yl)benzenesulfinamide, OSM-A-6



Representative Example: http://malaria.ourexperiment.org/uri/462
Prepared according to General Procedure **B** from: phosphoryl chloride (0.19 mL, 1.5 mmol, 1.2 equiv.) and **OSM-A-5** (0.32 g, 13 mmol, 1.0 equiv) in DMF (1.8 mL); 0 ˚C to rt, 30 min; recrystallization in acetonitrile gave brown solid (0.11 g, 33%); **m.p** 203–207 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): 9.89 (s, 1H), 8.07 (d, 2H), 7.32 (d, 2H), 6.41 (s, 1H), 3.19 (s, 2H), 3.10 (s, 2H), 2.3 (m, 3H), 2.01 (m, 3H); **IR** ν_{max} (neat) peaks not labelled, however, spectra showed benzene ring, carbonyl peak, the presence of single and double carbon-carbon bonds, and amine.
InChI=1S/C13H14N2O2S/c1-9-7-11(8-16)10(2)15(9)12-3-5-13(6-4-12)18(14)17/h3-8H,14H2,1-2H3

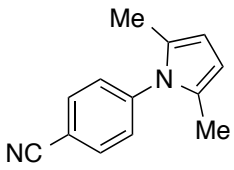
4-(2,5-Dimethyl-3-((Z)-((Z)-4-oxo-2-(phenylimino)thiazolidin-5-ylidene)methyl)-1H-pyrrol-1-yl)benzenesulfinamide, OSM-A-1



Representative Example: http://malaria.ourexperiment.org/uri/462
Prepared according to General Procedure **H** from: **OSM-S-286** (78 mg, 0.38 mmol), piperidine (60 µL, 0.56 mmol) and **OSM-A-6** (0.1 g, 0.38 mmol) in EtOH; reflux (60 ˚C), overnight; vacuum filtration (EtOH) afforded brown solid crystals (67 mg, 67%). **m.p** Decomposed at 250 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (1H, s), 8.20–8.02 (2H, m), 7.28-7.14 (8H, m), 3.19-3.09 (2H, d); **IR** ν_{max} (neat) /cm^{-1} 3401, 3094, 3054, 2943, 2744, 1628, 1590, 1537, 1497 cm^{-1}.

InChI=1S/C22H20N4O2S2/c1-14-12-16(15(2)26(14)18-8-10-19(11-9-18)30(23)28)13-20-21(27)25-22(29-20)24-17-6-4-3-5-7-17/h3-13H,23H2,1-2H3,(H,24,25,27)/b20-13-

4-(2,5-Dimethyl-1H-pyrrol-1-yl)benzonitrile, OSM-A-7

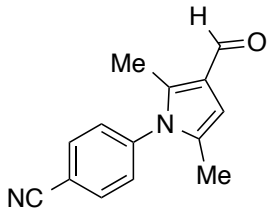


Representative Example: http://malaria.ourexperiment.org/uri/461

Prepared according to General Procedure **A** from: 4-aminobenzonitrile (1.4 g, 10 mmol), 2,5-hexanedione (1.4 mL, 12 mmol) and sulfamic acid (50 mg, 0.5 mmol, 5 mol%); capped tube, 130 ˚C overnight; solid recrystallised from hot EtOH to give a tan powder (1.40 g, 63%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (2H, d *J* 8.4), 7.33 (2H, d *J* 8.8), 5.93 (2H, s), 2.05 (6H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 143.2, 133.2, 129.1, 128.6, 118.3, 111.6, 107.3, 13.1; **IR** ν_{max} (neat) 3089, 3060, 2918, 2226, 1605, 1506, 1400, 1324, 1175, 1102, 1039, 1000.

InChI=1S/C13H12N2/c1-10-3-4-11(2)15(10)13-7-5-12(9-14)6-8-13/h3-8H,1-2H3

4-(3-Formyl-2,5-dimethyl-1*H*-pyrrol-1-yl)benzonitrile, OSM-A-8

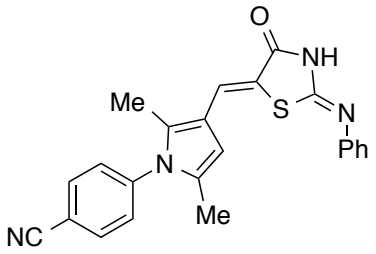


Representative Example: http://malaria.ourexperiment.org/uri/461

Prepared according to General Procedure **B** from: phosphoryl chloride (0.14 mL, 1.5 mmol) and **OSM-A-7** (0.20 g, 1.0 mmol) in DMF (0.80 mL); 0 ˚C to rt, 25 min; filtered and resulting grey crystal purified by trituration in MeCN and filtered to afford the title compound (90 mg, 40%) as brown crystals; **m.p.** 162–164 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.90 (1H, s), 7.86 (2H, d, *J* 8.4), 7.36 (2H, d, *J* 8.4), 6.42 (1H, s), 2.29 (3H, s), 2.01 (3H, s); **IR** ν_{max} (neat) /cm^{-1} 3094, 3060, 2956, 2923, 2837, 2755, 2229, 1651, 1603.

InChI=1S/C14H12N2O/c1-10-7-13(9-17)11(2)16(10)14-5-3-12(8-15)4-6-14/h3-7,9H,1-2H3

4-(2,5-Dimethyl-3-((Z)-((Z)-4-oxo-2-(phenylimino)thiazolidin-5-ylidene)methyl)-1H-pyrrol-1-yl)benzonitrile, OSM-A-2

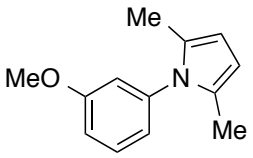


Representative Example: http://malaria.ourexperiment.org/uri/461

Prepared according to General Procedure **H** from: **OSM-A-8** (72 mg, 0.32 mmol) **OSM-S-286** (61 mg, 0.32 mmol) and piperidine (48 µL, 0.48 mmol) in EtOH (4.8 mL); 60 ˚C, 90 min; filtered and precipitate washed with EtOH to give the title compound (57 mg, 49%) as a yellow solid; **m.p.** 315 ˚C (decomposed); **^{1}H NMR** (400 MHz, DMSO–d_6 at 60 ˚C) δ: 11.5 (1H, br), 7.99 (2H, d, *J* 8.6), 7.53 (3H, app d), 7.38 (2-3H, app t), 7.15 (2H, app t), 6.10 (1H, s), 2.10 (3H, s), 1.97 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 165.3, 163.3, 141.6, 134.4, 133.3, 131.0, 129.4, 128.9, 126.6, 125.1, 121.9 117.7, 116.5, 112.8, 106.4, 110.5, 12.8, 11.2; **IR** ν_{max} (neat) /cm^{-1} 3066, 2978, 2792, 2232, 1700, 1641, 1600.

InChI=1S/C23H18N4OS/c1-15-12-18(16(2)27(15)20-10-8-17(14-24)9-11-20)13-21-22(28)26-23(29-21)25-19-6-4-3-5-7-19/h3-13H,1-2H3,(H,25,26,28)/b21-13-

1-(3-Methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole, OSM-A-9



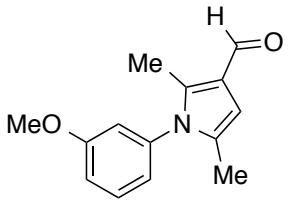
Representative Example: http://malaria.ourexperiment.org/uri/460

Prepared according to General Procedure **A** from: *m*-anisidine (0.57 mL. 5.0 mmol) and 2,5-hexanedione (0.53 mL, 4.5 mmol); 130 ˚C overnight. The reaction was combined with diethyl ether (10 mL) and citric acid (10 mL) and the organic layer was separated and washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) filtered and evaporated. The residue purified by flash chromatography over silica (hexanes-ethyl acetate, 8:1) to give the title compound as a brown oil (0.35 g, 35%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (1H, t), 6.94 (1H, dd), 6.81 (1H, dd), 6.75 (1H, d), 5.89 (2H, s), 3.80 (3H, s), 2.05 (6H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1, 140.1,

129.7, 128.8, 120.6, 113.9, 113.5, 105.7, 55.4, 13.0; **IR** ν_{max} (neat) /cm^{-1} 3063, 2918, 2834, 1596, 1489, 1398, 1282, 1243, 1203, 1032, 851, 751.

InChI=1S/C13H15NO/c1-10-7-8-11(2)14(10)12-5-4-6-13(9-12)15-3/h4-9H,1-3H3

1-(3-Methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole-3-carbaldehyde, OSM-A-10

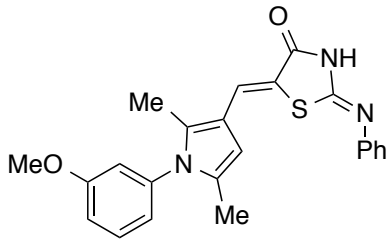


Representative Example: http://malaria.ourexperiment.org/uri/460

Prepared according to General Procedure **B** from: phosphoryl chloride (0.19 mL) and **OSM-A-9** (0.35 g, 1.7 mmol). On completion, the pH was adjusted to 11 using NaOH (10%). The reaction was extracted with EtOAc and combined organic layers washed with water, brine and then dried ($MgSO_4$), filtered and solvent evaporated under reduced pressure to give the title compound as a colourless oil (0.12 g, 29%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.87 (1H, s), 7.42 (1H, t), 7.02 (1H, m), 6.79 (1H, m), 6.73 (1H, d, *J* 2), 6.38 (1H, s), 3.85 (3H, s), 2.30 (3H, s), 2.01 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 185.3, 160.4, 139.1, 137.9, 131.1, 130.3, 121.8, 120.1, 114.4. 113.7, 105.6, 55.5, 12.6, 11.1; **IR** ν_{max} 2921, 2837, 1735, 1655 cm^{-1}.

InChI=1S/C14H15NO2/c1-10-7-12(9-16)11(2)15(10)13-5-4-6-14(8-13)17-3/h4-9H,1-3H3

(2Z,5Z)-5-((1-(3-Methoxyphenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-A-3



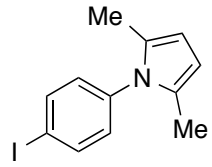
Representative Example: http://malaria.ourexperiment.org/uri/460

Prepared according to General Procedure **H** from: **OSM-S-286** (96 mg, 0.50 mmol) was dissolved in EtOH (2 mL) and piperidine (78 µL) was added. This was combined with **OSM-A-10** (0.12 g, 0.50 mmol); heated to 60 ˚C for 4.5 h; product precipitated and was filtered and washed with EtOH to provide the title compound as a

tan powder (68 mg, 34%); **m.p.** 251–255 ˚C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.40 (m, 3H), 7.8 (m, 3H), 6.99 (m, 1H), 6.75 (m, 1H), 6.69 (t, 1H), 3.83 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 160.4, 138.7, 135.4, 131.6, 130.2, 129.4, 125.0, 121.8, 120.2, 115.5, 114.3, 113.7, 105.2, 55.5, 12.7, 11.1; **IR** ν_{max} 2961, 2794, 1683, 1623 cm^{-1}.

InChI=1S/C23H21N3O2S/c1-15-12-17(16(2)26(15)19-10-7-11-20(14-19)28-3)13-21-22(27)25-23(29-21)24-18-8-5-4-6-9-18/h4-14H,1-3H3,(H,24,25,27)/b21-13-

1-(4-Iodophenyl)-2,5-dimethyl-1H-pyrrole, OSM-A-11

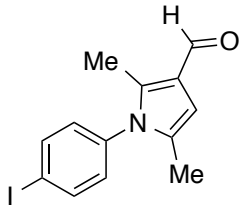


Representative Example: http://malaria.ourexperiment.org/uri/45f

Prepared according to General Procedure **A** from: 4-iodoaniline (2.2 g, 10 mmol), 2,5-hexanedione (1.4 mL, 12 mmol) and sulfamic acid (50 mg, 0.5 mmol, 5 mol%) combined in capped tube and stirred for 1 h until the solution crystallised; recrystallised from hot EtOH to give the desired compound as a peach-coloured needles (1.7 g, 55%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* 8.8), 6.96 (2H, d, *J* 8.8), 5.90 (2H, s), 2.03 (6H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.8, 138.4, 130.2, 128.7, 106.2, 93.0, 13.1.

InChI=1S/C12H12IN/c1-9-3-4-10(2)14(9)12-7-5-11(13)6-8-12/h3-8H,1-2H3

1-(4-Iodophenyl)-2,5-dimethyl-1H-pyrrole-3-carbaldehyde, OSM-A-12



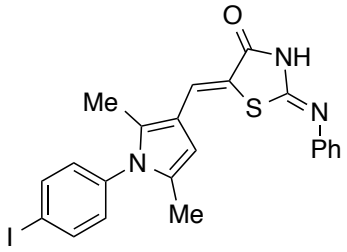
Representative Example: http://malaria.ourexperiment.org/uri/45f

Prepared according to General Procedure **B** from: phosphoryl chloride (0.12 mL, 1.3 mmol, 1.9 equiv.) and **OSM-A-11** (0.20 g, 0.68 mmol, 1.0 equiv.) in DMF (2.0 mL) was added; rt, 45 min; reaction poured over ice (10 mL), stirred, and basified to pH 11 with a 10% aqueous solution of NaOH. The resulting precipitate was collected by filtration to yield the title compound as a sticky beige solid (>100% due to residual solvent); **m.p.** 136–138 ˚C; **IR** ν_{max} (film) 3387, 1641 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.86 (1H, s), 7.86 (2H, d, *J* 8.4),

6.96 (2H, d, *J* 8.8), 6.38 (1H, d, *J* 1.2), 2.28 (3H, s), 1.99 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 185.3, 139.1, 138.9, 136.5, 130.9, 130.6, 122.1, 105.7, 95.8, 12.8, 11.1.

InChI=1S/C13H12INO/c1-9-7-11(8-16)10(2)15(9)13-5-3-12(14)4-6-13/h3-8H,1-2H3

(2Z,5Z)-5-((1-(4-Iodophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-2-(phenylimino)thiazolidin-4-one, OSM-A-4

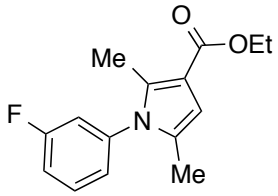


Representative Example: http://malaria.ourexperiment.org/uri/45f

Prepared according to General Procedure **H** from: **OSM-S-286** (70 mg, 0.35 mmol, 1.0 equiv.) and **OSM-A-12** (0.11 g, 0.35 mmol, 1.0 equiv.), piperidine (50 µL, 0.52 mmol, 1.5 equiv.) in EtOH (5 mL); refluxed at 60 ˚C overnight; cooled to rt and filtered to give the title compound as a yellow powder (0.11 g, 61%): **m.p.** 309 ˚C (decomposed); **IR** ν_{max} (neat) 3057, 2947, 2776, 1699, 1640 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (2H, m), 7.70 (1H, s), 7.41 (2H, t), 7.21 (1H, t), 7.15 (2H, bs), 6.93 (2H, d), 6.12 (1H, s), 2.14 (3H, s), 1.98 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.8, 137.3, 135.0, 129.8, 129.4, 125.1, 121.7, 105.7, 12.7, 11.1.

InChI=1S/C22H18IN3OS/c1-14-12-16(15(2)26(14)19-10-8-17(23)9-11-19)13-20-21(27)25-22(28-20)24-18-6-4-3-5-7-18/h3-13H,1-2H3,(H,24,25,27)/b20-13-

Ethyl 1-(3-fluorophenyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate, OSM-L-2



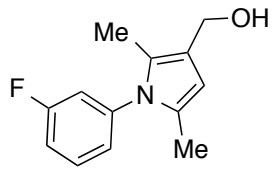
Representative example: http://malaria.ourexperiment.org/uri/86

Prepared according to General Procedure **C** from: ethyl acetoacetate (2 mL, 15.7 mmol, 1 equiv), K_2CO_3 (2.8 g, 20 mmol, 1.3 equiv), chloroacetone (1.6 mL, 17 mmol, 1.1 equiv) and NaI (2.7 g, 18 mmol, 1.2 equiv) in MeCN (40 mL); 80 ˚C, 3 h. The crude intermediate (2.1 g, 11 mmol, 1 equiv. of a possible 3.60 g) was treated with 3-fluoroaniline (1.26 mL, 13 mmol, 1.2 equiv.); 90 ˚C, 3 h; crude yellow oil was purified by flash column chromatography over silica gel (3–5 % EtOAc in hexane) to afford the pure product as yellow oil (1.7 g, 50%);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53–7.41 (1H, m), 7.23–7.13 (1H, m), 7.04–6.87 (2H, m), 6.37 (1H, s), 4.28 (2H, q, *J* 7.1), 2.30 (3H, s), 1.99 (3H, s), 1.34 (3H, t, *J* 7.1); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 166.1, 163.3 (d, *J* 249.2), 139.7 (d, *J* 9.3), 136.4, 131.0 (d, *J* 9.0), 129.0, 124.6 (d, *J* 3.2), 116.3 (d, *J* 22.5), 116.2 (d, *J* 21.0), 112.4, 108.4, 59.7, 15.0, 13.0, 12.8; **^{19}F{H} NMR** (376 MHz, $CDCl_3$) δ: -110.8; **IR** ν_{max} (neat) /cm^{-1} 3567, 3019, 2778, 1688, 1218; **HRMS** (ESI^+) found 262.12382 [M+H], $C_{15}H_{17}NO_2F$ requires 262. 12378.

InChI=1S/C15H16FNO2/c1-4-19-15(18)14-8-10(2)17(11(14)3)13-7-5-6-12(16)9-13/h5-9H,4H2,1-3H3

(1-(3-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrol-3-yl)methanol, OSM-L-3

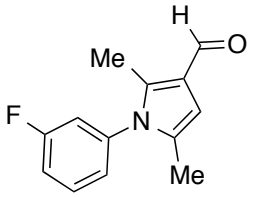


Representative example: http://malaria.ourexperiment.org/uri/91

OSM-L-2 (640 mg, 2.45 mmol, 1 equiv.) was stirred in THF (20 mL) at 0 ˚ C. $LiAlH_4$ (112 mg, 2.94 mmol, 1.2 equiv.) was added portion-wise at 0 ˚ C and stirred at this temperature for 20 min and then allowed to warm to rt and stirred for a further 3 h. The reaction mixture was then heated to 70 ˚C for 30 min, cooled to rt and quenched by the addition of a saturated solution of sodium tartrate (2 mL). The colloidal mixture was filtered through Celite^{TM}, washed with THF (40 mL) and concentrated prior to flash column chromatography over silica gel (25% EtoAc in hexane) to yield the desired alcohol (182 mg) along with impurities. The alcohol was used without further purification in the next step; **^{1}H NMR** (300 MHz, $CDCl_3$): 7.54–7.40 (1H, m), 7.23–7.10 (1H, m), 7.09–6.92 (2H, m), 6.00 (1H, bs), 4.54 (2H, s), 2.05 (6H, s).

InChI=1S/C13H14FNO/c1-9-6-11(8-16)10(2)15(9)13-5-3-4-12(14)7-13/h3-7,16H,8H2,1-2H3

1-(3-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrole-3-carbaldehyde, OSM-L-4

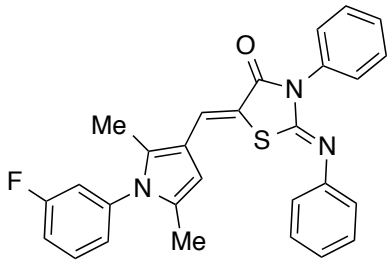


Representative example: http://malaria.ourexperiment.org/uri/97

OSM-L-3 (262 mg, 1.19 mmol, 1.0 equiv.) was stirred in anhydrous CH_2Cl_2 (5 mL) at rt. Activated MnO_2 (512 mg, 5.95 mmol, 5.0 equiv.) was added quickly at rt and the reaction stirred at rt for 3.5 h, after which time MnO_2 (512 mg, 5.95 mmol, 5.0 equiv.) was added. The reaction mixture was stirred for a further 2 h and then filtered through Celite™ and washed with CH_2Cl_2 (20 mL). The filtrate was evaporated under reduced pressure to yield a blackish gummy crude product that was purified by flash column chromatography over silica gel (25% EtoAc in hexane) to afford the title compound (172 mg) along with minor impurities; **^{1}H NMR** (300 MHz, $CDCl_3$): 9.89 (1H, s), 7.56–7.46 (1H, m), 7.27–7.18 (2H, m), 7.06–6.93 (1H, m), 6.40 (1H, s), 2.31 (3H, s), 2.01 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 185.7, 163.3 (d, *J* 249.8), 138.9 (× 2), 138.8, 131.3 (d, *J* 9.4), 124.4 (d, *J* 2.8), 122.6, 116.6 (d, *J* 21.8), 116.1 (d, *J* 21.8), 106.6, 13.0, 11.6; **^{19}F{H} NMR** (376 MHz, $CDCl_3$) δ: -110.3; **IR** ν_{max} (neat) /cm^{-1} 3473, 3390, 2363, 1655, 1606, 1531, 1491, 1425; **HRMS** (ESI$^+$) found 218.09747 [M+H], $C_{13}H_{13}NOF$ requires 218. 09756.

InChI=1S/C13H12FNO/c1-9-6-11(8-16)10(2)15(9)13-5-3-4-12(14)7-13/h3-8H,1-2H3

(2*Z*,5*Z*)-5-((1-(3-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrol-3-yl)methylene)-3-phenyl-2-(phenylimino)thiazolidin-4-one, OSM-L-1



Representative example: http://malaria.ourexperiment.org/uri/ab

OSM-S-47 (123 mg, 0.46 mmol, 1 equiv.) was stirred in EtOH (10 mL) at rt, piperidine (67 µL, 0.69 mmol, 1.5 equiv.) was added and then the reaction mixture solution was heated to 60 ˚C for 40 min prior to the dropwise addition of an ethanolic solution of **OSM-L-4** (0.10 g, 0.46 mmol, 1.0 equiv.). The reaction mixture was stirred at 60 ˚C overnight, allowed to cool and then EtOH was evaporated under reduced pressure to obtain a yellow oil

semi-solid mass. The residue was partitioned between EtOAc (40 mL) and water (20 mL) and the organic layer washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography over silica gel (25% EtOAc in hexane) to afford the title compound as yellow solid (72 mg, 33 % yield); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.80 (1H, s), 7.57–7.41 (6H, m), 7.41–7.32 (2H, m), 7.23–7.11 (2H, m), 7.04–6.97 (3H, m), 6.97–6.90 (1H, m) 6.17 (1H, s), 2.16 (3H, s), 2.00 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 167.5, 163.3 (d, *J* 249.2), 152.6, 149.2, 139.6, 139.5, 131.7, 131.2 (d, *J* 9.1), 129.6 (d, *J* 3.4), 129.1, 128.7, 128.5, 126.0, 125.1, 124.9, 124.4 (× 2), 121.8, 121.3, 116.4 (d, *J* 22.9), 116.1 (d, *J* 22.6), 114.5, 106.3, 13.1, 11.5; **^{19}F{H} NMR** (376 MHz, $CDCl_3$) δ: -110.5; **IR** ν_{max} (neat) /cm^{-1} 3768, 3690, 3538, 2929, 1700, 1634, 1492, 1366, 1301; **m/z** (ESI+) 468.2 $[M+H]^+$; **HRMS** (ESI^+) found 468.15360 [M+H], $C_{28}H_{23}N_3OFS$ requires 468. 15403.

InChI=1S/C28H22FN3OS/c1-19-16-21(20(2)31(19)25-15-9-10-22(29)18-25)17-26-27(33)32(24-13-7-4-8-14-24)28(34-26)30-23-11-5-3-6-12-23/h3-18H,1-2H3/b26-17-,30-28-

5. Synthetic Attempts Towards the Ether Analog (OSM-S-236)

One route to OSM-S-236 involved successful reduction of the relevant aldehyde (OSM-S-2) to the alcohol OSM-S-11 (found to be superior to reduction of the ester using $LiAlH_4$) and attempted alkylation with bromoacetamide, but multiple attempts at this reaction (employing bases such as NaH, K_2CO_3, KO^tBu and Ag_2CO_3) gave only mixtures of starting material and traces of minor products. Model etherification reactions using NaH and benzyl bromide or bromoacetonitrile in place of bromoacetamide gave either starting material or, under harsher conditions, decomposition. An alternative reductive synthesis of the ether from ester OSM-S-5 with indium tribromide and triethylsilane[35] also failed to yield the desired product. An attempted conversion of the alcohol to the bromide (with PBr_3) or mesylate gave only decomposition of starting material.

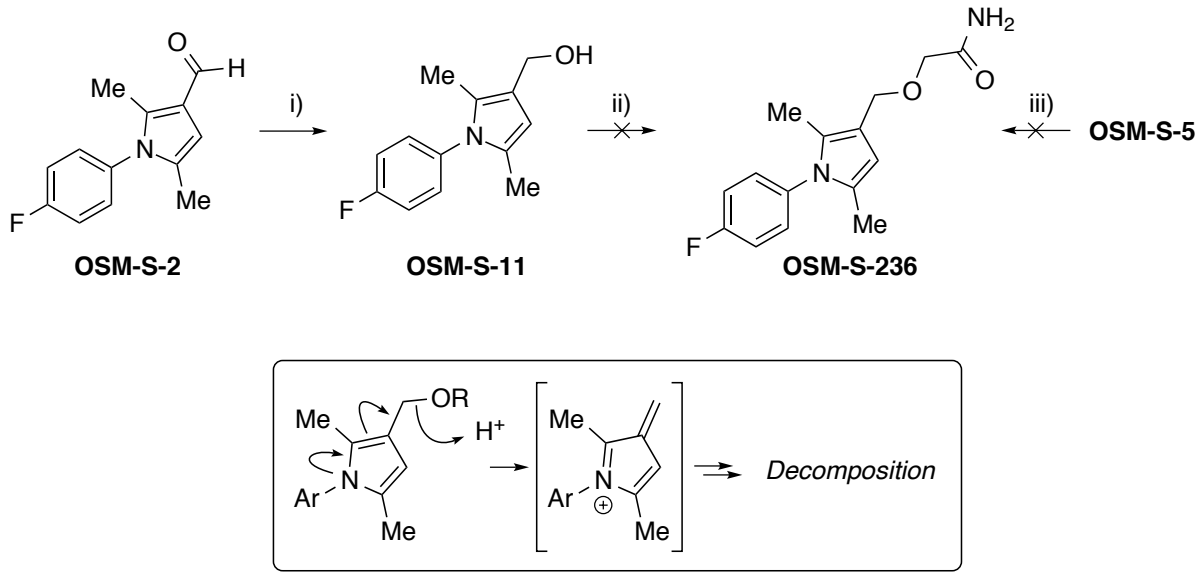


Fig SC6. Attempted syntheses of ether analog OSM-S-236 and suggested pathway of decomposition. Reagents and Conditions: i) $NaBH_4$, MeOH, 4.5 h. rt, 94%; ii) 2-bromoacetamide, various conditions; iii) indium tribromide, triethylsilane, chloroform, 60˚C.

6. Amines

Amine analogs were prepared by reductive amination of aldehyde OSM-S-2 with a selection of commercially-available amines in the presence of sodium cyanoborohydride to provide OSM-S-58, -94 and -95 (Fig SC7). 2-(Methylamino)acetamide was synthesised by a double reductive alkylation of glycinamide hydrochloride (first with benzaldehyde, then with formaldehyde) and subsequent hydrogenolysis prior to its reductive amination with OSM-S-2 to give OSM-S-60. Three commercial amines were purchased (OSM-S-88 to -90).

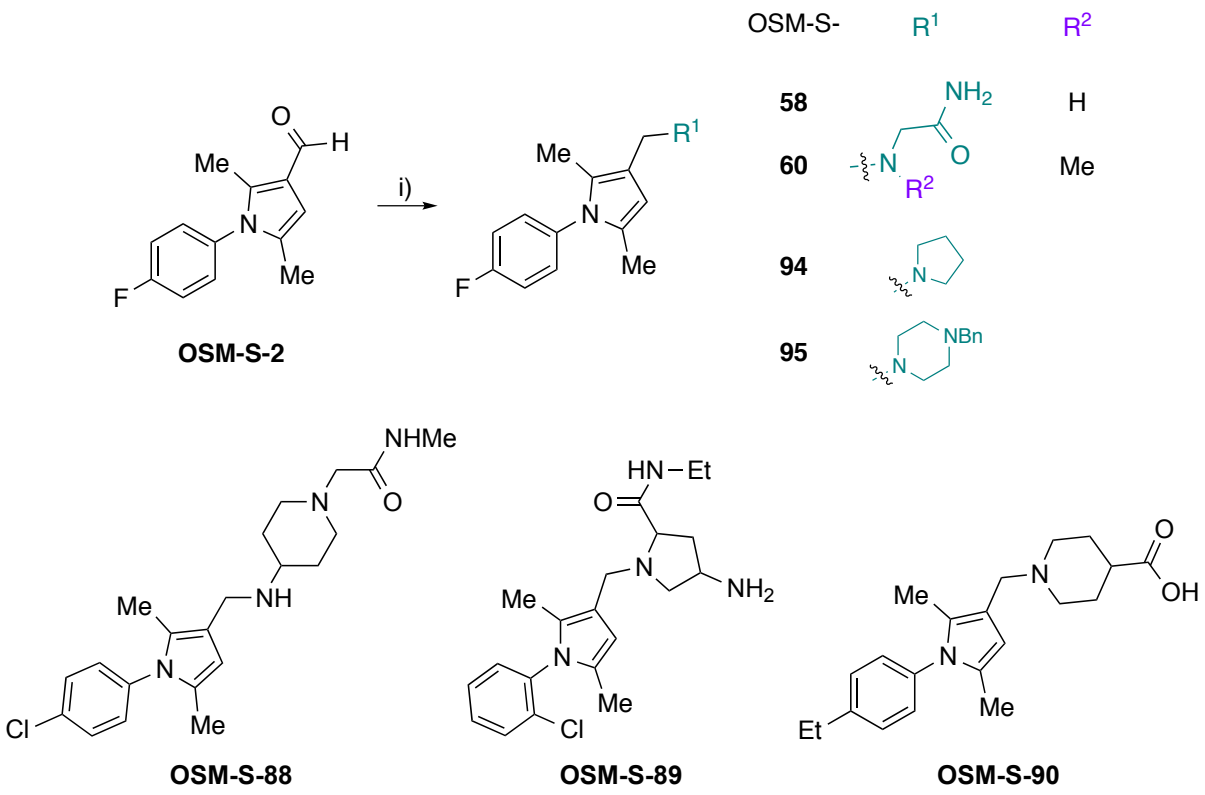
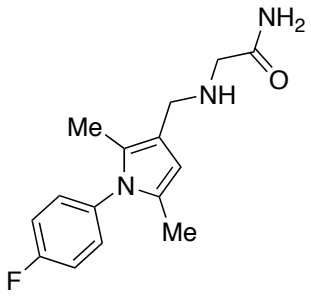


Fig SC7. Synthesis of Amine Analogs. Reagents and Conditions: i) amine, sodium cyanoborohydride, MeOH/AcOH, 18-21 h, rt.

2-(((1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methyl)amino)acetamide, OSM-S-58



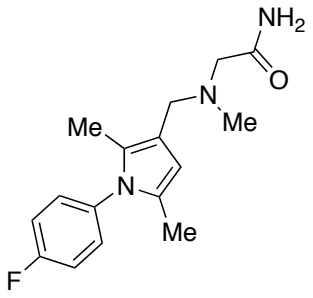
Representative example: http://malaria.ourexperiment.org/uri/11e

Glycinamide hydrochloride (132 mg, 1.20 mmol, 1.3 equiv.) was dissolved in water (0.2 mL), Sodium hydroxide (48.0 mg, 1.20 mmol, 1.3 equiv.) was added and the reaction stirred for 10 min, then concentrated under reduced pressure. **OSM-S-20** (200 mg, 0.921 mmol, 1 equiv.) was added and the mixture dissolved in MeOH (10 mL) and acetic acid (0.25 mL). Sodium cyanoborohydride (64.0 mg, 1.01 mmol, 1.1 equiv.) was added in 3 portions over 3 min and the reaction stirred at rt for 18 h. The mixture was concentrated under reduced pressure then treated with 1 M NaOH (10 mL). The mixture was then extracted with CH_2Cl_2 (3 × 15 mL). The extracts were washed with brine then dried ($MgSO_4$) and concentrated to an orange solid and then purified by flash column chromatography over silica (2-8% MeOH/ CH_2Cl_2 then NH_4OH/MeOH/CH_2Cl_2 3:8:89) to provide the desired product (200 mg, 79%) along with some *bis*-alkylated material (22 mg); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.38–7.12 (4H, m), 6.20 (1H, bs), 5.99 (1H, s), 3.72 (2H, s), 3.42 (2H, s), 2.09 (3H, s), 2.05 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 175.2, 161.9 (d, *J* 247.6), 134.7 (d, *J* 1.9), 129.8 (d, *J* 8.6), 128.3, 126.0, 116.8, 116.5, 116.1, 115.8, 106.5, 51.8, 45.6, 12.6, 10.5; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -113.8; **HRMS** (ESI^+) found 298.13340 [M+Na], $C_{15}H_{18}N_3OFNa$ requires 298.13261.

InChI=1S/C13H14N4O2/c1-9-11(13(19)15-8-12(14)18)7-16-17(9)10-5-3-2-4-6-10/h2-7H,8H2,1H3,(H2,14,18)(H,15,19)

All attempts: http://malaria.ourexperiment.org/uri/2fe

2-(((1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methyl)(methyl)amino)acetamide, OSM-S-60



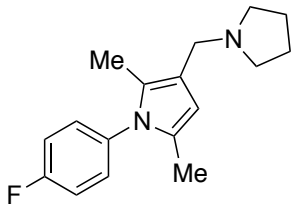
Representative example: http://malaria.ourexperiment.org/uri/11d

Prepared according to General Procedure **I** from: **OSM-S-2** (0.2 g, 0.92 mmol, 1.0 equiv.) and crude **OSM-S-285** (0.15 g, 1.7 mmol, 1.9 equiv.) in anhydrous MeOH (10 mL) and AcOH (0.25 mL); rt for 1h then sodium cyanoborohydride (64 mg, 1.0 mmol, 1.1 equiv) in 3 portions over 3 min; rt for 18 h. 1 M NaOH (10 mL) and CH_2Cl_2 (20 mL) was added and the reaction stirred for 10 min. The reaction was extracted with further CH_2Cl_2 (2 × 15 mL). Combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to yield a pale yellow gum. Flash column chromatography on silica (1-10% MeOH/ CH_2Cl_2) provided the title compound (148 mg, 56% yield); **^{1}H NMR** (300 MHz, $CDCl_3$): δ: 7.25–7.14 (4H, m), 5.86 (1H, bs), 3.42 (2H, s), 3.03 (2H, s), 2.34 (3H, s) 1.98 (3H, s), 1.94 (3H, s); **HRMS** (ESI+) found 312.14899 [M+Na], $C_{16}H_{20}N_3OFNa$ requires 312.14826.

InChI=1S/C16H20FN3O/c1-11-8-13(9-19(3)10-16(18)21)12(2)20(11)15-6-4-14(17)5-7-15/h4-8H,9-10H2,1-3H3,(H2,18,21)

All attempts: http://malaria.ourexperiment.org/uri/300

1-(4-Fluorophenyl)-2,5-dimethyl-3-(pyrrolidin-1-ylmethyl)-1H-pyrrole, OSM-S-94



Representative example: http://malaria.ourexperiment.org/uri/185

Prepared according to General Procedure **I** from: **OSM-S-2** (0.10 g, 0.46 mmol) and pyrrolidine (43 mg, 50 µL, 0.60 mmol) in anhydrous MeOH (5 mL) and AcOH (0.12 mL); rt for 1 h then sodium cyanoborohydride (32 mg, 0.51 mmol); rt for 16 h. MeOH removed *in vacuo* and then the crude orange oil treated with 1 M NaOH (5 mL).

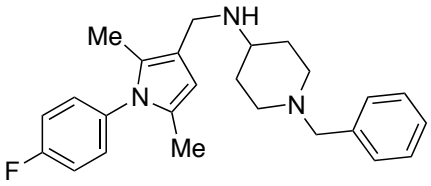
The mixture was then extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were washed with brine then dried ($MgSO_4$) and concentrated to give an orange oil. Flash column chromatography over silica (1–10% MeOH in CH_2Cl_2) gave the desired product as an orange oil (23 mg, 18%); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.18–7.12 (4H, m), 6.04 (1H, s), 4.06 (2H, s), 3.64 (2H, bs), 2.91 (2H, bs), 2.21 (2H, bs), 2.09–1.87 (8H, m).

**Product unstable and attempts to measure spectra led to decomposition, HRMS not obtained.*

InChI=1S/C17H21FN2/c1-13-11-15(12-19-9-3-4-10-19)14(2)20(13)17-7-5-16(18)6-8-17/h5-8,11H,3-4,9-10,12H2,1-2H3

All attempts: http://malaria.ourexperiment.org/uri/322

1-Benzyl-N-((1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methyl)piperidin-4-amine, OSM-S-95



Representative example: http://malaria.ourexperiment.org/uri/179

Prepared according to General Procedure **I** from: **OSM-S-2** (50 mg, 0.23 mmol, 1.0 equiv.) and 4-amino-1-benzylpiperidine (61 mg, 0.30 mmol, 1.3 equiv.) in MeOH (2.5 mL) and acetic acid (60 µL,); 2 h at rt and then sodium cyanoborohydride (16 mg, 0.25 mmol); 21 h at rt. Flash column chromatography over silica (1–10% MeOH in CH_2Cl_2) gave the desired product as a pale yellow oil (19 mg, 21%); **^{1}H NMR** (200 MHz, $CDCl_3$): 7.35–7.22 (5H, m), 7.13 (4H, d, *J* 6.6), 6.14 (1H, s), 3.88 (2H, s), 3.49 (2H, s), 2.93–2.80 (3H, m), 2.14–1.83 (13H, m).

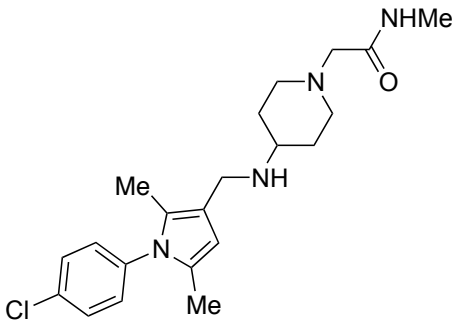
**Product unstable and attempts to measure spectra led to decomposition, HRMS not obtained.*

InChI=1S/C25H30FN3/c1-19-16-22(20(2)29(19)25-10-8-23(26)9-11-25)17-27-24-12-14-28(15-13-24)18-21-6-4-3-5-7-21/h3-11,16,24,27H,12-15,17-18H2,1-2H3

All attempts: http://malaria.ourexperiment.org/uri/323

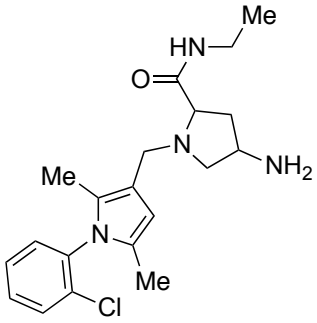
6.1 Commercial amines

2-(4-(((1-(4-Chlorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methyl)amino)piperidin-1-yl)-N-methylacetamide, OSM-S-88



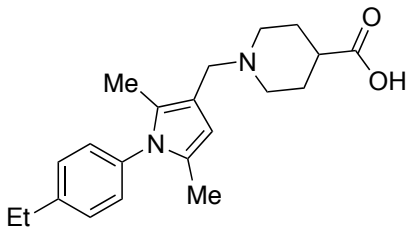
InChI=1S/C21H29ClN4O/c1-15-12-17(16(2)26(15)20-6-4-18(22)5-7-20)13-24-19-8-10-25(11-9-19)14-21(27)23-3/h4-7,12,19,24H,8-11,13-14H2,1-3H3,(H,23,27)

4-Amino-1-((1-(2-chlorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methyl)-N-ethylpyrrolidine-2-carboxamide, OSM-S-89



InChI=1S/C20H27ClN4O/c1-4-23-20(26)19-10-16(22)12-24(19)11-15-9-13(2)25(14(15)3)18-8-6-5-7-17(18)21/h5-9,16,19H,4,10-12,22H2,1-3H3,(H,23,26)/t16,19+/m0/s1

1-((1-(4-Ethylphenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methyl)piperidine-4-carboxylic acid, OSM-S-90



InChI=1S/C21H28N2O2/c1-4-17-5-7-20(8-6-17)23-15(2)13-19(16(23)3)14-22-11-9-18(10-12-22)21(24)25/h5-8,13,18H,4,9-12,14H2,1-3H3,(H,24,25)

7. Modified Esters

A direct functionalization of carboxylic acid OSM-S-4 with 2-bromo-2-methylpropanamide was achieved in the presence of freshly prepared silver oxide in partially aqueous acetonitrile to furnish compound OSM-S-68 (Fig 12).[36] The corresponding monomethyl derivative OSM-S-116 could not be obtained directly from the acid but rather *via* the corresponding ethyl ester (OSM-S-99). Hydrolysis at room temperature selectively cleaved the terminal ester in good yield to give the acid OSM-S-100 and subsequent amidation provided the desired terminal amide.

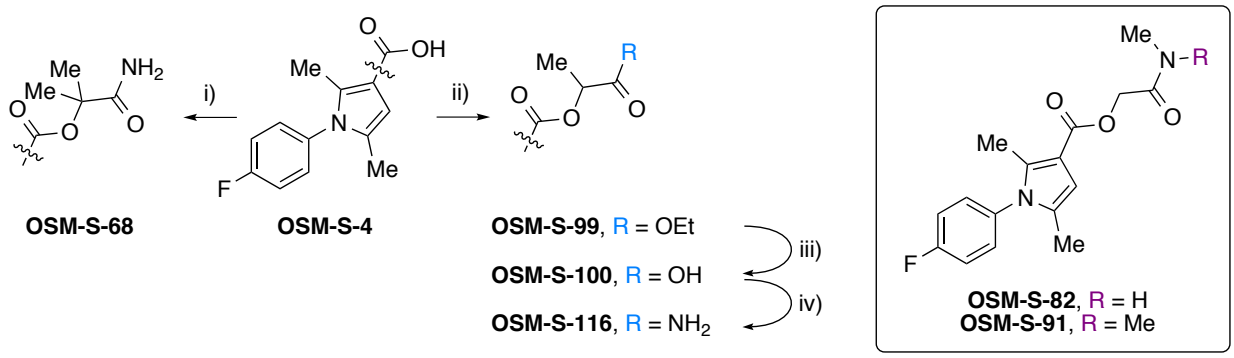
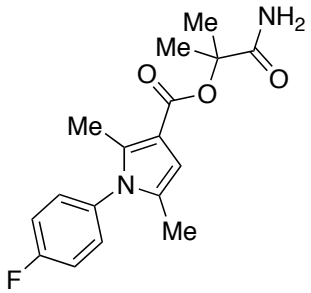


Fig SC8. Synthesis of Modified Esters. Reagents and Conditions: i) 2-bromo-2-methylpropanamide, silver (II) oxide, 5% aq. acetonitrile, dark, 4 h, rt; ii) ethyl-2-bromopropionate, potassium carbonate, dimethylformamide, 20 h, rt; iii) 20% aqueous sodium hydroxide, ethanol, 1.5 h, rt; iv) ammonia, EDCI.HCl, HOBt, dichloromethane, overnight, rt. Compounds OSM-S-82 and OSM-S-91 were purchased.

1-Amino-2-methyl-1-oxopropan-2-yl 1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, OSM-S-68



Representative example: http://malaria.ourexperiment.org/uri/165

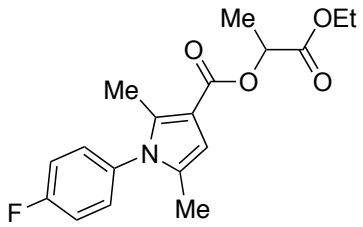
OSM-S-4 (1.0 g, 4.3 mmol, 1.0 equiv.) and 2-bromo-2-methylpropanamide (0.71 g, 4.3 mmol, 1.0 equiv.) were dissolved in 5% aqueous MeCN (25 mL). Freshly prepared silver(I) oxide (2.0 g, 8.5 mmol, 2.0 equiv.) was added and the reaction mixture stirred at rt whilst covered in aluminium foil to maintain a dark reaction

environment. The reaction mixture was stirred at rt for 8 h. 2-Bromo-2-methylpropanamide (0.36 g, 2.15 mmol, 0.5 equiv) was added and the reaction stirred at rt overnight and then filtered through Celite™ and washed with MeOH. The crude mixture was concentrated to give an orange oil and then purified by flash chromatography over silica (50:50 hexane/EtOAc to 100% EtOAc) to give an orange powder (0.91 g, 2.86 mmol, 67% yield); **IR** ν_{max} (film) 3343, 2981, 2934, 1666, 1534, 1512, 1468, 1414; **^{1}H NMR** (200 MHz, $CDCl_3$) δ; 7.23–7.12 (4H, m), 6.33 (1H, d, *J* 0.9), 6.03 (1H, bs), 5.33 (1H, bs), 2.28 (3H, s), 1.97 (3H, s), 1.74 (3H, s); **^{19}F{1H} NMR** (282 MHz, $CDCl_3$) δ: -112.0; **HRMS** (ESI^+) found 341.12719 [M+Na], $C_{17}H_{19}N_2OFNa$ requires 341.12715.

InChI=1S/C17H19FN2O3/c1-10-9-14(15(21)23-17(3,4)16(19)22)11(2)20(10)13-7-5-12(18)6-8-13/h5-9H,1-4H3,(H2,19,22)

All attempts: http://malaria.ourexperiment.org/uri/308

1-Ethoxy-1-oxopropan-2-yl 1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, OSM-S-99



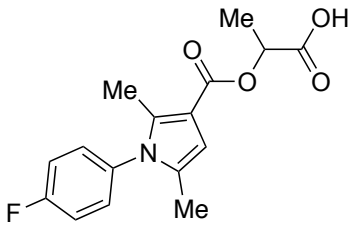
Representative example: http://malaria.ourexperiment.org/uri/3e2

OSM-S-4 (500 mg, 2.14 mmol, 1 equiv.) was dissolved in DMF (8 mL) and oven-dried potassium carbonate (741 mg, 5.35 mmol, 2.5 equiv.) was added. The mixture was stirred at rt for 20 min, followed by addition of ethyl-2-bromopropionate (0.36 mL, 2.78 mmol, 1.3 equiv.). Reaction mixture stirred for 20 h at rt. Water was added and then reaction mixture partitioned between EtOAc and water. The aqueous layer was removed and the organic layer washed with water, brine and dried ($MgSO_4$), filtered and evaporated to give a dark orange oil. The crude mixture was purified by flash column chromatography over silica (100% petroleum ether to remove DMF, and then 2:1 petrol:EtOAc) to give a pale yellow/orange oil that was dried further *in vacuo* to give a viscous orange oil that slowly crystallised to a yellow semi-solid (680 mg, 95%); **IR** ν_{max} (film) 2986, 2941, 1751, 1703, 1579, 1416, 1375, 1333; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.22–7.13 (4H, m), 6.43 (1H, bs), 5.24 (1H, q, *J* 7.0), 4.23 (2H, q, *J* 7.1), 2.28 (3H, s), 1.96 (3H, s), 1.57 (3H, d, *J* 7.0), 1.29 (3H, t, *J* 7.1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 171.5, 164.6, 162.4 (d, *J* 249.0), 137.0, 133.6 (d, *J* 3.1), 129.9 (d, *J* 8.7), 128.9, 116.4 (d, *J* 22.8), 110.7, 107.9, 67.8, 61.0, 17.2, 14.1, 12.5, 12.4; **^{19}F{1H} NMR** (376 MHz, $CDCl_3$) δ: -112.4; **HRMS** (ESI^+) found 356.12686 [M+Na], $C_{18}H_{20}NO_4FNa$ requires 356.12687.

InChI=1S/C18H20FNO4/c1-5-23-17(21)13(4)24-18(22)16-10-11(2)20(12(16)3)15-8-6-14(19)7-9-15/h6-10,13H,5H2,1-4H3

All attempts: http://malaria.ourexperiment.org/uri/327

2-((1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl)oxy)propanoic acid, OSM-S-100



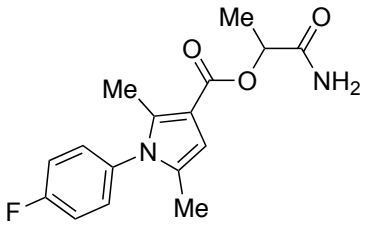
Representative example: http://malaria.ourexperiment.org/uri/3e5

Prepared according to General Procedure **D** from: **OSM-S-99** (585 mg, 1.75 mmol), 20% NaOH (2.6 mL, 9 equiv.) in EtOH (27 mL); rt for 1.5 h to yield a white solid that was used without further purification (452 mg, 1.38 mmol, 79% yield); **IR** ν_{max} (film) 2924, 1699, 1579, 1535, 1510, 1417; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.22–7.14 (4H, m), 6.42 (1H, d, *J* 0.9), 5.29 (1H, q, *J* 7.1), 2.28 (3H, s), 1.96 (3H, s), 1.62 (3H, t, *J* 7.1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 176.6, 164.7, 162.4 (d, *J* 249.1), 137.4, 133.5 (d, *J* 3.4), 129.9 (d, *J* 8.7), 129.1, 116.4 (d, *J* 22.8), 110.3, 107.8, 67.3, 17.0, 12.6, 12.4; **^{19}F{1H} NMR** (377 MHz, $CDCl_3$) δ: -112.3; **HRMS** (ESI^+) found 328.09556 [M+Na], $C_{16}H_{16}NO_4FNa$ requires 328.09565.

InChI=1S/C16H16FNO4/c1-9-8-14(16(21)22-11(3)15(19)20)10(2)18(9)13-6-4-12(17)5-7-13/h4-8,11H,1-3H3,(H,19,20)

All attempts: http://malaria.ourexperiment.org/uri/328

1-Amino-1-oxopropan-2-yl 1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, OSM-S-116



Representative example: http://malaria.ourexperiment.org/uri/3ec

Prepared according to General Procedure **E** from: **OSM-S-100** (80 mg, 0.26 mmol, 1 equiv.), EDCI (60 mg, 0.31 mmol, 1.2 equiv.) and HOBt (3.5 mg, 30 µmol, 0.1 equiv.) in CH_2Cl_2 (2.6 mL) for 20 min; then ammonia (28% aqueous soln., 0.24 mL, 0.39 mmol, 1.5 equiv.); rt 20 h; purified by flash column chromatography over silica (1-10% MeOH in CH_2Cl_2) to give an off white semi-solid (52 mg, 66% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.23–7.14 (4H, m), 6.37 (1H, s), 6.25 (1H, bs), 5.86 (1H, bs), 5.43 (1H, q, *J* 6.9), 2.29 (3H, s), 1.97 (3H, s), 1.56 (3H, t, *J* 6.9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 174.1, 163.8, 162.4 (d, *J* 249.4), 137.6, 133.3 (d, *J* 3.3), 129.8 (d,

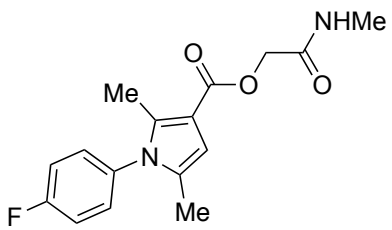
J 8.7), 129.3, 116.5 (d, *J* 22.8), 110.3, 107.3, 69.0, 17.8, 12.6, 12.4; **^{19}F{1H} NMR** (471 MHz, $CDCl_3$) δ: -111.7; **HRMS** (ESI^+) found 327.11154 [M+Na], $C_{16}H_{17}N_2O_3FNa$ requires 327.11159.

InChI=1S/C16H17FN2O3/c1-9-8-14(16(21)22-11(3)15(18)20)10(2)19(9)13-6-4-12(17)5-7-13/h4-8,11H,1-3H3,(H2,18,20)

All attempts: http://malaria.ourexperiment.org/uri/338

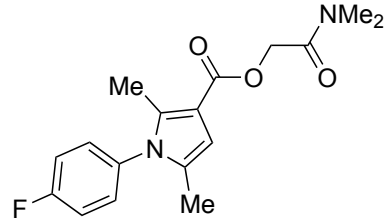
7.1 Commercial esters

2-(Methylamino)-2-oxoethyl1-(4-fluorophenyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate, OSM-S-82



InChI=1S/C16H17FN2O3/c1-10-8-14(16(21)22-9-15(20)18-3)11(2)19(10)13-6-4-12(17)5-7-13/h4-8H,9H2,1-3H3,(H,18,20)

2-(Dimethylamino)-2-oxoethyl 1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate, OSM-S-91



InChI=1S/C17H19FN2O3/c1-11-9-15(17(22)23-10-16(21)19(3)4)12(2)20(11)14-7-5-13(18)6-8-14/h5-9H,10H2,1-4H3

8. Ketones

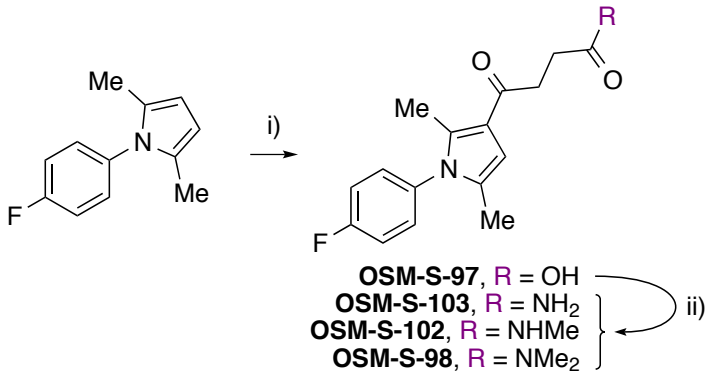
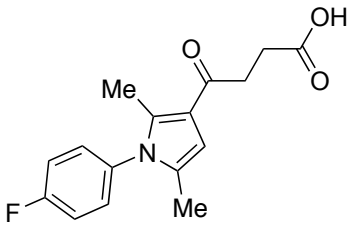


Fig SC9. Ketone analogs *via* Friedel-Crafts acylation. Reagents and Conditions: i) succinic anhydride, $AlCl_3$, dichloromethane, 18 h, rt; ii) dimethylamine, methylamine or ammonium hydroxide (28%), EDCI.HCl, HOBt, dichloromethane, 5–16 h, rt.

4-(1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)-4-oxobutanoic acid, OSM-S-97



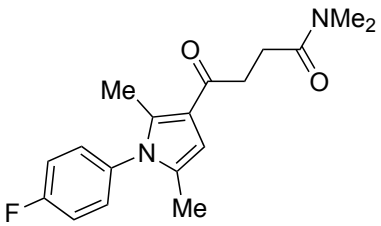
Representative example: http://malaria.ourexperiment.org/uri/1b2

$AlCl_3$ (1.1 g, 7.9 mmol) was added to a solution of succinic anhydride (0.44 g, 4.4 mmol) and **OSM-S-1** (0.75 g, 4.0 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at rt for 18 h and then concentrated under reduced pressure. The reaction mixture was partitioned between water (6 mL) and EtOAc (15 ml), aqueous layer was extracted with EtOAc (3 × 15 mL) and combined organic layers were dried ($MgSO_4$), filtered and evaporated to yield a red solid (1.5 g) which was purified by flash column chromatography over silica (40-60% EtOAc/Hexane) to yield the title compound (0.34 g, 30%) as a pale red solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 9.86 (1H, bs), 7.22–7.15 (4H, m), 6.37 (1H, s), 3.13 (2H, t, *J* 6.5), 2.75 (2H, t, *J* 6.5), 2.30 (3H, s), 1.98 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 194.8, 178.7, 170.7, 167.4 (d, *J* 249.5), 160.7, 136.4, 133.2, 129.7 (d, *J* 8.7), 129.0, 119.4, 116.4 (d, *J* 23.0), 107.3, 34.7, 28.3, 12.5; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.1; **HRMS** (ESI+) found 312.10061 $[M+Na]^+$, $C_{16}H_{16}FNO_3Na$ requires 312.10064.

InChI=1S/C16H16FNO3/c1-10-9-14(15(19)7-8-16(20)21)11(2)18(10)13-5-3-12(17)4-6-13/h3-6,9H,7-8H2,1-2H3,(H,20,21)

All attempts: http://malaria.ourexperiment.org/uri/325

4-(1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)-N,N-dimethyl-4-oxobutanamide, OSM-S-98



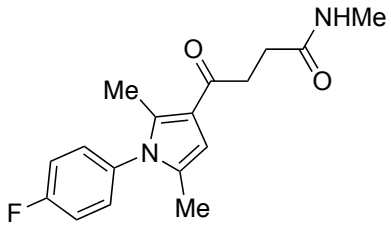
Representative example: http://malaria.ourexperiment.org/uri/1b7

Prepared according to General Procedure **E** from: EDCI (83 mg, 0.44 mmol), HOBt (5.0 mg, 40 µmol), **OSM-S-97** (105 mg, 0.36 mmol) and dimethylamine (~5.6 M in absolute EtOH, 0.097 mL, 0.54 mmol) in CH_2Cl_2 (5 mL); rt for 5 h. Flash column chromatography over silica (50-75% EtOAc/Hexane) gave the title compound as an orange oil (35 mg, 30%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.22–7.13 (4H, m), 6.44 (1H, s), 3.15 (2H, t, *J* 6.8), 3.08 (3H, s), 2.96 (3H, s), 2.73 (2H, t, *J* 6.8), 2.30 (3H, s), 1.97 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 195.9, 172.2, 162.2 (d, *J* 249.5), 135.8, 137.3 (d, *J* 2.7), 129.7 (d, *J* 8.7), 128.6, 120.0, 116.3 (d, *J* 22.8), 107.6, 37.0, 35.4, 35.2, 27.3, 12.8, 12.6; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.4; **HRMS** (ESI+) found 399.14794 $[M+Na]^+$, $C_{18}H_{21}FN_2O_2Na$ requires 399.14793.

InChI=1S/C18H21FN2O2/c1-12-11-16(17(22)9-10-18(23)20(3)4)13(2)21(12)15-7-5-14(19)6-8-15/h5-8,11H,9-10H2,1-4H3

All attempts: http://malaria.ourexperiment.org/uri/326

4-(1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)-N-methyl-4-oxobutanamide, OSM-S-102



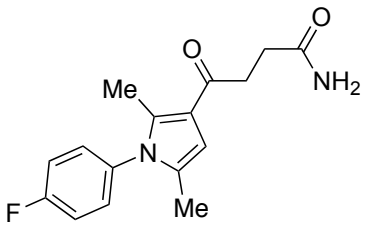
Representative example: http://malaria.ourexperiment.org/uri/1ba

Prepared according to General Procedure **E** from: EDCI (0.11 g, 0.48 mmol), HOBt (7.0 mg, 50 µmol), **OSM-S-97** (0.14 g, 0.48 mmol), methylamine in water (35%, 0.5 mL in CH_2Cl_2 (7 mL); rt for 16 h. Flash column chromatography over silica (75-100% EtOAc/Hexane) to give the title compound as white crystals (54 mg, 37%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.23–7.13 (4H, m), 6.35 (1H, s), 6.18 (1H, bs), 3.16 (2H, t, *J* 6.6), 2.78 (3H, d, *J* 4.8), 2.54 (2H, t, *J* 6.6), 2.28 (3H, s), 1.95 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 195.9, 173.5, 162.4 (d, *J* 249.4), 136.1, 133.2 (d, *J* 2.8), 129.7 (d, *J* 8.6), 128.9, 119.7, 116.4 (d, *J* 23.0), 107.5, 35.9, 30.5, 26.3, 12.9,

12.6; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.2; **HRMS** (ESI+) found 325.13236 $[M+Na]^+$, $C_{17}H_{19}FN_2O_2Na$ requires 325.13228.

All attempts: http://malaria.ourexperiment.org/uri/32a

4-(1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)-4-oxobutanamide, OSM-S-103



Representative example: http://malaria.ourexperiment.org/uri/1be

Prepared according to General Procedure **E** from: EDCI (0.80 g, 0.41 mmol), HOBt (5.0 mg, 30 µmol), **OSM-S-97** (0.1 g, 0.35 mmol), ammonium hydroxide (28%, 40 µL, 0.52 mmol) in CH_2Cl_2 (5 mL); rt 16 h. Flash column chromatography over silica (80-100% EtOAc/Hexane) gave the title product as a red oil (34 mg, 34%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.24–7.12 (4H, m), 6.37 (1H, s), 6.29 (1H, bs), 6.00 (1H, bs), 3.20–3.12 (2H, m), 2.67–2.59 (2H, m), 2.29 (3H, s), 1.97 (3H, s); **^{13}C NMR** (76 MHz, $CDCl_3$) δ: 195.6, 176.0, 162.4 (d, *J* 249.9), 136.3, 133.2 (d, *J* 2.8), 129.7 (d, *J* 8.6), 129.0, 119.6, 116.4 (d, *J* 23.0), 107.4, 35.6, 29.8, 12.9, 12.6; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.1; **HRMS** (ESI+) found 311.11662 $[M+Na]^+$, $C_{16}H_{17}FN_2O_2Na$ requires 311.11663.

InChI=1S/C16H17FN2O2/c1-10-9-14(15(20)7-8-16(18)21)11(2)19(10)13-5-3-12(17)4-6-13/h3-6,9H,7-8H2,1-2H3,(H2,18,21)

All attempts: http://malaria.ourexperiment.org/uri/32b

9. Sulfonamides

Treatment of OSM-S-1 with chlorosulfonic acid resulted in *bis*-chlorosulfonation (at both room temperature and –25 ˚C); treatment of this intermediate with sarcosine methyl ester then ammonia in methanol afforded the *bis*-amide product OSM-E-3 (Fig SC10). The corresponding (desired) mono-substituted derivative was instead obtained through a route involving an initial step of heating OSM-S-1 at reflux with pyridine-sulfur trioxide in toluene to afford the pyridinium salt OSM-E-12 in around 60% purity. This crude salt was treated with oxalyl chloride and then either glycine methyl ether hydrochloride or sarcosine methyl ester hydrochloride to furnish esters OSM-E-11 and OSM-E-10 respectively, which were then transformed into the corresponding amides OSM-E-2 and OSM-E-1.

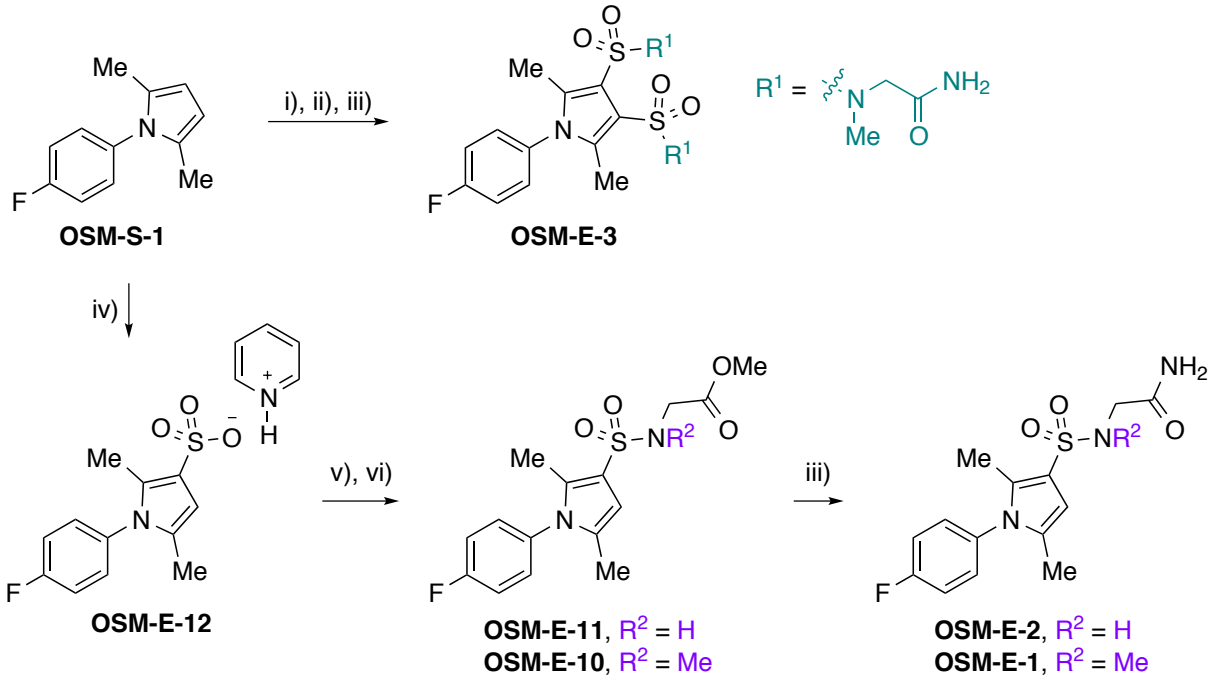
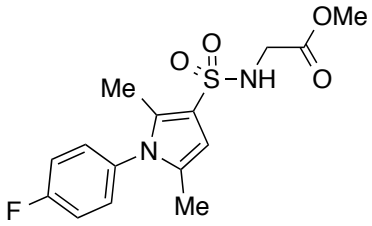


Fig SC10. Synthesis of Sulfonamides. Reagents and Conditions i) $ClSO_3$,CH_2Cl_2, rt; ii) sarcosine methyl ether, pyridine, rt;, iii) NH_3, MeOH, rt; iv) Py.SO_3, toluene, reflux; v) oxalyl chloride, cat. DMF, CH_2Cl_2, rt; vi) sarcosine methyl ester hydrochloride *or* glycine methyl ether hydrochloride, pyridine

Methyl 2-[1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-sulfonamido]acetate, OSM-E-11



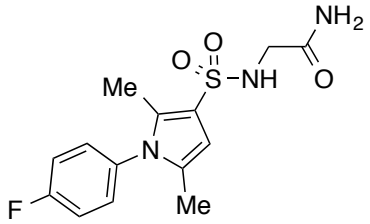
Representative example: http://malaria.ourexperiment.org/uri/29f

OSM-S-1 (0.75 g, 4.0 mmol) and sulfur trioxide-pyridine (0.60 g, 4.0 mmol) were dissolved in toluene (6 mL) and heated to reflux for 16 h. The reaction mixture was cooled to rt, then diluted with distilled water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was evaporated to recover starting material (56%). The aqueous phase was evaporated to dryness to give a dark solid (**OSM-E-12**). A portion of the dark solid (0.12 g, 62% purity, 0.20 mmol) was suspended in 1 mL of dry CH_2Cl_2 and to this was added dry DMF (15 µL, *ca*. 1 drop) followed by dropwise addition of oxalyl chloride (0.14 mL, 1.6 mmol). The reaction mixture was stirred at rt under an atmosphere of dry nitrogen for 3 h, then diluted with CH_2Cl_2 (25 ml) and washed with water (25 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil (**OSM-E-9**, 0.13 g). The oil was suspended in dry pyridine (10 ml) and to this was added glycine methyl ester hydrochloride (0.13 g, 1.0 mmol). The reaction mixture was stirred at rt for 3 h and then solvents removed *in vacuo* and the residue purified by dry column vacuum chromatography (EtOAc/heptane, 25-100%) to give the title compound as a tan oil (17 mg, 48 µmol, 24%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.24-7.16 (4H, m), 6.26 (1H, s), 4,97 (1H, s), 3.73 (3H, s), 2.23 (3H, s), 2.06 (2H, s), 1.97 (3H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 207.0, 171.1, 169.8, 163.6, 161.6, 133.1 (m) 129.8 (m), 129.4, 116.7 (m), 106.9, 60.4, 52.5, 31.9, 30.9, 22.7, 21.1, 14.2, 12.6, 11.6.

InChI=1S/C14H16FN3O3S/c1-9-7-13(22(20,21)17-8-14(16)19)10(2)18(9)12-5-3-11(15)4-6-12/h3-7,17H,8H2,1-2H3,(H2,16,19)

All attempts: http://malaria.ourexperiment.org/uri/699

2-[1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-sulfonamido]acetamide, OSM-E-2



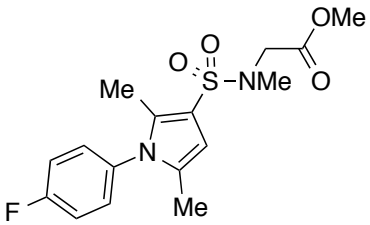
Representative example: http://malaria.ourexperiment.org/uri/2fc

OSM-E-11 (17 mg 49 µmol), was suspended in MeOH (10 ml) and saturated aqueous ammonia (10 mL) and stirred for 30 min. The reaction was concentrated *in vacuo* and the residue was purified by dry column vacuum chromatography (gradient: 50-100% EtOAc in petroleum ether) and dried *in vacuo* to give the title compound as a white solid (7.0 mg, 21 µmol, 43%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.24-7.16 (4H, m), 6.52 (1H, bs), 6.26 (1H, s), 5.60 (1H, br s), 5.17 (1H, s), 3.68 (2H, m), 2.24 (3H, s), 1.98 (3H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 171.0, 168.6, 161.7, 133.4, 132.9 (m), 129.9 (m), 116.7 (m), 116.0, 106.6, 49.8, 12.6, 11.6; **LRMS** (ESI+): 348.1 $[M+Na]^+$, 672.7 $[2M+Na]^+$; **HRMS** (ESI+): found 325.08881, $C_{14}H_{16}O_3N_3FS$ M^+ 325.08909.

InChI=1S/C15H17FN2O4S/c1-10-8-14(23(20,21)17-9-15(19)22-3)11(2)18(10)13-6-4-12(16)5-7-13/h4-8,17H,9H2,1-3H3

All attempts: http://malaria.ourexperiment.org/uri/690

Methyl 2-[N-methyl-1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-sulfonamido]acetate, OSM-E-10



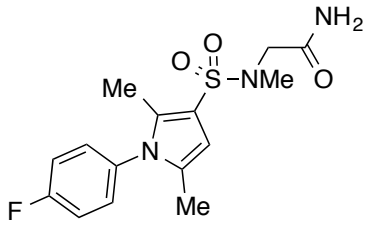
Representative example: http://malaria.ourexperiment.org/uri/28b

OSM-S-1 (0.75 g, 4.0 mmol) and sulfur trioxide-pyridine (0.60 g, 4.0 mmol) were dissolved in toluene (6 mL) and heated to reflux for 16 h. The reaction mixture was cooled to rt, then diluted with distilled water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was evaporated to recover starting material (56%). The aqueous phase was evaporated to dryness to give a dark solid (**OSM-E-12**). A portion of the dark solid (0.12 g, 62% purity, 0.2 mmol) was suspended in 1 mL of dry CH_2Cl_2 and to this was added dry DMF (14 mg, 15 µL, *ca*. 1 drop) followed by dropwise oxalyl chloride (0.14 mL, 1.6 mmol). The reaction mixture was stirred at rt under an atmosphere of dry nitrogen overnight, then diluted with CH_2Cl_2 (25 ml) and washed with water (25

mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil (**OSM-E-9**, 0.10 g). The oil was suspended in dry pyridine (10 mL) and to this was added sarcosine methyl ester hydrochloride (0.13 g, 1.0 mmol). The reaction mixture was stirred at rt overnight and then solvents were removed *in vacuo* and the residue purified by dry column vacuum chromatography (EtOAc/heptane, 25%) to give the title compound as a white oil (50 mg, 0.14 mmol, 70%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.18-7.24 (4H, m), 6.25 (1H, s), 3.98 (2H, s), 3.75 (3H, s), 2.93 (3H, s), 2.23 (3H, s), 1.98 (3H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 169.4, 163.5, 161.6, 133.2 (m), 133.1, 129.8 (m), 116.6 (m), 116.7, 107.0, 52.1, 51.0, 35.6, 12.6, 11.7; **LRMS** (ESI+): 377 $[M+Na]^+$, 731 $[2M+Na]^+$; **HRMS** (ESI+): found 354.10425, $C_{16}H_{19}O_4N_2FS$ M^+ 354.10441.

InChI=1S/C16H19FN2O4S/c1-11-9-15(24(21,22)18(3)10-16(20)23-4)12(2)19(11)14-7-5-13(17)6-8-14/h5-9H,10H2,1-4H3

2-[N-Methyl-1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-sulfonamido]acetamide, OSM-E-1



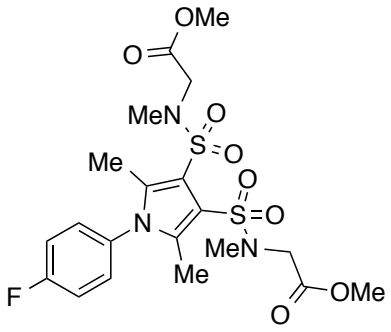
Representative example: http://malaria.ourexperiment.org/uri/291

OSM-E-10 (42 mg 0.12 mmol), was suspended in MeOH (10 ml) and saturated aqueous ammonia (10 mL) and stirred for 1 h. The reaction was concentrated *in vacuo* and the residue was purified by dry column vacuum chromatography (gradient: 50-100% EtOAc in petroleum ether) to give the title compound as a white foam (28 mg, 82 µmol, 69%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.20-7.27 (4H, m), 6.74 (1H, br s), 6.23 (1H, s), 5.55 (1H, br.s), 3.68 (2H, s), 2.88 (3H, s), 2.26 (3H, s), 1.99 (3H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 171.0, 163.7, 161.7, 133.5, 132.9 (m), 129.8 (m), 116.9 (m), 113.6, 106.7, 54.3, 37.0, 12.6, 11.9; **LRMS** (ESI+): 361 $[M+Na]^+$, 701 $[2M+Na]^+$; **HRMS** (ESI+): found 339.10460, $C_{15}H_{18}O_3N_3FS$ M^+ 339.10474.

InChI=1S/C15H18FN3O3S/c1-10-8-14(23(21,22)18(3)9-15(17)20)11(2)19(10)13-6-4-12(16)5-7-13/h4-8H,9H2,1-3H3,(H2,17,20)

All attempts: http://malaria.ourexperiment.org/uri/68f

Methyl 2-[N-methyl-1-(4-fluorophenyl)-4-[(2-methoxy-2-oxoethyl)(methyl)sulfamoyl]-2,5-dimethyl-1H-pyrrole-3-sulfonamido]acetate, OSM-E-13



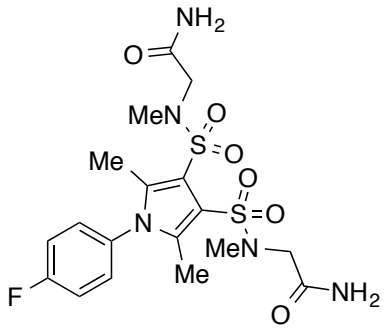
Representative example: http://malaria.ourexperiment.org/uri/241

OSM-S-1 (567 mg, 1.00 mmol) was dissolved in dry CH_2Cl_2 (1 mL), chlorosulfonic acid (350 mg, 200 µL, 3.00 mmol) was added and the reaction mixture was stirred at rt under an atmosphere of dry nitrogen overnight. Sarcosine methyl ester hydrochloride (627 mg, 5.0 mmol) was suspended in CH_2Cl_2 (*ca*. 25 mL) and washed with 10% NaOH solution. After drying over $MgSO_4$, most of the CH_2Cl_2 was carefully evaporated and the residue taken up in pyridine (2 mL). The solution was added to the reaction mixture dropwise at 0 ˚C, and the reaction stirred whilst warming to rt for a further 4 h. The reaction mixture was diluted with EtOAc (40 mL) and washed with a saturated aqueous solution of sodium carbonate (50 mL), hydrochloric acid (2 M, 50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown-red oil (87 mg) which was purified by dissolving in EtOAc and passing through a plug of silica with 88% recovery to give the title compound as a pale green oil (68.0 mg, 131 µmol, 13%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.28 (2H, m), 7.20 (2H, m), 4.21 (4H, s), 3.74 (6H, s), 2.95 (6H, s), 2.28 (6H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 170.1, 137.4, 132, 130.2, 117.3 (m), 116.2, 52.0, 51.4, 35.2, 14.2, 13.3; **LRMS** (ESI+): 542 $[M+Na]^+$.

InChI=1S/C20H26FN3O8S2/c1-13-19(33(27,28)22(3)11-17(25)31-5)20(34(29,30)23(4)12-18(26)32-6)14(2)24(13)16-9-7-15(21)8-10-16/h7-10H,1

All attempts: http://malaria.ourexperiment.org/uri/69b

2-{N-methyl-4-[(carbamoylmethyl)(methyl)sulfamoyl]-1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrole-3-sulfonamido}acetamide, OSM-E-3



Representative example: http://malaria.ourexperiment.org/uri/254

OSM-E-13 (68.3 mg, 131 µmol) was dissolved in MeOH (20 mL) and to this was added concentrated aqueous ammonia (10 mL). The resulting suspension was stirred vigorously overnight. The reaction was concentrated *in vacuo* and the residue was purified by dry column vacuum chromatography (50-100% EtOAc/heptane, then 0-5% MeOH in EtOAc) to give the title compound as a tan oil (17.0 mg, 26%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.41 (2H, br s), 7.3 (2H, m), 7.22 (2H, m), 5.57 (2H, br s), 3.82 (4H, s), 2.99 (6H, s), 2.30 (6H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 170.8, 162.3, 140.2, 131.2 (m), 130.0 (m), 117.6 (m), 113.6, 52.1, 35.5, 12.9; **LRMS** (ESI+): 512 $[M+Na]^+$, 1001 $[2M+Na]^+$; **HRMS** (ESI+): found 489.11439, $C_{13}H_{24}O_6FS_2$ M^+ 489.11466.

InChI=1S/C18H24FN5O6S2/c1-11-17(31(27,28)22(3)9-15(20)25)18(32(29,30)23(4)10-16(21)26)12(2)24(11)14-7-5-13(19)6-8-14/h5-8H,9-

All attempts: http://malaria.ourexperiment.org/uri/691

10. Pyrazoles

Esters OSM-S-23 and OSM-S-241 were formed from the condensation of ethyl acetoacetate, dimethylformamide dimethyl acetal and the relevant arylhydrazine (Fig SC11). Saponification gave the corresponding acids OSM-S-24 and OSM-S-242. The desired pyrazole analog OSM-S-57 could be obtained from direct elaboration of OSM-S-24 with 2-bromoacetamide or *via* addition of bromoacetonitrile followed by acidic hydrolysis. A *des*-methyl pyrazole series was synthesised *via* condensation of ethyl (2*E*)-2-cyano-3-ethoxy-2-propenoate with *para*-fluoro phenylhydrazine, deamination with isoamyl nitrite to furnish ester OSM-S-244, hydrolysis to give the acid followed by alkyation with 2-bromoacetamide in DMF to yield OSM-S-92.[37]

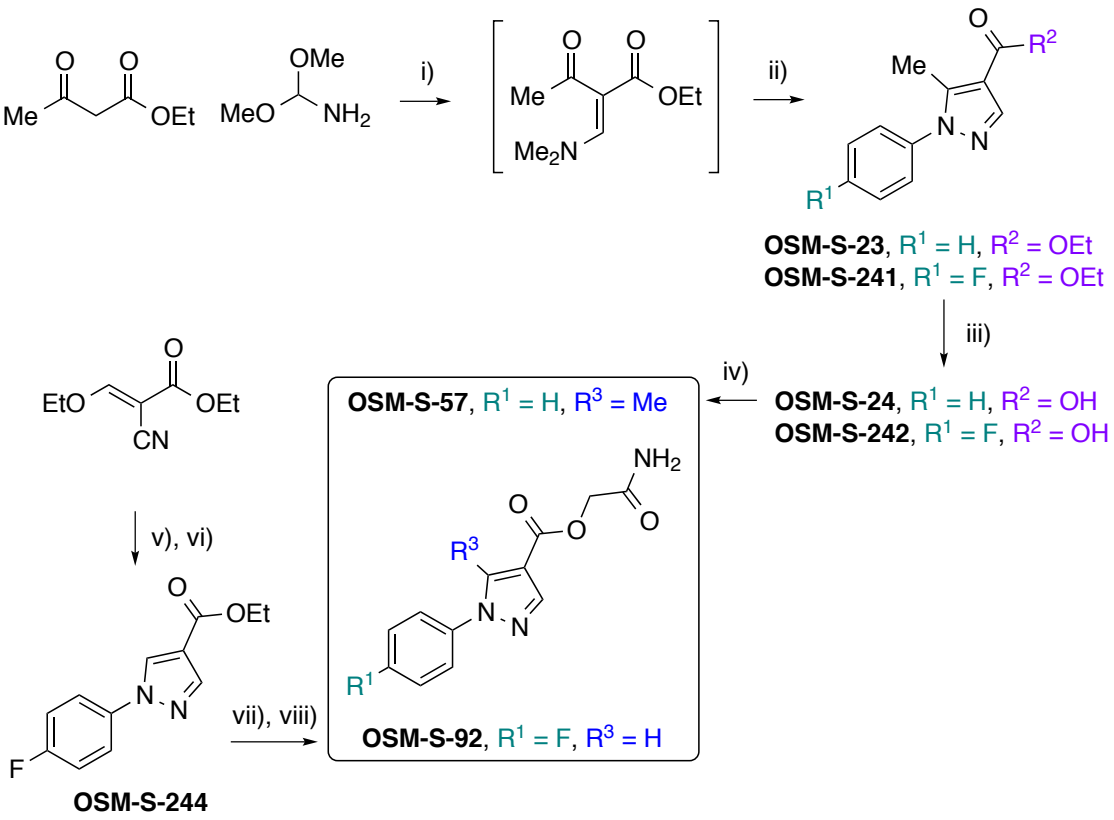
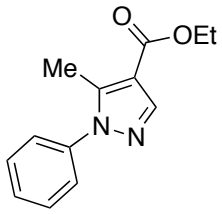


Fig SC11. Synthesis of Pyrazole Analogs. Reagents and Conditions: i) 50 min, 100 ˚C; ii) $ArNHNH_2$, EtOH, 2 h, reflux; iii) sodium hydroxide solution, EtOH, 1.5 h, reflux; iv) 2-bromoacetamide, potassium carbonate, DMF, rt; or bromoacetonitrile, K_2CO_3, acetone, reflux then TFA:H_2SO_4 (4:1), rt; v) sodium acetate trihydrate, acetic acid/water, overnight, 100 ˚C; vi) isoamyl nitrite, THF, 19 h, reflux; vii) sodium hydroxide solution, EtOH, 1.5 h, reflux; viii) 2-bromoacetamide, potassium carbonate, DMF, rt.

Ethyl 5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate, OSM-S-23



Representative example: http://malaria.ourexperiment.org/uri/c0

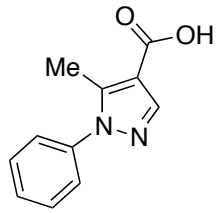
Ethyl acetoacetate (2.0 mL, 16 mmol, 1.0 equiv.) and dimethylformamide dimethyl acetal (2.2 mL, 17 mmol, 1.1 equiv.) were mixed and heated to 90 ˚C for 70 min. The reaction was cooled to rt and concentrated under reduced pressure to yield a red oil which was dissolved in EtOH (20 mL). Phenylhydrazine (1.5 mL, 16 mmol, 1.0 equiv.) in EtOH (20 mL) was added dropwise to the reaction over 5 min. The reaction was then heated to reflux for 2 h. The reaction was cooled to rt and then concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (40 mL), washed with water (20 mL), 10% $NaHCO_3$ (20 mL), brine dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a crude brown oil (3.5 g, 96% over 2 steps) that was used without further purification in the next step; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.02 (1H, s), 7.53–7.39 (4H, m), 4.32 (2H, q, *J* 7.1), 2.36 (3H, s), 1.37 (3H, t, *J* 7.1).

InChI=1S/C13H14N2O2/c1-3-17-13(16)12-9-14-15(10(12)2)11-7-5-4-6-8-11/h4-9H,3H2,1-2H3

All attempts: http://malaria.ourexperiment.org/uri/2d9

Prepared according to a literature precedent.[38, 39]

5-Methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid, OSM-S-24



Representative example: http://malaria.ourexperiment.org/uri/c4

OSM-S-23 (3.46 g, 15.0 mmol, 1.0 equiv.) was dissolved in EtOH (20 mL). 5 M NaOH (20.0 mL, 100 mmol, 6.7 equiv.) was added and the mixture heated to reflux for 9 h. The reaction mixture was cooled in ice, acidified with 6 M HCl (pH 1) and the resulting amber precipitate was allowed to ripen for 20 min at 0 ˚C, filtered and dried under reduced pressured. The amber product was recrystallised from Et_2O (approx 50 mL) to obtain the

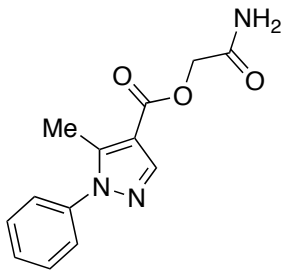
product as colourless plates (1.26 g, 74%); **m.p.** 167–168 ˚C (Et_2O) decomposition (lit. 169 ˚C)[40]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.36 (1H, s), 7.56–7.41 (4H, m), 2.60 (3H, s); **m/z** (APCI+) 298 $[M+H]^+$.

InChI=1S/C11H10N2O2/c1-8-10(11(14)15)7-12-13(8)9-5-3-2-4-6-9/h2-7H,1H3,(H,14,15)

All attempts: http://malaria.ourexperiment.org/uri/2da

Data in agreement with literature precedent.[40]

2-Amino-2-oxoethyl 5-methyl-1-phenyl-1H-pyrazole-4-carboxylate, OSM-S-57



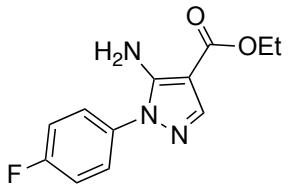
Representative example: http://malaria.ourexperiment.org/uri/106

OSM-S-24 (0.20 g, 1.0 mmol, 1.0 equiv.) was stirred in toluene (2 mL) at 0 ˚C, thionyl chloride (0.15 mL, 2.1 mmol, 2.1 equiv.) and a drop of DMF were added and the reaction mixture heated to reflux for 1.5 h. The reaction was cooled and concentrated under reduced pressure and the resulting solid was dissolved in THF (4 mL). Glycolamide (82 mg, 1.1 mmol, 1.1 equiv.), 4-DMAP (48 mg, 0.40 mmol, 0.4 equiv.) and DIPEA (0.35 mL, 2.0 mmol, 2.0 equiv.) were stirred in THF (4 mL) at rt. The solution of acid chloride was added dropwise and the mixture stirred overnight. Concentration under reduced pressure afforded an orange gum that was purified by flash column chromatography on silica (40–80% EtOAc/hexane) to give the title compound as a white solid (143 mg, 56%); **m.p.** 153–155 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.06 (1H, s), 7.55–7.40 (4H, m), 6.19 (1H, bs), 6.09 (1H, bs), 4.77 (2H, s), 2.58 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 170.1, 162.1, 144.7, 141.6, 138.5, 129.3, 128.9, 125.5, 111.4, 74.0, 62.1, 11.9; **IR** ν_{max} (neat) /cm^{-1} 3349, 1684, 1559, 1504, 1405, 1234, 1104, 939, 771, 697; **m/z** (APCI+) 283 $[M+Na]^+$; **HRMS** (ESI^+) found 282.08456 $[M+Na]^+$, $C_{13}H_{13}N_3O_3Na$ requires 282.08491.

InChI=1S/C13H13N3O3/c1-9-11(13(18)19-8-12(14)17)7-15-16(9)10-5-3-2-4-6-10/h2-7H,8H2,1H3,(H2,14,17)

All attempts: http://malaria.ourexperiment.org/uri/2fb

Ethyl 5-amino-1-(4-fluorophenyl)-1*H*-pyrazole-4-carboxylate,[41] OSM-S-243



Representative example: http://malaria.ourexperiment.org/uri/18a

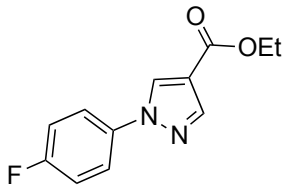
4-Fluorophenylhydrazine hydrochloride (0.81 g, 5.0 mmol), ethyl 2-cyano-3-ethoxyacrylate (0.94 g, 5.5 mmol) and sodium acetate trihydrate (1.5 g, 11 mmol) were stirred in acetic acid (7.5 ml) and water (2.5 mL). The mixture was heated to 100 ˚C. After overnight heating, the reaction was poured over ice and the resulting precipitate was filtered and recrystallised (MeOH/water) to obtain pale tan needles (0.98 g, 78%); **m.p.** 152–153 ˚C (MeOH/H_2O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.77 (1H, s), 7.54–7.49 (2H, m), 7.32 (2H, t, *J* 8.7), 5.25 (2H, s), 4.30 (2H, q, *J* 7.0), 1.36 (3H, t, *J* 7.0); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 164.5, 149.1, 140.7, 133.7, 126.1, 125.9, 116.9, 116.6, 96.3, 59.7, 14.5; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.4.

InChI=1S/C12H12FN3O2/c1-2-18-12(17)10-7-15-16(11(10)14)9-5-3-8(13)4-6-9/h3-7H,2,14H2,1H3

All attempts: http://malaria.ourexperiment.org/uri/6a4

Data in accordance with literature precedent.[41]

Ethyl 1-(4-fluorophenyl)-1*H*-pyrazole-4-carboxylate, [41] OSM-S-244



Representative example: http://malaria.ourexperiment.org/uri/18e

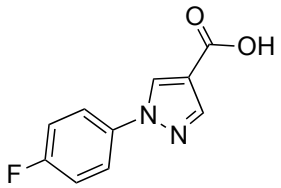
Aminopyrazole **OSM-S-243** (700 mg, 2.81 mmol) was dissolved in THF (15 mL) and isoamyl nitrite (1.50 mL, 11.2 mmol) was added and reaction was heated to reflux. After 19 h, the reaction was concentrated under reduced pressure and the yellow residue recrystallised from hot EtOH and once again from (EtOH/water) to give white needles (0.44 g, 66%); **m.p.** 121–122 ˚C (EtOH); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.35 (1H, s), 8.09 (1H, s), 7.71–6.45 (2H, m), 7.22–7.14 (2H, m), 4.34 (2H, q, *J* 7.2), 1.38 (3H, t, *J* 7.2).

InChI=1S/C12H11FN2O2/c1-2-17-12(16)9-7-14-15(8-9)11-5-3-10(13)4-6-11/h3-8H,2H2,1H3

All examples: http://malaria.ourexperiment.org/uri/6a5

Data in accordance with literature precedent.[41]

1-(4-Fluorophenyl)-1*H*-pyrazole-4-carboxylic acid, OSM-S-245



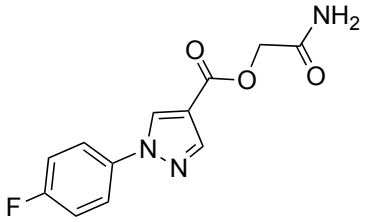
Representative example: http://malaria.ourexperiment.org/uri/192

Prepared according to General Procedure **D** from: **OSM-S-244** (324 mg, 1.38 mmol) in EtOH (~6 mL) and 20% NaOH(aq) (~20mL); reflux for 2 h; fine white solid (253 mg, 89%); **^{1}H NMR** (200 MHz, DMSO *d*-$_6$): δ 12.7 (1H, bs), 9.00 (1H, s), 8.07 (1H, s), 7.99–7.92 (2H, m), 7.41–7.32 (2H, m).

InChI=1S/C10H7FN2O2/c11-8-1-3-9(4-2-8)13-6-7(5-12-13)10(14)15/h1-6H,(H,14,15)

All attempts: http://malaria.ourexperiment.org/uri/6a6

2-Amino-2-oxoethyl 1-(4-fluorophenyl)-1H-pyrazole-4-carboxylate, OSM-S-92



Representative example: http://malaria.ourexperiment.org/uri/197

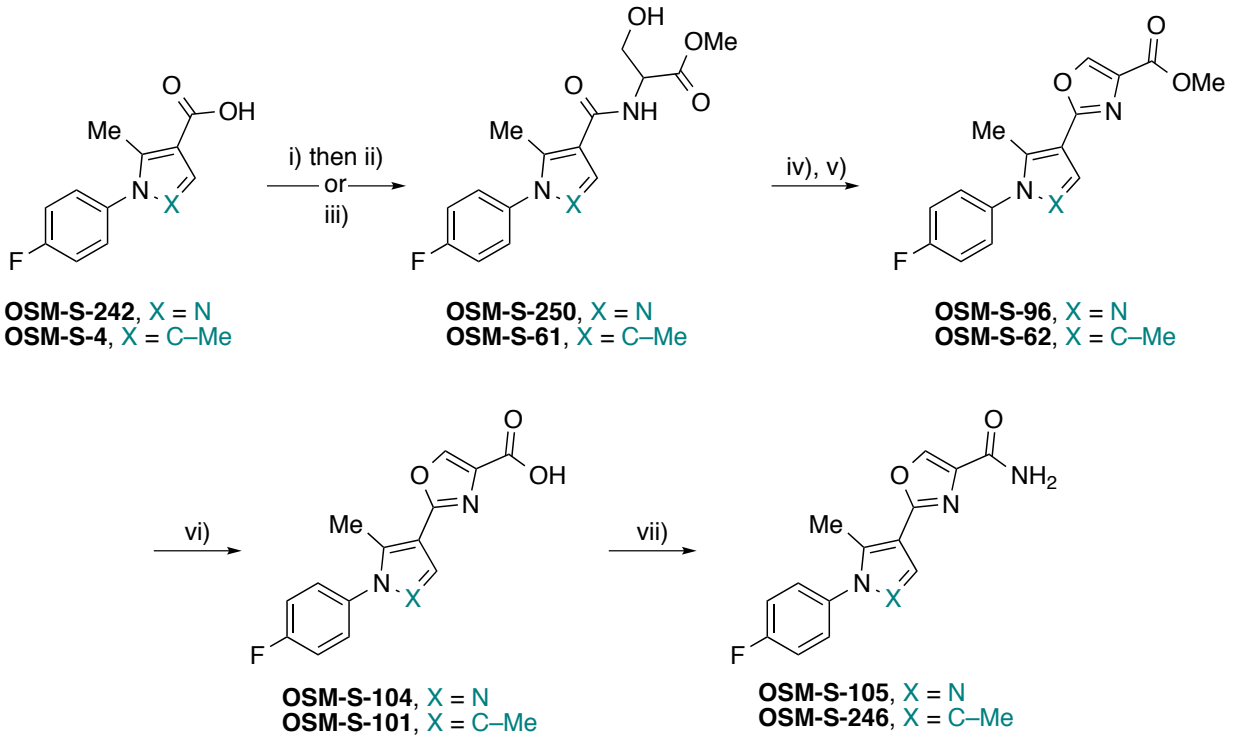
Prepared according to General Procedure **H** from: **OSM-S-245** (83 mg, 0.40 mmol), 2-bromoacetamide (59 mg, 0.43 mmol) and potassium carbonate (98 mg, 0.71 mmol) in DMF (2 mL); rt 16 h; crude white solid recrystallised from hot methanol (approx. 4 mL) to obtain colourless needles (10 mg, 9%); **m.p.** 220–221 ˚C (MeOH); **^{1}H NMR** (200 MHz, DMSO-*d*$_6$) δ: 9.21 (1H, s), 8.25 (1H, s), 8.04–7.90 (2H, m), 7.54 (1H, bs), 7.47–7.34 (3H, m), 4.61 (2H, s); **m/z** (APCI+) 264 $[M+H]^+$; **HRMS** (ESI+) found 286.05979 [M+Na], $C_{12}H_{10}N_3O_3FNa$ requires 286.05984.

InChI=1S/C12H10FN3O3/c13-9-1-3-10(4-2-9)16-6-8(5-15-16)12(18)19-7-11(14)17/h1-6H,7H2,(H2,14,17)

All attempts: http://malaria.ourexperiment.org/uri/320

11. Oxazoles

Oxazole analogs were prepared by amidation of the carboxylic acid of the corresponding pyrazole (OSM-S-242) or pyrrole (OSM-S-4) with DL-serine methyl ester hydrochloride (Fig SC12). A two-step cyclodehydration employing XtalFluorE^{TM} and then bromotrichloromethane led to the synthesis of methyl esters OSM-S-96 and OSM-S-62, which could be saponified to their acids. Conversion to the desired primary amide was successful for the pyrazole series (giving OSM-S-105) but could not be completed for the pyrrole series, even *via* a separate attempt in which acid OSM-S-4 was successfully coupled to serinamide directly (to give OSM-S-249, not shown) and cyclised. The poor solubility of acid and amide analogs in many common organic solvents was probably responsible for the low yields of isolated products in several steps in this sequence.



OSM-S-242, X = N
OSM-S-4, X = C–Me

OSM-S-250, X = N
OSM-S-61, X = C–Me

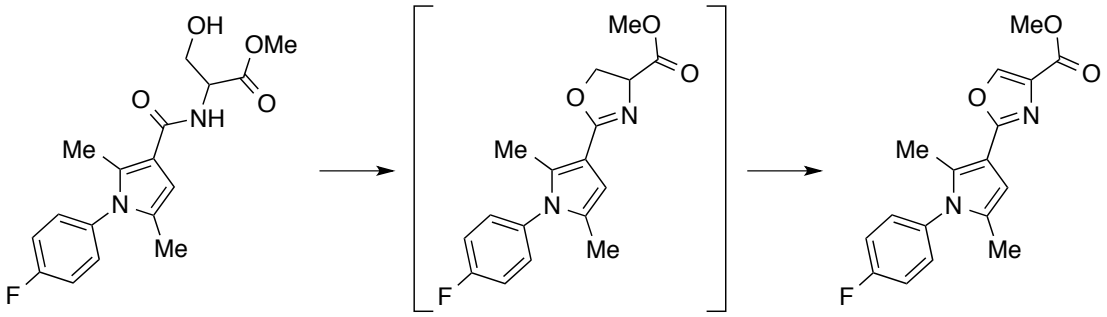
OSM-S-96, X = N
OSM-S-62, X = C–Me

OSM-S-104, X = N
OSM-S-101, X = C–Me

OSM-S-105, X = N
OSM-S-246, X = C–Me

Fig SC12. Synthesis of Oxazole Analogs. Reagents and Conditions: i) thionyl chloride (2 equiv.), toluene, 4 h, 0 ˚C to rt; ii) DL-serine methyl ester hydrochloride, diisopropylethylamine, 16 h, rt; iii) DL-serine methyl ester hydrochloride, EDCI, HOBt, diisopropylethylamine, dichloromethane, 19 h, rt; iv), XtalFluor-E, dichloroethane 16 h, 90 ˚C; v) bromotrichloromethane, DBU, dichloromethane, 18 h, 15 ˚C; vi) sodium hydroxide solution, EtOH, 2.5 – 3 h, reflux; vii) ammonium hydroxide, EDCI, HOBt, diisopropylethylamine, dichloromethane, 4 h, rt.

Methyl 2-(1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)-4,5-dihydrooxazole-4-carboxylate, OSM-S-63 and methyl 2-(1-(4-fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)oxazole-4-carboxylate, OSM-S-62



OSM-S-63 **OSM-S-62**

Representative example: http://malaria.ourexperiment.org/uri/128

OSM-S-61 (1.00 g, 3.0 mmol, 1.0 equiv.) was stirred in 1,2-DCE (40 mL). XtalFluor-E (1.40 g, 6.0 mmol, 2.0 equiv.) was added and the reaction heated to 90 ˚C under N_2 for 18 h. The reaction was cooled to rt and a solution Na_2CO_3 (1:1 saturated aq. solution/water, ~30 mL) was added. The reaction was stirred for 10 min and then separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to a brown foam, **OSM-S-63** (1.04 g, 110% of theory); **^{1}H NMR** (300 MHz, $CDCl_3$): δ: 7.19–7.12 (4H, m), 6.35 (1H, s), 4.86 (1H, dd, *J* 10.4 and 2.9), 4.62-4.36 (2H, m), 3.78 (3H, s), 2.25 (3H, s), 1.95 (3H, s). **OSM-S-63** was dissolved in CH_2Cl_2 (50 mL). DBU (1.3 mL, 8.7 mmol, 2.9 equiv.) and bromotrichloromethane (0.88 mL, 8.9 mmol, 3.0 equiv.) were added and the reaction was heated to reflux for 3.5 h and then stirred at 25 ˚C overnight. The reaction was concentrated under reduced pressure and purified by flash column chromatography on silica (5–20% acetone/hexane) to provide the title compound as a pale yellow solid (322 mg, 34%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.16 (1H, s), 7.19 (1H, d, *J* 6.5), 6.48 (1H, s), 3.91 (3H, s), 2.35 (3H, s), 2.00 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 162.3, 162.3 (d, *J* 248.9), 161.5, 141.8, 133.7, 133.6, 131.7, 129.9 (d, *J* 8.7), 116.4 (d, *J* 23.0), 110.0, 107.8, 105.9, 52.0, 12.7, 12.4; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -114.1; **HRMS** (ESI+) found 337.09628 [M+Na], $C_{17}H_{15}N_2O_3FNa$ requires 337.09589.

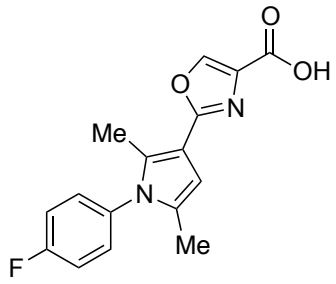
OSM-S-63 *InChI=1S/C17H17FN2O3/c1-10-8-14(16-19-15(9-23-16)17(21)22-3)11(2)20(10)13-6-4-12(18)5-7-13/h4-8,15H,9H2,1-3H3*

OSM-S-62 *InChI=1S/C17H15FN2O3/c1-10-8-14(16-19-15(9-23-16)17(21)22-3)11(2)20(10)13-6-4-12(18)5-7-13/h4-9H,1-3H3*

All attempts: **OSM-S-62** http://malaria.ourexperiment.org/uri/302 and
OSM-S-63 http://malaria.ourexperiment.org/uri/303.

Prepared according to literature.[42]

2-(1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)oxazole-4-carboxylic acid, OSM-S-101



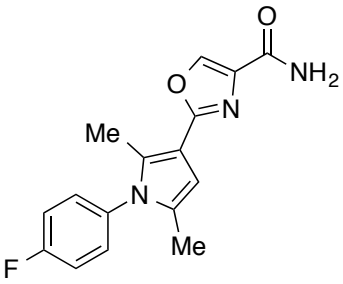
Representative example: http://malaria.ourexperiment.org/uri/1a7

OSM-S-62 (240 mg, 0.76 mmol, 1 equiv.) was dissolved in hot MeOH (15 mL). 5 M $NaOH_{(aq)}$ (4 mL) was added and the reaction refluxed for 30 min. The reaction mixture was acidified using 6 M HCl and cooled in a salt/ice bath to yield pale yellow crystals that were filtered, washed with water then dried *in vacuo* to provide the title compound (146 mg, 64%); **HRMS** (ESI+) found 301.14097 $[M+Na]^+$, $C_{16}H_{13}FN_2O_3Na$ requires 301.09830.

InChI=1S/C16H13FN2O3/c1-9-7-13(15-18-14(8-22-15)16(20)21)10(2)19(9)12-5-3-11(17)4-6-12/h3-8H,1-2H3,(H,20,21)

All attempts: http://malaria.ourexperiment.org/uri/329

2-(1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)oxazole-4-carboxamide, OSM-S-246



Representative example: http://malaria.ourexperiment.org/uri/1aa

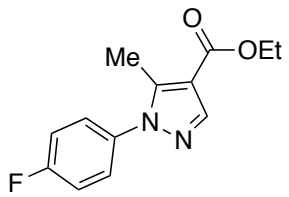
OSM-S-101 (0.10 g, 0.34 mmol, 1.0 equiv.) was stirred in CH_2Cl_2 (7 mL, 0.05 M). Partial solution. EDC.HCl (0.85 g, 0.44 mmol, 1.3 equiv.) and HOBt (~4.0 mg, 0.10 equiv.) were added. After 10 min, clear solution with some needles. After 20 min, 28% NH_4OH (1 mL) was added and the reaction left to stir o/n. A saturated solution of $NH_4Cl_{(aq)}$ was added, layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to a pale yellow solid

(0.11 g). Purified by chromatography on silica (5% MeOH, 1% NH_4OH/ CH_2Cl_2) to give a slightly yellow solid (84 mg).

All attempts: http://malaria.ourexperiment.org/uri/6a9

InChI=1S/C16H14FN3O2/c1-9-7-13(16-19-14(8-22-16)15(18)21)10(2)20(9)12-5-3-11(17)4-6-12/h3-8H,1-2H3,(H2,18,21)

Ethyl 1-(4-fluorophenyl)-5-methyl-1H-pyrazole-4-carboxylate, OSM-S-241



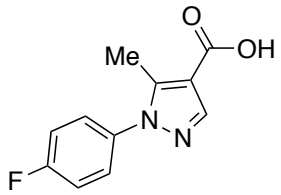
Representative example: http://malaria.ourexperiment.org/uri/13f

Dimethylformamide dimethyl acetal (910 µL, 7.21 mmol) was added with stirring to ethyl acetoacetate (919 µL, 7.21 mmol) and the mixture was heated to reflux at 100 ˚C for 2 h. In a separate vessel, NaOH (4 mL, 2 M aq. soln) was added to 4-fluorophenylhydrazine hydrochloride (1.00 g, 6.17 mmol) and the salt was dissolved with the aid of heating, extracted with EtOAc (3 × 10 mL), washed with brine (10 mL) and dried ($MgSO_4$) and solvent removed under reduced pressure to give 4-fluorophenylhydrazine (733 mg) as a yellow oil. 4-Fluorophenylhydrazine (0.73 g, 5.8 mmol) was dissolved in EtOH (20 mL) and added dropwise, and the reaction heated to reflux for 1.5 h and then stirred at rt overnight. The reaction mixture was filtered through a silica pad and washed with EtOAc / hexane (5–10%) to give a yellow solution which was concentrated and then purified by flash column chromatography over silica using (10% EtOAc in hexane) to give a yellow oil (0.96 g, 3.9 mmol, 73%); **m.p.** 45–46 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.04 (s, 1H), 7.44–7.40 (m, 2H), 7.24–7.19 (m, 2H), 4.36 (q, 4H, *J* 7.1), 2.57 (s, 1H), 1.40 (t, 2H, *J* 7.0); **^{13}C NMR** (76 MHz, $CDCl_3$) δ: 163.7, 162.3 (d, *J* 249.3), 143.6, 141.9, 135.0 (d, *J* 2.3), 127.4 (d, *J* 8.9), 116.2 (d, *J* 23.2), 113.0, 60.0, 14.4, 11.8; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.2; **IR** ν_{max} (film) / cm^{-1} 2984, 1736, 1517, 1447, 1373, 1300, 1232, 1098, 1043, 938, 918, 846; **m/z** (ESI) 249 $[2M+H]^+$; **HRMS** (ESI+) found 271.08524 [M+Na], $C_{13}H_{13}N_2O_2FNa$ requires 271.08533.

InChI=1S/C13H13FN2O2/c1-3-18-13(17)12-8-15-16(9(12)2)11-6-4-10(14)5-7-11/h4-8H,3H2,1-2H3

All attempts: http://malaria.ourexperiment.org/uri/6a2

1-(4-Fluorophenyl)-5-methyl-1H-pyrazole-4-carboxylic acid, OSM-S-242



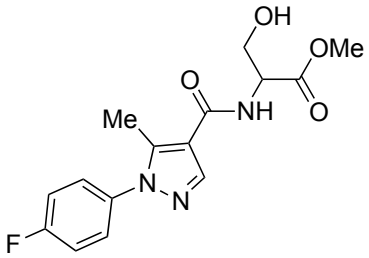
Representative example: http://malaria.ourexperiment.org/uri/159

Prepared according to General Procedure **D** from: NaOH (5 M, 4.8 mL, 24 mmol) and **OSM-S-241** (0.84 g, 3.4 mmol) in EtOH (4.5 mL); heated to reflux for 1 h. Cream precipitate was isolated and filtered and then recrystallised from diethyl ether (15 mL). First crop gave the carboxylic acid (0.30 g, 1.4 mmol, 41%) as white needles; **m.p.** 168-169 ˚C (EtOH); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 12.4 (s, 1H), 7.96 (s, 1H), 7.62-7.57 (m, 2H), 7.43-7.37 (m, 2H), 2.48 (s, 3H); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 164.5, 161.5 (d, *J* 245.3), 143.5, 141.6, 135.0, 127.7 (d, *J* 11.0), 116.2 (d, *J* 22.0), 113.0, 11.4; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -113.0; **IR** ν_{max} (film) / cm^{-1} 3082, 2958, 2648, 1678, 1560, 1514, 1223, 841; **m/z** (ESI) 249 $[2M+H]^+$; **HRMS** (ESI+) found 221.07207 [M+H], $C_{11}H_{10}N_2O_2F$ requires 221.07208.

InChI=1S/C11H9FN2O2/c1-7-10(11(15)16)6-13-14(7)9-4-2-8(12)3-5-9/h2-6H,1H3,(H,15,16).

All attempts: http://malaria.ourexperiment.org/uri/6a3

Methyl 2-(1-(4-fluorophenyl)-5-methyl-1H-pyrazole-4-carboxamido)-3-hydroxypropanoate, OSM-S-250



Representative example: http://malaria.ourexperiment.org/uri/1a1

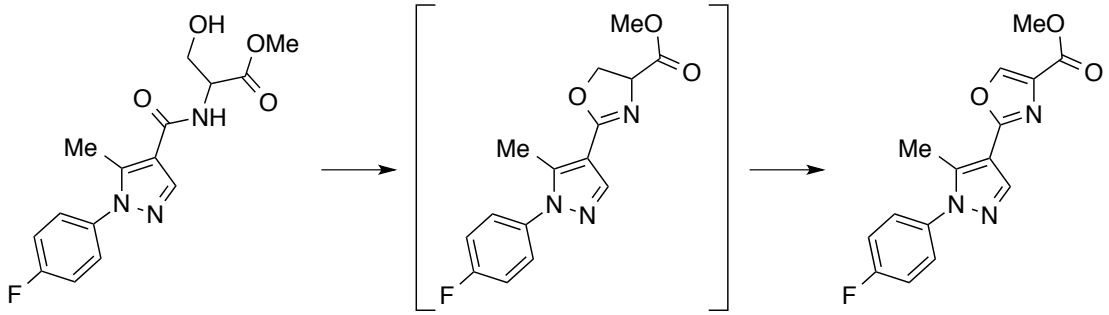
Prepared according to General Procedure **E** from: **OSM-S-242** (1.3 g, 5.7 mmol), EDCI (1.2 g, 6.3 mmol), HOBt (0.085 g, 0.63 mmol) and DIPEA (2.2 mL, 12.6 mmol) in CH_2Cl_2 (40 mL) under N_2; 10 min rt then serine methyl ester hydrochloride (977 mg, 6.3 mmol) was added; 19 h rt. A saturated aqueous solution of NH_4Cl (20 mL) was added to the reaction mixture followed by an aqueous solution of HCl (1 M) until the solution reached pH 1. The organic layer was then extracted and washed with water (3 × 20 mL), a saturated aqueous solution of Na_2CO_3 (20 mL), water (3 × 20 mL), brine (20 mL), dried over ($MgSO_4$) and concentrated to a white foam (0.55 g). The crude product was purified by flash column chromatography over silica (5–10% MeOH in CH_2Cl_2) to

provide the title product as a white foam (0.44 g, 25%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.91 (1H, s), 7.40–7.37 (2H, s), 7.22–7.16 (2H, m), 6.82 (1H, s), 4.87–4.82 (1H, m), 4.04 (2H, s), 3.83 (3H, s), 3.05 (1H, s), 2.54 (3H, s); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: *δ* 176.1, 171.2, 163.8, 142.7, 138.7, 134.8 (d, *J* 4.0), 127,4 (d, *J* 7.4), 116.3 (d, *J* 26.0), 114.9, 63.6, 54.6, 52.9, 11.8; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ: -112.0; **IR** ν_{max} (film) / cm^{-1} 3352, 2955, 1739, 1635, 1565, 1510, 1437, 1397; **m/z** (ESI) 322 $[M+H]^+$; **HRMS** (ESI+) found 344.10169 $[M+Na]^+$, $C_{15}H_{16}N_3O_4FNa$ requires 344.10171.

InChI=1S/C15H16FN3O4/c1-9-12(14(21)18-13(8-20)15(22)23-2)7-17-19(9)11-5-3-10(16)4-6-11/h3-7,13,20H,8H2,1-2H3,(H,18,21)/t13-/m0/s1

All attempts: http://malaria.ourexperiment.org/uri/6ad

Methyl 2-(1-(4-fluorophenyl)-5-methyl-1H-pyrazol-4-yl)oxazole-4-carboxylate, OSM-S-96



OSM-S-250 **OSM-S-96**

Representative example: http://malaria.ourexperiment.org/uri/1a9

OSM-S-250 (0.44 g, 1.4 mmol) was stirred in 1,2-DCE (20 mL). XtalFluor-E (0.64 g, 2.8 mmol) was added and the mixture heated to reflux at 90 ˚C under a nitrogen atmosphere. After 40 min the reaction was allowed to cool to rt before a solution of Na_2CO_3 (1:1 saturated soln/water, ~30 mL) was added. The reaction was stirred for 10 min and then separated. The aqueous layer was washed with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts washed with brine (~20 mL), dried ($MgSO_4$) and concentration to give the intermediate (0.47 g, 1.5 mmol) as a viscous dark brown oil that was consistent with expected product by ^{1}H NMR spectroscopy. The intermediate (0.40 g, 1.3 mmol) was dissolved in CH_2Cl_2 (15 mL) and then bromotrichloromethane (0.39 mL, 4.0 mmol) and DBU (0.59 mL, 4.0 mmol) were added and the reaction stirred under a nitrogen atmosphere for 45 min. The reaction mixture was then concentrated to a viscous dark brown oil and then purified by flash column chromatography over silica (5–10% acetone / hexane) to provide the title compound as a yellow-white solid (0.37 g, 90%); **m.p.** 130-134 ˚C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.24 (s, 1H), 8.16 (s, 1H), 7.47–7.42 (m, 2H), 7.24-7.18 (m, 2H), 3.95 (s, 3H), 2.66 (s, 3H); **^{13}C NMR** (76 Hz, $CDCl_3$) δ: 162.3 (d, *J* 250.0), 161.9, 158.4, 142.6, 139.9, 139.6, 135.0 (d, *J* 2.8), 133.9, 127.3 (d, *J* 8.8), 116.3 (d, *J* 23.2), 109.3, 52.1, 12.0; **^{19}F{^{1}H} NMR**

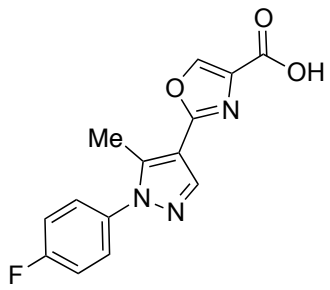
(282 MHz, $CDCl_3$) δ: -112.2; **IR** ν_{max} (film) / cm^{-1} 1744, 1720, 1629, 1515, 1228, 1114, 940, 843; **m/z** (ESI) 625 $[2M+H]^+$; **HRMS** (ESI+) found 302.09359 $[M+H]^+$, $C_{15}H_{13}N_3O_3F$ requires 302.09355.

InChI=1S/C15H12FN3O3/c1-9-12(14-18-13(8-22-14)15(20)21-2)7-17-19(9)11-5-3-10(16)4-6-11/h3-8H,1-2H3

All attempts: http://malaria.ourexperiment.org/uri/324

Preparation adapted from literature procedure.[42]

2-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)oxazole-4-carboxylic acid, OSM-S-104



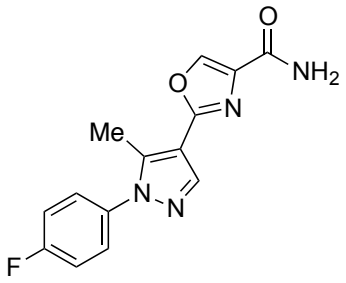
Representative example: http://malaria.ourexperiment.org/uri/1c0

Prepared according to General Procedure **D** from: NaOH (200 mg, 4.98 mmol) **OSM-S-96** 150 mg, 0.50 mmol) in EtOH (2 mL) and water (1 mL); heated to reflux for 3 h. White precipitate was filtered and rinsed with water to yield an off-white solid (94 mg, 66%.); **^{1}H NMR** (400 MHz, DMSO-d_6): δ: 13.1 (1H, bs), 8.79 (1H, s), 8.20 (1H, s), 7.75–7.60 (2H, m), 7.53–7.38 (2H, m), 2.65 (3H, s); **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 162.5 (d, *J* 246.4), 163.0, 158.2, 144.8, 140.8, 139.8, 135.9 (d, *J* 2.7), 134.9, 128.4 (d, *J* 8.6), 117.1 (d, *J* 23.1), 109.7, 12.5; **^{19}F{^{1}H} NMR** (282 MHz, MeOD) δ: -114.1; **HRMS** (ESI+) found 310.05976 $[M+Na]^+$, $C_{14}H_{10}FN_3O_3Na$ requires 310.05984.

InChI=1S/C14H10FN3O3/c1-8-11(13-17-12(7-21-13)14(19)20)6-16-18(8)10-4-2-9(15)3-5-10/h2-7H,1H3,(H,19,20)

All attempts: http://malaria.ourexperiment.org/uri/32c

2-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)oxazole-4-carboxamide, OSM-S-105



Representative example: http://malaria.ourexperiment.org/uri/1c4

Prepared according to General Procedure **E** from: EDCI (56 mg, 0.29 mmol), HOBt (3 mg, 0.02 mmol) **OSM-S-104** (70 mg, 0.24 mmol) and ammonium hydroxide (28%, 0.1 mL) in CH_2Cl_2 (3 mL); rt for 4 h. Flash column chromatography over silica (100% EtOAc) gave the title compound as a white solid (40 mg, 57%); **^{1}H NMR** (300 MHz, MeOD) δ 8.41 (1H, s), 8.17 (1H, s), 7.65–7.53 (2H, m), 7.44–7.30 (2H, m), 2.68 (3H, s); **^{13}C NMR** (76 MHz, MeOD) δ: 65.7, 164.1 (d, *J* 248.6), 159.0, 142.0, 141.8, 140.2, 137.8, 136.3 (d, *J* 2.2), 129.1 (d, *J* 9.2), 117.4 (d, *J* 23.3), 110.5, 12.0; **^{19}F{^{1}H} NMR** (282 MHz, MeOD) δ: -114.1; **HRMS** (ESI+) found 309.07580 $[M+Na]^+$, $C_{14}H_{11}N_4O_2FNa$ requires 309.07582.

InChI=1S/C14H11FN4O2/c1-8-11(14-18-12(7-21-14)13(16)20)6-17-19(8)10-4-2-9(15)3-5-10/h2-7H,1H3,(H2,16,20)

All attempts: http://malaria.ourexperiment.org/uri/32d

12. Triazoles

Propargylic ether OSM-E-14 (Fig SC13) was synthesised from commercial starting materials and submitted to a copper-catalysed cycloaddition reaction with *para*-fluorophenyl azide to give the desired methyl ester OSM-E-6 along with three other isolable side products (OSM-E-4, -5 and -7), which were all evaluated for potency. The methyl ester OSM-E-6 was reacted with aqueous ammonia in methanol to afford the ultimately desired triazole amide analogue of OSM-E-8, which was also evaluated, but all compounds were found to be inactive (Dataset S18 Dundee 2).

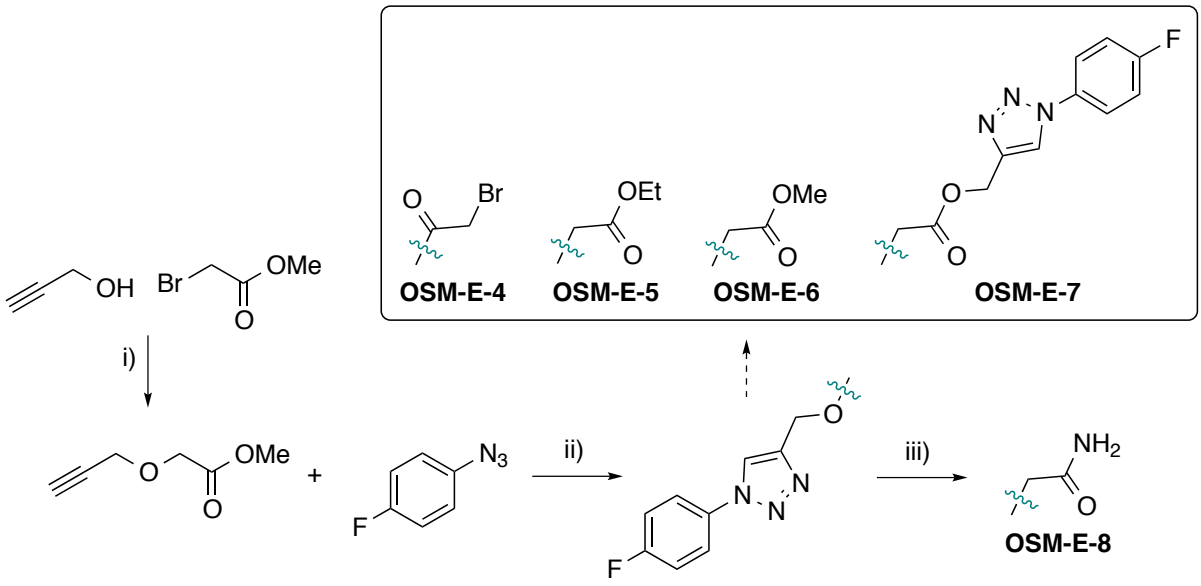
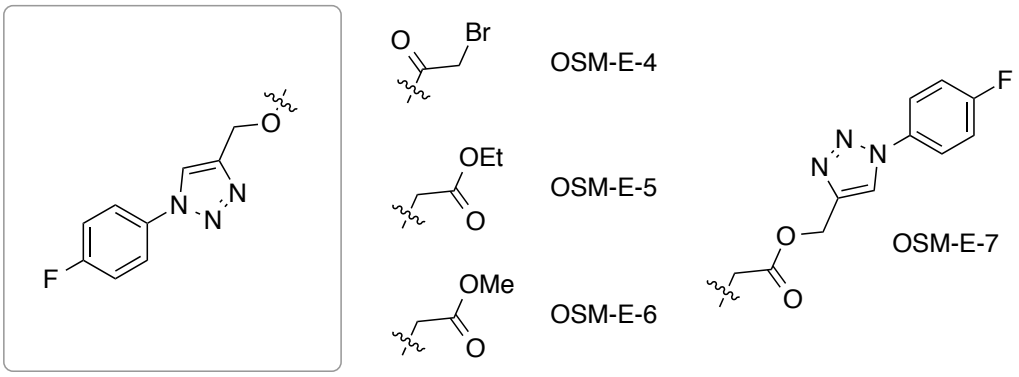


Fig SC13. Synthesis of Triazole Analogs. Reagents and Conditions i) NaH, THF, rt; ii) $CuSO_4$, sodium ascorbate, CH_2Cl_2/H_2O, rt; iii) NH_3, MeOH, rt.

[1-(4-Fluorophenyl)-1H-1,2,3-triazol-4-yl]methyl 2-bromoacetate, OSM-E-4;
Ethyl 2-{[1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}acetate, OSM-E-5;
Methyl 2-{[1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}acetate, OSM-E-6
and
1-(4-Fluorophenyl)-1H-1,2,3-triazol-4-yl]methyl 2-{[1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}acetate, OSM-E-7



Representative example: http://malaria.ourexperiment.org/uri/3a4

Methyl propynyloxyacetate was prepared by the procedure of Carrol[43] and unreacted propargyl alcohol was removed by distillation as described (*N.B. incomplete purification but material was used for synthesis*). 4-Fluorophenyl azide (0.38 g, 2.7 mmol) and methyl propynyloxyacetate (127 mg, 0.99 mmol) were dissolved in CH_2Cl_2:H_2O (5 mL, 3:2 mL) and stirred overnight with copper sulfate (12 mg, 0.08 mmol) and sodium ascorbate (20 mg, 0.10 mmol). The mixture was diluted with CH_2Cl_2 and the organic layer washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give 272 mg of yellow solid which was purified by dry column vacuum chromatography (40% EtOAc in heptane, followed by 100% EtOAc after 20 fractions) to give four products:

[1-(4-Fluorophenyl)-1H-1,2,3-triazol-4-yl]methyl 2-bromoacetate, OSM-S-4

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06 (1H, s), 7.73 (2H, m), 7.26 (2H, m), 5.43 (2H, s), 3.91 (2H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 167.25, 142.82, 122.72, 166.96, 59.12, 25.58.

InChI=1S/C11H9BrFN3O2/c12-5-11(17)18-7-9-6-16(15-14-9)10-3-1-8(13)2-4-10/h1-4,6H,5,7H2

Ethyl 2-{[1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}acetate, OSM-E-5

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.04 (1H, s), 7.74 (2H, m), 7.26 (2H, m), 4.88 (2H, s), 4.27 (2H, m), 4.24 (2H, s), 1.32 (3H, m); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 170.12, 163.51, 161.52, 145.32, 122.63, 133.31 131.36, 116.80, 67.62, 64.06, 61.06, 14.22; **LRMS** (ESI+): 302 $[M+Na]^+$, 580.7 $[2M+Na]^+$; **HRMS** (ESI+): found 302.0911, $C_{13}H_{14}O_3N_3FNa$ M^+ 302.0917.

InChI=1S/C13H14FN3O3/c1-2-20-13(18)9-19-8-11-7-17(16-15-11)12-5-3-10(14)4-6-12/h3-7H,2,8-9H2,1H3

Methyl 2-{[1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}acetate, OSM-E-6

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.04 (1H, s), 7.73 (2H, m), 7.26 (2H, m), 4.88 (2H, s), 4.27 (2H, s), 3.80 (3H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 170.53, 163.51, 161.53, 145.21, 133.30, 122.66, 121.38, 116.80, 67.48, 64.65, 51.98; **LRMS** (ESI+): 288 $[M+Na]^+$; **HRMS** (ESI+): found 288.0752, $C_{12}H_{12}O_3N_3FNa$ M^+ 288.0760.

InChI=1S/C12H12FN3O3/c1-18-12(17)8-19-7-10-6-16(15-14-10)11-4-2-9(13)3-5-11/h2-6H,7-8H2,1H3

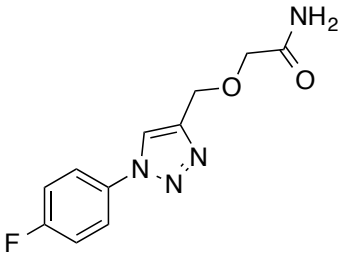
1-(4-Fluorophenyl)-1H-1,2,3-triazol-4-yl]methyl2-\\{[1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}acetate, OSM-E-7

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.10 (1H, s), 8.04 (1H, s), 7.74 (4H, m), 7.26 (4H, m), 5.43 (2H, s), 4.88 (2H, s), 4.30 (2H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 170.13, 143.17, 121.48, 122.68, 122.53, 116.90, 116.70, 67.41, 64.63, 57.97; **LRMS** (ESI+): 449 $[M+Na]^+$, 874.6 $[2M+Na]^+$; **HRMS** (ESI+): found 449.1144, $C_{20}H_{16}O_3N_6F_2Na$ M^+ 449.1150.

InChI=1S/C20H16F2N6O3/c21-14-1-5-18(6-2-14)27-9-16(23-25-27)11-30-13-20(29)31-12-17-10-28(26-24-17)19-7-3-15(22)4-8-19/h1-10H,11-13H2

All attempts: http://malaria.ourexperiment.org/uri/692, http://malaria.ourexperiment.org/uri/693, http://malaria.ourexperiment.org/uri/694 and http://malaria.ourexperiment.org/uri/695

2-{[1-(4-Fluorophenyl)-1H-1,2,3-triazol-4-yl]methoxy}acetamide, OSM-E-8



Representative example: http://malaria.ourexperiment.org/uri/3a5

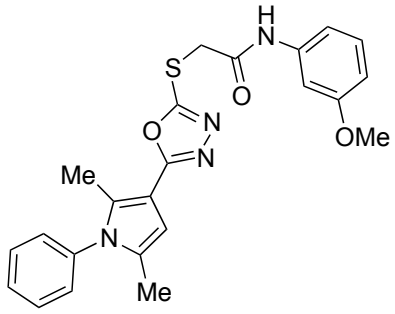
OSM-E-6 (24 mg, 90 μmol) was suspended in MeOH (2 mL) and ammonia (4 mL, saturated aqueous) and stirred for 1 h, then concentrated *in vacuo* to give the title compound as a white solid (22 mg, 98%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.98 (1H, s), 7.73 (2H, m), 7.27 (2H, m), 6.71 (1H, br s), 5.63 (1H, br s), 4.83 (2H, s), 4.13 (1H, s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 171.95, 163.61, 161.69, 144.51, 133.12, 122.66, 121.17, 116.80, 69.68, 64.51; **LRMS** (ESI+): 251.0 $[M+H]^+$, 273.0 $[M+Na]^+$, 522.6 $[2M+Na]^+$; **HRMS** (ESI+): found 251.0939, $C_{11}H_{12}O_2N_4F$ M^+ 251.0944.

InChI=1S/C11H11FN4O2/c12-8-1-3-10(4-2-8)16-5-9(14-15-16)6-18-7-11(13)17/h1-5H,6-7H2,(H2,13,17)

All attempts: http://malaria.ourexperiment.org/uri/696

13. Commercial Oxadiazole

2-((5-(2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)-1,3,4-oxadiazol-2-yl)thio)-*N*-(3-methoxyphenyl)acetamide, OSM-S-85



InChI=1S/C23H22N4O3S/c1-15-12-20(16(2)27(15)18-9-5-4-6-10-18)22-25-26-23(30-22)31-14-21(28)24-17-8-7-11-19(13-17)29-3/h4-13H,14H2,1-3H3,(H,24,28)

References for Chemical Protocols

[1] Gu, X. P.; Nishida, N.; Ikeda, I.; Okahara, M. 2-(Chloromethyl)-3,5-dioxahex-1-ene. An effective acetonylating reagent. *J. Org. Chem.* **1987**, *52*, 3192–3196. (10.1021/jo00391a003)

[2] Greiner, A.; Ortholand, J.-Y. Chirality transfer from lactic acid selective synthesis of 2,2-disubstituted-1,3-dioxolan-4-ones from ketones and acetals. *Tet. Lett.* **1990**, *31*, 2135–2138. (10.1016/0040-4039(90)80091-Y)

[3] Daryaee, F.; Kobarfard, F.; Khalaj, A.; Farnia, P. Synthesis and evaluation of *in vitro* anti-tuberculosis activity of *N*-substituted glycolamides. *Eur. J. Med. Chem.* **2009**, *44*, 289–295. (10.1016/j.ejmech.2008.02.022)

[4] Manetti, F.; Magnani, M.; Castagnolo, D.; Passsalacqua, L.; Botta, M. *et al*. Ligand-Based Virtual Screening, Parallel Solution-Phase and Microwave-Assisted Synthesis as Tools to Identify and Synthesize New Inhibitors of *Mycobacterium tuberculosis*. *Chem. Med. Chem.* **2006**, *1*, 973–989. (10.1002/cmdc.200600026))

[5] Gangjee, A.; Patel, J.; Kisliuk, R. L.; Gaumont, Y. 5,10-Methylenetetrahydro-5-deazafolic acid and analogs: synthesis and biological activities. *J. Med. Chem.* **1992**, *35*, 3678–3685. (10.1021/jm00098a013)

[6] Kazembe, T. C.-G.; Taylor, D. A. Synthesis of pyrrolo[1,2-a]indoles: vilsmeier formylation of some 3-methylindol-2-yl ketones and 3(3-methylindol-2-yl)propenoic ester. *Tetrahedron* **1980**, *36*, 2125–2132. (10.1016/0040-4020(80)80102-5)

[7] Dunetz, J. R.; Xian, Y.; Baldwin, A.; Ringling, J. General and Scalable Amide Bond Formation with Epimerization-Prone Substrates Using T3P and Pyridine. *Org. Lett.* **2011**, *13*, 5048–5051. (10.1021/ol201875q)

[8] Sudha, B. N.; Sridhar, C.; Reddy, Y. S. R.; Swathi, K.; Joythi, S.; Prasad, E. V. S.; Naresh, P.; Chakraborty, R.; Sen, S. Synthesis and characterization of several valinamide derivatives. *J. Chem. Pharm. Res.* **2010**, *2*, 410–414. (http://jocpr.com/vol2-iss4-2010/JCPR-2-4-410-414.pdf)

[9] Tripathi, M.; Verma, M.; Palit, G.; Shanker, K. Antipyrine congeners as antidepressant agents. *Arzneimittelforschung* **1993**, *43*, 1045–1049. (http://www.ncbi.nlm.nih.gov/pubmed/8267666)

[10] Lang, A.; Hatscher, C.; Wiegert, C.; Kuhl, P. Protease-catalysed coupling of N-protected amino acids and peptides with 4-aminoantipyrine. *Amino Acids* **2009**, *36*, 333–340. (10.1007/s00726-008-0074-1)

[11] Flatt, B.; Gu, X. H.; Martin, R.; Mohan, R.; Murphy, B.; Nyman, M.; Stevens, W. C.; Wang, T. L. Heterocyclic carboxamide compounds as steroid nuclear receptor ligands. *Patent WO2006076202* available at http://www.wipo.int/patentscope/search/en/WO2006076202, **2006**.

[12] Chiaki, S.; Shozo, I.; Atsushi, K.; Toshimasa, O.; Motoshige, T.; Manabu, U. Preparation process of aminoacetamide derivative. *Patent EP0714885 (A2)* available at http://worldwide.espacenet.com/publicationDetails/biblio?FT=D&date=19960605&DB=EPODOC&locale=en_EP&CC=EP&NR=0714885A2&KC=A2&ND=4, **1996**.

[13] Drabina, P.; Sedlák, M.; Růžička, A.; Malkov, A. V.; Kočovský, P. Synthesis of (R)- and (S)-2-N-methylamino-2,3-dimethylbutanamides and (R)- and (S)-(5-isopropyl-1,5-dimethyl-4,5-dihydro-1H-imidazol-4-on-2-yl)pyridines. *Tetrahedron: Asymmetry* **2008**, *19*, 384–390. (10.1016/j.tetasy.2008.01.016)

[14] De, S. K. Sulfamic Acid as a Novel, Efficient, Cost-Effective, and Reusable Solid Acid Catalyst for the Synthesis of Pyrroles under Solvent-Free Conditions. *Synth. Comm.* **2008**, *38*, 803–809. (10.1080/00397910701821051)

[15] Bhandari, S. V.; Bothara, K. G.; Patil, A. A.; Chitre, T. S.; Sarkate, A. P. *et al*. Design, Synthesis and Pharmacological Screening of Novel Antihypertensive Agents Using Hybrid Approach. *Bioorgan. Med. Chem.* **2009**, *17*, 390–400. (10.1016/j.bmc.2008.10.032)

[16] Urbano, M.; Guerrero, M.; Velaparthi, S.; Crisp, M.; Chase, P.; Hodder, P. *et al*. Discovery, synthesis and SAR analysis of novel selective small molecule $S1P_4$-R agonists based on a (2*Z*,5*Z*)-5-((pyrrol-3-yl)methylene)-3-alkyl-2-(alkylimino)thiazolidin-4-one chemotype. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6739–6745. (10.1016/j.bmcl.2011.09.049)

[17] Singh, T.; Sharma, P. K.; Mondal, S. C.; Kumar, N. Difference in Rate of Reaction of Some Thiazolidinone Derivatives with Synthesis and Spectral Characterization. *J. Adv. Sci. Res.* **2011**, *2*, 58–61. (http://www.sciensage.info/journal/1339778700JASR_2206111.pdf, accessed December 8th 2015)

[18] Ylioja, P. M. Reduction of 4-fluoro near-neighbour Michael-acceptor (PMY 36-2). *OSM ELN*, http://malaria.ourexperiment.org/near_neighbours/2237, **2012**.

[19] Ylioja, P. M. Reduction of 4-fluoro near-neighbour (N-H- Michael-acceptor (PMY 39-1). *OSM ELN*, http://malaria.ourexperiment.org/near_neighbours/2259, **2012**.

[20] Ylioja, P. M. Reduction of 4-fluoro near-neighbour Micheal-acceptor (PMY 36-1). *OSM ELN*, http://malaria.ourexperiment.org/near_neighbours/2181, **2012**.

[21] Ylioja, P. M. Testing reactivity of Michael-acceptor of ZYH 6-2 (PMY 41-1). *OSM ELN*, http://malaria.ourexperiment.org/near_neighbours/2523, **2012**.

[22] Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. Triazole-Au(l) Complexes: A New Class of Catalysts with Improved Thermal Stability and Reactivity for Intermolecular Alkyne Hydroamination. *J. Am. Chem. Soc.* **2009**, *131*, 12100–12102. (10.1021/ja9041093)

[23] Copyright Bio-Rad Laboratories. All Rights Reserved. Accessible through SciFinder, spectra for compound CAS: 5159-70-6.

[24] Chen, J.-X.; Liu, M.-C.; Yang, X.-L.; Ding, J.-C.; Wu, H.-Y. Indium (III)-catalyzed synthesis of *N*-substituted pyrroles under solvent-free conditions. *J. Braz. Chem. Soc.* **2008**, *19*, 1678–1790. (10.1590/S0103-50532008000500011)

[25] Copyright Bio-Rad Laboratories. All Rights Reserved. Accessible through SciFinder, spectra for compound CAS: 52034-37-4.

[26] Bhandari, S. V.; Bothar, K. G.; Patil, A. A.; Chitre, T. S.; Sarkate, A. P.; Gore, S. T.; Dangre, S. C.; Khachane, C. V. Design, Synthesis and Pharmacological Screening of Novel Antihypertensive Agents Under Hybrid Approach. *Bioorganic and Medicinal Chemistry*, **2009**, *17*, 390–400. (10.1016/j.bmc.2008.10.032)

[27] Caille, S.; Bercot, E. A.; Cui, S.; Faul, M. M. New Methods for the Synthesis of 2-Aminothiazolones. *J. Org. Chem.* **2008**, *73*, 2003–2006. (10.1021/jJo702369f)

[28] Mahboobi, S.; Sellmer, A.; Höcher, H.; Eichhorn, E.; Bär, T.; Schmidt, M.; Maier, T.; Stadlwieser, J. F.; Beckers, T. L. [4-(Imidazol-1-yl)thiazol-2-yl]phenylamines. A Novel Class of Highly Potent Colchicine Site Binding Tubulin Inhibitors: Synthesis and Cytotoxic Activity on Selected Human Cancer Cell Lines. *J. Med. Chem.* **2006**, *49*, 5769–5776 (10.1021/jm060545p)

[29] Preparation of 2,5-Dimethylpyrrole (http://www.lookchem.com/Chempedia/Chemical-Technology/Organic-Chemical-Technology/16247.html)

[30] http://www.sigmaaldrich.com/catalog/product/aldrich/d183601?lang=en&region=AU

[31] Pindur, U.; Flo, C. First reactions of dialkoxycarbenium tetrafluoroborates with pyrroles, 5*H*-dibenz[*b*,*f*]azepines and electron-rich arenes. *J. Heterocyclic Chem*. **1989**, *26*, 1563–1568. (10.1002/jhet.5570260611)

[32] Sakai, N.; Moriya, T.; Konakahara, T. An efficient one-pot synthesis of unsymmetrical ethers: a directly reductive deoxygenation of esters using and $InBr_3/Et_3SiH$ catalytic system. *J. Org. Chem.* **2007**, *72*, 5920–5922. (10.1021/jo070814z)

[33] Vachal, P.; Fletcher, J. M.; Hagmann, W. K. Direct functionalization of teriary alkyl bromides with O-, N-, and C-nucleophiles. *Tetrahedron Lett.* **2007**, *48*, 5761-5765. (10.1016/j.tetlet.2007.06.091)

[34] Sutherland, H. S.; Blaser, A.; Kmentova, I.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z.; Palmer, B. D.; Denny, W. A.; Thompson, A. M. Synthesis and structure-activity relationships of antitubercular 2-nitroimidazooxazines bearing heterocyclic side chains. *J. Med. Chem.* **2010**, *53*, 855–866. (10.1021/jm901378u)

[35] Menozzi, G.; Mosti, L.; Schenone, P. Reaction of 2-dimethylaminomethylene-1,3-diones with dinucleophiles. VI. Synthesis of ethyl or methyl 1,5-disubstituted 1*H*-pyrazole-4-carboxylates. *J. Heterocyclic Chem.* **2009**, *24*, 1669–1675. (10.1002/jhet.5570240634)

[36] Persson, T.; Nielsen, J. Synthesis of *N*-Methoxy-*N*-methyl-β-enaminoketoesters: New Synthetic Precursors for the Regioselective Synthesis of Heterocyclic Compounds *Org. Lett.* **2006**, *8*, 3219–3222. (10.1021/ol0611088)

[37] Schenone, P.; Mosti, L.; Menozzi, G. Reaction of 2-dimethylaminomethylene-1,3-diones with dinucleophiles. I. Synthesis of 1,5-disubstituted 4-acylpyrazoles. *J. Heterocyclic Chem.* **2009**, *19*, 1355–1361. (10.1002/jhet.5570190620)

[38] Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. Synthesis of 2-oxazolines and related N-containing heterocycles using $[Et_2NSF_2]BF_4$ as a cyclodehydration agent. *Tetrahedron Lett.* **2012**, *53*, 4121–4123. (10.1016/j.tetlet.2012.05.130)

[39] Altenbach, R. J.; Agrios.; K, Drizin, I.; Carroll, W. A. 5-Amino-2H-pyran-3(6H)-one, 1, a Convenient Intermediate in the Synthesis of Pyran Containing 1,4-Dihydropyridines. *Synth Commun.* **2004**, *4*, 557–565. (10.1081/SCC-120027702)

Biological Protocols for All Assays and Selected Biological Results

Table SB1. Evaluation of Resynthesized Hits and Potential Prodrug Fragments

Entry	Compound	IC_{50} (nM) (3D7[a,b,c])	K1 (nM)[c]	HEK293[c,d]
1	OSM-S-5	610, 818, 404, 177[e]	375	20
2	OSM-S-6	387, 245, 345	152	20
3	OSM-S-2	>1000, >5000, 60% at 120 μM	50% at 120 μM	25
4	OSM-S-3	>1000, >5000, 11960	12400	25
5	OSM-S-4	>1000, >5000, 75% at 120 μM	50% at 120 μM	20
6	chloroquine	21, 52.3, 18.7	266	100
7	artemisinin	6[c]	0.61	25
8	artesunate	19.4[b]	n/a	n/a

[a] Dataset S3 Ralph 1. [b] Dataset S4 GSK 1. [c] Dataset S5 Avery 1. [d] % inhibition at 120 μM. [e] Text S1 PRR Assay. n/a = not measured.

Table SB2. Evaluation of Synthetic and Commercial Amide Analogs (for structures see Fig SC2 in Text S1 Chemical Protocols)

Entry	OSM-S-	IC_{50} (μM)
1	19	inactive[a], >5[b], 25-80% at 80 μM[c]
2	21	inactive[a], >5[b], 31 μM - 100% at 80 μM[c]
3	8	inactive[a], >5[b], 100% at 80 μM[c]
4	59	inactive[d]
5	93	inactive[e]
6	81	inactive[e]
7	84	70% at 40 μM[e]
8	7	>>1[f], >5[g], 7.8 (3D7), 4.6 (K1)[h]
9	61	inactive[d]
10	83	inactive[e]
11	86	inactive[e]

12	87	85% at 40 μM[e]
13	85	inactive[e]
14	16	inactive[a], >5[b], inactive[c]

[a] 3D7, Dataset S8 Ralph 2, Text S3 Ralph 2, chloroquine control. [b] 3D7A, Dataset S9 GSK 2, chloroquine and artemisinin used as controls. [c] 3D7, Dataset S10 Avery 2, artemisinin, pyrimethamine, pyronaridine and chloroquine used as controls. [d] 3D7, Dataset S11 Avery 3a, artemisinin control. [e] 3D7, Dataset S12 Avery 3b, Fig S12 Avery 3b, artemisinin control (IC_{50} % inhibition at 120 μM.) [f] see footnote a, Table SB1. [g] see footnote b, Table SB1. [h] see footnote c, Table SB1.

Table SB3. Evaluation of Near Neighbour Series.

Entry	OSM-	IC_{50} (nM)	HEK293 IC_{50}[k]
1	S-35	11[d], 36[e], 26[f], 38[g], 12[l]	57[g]
2	S-10	201[a], 176 (3D7),[c] 361 (K1)[c], 32[l]	25% at 120 μM[c]
3	S-38	205[d], 29[e], 2[f]	
4	S-37	9[d], 28[e], 15[f], 161 (3D7),[i] 176 (K1)[i], 15[l]	
5	S-39	5[d], 7[e], 1[f], 121[l]	
6	S-48	339[d], 267[e], 169[f]	
7	S-109	262[g]	0[g]
8	S-111	146[g], 147 (3D7),[i] 204 (K1)[i]	32[g]
9	S-138	2300[h]	
10	A-1	3050 (3D7),[i] 4379 (K1)[i]	
11	A-2	574 (3D7),[i] 1829 (K1)[i]	
12	A-3	98 (3D7),[i] 140 (K1)[i]	
13	A-4	1745 (3D7),[i] 3162 (K1)[i]	
14	S-49	28[d], 85[e], 63[f]	
15	S-9	23[a], 47[b], 47 (3D7),[c] 66 (K1)[c]	75% at 120 μM[c]
16	S-45	8[d], 26[e], 12[f]	
17	S-50	156[d], 25[e], 326[f]	

18	S-54	520[d], 276[e], 34[f]	
19	S-52	485[d], 372[e], 54[f]	
20	L-1	3200 (3D7),[J] >5000 (K1)[J]	92[J]
21	S-110	2300[g]	26[g]
22	S-112	1600[g]	38[g]
23	S-114	1200[g]	42[g]
24	S-115	1800[g]	35[g]
25	S-51	442[d], 309[e], 307[f], 48[l]	
26	S-113	inactive[g]	
27	S-42	inactive[d], >5000[e], nd[f]	
28	S-43	inactive[d], >5000[e], 3120[f]	
29	S-108	1200[g]	44[g]
30	S-55	inactive[d], >5000[e], 100% at 40 μM[f]	

[a] Dataset S3 Ralph 1. [b] Dataset S4 GSK 1. [c] Dataset S5 Avery 1. [d] Dataset S8 Ralph 2, Text S3 Ralph 2. [e] Dataset S9 GSK 2. [f] Dataset S10 Avery 2. [g] Fig S13 Avery 4. [h] Dataset S14 Avery 5. [i] Dataset S15 Guy 1. [j] Fig S14 Batra, Text S4 Batra Controls, Text S5 Assay Protocol Batra, CC_{50} cytotoxicity (MTT) value in micromolar. [k] % inhibition at 40 μM unless otherwise stated. [l] Text S1 PRR Assay. nd = not determined due to solubility problem or optical interference.

Evaluation of Amine Analogs

OSM-S-58 and -60: Dataset S11 Avery 3a.
OSM-S-88, -89, -90, -94, -95: Fig S12 Avery 3b, Dataset S12 Avery 3b.

Table SB4. Evaluation of Modified Ester Analogs (All structures in Text S1 Chemical Protocols, Fig SC8)

Entry	OSM-S-	IC_{50} (nM)
1	116	11000[a]
2	68	inactive[b]
3	99	inactive[c]
4	100	inactive[c]
5	82	9400[d]
6	91	11300[d]

[a]Fig S13 Avery 4. [b] Dataset S11 Avery 3a. [c] Dataset S16 Avery 3c, Fig S26 Avery 3c. [d] Dataset S12 Avery 3b, Fig S11 Avery 3b.

Evaluation of Ketone Analogs

OSM-S-98, OSM-S-102, OSM-S-103: Dataset S16 Avery 3c, Fig S26 Avery 3c.

Evaluation of Sulfonamides (Structures in Fig SC10)

OSM-E-1, OSM-E-2, OSM-E-3: Dataset S17 Dundee 1.

Evaluation of Pyrazoles (Structures in Fig SC11)

OSM-S-57: Dataset S11 Avery 3a
OSM-S-92: Dataset S12 Avery 3b, Fig S11 Avery 3b

Evaluation of Oxazoles (Structures in Fig SC12)

OSM-S-61 and -62: Dataset S11 Avery 3a
OSM-S-96, -101, -104 and -105: Dataset S16 Avery 3c, Fig S26 Avery 3c

Evaluation of Triazoles (Structures in Fig SC13)

OSM-E-4, OSM-E-5, OSM-E-6, OSM-E-7, OSM-E-8: Dataset S18 Dundee 2

Potency Evaluation, Ralph Data, Round 1
Corresponding raw data may be found in **Dataset S3 Ralph 1**.
Method: Screening performed using a malaria SYBR green I- based fluorometric assay. Asynchronous parasites (standard laboratory strain 3D7) were prepared in 96-well plates for a twofold-dilution of the compounds (highest concentration = 1000 nM). Chloroquine was used as a positive control, negative control was vehicle alone (1% DMSO) and a lane of red blood cells served for subtraction of background. Parasites were grown for 48 h (Gamo *et al*[1] did 72 h incubation to include possible delay death effects).
Original location: http://malaria.ourexperiment.org/biological_data/1389

Potency Evaluation, Ralph Data, Round 2
Corresponding raw data may be found in **Dataset S8 Ralph 2** and **Text S3 Ralph 2**.
Method: Compounds were tested for inhibition of Plasmodium falciparum growth using a SYBR green I fluorescence based assay. Dose response curves were generated comprising of 8 points using a 2-fold serial dilution for the maximum final concentration of 1000 nM. The lowest concentration tested was 7.81 nM.
Original location: http://malaria.ourexperiment.org/biological_data/3152

Potency Evaluation, GSK Data, Round 1
Corresponding raw data may be found in **Dataset S4 GSK 1**.
Method: Literature methods.[2] Strain: 3D7A.
Original location: http://malaria.ourexperiment.org/biological_data/1438

Potency Evaluation, GSK Data, Round 2
Corresponding raw data may be found in **Dataset S9 GSK 2**.
Method: Control "ARTE" is artemisinin.

Original location: http://malaria.ourexperiment.org/biological_data/2722

Potency Evaluation, Avery Data, Round 1
Corresponding raw data may be found in **Dataset S5 Avery 1**.
Method: IC_{50} values determined from 21 point dose response curves for both K1 and 3D7 strains. This was performed in two separate screening rounds, 4 data points per dose. Plus, HEK-293 cytox data - duplicate point single experiment.
Original location: http://malaria.ourexperiment.org/biological_data/1393

Potency Evaluation, Avery Data, Round 2
Corresponding raw data may be found in **Dataset S10 Avery 2**.
Method: As for Avery Round 1.
Original Location: http://malaria.ourexperiment.org/biological_data/2430

Potency Evaluation, Avery Data, Round 3a
Corresponding raw data may be found in **Dataset S11 Avery 3a**.
Method: Artemisinin control. 3D7.
Original location: http://malaria.ourexperiment.org/biological_data/5010

Potency Evaluation, Avery Data, Round 3b
Corresponding raw data may be found in **Dataset S12 Avery 3b** and **Figure S11 Avery 3b**
Original location: http://malaria.ourexperiment.org/biological_data/5521

Potency Evaluation, Avery Data, Round 3c
Corresponding raw data may be found in **Dataset S16 Avery 3c and Figure S26 Avery 3c**
Method: 3D7.
Original location: http://malaria.ourexperiment.org/biological_data/5981

Potency Evaluation, Avery Data, Round 4
Corresponding raw data may be found in **Figure S13 Avery 4**
Original location: http://malaria.ourexperiment.org/biological_data/6734

Potency Evaluation, Avery Data, Round 5
Corresponding raw data may be found in **Dataset S14 Avery 5**
Original location: http://malaria.ourexperiment.org/biological_data/7372

Potency Evaluation, Batra Data
Corresponding raw data may be found in **Figure S14 Batra**
Method: Detailed in **Text S4 Assay Protocol Batra.** Controls: CQ and OSM-S-5 (PMY 10-6) described in **Text S5 Batra Controls**.
Original location: http://malaria.ourexperiment.org/biological_data/2982

Potency Evaluation, Dundee Data, Round 1
Corresponding raw data may be found in **Dataset S17 Dundee 1**
Original location: http://malaria.ourexperiment.org/biological_data/7446

Potency Evaluation, Dundee Data, Round 2
Corresponding raw data may be found in **Dataset S18 Dundee 2**
Original location: http://malaria.ourexperiment.org/biological_data/7709

Potency Evaluation, Guy Data 1
Corresponding raw data may be found in **Dataset S15 Guy 1**
Method: Two *P. falciparum* strains were used in this study and were provided by the MR4 Unit of the American Type Culture Collection (ATCC, Manassas, VA). Those two strains were the chloroquine sensitive strain 3D7 and the chloroquine resistant strain K1.
Growth of parasites and IC50 determinations. Asynchronous parasites were maintained in culture based on the method of Trager.[3] Parasites were grown in presence of fresh group O-positive erythrocytes (Key Biologics, LLC, Memphis, TN) in Petri dishes at a hematocrite of 4% in RPMI based media (RPMI 1640 supplemented with 0.5% AlbuMAX II, 25 mM HEPES, 25 mM $NaHCO_3$ (pH 7.3), 100 µg/mL hypoxanthine, and 5 µg/mL gentamycin). Cultures were incubated at 37°C in a gas mixture of 90% N_2, 5% O_2, 5% CO_2. For IC_{50} determinations, 20 µL of RPMI 1640 with 5µg/mL gentamycin were dispensed per well in an assay plate (Corning 384-well microtiter plate, clear bottom, tissue culture treated, catalog no. 8807BC). An amount of 60 nL of compound, previously serial diluted in a separate 384-well white polypropylene plate (Corning, catalog no. 8748BC), was dispensed to the assay plate by hydrodynamic pin transfer (FP1S50H, V&P Scientific Pin Head) and then an amount of 20 µL of a synchronized culture suspension (1% rings, 4% hematocrite) was added per well, thus making a final hematocrite and parasitemia of 2% and 1%, respectively. Assay plates were incubated for 72 h, and the parasitemia was determined by a method previously described.[4] Briefly, an amount of 10 uL of the following solution in PBS (10X Sybr Green I, 0.5% v/v triton, 0.5 mg/mL saponin) was added per well. Assay plates were shaken for 1 min, incubated in the dark for 90 min, then read with the Envision spectrophotomer at Ex/Em of 485 nm/535 nm. IC_{50}s were calculated with the robust investigation of screening experiments (RISE) with four-parameter logistic equation.
Original location: http://malaria.ourexperiment.org/biological_data/11103

Table SB5. Solubility and Metabolic Stability of Selected Compounds

OSM-S-	Kinetic Solubility (µg/mL)[a]	Degradation Half Life in Human Liver Microsomes (min)	*in vitro* CL_{int} (µL/min/mg protein)	Degradation Rate Classification
5	50.0–100.0	59	29	moderate
6	12.5–25.0	29	60	moderate
9	<1.6	*(rapid hydrolysis of test compound to OSM-S-10)*		
10[b]	<1.6	113	15	moderate
10[c]		92	19	moderate
37[d]	<1.6	245	7	Low
38[b]	<1.6	>250	<7	Low
38[c]		>250	<7	Low
39[b]	<1.6	>250	<7	Low
39[c]		>250	<7	Low
54[d]	<1.6	121	14	moderate
111[e]	1.6–3.1[f]	207	8	Low

[a]Values the same at pH 2 and 6.5; [b]Major isomer, earlier retention time; [c]Minor isomer, later retention time; [d]Isomers were present, but did not separate, so had to be integrated together. [e]Values for OSM-S-111 from Dataset S21 Charman 2, all others from Dataset S20 Charman 1. [f]Range is for pH 2; at pH 6.5 value is <1.6. For structures see: Fig 2 (OSM-S-5 and -6) or Fig 4.

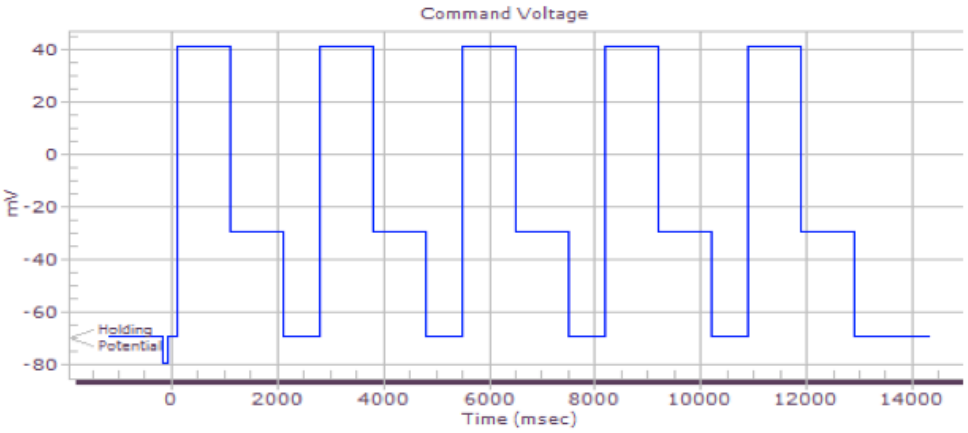
Charman Data Round 1
Corresponding raw data may be found in **Dataset S20 Charman 1**
Method: Note that the <1.6 µg/mL solubility window means that the solubility was less than the lowest concentration tested which in this assay is 1.6 µg/mL. Method used identical to method described below for Dataset S21 Charman 2. The rate of metabolism for the acyl substituted compound OSM-S-9 could not be determined since it was observed to rapidly hydrolyse to the parent compound, OSM-S-10. For three of the compounds (OSM-S-10, -38 and -39) two isomeric peaks were present in the chromatogram with peak area ratios being approximately 4:1 and remaining constant throughout the course of the degradation experiment.
Original location: http://malaria.ourexperiment.org/biological_data/3101

Charman Data Round 2
Corresponding raw data may be found in **Dataset S21 Charman 2**
Methods:
Kinetic Solubility Assessment
10 mg/mL DMSO stock solutions of each compound were diluted 1:100 into aqueous test media (either pH 2 0.01 M HCl or pH 6.5 phosphate buffer) in a 96-well plate. Serial dilutions were then conducted to provide final concentrations of compound over the range of 1.6 to 100 µg/mL. Plates were allowed to stand for 30 minutes at room temperature, after which the extent of compound precipitation in each well was measured by nephelometry. The kinetic solubility range was determined as being between the concentrations where precipitation was detected and absent. Note that 1.6 µg/mL was the lowest concentration tested.

Metabolic Stability Assay
A solution of each test compound (and quality control compounds) prepared in 50% acetonitrile/water was spiked into microsomal matrix (human liver microsomes from XenoTech LLC, Lenexa, Kansas City, suspended in 0.1 M phosphate buffer, pH 7.4) at a compound concentration of 1 µM and a protein concentration of 0.4 mg/mL, and incubated at 37 ˚C. The reaction was initiated by the addition of NADPH (the cofactor for CYP450-mediated metabolism) and then quenched at various time points over a 60 minute period by the addition of ice-cold acetonitrile. Additional control samples were also included to monitor for potential compound degradation in the absence of cofactor. Quenched samples were centrifuged for 3 min at 10,000 rpm to remove microsomal proteins and the amount of parent compound remaining in the supernatant quantified by UPLC-MS (Waters Micromass Xevo G2 QTOF coupled to a Waters Acquity UPLC) to determine the extent and rate of loss of parent compound. The depletion rate constant for each compound was used to calculate a degradation half-life and *in vitro* intrinsic clearance as previously described.[5]
Original location: http://malaria.ourexperiment.org/biological_data/7661

hERG assay
Assay performed by Essen Bioscience 17th April 2012
Corresponding data may be found in **Dataset S26 hERG.**
Method: Compounds were tested for inhibition of the human ether a go-go related gene (hERG) K^+ channel using IonWorks patch clamp electrophysiology. 8-Point concentration-response curves were generated using 3-fold serial dilutions from the maximum final assay concentration shown in **Text S9 hERG Curves**.

Electrophysiological recordings were made from a Chinese Hamster Lung cell line stably expressing the full length hERG channel. Single cell ionic currents were measured in the perforated patch clamp configuration (100 μg mL^{-1}) amphoterocin) at room temperature (21-23 °C) using an IonWorks Quattro instrument. The internal solution contained (mM): 140 KCl, 1 $MgCl_2$, 1 EGTA, 20 HEPES and was buffered to pH 7.3. The external solution contained (mM): 138 NaCl, 2.7 KCl, 0.9 $CaCl_2$, 0.5 $MgCl_2$, 8 Na_2HPO_4, 1.5 KH_2PO_4 also buffered to pH 7.3. Cells were clamped at a holding potential of –70 mV for 30 s and then stepped to +40 mV for 1 s. This was followed by a hyperpolarising step of 1 s to –30 mV to evoke the hERG tail current. This sequence was repeated 5 times at a frequency of 0.25 Hz. Currents were measured from the tail step at the 5th pulse, and referenced to the holding current. Compounds were then incubated for 6–7 minutes prior to a second measurement of the hERG signal using an identical pulse train.



The following QC conditions were applied:

(1) Individual cells with any of the following properties were excluded from subsequent analysis: (1) seal resistances <50 MOhms (2) hERG currents <150 pA (3) seal resistances that changed by >50% during the experiment

(2) A minimum of 17 cells were required for each pIC_{50} curve fits

(3) pIC_{50} curve fits with a 95% confidence limit of > ±0.5 log were failed

(4) Entire assay plates in which the pIC_{50} of the standard compound (quinidine) was outside of the normal range [5.6–6.3] were failed.

Original location of data: http://malaria.ourexperiment.org/biological_data/2999
Original description of results: http://www.thesynapticleap.org/node/402

Avery Late Stage Gametocyte Assay 1
Corresponding data may be found in **Dataset S27 Avery LSG**
Method: Four compounds from the arylpyrrole series tested in a late stage anti-gametocyte imaging assay. The assay involves the use of a Pfs16-GFP transgenic NF54 Plasmodium falciparum strain kindly provided by Dr David Fidock (Columbia University).

Compounds were benchmarked against a range of positive and negative controls:

Controls	
Chloroquine	86% at 120 μM
Pyrimethamine	50% at 120 μM
Tafenoquine	2800
Pyronaridine	2960
Epoxomicin	0.3
Artemisinin	2.4 nM (67% max response)
Artesunate	1.1 nM (88% max response)

All data were normalised to 5 μM puromycin and expressed as % inhibition for calculation of IC_{50} values.

Compound is added to 384 well imaging plates containing 20,000 highly synchronous late stage IV gametocytes. The plates are incubated for 72 hours in standard incubation conditions (5% CO_2, 5% O_2, 37 ºC, 5% humidity). After incubation the viability marker MitoTracker Red CM-H 2 XRos is added to the wells. The plates are then imaged on the OPERA confocal high-throughput imaging system. The images obtained are then analysed using an algorithm for determining the number of viable gametocytes still remaining in the compound treated wells based on viability marker fluorescent intensity and the morphology of the GFP expressing parasite.

The number of gametocytes per well in this assay is the same number of parasites used in the asexual imaging assay for 3D7 and K1.

Note: It has to be noted that the compounds have been in storage for a while and the plates defrosted several times for screening. The inactive compound could have lost asexual activity at the same time due to some instability. This was not tested.

Effect on Parasite Morphology

Viable gametocytes have an elongated solid green fluorescent protein (GFP) morphology and a MitoTracker Red CM-H_2XRos (MTR) fluorescent staining pattern of a small intense spot within the GFP body of the gametocyte image. The MTR object is classified based on its relative fluorescent intensity, radius and contrast to background. Gametocytes when treated with 5 μM puromycin lose the elongated morphology, becoming a small disorganised object with no classified MTR objects. Essentially the gametocytes are destroyed in structure and have no centralised or recognisable MTR signal. Gametocytes treated with OSM-S-111 demonstrated a different phenotype to puromycin treated

gametocytes. The parasite morphology is still intact as demonstrated by the GFP fluorescence but the MTR signal has no concentrated spot of intensity. There is a small low fluorescent MTR staining pattern distributed throughout the parasite structure but there is no singular intense localised MTR signal to identify as an active mitochondrion. Compounds with this phenotype may be determined as not active if Giemsa staining and light microscopy were performed to determine compound action. This phenotype was seen for small numbers of other compounds tested in the same assay. At present the reason for the occurrence of this different phenotype is not clear, but it is possible that it could be related to a slow acting mechanism whereby the parasite slowly dies due to a direct effect on mitochondrial metabolism but not exclusively so. As the compound action is slow, the parasite structure is still intact within the assay time frame of a total of 96 hours. Compounds with this activity phenotype have not yet been tested for longer treatment times as the total of 96 hours is already a significant activity timeframe.

Original location: http://malaria.ourexperiment.org/biological_data/3066

Avery Late Stage Gametocyte Assay 2
Corresponding data may be found in **Dataset S28 Avery LSG2**
Method: As above
Original location: http://malaria.ourexperiment.org/biological_data/8329

Imperial DGFA Assay
Corresponding data may be found in **Text S10 DGFA**
Method: As per data file
Original location: http://malaria.ourexperiment.org/biological_data/13764

***In Vivo P. berghei* Assay**
Corresponding raw data may be found in **Dataset S22 Berghei**
Method: A *p.o. Plasmodium berghei* mouse study at 50 mg/kg revealed no efficacy of OSM-S-35 (ZYH 3-1), OSM-S-5 (TCMDC-123812) or OSM-S-6 (TCMDC-123794) relative to control. Experiments carried out in the group of Dr Sergio Wittlin at Swiss TPH (Unit of Prof. Reto Brun). Compounds assessed against the *P. berghei* GFP ANKA strain *in vivo*. Mice infected intravenously with parasitized red blood cells on day 0 (2 x 107 parasitized erythrocytes per mL). Experimental mice are generally treated at 4, 24, 48, and 72 hours post-infection with an oral dose of the compound (4-day test by Peters) and are compared to an infected control group for reduction in parasitaemia on day 4 (96 hours post-infection) in % and for mean survival (monitored up to 30 days post-infection). A compound is considered curative, if the animal survives to day 30 after infection with no detectable parasites. Other delivery route (intravenous, intraperitoneal, subcutaneous) and dosing regimen (e.g. single dose) are possible. Percent activities below 40% are regarded as inactive.
Original location: http://malaria.ourexperiment.org/biological_data/3160

P. berghei Pharmacokinetics Measurements
Corresponding raw data may be found in **Dataset S23 Berghei PK**
Method: Frozen plasma samples collected from *in vivo P. berghei* were assayed for quantity of OSM-S-5 at 1, 4 and 24 hours. OSM-S-5 was taken to have a 3D7 IC_{50} of 0.4–0.8 μM, for the purposes of the calculation.
Original location: http://malaria.ourexperiment.org/biological_data/3825

Charman Plasma Stability Studies
Corresponding raw data may be found in **Dataset S24 Charman Plasma.**

Method: The stability of OSM-S-5 in human and mouse plasma was assessed *ex vivo* by spiking the compound into human plasma (plasma from the Australian Red Cross Blood Service and pooled from three individual donors) or mouse plasma (pooled from male Swiss outbred mice) at a nominal compound concentration of 500 ng/mL. Spiked plasma samples were incubated at 37°C with aliquots taken at various time points over 240 minutes and snap frozen in dry-ice to prevent further degradation. Following protein precipitation with acetonitrile and centrifugation, the amount of OSM-S-5 remaining in the supernatant of each sample was quantified by UPLC (Waters Micromass Quattro Premier coupled to a Waters Acquity UPLC) and compared to the concentration present at 2 minutes. The activity of esterases in the human and mouse plasma used in this assay was confirmed qualitatively by assessing the hydrolysis of *p*-nitrophenol acetate to *p*-nitrophenol in a parallel set of incubations.
Original location: http://malaria.ourexperiment.org/biological_data/3598

Charman Glutathione Trapping Experiments
Corresponding raw data may be found in **Dataset S25 Charman Glutathione.**
Method: In order to promote metabolite formation for the purpose of detection and identification, OSM-S-35 was incubated in human liver microsomes (XenoTech LLC, Lenexa, Kansas City) at a concentration of 10 µM and a protein concentration of 1 mg/mL. The reaction was initiated by the addition of NADPH and samples were incubated at 37°C for up to 120 minutes. Glutathione ethyl ester (GSH-EE, 1 mM) was included for the purpose of trapping reactive species formed during the incubation. Paracetamol was included as a positive control to confirm the ability of the test system to detect reactive metabolites in the presence of GSH-EE. Incubations without NADPH were also included as controls. At selected time points, samples were quenched by addition of ice-cold acetonitrile, and following centrifugation (3 min at 10,000 rpm) the supernatant was removed and analysed for metabolite formation by LCMS (Waters Micromass Xevo G2 QTOF coupled to a Waters Acquity UPLC). The identity of putative metabolites was confirmed by accurate mass and high collision energy data where possible.
Original location: http://malaria.ourexperiment.org/biological_data/6729

Liver Stage Assay
Corresponding raw data may be found in **Dataset S29 Liver Stage**
Method:
Parasites: *P. berghei* Luciferase sporozoites are obtained by dissection of infected *Anopheles stephensi* mosquito salivary glands supplied by the New York University Insectary. Dissected salivary glands were homogenized in a glass tissue grinder and filtered twice through Nylon cell strainers (40 µm pore size, BD Falcon), spun down at 10,000 × g, resuspended in media and counted using a hemocytometer. The sporozoites are diluted to a final concentration of 200 sporozoites per µL and kept on ice until needed.

Cell lines: HepG2-A16-CD81EGFP cells stably transformed to express a GFP-CD81 fusion protein,[6] are cultured at 37 ˚C in 5% CO_2 in DMEM (Invitrogen, Carlsbad, USA) supplemented with 10% FCS, 0.29 mg/mL glutamine, 100 units penicillin and 100 µg/mL streptomycin.

Sporozoite invasion assay: 3×10^3 HepG2-A16-CD81EGFP cells in 5 µL of medium (2×10^5 cells/mL, 5% FBS, 5xPen/Strep/Glu) are seeded in 1536-well plates 20–26 hours prior to the actual infection. 18 hours prior to infection, 50 nL of compound in DMSO (0.5% final DMSO concentration per well) are transferred with a PinTool (GNF Systems) into the assay plates (10 µM final concentration). Atovaquone and 0.5% DMSO are used as positive and negative controls, respectively. Penicillin and streptomycin are added to the sporozoite preparation for a final 5×-fold increased concentration in the well. The HepG2-A16-CD81EGFP cells were then infected with 10^3 sporozoites

per well (5 μL) with a single tip Bottle Valve liquid handler (GNF), and the plates spun down at 37°C for 3 minutes in an Eppendorf 5810 R centrifuge with a centrifugal force of 330× on lowest acceleration and brake setting. After incubation at 37 ˚C for 48 hours the EEF growth was quantified by bioluminescence.

Bioluminescence quantification of exo-erythrocytic forms (EEFs): Media is removed by spinning the inverted plates at 150 × g for 30 seconds. 2 μL BrightGlo (Promega) are dispensed with the MicroFlo (BioTek) liquid handler. Immediately after addition of the luminescence reagent, plates are vortexed at the median intensity setting for 10 seconds and read by the Envision Multilabel Reader (PerkinElmer). IC_{50} values are obtained using measured bioluminescence intensity and a non-linear variable slope four parameter regression curve fitting model in Prism 6 (GraphPad Software Inc).
Original location: http://malaria.ourexperiment.org/biological_data/7840

Nislow Mode of Action Studies

Compounds originally evaluated:

Actives: OSM-S-5, -6, -9, -10, -35, -37, -39 and -51 (structures shown in paper Figs 2 and 4) Inactives: OSM-S-19, -21 and -55 as well as inactive *N*-phenyl pyrrole carboxylic acid and ester fragments OSM-S-12 and -31 (for structures see Dataset S3 Ralph 1, Dataset S4 GSK 1 and Dataset S5 Avery 1).

Briefly, compounds were dissolved in DMSO and titrated to determine a dose that inhibited wild-type yeast at approximately 20%. For those cases in which compounds did not show detectable inhibition of wild type yeast, compounds were screened at the solubility maximum. Mutants comprising the entire yeast genome as 1200 barcoded heterozygous diploids and 4800 non-essential homozygous diploids were screened in parallel, ranked according to their sensitivity and analyzed using Gene Set Enrichment Analysis[118] to identify any sensitive biological processes. Significant enrichments were detected for OSM-S-9, -31 and -51.

Corresponding raw data may be found in **Dataset S32 Nislow1** (log2 intensity ratios (control/treatment) which are proportional to the strains sensitivity to the compound. Also contains a list of sensitive genes for all compound tested and a description of the cellular compartment, the metabolic process and the gene function for each strain), **Dataset S33 Nislow2** (Spotfire file containing all data plots), **Dataset S34 Nislow3** (Powerpoint file of data plots; Y axis shows log2 ratios (control/treatment), X axis shows genes), **Dataset S35 Nislow4** (Excel file of the fitness defect scores for all deletion strains) and **Figure S32 Nislow9**, **Figure S33 Nislow12**, **Figure S34 Nislow31**, **Figure S35 Nislow39** and **Figure S36 Nislow51** for the enrichment maps for OSM-S-9 (500 μM), -12 (1 mM), -31 (1 mM), -39 (500 μM) and -51 (125 μM) respectively.

Cytoscape Maps. Biological processes associated with sensitivity to the compounds. Each node represents a biological process significantly enriched amongst genes associated with sensitivity to a compound (FDR ≤ 0.1). The size of a node is proportional to the level of significance at which the process is enriched [i.e. proportional to $-\log_{10}(\text{FDR})$]. The width of an edge is proportional to the level of gene overlap between the two connected processes. Edges are not shown where the overlap coefficient is less than 0.5. The color of a node shows cluster membership, where clustering is based on the level of overlap between processes and thus groups together related processes.

Method:

Gene-set Enrichment Analysis (GSEA)

GSEA[7] was used to identify biological processes enriched amongst genes associated with sensitivity to the compounds, when individually deleted in diploid deletion strains. Specifically, the chemogenomic profile of each compound was analyzed by GSEA v2.07 in pre-rank mode (Java implementation). All default parameters were used except that the minimum and maximum gene set sizes were restricted to 5 and 300, respectively. Our gene sets were defined with Gene Ontology biological process gene annotations obtained from the *Saccharomyces* Genome Database on May 26, 2012.

The enrichment maps were generated with the Enrichment Map Plugin v1.2[8] developed for Cytoscape.[9] All default parameters were used. For each node (i.e. enriched gene set) in each map, we computed *significance* = $-\log_{10}$(FDR) where FDR was estimated by GSEA. For nodes were *significance* equals infinity, *significance* was changed to equal 2 + the maximum non-infinite *significance* value in the given map. Node sizes were changed to be proportional to *significance*. In addition, the nodes in the map were clustered with the Markov clustering algorithm,[10] using the overlap coefficient computed by the plugin as the similarity metric (coefficients less than 0.5 were set to zero) and an inflation of 2. Node colors were changed to indicate cluster membership.

Original location: http://malaria.ourexperiment.org/biological_data/5911

Methods associated with ***Dataset S35 Nislow4***

File lists the significantly sensitive strains derived from Tag4 microarray hybridizations as described in the literature.[11]

Raw data normalization and removal of problematic tags: Each probe on the Genflex tag16k array (Affymetrix, Santa Clara, CA), i.e. the Tag4 array, is represented by 5 replicate features. These replicates allow the removal of outliers that may for example, arise from small debris in the hybridization solution. To identify and remove probes defined as outliers, we used a previously described masking algorithm. We next defined the 'raw average' of each tag as the average of all remaining probe replicates for a particular tag. We then removed all tags corresponding to the control strain. For each array, uptags and downtags were normalized separately, as were heterozygous and homozygous strains, creating 4 sets: uptag/het, uptag/hom, downtag/het, downtag/hom. To simplify our dataset, we removed strains where the deletions no longer correspond to valid genes according to the Saccharomyces Genome Database (SGD).

The fitness defect (FD) score: We devised a fitness defect (FD) score that quantifies the sensitivity of each deletion strain to a chemical perturbation by comparing the signal of a strain following chemical treatment to the signal of the strain from control samples (i.e. DMSO-treated samples). Specifically, log2ratios were calculated for each strain as follows: log2ratio = log2[chemical/DMSO control]

Identification of significant chemical-genetic interactions: We defined significant chemical-genetic interactions by identifying FD scores that deviated significantly from other FD scores in a given screen (heterozygous and homozygous strains were considered separately). This approach is based on the assumption that, at chemical concentrations that only minimally inhibit growth of the pool, most strains will not exhibit a fitness defect.

Original location: http://malaria.ourexperiment.org/biological_data/5911

Parasite Rate of Reduction (PRR, "Rate of Killing") assay

Corresponding raw data may be found in **Text S1 PRR Assay** and **Figure S37 PRR Data**

Method: Described in **Text S1 PRR Assay**

Original Location: http://malaria.ourexperiment.org/biological_data/13274

***In Silico* Prediction of Target**
Corresponding raw data may be found in **Text S11 Wallace**
Method: Computationally predicted protein targets were calculated based on the compound structure information using a statistical model derived from the ChEMBL database. Specifically, we used a multi-category Naive Bayes statistical model that identifies compound structural features (specific sets of atoms and bonds generated using the ECFP_4 fingerprint) that are correlated with a particular data class (i.e. protein target). A set of active compounds was created for proteins in the ChEMBL database for which at least 50 compounds (to ensure a robust model) were annotated to an activity <10 μM. A multi-category model was then built with PipelinePilot for each of these compounds (i.e. active against this protein) versus all of the other compounds (assumed inactive). By scoring each compound with all 1,287 models, a ranked list of up to the top 50 predicted protein targets (with a model score >0) for each compound is generated. The scores for each individual protein target were standardized by comparing to the scores obtained for a random set of >10,000 compounds.
Original location: http://malaria.ourexperiment.org/in_silico_prediction/2675

DHODH Assay
Corresponding raw data may be found in **Dataset S36 DHODH**
Method: See **Text S12 DHODH**
Original location: http://malaria.ourexperiment.org/biological_data/10811

Kirk Ion Regulation Assay
Corresponding raw data may be found in **Dataset S37 Ion Regulation** and **Figure S38 Ion Regulation**
Method: Compounds were tested at 150 μM and 1 μM. At 150 μM OSM-S-5 appeared to increase [Na+]i within the parasite. At 150 μM OSM-S-4 did not cause an increase in [Na+]i, and the remaining four compounds (35, 51, 106, 111) caused an 'optical effect'. In this assay, excitation wavelengths are 340 nm and 380 nm, while emission is measured at 520 nm. An 'optical effect' occurs when the addition of a compound causes a disturbance at one of these wavelengths.
At 1 μM OSM-S-4, OSM-S-5 and OSM-S-111 showed no effect on [Na+]i within the parasite, and OSM-S-35, OSM-S-51 and OSM-S-106 showed slight 'optical effects'.
Fluorescence intensity (FI) was calibrated to [Na+]i for the traces showing compounds tested at 150 μM. Fluorescence intensity was not calibrated for traces showing compounds tested at 1 μM. Control: NITD246
Original location: http://malaria.ourexperiment.org/biological_data/10343

Similarity Mapping
Corresponding raw data may be found in **Dataset S38 Wallace Similarity**
Method: All compounds (nodes) were compared to each other, and were connected with an edge if they possessed a similarity of >0.3 using ECFP_4 fingerprints and a Tanimoto similarity. Original network generated with Pipeline Pilot and visualized using Cytoscape (http://www.cytoscape.org/), requiring ChemViz (http://www.cgl.ucsf.edu/cytoscape/chemViz/) plugin, allowing one to right-click a node and view the structure and to view the target of the compound.[12] See also **Figure S39 Wallace Similarity**
Original location: http://malaria.ourexperiment.org/in_silico_prediction/2913

References for Biological Protocols

[1] Gamo, F. J; Sanz, L. M.; Vidal, J.; de Cozar, C.; Alvarez, E. *et al.* Thousands of chemical starting points for antimalarial lead identification. *Nature* **2010**, *465*, 305–310. (10.1038/nature09107)

[2] Calderón, F.; Barros, D.; Bueno, J. M.; Coterón, J. M.; Fernández, E.; Gamo, F. J. *et al*. An invitation to open innovation in malaria drug discovery: 47 quality starting points from the TCAMS. *ACS Med. Chem. Lett.* **2011**, *2*, 741–746. (10.1021/ml200135p)

[3] Trager, W.; Jensen, J. B. Human malaria parasites in continuous culture. *Science* **1976**, *193*, 673–675. (10.1126/science.781840)

[4] Smilkstein, M.; Sriwilaijaroen N.; Kelly, J. X.; Wilairat, P.; Riscoe, M. Simple and inexpensive fluorescence-based technique for high-throughput antimalarial drug screening. *Antimicrob. Ag. Chemother.* ***2004,*** *48*, 1803–1806 (10.1128/AAC.48.5.1803-1806.2004)

[5] Obach, R. S. Prediction of human clearance of twenty-nine drugs from hepatic microsomal intrinsic clearance data: an examination of in vitro half-life approach and nonspecific binding to microsomes. *Drug Metab. Dispos.* **1999**, *27*, 1350–1359

[6] Silvie, O. O.; Greco, C. C.; Franetich, J. F. J.; Dubart-Kupperschmitt, A. A.; Hannoun, L. L.; van Gemert, G. J. G. *et al.* Expression of human CD81 differently affects host cell susceptibility to malaria sporozoites depending on the Plasmodium species. *Cellular Microbiology* **2006**, *8*, 1134–1146. (10.1111/j.1462-5822.2006.00697.x)

[7] Subramanian, A.; Tamayo, P.; Mootha, V. K.; Mukherjee, S.; Ebert, B. L.; Gillette, M. A. *et al.* Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 15545–15550. (10.1073/pnas.0506580102)

[8] Merico, D.; Isserlin, R.; Stueker, O.; Emili, A.; Bader, G. D. Enrichment map: a network-based method for gene-set enrichment visualization and interpretation. *PLoS ONE* **2010**, *15*, e13984. (10.1371/journal.pone.0013984)

[9] Smoot, M. E.; Ono, K.; Ruscheinski, J.; Wang, P. L.; Ideker, T. Cytoscape 2.8: new features for data integration and network visualization. *Bioinform*. **2011**, *27*, 431–432. (10.1093/bioinformatics/btq675)

[10] van Dongen, S. A cluster algorithm for graphs. *Technical Report INS-R0010*, *National Research Institute for Mathematics and Computer Science in the Netherlands, Amsterdam,* **2000**, 1386–3681

[11] Lee, A. Y.; St Onge, R. P.; Proctor, M. J.; Wallace, I. M.; Nile, A. H.; Spagnuolo, P. A. *et al.* Mapping the cellular response to small molecules using chemogenomic fitness signatures. *Science* **2014**, *344*, 208–211. (10.1126/science.1250217)

[12] Wallace, I. M.; Bader, G. D.; Giaever, G.; Nislow, C. Displaying chemical information on a biological network using Cytoscape. *Methods Mol. Biol.* **2011**, *781*, 363–376. (10.1007/978-1-61779-276-2_18)

do more
feel better
live longer

Diseases of the Developing World-Tres Cantos

MALARIA DPU
Microbial Biochemistry and Parasitology

STUDY TITLE

Determination of *in vitro* killing effects for MMV019247 (Batch: MMV019247-01), MMV689017 (Batch: MMV689017-01), MMV689018 (Batch: MMV689018-01), MMV689019 (Batch: MMV689019), MMV689020 (Batch: MMV689020-01), MMV689021 (Batch:MMV689021-01) after 24 and 48 hrs treatment (MMV project MMV11/0040).

EXPERIMENT CODE

20150803_
MMV019247_MMV689017_MMV689018_MMV689019_MMV689020_MMV899021_PRR_
24 and 48 hrs treatment
The original report, raw data, and experimental details pertaining to this study are held in GSK Archives.

EXPERIMENT AUTHORS

Benigno Crespo

REPORT AUTHOR

Laura Sanz

DATE OF ISSUE

03rd August 2015

REVIEWED AND AUTHORIZED

Francisco Javier Gamo
Manager, Microbial biochemistry and Parasitology

DATE OF REVIEW

1st September 2015

OBJECTIVE

In vitro studies to determine parasite viability (*P. falciparum* 3D7A) after treatment with MMV019247, MMV689017, MMV689018, MMV689019, MMV689020 and MMV899021 compounds.

PROTOCOL DESCRIPTION

IC_{50} determination
Prior to initiating the PRR assay, an IC_{50} for the compound must be determined using the standard *in vitro* ^{3}H-hypoxanthine incorporation assay .

IC50 determination

Table 1. Summary of method used to carry out *in vitro* activity assay.

Assay	*In vitro* activity of drugs against *P.falciparum* Whole Cell Assay.
Methodology	[^{3}H] Hypoxanthine incorporation assay.
Replicates	2 independent experiments (7 replicates per assay)
Strains	*Plasmodium falciparum* 3D7A, (from the Malaria Research and Reference Reagent Resource Center MR4)
% Initial Parasitemia	0.5%
Hematocrit	2%
Red blood cells	Human A+, supplied by Spanish Red Cross
Culture medium	RPMI 1640 (Sigma Catalog Number R5886), 25mM HEPES and $NaHCO_3$ without L-glutamine supplemented with an albumax solution containing : Albumax II 100g/L(Gibco, Catalog Number 11021-037), D-Sucrose 40g/L (#Sigma 68720), L-glutamine 6 g/L (Merck, Catalog Number 1.00229), Hypoxanthine 0.150 mM (Fluka, Catalog Number: 5670)
Culture volume	100 µl in 96-well flat bottom microtiter plates (Costar, Catalog #3599)
Incubation conditions	37ºC, 5% CO_2, 5% O_2, 90% N_2
Incubation time	48 h
Compound/ Cmax	(Cmax:5uM)
Controls	Chloroquine
Maximum concentration of controls	C_{MAX} Chloroquine :1 µM , 9 dilutions (2 fold serial dilutions)
Number of dilutions	9 dilutions (3 fold serial dilutions)
Solvent	0.5% DMSO (# Sigma D6250)
Measured parameter	IC_{50} value
Data analysis	Microsoft Excel and Grafit

This assay relies on the parasite incorporation of labeled hypoxanthine that is proportional to *P. falciparum* growth.
A culture of parasitized red blood cells (RBC) of strain 3D7A with a 0.5% parasitemia and 2% haematocrit in RPMI-1640, albumax and 5 uM hypoxanthine is exposed to 3-fold serial dilutions of the compound. Plates are incubated 48h at 37ºC, 5% CO_2, 5%O_2, 90% N_2. After 24h of incubation, ^{3}H-hypoxanthine is added and plates are incubated for another

24h.
After that period, plates are harvested on a glass fiber filter using a TOMTEC Cell harvester 96. Filters are dried and melt-on scintillator sheets are used to determine the incorporation of ^{3}H-hypoxanthine. Radioactivity is measured using a microbeta counter. Data are normalized using the incorporation of the positive control, (parasitized red blood cells without drug). IC_{50}s are determined using Excel and Grafit 7 software.

PRR assay. Parasite treatment
Note: This method includes renewal of the drug and washing before serial dilution

The assay uses limiting dilution technique to quantify number of parasites that remain viable after drug treatment.
P. falciparum strain 3D7A (MR4) is treated with the selected drug at concentration corresponding to 10x respective IC_{50s} .
Parasitic conditions are 2% haematocrit, 0.5% parasitemia.
Samples of parasites are taken from treated cultures after 24 and 48 hrs.
Drug is renewed after 24 hrs by taken out old media and replenishing an equal amount of media at 10x IC_{50}.
To avoid interference by drug, parasite samples are washed out by centrifugation before making serial dilutions. Then, 10 fold- serial dilution of treated samples are made in 96 well plates by adding fresh erythrocytes and new culture medium to quantify the number of viable parasites. Parasites are cultured in microtiter plates to allow wells with less parasite load to render detectable parasitemia.
Number of viable parasites is determined by counting the number of wells with growth. After 21 days of culturing, samples are taken to examine growth. Additional sampling is done after 28 days to confirm growth/ no growth.
Two independent serial dilutions were done with each sample to correct for experimental variation.

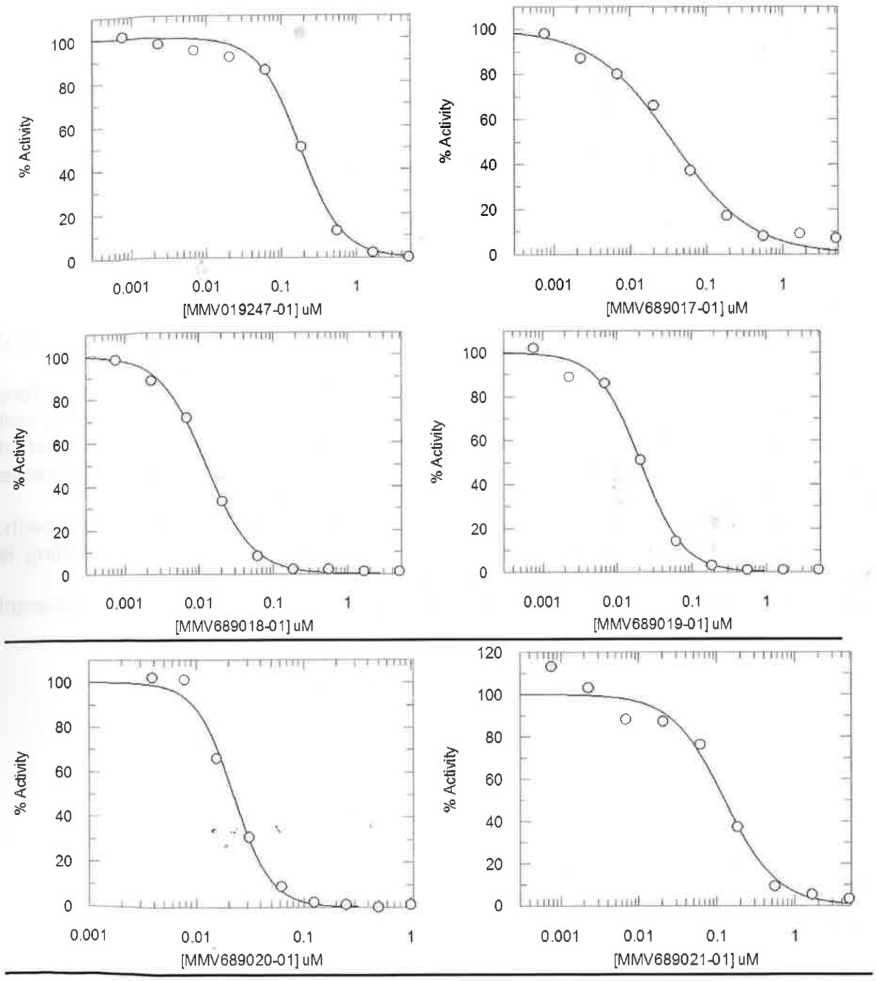
The assay allows to determine the reduction of viable parasites after drug treatment.

RESULTS

IC_{50} values

Compound	3D7 *P. falciparum* IC_{50} (µM)
MMV019247	0.177 ± 0.039
MMV689017	0.032 ± 0.011
MMV689018	0.012 ± 0.002
MMV689019	0.015 ± 0.006
MMV689020	0.121 ± 0.048
MMV689021	0.048 ± 0.006
Control	
Chloroquine	0.014 ± 0.006

Figure 1. Profiles of *in vitro* ^{3}H-hypoxanthine incorporation for parasites exposed to serial dilution of MMV019247, MMV689017, MMV689018, MMV689019, MMV689020 or MMV689021 compounds.

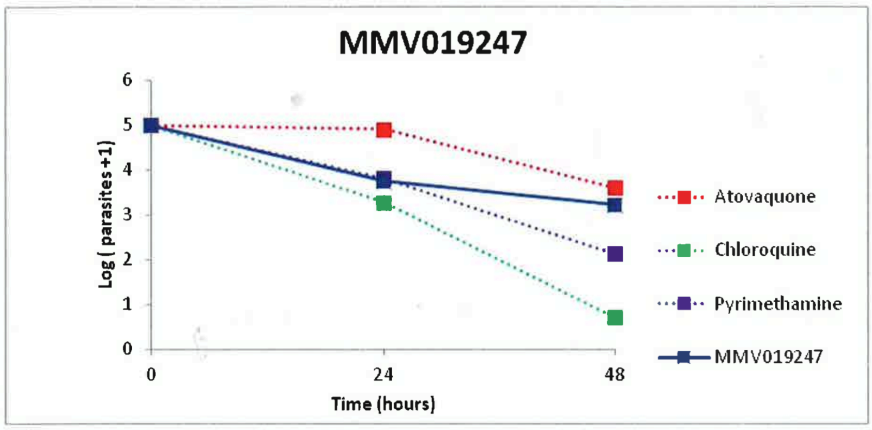


PRR determination

The number of viable parasites, as log base 10 (viable parasites+1) after 24 and 48 h of treatment have been determined.

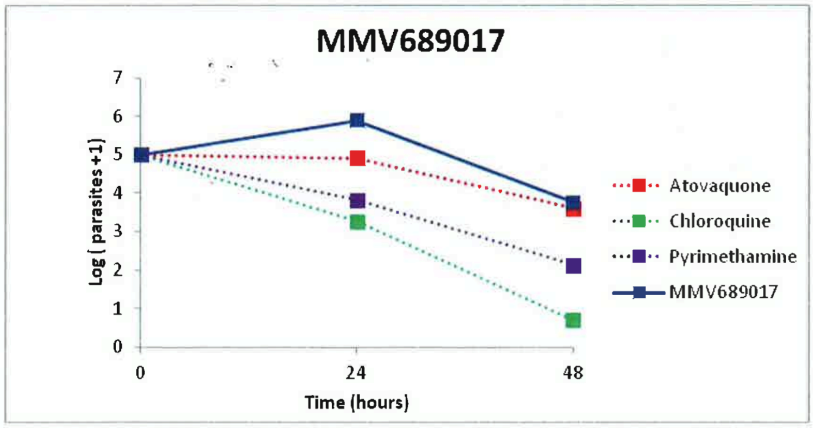
Chloroquine, Atovaquone and Pyrimethamine were included as controls at concentrations corresponding to 10x their respective IC50s and worked as expected.

Figure 2. Number of viable parasites after MMV019247 treatment



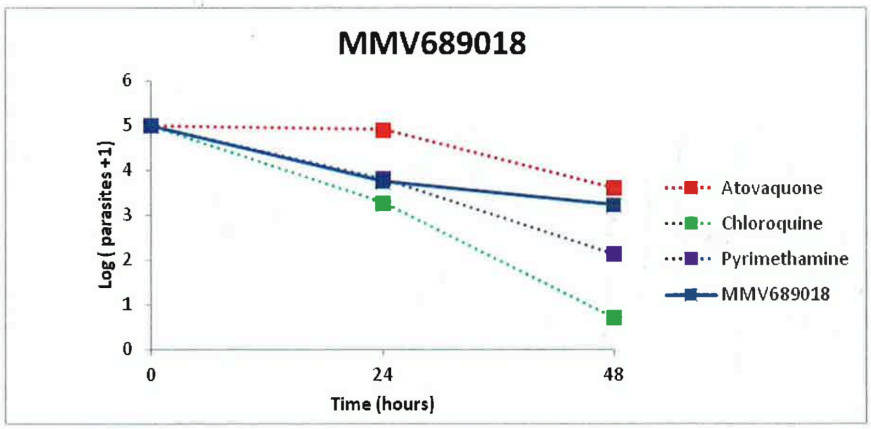
	time of treatment (h)		
Compound	0	24	48
MMV019247	5	3.75	3.21
Chloroquine	5	3.27	0.71
Pyrimethamine	5	3.82	2.13
Atovaquone	5	4.91	3.61

Figure 3. Number of viable parasites after MMV689017 treatment



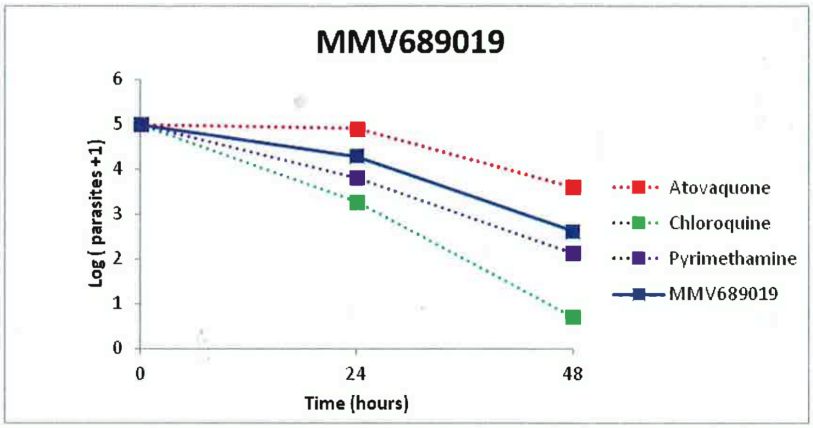
	time of treatment (h)		
Compound	0	24	48
MMV689017	5	5.89	3.75
Chloroquine	5	3.27	0.71
Pyrimethamine	5	3.82	2.13
Atovaquone	5	4.91	3.61

Figure 4. Number of viable parasites after MMV689018 treatment



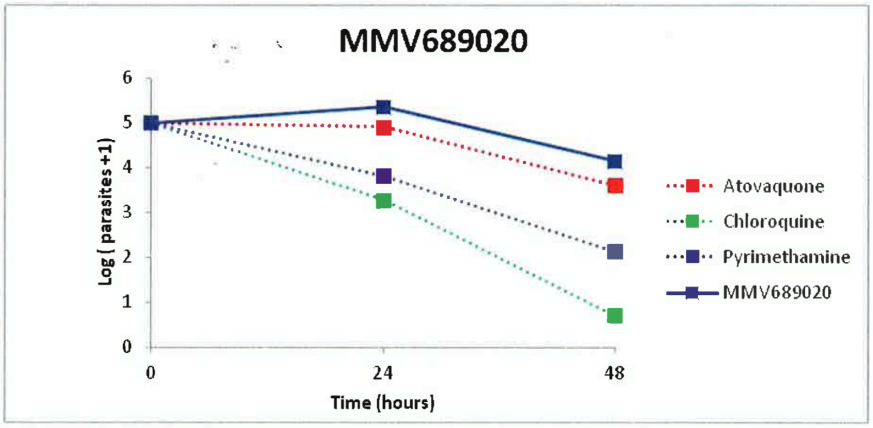
	time of treatment (h)		
Compound	0	24	48
MMV689018	5	3.75	3.21
Chloroquine	5	3.27	0.71
Pyrimethamine	5	3.82	2.13
Atovaquone	5	4.91	3.61

Figure 5. Number of viable parasites after MMV689019 treatment



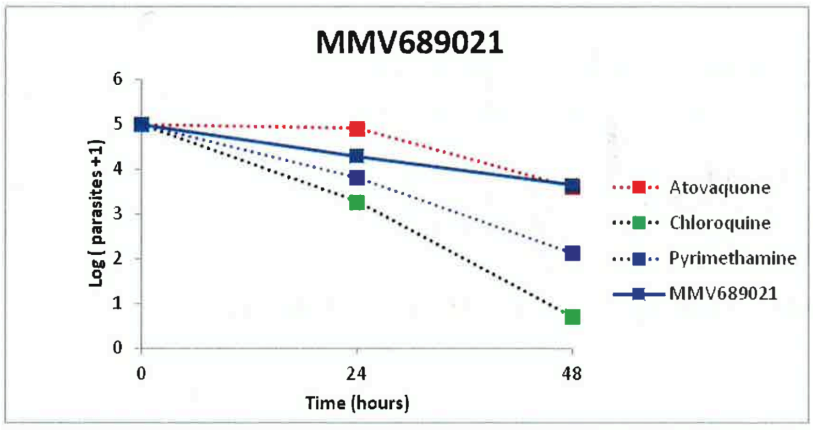
	time of treatment (h)		
Compound	0	24	48
MMV689019	5	4.29	2.61
Chloroquine	5	3.27	0.71
Pyrimethamine	5	3.82	2.13
Atovaquone	5	4.91	3.61

Figure 6. Number of viable parasites after MMV689020 treatment



	time of treatment (h)		
Compound	0	24	48
MMV689020	5	5.36	4.14
Chloroquine	5	3.27	0.71
Pyrimethamine	5	3.82	2.13
Atovaquone	5	4.91	3.61

Figure 7. Number of viable parasites after MMV689021 treatment



	time of treatment (h)		
Compound	0	24	48
MMV689021	5	4.29	3.64
Chloroquine	5	3.27	0.71
Pyrimethamine	5	3.82	2.13
Atovaquone	5	4.91	3.61

CONCLUSIONS

Teh compounds tested have shown the following effects when comparing with standard antimalarials tested in the same assay:

Compound	Effect
MMV019247	Moderate-slow
MMV689017	slow
MMV689018	Moderate-slow
MMV689019	moderate
MMV689020	slow
MMV689021	slow

Note: a screening format was used. Full time course or a more detailed study should be done to confirm results.

Text S2. Methods Employed in Commercial Acquisition of Compounds.

At various points in the project databases of commercially-available molecules were searched and relevant compounds were purchased.

Example 1
Purchasable Chemical Space Map Centered on GSK's Prioritised Hit Compounds
Original Location: http://malaria.ourexperiment.org/in_silico_prediction/2925

Method:
A structural similarity map of compounds from the publication grouping GSK's compounds into high priority compound lead series (http://pubs.acs.org/doi/abs/10.1021/ml200135p) including very close purchasable structural neighbours.

The Fast track publication contains ~550 compounds grouped into ~40 compound series' for follow up by the community. Original compounds are shown as red nodes and purchasable compounds from E-Molecules as blue nodes (code shown). Nodes are connected by an edge if compounds have a structural similarity of > 0.7 Tanimoto co-efficient with ECFP_4 fingerprints (i.e very similar compounds)

The map is best viewed with Cytoscape (http://www.cytoscape.org/) and the ChemViz plugin (http://www.cgl.ucsf.edu/cytoscape/chemViz/). Nodes can be right clicked to view compound structure. IDs and smiles strings can also be copied out of Cytoscape in to a text editor.

The E-molecule compounds can be retrieved from the E-molecules list view (http://www.emolecules.com/cgi-bin/rene/list_search_setup.cgi), selecting E-molecules ID from the drop down and inputting the list of ids to be retrieved.

Map: Fig S7 ACS Network Similarity
Data: Dataset S6 ACS Network Similarity

Example 2
Purchasable Chemical Space Map Centered on Early OSM Compounds
Original Location: http://malaria.ourexperiment.org/in_silico_prediction/2929

Method:
Map is generated as before, except two thresholds were used. 0.7 for very similar compounds, and 0.5 for similar compounds. The lower the threshold the more connections and nodes in the network.

A small network is also shown which contains all the neighbours of ZYH-3-1 from the similar map. This can be generated by selecting the node of interest (search box is useful), choosing "Select -> Nodes -> First neighbours of Selected Nodes", then "File -> New Network -> From Selected Nodes All Edges"

Map around OSM-S-35: Fig S8 Purchasable Map Around 35
Full Dataset: Dataset S7 Purchasable Around OSM

For related discussion, see:
http://www.thesynapticleap.org/node/399 (Fig S9 Synaptic Leap Node 399)
http://www.thesynapticleap.org/node/404 (Fig S10 Synaptic Leap Node 404)
http://cdsouthan.blogspot.se/2012/05/shop-till-you-hit-chemical-suppliers.html (Fig S11 Southan Purchaseable)

Series 2 - Arypyrroles

SYBR green I Assay @ Ralph lab, Bio21 Institute

6th May 2012

Methods overview

Compounds were tested for inhibition of *Plasmodium falciparum* growth using a SYBR green I fluorescence based assay. Dose response curves were generated comprising of 8 points using a 2-fold serial dilution for the maximum final concentration of 1000 nM. The lowest concentration tested was 7.81 nM. The raw data and generated dose-response curves can be viewed here.

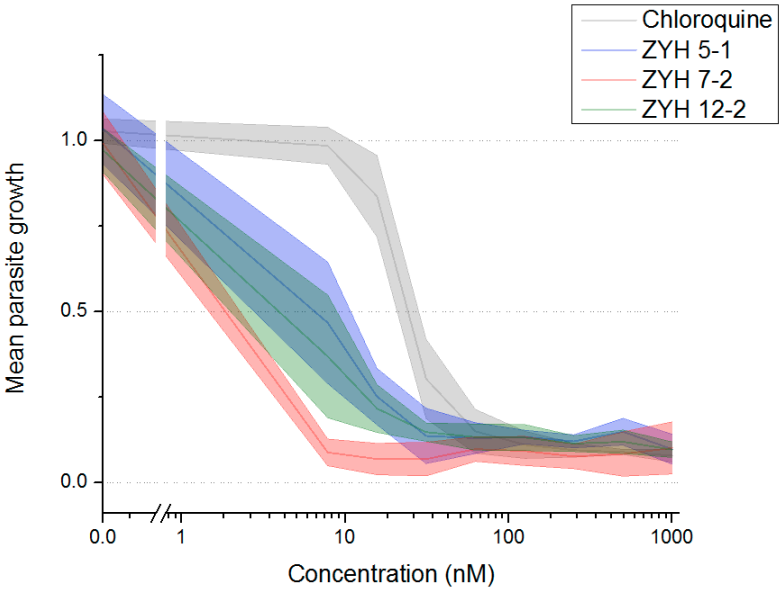
Detailed method

The compounds were first dissolved to a stock concentration of 10 mM in DMSO. A subsequent dilution was performed with MilliQ H2O to a working concentration of 100µM. Master and daughter plates were prepared and stored at -80°C until required. Asynchronous asexual blood stage *Plasmodium falciparum* (3D7 strain) parasites were used to perform the *in vitro* growth inhibition assays. SYBR green I assay was performed as described in Smilkstein *et. al.,* 2004, with modifications. The human blood (O+) used for cultivation and compound screening was washed twice with complete RPMI media before use. The SYBR green I assay was set up in FALCON® 96 well flat bottom plates; not using the outermost wells to avoid for evaporation ie. border-effect. Compounds were prepared in triplicates and 2-fold serial dilution was used to prepare 8-points starting at 1000 nM final concentration. The final conditions for the dose response assays were 2% hematocrit and 0.5% parasitaemia. After 48 hours, the plates were assayed for fluorescence with a plate-reader. IC50 were calculated using a point-to-point method.

Analysis overview

TABLE 1. The mean IC50 concentrations for the compounds from two independent experiments. NA denotes curves displaying no or less than 50% inhibition. (*) This compound displayed complete growth inhibition at all tested concentrations.

Compound ID	IC50 (nM)	Compound ID	IC50 (nM)
PMY 12-5	NA	ZYH 10-2 B	NA
PMY 27-2	NA	ZYH 12-2	7.65±2.78
PMY 31-5	NA	ZYH 15-1	338.88±139.88
PMY 34-1	NA	ZYH 16-1	27.59±15.40
ZYH 3-1	10.89±3.66	ZYH 17-1	155.96±77.86
ZYH 5-1	9.21±3.22	ZYH 18-1	442.4±248.40
ZYH 6-2	205±191.43	ZYH 19-1	484.73±22.01
ZYH 7-2*	4.66±0.42	ZYH 22-3	520.1±66.76
ZYH 10-2 A	NA	ZYH 23-1	NA



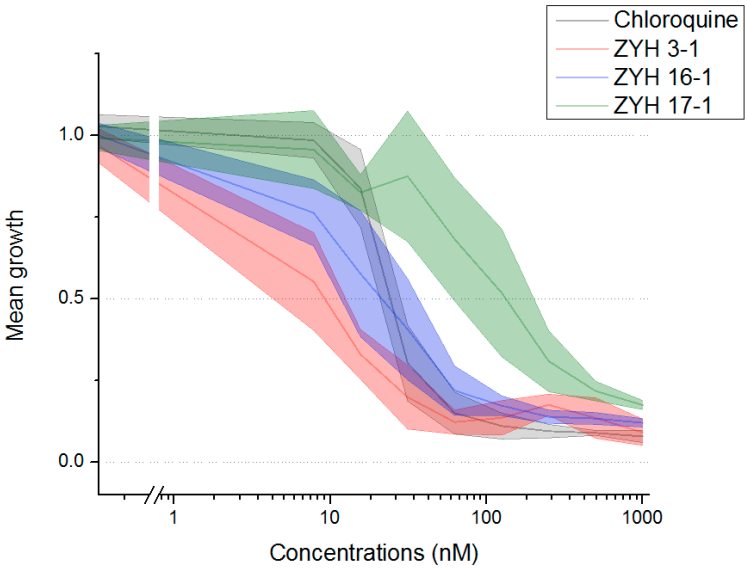


FIGURE 1. Dose response curves for compounds against parasite growth; A: ZYH 5-1, 7-2 and 12-2; B: ZYH 3-1, 16-1, and 17-1. The mean is represented as a solid line and the standard deviation is shown as a transparent solid in the colour specified as per the legend. Graphs were generated using the Origin 8.6 graphing software (Windows7).

Table 1 summarises the mean IC50 values calculated for each compound using a point-to-point method i/e. manual inspection and derived from generated dose-response curves. In general, for the concentration range tested and the overall shape of the inhibition profile, did not allow for use of curve-fitting software. A sigmoidal curve and an upper and lower asymptote are required for the algorithms to be properly utilised in those software packages.

Only 7 out of 18 compounds tested did not display any or strong inhibition at concentrations below 1 µM. More encouraging is the presence of 4 compounds which display potent IC50

concentrations below 10 nM. Furthermore, compound ZYH 7-2 in figure 1, shows strong inhibition displayed complete inhibition across all concentrations tested. The estimated IC50 in table 1 is made by extrapolation back to 0 nM; and therefore will require additional dose-response assays to determine the correct IC50 values.

Detailed analysis

Whisker-box-plots were constructed for the derived IC50 values from two independent experiments. The box shows the middle 50% of the data (interquartile range),the middle bar is the median and the open box is the calculated mean. These box plots were made to visually represent the spread of data, and can help flag possible issues. For example in figure 2, most of the IC50 for the compounds appear contained but focusing on ZYH 16-1 shows there is more variability with the derived IC50 values between my repeated experiments. It could simply be a technical error and requires another repeat to correct for. Another possibility could be due to the compound hitting several targets that may be stage specific and is therefore affected by the initial composition of the asynchronous culture.

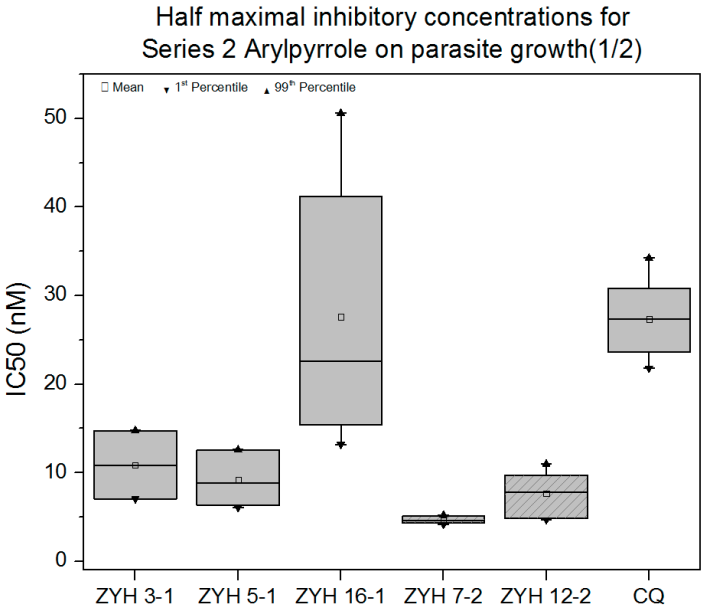


FIGURE 2. Whisker-box plot for the various compound IC50 concentrations. Symbols as described in legend.

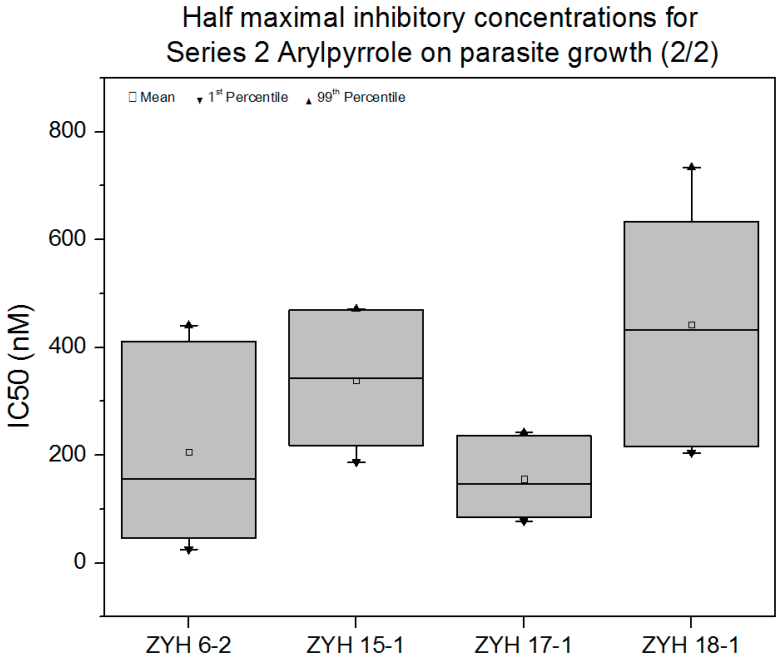


FIGURE 3. Whisker-box plot for the various compound IC50 concentrations. Symbols as described in legend.

This issue of IC50 spread is more pronounced in figure 3. The first and easiest explanations is to assume some sort of technical error has occurred, and simply requires another repeat of the experimental conditions to determine which data set was properly performed. A possible explanations for the resulting differences in dose-response curves despite the same testing conditions, is the thawing of a new daughter plate, after leaving a pre-existing daughter plate in the incubator over the weekend (this plate was discarded and never used for the collection of this presented data). Looking at the ratio of the IC50, there seems to be a greater change observed for the second testing of compounds C10 - C18 - when the new daughter plate was used. From previous experience, compounds have been observed to lose activity over extended periods of storage at -20°C and also after several freeze-thaw cycles, so this effect could be due to the degeneration of the compounds - a chemist will have to interject here.

Next experiments

1. Repeat experiment for compounds C10-C18, especially where the difference in the mean IC50 was >30%.
2. Perform a dose-response assay at a lower concentration ~sub-nanomolar to determine the IC50 for compounds like ZYH 7-2.
3. Suggestions? Looking at parasite metabolic activity via dye stain? Multidrug resistance Pf strains?

Comments/Feedback

Text S4. Results from Assay Performed by Batra Laboratory.

Date: 13/04/12

TCMDC-123812

Test model: *In vitro P. falciparum* (**3D7 strain**)

S. No.	Sample Code	IC_{50} (μM)	CC_{50} (μM)	SI	Remark
1	PMY-10-6 (ref drug)	0.581	nd	-	
Reference drug -Chloroquine		0.0083	125.85	15162.7	

Test model: *In vitro P. falciparum* (**K1 strain**)

S. No.	Sample Code	IC_{50} (μM)	CC_{50} (μM)	SI	Remark
1	PMY-10-6 (ref)	0.641	nd	-	
Reference drug -Chloroquine		0.252	125.85	499	

Kumkum Srivastava, Parasitology Division, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031. e-mail - kumkum_srivastava@cdri.res.in

Biological Assays

***In vitro* antiplasmodial assay**

The compounds were evaluated for antimalarial activity against 3D7 (CQ^S) or K1 (CQ^R) strains of *P. falciparum* using Malaria SYBR Green I nucleic acid staining dye based fluorescence (MSF) assay.[1] The stock (5 mg/ml) solution was prepared in DMSO and test dilutions were prepared in culture medium (RPMI-1640-FBS). Chloroquine-diphosphate was used as reference drug.

Test Technique – 50 µL of culture medium was dispensed in 96 well plate followed by addition of 50 µL of highest concentration of test compounds (in duplicate wells) in row B. Subsequent two-fold serial dilutions were prepared and finally 50 µL of 1.0% parasitized cell suspension containing 0.8% parasitaemia was added to each well except 4 wells in row 'A' received non parasitized erythrocyte suspension. The plates were incubated at 37ºC in CO_2 incubator in an atmosphere of 5% CO_2 and air mixture and 72 h later 100 µL of lysis buffer containing 2 x concentration of SYBR Green-I (Invitrogen) was added to each well and incubated for one hour at 37ºC. The plates were examined at 485±20nm of excitation and 530±20nm of emission for relative fluorescence units (RFUs) per well using the fluorescence plate reader (FLX800, BIOTEK)

Statistical analysis- Data was transferred into a graphic programme (EXCEL) and IC_{50} values were obtained by Logit regression analysis of dose response curves using pre-programmed Excel spread sheet.

Cytotoxicity assay- Cytotoxicity of the compounds was carried out using Vero cell line (C1008; Monkey kidney fibroblast) following the literature method.[2] Cells were incubated with compound-

dilutions for 72 h and MTT was used as reagent for detection of cytotoxicity. 50% cytotoxic concentration (CC_{50}) was determined using nonlinear regression analysis of dose response curves.

References

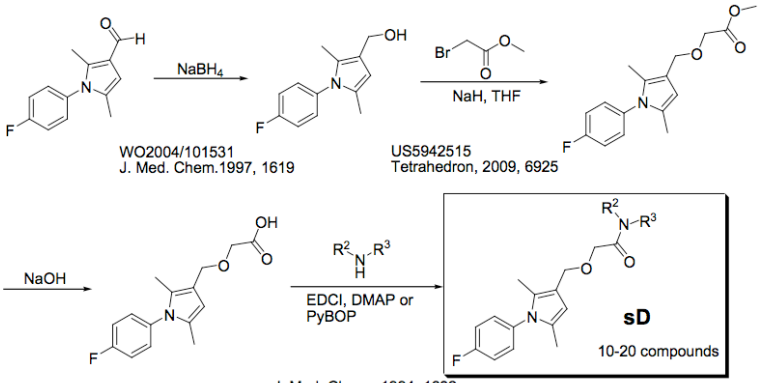
1. Singh, S.; Srivastava, R. K.; Srivastava, M.; Puri, S. K.; Srivastava, K. In-vitro culture of *Plasmodium falciparum*: Utility of modified (RPNI) medium for drug-sensitivity studies using SYBR Green I assay. *Exptl. Parasitol.* **2011**, *127*, 318-321.

2. Sashidhara K. V.; Kumar, M.; Modukuri, R. K.; Srivastava, R. K.; Soni, A.; Srivastava, K.; Singh, S. V.; Saxena, J. K.; Gauniyal, H. M.; Puri, S. K. Antiplasmodial activity of novel keto-enamine chalcone-chloroquine based hybrid pharmacophores. *Bioorg. Med. Chem.* **2012**, *20*, 2971–2981.

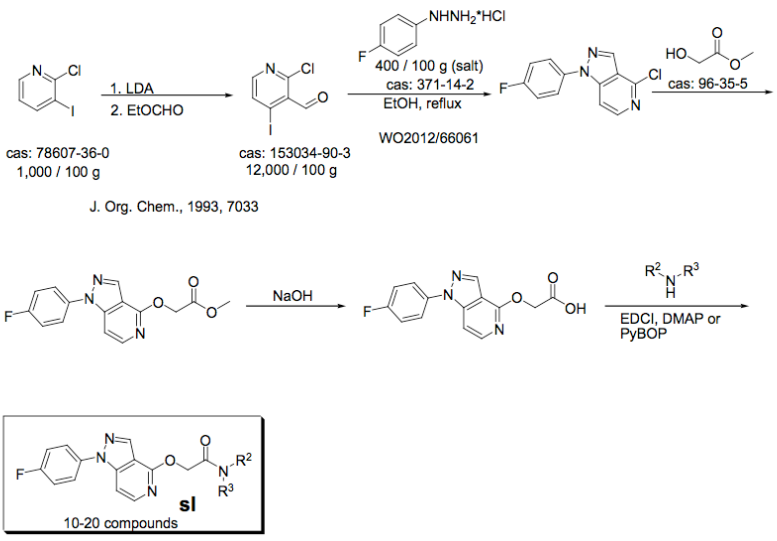
Text S6. Synthetic Planning by Asclepia for Ether Compound (OSM-S-236).

OSDD Malaria project – Suggested synthesis routes by Asclepia (Frederik Deroose)
October 24th 2012

Library sD:



Library sI:



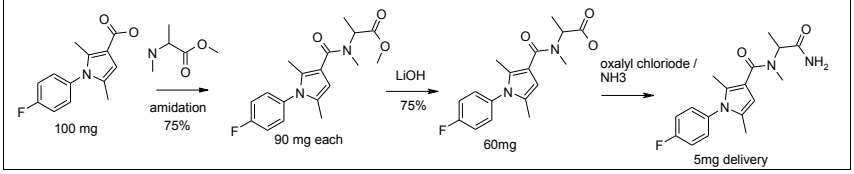
Text S7. Synthetic Planning by Asclepia for Miscellaneous Compounds.

ASCLEPIA
OUTSOURCING SOLUTIONS

Proposal for 5 compounds
Amount: 5 mg (>90% by LCMS, identification by NMR)

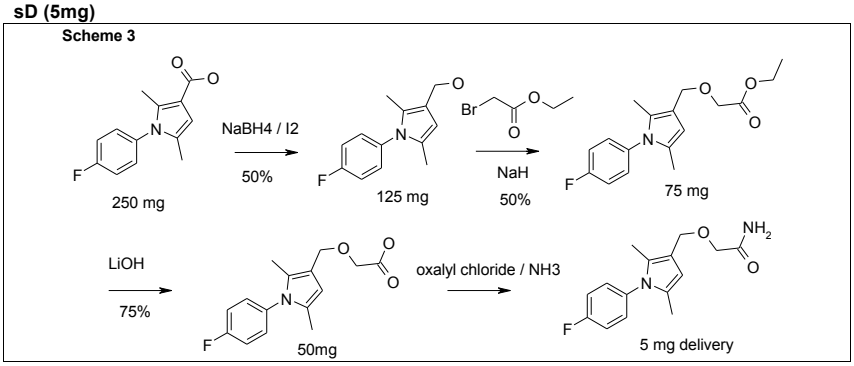
sC (5mg)

Scheme 1



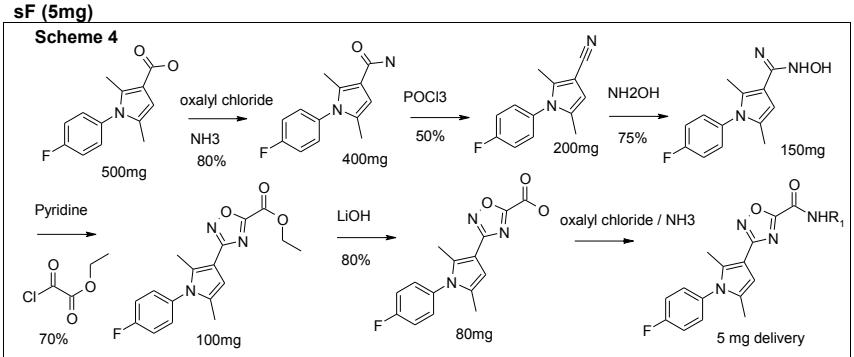
sD (5mg)

Scheme 3



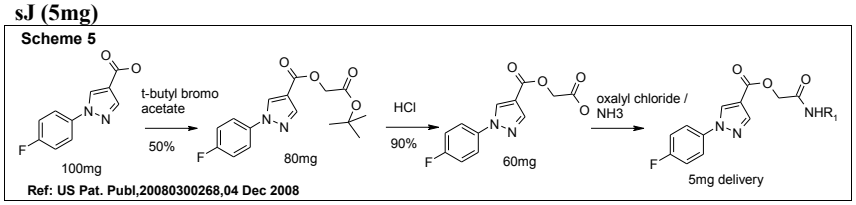
sF (5mg)

Scheme 4

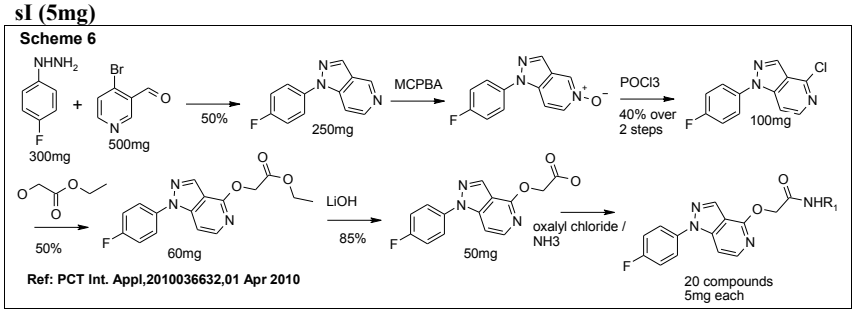


Ref: PCT Int. Appl.,2011121137,06 Oct 2011
PCT Int. Appl.,2019127686,22 Oct 2011

sJ (5mg)



sI (5mg)



Note:

- Synthesis of scaffold for sI series has no relevant literature precedence after step-1, but we are quite familiar with this kind of chemistry.

Chemicals needed:

Name	cas no	Vendor	amount	price in USD	Lead time
N-methyl alanine methyl ester hydrochloride	52060-77-2	Chembridge	1g	405	Min pack
t-butyl bromo acetae	5292-43-3	Aldrich	10g	20	Min pack
4-fluoro phenyl hydrazine hydrochloride	823-85-8	Aldrich	10g	35	Min pack
4-bromopyridine-3-carboxaldehyde	154105-64-3	Arkphar minc	1g	410	7 days back order
1-(4-fluorophenyl)-1H-pyrazole-4-carboxylic acid	138907-81-0	Matrix	500mg	305	5 days back order
1-(4 flurophenyl)-2,5-dimethyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid	519151-74-7	Enamine	1g	348	10 days back order
Ethylchlorooxoacetate	4755-77-5	Aldrich	25g	20	Min pack
Total				**1543**	

Effort cost: 6500 USD
Chemical cost: 1500 USD
Total cost: 7500 USD for 5 compounds i.e 1500 USD / compound
Delivery in 5 weeks
Please let me know if you have any questions,

Best regards
Frederik Deroose

Frederik Deroose, PhD
CEO

Damvalleistraat 49 B-9070 Destelbergen
Belgium
Mobile: +32 468 13 70 14
Fax: +32 9 251 56 08
Email: *frederik.deroose@asclepia.com*
Website: www.asclepia.com

Text S8. Description of Procedures Used in Bioisostere Analysis.

Original location: http://malaria.ourexperiment.org/in_silico_prediction/2954

Cytoscape maps were generated based on transformations for compounds synthesized using both the Classic Transformation (transforming the original molecule based on a set of ~200 commonly used transformations, such as replacing a hydroxyl with a sulfonamide) and Database Transformation (algorithm described in this paper
http://www.ncbi.nlm.nih.gov/pubmed/16562998
"M. Wagener, J.P.M. Lommerse, "The Quest for Bioisomeric Replacements", J. Chem. Info. Modeling, 2006, 46(2), 677- 685) components in Pipeline Pilot.

Map Data: Dataset S19 Bioisostere

Node ID shows the type of transformation
Node size reflects the ALogP of the compound, larger nodes have LOWER values. The smallest nodes have ALOGP >5
Node colour reflects the change in AlogP of the child compound vs the original. Red nodes indicate in a drop of >1, Green nodes a change of >0.5 while Blue nodes indicate an INCREASE ALogP

Two reports were generated focusing on just OSM-S-35 child compounds that would have a ALogP<5 resulting from both types of transformations. There is also a pdf showing a map centered on OSM-S-35.

Fig S27 Bioisostere Classic
Fig S28 Bioisostere Database
Map Diagram: Fig S29 Bioisostere Map 35

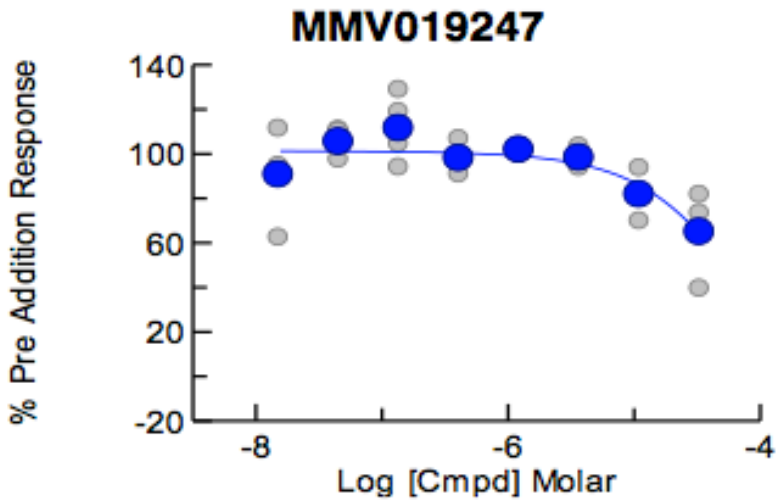
Original Contribution: http://www.thesynapticleap.org/node/400 (Fig S30 Synaptic Leap Node 400)

Text S9. Potency Curves Derived from hERG Assay.

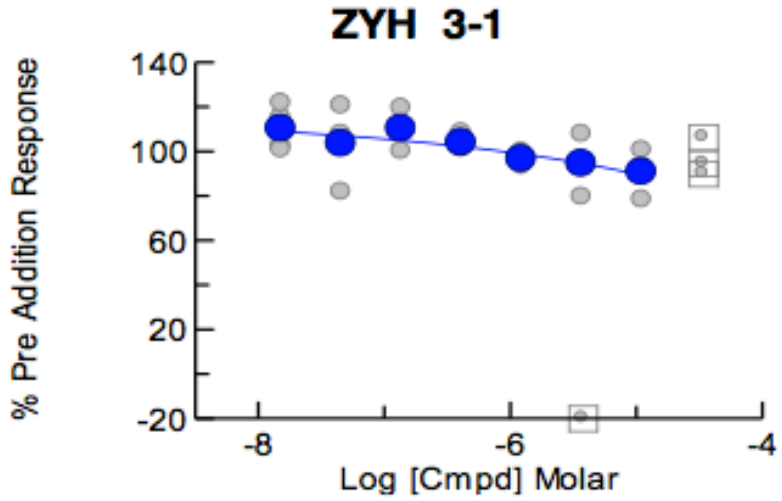
hERG – Graphical Outputs
Assay performed by Essen Bioscience 17th April 2012
Corresponding data may be found in **File Dataset SX**
Method: See **File Text SX**.

Original location: http://malaria.ourexperiment.org/biological_data/2999

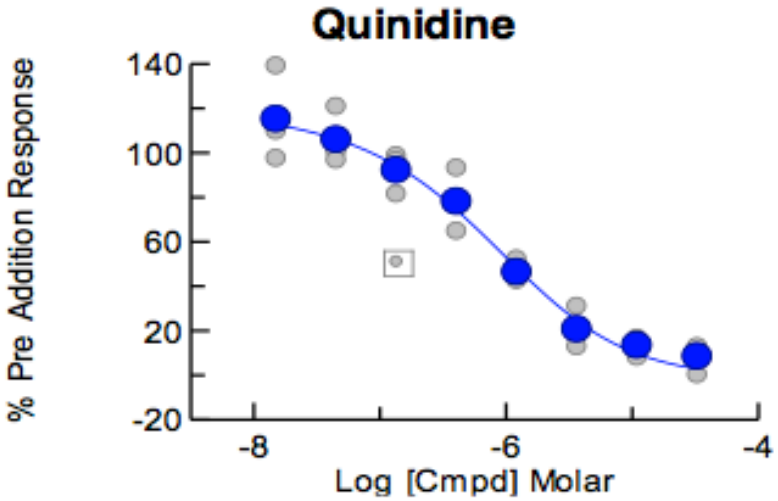
OSM-S-5



OSM-S-35



Quinidine



In each graph the log of molar concentration of test compound is plotted against the effect of the compound on the hERG current, expressed as a percentage of the pre-compound signal. In this experiment an average of 9±3% signal decay was observed in the time- and vehicle (DMSO) control. Data are normalised for this vehicle-response such that a value of 100% = no drug effect. The smaller grey symbols represent data from individual cells. The larger blue points show the mean data at each test concentration. The line of best fit (4 parameter logistic equation) is generated from the individual cell data points. Outlier data points (boxed symbols) were manually excluded from the curve fit. No more than two per curve were excluded, other than where compounds were visibly out of solution.

Text S10. Data and Method for the Dual Gamete Formation Assay.

Imperial College London

MMV Medicines for Malaria Venture

Data report

- Imperial College London -

Goal of the study

To determine the transmission-blocking efficacy of four compounds from University of Sydney.

Assay(s) performed

1. *P. falciparum* dual gamete formation assay

Summary of data

	% inhibition at 1µM			
	Male			
	OSM-S-5	**OSM-S-38**	**OSM-S-39**	**OSM-S-111**
Expt 1	4.44	19.76	39.52	20.56
Expt 2	0.22	18.32	32.50	15.88
Expt 3	9.66	19.08	22.90	23.49
Expt 4	6.09	49.01	49.43	24.36
Mean	**5.10**	**26.54**	**36.09**	**21.07**
SD	3.92	14.99	11.20	3.83
SEM	1.96	7.49	5.60	1.91
	Female			
	OSM-S-5	**OSM-S-38**	**OSM-S-39**	**OSM-S-111**
Expt 1	10.95	23.19	32.10	18.00
Expt 2	14.47	-5.82	6.84	18.40
Expt 3	9.00	14.25	27.62	28.41
Expt 4	19.60	50.42	58.53	65.25
Mean	**13.51**	**20.51**	**31.27**	**32.51**
SD	4.65	23.34	21.24	22.35
SEM	2.33	11.67	10.62	11.17

Biological context

Gametocytes differentiate from sexually committed merozoites that invade red blood cells (RBCs) in the human host. Therein they mature (48 hours in *P. vivax*; ~10 days in *P. falciparum*). Maturation entails an initial period of cell growth (approximately 60% of the maturation period), during which they are susceptible to schizontocidal compounds, followed by

cell cycle arrest and insensitivity to most schizonticides. The mature, infectious *P. falciparum* gametocyte has a half-life of 4-7 days, and a population lifespan of 22 days. In the field, patients often present to the clinic with mature gametocytes already in their bloodstream, therefore interventions that also target transmission will be important for any eradication strategy.

Upon uptake into the mosquito blood meal, the previously arrested gametocytes are activated by a fall in temperature and the presence of mosquito-derived xanthurenic acid (XA), and undergo gametogenesis. This explosive development is often completed in the first 20 minutes, and in the female cell, is mediated by pre-existing proteins, or those translated from stored mRNA. Constituent cell processes occurring during male gametogenesis include egress from the red blood cell, axoneme assembly and activation, and three rounds of DNA replication. Immediately following gamete formation and fertilization, the extracellular parasite initiates transcription of the hybrid genome, undergoes meiosis and develops into the motile ookinete ~22hrs after blood feeding. The ookinete 'glides' to and through the mosquito gut epithelium where it contacts the basal lamina and transforms into an oocyst. These processes occur within an environment almost totally derived from host blood (in which drugs can be effectively delivered).

Description of assay

Assay 1: *P. falciparum* dual male and female gamete formation assay. This assay reports on the ability of a drug to either kill the mature *P. falciparum* male and female gametocytes directly or damage them in such a way that they cannot undergo onward development and form gametes - a process known as exflagellation for male gametocytes and activation for female gametocytes. Therefore this assay does not report only on gamete formation *per se*, rather reports on the functional viability of the mature Stage V gametocyte.The dual readout is performed on exactly the same cells and so inhibition of male gamete formation and female gamete formation can be directly compared for test compounds in the same assay. Male gametes are highly motile cells and are readily identified microscopically around 20min after induction of gamete formation as "exflagellation centres" clustered around the residual gametocyte. Female gametes are readily identified by the surface expression of Pfs25 which begins to be detectable 2 hours after induction of gamete formation and is maximal by 24 hours.

Mature Pf NF54 gametocyte cultures already showing the ability to form gametes are taken and divided into wells of a 96 well plate each containing the drug to be tested at 1μM. Final DMSO concentration of the microculture does not exceed 0.5%. Gametocytes in the wells are incubated for 24hrs in the presence of the drug before being stimulated to form gametes by temperature decrease from 37°C to 26°C and addition of the gametocyte activating factor xanthurenic acid (2.5μM). At 20min after induction, exflagellation of each well is recorded by automated timelapse microscopy using x10 objective and a custom algorithm. This process is repeated to obtain three readings from each well and after image processing, the mean of each replicate is calculated. Typically between 15 and 100 exflagellation centres are recorded per field in the negative controls, dependent on the overall exflagellation of the source parent culture. DMSO is used as a negative control and 10μM methylene blue is used as a positive control. After data collection, the plate is returned to a 26°C incubatior for 24hrs and then female gamete formation is assessed by live staining with a Cy3-labelled anti-Pfs25 monoclonal antibody. Cells are resuspended when adding the antibody and left to stain and re-settle for 2hrs before being recorded by automated microscopy using the x20 objective and identified and counted by a custom algorithm. Four fields of view are recorded and the mean taken. Typically 150-400 female gametes are recorded per field in the controls.

% inhibition of male or female gamete formation is calculated with respect to the positive and negative controls and the whole experiment repeated 4 times using independent cultures. Those compounds selected for further investigation undergo dose response analysis and IC50 curves for both male and female gamete formation are generated.

Results

1. *P. falciparum* dual gamete formation assay

See above

Conclusion

All compounds tested were inactive at 1µM.

Text S11. Target Prediction Analysis for OSM-S-39.

Predicted targets in malaria for ZYH_72

Number of molecules with a predicted target: 1 out of 1

Overview

Computationally predicted protein targets were calculated based on the compound structure information using a statistical model derived from the ChEMBL database. Specifically, we used a multi-category Naive Bayes statistical model that identifies compound structural features (specific sets of atoms and bonds generated using the ECFP_4 fingerprint) that are correlated with a particular data class (i.e. protein target). A set of active compounds was created for proteins in the ChEMBL database for which at least 50 compounds (to ensure a robust model) were annotated to an activity <10uM. A multi-category model was then built for each of these compounds (i.e. active against this protein) versus all of the other compounds (assumed inactive). By scoring each compound with all 1,287 models, a ranked list of up to the top 50 predicted protein targets (with a model score >0) for each compound is generated. The scores for each individual protein target were standardized by comparing to the scores obtained for a random set of >10,000 compounds.

Predicted targets for each compound are then limited to only those of relevance to malaria. The proteome is defined as the complete proteome set for Plasmodium falciparum (isolate 3D7) as listed in Uniprot reference proteome, a total of 5353 proteins.
1.Any protein sharing the same accension as those in ChEMBL are included
2.Any protein clustered into the same group according to Homologene are included. This involves matching ids.
3.Any protein annotated into the same group according to orthoMCL are included. This match is protein sequence based.

There are 22 organism specific sequence in ChEMBL.
There are 185 ChEMBL targets with a homolog from 104 homologene clusters.
There are 962 ChEMBL targets with homolog in 337 OrthoMCL clusters

All targets with a standard score > 1 are listed in a table including the standard score, the target name in ChEMBL, the uniprot accession of the malaria protein, and a corresponding protein name

An image of the compound and a bar plot showing the standard scores for predicted targets is also shown

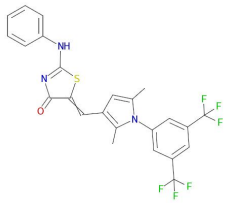
Caveat Emptor: This report, and the models that it is based on, represent very prelimnary work.

Author: Iain Wallace

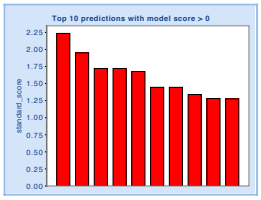
Date: 03/16/12

Compound name is ZYH_72

Cc1n(c2cc(C(F)(F)F)cc(C(F)(F)F)c2)c(C)c(C=C3C(=O)N=C(Nc4ccccc4)S3)c1



ZYH_72



Top 5 predicted targets score > cut_off

Name in ChEMBL	Z-Score	Protein ID	Protein Name
Carboxy-terminal domain RNA polymerase II polypeptide A small phosphatase 1	2.2350	Q8I3U9	Protein phosphatase, putative
Dihydroorotate dehydrogenase	1.9501	Q08210	Dihydroorotate dehydrogenase (quinone), mitochondrial (DHOdehase) (EC 1.3.5.2) (Dihydroorotate oxidase)
SUMO-activating enzyme subunit 2	1.7208	Q8I553	Ubiquitin-activating enzyme, putative
SUMO-activating enzyme subunit 1	1.7208	Q8IHS2	Ubiquitin activating enzyme (E1) subunit Aos1, putative
Cyclin-dependent kinase 1	1.6767	P61075	Cell division control protein 2 homolog (EC 2.7.11.22) (EC 2.7.11.23)

Author: Iain Wallace

Date: 03/16/12

Text S12. Data and Methods Employed in DHODH Assay.

Diseases of the Developing World-Tres Cantos

Malaria DPU
Microbial Biochemistry and Parasitology Group

STUDY TITLE

To study the inhibition of *P. falciparum* Dihydroorotate dehydrogenase by arylpyrrol compounds.

REPORT AUTHOR

María José Lafuente

PERSONNEL INVOLVED

Maria Jose Lafuente

DATE OF ISSUE

August 20130718

REVIEWED AND AUTHORIZED

Francisco Javier Gamo Benito
Manager, Parasitology and Biochemistry

DATE OF REVIEW

August 20130718

ABSTRACT

Plasmodium falciparum is the causative agent of the most serious and fatal malarial infections, and it has developed resistance to commonly employed chemotherapeutics. The *de novo* pyrimidine biosynthesis enzymes offer potential as targets for drug design, because, unlike the host, the parasite does not have pyrimidine salvage pathways.

In *P*. *falciparum*, like in most of eukaryotic cells, DHODH is a flavin-dependent mitochondrial enzyme placed in the outer face of the inner mitochondrial membrane and uses mitochondrial ubiquinone as final electron acceptor (Baldwin *et al*. 2002). Recently, *P*. *falciparum* DHODH inhibitors (N-alkyl-5-(1Hbenzimidazol-1-yl)thiophene-2-carboxamides and triazolopyrimidines) have been identified which can suppress *Plasmodium* growth *in vivo*, validating DHODH as a new target for anti-malarial chemotherapy.

OBJECTIVE

To determine if compounds belonging to the Arypyrrole series are able to inhibit PfDHODH. Compounds assayed are based in the structures of TCMDC-123812 and TCMDC-123794.

PROTOCOL DESCRIPTION

Dihydroorotate dehydrogenase activity

Assay	Absorbance – Kinetic – IC50
Experimental procedure	DHODH is evaluated using a standard colorimetric assay that monitors 2,6-dichloroindophenol (DCIP) reduction at 600 nm. Decylubiquinone is used as final electron acceptor for P. falciparum. The assay buffer contains 100 mM Hepes pH 8.0, 150 mM NaCl, 10% glycerol, 0.05 % Triton X-100, 500 µM L-dihydroorotate, 100 µM Decylubiquinone and 60 µM DCIP in all cases. Each compound is prepared as a 5 mM stock in DMSO, a 1:3 serial dilution was prepared, and of that, 0.5 µl is transferred to the assay mixture testing 9 different concentrations. The reaction is started by the addition of 20 nM enzyme.
Biological Reagent	Recombinant *P*. *falciparum* DHODH.
Controls	TCMDC-125840, TCMDC-123822 and lapachol
Solvent	DMSO.
Data analysis	SoftMax Pro software provides data acquisition. Non-linear regression analysis is used to fit the normalized results of the dose response curves and IC50s determined using the Grafit5 software package (Grafit program; Erithacus Software, Horley, Surrey, UK).
Marker	**DCPIP reduction, Absorbance**

RESULTS

To examine the possibility that arylpyrrole series could be inhibitors of the *P. falciparum* Diihydroorotate dehydrogenase we have evaluated a set of compounds against PfDHODH and we have found that the compounds are inactive at the maximum concentration tested (50 μM) (Table 1).

Table 1. Sensitivity of *P.falciparum* DHODH to different inhibitors. TCMDC-125840 and TCMDC-123822 are used as positive controls of inhibition.

Compound	PfDHODH IC50 (μM)
PMY 12-5	>50
PMY 27-2	>50
PMY 31-5	>50
PMY 34-1	>50
ZYH 3-1	>50
ZYH 5-1	>50
ZYH 6-1/6-2	>50
ZYH 7-2	>50
ZYH 10-2 A	>50
ZYH 10-2 B	>50
ZYH 12-1/12-2	>50
ZYH 15-1	>50
ZYH 16-1	>50
ZYH 17-1	>50
ZYH 18-1	>50
ZYH 19-1	>50
ZYH 22-3	>50
ZYH 23-1	>50
PMY12-1	>50
PMY 2-4	>50
PMY 6-1	>50
PMY 8-2	>50
PMY 11-2 (TCMDC-123794)	>50
PMY 10-2 (TCMDC-123812)	>50
PMY 14-1	>50
TCMDC-125840	0.005
TCMDC-123822	0.048
Lapachol	>100

CONCLUSION

Arylpyrroles series don´t inhibit PfDHODH activity.

REFERENCES

Baldwin J., Farajallah, A. M., Malmquist, N. A., Rathod, P. K. and Phillips M. A. (2002) "Malarial dihydroorotate dehydrogenase: substrate and inhibitor specificity. *J*. *Biol*. *Chem*. 277, 41827-41834.

.

Fig S1. Screengrab of Synaptic Leap Node 343 (http://www.thesynapticleap.org/node/343), Open Source Drug Discovery for Malaria, Matthew Todd, 2011. Description of Laws Governing Project.

The Synaptic Leap
Open Source Biomedical Research

Search

HOME COMMUNITIES GETTING STARTED RESOURCES NEEDED ABOUT

You are here: Home » Blogs » MatTodd's blog

Open Source Drug Discovery for Malaria

25 Jul

Published by MatTodd
Community
malaria research community

We're starting a new project – open source drug discovery for malaria. Initially the participants are my group at the University of Sydney and the Medicines for Malaria Venture (MMV), but naturally as an open project we need to expand beyond this. If you're reading this, you can join us. Check here for what's needed at the moment.

In brief the idea is this: we start with some known compounds released into the public domain as part of the 2010 deposition of data by GSK Tres Cantos and others. These lead compounds, selected by a team at MMV, will first be resynthesised and their activity confirmed. The initial funding we have received from MMV is intended to achieve this.

MMV have also committed funding to a "Linkage grant" we have submitted to the Australian Research Council for funding. We will hear whether we have been successful later in 2011, but those funds would then allow us to progress to a full medicinal chemistry/drug discovery project. i.e. the synthesis of analogs, and prosecution of a hit to lead campaign.

We'll initially be working with MMV, GSK Tres Cantos, and the OSDD project based at Lucknow in India, who are also applying for funds from the Indian agency CSIR, to start up a malaria project. This core must grow. If you have an interest in drug discovery, chemistry, biology, bioinformatics, toxicology, clinical trials, and so on, please get on board – this project will be an interesting test case of how all these disparate fields can get together. Open projects mean you can showcase your expertise/tools/software without any IP worries.

We (my group and MMV) are starting this project off, and we're super excited to lead it when we are able. But we do not "own" the project. If you would like to join in, understand that you can, at any level. With one proviso – that by taking part you understand that whatever you do needs to be recontributed back to the project in full. Please do not even think about participating if you're not completely clear about the need, and spectacular benefits, of sharing all your data and ideas in public.

More will come soon – there's a lot to say about a project like this. For now, a word about the general structure. There are several components, as far as I can see:

1) The Synaptic Leap site can be a good place for overall project discussion and coordination. We're hoping to change it around a little to make it easier to comment and post.
2) We'll use a wiki as a place to describe the project status. We've started this here. Chemists: you can see the structures of the first two molecules we'll go after here.
3) The raw synthetic data will be hosted on publicly available electronic lab notebooks. Every experiment, every spectrum. Screening data will hosted publicly elsewhere when we start to acquire them. If you want to make molecules as part of the project, it would be great if you used the same lab book, but it's not essential.
4) We'll try to start up a web presence for updates and feeds – the Twitter feed is active already.

Taking a look at what we're about to start here is both exciting and alarming. I'll try to post about this elsewhere, to keep this first post short. But here are some basic principles:

1) First law: All data are open and all ideas are shared
2) Second Law: Anyone can take part at any level of the project
3) Third Law: There will be no patents
4) Fourth Law: Suggestions are the best form of criticism
5) Fifth Law: Public discussion is much more valuable than private email
6) Sixth Law: The project is bigger than, and is not owned by, any given lab. The aim is to find a good drug for malaria, by whatever means, as quickly as possible.

MatTodd's blog Add new comment

User login

Username *

Password *

Create new account

Request new password

Log in

Recent posts

Biological Results for ATP Series from April 2013
1 May 2013 - 3:48am By MatTodd
Replies: 0

Biological Data
1 May 2013 - 3:39am By MatTodd
Replies: 0

The GSK Aminothienopyrimidine (ATP) Series
1 May 2013 - 3:38am By MatTodd
Replies: 0

more

Recent comments

anacardic compounds to cure TB 5 March 2014 - 12:27am

Protein available 24 September 2013 - 8:20pm

Hi there, just watched Tom's 17 May 2013 - 11:32am

Meeting Recording and Minutes 21 March 2013 - 2:57am

SOLVED-onamides - perhaps! 28 February 2013 - 5:44pm

more

Comments

Great laws!

Just to clarify, ideas are Open too, right?

Egon Willighagen (not verified)
Sep 16 2011

REPLY

MatTodd
Sep 17 2011

Ideas are open too

Yes. You know, that's really one of the key aspects to me of open research. Sharing open data is good, and sharing lab books is an excellent idea, but if you don't share what you need, or what you're currently thinking, then people will rightly think that they can't influence the current direction of the project. Our recent posts on some of the malaria stuff are guided by this idea. The advice we need is about current problems we might have, sure, but it's also about bigger picture things, such as which analogs ought we to be making, and what kinds of biological data are needed for drug development guys to be convinced that we are working on a promising lead?

(Still need to do that Open Tox prediction on our two leads, though. I stalled on it. You don't want to run it, by any chance? ;))

REPLY

excellent steps in the right

excellent steps in the right direction - I'll give some friends/collaborators the heads-up to see if we cant get this ball rolling a little fast.

Sajid (not verified)
Sep 20 2011

REPLY

Open Source Drug Discovery (OSDD)

Hello all,

This is clearly a good initiative and I think that it is in collaboration with the OSDDm project of Council of Scientific and Industrial Research (CSIR) and CDRI, India . You all can collaborate.

Here are a few links :

https://sites.google.com/a/osdd.net/malaria/
http://portal.osdd.jnu.ac.in/tags/osddm
www.osdd.net

Regards,
Anurag

Anurag Passi (not verified)
Jan 05 2012

REPLY

MatTodd
Jan 09 2012

Already started!

Yes certainly - we've already started this collaboration. See this link. We need more interactions and people to combine. Anyone can be part of the worldwide project provided that all data and ideas are freely shared. That necessitates public electronic laboratory notebooks and no patents.

REPLY

IP Guidelines

TSL Privacy Policy

We respect your privacy.

Fig S2. Screengrab of Synaptic Leap Node 349 (http://www.thesynapticleap.org/node/349), Known Near Neighbours of Initial Tres Cantos Leads, Matthew Todd, 2011.

The Synaptic Leap
Open Source Biomedical Research

Search

HOME COMMUNITIES GETTING STARTED RESOURCES NEEDED ABOUT

Known Near Neighbours of Initial Tres Cantos Leads

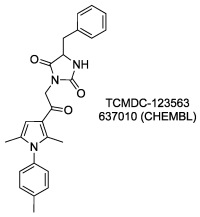
Published by MatTodd on 28 August 2011 - 7:01am

Community

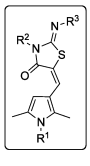
malaria research community

We're starting with the resynthesis of two leads from the GSK Tres Cantos dataset. The obvious question is: are there other, related structures in the dataset that might give us information on what to change next?

Paul Willis from MMV did a quick "near neighbour" search (25 Aug 2011), particularly with an eye to getting rid of the ester in the lead structures. Structures below. As he said: "The first compound is a ketone analogue of the ester lineage – it's a singleton and not an ideal group from a drug discovery perspective but indicates other groups may be tolerated. The next set is the entire cluster output of another near neighbor I spotted – all have replacements for the ester group (again not especially drug like but possible indication that wide variation possible at this position) and interestingly some contain variations on the 4-F-Ph"



TCMDC-123563
637010 (CHEMBL)

	TCMDC-125698 627784 (CHEMBL)	TCMDC-125697 640978 (CHEMBL)	TCMDC-125659 626220 (CHEMBL)	TCMDC-124103 643107 (CHEMBL)	TCMDC-124456 640006 (CHEMBL)
					
R^1					Ethyl
R^2				H	H
R^3					

Cc1ccc(cc1)n2c(cc(c2C)C(=O)CN3C(=O)C(NC3=O)Cc4ccccc4)C
Cc1cc(c(n1c2ccc(cc2)Cl)C)C=C3C(=O)N(C(=Nc4ccccc4)S3)C5CCCC5
Cc1ccnc(c1)n2c(cc(c2C)C=C3C(=O)N(C(=Nc4ccccc4)S3)Cc5ccco5)C
Cc1cc(cc(c1)n2c(cc(c2C)C=C3C(=O)NC(=Nc4ccc(cc4Cl)S3)C)C
CCOC(=O)c1ccc(cc1)n2c(cc(c2C)C=C3C(=O)N(C(=Nc4ccccc4)S3)C5CCCC5)C
CCn1c(cc(c1C)C=C2C(=O)NC(=Nc3ccccc3)S2)C

Questions:

1) Are there other structures that are "similar" in the GSK set - searchable at Chembl.

2) What do these structures tell us about what to change next in the lead compounds?

User login

Username *

Password *

Create new account

Request new password

Log in

Malaria Research Community

Current Projects for Malaria
- Functional Reconstitution of the Plasmodium GPI:protein transamidase Complex
- Gene Wiki Overview
- Open Source Drug Discovery for Malaria Meeting - February 2012 - Why?
- Open Source Drug Discovery for Malaria Project Meetings
- Open Source Drug Discovery: The GSK Arylpyrrole Series
  - A list of what's needed in the OSDD Malaria project
  - Analog Synthesis - Variation of the Aryl Ring
  - Availability of TCMDC-123812 and TCMDC-123794
  - Biological Evaluation of Arylpyrrole Series
  - Druggability of the Arylpyrrole leads (TCMDC-123794 etc)
  - Known Near Neighbours of Initial Tres Cantos Leads
    - Synthesis Strategy for Near Neighbours
  - Prediction of Biological Targets of Actives
  - Proposed resynthesis strategy for TCMDC-123812 and TCMDC-123794

THE SUBCELLULAR DRUG TRANSPORT LABORATORY: Cellular pharmacokinetic analysis of antimalarials

The GSK Aminothienopyrimidine (ATP) Series

3) Importantly, **can we gain access to analogous structures that have been evaluated but not reported?**

Interestingly this includes compounds that are related to the TC hits above but which were perhaps assayed against other targets.

Data for the above compounds will be posted to the wiki page. Discussion of them can more easily happen in comments below.

- Synthesis Strategy for Near Neighbours

‹ Druggability of the Arylpyrrole leads (TCMDC-123794 etc) up Synthesis Strategy for Near Neighbours ›

Printer-friendly version Add new comment

Comments

Synthesis of near neighbour analogues

I've just started testing out a synthesis to these near neighbours (PMY 14-1). I'm going after an analogue of the compounds I already have to hand though.

pylioja
Oct 11 2011

REPLY

Update on the near neighbour thread...

The near neighbours were to some extent included in the project, though not all of the structures included above have, to date, been included. See the overall Story so Far for the current situation. Some of these near neighbours were very insoluble, though they did show significant late stage gametocyte activity. The compounds remain of interest.

MatTodd
Dec 15 2012

REPLY

Completed Projects for Malaria

Toxoplasma Research Community

Recent posts

Biological Results for ATP Series from April 2013
1 May 2013 - 3:48am By MatTodd
Replies: 0

Biological Data
1 May 2013 - 3:39am By MatTodd
Replies: 0

The GSK Aminothienopyrimidine (ATP) Series
1 May 2013 - 3:38am By MatTodd
Replies: 0

more

Recent comments

anacardic compounds to cure TB 5 March 2014 - 12:27am

Protein available 24 September 2013 - 8:20pm

Hi there, just watched Tom's 17 May 2013 - 11:32am

Meeting Recording and Minutes 21 March 2013 - 2:57am

SOLVED-onamides - perhaps! 28 February 2013 - 5:44pm

more

IP Guidelines

TSL Privacy Policy

We respect your privacy.

Fig S3. Screengrab of Synaptic Leap Node 344 (http://www.thesynapticleap.org/node/344), Proposed Resynthesis Strategy for TCMDC-123812 and TCMDC-123794, Paul Ylioja, 2011.

The Synaptic Leap
Open Source Biomedical Research

Search

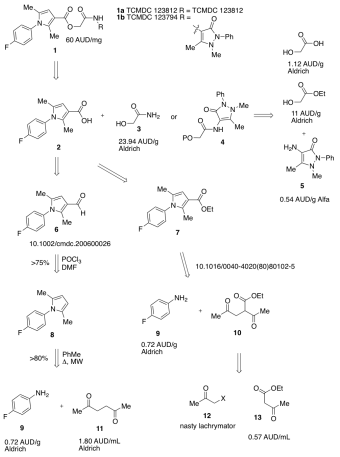
HOME COMMUNITIES GETTING STARTED RESOURCES NEEDED ABOUT

Proposed resynthesis strategy for TCMDC-123812 and TCMDC-123794

Published by pylioja on 18 August 2011 - 5:08am

Community
malaria research community

Below is a proposed synthesis strategy to the two members of the TCMDC aryl pyrrole series. Please comment, give your thoughts and improvements.
Experimental attempts are documented on an electonic lab notebook found here: malaria.ourexperiment.org/tcmdc_ap/



‹ Purchasable compound similarity maps up THE SUBCELLULAR DRUG TRANSPORT LABORATORY: Cellular pharmacokinetic analysis of antimalarials ›

Printer-friendly version Add new comment

Comments

Paal-Knorr Advice

(Posting on behalf of a TSL member who emailed)
Have you tried toluene with lower temps than reflux? If you need the heat I would go with a solvent like NMP and do the reaction in a sealed tube. Or try the reaction

User login

Username *

Password *

Create new account

Request new password

Log in

Malaria Research Community

Current Projects for Malaria
Functional Reconstitution of the Plasmodium GPI:protein transamidase Complex
Gene Wiki Overview
Open Source Drug Discovery for Malaria Meeting - February 2012 - Why?
Open Source Drug Discovery for Malaria Project Meetings
Open Source Drug Discovery: The GSK Arylpyrrole Series
A list of what's needed in the OSDD Malaria project
Analog Synthesis - Variation of the Aryl Ring
Availability of TCMDC-123812 and TCMDC-123794
Biological Evaluation of Arylpyrrole Series
Druggability of the Arylpyrrole leads (TCMDC-123794 etc)
Known Near Neighbours of Initial Tres Cantos Leads
Prediction of Biological Targets of Actives
Proposed resynthesis strategy for TCMDC-123812 and TCMDC-123794
THE SUBCELLULAR DRUG TRANSPORT LABORATORY: Cellular pharmacokinetic analysis of antimalarials
The GSK Aminothienopyrimidine (ATP) Series
Completed Projects for Malaria
Toxoplasma Research Community

Aug 22 2011

in a sealed tube with toluene. I always had better results with sealed tubes than with microwave. Just some simple modifications since you are getting product, but I would be concerned about the blue color change.

Darren Dressen, M.S.
Former medicinal chemist with Elan Pharmaceuticals
Chemistry teacher at Los Altos High School in California

REPLY

pylioja
Aug 24 2011

Thanks for the input. It

Thanks for the input. It looks like it's working pretty well in a neat open reaction. The reaction is very clean and can be purified by a simple recryst. As for the blue colour, the HCl wash could be the cause. Whatever is causing it is only present in trace quantities as the NMR of the material was pretty clean. None of the subsequent samples have changed colour. If you have any further thoughts on the later steps, please get in touch. Any nice aldehyde to acid oxidations? I'm currently playing with permanganate oxidations and possibly chlorite oxidations. They seem to have the best precedent going for them.

REPLY

CreativeChemistry
Sep 01 2011

Vilsmier

Matt
I would suggest that, with the Vilsmier formylation, the mixture is aged at about pH 5 overnight after the quench; we have just been doing some large scale ones on an indole and the intermediate needs an overnight stir to fully hydrolyse. After basification and filtration, the yields are coming out close to quantitative.

Also, on the oxidation you may want to try peroxide/potassium carbonate in methanol which we have used with good results (though not on the above project).
Bill

REPLY

pylioja
Sep 05 2011

Vilsmeier and Oxidation

Hi Bill, Thanks. I'll definitely give both of those a go.

REPLY

CreativeChemistry
Sep 05 2011

Oxidation

Ref for the peroxide reaction is
Synthesis, 1986, 1024

REPLY

Recent posts

Biological Results for ATP Series from April 2013
1 May 2013 - 3:48am By MatTodd
Replies: 0

Biological Data
1 May 2013 - 3:39am By MatTodd
Replies: 0

The GSK Aminothienopyrimidine (ATP) Series
1 May 2013 - 3:38am By MatTodd
Replies: 0

more

Recent comments

anacardic compounds to cure TB 5 March 2014 - 12:27am

Protein available 24 September 2013 - 8:20pm

Hi there, just watched Tom's 17 May 2013 - 11:32am

Meeting Recording and Minutes 21 March 2013 - 2:57am

SOLVED-onamides - perhaps! 28 February 2013 - 5:44pm

more

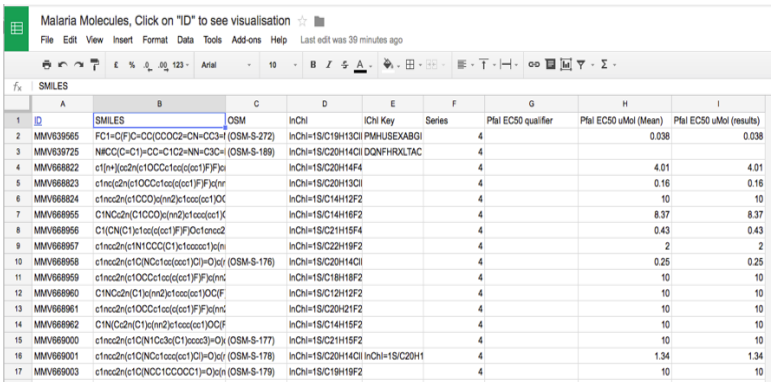
Fig S4. Screengrab of MacinChem (http://macinchem.org/reviews/vortex/tut26/scripting_vortex26.php), Importing Open Source Malaria Project Data, Chris Swain 2015.

Macs in Chemistry

Insanely great science

Importing Open Source Malaria Project data

The Open Source Malaria project is trying a different approach to curing malaria. Guided by open source principles, everything is open and anyone can contribute. To date a lot of people around the world have made contributions and the project is at a very exciting stage. Whilst everyone can see the compounds that have been made and the biological data, it is often spread over multiple web pages and can be tricky to link molecule with identifier with data. Over the last couple of months a significant effort has been put into populating a spreadsheet with all the information.



Malaria Molecules, Click on "ID" to see visualisation

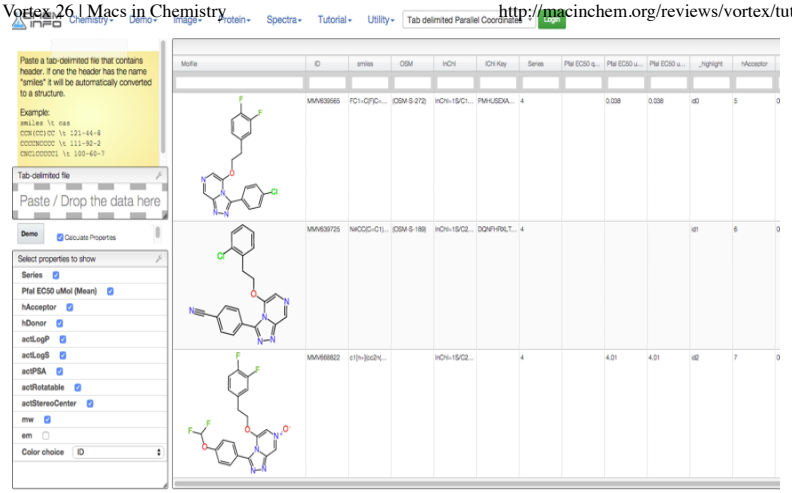
File Edit View Insert Format Data Tools Add-ons Help Last edit was 39 minutes ago

SMILES

	A	B	C	D	E	F	G	H	I
1	ID	SMILES	OSM	InChI	ICh Key	Series	Pfal EC50 qualifier	Pfal EC50 uMol (Mean)	Pfal EC50 uMol (results)
2	MMV639565	FC1=C(F)C=CC(CCOC2=CN=CC3=(	(OSM-S-272)	InChI=1S/C19H13Cl	PMHUSEXABGI	4		0.038	0.038
3	MMV639725	N#CC(C=C1)=CC=C1C2=NN=C3C=(	(OSM-S-189)	InChI=1S/C20H14Cl	DQNFHRXLTAC	4			
4	MMV668822	c1[n+](cc2n(c1OCCc1cc(c(cc1)F)F)c		InChI=1S/C20H14F4		4		4.01	4.01
5	MMV668823	c1nc(c2n(c1OCCc1cc(c(cc1)F)F)c(nn		InChI=1S/C20H13Cl		4		0.16	0.16
6	MMV668824	c1ncc2n(c1CCO)c(nn2)c1ccc(cc1)OC		InChI=1S/C14H12F2		4		10	10
7	MMV668955	C1NCc2n(C1CCO)c(nn2)c1ccc(cc1)C		InChI=1S/C14H16F2		4		8.37	8.37
8	MMV668956	C1(CN(C1)c1cc(c(cc1)F)F)Oc1cncc2		InChI=1S/C21H15F4		4		0.43	0.43
9	MMV668957	c1ncc2n(c1N1CCC(C1)c1ccccc1)c(ni		InChI=1S/C22H19F2		4		2	2
10	MMV668958	c1ncc2n(c1C(NCc1cc(ccc1Cl)=O)c(r	(OSM-S-176)	InChI=1S/C20H14Cl		4		0.25	0.25
11	MMV668959	c1ncc2n(c1OCCc1cc(c(cc1)F)F)c(nn		InChI=1S/C18H18F2		4		10	10
12	MMV668960	C1NCc2n(C1)c(nn2)c1ccc(cc1)OC(F		InChI=1S/C12H12F2		4		10	10
13	MMV668961	c1ncc2n(c1OCCc1cc(c(cc1)F)F)c(nn		InChI=1S/C20H21F2		4		10	10
14	MMV668962	C1N(Cc2n(C1)c(nn2)c1ccc(cc1)OC(F		InChI=1S/C14H15F2		4		10	10
15	MMV669000	c1ncc2n(c1C(N1Cc3c(C1)cccc3)=O)c	(OSM-S-177)	InChI=1S/C21H15F2		4		10	10
16	MMV669001	c1ncc2n(c1C(NCc1ccc(cc1Cl)=O)c(r	(OSM-S-178)	InChI=1S/C20H14Cl	InChI=1S/C20H1	4		1.34	1.34
17	MMV669003	c1ncc2n(c1C(NCC1CCOCC1)=O)c(n	(OSM-S-179)	InChI=1S/C19H19F2		4		10	10

The plan is that all new molecules will be added to the spreadsheet and new assays will added as additional columns. Storing the structures in a text format like SMILES provides a compact and efficient way to store molecular information which does not require any specials software. Whilst this provides a useful repository it is not particularly helpful for the chemists who would actually prefer to see the structures of the molecules.

In collaboration with Luc Patiny at http://www.cheminfo.org/ we have been able to provide a visualiser that pulls data directly from the spreadsheet. This currently requires Google Chrome. Link to visualiser. This also calculates a number of physicochemical properties on the fly.



Whilst this is very, very useful for viewing results it is not ideal for trying to build predictive models. Vortex is a chemically intelligent data analysis and visualisation platform. This script provides a one-click access to the OSM data and creates a new workspace containing the data, and since it is linked to the live spreadsheet you will always have access to the latest data.

OSMdata Vortex script

The first part of the script imports the data from the google spreadsheet as tab separated values, we then store the data as an array in list1.

We can then get the column names by parsing the first line of list1.

We then get the data by parsing each line of list1 starting at the second line.

Finally we create a new workspace.

```
# Vortex imports
import urllib2
import urllib
import csv
import sys
from com.xhaus.jyson import JysonCodec as json

# Vortex imports
import com.dotmatics.vortex.util.Util as Util
import com.dotmatics.vortex.mol2img.jni.genImage as genImage
import com.dotmatics.vortex.mol2img.Mol2Img as mol2Img
import com.dotmatics.vortex.table.VortexTableModel as vtm
import jarray
import binascii
import string
import os

# Example search string
# http://docs.google.com/spreadsheets/d/1Rvy6OiM291d1GN_cyT6eSw_C3lSuJ1jaR7AJa8hgGsc/export?format=tsv

mystr = "http://docs.google.com/spreadsheets/d/1Rvy6OiM291d1GN_cyT6eSw_C3lSuJ1jaR7AJa8hgGsc/export?format=tsv"

myreturn = urllib2.urlopen(mystr).read()
list1 = myreturn.split('\n')

TableName = "OSMData"

# Get column names
column_names = list1[0].split('\t')

rows = []
for i in list1[1:]:
    row = i.split('\t')
    rows.append(row)


arrayToWorkspace(rows, column_names, TableName)
```

The results are shown below.

The script can be downloaded from here why not give it a try and then contribute your findings and suggestions to the Open Source Malaria project.

Page Updated 24 June 2015

Fig S5. Screengrab of MacinChem (http://www.macinchem.org/reviews/osm/osmipython.php), Accessing Open Source Malaria Data using an iPython Notebook, Chris Swain, 2015.

Macs in Chemistry

Insanely great science

Accessing Open Source Malaria Data using an iPython Notebook

The Open Source Malaria project is trying a different approach to curing malaria. Guided by open source principles, everything is open and anyone can contribute. To date a lot of people around the world have made contributions and the project is at a very exciting stage. Whilst everyone can see the compounds that have been made and the biological data, it is often spread over multiple web pages and can be tricky to link molecule with identifier with data. Over the last couple of months a significant effort has been put into populating a spreadsheet with all the information.

Malaria Molecules, Click on "ID" to see visualisation

File Edit View Insert Format Data Tools Add-ons Help Last edit was 39 minutes ago

	A	B	C	D	E	F	G	H	I
1	ID	SMILES	OSM	InChI	IChI Key	Series	Pfal EC50 qualifier	Pfal EC50 uMol (Mean)	Pfal EC50 uMol (results)
2	MMV639565	FC1=C(F)C=CC(CCOC2=CN=CC3=I	(OSM-S-272)	InChI=1S/C19H13CII	PMHUSEXABGI	4		0.038	0.038
3	MMV639725	N#CC(C=C1)=CC=C1C2=NN=C3C=I	(OSM-S-189)	InChI=1S/C20H14CII	DQNFHRXLTAC	4			
4	MMV668822	c1[n+](cc2n(c1OCCc1cc(c(cc1)F)F)c		InChI=1S/C20H14F4		4		4.01	4.01
5	MMV668823	c1nc(c2n(c1OCCc1cc(c(cc1)F)F)c(nr		InChI=1S/C20H13CII		4		0.16	0.16
6	MMV668824	c1ncc2n(c1CCO)c(nn2)c1ccc(cc1)OC		InChI=1S/C14H12F2		4		10	10
7	MMV668955	C1NCc2n(C1CCO)c(nn2)c1ccc(cc1)(		InChI=1S/C14H16F2		4		8.37	8.37
8	MMV668956	C1(CN(C1)c1cc(c(cc1)F)F)Oc1cncc2		InChI=1S/C21H15F4		4		0.43	0.43
9	MMV668957	c1ncc2n(c1N1CCC(C1)c1ccccc1)c(n		InChI=1S/C22H19F2		4		2	2
10	MMV668958	c1ncc2n(c1C(NCc1cc(ccc1)Cl)=O)c(r	(OSM-S-176)	InChI=1S/C20H14CII		4		0.25	0.25
11	MMV668959	c1ncc2n(c1OCCc1cc(c(cc1)F)F)c(nn2		InChI=1S/C18H18F2		4		10	10
12	MMV668960	C1NCc2n(C1)c(nn2)c1ccc(cc1)OC(F		InChI=1S/C12H12F2		4		10	10
13	MMV668961	c1ncc2n(c1OCCc1cc(c(cc1)F)F)c(nn2		InChI=1S/C20H21F2		4		10	10
14	MMV668962	C1N(Cc2n(C1)c(nn2)c1ccc(cc1)OC(F		InChI=1S/C14H15F2		4		10	10
15	MMV669000	c1ncc2n(c1C(N1Cc3c(C1)cccc3)=O)(	(OSM-S-177)	InChI=1S/C21H15F2		4		10	10
16	MMV669001	c1ncc2n(c1C(NCc1ccc(cc1)Cl)=O)c(r	(OSM-S-178)	InChI=1S/C20H14CII	InChI=1S/C20H1	4		1.34	1.34
17	MMV669003	c1ncc2n(c1C(NCC1CCOCC1)=O)c(n	(OSM-S-179)	InChI=1S/C19H19F2		4		10	10

The plan is that all new molecules will be added to the spreadsheet and new assays will added as additional columns. Storing the structures in a text format like SMILES provides a compact and efficient way to store molecular information which does not require any specials software. Whilst this provides a useful repository it is not particularly helpful for the chemists who would actually prefer to see the structures of the molecules. In collaboration with Luc Patiny at http://www.cheminfo.org/ we have been able to provide a visualiser that pulls data directly from the spreadsheet. This currently requires Google Chrome. Link to visualiser. This also calculates a number of physicochemical properties on the fly. There is also a Vortex script that can be used to import data directly.

iPython Notebooks are becoming increasingly popular formats for combining combine code execution, rich text, mathematics, plots, chemical structures etc. For a brief introduction to getting started using iPython read this page.

The iPython notebook example shown below first downloads the data from the Google document as tab delimited text then, we read the file into a pandas data frame.

```
datafile = pd.read_table('./export?format=tsv')
```

We can browse the data in the iPython notebook or select a particular cell, since this is a SMILES string one of the nice features is we can use rdkit to render the structure within the notebook

```
smiles = datafile['SMILES'].loc[2]
mol = Chem.MolFromSmiles(smiles)
mol
```

Or we can begin the analysis of the data, and plot the results in the notebook.

```
datafile['PfaI EC50 uMol (Mean)'].hist()
```

Why not give it a try and then contribute your findings and suggestions to the Open Source Malaria project.

The iPython Notebook

In [1]:
```
!wget http://docs.google.com/spreadsheets/d/1Rvy6OiM291d1GN_cyT6eSw_C3lSuJ1jaR7AJa8hgGsc/export?format=tsv
```

```
--2015-07-21 16:21:48--  http://docs.google.com/spreadsheets/d/1Rvy6OiM291d1GN_cyT6eSw_C3lSuJ1jaR7AJa8hgGsc
/export?format=tsv
Resolving docs.google.com... 216.58.210.46, 2a00:1450:4009:800::200e
Connecting to docs.google.com|216.58.210.46|:80... connected.
HTTP request sent, awaiting response... 301 Moved Permanently
Location: https://docs.google.com/spreadsheets/d/1Rvy6OiM291d1GN_cyT6eSw_C3lSuJ1jaR7AJa8hgGsc/export?format=tsv
[following]
--2015-07-21 16:21:49--  https://docs.google.com/spreadsheets/d/1Rvy6OiM291d1GN_cyT6eSw_C3lSuJ1jaR7AJa8hgGsc
/export?format=tsv
Connecting to docs.google.com|216.58.210.46|:443... connected.
HTTP request sent, awaiting response... 200 OK
Length: unspecified [text/tab-separated-values]
Saving to: 'export?format=tsv.1'

export?format=tsv.1     [ <=>                  ]  76.35K  --.-KB/s   in 0.04s

2015-07-21 16:21:49 (1.83 MB/s) - 'export?format=tsv.1' saved [78183]
```

In [1]:
```
from rdkit import Chem
from rdkit.Chem.Draw import IPythonConsole
from rdkit.Chem import PandasTools
from rdkit.Chem import Draw
import pybel


import pandas as pd
datafile = pd.read_table('./export?format=tsv')
```

In [2]:
```
%matplotlib inline
```

In [3]:
```
datafile
```

Out[3]:

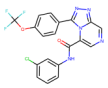
	ID	SMILES	OSM	
0	MMV639565	FC1=C(F)C=CC(CCOC2=CN=CC3=NN=C(C4=CC=C(Cl)C=C4)N32)=C1	(OSM-S-272)	InChI=1S/C19H13ClF2N4O/c20-14-4-2-13(3-5-1 /h1-6,9-11H,7-8H2
1	MMV639725	N#CC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC4=CC=CC=C4Cl)N32	(OSM-S-189)	InChI=1S/C20H14ClN5O/c21-17-4-2-1-3-15(17) /h1-8,12-13H,9-10H2
2	MMV657963	O=C(NC1=CC(Cl)=CC=C1)C2=CN=CC(N23)=NN=C3C4=CC=C(OC(F)(F)F)C=C4	OSM-S-271	InChI=1S/C19H11ClF3N5O2 /c20-12-2-1-3-13(8-12)25-18(29)15-9-24-10-1
3	MMV668822	c1[n+](cc2n(c1OCCc1cc(c(cc1)F)F)c(nn2)c1ccc(cc1)OC(F)F)[O-]	NaN	InChI=1S/C20H14F4N4O3 /c21-15-6-1-12(9-16(15)22)7-8-30-18-11-27(2
4	MMV668823	c1nc(c2n(c1OCCc1cc(c(cc1)F)F)c(nn2)c1ccc(cc1)OC(F)F)Cl	NaN	InChI=1S/C20H13ClF4N4O2 /c21-17-19-28-27-18(12-2-4-13(5-3-12)31-20
5	MMV668824	c1ncc2n(c1CCO)c(nn2)c1ccc(cc1)OC(F)F	NaN	InChI=1S/C14H12F2N4O2/c15-14(16)22-11-3-1-
6	MMV668955	C1NCc2n(C1CCO)c(nn2)c1ccc(cc1)OC(F)F	NaN	InChI=1S/C14H16F2N4O2/c15-14(16)22-11-3-1-
7	MMV668956	C1(CN(C1)c1cc(c(cc1)F)F)Oc1cncc2n1c(nn2)c1ccc(cc1)OC(F)F	NaN	InChI=1S/C21H15F4N5O2 /c22-16-6-3-13(7-17(16)23)29-10-15(11-29)31 /h1-9,15,21H,10-11H2
8	MMV668957	c1ncc2n(c1N1CCC(C1)c1ccccc1)c(nn2)c1ccc(cc1)OC(F)F	NaN	InChI=1S/C22H19F2N5O /c23-22(24)30-18-8-6-16(7-9-18)21-27-26-19- /h1-9,12-13,17,22H,10-11,14H2
9	MMV668958	c1ncc2n(c1C(NCc1cc(ccc1)Cl)=O)c(nn2)c1ccc(cc1)OC(F)F	(OSM-S-176)	InChI=1S/C20H14ClF2N5O2 /c21-14-3-1-2-12(8-14)9-25-19(29)16-10-24- (H,25,29)
10	MMV668959	c1ncc2n(c1OCCc1cc(c(cc1)F)F)c(nn2)C1CCOCC1	NaN	InChI=1S/C18H18F2N4O2/c19-14-2-1-12(9-15(1 /h1-2,9-11,13H,3-8H2
11	MMV668960	C1NCc2n(C1)c(nn2)c1ccc(cc1)OC(F)F	NaN	InChI=1S/C12H12F2N4O/c13-12(14)19-9-3-1-8(
12	MMV668961	c1ncc2n(c1OCCc1cc(c(cc1)F)F)c(nn2)C1CCN(CC1)C(C)=O	NaN	InChI=1S/C20H21F2N5O2/c1-13(28)26-7-4-15(5 /h2-3,10-12,15H,4-9H2,1H3
13	MMV668962	C1N(Cc2n(C1)c(nn2)c1ccc(cc1)OC(F)F)C(CN)=O	NaN	InChI=1S/C14H15F2N5O2/c15-14(16)23-10-3-1-
14	MMV669000	c1ncc2n(c1C(N1Cc3c(C1)cccc3)=O)c(nn2)c1ccc(cc1)OC(F)F	(OSM-S-177)	InChI=1S/C21H15F2N5O2 /c22-21(23)30-16-7-5-13(6-8-16)19-26-25-18-

In [4]:
```
smiles = datafile['SMILES'].loc[2]
```

In [5]:
```
mol = Chem.MolFromSmiles(smiles)
```

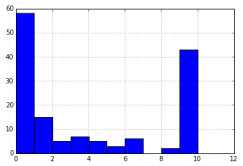
In [6]:
```
mol
```

Out[6]:



In [7]: [redacted]

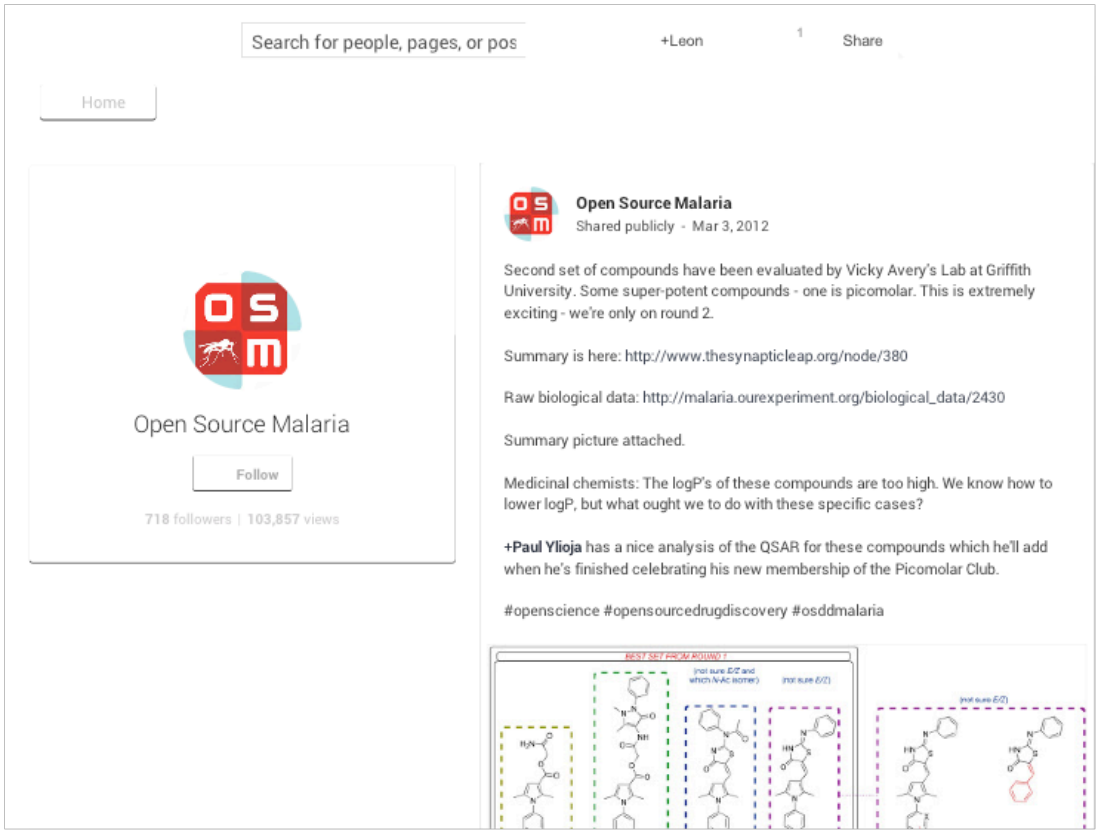
Out[7]: <matplotlib.axes._subplots.AxesSubplot at 0x1137a2f50>

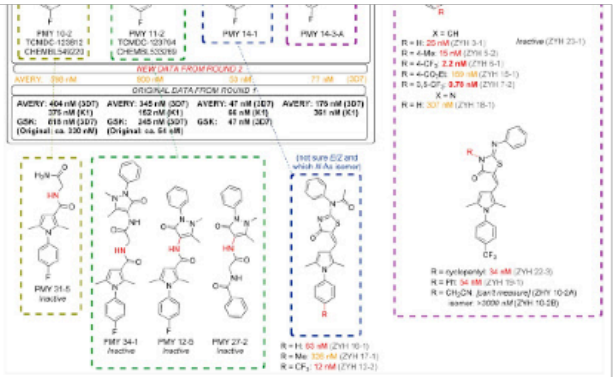


The python notebook can be downloaded from here

Last updated 21 July 2015.

Fig S6. Screengrab of Open Source Malaria Google+ discussion (https://plus.google.com/114702323662314783325/posts/Pma1Ddk2XCy), Discussion of Potential Assay Bias, 2012.





2 1

26 comments

Stuart Ralph Mar 4, 2012 +1

Maybe we should have discussed this last week, but this only occured to me when reading this. I think it is potentially important that if we have multiple labs conducting tests on the same compounds, that the labs conducting the later tests should not look at the specific results of the earlier test until they complete their own assays. I see that there is one or more potent compounds in this series, but I think I and people in my lab should maybe avoid looking at specific these data until we redo the assays independently. There is very little room for subjective interpretation of the data, so I am not too concerned about us biasing our interpretation, but maybe individuals might poison themselves against particular compounds if they see that they are not potent in others hands, (or throw out assays that seem to be non-potent, failed assays if reproducibility is low). What do others thing about this? Certainly a benefit of early sharing is that it eggs us on to follow up quickly, and maintains

enthusiasm when sharing great results, but maybe one solution is for the scientists conducting the assays to blind themselves from the previous results for specific compounds. Of course, this also highlights our need to share SOPs and to agree on common negative and positive controls too, as discussed last week.
cheers
Stuart

Christopher Southan Mar 4, 2012
It would be useful to include SMILES in the SAR summary sheets even as a cross-check against the InChI. If I find out anything useful in the databases I can report back. Cheers, Chris

Matthew Todd Mar 4, 2012
Stuart - very interesting point. I don't know. It's possible that the "negatives" might be less well looked at, yes. For the positive/negative control angle, the full data are here: http://malaria.ourexperiment.org/biological_data/2430 and we can certainly adopt a recommended set of standard. I think chloroquine and artemisinin were recommended at the meeting, and that 3D7 was standard, but quite how the assays are done is, to me, not clear. When we write this up is a good time to confront differences.

Christopher - good question - one for **+Paul Ylioja** . Which databases are you thinking of? I wanted with these data to bring in **+John Overington** and see what we could do about getting these data into ChEMBL.

Christopher Southan Mar 4, 2012
Matt, As you can see from http://cdsouthan.blogspot.com/ and our recent PubMed IDs I enjoy ferreting around in PubChem, ChEMBL and just about anywhere else. In regard to getting your new structures publicly surfaced quickly PubChem and/or ChEMBL should do nicely. JPO will help on the latter and I can give you contacts for the former. You could set up your own AID (assay) and feed in that way. As a precedent have you asked GSK (or any other pharma in fact) if they can just search your new structures against their entire collection including 3D/isostere ? If they did offer, quite how they decided to tell you about the results would be interesting ..... Cheers

John Overington Mar 4, 2012
We have some resource now available to do this sort of thing now - basically

hunting down datasets for malaria and getting them loaded into ChEMBL-NTD, better query capabilities for HTS data, compound filtering by availability - community annotation, etc. We should set up a call to discuss timing and options.

John Overington Mar 5, 2012
The person working on this in our group is Iain Wallace - he'll connect up with you shortly.

Matthew Todd Mar 5, 2012
Great, thanks John - here or email then we can TC

Iain Wallace Mar 6, 2012
Hi all, I am the new person in John's group. I was just wondering if anybody had a rough guess-timate of the %conservation between P. falciparum. and S. cerevisiae/H. sapiens. There are some really nice target id assays available in S. cerevisiae (http://chemogenomics.stanford.edu/) which might be useful. Thanks!

Open Source Malaria Mar 6, 2012
No idea, sorry. Shall we talk on Skype about data uploads etc?

Stuart Ralph Mar 7, 2012
Hi Iain, do you mean at an average per protein % similarity level? or in terms of divergence time?

Christopher Southan Mar 7, 2012
You may have done this already but, assuming I got the conversions right, ZHY7-2 has 10, 95% Tanimoto analogs in PubChem, most of which have a chemical supplier. They don't have those triflouros though and some have dodgy stero.

Iain Wallace Mar 7, 2012
Hi Stuart, I meant a guest-imate of the % of proteins in P. falciparum have a homolog in S. Cerevisiae or H. Sapiens. I get quite different numbers (10% vs. 20%) when I look at Homologene and InParanoid. Homologene has ~400 homolog clusters compared to ~1,000 in inParanoid for P. flaciparum/S. Cerevisiae. It would be nice to know if there was a rough expert expected ball park number for P. falciparum/H. Sapiens for comparison.

Matthew Todd Mar 7, 2012
+Christopher Southan the original hits from GSK came from a commercial library, so we'd expect some similar compounds to be available. The ones we're making now and ones planned are probably not, but we ought always to do that check, **+Paul Ylioja** , particularly when we're thinking about new heterocycles to replace/merge with the central pyrrole.

Christopher Southan Mar 7, 2012
Matt/Paul, like most screening collections they were an eclectic mix, including newish patent cpds and old ones from the Wellcome days. As you suggest Paul could pop the SMILES from what you have/are going to make into PubChem and do a 2D-walk and a 3D-walk if so inclined. NOBA you could x-check ChemSpider because the content does not overlap completely.

Matthew Todd Mar 7, 2012
+Christopher Southan Interesting. A 3-D walk sounds a little outside our level of expertise. Do you have capacity/interest in doing that, based on e.g. ZYH 7-2 ? (InChI=1S/C24H17F6N3OS/c1-13-8-15(9-20-21(34)32-22(35-20)31-18-6-4-3-5-7-18)14(2)33(13)19-11-16(23(25,26)27)10-17(12-19)24(28,29)30/h3-12H,1-2H3,(H,31,32,34)/b20-9-)

Christopher Southan Mar 7, 2012
OK, assuming its c3ccccc3NC(=NC2=O)SC2=Cc1cc(C)n(c1C)-c4cc(C(F)(F)F)cc(C(F)(F)F)c4. Hey - all I do is click on the "conformer" buttons, Evan Boulton's papers are heavy going ....

Matthew Todd Mar 7, 2012
Correct on SMILES, with the proviso that it handles tautomers on the thiazolone...

Christopher Southan Mar 7, 2012
Rats, I get errors on "conformer" with SMILES or .mol. Should you contemplate setting up an AID and submitting (even the virtuals) you'll get your own CIDs, all your intersects and proximities pre-computed, and the option to set auto-alerts (via MyNCBI)

OK, unique SMILEs seems to work and I have 32 conformer matches to walk through. How can I post the image results here ?

Christopher Southan Mar 7, 2012

I have uploaded a picture- There are high PubChem 3D shape matches between ZYH 7-2 and CIDs 53451274, 41011509, 1232848 but these have carboxylate anions where the flourines are

Paul Ylioja Mar 7, 2012 +1

Generally searching around the substructure, there are approximately 1000 "commercial compounds" on Scifinder. There are also about another 1000 known in literature. It would be great to get our hands on some more of these to help explore the SAR without too much synthetic effort. It looks like a lot of the hits though are duplicates due to either defined or undefined stereochemistry. The 3D structures you showed are quite different from the crystal structures we have obtained (to be posted up soon).

Pharmacophore modelling using our data and the original GSK dataset would be a useful exercise as we now have reliable 3D structure data. Would someone like to get this started?

Christopher Southan Mar 8, 2012

Matt/Paul, maybe you laid it out in the webinar last week but I'm missing the OSDD master-plan in terms of what we can offer to pitch in with. If you want to go analog shopping via SciFinder substructures - best of luck - I don't have access. Tanimoto walking through PubChem vendors and/or e-molecules via ChemSpider, is different. Ditto having one solid-phase structure is not per se SAR pharmacophore modeling, although it helps (and there's reasons why it may not match the computed PubChem 3D conformer sets). While a focus on the GSK set is understandable you also might want to subsume the GBF St Judes and NCGC results into this exercise. In this context I'm also missing the target deconvolution strategy i.e. you don't know if you're dealing with single or multiple pharmacophores.

Matthew Todd Mar 8, 2012

Well there's some background here: http://www.thesynapticleap.org/node/343. We're starting with some sets from the GSK set, just because we have to start somewhere, and the GSK team are part of the consortium - i.e. they're happy to work with us. The hits are also very good. These compounds are from whole cell assays, so no targets known. Gut medchem feeling optimization of our hits is what's next, but MMV are keen I think to move in vivo pretty soon. One of the ideas behind the similarity searches is to find compounds that are similar to the ones we're

looking at that may already have been made - i.e. that are actually sitting in lab fridges as we speak, and which could therefore be screened without having to be made.

Open Source Malaria Mar 9, 2012 +1
Sorry missed you - we were hosting a visiting speaker so the day was full. Next week sometime? mattodd on Skype

Stuart Ralph Mar 20, 2012
+Iain Wallace I don't have a more expert estimate of orthology, but OrthoMCL, developed by the roos lab with a particular interest in Plasmodium, has 1400 P. falciparum genes with a yeast ortholog, 1700 falciparum genes with a human orthologue. This is out of ~5400 falciparum genes. These translate to about 25-30% of the falciparum proteome. 10% certainly seems way too low to me.

Open Source Malaria Mar 21, 2012 +1
Biological activity of second set of compounds largely confirmed by GSK - data are here: http://malaria.ourexperiment.org/biological_data/2722

Open Source Malaria Mar 22, 2012
+Iain Wallace GSK going to check your DHODH prediction! http://www.thesynapticleap.org/node/385#comment-797

Add a comment...

Fig S7. Similarity Network Map to identify Purchasable Compounds Around the GSK Lead Series (Related to Text S2)

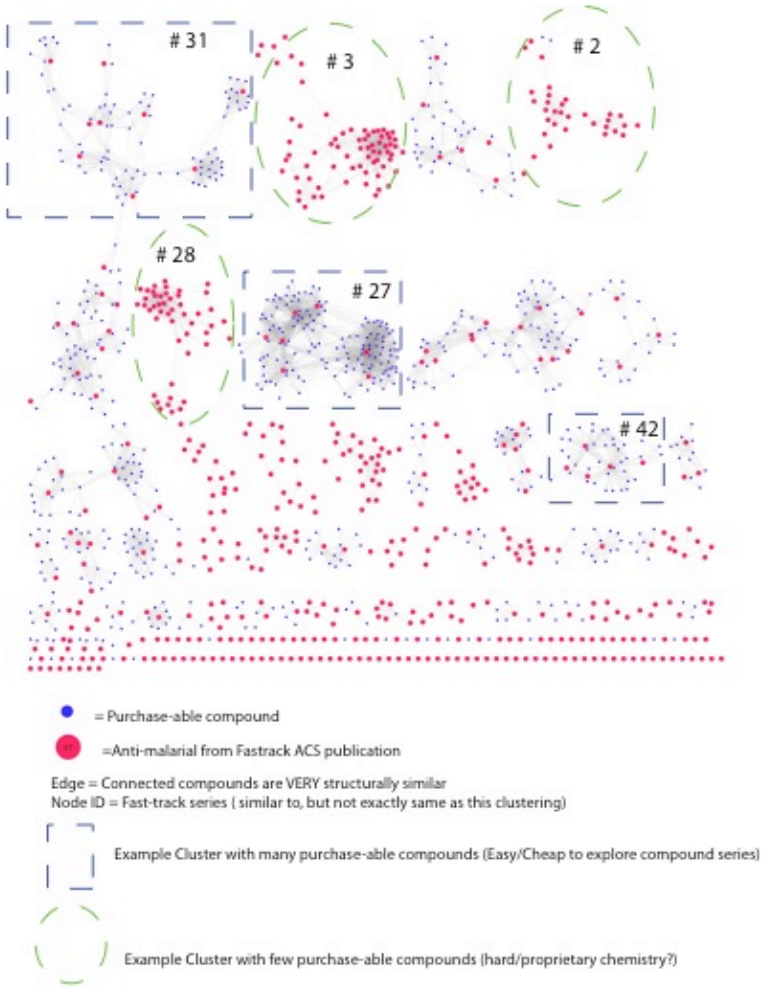


Fig S8. Similarity Map of Purchaseable Compounds around OSM-S-35. (Related to Text S2)

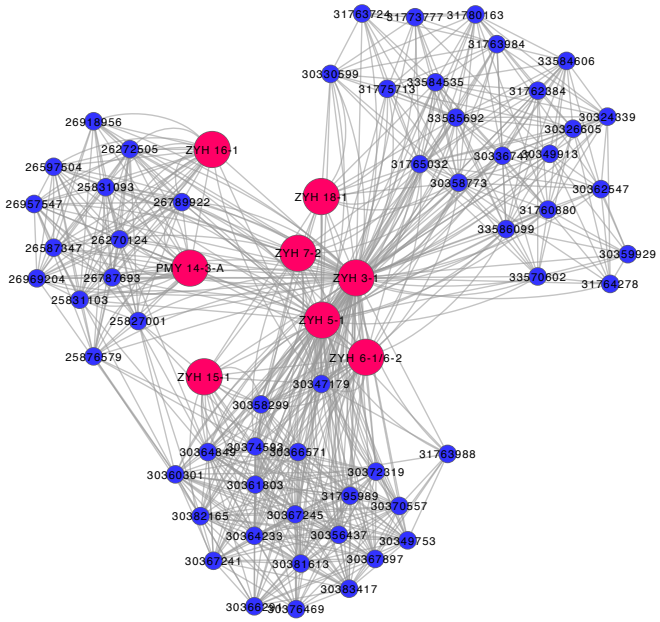


Fig S9. Screengrab of Synaptic Leap Node 399 (http://www.thesynapticleap.org/node/399), Purchasable Compound Similarity Maps, Iain Wallace, 2012. (Related to Text S2)

The Synaptic Leap
Open Source Biomedical Research

Search

HOME COMMUNITIES GETTING STARTED RESOURCES NEEDED ABOUT

You are here: Home » Malaria Research Community » Current Projects for Malaria » Open Source Drug Discovery: The GSK Arylpyrrole Series » Prediction of Biological Targets of Actives

Purchasable compound similarity maps

Published by wallacei on 11 April 2012 - 4:38pm

Community
malaria research community
Subject
Request for Help

There are over 5 million compounds that are available to purchase according to the meta service, E-molecules (http://www.emolecules.com).
It is worth exploring these in the context of the OSDD project as it will identify compound series' that are very easy to explore by purchasing analogues (i.e SAR by catalogue) aswell as identifying compounds that are potentially more sythetically accessible than others (i.e. if there many close neighbours these compounds might be easier to make than others).
To this end I have generate three chemical similarity maps, showing compounds that are very similar to known anti-malarial's that can be purchased.

Maps generated

1) Centered on ~40 compounds synthesized by OSDD:
http://malaria.ourexperiment.org/in_silico_prediction
/2929/purchasable_chemical_space_map_centered_on_OSDD_synthesised_compounds.html
This is particularly interesting, as there are many compounds similar to ZYH 3-1 that could be purchased exploring both ends of the molecule.
2) Centered on ~550 compounds from GSK priortized into ~40 compounds series
http://malaria.ourexperiment.org/in_silico_prediction
/2925/purchasable_chemical_space_map_centered_on_GSKs_prioritised_hit_compounds.html
This is interesting as it clearly identifies high priority series that are easier to follow up on than others based on the premise that if there are many close analogs available, it should be cheaper/easier to follow up on these clusters compared to clusters with no close analogs available.For example, the paper highlights five clusters for follow on work. #31 has the most similar available compounds (~100 compounds), while #18 has the least, 1, which would suggest to me that it is much more efficient to follow up on the compounds in cluster #31 than any of the other high priority clusters. There are other very interesting clusters too, which perhaps have more interesting chemistry.
3) Centered on ~400 compounds in the Malaria open box
http://malaria.ourexperiment.org/in_silico_prediction
/2919/purchasable_chemical_space_map_centered_on_Malaria_Open_Box_compounds.html
Likewise, certain compounds in the Malria open box have many more close neighbours than others which could help prioritize compounds for the community.

It would be great to get feedback on this approach, namely:

1) Does this type of visualization work for chemists? Is it straightforward to download cytoscape, install ChemViz and load the network?
2) What do we know about the SAR about these compounds? This would help to priortize/focus our search on chemical space. While I used ECFP_4 fingerprints, other similarity measures can prioritize other features differently (e.g. if we know a paticular substructure is key, then all compounds should contain it etc)
3) While I think the network view is great for a global overview of the compounds available (and can be overlayed with any other types of data that we can thing of, such as predicted targets etc), perhaps there is a better visualization for a smaller number of compounds?

‹ Compound Similarity Networks from Iain up Proposed resynthesis strategy for TCMDC-123812 and TCMDC-123794 ›

Printer-friendly version Add new comment

User login

Username *

Password *

Create new account

Request new password

Log in

Malaria Research Community

Current Projects for Malaria
Functional Reconstitution of the Plasmodium GPI:protein transamidase Complex
Gene Wiki Overview
Open Source Drug Discovery for Malaria Meeting - February 2012 - Why?
Open Source Drug Discovery for Malaria Project Meetings
Open Source Drug Discovery: The GSK Arylpyrrole Series
A list of what's needed in the OSDD Malaria project
Analog Synthesis - Variation of the Aryl Ring
Availability of TCMDC-123812 and TCMDC-123794
Biological Evaluation of Arylpyrrole Series
Druggability of the Arylpyrrole leads (TCMDC-123794 etc)
Known Near Neighbours of Initial Tres Cantos Leads
Prediction of Biological Targets of Actives
Bioisosteric transformation maps
Compound Similarity Networks from Iain
Purchasable compound similarity maps
Proposed resynthesis strategy for TCMDC-123812 and TCMDC-123794
THE SUBCELLULAR DRUG TRANSPORT LABORATORY: Cellular

Comments

MatTodd
Apr 11 2012

Structures in purchasable similarity networks

Iain - this is very interesting. Cytoscape/chemviz are a doddle to install. So - let me clarify three things

1) If a compound appears in one of the three maps you posted above then it's commercially available? (was that through emolecules?)
2) How do we visulaise structures? I see there is a SMILES when I click once, but is there a possibility of a little window displaying the structure?
3) (Non-essesntial) One of the next steps would be to contact suppliers. It would save a non-trivial amount of time if we could group availability of compounds by vendor. Non-essential, just convenient!

Each of the maps is interesting in its own right, but I will flag the GSK one up to Javier and Felix at Tres Cantos - it's a very nice layer on top of their "Open Invitation" paper and could have ramifications for target prioritization. It's also important for us (at Sydney) to look at the other two targets Jimmy Cronshaw is pursuing.

REPLY

wallacei
Apr 12 2012

Exploring the maps

1) Yeah, if a node is blue it means it was found in E-Molecules. The node label is the e-molecules id. The downloaded dataset was from 1-Mar-2012, so will not all molecules will neccessarily be available today
2) This is what I posted in response to a comment on Google+ (https://plus.google.com/u/0/114702323662314783325/posts/fp4qfLsBkUe)
Once it is installed, you can either
1) Right click on a node and select "Cheminformatics Tools" -> "Depict 2D Structure" -> "Show 2D Structures from this Node"
Alternatively, if that doesn't work (occasionally it doesn't)
2) Select node/nodes of interest then
Select from the menu bar, "Plugins" -> "Cheminformatic Tools" -> "Show table of compounds from selected nodes"
This will generate a table showing some information from various attributes. Columns can be deleted or resized.
There is some more details on general cytoscape usage linked there as well.
3) To get suppliers, you can
From the Cytoscape menu, press "Select" -> "Nodes" -> "All Nodes"
In the node attribute browser at the bottom of the screen you can then select all the id's by clicking the first one and holding shift and then pressing the down arrow. Once all the ids are selected/highlighted in the table, right click and select "Copy".
Now the id's can be pasted into the emolecules website
http://www.emolecules.com/ -> click "Enter a list"
On list page, select "Emolecules ID' and paste id list and search.
On the results page, click "Export" -> "Excel Spreadsheet"

REPLY

pylioja
Apr 13 2012

Shopping!

Iain, These are brilliant. Thank you so much for doing this. I'm going to export a list of likely candidates and see if we can go about procuring them.

REPLY

wallacei
Apr 14 2012

So many options!

Great!
It will be very interesting to see which (and why) you identify as likely candidates. As I mentioned above, it is possible to regenerate the maps based on the type of compounds you want to purchase.

pharmacokinetic analysis of antimalarials

The GSK Aminothienopyrimidine (ATP) Series

Completed Projects for Malaria

Toxoplasma Research Community

Recent posts

Biological Results for ATP Series from April 2013
1 May 2013 - 3:48am By MatTodd
Replies: 0

Biological Data
1 May 2013 - 3:39am By MatTodd
Replies: 0

The GSK Aminothienopyrimidine (ATP) Series
1 May 2013 - 3:38am By MatTodd
Replies: 0

more

Recent comments

anacardic compounds to cure TB 5 March 2014 - 12:27am

Protein available 24 September 2013 - 8:20pm

Hi there, just watched Tom's 17 May 2013 - 11:32am

Meeting Recording and Minutes 21 March 2013 - 2:57am

SOLVED-onamides - perhaps! 28 February 2013 - 5:44pm

more

REPLY

MatTodd
Apr 19 2012

Many purchasable analogs makes a series more attractive?

Reproduction (with permission) of an email correspondence on this question:

Javier Gamo from GSK:

"Hi Matt,
You rationale is good but amenability of the chemistry (i.e. easy chem to have a good number of derivatives in a short time) should be another one if the initial goal is to get as many derivatives as possible to establish an preliminary SAR. This could be a good possibility providing there is no other major differences...in any case I should feel more comfortable driving the choice by a good biological profile. This could give you a better opportunity of starting with a good parasite target from the beginning and increasing chances of getting your desired therapeutic profile

Comments?

Javier"

Iain Wallace responded, also by email:

"Hi Javier,

I would be very interested to know if the number of available compounds commercially correlated with amenability of chemistry. Or maybe this is very lab specific?

Regardless, I would agree the biological profile should be the main driver of deciding which compounds to screen. However, my understanding (admittedly naive) is that all of these compounds equally attractive starting points, with no additional biological information available, other than that they are potent against the parasite?

Cheers,

Iain

REPLY

wallacei
Apr 22 2012

SAR Information

We can also use this maps to identify which compound series is the largest. A cluster containing many known anti-malarials should have alot of SAR information that could be used to guide synthesis design.
Conversly, a cluster containing only one known anti-malarial or a singleton would not be a great starting point for a lead optimization as we would have no SAR information.

REPLY

MatTodd
Apr 23 2012

SAR Information - but

Yes, BUT, sometimes we like the small series or singletons because those may represent unusual compounds with new mechanisms of action, that may complement what's known. So a cluster may be a safer bet for deriving a new bioactive, but not necessariy the best for diversity. There must be an analogy there...

REPLY

wallacei
Apr 23 2012

SAR information - all depends....

Yeah, I think it all depends on what you would like to do and what the ideal end result would be.
For example, if you wanted to identify compounds that have good anti-malarial properties, that you can quickly build a structure activity relationship data for, you could prioritize compounds that
1) already have lots of SAR info from the large publically availble screens
2) have lots of purchasable analogs
3) are easy to make
4) and importantly don't look similar to known anti-malaria compounds

in the clinic.

Alternatively, if you wanted to identify novel, unique anti-malarial compounds then you could
1) looking for active singletons
2) that don't have any purchasable analogs
3) that don't appear in the patent literature

The second option seems to be much more costly and difficult, but that is just my risk adverse two cents. There are probably other aspects that I haven't considered either, which might be much more important. Personally, I don't understand the drive for diversity for diversity's sake, because if that was all that mattered we should be just screening and making natural products. And I am not sure how much the concept novel diverse compound = unique mode of action holds up. According to people who screen natural products, the same mode of action is repeatedly found despite being structurally different (this is a really nice review of Natural Products for anti-bacterial compounds carried out in Merck http://www.sciencedirect.com/science/article/pii/S1074552111000354).

REPLY

cdsouthan
May 07 2012

SAR-lite vs SAR-pro

Mat/Ian, my takes are somewhat orthogonal to yours but I hope add to the discussion.

1. Pharma's need to generate IP has impelled them to pack their screening collections with Chinese/Indian/Russian libraries that have designed-in novelty and diversity but also a high proportion of "no hitters" because they are too divergent from known bioactives. We don't have this problem and should therefore be circumspect about such strategies.
2. IMCO the best predictor of possible new (antimalarial) bioactivity is simply any previous bioactivity, in vitro or in vivo, from any source (paper, patent, poster or public assay)
3. This thus includes ~ 40K old drug leads, ~ 200K NPs, ~ 3-5 millon actives from patents and ~ 1 million from ChEMBL (that includes the confirmed PubChem BioAssay hits).
4. What we might want to emulate from pharma is their strategy of working up several series of diverse chemotypes that can serve as back-ups when one of them runs into trouble. They can also (on a good day) cross-corroborate pharmacophores/isosteres and other types of VS models.
5. However, as has been pointed out, with our "bag of targets" different series may have different molecular moas. This can obviously have advantages but may confound SAR modeling between series
6. Verified (and QC'd) singeltons can be valuable founders of new series depending on why they are singletons e.g. if analogues are sparse or they have idiosyncratic discontinuous SAR.
7. Exploring off-the-shelf analogues is obviously efficient and potentially informative but I think we need to be wary of "SAR-lite" circularity (i.e. easy/cheap commercial compounds > screening collections > hits > clusters > more commercial analogues > more hits > …)
8. As we know "SAR-pro" involves the classic design-make-test-analyse cycle that can utilize much tougher and/or novel chemistry (e.g. http://www.ncbi.nlm.nih.gov/pubmed/21963616)
9. I'm sure we'd agree a mix of SAR-lite and SAR-pro is a good way forward but it's a challenge to optimize resourcing between the approaches.

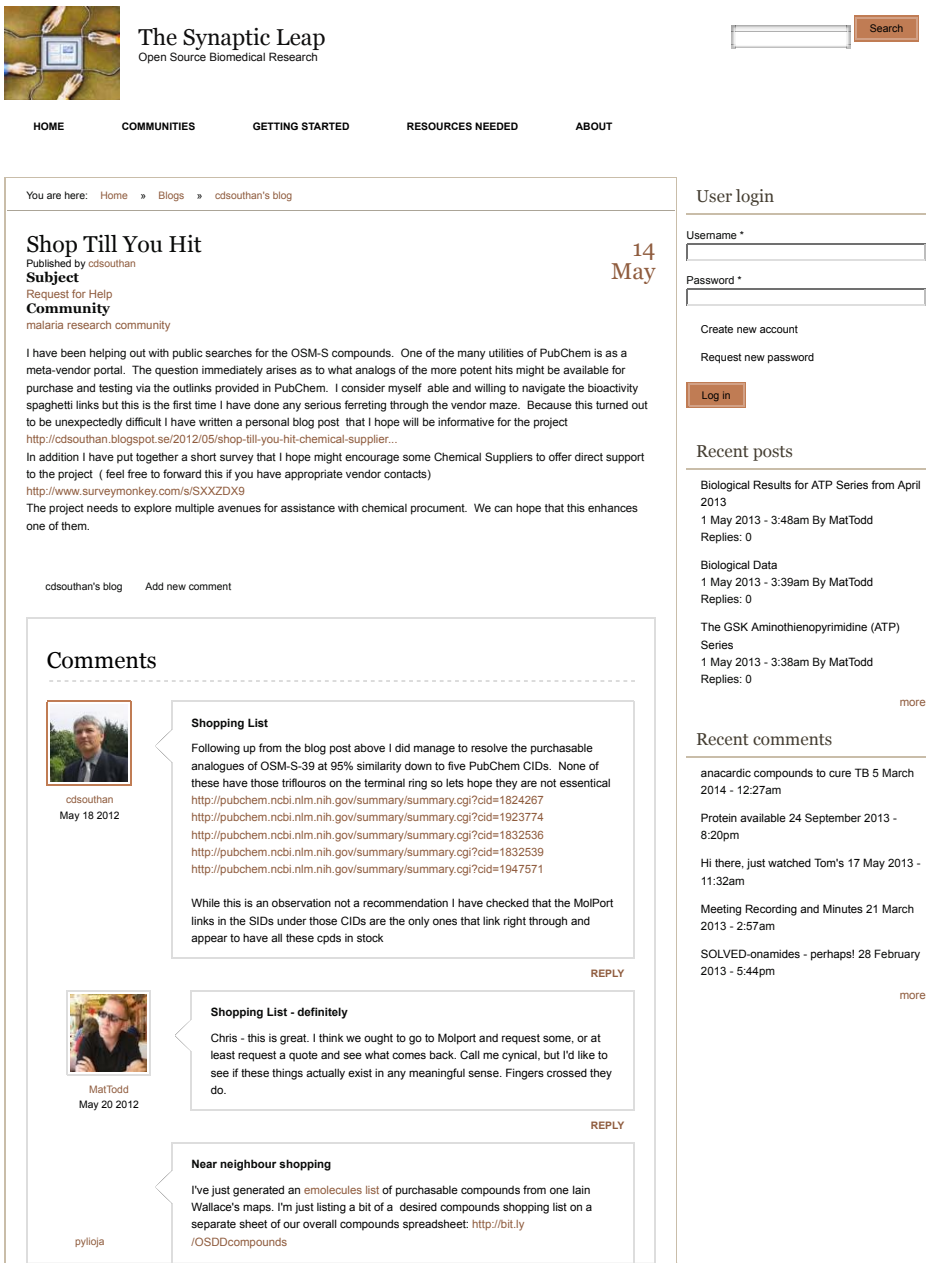
REPLY

IP Guidelines

TSL Privacy Policy

We respect your privacy.

Fig S10. Screengrab of Synaptic Leap Node 404 (http://www.thesynapticleap.org/node/404), Shop Till You Hit, Chris Southan, 2012. (Related to Text S2)



The Synaptic Leap
Open Source Biomedical Research

Search

HOME COMMUNITIES GETTING STARTED RESOURCES NEEDED ABOUT

You are here: Home » Blogs » cdsouthan's blog

Shop Till You Hit

Published by cdsouthan
Subject
Request for Help
Community
malaria research community

14 May

I have been helping out with public searches for the OSM-S compounds. One of the many utilities of PubChem is as a meta-vendor portal. The question immediately arises as to what analogs of the more potent hits might be available for purchase and testing via the outlinks provided in PubChem. I consider myself able and willing to navigate the bioactivity spaghetti links but this is the first time I have done any serious ferreting through the vendor maze. Because this turned out to be unexpectedly difficult I have written a personal blog post that I hope will be informative for the project
http://cdsouthan.blogspot.se/2012/05/shop-till-you-hit-chemical-supplier...
In addition I have put together a short survey that I hope might encourage some Chemical Suppliers to offer direct support to the project (feel free to forward this if you have appropriate vendor contacts)
http://www.surveymonkey.com/s/SXXZDX9
The project needs to explore multiple avenues for assistance with chemical procument. We can hope that this enhances one of them.

cdsouthan's blog Add new comment

Comments

cdsouthan
May 18 2012

Shopping List

Following up from the blog post above I did manage to resolve the purchasable analogues of OSM-S-39 at 95% similarity down to five PubChem CIDs. None of these have those triflouros on the terminal ring so lets hope they are not essentical
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=1824267
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=1923774
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=1832536
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=1832539
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=1947571

While this is an observation not a recommendation I have checked that the MolPort links in the SIDs under those CIDs are the only ones that link right through and appear to have all these cpds in stock

REPLY

MatTodd
May 20 2012

Shopping List - definitely

Chris - this is great. I think we ought to go to Molport and request some, or at least request a quote and see what comes back. Call me cynical, but I'd like to see if these things actually exist in any meaningful sense. Fingers crossed they do.

REPLY

Near neighbour shopping

I've just generated an emolecules list of purchasable compounds from one Iain Wallace's maps. I'm just listing a bit of a desired compounds shopping list on a separate sheet of our overall compounds spreadsheet: http://bit.ly /OSDDcompounds

pylioja

User login

Username *

Password *

Create new account

Request new password

Log in

Recent posts

Biological Results for ATP Series from April 2013
1 May 2013 - 3:48am By MatTodd
Replies: 0

Biological Data
1 May 2013 - 3:39am By MatTodd
Replies: 0

The GSK Aminothienopyrimidine (ATP) Series
1 May 2013 - 3:38am By MatTodd
Replies: 0

more

Recent comments

anacardic compounds to cure TB 5 March 2014 - 12:27am

Protein available 24 September 2013 - 8:20pm

Hi there, just watched Tom's 17 May 2013 - 11:32am

Meeting Recording and Minutes 21 March 2013 - 2:57am

SOLVED-onamides - perhaps! 28 February 2013 - 5:44pm

more

Fig S11. Screengrab of Blog Post (http://cdsouthan.blogspot.se/2012/05/shop-till-you-hit-chemical-suppliers.html), Shop Till You Hit: Chemical Suppliers and Malaria OSDD, Chris Southan, 2012. (Related to Text S2)

Shop Till You Hit: Chemical Suppliers and Malaria OSDD

Updates 14th May and 27 July, mainly corrections related to comments (with thanks). Also, please see sequel post shop-till-you-hit-part-II [http://cdsouthan.blogspot.se/2012/07/shop-till-you-hit-part-ii.html] .

****

I am pleased to be participating in the OSDD antimalarial project (AMP) in a small way and have been following the interesting implications for open drug discovery for major tropical diseases. You can find background information at the Synaptic Leap [http://www.thesynapticleap.org/] . As a starting point for this post I can draw on my experience as an experimental biochemist. This means I understand the importance of ordering things that arrived in small bottles, weighing them out to use in experiments and, crucially, being assured that said bottle contained what we inferred from the label. One learned the hard way not to take this for granted when either; said bottles never turned up, you had picked the wrong name/catalog number (and lost the invoice), static charge spattered the contents all over the balance, or, for proteins and peptides, my own HPLC runs [http://www.citeulike.org/user/cdsouthan/article/7558365] showed many peaks. I can even tell the tale of a head of research at large R&D operation (now lost in M&A history) who issued an edict that we should stop ordering from a certain major supplier because internal QC revealed too many cases where the stuff was clearly not what it said on the label. The context of this is that as the AMP runs into the chemical supplier maze I have a practical and not just an abstract appreciation of the problems. I can also draw on more recent experience since we grappled with incorporating chemical suppliers as sources in Chemistry Connect [http://www.citeulike.org/user/cdsouthan/article/9935552] (see fig. 2d)

The good news is that, freed from the tyranny of having to stake out IP estate by continually synthesizing novel structures, AMP can, in theory, merrily just go shopping in the 2D and 3D analogue proximity around their openly confirmed hits (i.e. "SAR lite" by credit card). The bad news is this turns out to be an unexpectedly difficult undertaking. What I can do here is outline some observations from sources and links that might increase awareness of the challenges, and at least some approaches to solutions. Before that I should point to the excellent work already done by IW in support of AMP, where he has clustered the GSK antimalarial [http://www.thesynapticleap.org/node/399] hits in Tanimoto space against a download of e-molecules.

Chemical suppliers remind me of Greek souvenir shops in that there are so many you wonder how any of them are commercially viable. PubChem currently lists ~70 vendor sources [http://pubchem.ncbi.nlm.nih.gov/sources/sources.cgi?mode=substanceinfo] containing between

one [http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?sid=124391270] (!) and ~7 million SIDs. Only nine are close to or above one million and I think these are all are meta-sources that aggregate primary suppliers. The vendor classification adds up to just below 40 mill [http://www.ncbi.nlm.nih.gov/pcsubstance?db=pcsubstance&cmd=search&term=all[filt]%20AND%20%28has_src_vendor[filt]%29&loc=s_frm] or 43% of the total PubChem substance links. This rises to nearly 21 mill, or just over 60%, for compounds. This means, for example, ~15% of ChEMBL and ~13% of the GSK antimalarial hits (that are also in ChEMBL) should be available off-the-shelf and, of course, there are substantial numbers of analogues with similarity high enough to warrant testing.

However, looking at the wider vendor ecosystem reveals a complex picture. I have no idea what the total number of independent suppliers is but I guess somewhere north of 500. The challenges of picking a good one are not new and there is a long and heavily commented list in this 2010 "In The Pipeline" chemical suppliers customer reviews [http://pipeline.corante.com/archives/2010/03/19/the_chemical_suppliers_customer_reviews.php] post. While PubChem and ChemSpider are the *de-facto* largest open meta-source aggregators it's not easy to determine which vendors are in one, t'other, both, or neither. Adding to the confusion some have partial representations and/or nestings in either, or both of the two portals, in addtion to their stand-alone search offerings. For example, e-molecules [http://www.emolecules.com/] declare 5.3 mill to be searchable on their own site but they do not submit directly to PubChem. However, selecting e-molecules in ChemSpider gives 4.8 mill, but they also have 4.6 mill links nested within ZINC, most of which you can click through to from PubChem. ZINC itself declares 21 mill for their own interface, but have only just over 7 mill links inside PubChem and 3.8 mill in ChemSpider. Some of the difference is the exclusion of virtual "make-on-demands [http://cdsouthan.blogspot.se/2011/06/shrinking-pubchem-aug-2009-yep-it-wuz.html] " from ZINC suppliers such as Enamine [http://www.enamine.net/] . While the website from the latter is well laid out they imply that their "Real" collection needs a 34-file download or purchase a CD (27 July CD is free, see comment) but omit to mention the 15 mill structures are directly searchable via ZINC. Analogously, Ambinter [http://www.ambinter.com/about] declare 18 millions (*sic*), have 5.5 mill in PubChem, 5.0 million in ZINC, only 2.6 million in-common between these, no mentions on the website and no SID out-links!

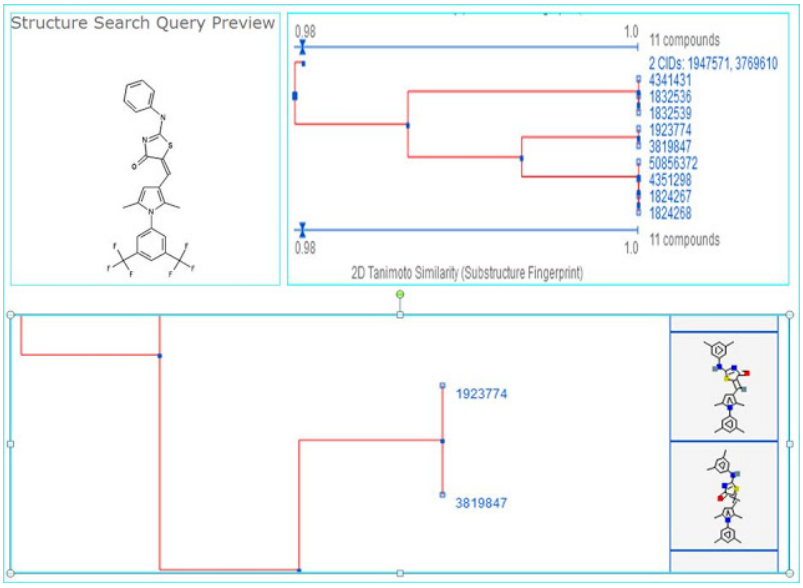
Finding out who might have what for sale where isn't made any simpler when sources such as ChemNavigator [https://www.chemnavigator.com/members/register.asp] , declare 55 mill structures from 300 suppliers as only accessible behind a registration wall, but also omit to mention the pre-2009 content thereof can be openly searched via the Chemical Structure Lookup Service. [http://cactus.nci.nih.gov/cgi-bin/lookup/search] This raises the key question as to which structures might be unique to a particular vendor because, understandably perhaps, they don't compare each others content. To add to the fun I came across a cryptic vendor in

PubChem. While ChemDiv [http://chemistryondemand.com:8080/eShop/] have an open search interface for their 1.2 million structures they are not a PubChem source. However, searching "ChemDiv1" in PubChem brings back ~ 0.3 mill CIDs, mostly from ChemBank. Inside PubChem of course you can always tell "who has what" providing you have the perspicacity to do the intersects and unions. An example is shown below that should be easy to read.

Search	Add to builder	Query	Items found
#21	Add	Search **((#18) AND #9) AND #6**	1273585
#20	Add	Search **((#18) OR #9) OR #6**	15304403
#18	Add	Search Limits: **Ambinter**	5524464
#9	Add	Search Limits: **ZINC**	8120629
#6	Add	Search Limits: **ABI Chem**	7712804

[http://3.bp.blogspot.com/-N5KO0gUDoQI/T7DtXoKfGUI/AAAAAAAAAbY/uJL2xokPN5s/s1600/CS4.JPG]

We can explore an example of supplier links directly relevant to AMP by popping their current sub-nM lead OSM-S-39 (Cc1cc(/C=C\2 /C(=NC(=Nc3ccccc3)S2)O)c(C)n1c1cc(cc(c1)C(F)(F)F)C(F)(F)F) against PubChem at 95% similarity. You get 11 CID matches that include only vendor SIDs as there are no data links in the set. However, as you can see below, the clustering looks quirky.



[http://4.bp.blogspot.com/-FFuCYmIY2GA/T6ucb1bNxPI/AAAAAAAAAa0/EGDnYqKJF5E/s1600/CS2.JPG]

The reason is that good-old stereo multiplexing from these vendors collapses the 11 CIDs to just four "same connectivity" sets. OK, so this will spare the credit card a bit but who do you go for ? I prefer to steer clear of those "crossed bond" versions so we'll take a look at just the 8 SIDs under CID 1947571. [http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&db=pcsubstance&term=1947571[cid]]

[http://3.bp.blogspot.com/-rTL3oQ8MYMA/T6ugP9l9JcI/AAAAAAAAAbA/7ayX5QhYJ2s/s1600/CS3.JPG]

This looks like three direct and four meta-suppliers but there is no flag or filter that can discriminate this. This adds up to only seven because ZINC appears in two SIDs (with different numbers) because it has been piggy-backed under a NextBio SID as a dead-link. In the real ZINC SID 60809296 [http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?sid=60809296&loc=es_rss] you can go out to the website (but be careful to use the back-button rather that get directed back-in via the deprecated CID 44173449 [http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=44173449]) or you can bypass straight to the nested individual vendor links that includes emolecules. Going back to the top of the list we can follow out SID 110765303 [http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?sid=110765303&loc=es_rss] . However, trying to actually order from ABI Chem

turns out to be problematic because neither the IUPAC nor their own ID retrieves anything! The next SID pointer to AKOS000324153 [http://akosservice.de/akossamplesservice/php/akossamplesretrieval.php?IDNUMBERS=AKOS000324153] at least indicates it is in stock but the dead-link enjoins you to e-mail them for a quote. Proceeding down the list, Molport [http://www.molport.com/buy-chemicals/moleculelink/JNYMIGKOGRELOP-XKZIYDEJBZ/2562616#building-block-section] , does appear to get you to a shopping cart for each of their three suppliers (no, I didn't try out my card..) but you might want to spin a coin for which one to select. Vitas M [http://www.request.vitasmlab.com/index.php?option=com_search_stk&Itemid=22&stk=STK159682&?utm_source=pubchem&utm_medium=p_search_link&utm_campaign=pubchem_search&utm_content=pubchem_slink] also indicated the compound was in stock but you have to fill out an extensive quote form. Last on the SID list takes you over to ChemSpider 1489859 [http://www.chemspider.com/Chemical-Structure.1489859.html] which points to seven vendors but most of those were nested under the previous links already.

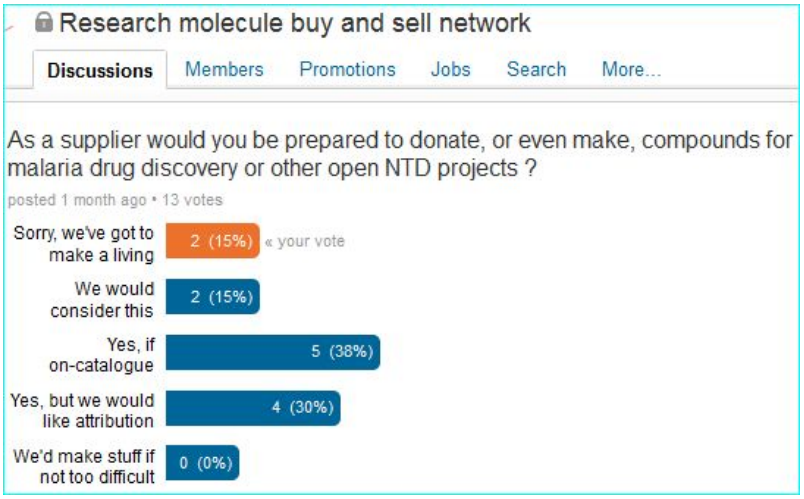
So where does this leave us ? From a personal viewpoint its obvious from my posts on this blog that following the link spaghetti for real data and documentation across different sources can be interesting, insightful and valuable. In contrast, I found the navigation of vendor spaghetti tedious and, at times, exasperatingly circular. It's not that I don't appreciate the essential contribution of chemical suppliers as a whole to medicinal chemistry and chemical biology. However, relentless proliferation and cryptic nesting does seem to have produced a "Greek souvenir shops" effect. Giving the benefit of the doubt that vendors don't want buying their stuff to be difficult or confusing, I can offer some suggestions:

1) Make it really easy to order (like Amazon) by linking straight through to what is in-stock with minimum effort (max one or two clicks, no quoting delays, registrations, form filling or ID re-inputing).
2) If you do expose a searching interface enable this for SMILES,/InChI/SDF inputs (and include these in the product specification) but please not just only sketchers, names, IUPACs or CAS numbers (anyone able to verify the latter might use them to order via SciFinder anyway).
3) If part or all of your content is nested under major meta-portals a) find this out and b) declare it.
4) Enable at least a limited batch upload searching and batch ordering from those results (even cluster visualisation?).
5) Try to get the structures that have links to in PubChem or ChemSpider correct, the ID-specific links working reciprocally, and clean up by re-submission what you may have out there already.
6) If anyone had the wherewithal to make a network display of which large primary suppliers were nested within which aggregation portals, this would be very useful.

7) If you enable 3D searching you could sell more.
8) You might consider proactively stocking up on same-structures and analogues around verified bioactivities of all types (ChEMBL being an obvious starting point).

Given the potentially testable analogue landscape around even just the antimalarial GSK actives is at least 100-fold higher than for just the single lead above, the procurement challenges and budget constraints faced by AMP become clear. You can read on the Synaptic Leap and associated G+ conversations that the AMP community is grappling towards some solutions for this. The analysis by IW has already been mentioned but there is also the interesting idea for a Molecular Craigslist [http://intermolecular.wordpress.com/2012/04/20/molecular-craigslist/] proposed by MT.

What I am going to try is an expansion of what you can see below as the results of a LinkIN poll specifically for Chemical Suppliers



[http://3.bp.blogspot.com/-1pIo9LDfIp8/T6vF3blBdbI/AAAAAAAAAbM/UlQUgksGBeA/s1600/CS1.JPG]

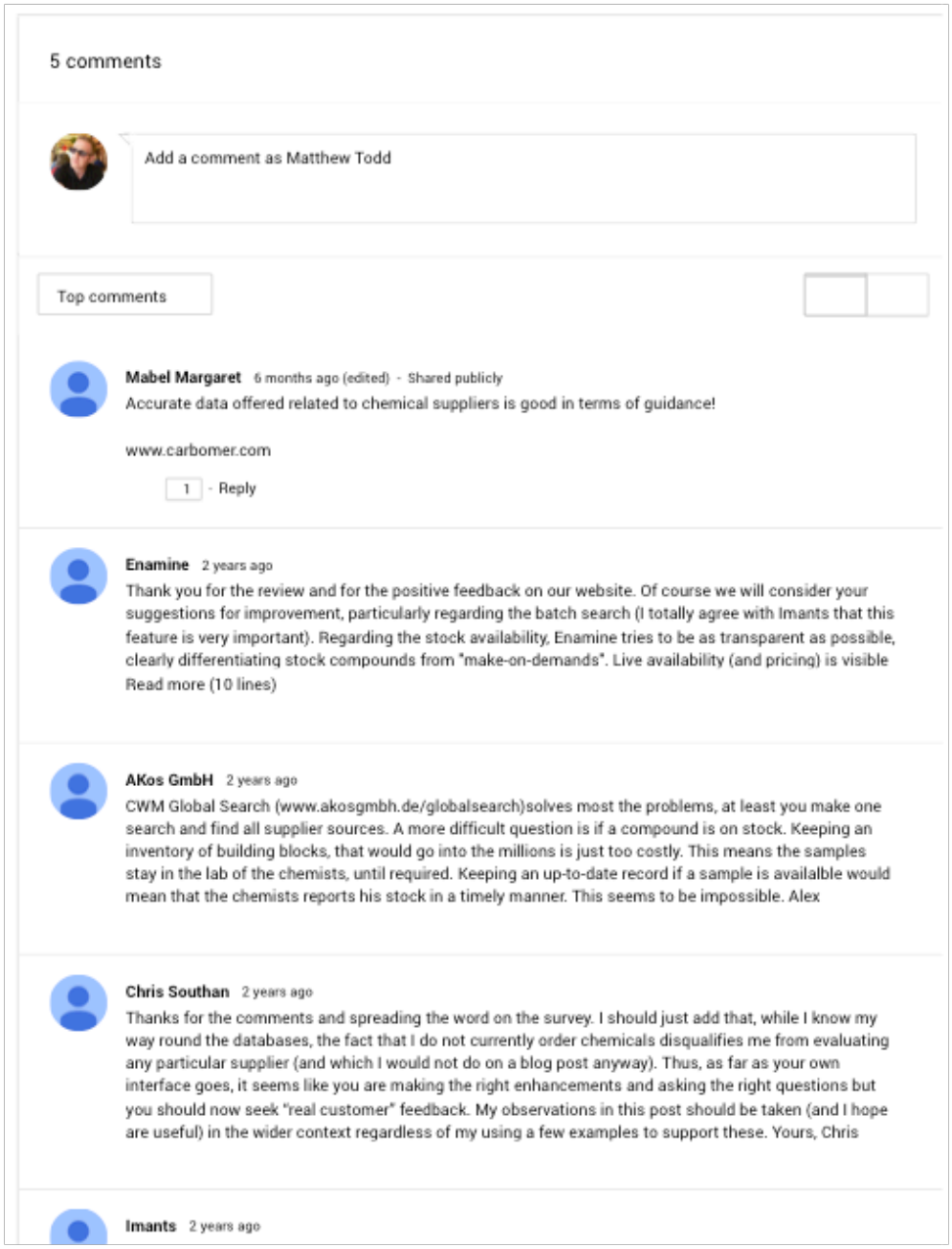
At 13 replies in a month this did not set the world alight, was uselessly anonymous and I had to make a dummy vote to see the results! Consequently I have now generated a Survey Monkey equivalent [http://www.surveymonkey.com/s/SXXZDX9] http://www.surveymonkey.com/s/SXXZDX9. I hope this will get a little more traction so please fill it in and/or forward if you have appropriate vendor contacts. I have posted a short comment with this link at the

Synaptic Leap. [http://www.thesynapticleap.org/node/404#comment-818]

Posted 9th May 2012 by Christopher Southan

Labels: antimalarials, chem

View comments



5 comments

Add a comment as Matthew Todd

Top comments

Mabel Margaret 6 months ago (edited) - Shared publicly
Accurate data offered related to chemical suppliers is good in terms of guidance!

www.carbomer.com

1 - Reply

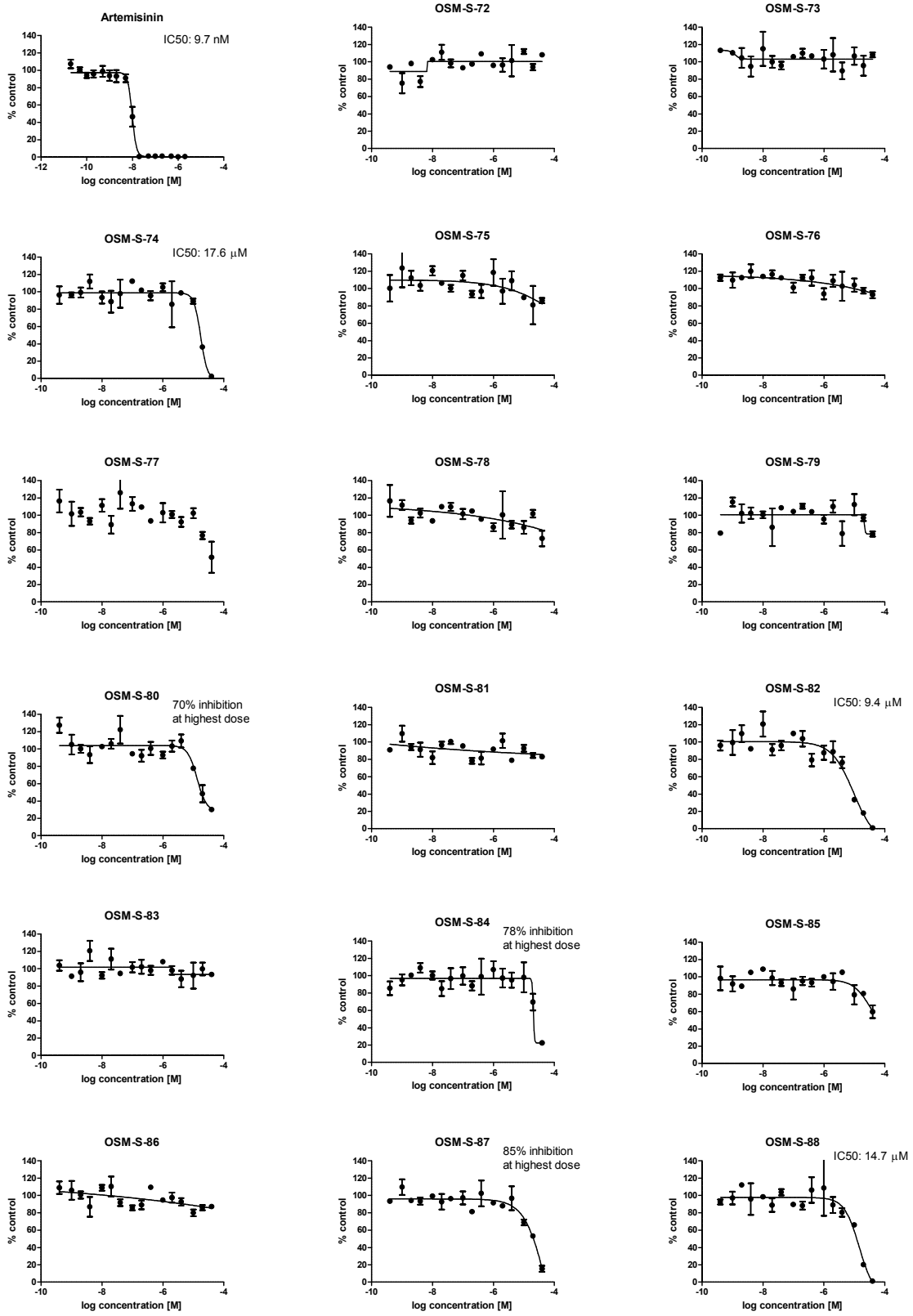
Enamine 2 years ago
Thank you for the review and for the positive feedback on our website. Of course we will consider your suggestions for improvement, particularly regarding the batch search (I totally agree with Imants that this feature is very important). Regarding the stock availability, Enamine tries to be as transparent as possible, clearly differentiating stock compounds from "make-on-demands". Live availability (and pricing) is visible
Read more (10 lines)

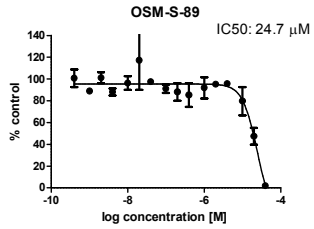
AKos GmbH 2 years ago
CWM Global Search (www.akosgmbh.de/globalsearch)solves most the problems, at least you make one search and find all supplier sources. A more difficult question is if a compound is on stock. Keeping an inventory of building blocks, that would go into the millions is just too costly. This means the samples stay in the lab of the chemists, until required. Keeping an up-to-date record if a sample is availalble would mean that the chemists reports his stock in a timely manner. This seems to be impossible. Alex

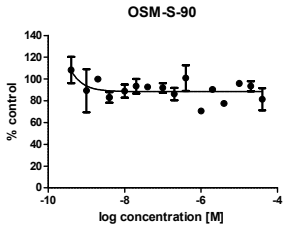
Chris Southan 2 years ago
Thanks for the comments and spreading the word on the survey. I should just add that, while I know my way round the databases, the fact that I do not currently order chemicals disqualifies me from evaluating any particular supplier (and which I would not do on a blog post anyway). Thus, as far as your own interface goes, it seems like you are making the right enhancements and asking the right questions but you should now seek "real customer" feedback. My observations in this post should be taken (and I hope are useful) in the wider context regardless of my using a few examples to support these. Yours, Chris

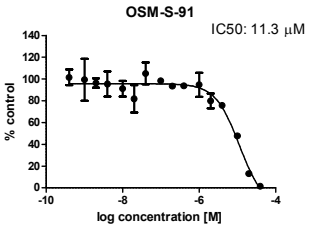
Imants 2 years ago

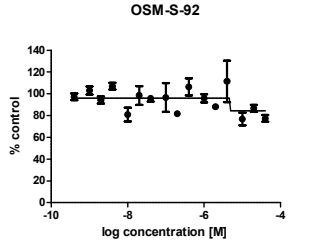
Fig S12. Potency Curves for OSM-S-72 to OSM-S-95

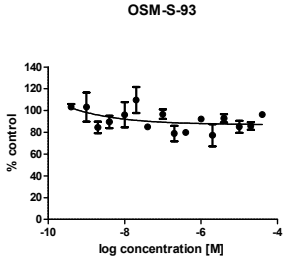


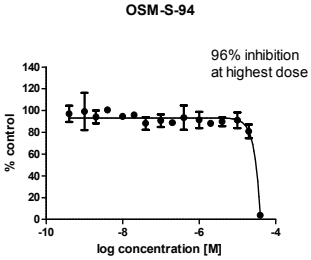

OSM-S-89
IC50: 24.7 μM
% control
log concentration [M]


OSM-S-90
% control
log concentration [M]


OSM-S-91
IC50: 11.3 μM
% control
log concentration [M]


OSM-S-92
% control
log concentration [M]


OSM-S-93
% control
log concentration [M]


OSM-S-94
96% inhibition
at highest dose
% control
log concentration [M]

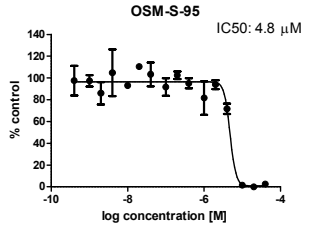
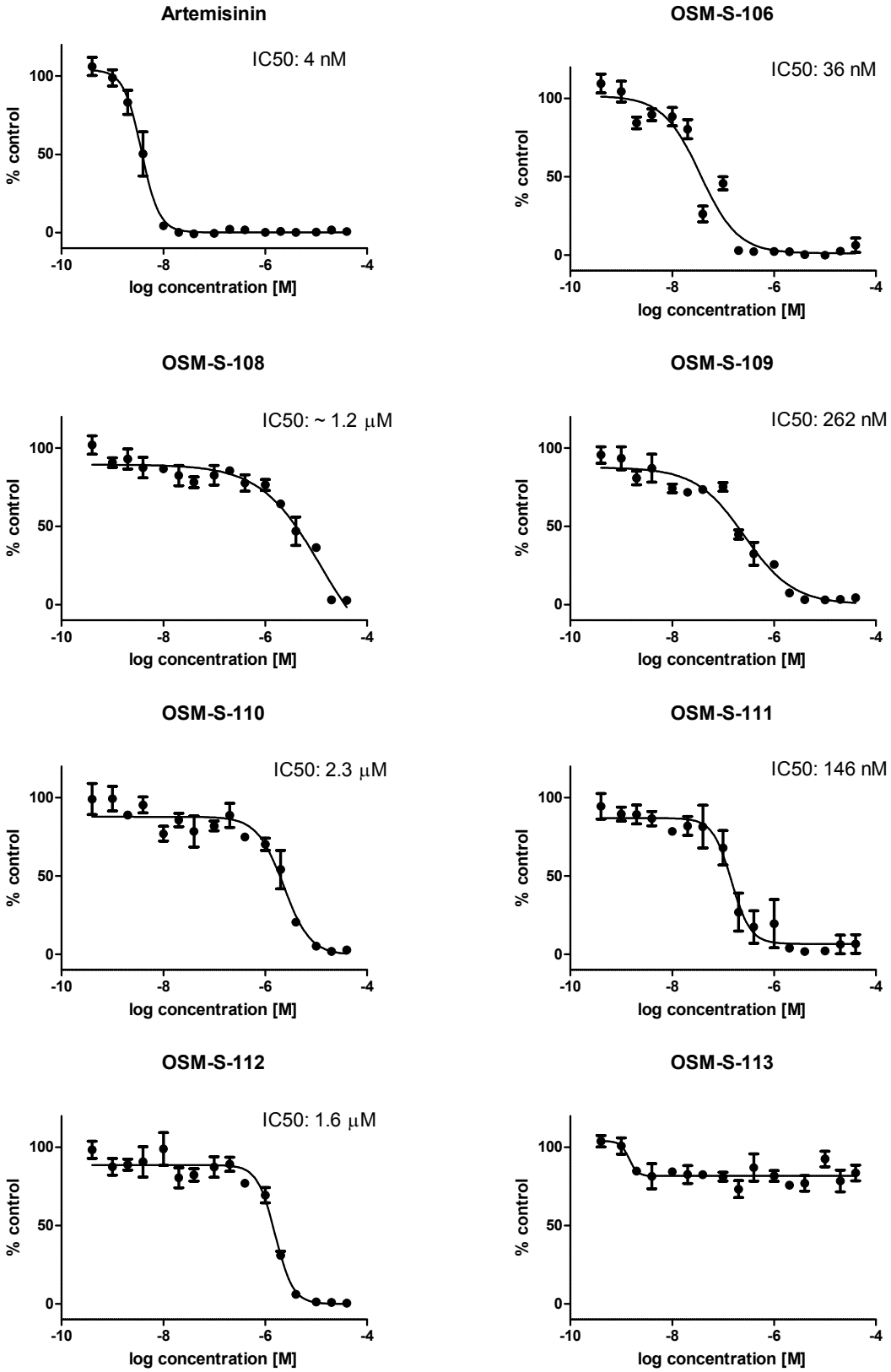
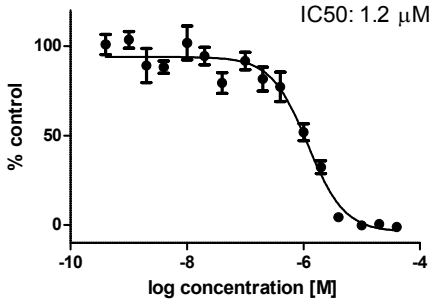

OSM-S-95
IC50: 4.8 μM
% control
log concentration [M]

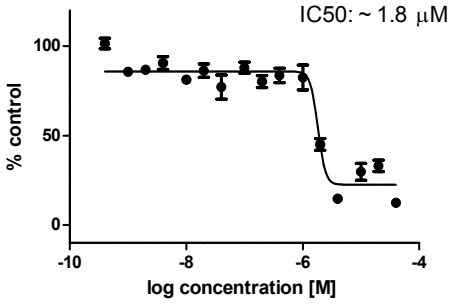
Fig S13. Potency Curves for OSM-S-35, OSM-S-106, OSM-S-108 to OSM-S-116



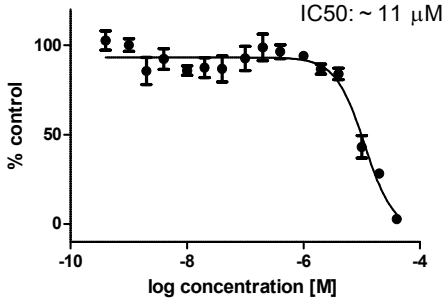
OSM-S-114



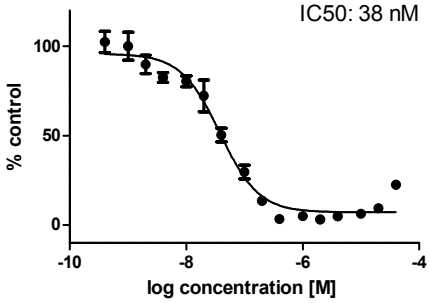
OSM-S-115

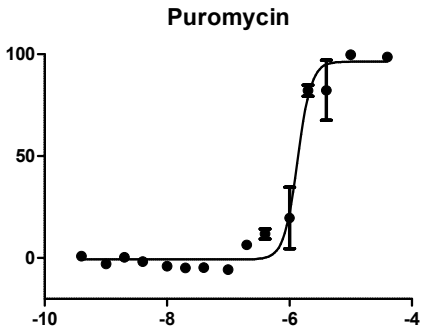


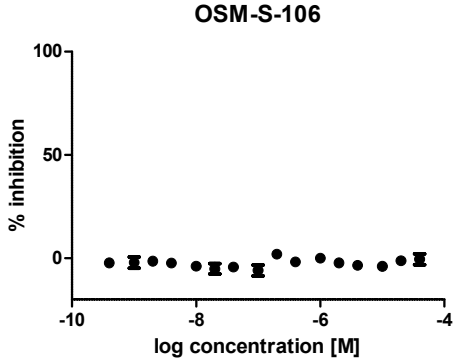
OSM-S-116

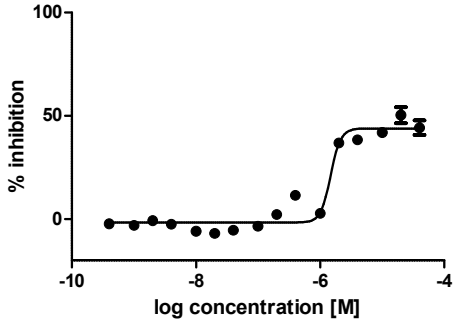


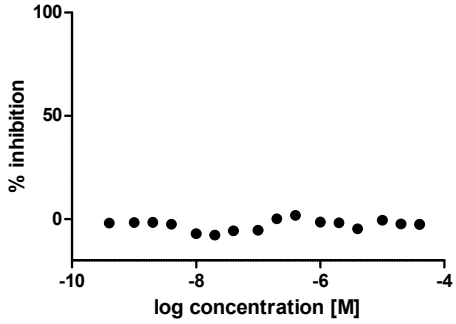
OSM-S-35

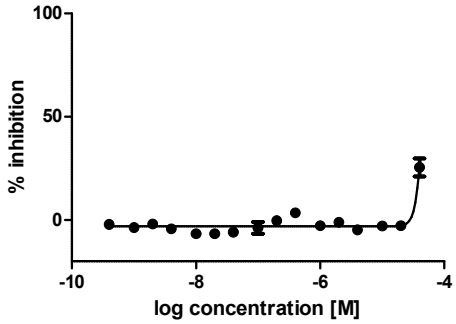


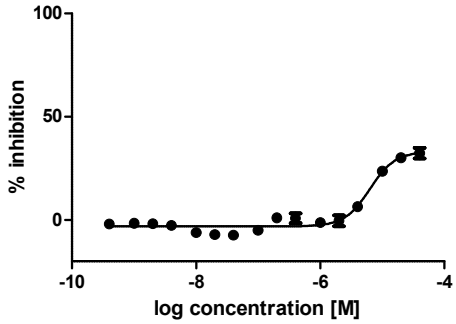

Puromycin
100
50
0
-10
-8
-6
-4

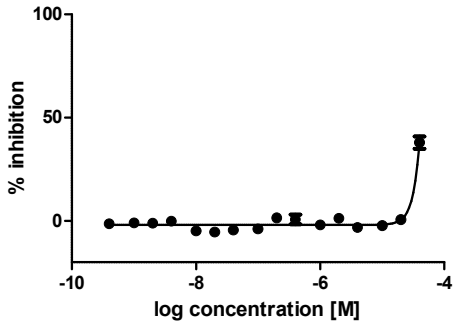

OSM-S-106
% inhibition
100
50
0
-10
-8
-6
-4
log concentration [M]


OSM-S-108
% inhibition
100
50
0
-10
-8
-6
-4
log concentration [M]


OSM-S-109
% inhibition
100
50
0
-10
-8
-6
-4
log concentration [M]


OSM-S-110
% inhibition
100
50
0
-10
-8
-6
-4
log concentration [M]


OSM-S-111
% inhibition
100
50
0
-10
-8
-6
-4
log concentration [M]


OSM-S-112
% inhibition
100
50
0
-10
-8
-6
-4
log concentration [M]

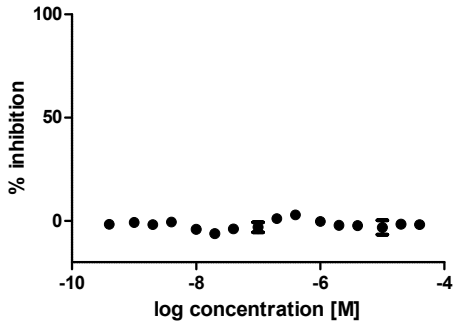

OSM-S-113
% inhibition
100
50
0
-10
-8
-6
-4
log concentration [M]

Fig S14. Screengrab of Biological Evaluation of Compounds ELN (http://malaria.ourexperiment.org/biological_data/2982), First Set of Biological Data from Sanjay Batra's Lab, CDRI, Lucknow, Matthew Todd, 2012.

Biological Evaluation of Compounds

Biological Data for Open Antimalarial Compounds

<< Next Post Previous Post >>

First set of biological data from Sanjay Batra's Lab, CDRI, Lucknow

19th April 2012 @ 04:51

Data obtained for compounds synthesised by Soumya Bhattacharyya and Sanjay Batra.

Conclusions:
1) 3-fluoro "near neighbour" derivative is much less active than closely related compounds described here.
2) The IC50 for PMY 10-6 broadly matches the results obtained by other labs, meaning this is a good control to use in conjunction with chloroquine.

Data for (3-fluorophenyl) pyrrole derivative SBBH-1-9 (or isomer) Synthesis of (3E)-3-((1-(3-fluorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methylene)-1-phenyl-5-(phenylimino)pyrrolidin-2-one or it's isomer (SBBH-1-9)

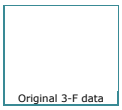
(Original data posted to G+ (with wrong name) - screenshot attached)

3D7:

Sample Code, IC50 (microM), CC50 (microM), SI
SBBH-1-9: 3.2, 92.4, 28.87
Chloroquine: 0.0063, 125.85, 19976.2

K1 strain:

Sample Code, IC50 (microM,) CC50 (microM), SI
SBBH-1-9: >5.0, 92.4, 18.48
Chloroquine: 0.235, 125.85, 535.53



Control compounds sent from Sydney was PMY 10-6 (TCMDC-123812) Synthesis of TCMDC-123812 via acid chloride (PMY 10-6), which was evaluated (13/04/2012) *vs.* chloroquine. Data attached

and results pasted here:

For 3D7:
PMY 10-6 IC50 0.581 microM, CC50 (cytotoxicity) nd, SI (selectivity index) -
CQ IC50 0.0083 microM, CC50 125.85, SI 15162.7

For K1:
PMY 10-6 IC50 0.641, CC50 nd, SI -

Search

This Post

Permalink
URI
URI Label
Revisions
Export:
XML

Archives

August 2014 (1)
July 2014 (3)
June 2014 (1)
May 2014 (3)
April 2014 (2)
February 2014 (2)
January 2014 (1)
December 2013 (2)
(more)

Authors

Patrick Thomson (2)
OSM ELN (10)
Stephan Meister (1)
Open Source Malaria (2)
Alice Williamson (5)
OSDD Malaria (6)
Matthew Todd (15)
Paul Ylioja (5)
(more)

Sections

3D7 IC50 Avery Lab (3)
Biology (35)
DMPK (1)
GSH-EE - Chapman Lab (2)
Kirk Lab (3)
MetID (2)
Potencies GSK (1)

Tools

Show/Hide QR Code
Show/Hide Keys

CQ IC50 0.252, CC50 125.85, SI 499

Method used for cytotoxicity assay:

cytotox assay SOP

Linked Posts

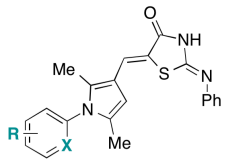
Attached Files

Controls | Original 3-F data | cytotox assay SOP

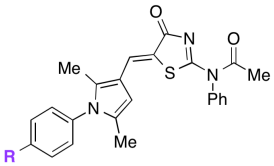
Matthew Todd | View Source | Biology | Comments (0)

<< Next Post Previous Post >>

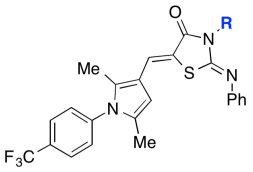
Fig S15. LogP Calculations for Representative Near Neighbour Compounds, ChemBioDraw Ultra v14.0.0.117.



X = CH	LogP
OSM-S-10, R = 4-F, 176 nM	3.32
OSM-S-35, R = H, 26 nM	3.16
OSM-S-37, R^1 = 4-Me, 15 nM	4.85
OSM-S-38, R^1 = 4-CF_3, 2.2 nM	4.08
OSM-S-39, R^1 = 3,5-CF_3, 0.78 nM	5.00
OSM-S-48, R^1 = 4-CO_2Et, 169 nnM	3.32
X = N	
OSM-S-51, R = H, 307 nM	1.82



	LogP
OSM-S-49, R = H, 63 nM	3.11
OSM-S-9, R = F, 47 nM	3.27
OSM-S-50, R = Me, 326 nM	3.60
OSM-S-45, R = CF_3, 12 nM	4.03



X = CH	LogP
OSM-S-38, R = H, 2.2 nM	4.08
OSM-S-54, R = Cyclopentyl, 34 nM	5.45
OSM-S-52, R = Ph, 54 nM	5.98
OSM-S-42, R = CH_2CN, no data	4.06
OSM-S-43, R = CH_2CN (isomer), >3000 nM	4.06

Fig S16. Correlation between LogP and Potency for Representative Near Neighbour Compounds

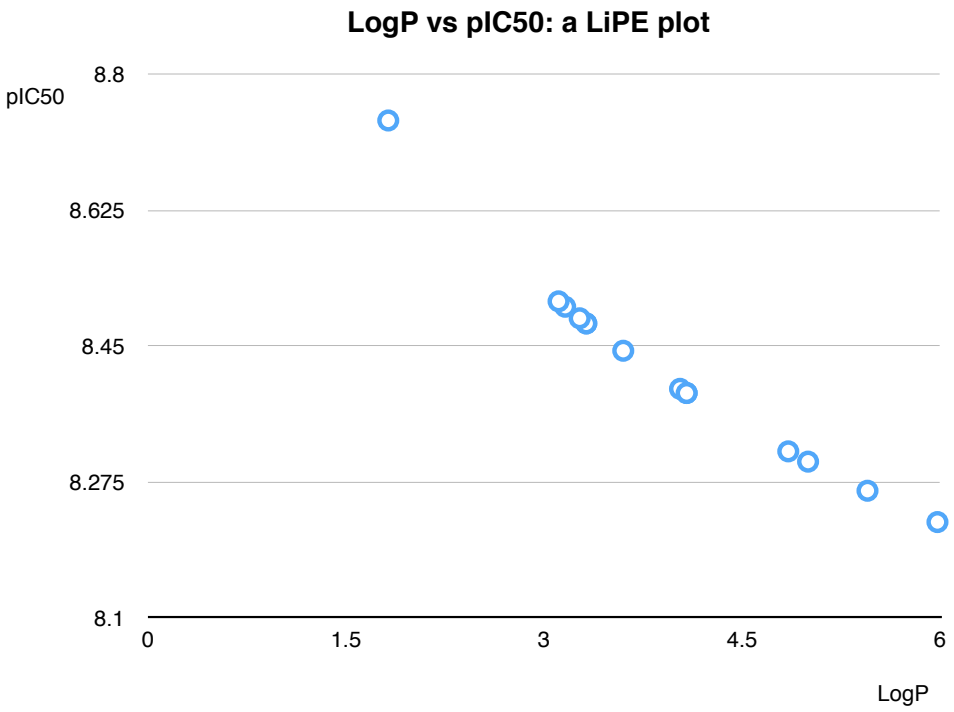


Fig S17. Screengrab of Synaptic Leap Node 367 (http://www.thesynapticleap.org/node/367), Biological Results for First Set of Compounds, Matthew Todd, 2012.

The Synaptic Leap
Open Source Biomedical Research

Search

HOME COMMUNITIES GETTING STARTED RESOURCES NEEDED ABOUT

You are here: Home » Malaria Research Community » Current Projects for Malaria » Open Source Drug Discovery: The GSK Arylpyrrole Series » Biological Evaluation of Arylpyrrole Series

Biological Results for First Set of Compounds

Published by MatTodd on 11 January 2012 - 12:12am

Community

malaria research community

The screening data from three separate labs have been obtained for the first set of compounds on the project. Data were obtained from the Ralph Lab at the University of Melbourne, and a second data set was provided just before Christmas by the Avery Lab at Griffith University. Yesterday the third set was provided by GSK Tres Cantos in Spain, who originally discovered the hits we're starting with. The current list of available compounds in this open project is here, with those that have been evaluated by at least one lab indicated in the relevant column.

Having data on the same compounds from three labs using different screening methods is useful as it provides contrasting ways of assaying effectiveness. In any given screening experiment on this project it's going to be important to include known actives, so that we have benchmarks, and this was done in these cases. It's also very important to be 100% sure about the effectiveness of a compound before we become too attached to it...

The data (below, but all available through the relevant lab book) show that the original TCAMS compounds are certainly active, though perhaps not quite as active as suggested by the original screen. Paul Willis at MMV had suggested we also check out some "near neighbors" of these compounds that were in the original data set. We made a couple and one (a novel compound with the code PMY 14-1, shown below and synthesized here) has shown promising activity in all three screens, with Avery/GSK IC50s coming back as low nanomolar. (Note that this project will never involve patents or closed data, giving us the freedom to discuss the compounds freely.)

What's next? In the short term: We're waiting for confirmation of the Melbourne data *via* a re-run of some of the experiments. But what we need is an expert qualitative assessment of these bioactivity data by someone familiar with such screening assays. Either in comments below this post, or on G+, not by email. First item of business in the lab is to generate a few variants of PMY 14-1. We already have some new relevant compounds and are now planning others. What should we make - i.e. how ought we to change PMY 14-1? Sanjay Batra has students who are about to make steric variations in the aryl pyrrole, and these could then be employed in the synthesis of PMY 14-1 variants, for example, but shouldn't we also be interested in changes in the "upper half" of the molecule?

In the long term: It would be good to find other labs which already have analogous compounds to the actives. Paul and Zoe found a paper from the Roberts lab at Scripps describing a number of such compounds, and I will write to them to ask

User login

Username *

Password *

Create new account

Request new password

Log in

Malaria Research Community

- Current Projects for Malaria
  - Functional Reconstitution of the Plasmodium GPI:protein transamidase Complex
  - Gene Wiki Overview
  - Open Source Drug Discovery for Malaria Meeting - February 2012 - Why?
  - Open Source Drug Discovery for Malaria Project Meetings
  - Open Source Drug Discovery: The GSK Arylpyrrole Series
    - A list of what's needed in the OSDD Malaria project
    - Analog Synthesis - Variation of the Aryl Ring
    - Availability of TCMDC-123812 and TCMDC-123794
    - Biological Evaluation of Arylpyrrole Series
      - Biological Results for First Set of Compounds
      - Biological Results for Second Set of Compounds
      - Biological Results for Third Set of Compounds
      - Late Stage Gametocyte Assay for Arylpyrroles
      - Metabolic Studies on a Set of Arylpyrroles
      - hERG Assay for Two Potent OSM-S Compounds
    - Druggability of the Arylpyrrole leads (TCMDC-123794 etc)
    - Known Near Neighbours of Initial Tres

whether they are interested in having the compounds be screened for their antimalarial activity. If anyone knows of any other possible sources, that would be great, since using existing compounds saves a lot of time in the lab.

‹ Biological Evaluation of Arylpyrrole Series up Biological Results for Second Set of Compounds ›

Printer-friendly version Add new comment

Comments

Paul MMV (not verified)
Jan 17 2012

Discussion of results

Great to see that that several analogues have been prepared and screened congratulations As one would expect, there is good agreement between the Avery and GSK data it would be helpful to detail the endpoints in each assay (apologies if I missed this data) It is encouraging that both PMY14-1 and PMY10-2 have low cytotoxicities (HEK 293) and similar potencies on the 3D7 and K1 (Chloroquine resistant) strains It would now be useful to further characterize these leads: solubility, in vitro metabolic stability (including GSH trapping?), lipophilicity, and plasma stability would be great. MMV can help generate some of this data is anyone else interested in contributing?

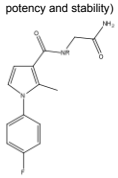
REPLY

MatTodd
Jan 18 2012

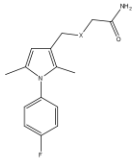
Further comments from Paul Willis

(Further suggestions from Paul Willis at MMV, since our image upload is a little tortuous...)

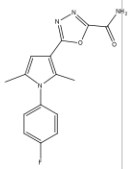
· Although PMY10-2 is less potent than PMY14-1, it can be considered a better lead due to its superior ligand-lipophilicity efficiency (4.7 vs 2.5) and ligand efficiency (0.41 vs 0.3)
· A key liability with PYM10-2 is likely the ester linkage. I would explore some simple ester replacements / isosteres, for example (main drive increase potency and stability)

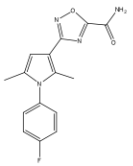


R=H, Me
also explore changes to primary amide



X =O, NH





REPLY

MatTodd
Jan 18 2012

Ligand efficiencies/compounds in progress

Paul - interesting. Those ligand efficiency values calculated by you or from Chembl? What's the sweet spot you're looking for?
Paul Ylioja is already on the case of the amide and ether-linked varieties - spreadsheet of currently-done compounds here. The amide bond is a pain to make for some reason, and one of the attractions of the near-neighbours is the requirement for a double bond there instead! Paul's going to summarize where he's at in the next day or so. The heterocycle isosteres should be simple from the carboxylic acid I'm guessing. Sanjay Batra's

Cantos Leads

Prediction of Biological Targets of Actives

Proposed resynthesis strategy for TCMDC-123812 and TCMDC-123794

THE SUBCELLULAR DRUG TRANSPORT LABORATORY: Cellular pharmacokinetic analysis of antimalarials

The GSK Aminothienopyrimidine (ATP) Series

Completed Projects for Malaria

Toxoplasma Research Community

Recent posts

Biological Results for ATP Series from April 2013
1 May 2013 - 3:48am By MatTodd
Replies: 0

Biological Data
1 May 2013 - 3:39am By MatTodd
Replies: 0

The GSK Aminothienopyrimidine (ATP) Series
1 May 2013 - 3:38am By MatTodd
Replies: 0

more

Recent comments

anacardic compounds to cure TB 5 March 2014 - 12:27am

Protein available 24 September 2013 - 8:20pm

Hi there, just watched Tom's 17 May 2013 - 11:32am

Meeting Recording and Minutes 21 March 2013 - 2:57am

SOLVED-onamides - perhaps! 28 February 2013 - 5:44pm

more

student is about to make variations in the fluorine that could be contributed to that series.
A question about the biological data: these arise from three different assay types. Is that a problem or a strength? In other words, is there a need for consistency?
I will contact Sue Charman at the outset to ask about ADME, unless a reader would like some of these compounds to play with.

REPLY

Martine (not verified)
Jan 22 2012

Hit dissemination

Hi Matthew,

It can be useful to deconstruct your hit molecule before optimising.

Why is PMY 14-1 more active than 10-2 - increased lipophilicity (N-Ph); extra HBA (acetyl); more rigid; determine E or Z (is this functionalality a michael acceptor?); more optimal position of HBA (the one closest to the pyrrole)?
Likewsie for 10-2 - amine or amide; NH2, NHR or NRR; ester, ether, amide or carbon linker; is ester HBA in optimal positoin for interactions - determine before making isosteres (extend and reverse); what activity value is the pyrrole N-aryl group and it's substituent?
If you have acces to molecular modeling, an overlay of 14-1 and 10-2 might be useful. If not, ball and stick models can be good enough to generate ideas.

Martine

REPLY

pylioja
Jan 23 2012

Molecular modelling, N-Aryl and so on

Hi Martine, Thanks for the input. These are exactly the kind of questions we're after. We're currently running some DFT of PMY 14-1 and PMY 14-3 to get an idea about how they look and behave. We've synthesised a good range of N-aryl analogues for the 14-1 set and some variety on the N-Acyl position. These are going to be sent for testing very soon, at the end of next week hopefully. I discuss some of these ideas here. If you have access to modelling software then it would be fantastic if you would like to contribute by investigating the pharmacophore? The next set of data should be available in the not too distant future but we could already start using the small set of biological data we have and the much larger published GSK data set.

REPLY

MatTodd
Feb 13 2012

Kinds of biological evaluation for Round 2?

Given that the first round of compounds have been shown to have no significant cytotoxicity against HEK293 and have equivalent activity for 3D7 and K1 parasite strains do we only need 3D7 data for the second round of testing, given that the compounds are analogous to the first set?

REPLY

MatTodd
Feb 14 2012

Some advice and replies by email..

In response to the above question, some replies came in via email overnight:
Stuart Ralph, Uni Melbourne: we would go for a drug resistant strain like w2mef first rather than 3d7. However finding a differential sensitivity between a drug sensitive and resistant line might be illuminating later on for compounds of particular interest.
Javier Gamo-Benito from GSK: I´d suggest to maintain 3D7 as standard to construct and guide SAR. To test a different genetic background harboring resistances could be a good approach to be sure we are not getting intro troubles.....for that W2 could be a good option.
Paul Willis from MMV: I agree with Javier: use 3D7 as our standard screen for SAR and once in the next few screening check a few representative compounds on a resistant strain: Dd2 or W2. Note in the initial HTS there was no difference in the % inhibition on 3D7 and Dd2, so there is flag of an issue.

So the consensus would seem to be to test this second batch of compounds on 3D7 only. Depending on the data, one or two might subsequently be tested on a resistant strain (with, presumably, a re-check for cytotoxicity).

REPLY

Jonathan (not verified)
Feb 04 2012

Pyrrole and alkene reactivity? PAINS?

It's great to see the interest in this area. One thing about PMY 14-1 druggability comments - what hasn't been raised is the potentially problematic nature of the groups therein. One never wants to become too jaded, especially in a wonderful endeavour such as this, but I'd just like to caution people on the potentially problematic nature of these groups. In fact, we have removed compounds that have similarities to both the top and or the bottom half, from recent HTS libraries because they light up our screens so often. Of course, not only may there be exceptions but also our focus is target-based HTS (this is changing though), and in phenotypic HTS (like here, just cidal readout) one obviously can view what may be biochemical probes differently. Without wanting to push my own publication, see Fut. Med. Chem. 2010 (2) 1529-1546. I should add that pulling electrons out of the pyrrole as in PMY 14-1 probably helps towards any tendency for retrosynthetic cyclocondensation and the imino thiazolidinone is not the hottest type of PAIN we see...i.e there are quite a few benign ones so in this context may be ok.

Just be cautious with these types of chemistries. Maybe getting access to the (blinded) HTS history for similar compounds to PMY 14-1 at GSK would be useful?

On the ester, it might be worth looking into being more evidence-based.....is it actually prone to esterases? It is in the 3 position of pyrrole, an e-rich aryl, and with a 2-methyl so may be more stable than anticipated?

REPLY

MatTodd
Feb 05 2012

PAINS

Jonathan - Thanks. This is an exceptionally important point. You know how much of a fan I am of your original paper. The importance of the work is to alert the community to promiscuous compounds and be more sceptical of molecules containing certain groups. Two questions:
1) I had thought that the problem was with certain HTS assays - we had three different low-throughput assays applied to these compounds, so the warning light hadn't gone off in my mind. Perhaps I misremembered that part of your talk/paper? Would the same caveats apply to the screens done to date on these compounds (as opposed to the original GSK screen)?
2) To evaluate directly whether this, or other compounds, are PAINS, what's the most direct test? Is there one?
We're about to send off round 2 for screening, which may throw some more light on this. I'll alert the screening teams to this post, though.

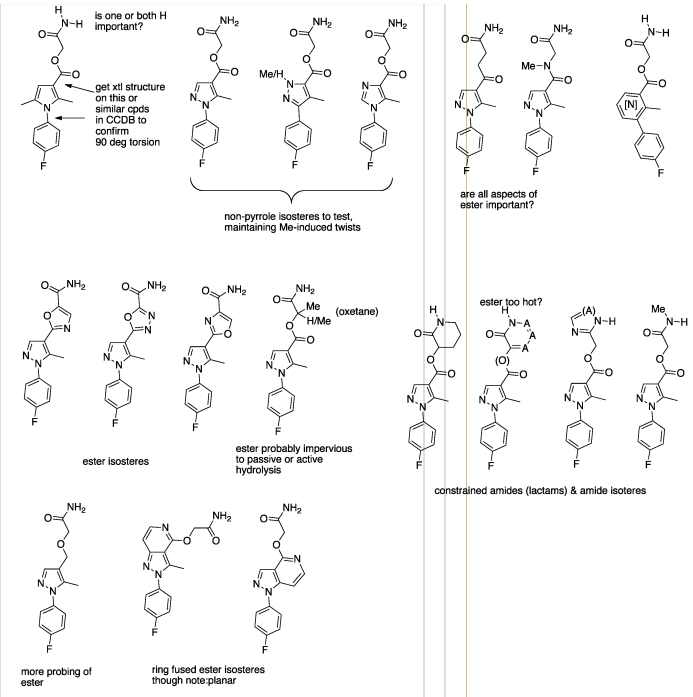
REPLY

Guest (not verified)
Feb 05 2012

PAINS reply

1) It is true that our assay conditions are particularly suited to pulling out inherently reactive compounds that may not light up other assays because we test at fairly high concs..eg. 25uM. But generally, we would say if our PAINS filters recognize a compound, deprioritize if a target-based screening hit and view cautiously even if phenotypic readout. But I don't want to become too dogmatic until we understand more on MOA of these.
2) Abbott's ALARM NMR is the industry standard to pick up protein reactives. I can put in a request to Andrew Petros there if you like to look at this cpd. A lot of places will now be setting up assays for cpds that may turn out to be protein-reactive intracellularly (but not necessarily in a test-tube).

With respect to medchem optimization of the the TCAMS pyrrole, I have emailed something that maybe you can upload on this site [Done below - Mat], which is how we would go about it. The message: optimize within your core first before extending. I'd be a little worried with your PMY cpd you may have moved into testing very different hypotheses.



REPLY

reply to PAINS reply

ZoeH
Feb 13 2012

Looking at the near neighbour compounds (PMY 14-1 analogues) in ChEMBL, they have IFIs of 0%, 4.7%, 3.65% and 6.67%, so while they have all clearly passed the thresholds they do have some propensity to hit different screens. Between the fact that GSK did take appropriate measures (the IFIs plus testing for assay interference, as well as doing cell based toxicity screens), and the fact that these are cell based assays, I'm not sure how we would see this sort of profile if the activity was completely non-specific - but I have had difficulty finding the question of false positives in cell based HTS assays vs binding type assays addressed directly in the literature, so I'm not sure how big a factor this is.
Regardless, if it's possible for us to get some of our compounds tested by ALARM-NMR, I think that would be fantastic as it will give us direct evidence of their reactivity towards proteins, and as I understand it can also provide an indication if activity is the result of a reactive contaminant.

REPLY

Reply to Pyrrole and alkene reactivity

ZoeH
Feb 05 2012

Hi Jonathan,
Looking at the original GSK paper, the GSK hits were assigned an "Inhibition Frequency Index" (IFI) to exclude promiscuous compounds which was basically a percentage of the HTS screens each compound had been used in where they showed 50% or more inhibition. They used a variable threshold, from 5 to 25% of screens, depending on the number of HTS screens a given compound had

been through.
Is this something you would see as an adequate measure? Our library doesn't give me access to your article in future med chem, but I had a look at your 2010 paper in J. med chem, and as I understood it you were taking something like activity in 4 out of 6 HTSs with one or two higher values as indicators of PAINS, so at face value the GSK thresholds would seem fairly reasonable?
Thanks very much,
Zoe

REPLY

Jonathan (not verified)
Feb 05 2012

Well answered Zoe. Yes that

Well answered Zoe. Yes that seems reasonable. One thing I would recommend with a pyrrole is to always retest on freshly HPLC-purified material, because an HTS history may vary with its age. That may have been done already for the original TCAMS compound...do you know if it has?
Jonathan

REPLY

Paul MMV (not verified)
Feb 06 2012

Frequent Hitters?

I checked ChEMBL and both TCMDC-123974 and TCMDC-123812 have a reported inhibition frequency index of 0 so there are no frequent hitter flags from the original screen - we could ask if GSK will reveal how many screens these compounds have now been tested in. This is an importnat issue: perhaps some groups will offer to screen the hits in their favourite assays so we can use the community to confirm these are not promiscious hitters. In addition, for information, the compounds have been resynthesised and the potencies confirmed in multiple assays using fresh samples.

REPLY

Fig S18. Screengrab of Blog Post, In the Pipeline (http://blogs.sciencemag.org/pipeline/archives/2010/02/08/polluting_the_literature_with_pains), Polluting the Literature with PAINS, Derek Lowe, 2010.

IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of *Science Translational Medicine*.

By Derek Lowe

Polluting the Literature with PAINs

By Derek Lowe | February 8, 2010

There's an **article out** from a group in Australia on the long-standing problem of "frequent hitter" compounds. Everyone who's had to work with high-throughput screening data has had to think about this issue, because it's clear that some compounds are nothing but trouble. They show up again and again as hits in all sorts of assays, and eventually someone gets frustrated enough to flag them or physically remove them from the screening deck (although that last option is often a lot harder than you'd think, and compound flags can proliferate to the point that they get ignored).

The larger problem is whether there are whole classes of compounds that should be avoided. It's not an easy one to deal with, because the question turns on how you're running your assays. Some things are going to interfere with fluorescent readouts, by absorbing or emitting light of their own, but that can depend on the wavelengths you're using. Others will mung up a particular coupled assay readout, but leave a different technology untouched.

And then there's the **aggregation problem**, which we've only really become aware of in the past few years. Some compounds just like to stick together into huge clumps, often taking the assay's itself is an assay-dependent phenomenon. Change the concentrations or added proteins, and

whoomph: compounds that were horrible before suddenly behave reasonably, while a new set of well-behaved structures has suddenly gone over to the dark side.

This new paper is another attempt to find "Pan-Assay Interference" compounds or PAINs, as they name them. (This follows a weird-acronym tradition in screening that goes **back** at least to Vertex's program to get undesirable structures out of screening collections, **REOS**, for "Rapid Elimination of, uh, Swill"). It will definitely be of interest to people using the AlphaScreen technology, since it's the result of some 40 HTS campaigns using it, but the lessons are worth reading about in general.

What they found was that (as you'd figure) that while it's really hard to blackball compounds permanently with any degree of confidence, the effort needs to be made. Still, even using their best set of filters, 5% of *marketed drugs* get flagged as problematic screening hits – in fact, hardly any database gives you a warning rate below that, with the exception of a collection of CNS drugs, whose properties are naturally a bit more constrained. Interestingly, they also report the problematic-structure rate for the collections of nine commercial compound vendors, although (frustratingly) without giving their names. Several of them sit around that 5% figure, but a couple of them stand out with 11 or 12% of their compounds setting off alarms. This, the authors surmise, is linked to some of the facile combinatorial-type reactions used to prepare them, particularly ones that leave enones or exo-alkenes in the final structures.

So what kinds of compounds are the most worrisome? If you're going to winnow out anything, you should probably start with these: **Rhodanines** are bad, which doesn't surprise me. (Abbott and Bristol Myers-Squibb have also reported them as troublesome). Phenol Mannich compounds and phenolic hydrazones are poor bets. And all sort of keto-heterocycles with conjugated exo alkenes make the list. There are several other classes, but those are the worst of the bunch, and I have to say, I'd gladly cross any of them off a list of screening hits.

But not everyone does. As the authors show, there are nearly 800 literature references to rhodanine compounds showing biological effects. A conspicuous example is **here**, from the good folks at Harvard, which was shown to be rather nonspecifically ugly **here**. What does all this do for you? Not much:

> *"Rather than being privileged structures, we suggest that rhodanines are polluting the scientific literature. . .these results reflect the extent of wasted resources that these nuisance compounds are generally causing. We suggest that a significant proportion of screening-based publications and patents may contain assay interference hits and that extensive docking computations and graphics that are frequently produced may often be meaningless. In the case of rhodanines, the answer set represents some 60 patents and we have found patents to be conspicuously prevalent for other classes of PAINS. This collectively represents an enormous cost in protecting intellectual property, much of which may be of little value. . ."*

11 comments on "Polluting the Literature with PAINs"

anchor

February 8, 2010 at 10:56 am

We encountered many of the problems discussed herein. Where I worked, the mangement wasted lot of time formulating thoughts as to what should happen next. The same sub-structure will show up for various program and we addtionally wasted even more time validating not only the structure but also the assay. But understand that from the time we hit it off, cross check, structural integrity and so on, an year rolls by with nothing to show. The people who head these program walk off with huge bonuses, while those who actually did the spade work were switched off to the next project.

Anonymous
February 8, 2010 at 12:42 pm

Actually, televancin (from Theravance) is a Mannich product of the bisphenol in vancomycin. So I wouldn't a priori eliminate that functionality.
What I have observed to be a ubiquitous hit from HTS were triamino triazines derived from cyanuric chloride. This was left over from the combichem heyday. They would show up in every screen regardless of what type of screen it was – enzyme, nuclear receptor, 7TM, ion channel ect. I would just shake my head anytime someone put one up as a bonafide hit from a screen. From my standpoint, they were just way too close to herbicides like atrazine. So I'd throw them out when I was filtering the screen but I would never tell management. They loved them because any idiot could make them and you could make a lot of them very quickly – you know, metrics and stuff. Maybe there's a drug out there with a triamino triazine but I don't know it. There IS a food supplement from China but that doesn't count since it's quite toxic.

Chris
February 8, 2010 at 12:45 pm

I thought this was a very interesting paper and I await with interest for a succession of comments with similar tales of woe.
Frequent hitters are pretty near the top of my list of things to eliminate during analysis of HTS results.

Questioner
February 8, 2010 at 3:38 pm

Question:
Is it worth separating "poorly behaved in HTS assays" from "never could be a drug?" Let me ask this another way, would any of you old hands be more amenable to working on a putative frequent hitter if, rather than coming from an HTS, it came from a microarry experiment, or high-throughput fragment crystal soaks, or Biacore, or some other technique which has a different "specious result profile" than HTS. Because all this paper is really saying is that these compounds don't work well with our man-made reductionist systems for interrogating chemical space, not that they don't work well for binding to and perturbing biological targets.
Or do the two correlate?

Mat Todd
February 8, 2010 at 3:56 pm

Baell gave this talk at Sydney a short while back, and it was fascinating. Would be nice if rhodanines were good for something else, given how many are probably kicking around in the back rooms of pharma.

DLIB
February 8, 2010 at 5:04 pm

@ Questioner:
You are correct sir.
Extensive studies have been performed on this question. Every technology you mentioned creates systematic biases. Some are orthogonal to each other some are not.
Right answers Schmight answers it's only $1Bn bucks ☹
The industry will not invest in new technology / instruments and the vendors are happy selling the fluorescent compounds and engineering new ones.
It funny how at the mercy the pharmaceutical industry is to the instrument vendors (who also own and engineer most of those great reagents — keep throwing them down the drain….they'll happily make you more)

Jonathan Baell
February 8, 2010 at 5:47 pm

Just to qualify – the fact our filters recognize a small percentage of drugs is not really meant as an indictment for the drug, but rather to illustrate that we do not claim that our filters perfectly discriminate between drug and non-drug….because they weren't designed to; our main point here is that HTS hits recognised by our filters are far more likely to be unoptimizable than end up going all the way, so removing them in the first place is more beneficial than the vanishingly small chance that they will end up being a drug. We further note that the moieties that cause these marketed drugs to be recognized by our filters oddly also tend to be associated with met/PK/tox issues. We discuss this extensively in the Suppl Info (pp S59-60
On triazines: apart from the problematic IP space, we too find some triazines (for reasons currently unknown to us) and briefly mention this class (see p "J" in the JMC ASAP and SI p 77 in supp)

Evorich
February 9, 2010 at 8:26 am

Surely the key is to maintain a dynamic, and relatively small (

Evorich
February 9, 2010 at 8:53 am

Amino triazines surely pop up in several drugs; e.g. lamotragine.

Anonymous
February 10, 2010 at 10:48 pm

@ Evorich: lamotragine is a 1,2,4-triazine and I was referring to 2,4,6-triamino-1,3,5-triazines which are derived from cyanuric chloride. Hope that clarifies things.....I wouldn't lump lamictal in that class.

Raphael Belcourt
August 12, 2012 at 9:48 am

Can I just now say such a relief to discover 1 who truly knows what theyre dealing with on-line. You in fact know how to bring a concern to light and earn it essential. Lots far more folks have to appear at this and see why side with the story. I cant believe youre not far more popular because you definitely develop the gift.

Comments are closed.

MORE FROM *SCIENCE TRANSLATIONAL MEDICINE*

- Archive
- Current Table of Contents
- In the Pipeline
- ▶ About Science Translational Medicine

RECENT COMMENTS

- anonymous on 3-Bromopyruvate: What a Mess
- loupgarous on The University of Malaya Is Not Having It
- loupgarous on The University of Malaya Is Not Having It
- loupgarous on Crap, Courtesy of a Major Scientific Publisher
- anon on 3-Bromopyruvate: What a Mess

CATEGORIES

- "Me Too" Drugs (30)
- Academia (vs. Industry) (142)
- Aging and Lifespan (74)
- Alzheimer's Disease (108)
- Analytical Chemistry (101)
- Animal Testing (39)
- Autism (23)
- Biological News (267)
- Birth of an Idea (43)
- Blink &#8250 (5)
- Blog Housekeeping (259)
- Book Recommendations (31)
- Business and Markets (966)
- Cancer (331)
- Cardiovascular Disease (154)
- Chem/Bio Warfare (15)
- Chemical Biology (88)

From [PAINS Go Mainstream (September 26, 2014)
(http://blogs.sciencemag.org/pipeline/archives/2014/09/26/pains_go_mainstream)]. Reprinted with permission from AAAS

Fig S19. Screengrab of Blog Post, In the Pipeline
(http://blogs.sciencemag.org/pipeline/archives/2014/09/26/pains_go_mainstream), PAINS Go Mainstream, Derek Lowe, 2014.

IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of *Science Translational Medicine*.

By Derek Lowe

PAINS Go Mainstream

By Derek Lowe | September 26, 2014

Well, I'm back in the Eastern Time Zone after flying in from Basel (and Amsterdam) yesterday. And the first thing I wanted to mention **was this article** from Jonathan Baell and Michael Walters in*Nature*, on the **PAINS compounds**. It's good to see the journal cover this issue (and I was impressed that they got *New Yorker* cartoonist **Roz Chast**Roz Chast to illustrate it).
PAINS are, of course, nasty frequent-hitting compounds that should be approached with great caution in any sort of **screen for activity**. This topic has come up many times on the blog (for someone writing about chemistry and drug discovery, there's no way it couldn't have), most recently just a ~~**few weeks ago**~~. There are a **lot** of these things out in the literature (and the **catalogs**), and they just **keep on** coming. Now a wider audience gets to hear about the problem:

> *Academic researchers, drawn into drug discovery without appropriate guidance, are doing muddled science. When biologists identify a protein that contributes to disease, they hunt for chemical compounds that bind to the protein and affect its activity. A typical assay screens many thousands of chemicals. 'Hits' become tools for studying the disease, as well as starting points in the hunt for treatments.*
> *But many hits are artefacts — their activity does not depend on a specific, drug-like*

> *interaction between molecule and protein. A true drug inhibits or activates a protein by fitting into a binding site on the protein. Artefacts have subversive reactivity that masquerades as drug-like binding and yields false signals across a variety of assays.*

That's the problem, all right. It's not like ugly-looking compounds can never become drugs, and it's not like they can't be **~~starting points~~** for research. But the odds are against them, and you have to realize that, and you also have to realize *why* this "hit" you've just uncovered may well be spurious (at worst) or need a lot of extra work (at best). Far, far too many papers from less

Appropriately, this piece calls out the rhodanines as perfect examples of the problem:

Rhodanines exemplify the extent of the problem. A literature search reveals 2,132 rhodanines reported as having biological activity in 410 papers, from some 290 organizations of which only 24 are commercial companies. The academic publications generally paint rhodanines as promising for therapeutic development. In a rare example of good practice, ***one of these publications*** *(by the drug company Bristol-Myers Squibb) warns researchers that these types of compound undergo light-induced reactions that irreversibly modify proteins. It is hard to imagine how such a mechanism could be optimized to produce a drug or tool. Yet this paper is almost never cited by publications that assume that rhodanines are behaving in a drug-like manner.*

Very occasionally, a PAINS compound does interact with a protein in a specific drug-like way. If it does, its structure could be optimized through medicinal chemistry. However, this path is fraught — it can be difficult to distinguish when activity is caused by a drug-like mechanism or something more insidious. Rhodanines also occur in some 280 patents, a sign that they have been selected for further drug development. However, to our knowledge, no rhodanine plucked out of a screening campaign is in the clinic or even moving towards clinical development. We regard the effort to obtain and protect these patents (not to mention the work behind them) as a waste of money.

Yeah, I wouldn't spend much on trying to stake a claim to these things, either. If you haven't done much screening, you may not appreciate just how many false positives are out there (and for difficult targets, how few real positives there may be). I see people in the literature screening little libraries of a few thousand compounds from a catalog and reporting hit after hit, even in very tricky systems, while in industry we're used to running hundreds of thousands of compounds past some of these things and coming up with squat. Well, after checking the "hits" for purity, aggregation behavior, reactivity, and profiles from past screening campaigns, that is. Here's the sad truth: If you're doing a small-molecule screen to affect transcription factors, protein-protein targets, or anything in general that doesn't have an evolutionary optimized small-molecule binding site, you'd better assume that the *vast majority* of any hits you get are false positives. There's almost no way that they can be anything else. The true hit rate for some of these things against any sort of typical compound collection is damn near zero, which means that the ways your compounds can be wrong far outnumber the ways that they can be right. Every single hit, for any assay, should be regarded with appropriate suspicion. Purity check first, LC/MS and NMR. Is it what it says on the label? You might be surprised how often it isn't (or isn't any more, even if it started out OK). If you have solid material and DMSO stock, check both of them, because things diverge on storage. It's a very good idea to take your interesting hits, run

them through a plug of silica gel, and test them again. That's especially true if they have any color to them (but keep in mind, some assay-killing contaminants are completely colorless). The gold standard is resynthesis: if you can make the compound again and purify it, and it still works, you at least know you can trust it that far. If you can't, well, how exactly is this compound going to do anyone any good?

Note that we haven't even gotten to the PAINS yet. There are a lot of clean, accurately labeled compounds that should be chucked into the waste can, too, which is where the **Baell PAINS list** comes in. You're going to want to **check for aggregation**: run your assay with some detergent in it, or do some dynamic light scattering or ~~**any**~~ of several **other techniques**. A lot of false-positive compounds are aggregators, and you can't completely predict which ones they might be (it varies according to assay conditions).

You're also going to want to run your hits through some other assays. How promiscuous are they? If you have access to data from multiple screening campaigns with the same compound collection, good for you. If you don't, you should strongly consider sending your hot compound(s) out for a commercial screening panel. Don't just pick the similar targets to screen – you want those, of course, but you want all kinds of other stuff. If a compound hits against widely disparate protein classes, it's a PAIN, and is set to cause trouble. Don't assume that they're clean – don't assume that *any* compound is clean, because it almost certainly isn't. That goes for marketed drugs, too – the question is, does it have selectivity that you can live with, or not?

Those are the big tests, and believe me, they'll clear out your initial list of screening hits for you. If your target is a tough one to start with, they may well clear out everything. Better that, though, than working on (and publishing) crap.

15 comments on "PAINS Go Mainstream"

David Borhani
September 26, 2014 at 9:58 am

Amen!

JAB
September 26, 2014 at 10:46 am

Amen twice!

Anonymous
September 26, 2014 at 11:08 am

Amen a third time, but I'd also be really interested to hear people's thoughts on how to identify suspect cpds.

There are a lot of methods – detergent sensitivity, Novartis' non-stochiometric binders assay, redox assays, looking at slope factors, promiscuity...the list goes on, but I've never really seen any recommendations as to what is best practise.

My personal prejudice would be to use the non-stochiometric binder assay in conjunction with slope factors and promiscuity against other targets. Detergent assays are OK when you ran your primary assay without detergent, but if you screened with it I'm not sure what they add and only do redox assays if you have a sensitive target

David Borhani
September 26, 2014 at 12:55 pm

@3: I'd love to hear Jonathan Baell's thoughts on your questions.
Something I think is reasonable to do, if your potentially PAINful compound has passed the easy hurdles (detergent, etc.) is to apply MedChem logic. It does take more work, however.
Take those arylidene rhodanines, for example: If I saturate the C=C double bond, or replace the C=S by C=O, do I still have an inhibitor? Toxoflavins: What happens if I replace some of the N atoms by CH? This sort of molecular deconstruction of hits, to enable building specific hypotheses about how each atom of the inhibitor may interact with the target, can be invaluable, in my opinion.

MAW
September 26, 2014 at 3:31 pm

Different PAINS require different techniques. A diligent MD/PHD student from Mayo Clinic (see our paper referred to in the Nature commentary) recently established ALARM NMR here at the UMN. It does not replace other methods, but we have found it a useful tool in the toolbox.
Always have a well-versed medicinal chemist on board when doing assay triage. Probably the simplest place to start.
I agree that atom replacements are key to understanding structure-interference liabilities in these compounds. Has anyone reduced the double bond in an "active" tetrahydroquinoline [C12=CC=CC=C1C3C(CC=C3)C(C4=CC=CC=C4)N2]; see Baell 2010FMC1529 for a discussion) and retained activity?

Jonathan Baell
September 26, 2014 at 6:09 pm

OK, I feel the need to respond.
Great summary Derek.
@3: you are quite correct. A recommended best practise has yet to be established, in part due to the subversive and complicated behaviour of PAINS in different settings…look at the excellent work of the Guy group on SJ-172550 in PlosOne a couple of years ago. Could a general assay be developed to detect such complicated behaviour? Maybe, but a lot of learning yet. Has anyone out there a protein like PTB1B pulls out lots of junk? A panel of these (such as the La protein that led to ALARM NMR) could be useful in addition to a couple of the redox assays now out there.
And @4 (hi dave) yes early SAR that tracks with the problematic structure has to be a concern. The importance of SAR is so often neglected. And @5…Mike/Jayme your efforts to establish ALARM NMR is brilliant. Re the tetrahydroquinoline…a good point about reduction….but another

complication…I've been told by Uli Schmitz (Giliead) these can chelate with heavy metals such as Gadolinium…so a metal strip should also be part of the process hit triage.

Jonathan Baell
September 26, 2014 at 6:18 pm

@6….I forgot to stress this is why structure alone is one of the most important red flags and so being familiar with as many PAINS classes as possible or at least the most common is very useful/important. Personally, I wouldn't actually bother following up target-based PAINS HTS hits in any sense with counter-assays unless accompanied by compelling data (less hot PAIN class, unusually potent, selective, polar etc, but even then…..)

Ed
September 27, 2014 at 3:51 am

It is also worth noting that there exist free and easy to use software solutions for filtering off PAINS, so there should be absolutely no reason for any group to chase up PAINS hits without being aware of it.
KNIME (a free, cross-platform equivalent to PipelinePilot) is very well supported by the cheminformatics and sbdd/fbdd/lbdd community (CDK, RDKit, Schrödinger, ChemAxon, Simulations+, MOE, BioSolveIT etc), and there are a number of freely downloadable workflows to achieve PAINS filtering.
as far as i know it installs without admin rights, so no need to trouble your IT team either.
https://www.knime.org/downloads/overview
ed (a happy medicinal chemist KNIME user)

cdsouthan
September 27, 2014 at 7:16 am

It would be a great community service if those so inclined could surface (and maintain) PAINS lists as PubChem submissions (SIDs). This would be the easiest way to warn the largest number of users.

cdsouthan
September 27, 2014 at 7:20 am

Alternative thoughts – just offer PubChem a robust consensus PAINS filter for them to includ as a default subset (i.e. on the right hand side of result sets)

Pete
September 27, 2014 at 11:33 am

I made these comments on the corresponding Practical Fragments post and they may have some relevance here as well.
I believe that we need to be thinking more about the criteria by which compounds are deemed to

be PAINS. For example has a compound been shown experimentally to be a PAIN or do we think it ought to be a PAIN because it includes a substructure that is believed to be PAINful? What do we mean when we assert that 8% of compounds in commercial libraries are PAINS. If we believe that a substructure is PAINful then exactly how strong is the link between the presence of the substructure and the observed PAINfulness? Is the PAINfulness restricted to a single type (i.e. detection technology) of assay or has it been observed over different types of assay? How much should we be worried about PAINfulness if affinity to the target has been measured directly and characterized by X-ray crystallography?

I'm certainly not denying that PAINS are a problem and we do need to be aware of potential screening artefacts. At the same time, we do need to find ways to better capture how much we really know about the PAIN levels associated with particular substructures, particularly when asserting literature pollution. As a cautionary tale, it's worth remembering that it was asserted (dx.doi.org/10.1038/nrd2445), "Lipophilicity plays a dominant role in promoting binding to unwanted drug targets" even though correlations were for median lipophilicity for each promiscuity level and the activity (>30% inhibition at 10 micromolar) threshold used to define promiscuity is unlikely to have any physiological relevance. Fast forward a bit and we see this work being cited in support of the assertion (dx.doi.org/10.1021/jm201388p) that lipophilicity, "... has an inevitable role in selectivity and promiscuity" which could be regarded as a form of inflation in its own right.

Jonathan Baell
September 29, 2014 at 1:11 am

@11....Pete, as I suggested in Dan's blog, I can recommend going back to the PAINS J. Med. Chem. 2010 and associated papers (Baell Fut. Med. Chem. 2010 and Baell Aust. J. Chem. 2013) as we discuss a number of these issues in quite some detail so there is no need to go over old ground. I certainly agree that we should not immediately think of this as a black and white issue and that evidence-driven decision-making is the way to go and the degree of evidence does vary from class to class. I also don't rule out that we may at some point in the future see an example or two where a PAIN (particularly from a less problematic class) has been prematurely progressed from a target-based screen but adventitious additional off-target activity has led to (possibly even clinical) efficacy and who knows maybe it goes all the way. That is, it has become a more traditional drug-discovery approach in a sense, associated with polypharmacology. Personally I'd not take this chance from a target-based screen without substantial reason to do so.

When we say 5-12% of libraries contains PAINS, this is defined by the original PAINS filters and what they recognise. There is much nuance and many concepts to discuss about this, which we do in the papers cited above (i.e. why in some cases a PAIN may not be a PAIN, and why in others a non-PAIN...that is a compound not recognized by the filters.....is actually a PAIN). The 1700 word/10 refs limit in the Nature article (where terms such as 'phenotypic' were seen as potentially too specific to a generalist audience) does not allow for such subtlety but does afford a valuable opportunity to send a strong message to try to put a halt to target-based (and many phenotypic-derived) PAINS publications, the overwhelming majority of which are a waste of precious (unaffordable) time and money.

I certainly appreciate that it is very hard for people to understand how much time PAINS can waste unless you are a H2L medicinal chemist who has worked on hit sets containing PAINS. I think most medicinal chemist who have gone down this path only to find it a cul-de-sac, would agree.

SP
September 29, 2014 at 8:20 am

I've faced biologists who were worse than ignorant of the general idea of "ugly" or promiscuous compounds based on substructure filters- they actively reject the notion that chemists can base these judgments on structure alone because they can always come up with a couple counterexamples, e.g. marketed drugs with "bad" groups. It's similar to the attitude that you have to follow up on EVERY SINGLE HIT even if it's not available, impure, etc. because that one hit out of your list of thousands is going to be the next drug. There's no sense of statistics or cost/benefit.

MAW
September 29, 2014 at 5:41 pm

@11...In most of my analyses, PAINS (or percent PAINS) simply means that this was the percent of compounds flagged by substructure filters implemented in Canvas (Schrodinger). The point is simply to say that most commercial libraries have suspect compounds in them, and researchers should be wary. I have found at least one 50k library that has no compounds flagged as PAINS. When doing HTS triage, I simply flag compounds as PAINS and decide by visual inspection how to prioritize them versus other actives. The same is true of any computational filter we use. After all, our groups don't have the resources to follow up on everything we find, so knowing what might be the risks of moving ahead on a series is important.
Presumably, pharmaceutical companies will sometimes employ even harsher filters to flag or remove compounds. REOS filtering is much stricter...usually on the order of 25-30% in large commercial libraries. But of course we don't throw out all nitro aromatics at the triage stage.
We are often approached by academic researchers who have developed compounds that we believe fit the PAINS substructure classes. In one case they have crystal structures. Of course, these crystals were formed under conditions that were not at all like the colormetric assays they were running to determine activity. (And the compounds weren't that potent anyhow, even after a library of ~400 compounds was prepared.) Before moving ahead with a collaboration, we proposed to derisk these compounds by performing simple redox cycling assays. After about 2 years we have yet to have access to any of their compounds.
The bottom line is we use many computational filters to flag compounds for prioritization. PAINS filtering is just one tool in this toolkit.
We are just completing work on structural interference studies on a few classes of interference compounds. I am in total agreement with JBaell. These studies have shown a wide range of interference with these classes. I suspect that following up on any of these non-interfering members would eventually lead to the discovery of the more deceptively "active" true interference compounds. But I don't know that for sure.

Lagorce David
October 1, 2014 at 10:11 am

As a follow up to those interesting discussions it is clear that educated decisions need to be made in the prioritization and optimization of hit compounds and especially when it comes to promiscuous associated substructures such as PAINS.
Having in hand the proper tool to flag such chemical moieties, rather than just reject them, is therefore essential to gain some knowledge and to anticipate any development failure later on in the process.
To this end, for several years we are developing a dedicated predicting tool and maintaining literature surveys on this matter in collaboration with Dr. J. Baell.
Indeed we provide a free online tool named FAFDrugs2 (http://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py?form=FAF-Drugs2#forms::FAF-Drugs2) which can either creating filtered libraries or analyzing a subset of hit compounds with the various physchem and chemistry rules including the essential concept of PAINS.
A dedicated website is available at http://fafdrugs2.mti.univ-paris-diderot.fr

Comments are closed.

MORE FROM *SCIENCE TRANSLATIONAL MEDICINE*

- Archive
- Current Table of Contents
- In the Pipeline
- ▶ About Science Translational Medicine

RECENT COMMENTS

- anonymous on 3-Bromopyruvate: What a Mess
- loupgarous on The University of Malaya Is Not Having It
- loupgarous on The University of Malaya Is Not Having It
- loupgarous on Crap, Courtesy of a Major Scientific Publisher
- anon on 3-Bromopyruvate: What a Mess

CATEGORIES

- "Me Too" Drugs (30)
- Academia (vs. Industry) (142)
- Aging and Lifespan (74)
- Alzheimer's Disease (108)
- Analytical Chemistry (101)
- Animal Testing (39)
- Autism (23)
- Biological News (267)
- Birth of an Idea (43)
- Blink &#8250 (5)
- Blog Housekeeping (259)
- Book Recommendations (31)
- Business and Markets (966)
- Cancer (331)
- Cardiovascular Disease (154)
- Chem/Bio Warfare (15)
- Chemical Biology (88)

- Chemical News (428)
- Clinical Trials (401)
- Closing Time (16)
- Current Events (145)
- Diabetes and Obesity (143)
- Drug Assays (282)
- Drug Development (498)
- Drug Industry History (360)
- Drug Prices (135)
- General Scientific News (166)
- Graduate School (64)
- How Not to Do It (39)
- How To Get a Pharma Job (32)
- In Silico (116)
- Infectious Diseases (173)
- Inorganic Chemistry (5)
- Intelligent Design (9)
- Job Postings (1)
- Life As We (Don't) Know It (24)
- Life in the Drug Labs (340)
- Lowe's Laws of the Lab (7)
- Metaphors, Good and Bad (2)
- Natural Products (31)
- Odd Elements in Drugs (12)
- Patents and IP (160)
- Pharma 101 (15)
- Pharmacokinetics (67)
- Press Coverage (97)
- Regulatory Affairs (202)
- Safety Warnings (19)
- Science Gifts (13)
- Snake Oil (94)
- The Central Nervous System (155)
- The Dark Side (206)
- The Scientific Literature (410)
- Things I Won't Work With (30)
- Things I'm Glad I Don't Do (6)
- Toxicology (169)
- Uncategorized (84)
- Who Discovers and Why (161)
- Why Everyone Loves Us (85)

ARCHIVES

Select Month




Fig S20. Screengrab of Near Neighbours ELN (http://malaria.ourexperiment.org/near_neighbours/2237), Reduction of 4-Fluoro Near-Neighbour Michael-Acceptor (PMY 36-2), Paul Ylioja, 2012. (Related to Fig SC5)

TCMDC Near Neighbours

Summer scholarship near neighbour synthesis

<< Next Entry Previous Entry >>

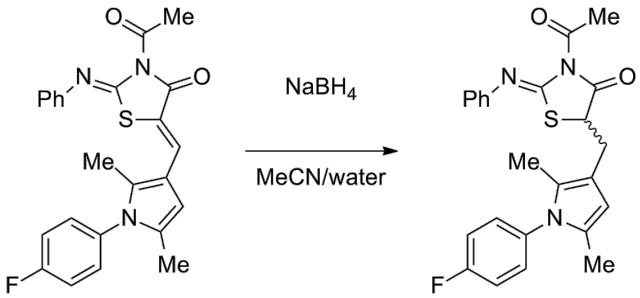
Reduction of 4-fluoro near-neighbour Michael-acceptor (PMY 36-2)

27th February 2012 @ 04:44

Reaction did not reduce the alkene of the product. The isolated material was mostly deacetylated product.

===

Reduction of 4-fluoro near-neighbour Michael-acceptor (PMY 36-2) using sodium borohydride.

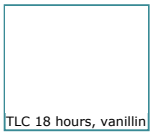


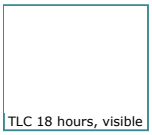
Reaction Start Time: 15.30 EST 27/02/12
PMY 36-1 (40 mg, 0.09 mmol, 1 equiv.) was dissolved in acetonitrile (11 mL, just soluble). The solution was cooled in ice/water and sodium borohydride (30 mg, 0.79 mmol, 8.6 equiv.) was added as a solution in water (approx 3 mL) was added. The reaction was allowed to warm to room temperature. The bright yellow solution turns noticeably less coloured (30 minutes). Reaction allowed to stir overnight. After 18 hours, TLC shows reaction complete. Water (15 mL) added, no precipitation. Forms hazy solution when cooled in ice. Mixture was extracted with EtOAc (3 × 15 mL) and the extracts washed with brine and dried ($MgSO_4$) then concentrated under reduced pressure to a yellow powder (35 mg). ^1H NMR matches de-acetylated product (e.g PMY 14-1).

TLC (10% MeOH/DCM) visualised with UV and vanillin:

NMR:

Sear
This
Perm
URI
URI L
Revis
Add
Edit
Expo
XML
Archi
Nove
Augu
April
Marc
Febr
Janu
June
April
Auth
Stefa
Zoe
Alice
Paul
Murr
Sect
Activ
Com
Data
need
Prod
Susp
Mnr
MNR
MNR


TLC 18 hours, vanillin


TLC 18 hours, visible


1H NMR

MNR
MNR
MNR
MNR

Too

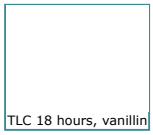
Show
Show

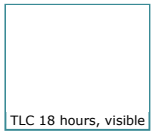
Risk and Hazard Assessment:
See: Reduction of 4-fluoro near-neighbour Micheal-acceptor (PMY 36-1) and Reduction of pyrrole-3-carbaldehyde using sodium borohydride (PMY 18-1)

Linked Posts

Attached Files


Scheme


TLC 18 hours, vanillin


TLC 18 hours, visible


1H NMR

Paul Ylioja | View Source | Completed | Comments (0)

<< Next Entry Previous Entry >>

Fig S21. Screengrab of Near Neighbours ELN (http://malaria.ourexperiment.org/near_neighbours/2259), Reduction of 4-Fluoro Near-Neighbour (N-H) Michael-Acceptor (PMY 39-1), Paul Ylioja, 2012. (Related to Fig SC5)

TCMDC Near Neighbours

Summer scholarship near neighbour synthesis

<< Next Entry Previous Entry >>

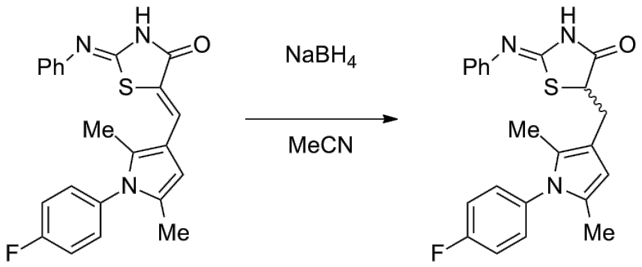
Reduction of 4-fluoro near-neighbour (N-H) Michael-acceptor (PMY 39-1)

28th February 2012 @ 04:14

Starting material recovered (90%) cleaner than original.

===

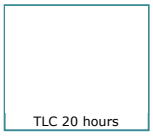
Reduction of the un-substituted near-neighbour PMY 14-4 to avoid the deacetylation seen in PMY 36-2.



Reaction Start Time: 14.50 28/02/12
PMY 14-4 (100 mg, 0.25 mmol, 1 equiv.) was stirred in acetonitrile (10 mL, slurry). Material did not dissolve on heating to reflux. MeOH (approx. 5 mL) was added. Dissolved on heating to reflux, precipiated on cooling to room temperature (not completely). Sodium borohydride (approx 50 mg, 1.3 mmol, 5 equiv.) was added, slight exotherm and bubbling observed. After 10 minutes bubbling had ceased, reaction heated briefly to reflux. On cooling, the reaction remained as a solution. TLC 1.5 hours, shows no reaction. Further sodium borohydride (approx 50 mg) was added and the reaction heated to 60 °C. After 20 hours, TLC shows no reaction, yellow colour remains. Water (10 mL) and EtOAc (20 mL) added. The layers separated. The organic layer was washed with water (2 × 10 mL), brine and dried ($MgSO_4$) then concentrated under reduced pressure to a yellow powder (90 mg). ^1H NMR shows very clean SM, cleaner than original PMY 14-4. Material to be used for biological testing.

TLC (50% EtOAc/hexane) visualised with UV and vanillin:

Sear
This
Perm
URI
URI L
Revis
Add
Edit
Expo
XML
Archi
Nove
Augu
April
Marc
Febr
Janu
June
April
Auth
Stefa
Zoe
Alice
Paul
Murr
Sect
Activ
Com
Data
need
Prod
Susp
Mnr
MNR
MNR



NMR:

See also:
Reduction of 4-fluoro near-neighbour Michael-acceptor (PMY 36-2)
Synthesis of 4-Fluoro substituted near neighbour (PMY 14-4)

Risk and Hazard Assessment:
See: Reduction of 4-fluoro near-neighbour Micheal-acceptor (PMY 36-1) and Reduction of pyrrole-3-carbaldehyde using sodium borohydride (PMY 18-1)

Linked Posts

Attached Files

Paul Ylioja | View Source | Completed | Comments (0)

<< Next Entry Previous Entry >>

MNR
MNR
MNR
MNR

Too

Show
Show

Fig S22. Screengrab of Near Neighbours ELN (http://malaria.ourexperiment.org/near_neighbours/2181), Reduction of 4-Fluoro Near-Neighbour Michael-Acceptor (PMY 36-1), Paul Ylioja, 2012. (Related to Fig SC5)

TCMDC Near Neighbours

Summer scholarship near neighbour synthesis

<< Next Entry Previous Entry >>

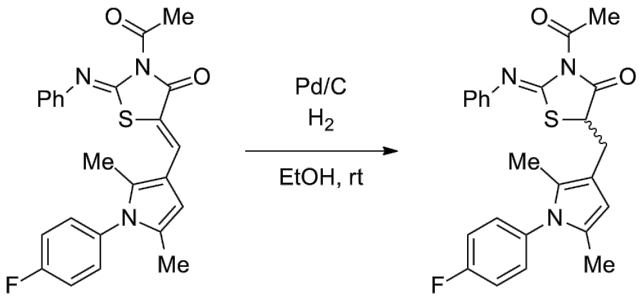
Reduction of 4-fluoro near-neighbour Micheal-acceptor (PMY 36-1)

22nd February 2012 @ 03:07

NMR showed disappearance of pyrrole-*H*, did not reduce alkene to a significant degree.

===

Reduction of 4-fluoro near-neighbour Micheal-acceptor PMY 35-1 by hydrogenation.



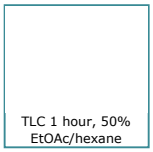
Reaction Start Time: 15.10 EST 22/02/12
10% Palladium on charcoal (approx. 20 mg) was stirred in EtOH (2 mL) at 0 °C under an inert atmosphere. PMY 35-1 (100 mg, 0.23 mmol, 1 equiv.) was suspended in EtOH (16 mL, partial solution) and added to the catalyst suspension. The reaction was placed under a hydrogen atmosphere (balloon) and the reaction allowed to warm to room temperature. TLC shows new product and SM at 1 hour. No change after 18 hours by TLC. Hydrogen was purged from the reaction (nitrogen). The reaction was filtered through celite and the filtrate concentrated under reduced pressure.

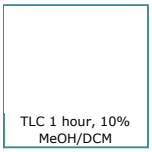
TLC visualised with UV and vanillin:

NMR:

Reference:

Sear
This
Perm
URI
URI L
Revis
Add
Edit
Expo
XML
Archi
Nove
Augu
April
Marc
Febr
Janu
June
April
Auth
Stefa
Zoe
Alice
Paul
Murr
Sect
Activ
Com
Data
need
Prod
Susp
Mnr
MNR
MNR





MNR
MNR
MNR
MNR

Too

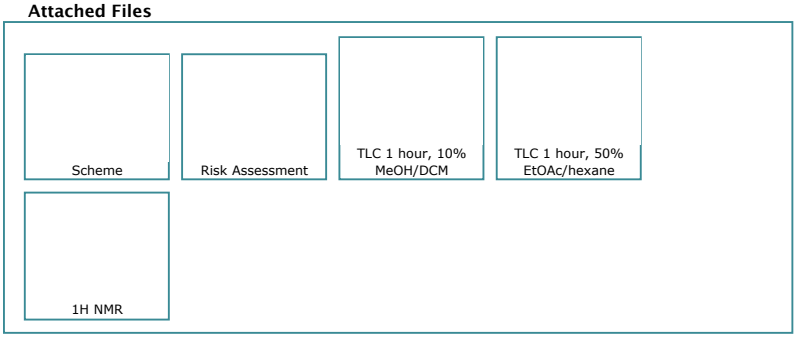
Show
Show

Patent:
WO2009137133 (A2)

Risk and Hazard Assessment:

Linked Posts

Attached Files



Paul Ylioja | View Source | Completed | Comments (0)

<< Next Entry Previous Entry >>

Fig S23. Screengrab of Near Neighbours ELN (http://malaria.ourexperiment.org/near_neighbours/2523), Testing Reactivity of Michael-Acceptor of ZYH 6-2 (PMY 41-1), Paul Ylioja, 2012. (Related to Fig SC5)

TCMDC Near Neighbours

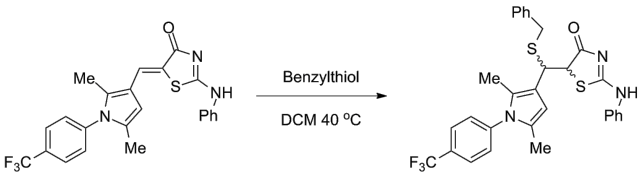
Summer scholarship near neighbour synthesis

<< Next Entry Previous Entry >>

Testing reactivity of Michael-acceptor of ZYH 6-2 (PMY 41-1)

9th March 2012 @ 03:22

Testing reactivity of Michael-acceptor of ZYH 6-2 (PMY 41-1) using benzylthiol at 40 °C (close to biological temperatures).



Reaction Start Time: 14.20 09/03/12

ZYH 6-2 (20 mg, 0.05 mmol, 1 equiv.) was stirred in DCM (10 mL). Benzylthiol (27 µL, 0.23 mmol, 5 equiv.) was added and the reaction heated to 40 °C. After 68 hours, solvent had evaporated. A sample of the mixture showed starting materials only by ^{1}H NMR. No peaks consistent with expected product. K_2CO_3 (approx 0.1 g) was added. After 1 hour, the reaction is a solution with solid base. Stirred at room temperature for approx 20 hours. ^{1}H NMR shows change but no obvious expected product peaks. TLC consistent with SM and some minor products. ESI mass spec. shows only SM. But no mass consistent with benzylthiol adducts.

NMR:

1H NMR 68 hours

Mass Spec:

ESI mass spec

Sear
This
Perm
URI
URI L
Revis
Add
Edit
Expo
XML
Arch
Nove
Augu
April
Marc
Febr
Janu
June
April
Aut
Stefa
Zoe
Alice
Paul
Murr
Sect
Activ
Com
Data
need
Prod
Susp
Mnr
MNR
MNR

Risk and Hazard Assessment:

Attached Files

Paul Ylioja | View Source | Active | Comments (0)

<< Next Entry Previous Entry >>

Powered by LabTrove 2.4 © University of Southampton

MNR
MNR
MNR
MNR

Too

Show
Show

Fig S24. Screengrab of Synaptic Leap Node 412 (http://www.thesynapticleap.org/node/412), Desired Compounds Consultation Phase 2, Matthew Todd, 2012.

The Synaptic Leap
Open Source Biomedical Research

Search

HOME COMMUNITIES GETTING STARTED RESOURCES NEEDED ABOUT

Desired Compounds Consultation Phase 2

Published by MatTodd on 28 June 2012 - 1:23pm

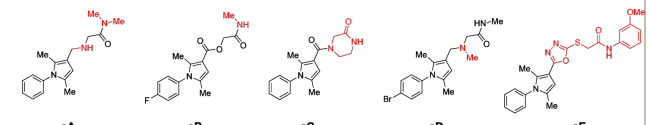
Community
malaria research community
Subject
Request for Help

The evaluation of the arylpyrroles has gone well, in that we've identified promising new antimalarial compounds. Besides their high potency, they exhibit high levels of activity in a late-stage gametocyte assay which is very exciting. (As an open source project, anyone may take these results and work on them - made easy by all our data being available.) It's for these reasons of potency that we're going to explore one more iteration of the series, despite three of the compounds showing no oral activity in mice. It's thought the problem could be low solubility. This round will only be including compounds with low (<5) logP, and we'd like to play around with the structure a little more.

If this round does not throw out any improved compounds we'll probably park the series. Hence it's important that we choose a good set of compounds to evaluate. We decided to list the top 10 "most wanted" compounds that we could access commercially, as well as a similar list of compounds we could not buy and wanted to make. We'd then attempt to source those commercial compounds, and ask the synthesis community to volunteer to make the other necessary compounds.

We're now assembling the lists. We'd compiled a first-pass list of attractive compounds. We've now modified that list to give two new lists of commercial vs. synthetic compounds - below. We now need to consult the community again on these new lists. Before embarking on synthesis or purchase we will have the compounds checked by the original authors of the GSK TCAMS set to see whether any of the compounds have been evaluated and found to be inactive - we'll send the SMILES of all these compounds to GSK and see what they say. We know that's a big ask.

First the compounds we'd like to get our hands on which are commercially-available:



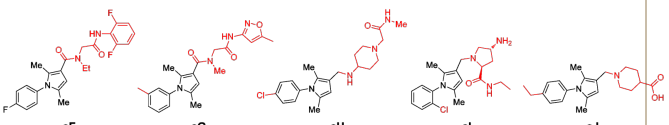
cA
Molecular Weight: 285.38402
Log P: 1.89
tPSA: 35.58
Enamine Z102381252

cB
Molecular Weight: 304.31618
Log P: 1.92
tPSA: 58.64
Enamine Z18964039

cC
Molecular Weight: 315.34212
Log P: 1.24
tPSA: 52.65
Enamine Z31603451

cD
Molecular Weight: 364.28008
Log P: 2.72
tPSA: 35.58
Enamine Z322133338

cE
Molecular Weight: 434.51078
Log P: 4.08
tPSA: 75.52
Enamine Z56895831



cF
Molecular Weight: 429.43489
Log P: 3.8
tPSA: 52.65
Enamine Z252425684

cG
Molecular Weight: 380.44026
Log P: 2.7
tPSA: 74.24
Enamine Z168527658

cH
Molecular Weight: 388.93416
Log P: 2.02
tPSA: 47.61
Enamine Z401944072

cI
Molecular Weight: 374.90758
Log P: 1.88
tPSA: 61.6
Chembridge 70163819

cJ
Molecular Weight: 340.45922
Log P: 3.84
tPSA: 43.78
ChemDiv C799-0833

If any of these are known by GSK, we'll fill up the spaces with compounds from these backups, or any others people might like to see tested:

User login

Username *

Password *

Create new account

Request new password

Log in

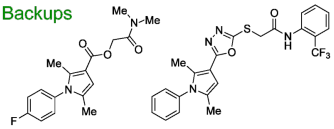
Malaria Research Community

Current Projects for Malaria
- Functional Reconstitution of the Plasmodium GPI:protein transamidase Complex
- Gene Wiki Overview
- Open Source Drug Discovery for Malaria Meeting - February 2012 - Why?
- Open Source Drug Discovery for Malaria Project Meetings
- Open Source Drug Discovery: The GSK Arylpyrrole Series
  - A list of what's needed in the OSDD Malaria project
    - Desired Compounds Consultation
      - Desired Compounds Consultation Phase 2
        - Consultation Outcome
- Analog Synthesis - Variation of the Aryl Ring
- Availability of TCMDC-123812 and TCMDC-123794
- Biological Evaluation of Arylpyrrole Series
- Druggability of the Arylpyrrole leads (TCMDC-123794 etc)
- Known Near Neighbours of Initial Tres Cantos Leads
- Prediction of Biological Targets of Actives
- Proposed resynthesis strategy for TCMDC-123812 and TCMDC-123794

THE SUBCELLULAR DRUG TRANSPORT LABORATORY: Cellular pharmacokinetic analysis of antimalarials

The GSK Aminothienopyrimidine (ATP)

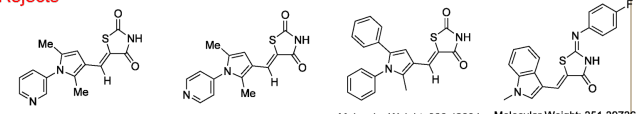
Backups



Molecular Weight: 318.34276
Log P: 0.65
tPSA: 49.85
Enamine Z18963831
Similar to cB

Molecular Weight: 472.48277
Log P: 4.57
tPSA: 66.29
Enamine
logP too high

Rejects



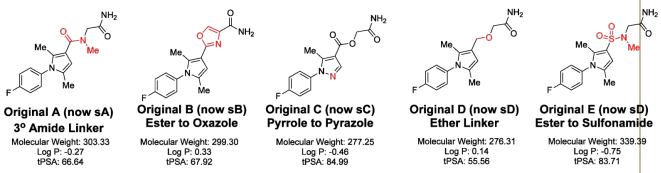
Molecular Weight: 299.34762
Log P: -0.3
tPSA: 61.77
Vitas M Labs STK629521

Molecular Weight: 299.34762
Log P: -0.3
tPSA: 61.77
Vitas M Labs STK594248

Molecular Weight: 360.42894
Log P: 3.11
tPSA: 49.41
Vitas M Labs STK621580

Molecular Weight: 351.39736
Log P: 3.85
tPSA: 44.7
Vitas M Labs STK578116

The compounds we'd like to evaluate which are not commercially-available are:



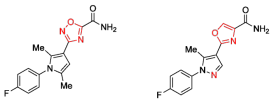
Original A (now sA)
3º Amide Linker
Molecular Weight: 303.33
Log P: -0.27
tPSA: 66.64

Original B (now sB)
Ester to Oxazole
Molecular Weight: 299.30
Log P: 0.33
tPSA: 67.92

Original C (now sC)
Pyrrole to Pyrazole
Molecular Weight: 277.25
Log P: -0.46
tPSA: 84.99

Original D (now sD)
Ether Linker
Molecular Weight: 276.31
Log P: 0.14
tPSA: 55.56

Original E (now sD)
Ester to Sulfonamide
Molecular Weight: 339.39
Log P: -0.75
tPSA: 83.71



Original F (now sF)
Ester to Oxadiazole
Molecular Weight: 300.29
Log P: 2.18
tPSA: 80.28

New G (now sG)
Pyrazole and Oxazole
Molecular Weight: 286.26
Log P: -0.31
tPSA: 80.28

New H

New I

New J

All compounds with terminal primary amides also need corresponding 2º and 3º amides made

(note that primary, secondary and tertiary terminal amides are all of interest here and ought to be made concurrently.

And again, these are the backups in case these compounds have already been evaluated:

Series

Completed Projects for Malaria

Toxoplasma Research Community

Recent posts

Biological Results for ATP Series from April 2013
1 May 2013 - 3:48am By MatTodd
Replies: 0

Biological Data
1 May 2013 - 3:39am By MatTodd
Replies: 0

The GSK Aminothienopyrimidine (ATP) Series
1 May 2013 - 3:38am By MatTodd
Replies: 0

more

Recent comments

anacardic compounds to cure TB 5 March 2014 - 12:27am

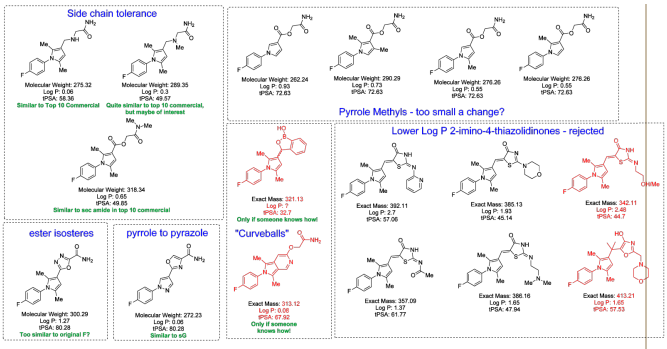
Protein available 24 September 2013 - 8:20pm

Hi there, just watched Tom's 17 May 2013 - 11:32am

Meeting Recording and Minutes 21 March 2013 - 2:57am

SOLVED-onamides - perhaps! 28 February 2013 - 5:44pm

more



In the synthesis set:

1) We've included a couple of pyrazoles. Fused pyrazoles quite different to the GSK hit compounds are commercially-available, and we've not included those because of the substantial differences - those options are shown here, and we could include some if needed.
2) We've taken the curveballs out as being a little speculative, but if anyone knows how to make these, or wants to have a go, please say.
3) We've de-prioritised the thiazolidinones as being too insoluble, even with some obvious tweaks. This means we have three slots available for the synthesis "top 10 most-wanted." Our final phase of consultation will be to fill those slots.

The final consultation will hopefully be a public hangout on the web for a final discussion, technology permitting. Date to be advised. This will finish the "Most Wanted" lists and begin the next phase of compound evaluation. **So this is where we stand - would anyone do this differently?**

On a side note, that will probably need a post of its own, the logPs in the above are approximate. We've been using available tools to calculate these, e.g. Chemdraw, but there's a lot of variability depending on the tool used. We have no access here to one that performs well, from ACDLabs. While it's likely the above figures are inaccurate (*vs.* truth) it's unlikely they are so far out as to invalidate a target).

- Consultation Outcome

‹ Desired Compounds Consultation up Consultation Outcome ›

Printer-friendly version Add new comment

Comments

Nicely presented!

Looks good, I really like the way that you have presented the compounds. It makes it clear what the aims of this stage of the project are.
My only suggestion would be to take each of the these 17 or so compounds (especially the to be synthesised list) and do a similarity search on E-Molecules.com to see if there are any more commercially available compounds of interest to you.
Iain

Iain Wallace (not verified)
Jun 29 2012

REPLY

Searching

Hi Iain. eMolecules is how we generated the commercially available lists. That is we took the "to be synthesised" list and trimmed by commercial availability to get the commercially available list. There are others of course in the similarity searches but they get quite different, quite quickly. The ones shown are some of the ones that probe the SAR that we're curious about.

pylioja
Jul 01 2012

REPLY

Jonathan Baell
(not verified)
Jul 11 2012

Top 10

Hi Matt
My thoughts would be to generally keep to small tweaks around the original 123812, along the lines of some targets some of us threw together a while ago (can't find the url on your site but it must be there somewhere). The reasoning is that at EC50 ca 330nM and multiple membranes possibly to traverse, intracellular target affinity could easily be ca 30nM or if competitive with substrate say 3nM...i.e. pretty tight fit to target and very small exploration of target space required. So 123794 with EC50 54nM but at the cost of a big chunk of added molecule is probably not the way to go: actives that are substantially changed may be introducing new targets (it is actually a bit of a worry how such big changes can also give rise to actives).
We typically find that commercially analogues may provide a little bit of useful SAR but almost always from an early stage we have to make SAR probes in-house....of course I realize chemistry resources are limiting hence a focus on available anlagues initially. But to find early on that e.g. a pyrazole can replace the pyrrole would be nice, the former I regard as a privileged structure. The pyrrole could complicate things but may be stable enough with e-withdrawing groups like ester (like lipitor with a 3-amide) but if one went to replace the ester, may not be a viable progression core...etc etc (actually, the ester may not be susceptible to esterases due to hindrance).
Anyway, just a few thoughts.
Jonathan

REPLY

pylioja
Jul 12 2012

Hi Jonathan, was the post you

Hi Jonathan, was the post you were thinking of this one? I linked to it on the first round of consultation.
I agree that commercial compounds aren't the best way of probing SAR but in this case the secondary and tertiary amides of TCMDC-123812 are commercially available (eg cB) so they would definitely be worth buying. Some of the larger changes might not be so useful but will help us build more data points without much effort.
In terms of the stability of the ester, we've found that it does seem to be metabolised quite readily, especially in mouse plasma, so the pyrrole methyl groups don't shield it enough. We are looking to nail down if this ester can be replaced with something more stable. We know that we can't use a secondary amide (OSM-S-19 and OSM-S-21 on http://bit.ly/OSDDcompounds) but we haven't yet tried a tertiary amide for the linker (e.g. sA).
The pyrroles seem quite stable, chemically at least. They stand up to quite harsh treatment without any issues, so I'm not overly worried about them. The pyrazole analogue (sC) is now ready and we'll certainly be investigating it.

REPLY

MatTodd
Jul 24 2012

Online consultation

An open online consultation about the way forward with this series (i.e. which compounds to make, which to buy) will be held on Wednesday July 25th 2012 at 4 pm Sydney time. Anyone who wants to join and advise can go here to do so: http://bit.ly/OSDDconsult. The proceedings will be up online shortly afterwards.

REPLY

MatTodd
Jul 24 2012

Known inactives

Felix Calderon from GSK Tres Cantos wrote to tell us that none of the compounds above are known inactives for malaria:

"Hi Matt,

From the list of 78 compounds that you sent, only 19 smiles strings are recognized as compound in the GSK collection and none of them have been tested as antimalarials.

The other 59 compounds or either are not in the collection or have either not been

recognized for our software.

Hope this helps,

Félix"

This is very useful advice, and an enormous help to the project from GSK. Thank you Felix. This means that all the compounds listed above on the synthetic and commercial lists are still of interest.

REPLY

MatTodd
Jul 24 2012

Comment from Vrinda Nandi on Linkedin

A comment on the series was received from Vrinda Nandi (drug discovery consultant, Bengaluru area, India) on a discussion thread on LinkedIn, which I wanted to repost here (with permission) for the sake of completeness:

"I would say you may have quite a few difficulties with the pyrroles. Being amide bioisosteres, the solubility is expected to be quite poor. And coupled with other amide functionalities would mean poorer solubilities in assays and in vivo. Have you plotted logP with activity? I note that the logP measured / calculated are variable, hence, it may be good to get hold of an ACD package or run a quick assay on a handful to see how lipophilic some of these might be. There may be a correlation of lipophilicity with extent of permeation into the parasite, so the more lipophilic compounds would tend to be more active. However, this can take you down a dubious route. As the program progresses, lipophilicity can markedly affect in vivo absorption and in turn you may fail to see efficacy.

How are you conducting your oral studies in mice? Sometimes, using cosolvents or solubilizing agents (small percentage of ethanol or a suitable cyclodextrin) may help to get a little more into the bloodstream. It will be challenging however, to demonstrate efficacy with early compounds that have low potency since getting sufficient amounts into the plasma could be difficult. Also do keep in mind that the phenyl ring (unsubstituted at 4-position) is susceptible to hydroxylation. This alongside amide hydrolysis in vivo will give you phenols or carboxylic acids which are poor at traversing membranes and may not have activity against the parasite. Thus, oxazoles and oxadiazoles should be good replacements.

Putting all this into perspective, I would say, test a handful, check in vivo exposures and call for a early "park" if necessary.

I think a sufficient property space has been planned for exploration in the proposed compounds. Good to see that the thiazolidinones have been rejected.

Good luck. I look forward to the next round of data."

Thank you Vrinda.

REPLY

Soumendranath Bhakat (not verified)
Aug 23 2012

Potential Antimalarials as NCEs

Hii;

I have designed a huge number of potential new antimalarials having great probability of activity predicted by PASS server and I believe these designed molecules will be active against artemisinin resistant strain.I do a PASS activity prediction of above described molecules but it is not showing significant probability of being an antimalarial molecule whereas my designed molecules are showing

better and even great probabilty of being antimalrial molecule.
But the main challenge lies with synthesis.If some of these sets molecules can be synthesised then we can overcome the resistancy problem and will ultimately find a new way of treatment.See the attached files for designed molecules.

File:
New Potent CHL Analogues.pdf

REPLY

MatTodd
Aug 24 2012

PASS prediction

Soumendranath - thanks, but perhaps you should firm up these arguments a little? If discovery of new medicines was as easy as using the PASS filter, we'd have solved a lot of the world's problems already!

How different are the scores for the molecules above (which you don't give - remember this is open science), and those you mention? Is the difference statistically significant? Perhaps you could enumerate why you think the molecules above are not likely to be antimalarials, and why yours are more likely (i.e. besides the data from the PASS prediction). How well does PASS work on predictions of activity in whole-cell screening (which is what we're doing here) vs isolated target prediction? Specifically why you think they would overcome the resistance problem (and resistance to what?).

If you want to discuss your series further, or request help on something, could you also start a new thread, on a new page? It's important to try to keep discussions focussed and relevant if we can.

REPLY

Fig S25. Screengrab of Synaptic Leap Node 416 (http://www.thesynapticleap.org/node/416), Consultation Outcome, Paul Ylioja, 2012.

The Synaptic Leap
Open Source Biomedical Research

Search

HOME COMMUNITIES GETTING STARTED RESOURCES NEEDED ABOUT

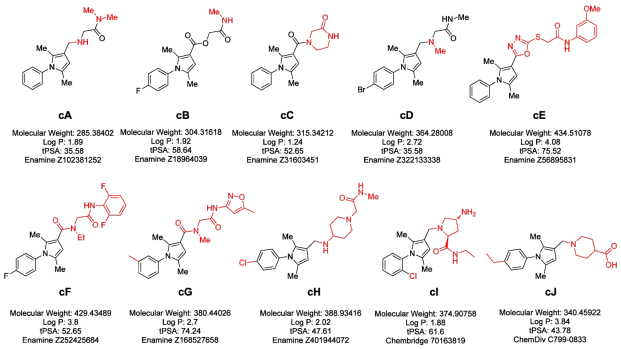
Consultation Outcome

Published by pylioja on 26 July 2012 - 6:59am

Community
malaria research community
Subject
Results

Firstly, thanks for coming to the online meeting. I found it worked quite well (minor glitches aside) but it would be great to hear your thoughts. We'll post the recording up in the near-ish future. The OpenWetWare wiki will soon be updated to reflect the outcomes of the meeting, along with SMILES. Of course if anyone is keen and beats me to it, then even better.

The discussion focused really on the selection of synthetic compounds. The list of commercial compounds (below) remained the same. The project is now looking for willing donors (ca. 5 mg) for these compounds.



The list of synthetic compounds saw some changes. Partially because some of the original list have already been made. The replacements were discussed and found for these and the blank spaces were filled. These compounds look to mitigate the problems observed with the previous rounds of testing. Please let us know if these structures aren't what you were expecting to see here. The two compounds highlighted in blue are one's that are currently receiving attention here at Sydney.

User login

Username *

Password *

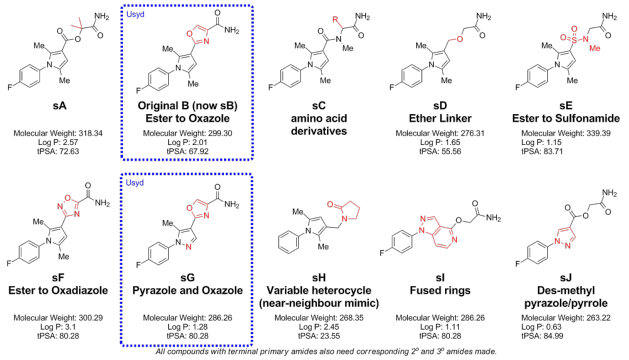
Create new account

Request new password

Log in

Malaria Research Community

Current Projects for Malaria
Functional Reconstitution of the Plasmodium GPI:protein transamidase Complex
Gene Wiki Overview
Open Source Drug Discovery for Malaria Meeting - February 2012 - Why?
Open Source Drug Discovery for Malaria Project Meetings
Open Source Drug Discovery: The GSK Arylpyrrole Series
A list of what's needed in the OSDD Malaria project
Desired Compounds Consultation
Desired Compounds Consultation Phase 2
Consultation Outcome
Analog Synthesis - Variation of the Aryl Ring
Availability of TCMDC-123812 and TCMDC-123794
Biological Evaluation of Arylpyrrole Series
Druggability of the Arylpyrrole leads (TCMDC-123794 etc)
Known Near Neighbours of Initial Tres Cantos Leads
Prediction of Biological Targets of Actives
Proposed resynthesis strategy for TCMDC-123812 and TCMDC-123794
THE SUBCELLULAR DRUG TRANSPORT LABORATORY: Cellular pharmacokinetic analysis of antimalarials
The GSK Aminothienopyrimidine (ATP)



The project now needs synthetic teams to investigate the other targets. Any groups looking for academic collaboration or industrial contributions would be gratefully received. It could potentially be a good way for a CRO to showcase their expertise in turning out compounds. We would be willing to provide starting material if necessary.

‹ Desired Compounds Consultation Phase 2 up Analog Synthesis - Variation of the Aryl Ring ›

Printer-friendly version Add new comment

Comments

cdsouthan
Jul 28 2012

List updating

Paul, I'd be please to take the short list of 20 round the databases again. When you update the Wiki with the SMILES you might want to check that chemicalize.org will convert the page OK. I also suggest you do belt and braces by including IUPAC and InChI (strings and keys). You might also want to formaly enumerate the synthetic proposals to explicit sets (i.e, for the R and amide permutations). I can check and send the PubMed CIDs for the ones on order. You might also give some more thought to your internal (and now de facto global) naming system and ID strings to reduce ambiguity (B < sB?). I guess when the virtuals become real you can give a three-digit PMY numbers (re-number old ones before it gets too crowded?) and when the purchases turn up. If you add the InChI key under your image displays that locks them down as well.
(BTW I am still regularly getting new password requests).

REPLY

pylioja
Jul 30 2012

ID strings

The naming system used above (cB, sB etc) is just temporary and only for the purposes of discussion. Once the compounds are made/received and become real, they'll receive the OSM- number and of course the batch number (e.g. PMY-XX-X or whatever supplier batch number they have). You're right about the formalising the R groups for ID purposes, but we are interested in pretty much any group there for the moment so we wanted the diagram to reflect that. As always, thanks.

REPLY

pylioja

The OpenWetWare wiki has been

The OpenWetWare wiki has been updated with the InChi's and smiles for the synthetic and commercial compounds.

Series

Completed Projects for Malaria

Toxoplasma Research Community

Recent posts

Biological Results for ATP Series from April 2013
1 May 2013 - 3:48am By MatTodd
Replies: 0

Biological Data
1 May 2013 - 3:39am By MatTodd
Replies: 0

The GSK Aminothienopyrimidine (ATP) Series
1 May 2013 - 3:38am By MatTodd
Replies: 0

more

Recent comments

anacardic compounds to cure TB 5 March 2014 - 12:27am

Protein available 24 September 2013 - 8:20pm

Hi there, just watched Tom's 17 May 2013 - 11:32am

Meeting Recording and Minutes 21 March 2013 - 2:57am

SOLVED-onamides - perhaps! 28 February 2013 - 5:44pm

more

Aug 07 2012

REPLY

cdsouthan
Sep 13 2012

Time for a fresh key-actives short list ?

Paul, I wonder if you could re-surface on OpenWetWare an updated but very brief summary of, say, the current top-ten actives (including any TCAMS re-tests) with their average activity. The reason for asking is that more open sources of patent-extracted structures have popped up recently http://cdsouthan.blogspot.se/2012/08/pubchem-pips-9-million-patent-extra... It could thus now be useful to take these leads for another walk through the databases.
If you could specify specify structures with the usual belt-and-braces IUPACs SMILES and InChIs, this makes for easy chemicalization and database checking.

REPLY

MatTodd
Aug 21 2012

A Recording of the Consultation

...can be found here: http://www.youtube.com/watch?v=ooM8kuo14Bg

Still (Aug 21 2012) really searching for CROs or other labs who might be interested in making one or two of these compounds. An update on that in the next comment.

REPLY

MatTodd
Aug 21 2012

An Update on Who's Doing What

Status of the compounds needing synthesis (August 21st 2012)

sA - Matin Dean, a student in Sydney, has started to look at this compound

sB - Paul Ylioja is working on this one (but is travelling now until the end of September)

sC - Sanjay Batra from CDRI Lucknow has said he'll make one of these compounds. All data will go online

sD - Nobody currently on this, though Paul had a few goes, e.g. here

sE - **Needed - nobody working on**

sF - **Needed - nobody working on**

sG - Being worked on by Paul and a Sydney undergrad student Matt Tarnowski Lab book

sH - **Needed - nobody working on**

sI - Sanjay is going to take this one - lab notebook coming

sJ - Sanjay will take this one too - lab notebook coming

News on the commercial compounds soon - ready to order, just clearing a few last hurdles.

REPLY

Dr.M.J.Karai (not verified)
Aug 22 2012

Compounds Required

Dear Matt,
Nice to learn of the eforts you are putting in.Who picksup the tabs for the synthesis of these devlopments?
Regards
Murzban.

REPLY

MatTodd
Aug 22 2012

Gratis!

Hi Murzban,

We're looking for people to make the compounds for zero charge. The compounds are not complex. Because this is an open project, all data need to be shared, and this acts as an excellent advertisment for a company's

synthetic abilities. There would also be co-authorship on a paper. For other reasons why industry might participate in a project like this see this previous comment.

REPLY

Alice Williamson
Sep 27 2012

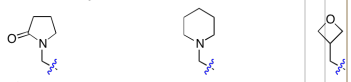
Compound Sh

Following so far unsuccessful attempts to synthesise Sd (post on its way!) I have decided to start focusing on compounds of type Sh. I just need to decide which heterocycle(s) to tether to the pyrrole 3-position.

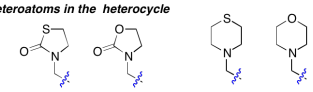
I have been thinking about heterocycles that would allow us to systematically develop the subsituent at this position position to effect more favourable in vivo results. The first row of compounds feature 1 heteroatom, the second row 2 heteroatoms and the third two nitrogen heteroatoms which would provide a handle for further derivitisation of the final compounds.

Does anyone have any thoughts regarding which compound(s) I should target first?

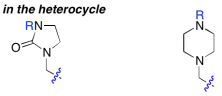
1 heteroatom in the heterocycle



2 heteroatoms in the heterocycle



3 heteroatoms in the heterocycle



REPLY

MatTodd
Oct 04 2012

All look good, Alice

These all look to be good options to me. I'd keep it simple, and what you're doing now seems perfectly reasonable.I like the thiazolidinone, but for no rational reason.

REPLY

MatTodd
Oct 06 2012

Metabolic instability of some sulfur-containing compounds

Jonathan Baell commented to me offline. To paraphrase. As a general rule an Sp3 S joined to a carbonyl always comes with higher risk of metabolic instability so we should probably go for the others first. The same holds for a thioether (more likely oxidation than hydrolysis in this case) but that there are always exceptions so this shouldn't be seen as black and white.

REPLY

MatTodd
Oct 04 2012

Second Update on Who's Doing What

The list as of **October 4th**:

(sA - Matin Dean has synthesised this compound).

sB - Paul Ylioja is nearly there.

sC - Sanjay Batra from CDRI Lucknow has said he'll make one of these compounds, but this one is **still needed**. People are asking which amino acids should be incorporated. The short answer is: at this stage, who cares? The long answer is: *rac*-alanine would be fine, but this can be changed to your favourite

amino acid.

sD - In progress. Paul had a few goes, e.g. here. Alice has had many attempts at this compound now, and it's proving to be a pain, e.g. here. Alice will post a summary...

sE - Matin is having a go at this one, e.g. here.

sF - **Still needed - nobody working on**

sG - Being worked on by Paul and a Sydney undergrad student Matt Tarnowski Lab book A version is also being worked on by one of the CDRI students, e.g. here.

sH - Alice is now taking a pop at this, e.g. here.

sI - Sanjay wanted to take this one, but **nobody currently working on it**.

sJ - Sanjay wanted this one too, but nobody working on it since last update. Paul wants to make it, like this.

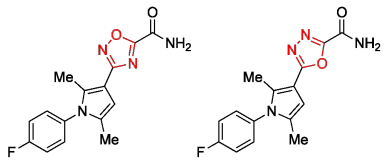
We've put in a quote request to both Assay Depot and Science Exchange, and are receiving inputs/quotes for a few of these molecules, which might be a way to go if we don't get any takers. I summarised the reasons why CROs might want to get involved in this part of the project here.

REPLY

MatTodd
Oct 04 2012

Oxadiazole (sF) isomers

...and the oxadiazole, incidentally, does not have to be as shown. When I spoke with Ed Tate recently he extolled the virtues of the "symmetrical" 1,3,4-isomer, which would be absolutely fine. Lots of nice precedence for synthesis, obviously.



REPLY

estier and pyrrole isosteres

Really looking forward with interest to the results of some of these, especially Si and Sj to move away from the pyrrole. btw nice review on oxdiazoles in JMC vol 55 (2012) 1817-1830.

REPLY

Jonathan (not verified)
Oct 05 2012

MatTodd
Oct 17 2012

Update on Who's Doing What October 17th

An update on where we are with finishing off the arylpyrrole set of compounds. The aim is to complete the synthesis of the 10 Most Wanted compounds above and have them biologically evaluated. The commercial compounds have been ordered from Molport and are on their way to us - arrival due Monday 22nd October if customs clearance goes well, at which point they will be re-vialled and bounced to Vicky Avery's lab at Eskitis.

sA - Done. Sent for testing already.
sB - Nearly there - Paul is confirming identity.
sC - To do. It may be prudent to wait for the evaluation of the related tertiary amide from the commercial set before worrying about the synthesis of more complex variants, but this is a judgement call.
sD - Need - despite our best efforts this compound is proving to be a pain. I wonder

if this could benefit from CRO input?
sE - Matin is working on this - he's just tried the penultimate step, a chlorination. If that's worked, coupling with an amine should be easy.
sF - Alice is working on one oxadiazole isomer, and John Wallis has indicated he might be interested in the other.
sG - Matt Tarnowski has been working on this molecule, but the end of semester is rapidly approaching. We reckon he can do it, but just in case, Murray (who's joined the project) is going to bring some material through so we can play with coupling conditions.
sH - Alice is on this set and has nearly finished purifying several.
sI - *Nobody on this yet.* We've had some interest from a CRO who have quoted us a price for making a few milligrams. The exact heterocyclic ring is not terribly important though. Maybe there are other possibilities. Murray and Alice are thinking this over. Alice was wondering about making a triazole via a click.
sJ - Paul says he's made this, and is acquiring the final characterization today.

Sanjay Batra's lab have been making a methyl isomer of one of the pyrazoles which will be a useful addition.

This is the state of play. If you're reading this, and want to take part by making a molecule, you can. Our next meeting is this Friday (Oct 19th) at about 4:30 pm Sydney time. Link coming for those who want to join in.

REPLY

Sanjay Batra (not verified)
Oct 18 2012

Preparation of methyl sJ and SI

We have been short of chemicals required for the desired synthesis and have therefore indented some of them. In the meantime Harikrishna is trying to standardize the synthesis using analogous compounds. The schemes for the synthesi of SJ and SI are being uploaded here.
For SJ, hydrolysis step is yet not complete. We have adopted this route as we did not have bromoacetamide in the lab.
For SI a tentative scheme is drawn and the synthesis is to be initiated.

File:
synthesis methyl SJ.pdf
proposed scheme for SI.pdf

REPLY

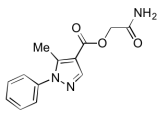
Alice Williamson
Nov 27 2012

Pyrazoles

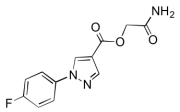
Hello Sanjay,

The route for SI looks good. However we have already synthesised and submitted the two pyrazoles shown below and found them to be inactive, so I don't think its so important to pursue this compound. What does everyone else think? Would be great to get SI though!

Alice



OSM-S-57
>100,000 nM



OSM-S-92
>100,000 nM

REPLY

IP Guidelines TSL Privacy Policy

Fig S26. Potency Curves for OSM-S-96 to OSM-S-105.

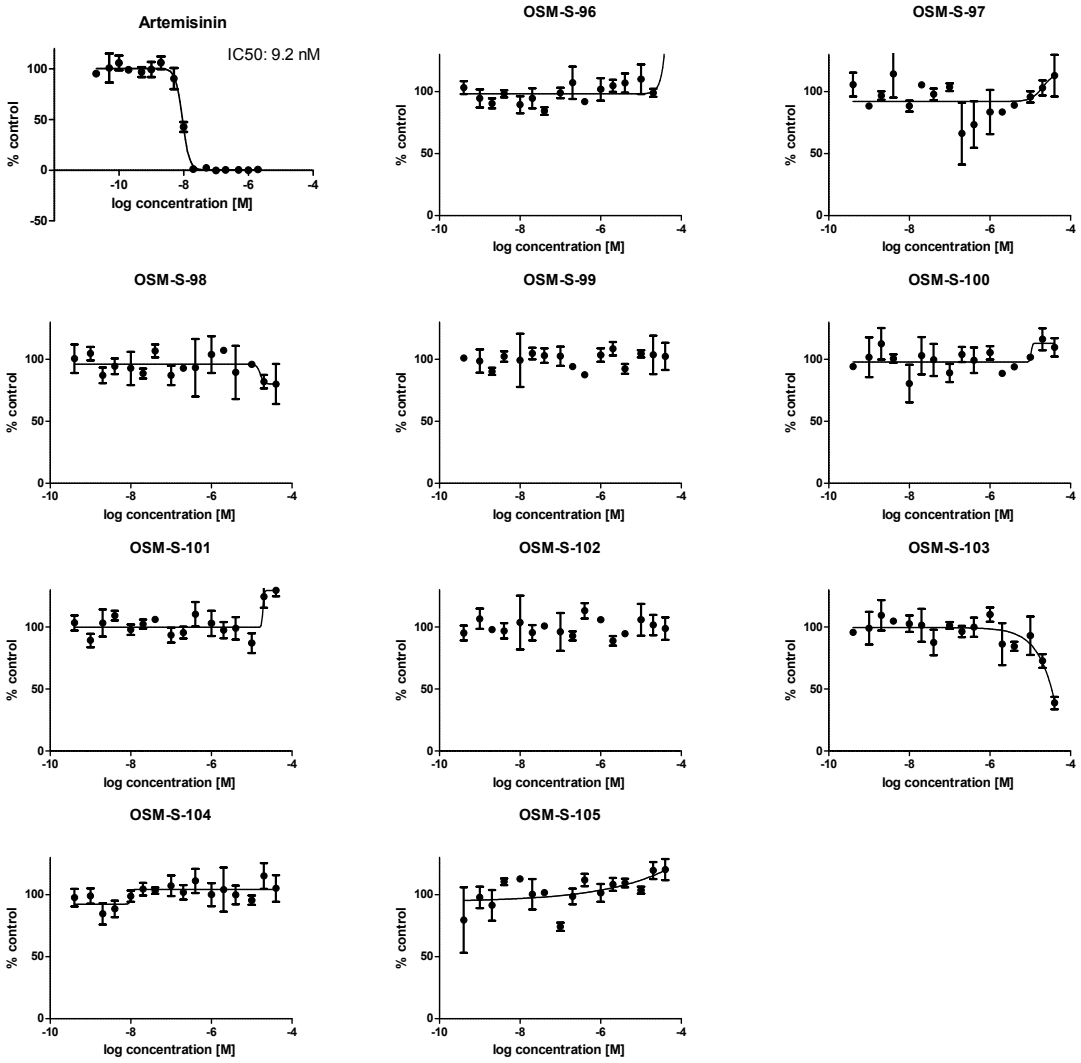
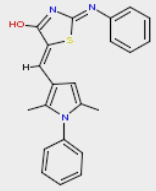
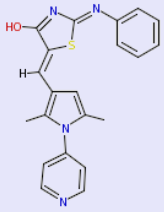
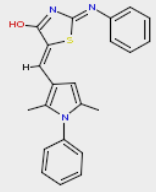
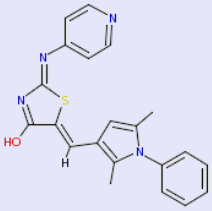
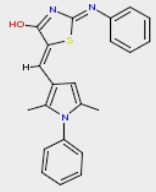
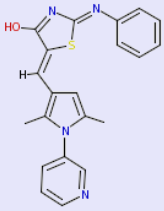
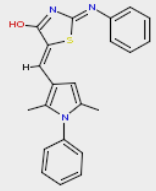
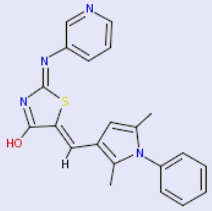
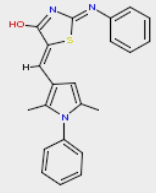
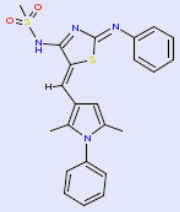


Fig S27. Targeted Bioisostere List for Pyrrole Phenyl Replacements. (Related to Text S8)

Classic Bioisoster Report for ZYH-3-1

Input Molecule	Transformed Molecule	Bioisosteric Transformation	New ALogP
 Original LogP =5.628		Phenyl to 4Pyridine	4.4780
 Original LogP =5.628		Phenyl to 4Pyridine	4.4780
 Original LogP =5.628		Phenyl to 3Pyridine	4.4780
 Original LogP =5.628		Phenyl to 3Pyridine	4.4780
 Original LogP =5.628		Hydroxyl to Sulfonamide	4.7810

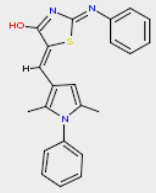
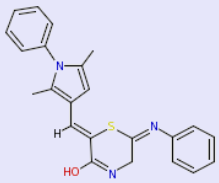
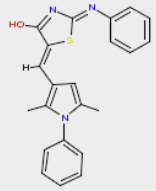
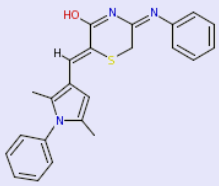
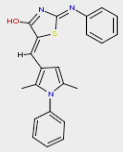
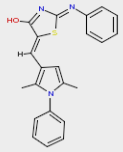
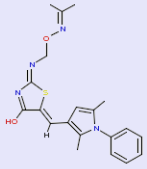
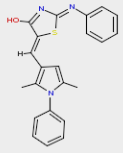
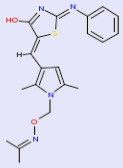
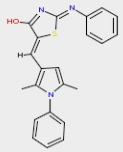
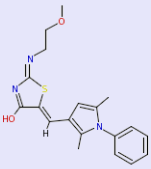
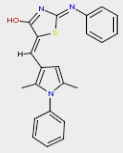
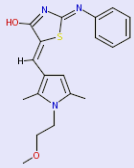
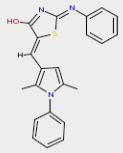
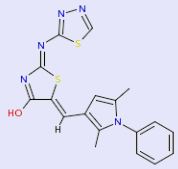
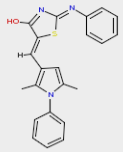
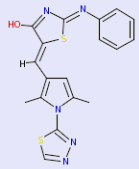
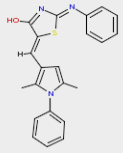
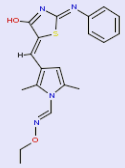
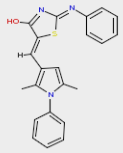
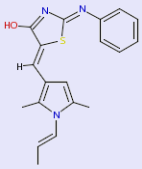
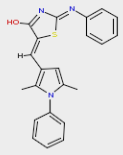
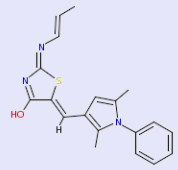
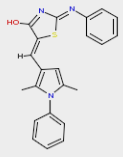
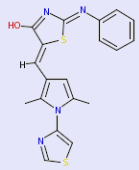
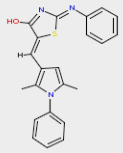
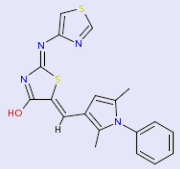
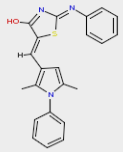
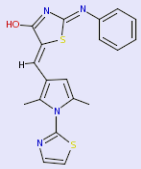
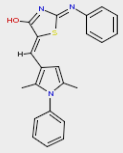
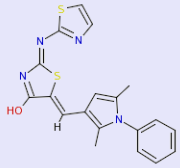
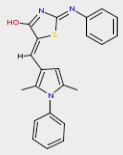
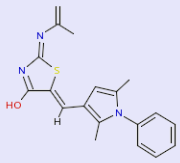
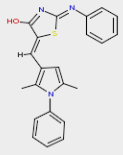
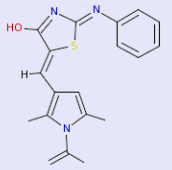
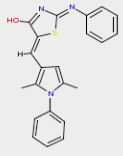
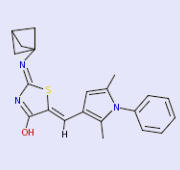
 Original LogP =5.628		Expand Ring by One	4.9080
 Original LogP =5.628		Expand Ring by One	4.9080

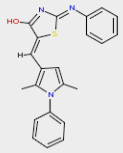
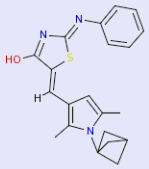
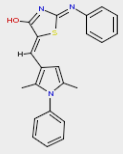
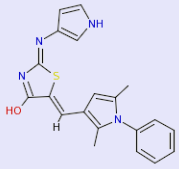
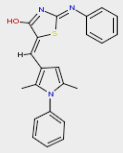
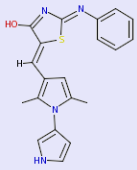
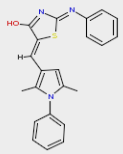
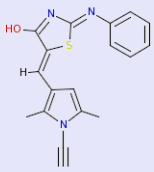
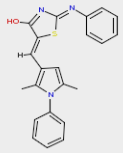
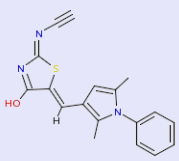
Fig S28. Broader Bioisostere Database for Pyrrole Phenyl Replacements. (Related to Text S8)

Database Bioisosteric Report for ZYH-3-1

Input Molecule	Transformed Molecule	Bioisosteric Transformation	References	New ALogP
 Original LogP =5.628		phenyl - oxime ether (RIN263)	Balsamo A et al, Bioorg Med Chem, 6() p. 2151, 1998; Balsamo A et al, Eur J Med Chem, 34() p. 283, 1999; Balsamo A et al, Eur J Med Chem, 38() p. 157, 2003; Breschi M C et al, Eur J Med Chem, 31() p. 159, 1996; Macchia B et al, J Med Chem, 37() p. 1518, 1994; de Fraine P J, Clough J M, Pestic Sci, 44() p. 77, 1995; see also Macchia B et al, J Med Chem, 28() p. 153, 1985	3.5660
 Original LogP =5.628		phenyl - oxime ether (RIN005)	Balsamo A et al, Eur J Med Chem, 31() p. 713, 1996; Balsamo A et al, Eur J Med Chem, 34() p. 283, 1999; Balsamo A et al, J Med Chem, 32() p. 1398, 1989; El Tayar N et al, J Med Chem, 31() p. 2072, 198 8; Macchia B et al, J Med Chem, 28() p. 153, 1985; Macchia B et al, J Med Chem, 33() p. 1423, 1990; Svendsen A, Pedersen L -E K, Pestic Sci, 18() p. 169, 1987; see also Breschi M C et al, Eur J Med Ch em, 31() p. 159, 1996	3.8550
 Original LogP =5.628		phenyl - oxime ether (RIN005)	Balsamo A et al, Eur J Med Chem, 31() p. 713, 1996; Balsamo A et al, Eur J Med Chem, 34() p. 283, 1999; Balsamo A et al, J Med Chem, 32() p. 1398, 1989; El Tayar N et al, J Med Chem, 31() p. 2072, 198 8; Macchia B et al, J Med Chem, 28() p. 153, 1985; Macchia B et al, J Med Chem, 33() p. 1423, 1990; Svendsen A, Pedersen L -E K, Pestic Sci, 18() p. 169, 1987; see also Breschi M C et al, Eur J Med Ch em, 31() p. 159, 1996	3.8550
 Original LogP =5.628		phenyl - alkoxyethyl (PHE037)	Cohen V I et al, J Med Chem, 34() p. 2989, 1991; Doherty G A et al, Bioorg Med Chem Lett, 12() p. 1501, 2002; Kongkathip B et al, Bioorg Med Chem, 13() p. 2167, 2005; see also Gogerty J H et al, J Med Chem, 20() p. 952, 1977	3.9210
 Original LogP =5.628		phenyl - alkoxyethyl (PHE037)	Cohen V I et al, J Med Chem, 34() p. 2989, 1991; Doherty G A et al, Bioorg Med Chem Lett, 12() p. 1501, 2002; Kongkathip B et al, Bioorg Med Chem, 13() p. 2167, 2005; see also Gogerty J H et al, J Med Chem, 20() p. 952, 1977	3.9210

Input Molecule	Transformed Molecule	Bioisosteric Transformation	References	New ALogP
 Original LogP =5.628		benzene - thiadiazole (BEN006)	Borras J et al, Bioorg Med Chem, 7() p. 2397, 1999; Marsham P R et al, J Med Chem, 34() p. 1594, 1991; Roberts E C, Shealy Y F, J Heterocycl Chem, 11() p. 547, 1974; Wasson B K et al, J Med Chem, 15() p. 651, 1972; see also Kubo H et al, J Agric Food Chem, 18() p. 60, 1970	4.1020
 Original LogP =5.628		benzene - thiadiazole (BEN006)	Borras J et al, Bioorg Med Chem, 7() p. 2397, 1999; Marsham P R et al, J Med Chem, 34() p. 1594, 1991; Roberts E C, Shealy Y F, J Heterocycl Chem, 11() p. 547, 1974; Wasson B K et al, J Med Chem, 15() p. 651, 1972; see also Kubo H et al, J Agric Food Chem, 18() p. 60, 1970	4.1020
 Original LogP =5.628		phenyl - oxime ether (RIN263)	Balsamo A et al, Bioorg Med Chem, 6() p. 2151, 1998; Balsamo A et al, Eur J Med Chem, 34() p. 283, 1999; Balsamo A et al, Eur J Med Chem, 38() p. 157, 2003; Breschi M C et al, Eur J Med Chem, 31() p. 159, 1996; Macchia B et al, J Med Chem, 37() p. 1518, 1994; de Fraine P J, Clough J M, Pestic Sci, 44() p. 77, 1995; see also Macchia B et al, J Med Chem, 28() p. 153, 1985	4.2120
 Original LogP =5.628		phenyl - alkene (CHA023b)	Beard R L et al, Bioorg Med Chem Lett, 4() p. 1447, 1994; Beautement K et al, Pestic Sci, 31() p. 499, 1991; Clinch K, Bioorg Med Chem Lett, 6() p. 467, 1996; Kim B T et al, Biosci Biotechnol Biochem, 56() p. 624, 1992; Posner G H et al, J Med Chem, 38() p. 4529, 1995; Procopiou P A et al, J Med Chem, 37() p. 3274, 1994; Simoni D et al, J Med Chem, 48() p. 723, 2005; Yue X et al, Tetrahedron Lett, 37() p. 8213, 1996; see also Wigerinck P et al, J Med Chem, 36() p. 538, 1993	4.5380
 Original LogP =5.628		phenyl - alkene (CHA023b)	Beard R L et al, Bioorg Med Chem Lett, 4() p. 1447, 1994; Beautement K et al, Pestic Sci, 31() p. 499, 1991; Clinch K, Bioorg Med Chem Lett, 6() p. 467, 1996; Kim B T et al, Biosci Biotechnol Biochem, 56() p. 624, 1992; Posner G H et al, J Med Chem, 38() p. 4529, 1995; Procopiou P A et al, J Med Chem, 37() p. 3274, 1994; Simoni D et al, J Med Chem, 48() p. 723, 2005; Yue X et al, Tetrahedron Lett, 37() p. 8213, 1996; see also Wigerinck P et al, J Med Chem, 36() p. 538, 1993	4.5380
 Original LogP =5.628		phenyl - thiazolyl (RIN452)	Hodson S J et al, J Med Chem, 37() p. 2112, 1994	4.6230

Input Molecule	Transformed Molecule	Bioisosteric Transformation	References	New ALogP
 Original LogP =5.628		phenyl - thiazolyl (RIN452)	Hodson S J et al, J Med Chem, 37() p. 2112, 1994	4.6230
 Original LogP =5.628		phenyl - thiazolyl (RIN452)	Hodson S J et al, J Med Chem, 37() p. 2112, 1994	4.6250
 Original LogP =5.628		phenyl - thiazolyl (RIN452)	Hodson S J et al, J Med Chem, 37() p. 2112, 1994	4.6250
 Original LogP =5.628		phenyl - alkene (CHA023b)	Beard R L et al, Bioorg Med Chem Lett, 4() p. 1447, 1994; Beautement K et al, Pestic Sci, 31() p. 499, 1991; Clinch K, Bioorg Med Chem Lett, 6() p. 467, 1996; Kim B T et al, Biosci Biotechnol Biochem, 56() p. 624, 1992; Posner G H et al, J Med Chem, 38() p. 4529, 1995; Procopiou P A et al, J Med Chem, 37() p. 3274, 1994; Simoni D et al, J Med Chem, 48() p. 723, 2005; Yue X et al, Tetrahedron Lett, 37() p. 8213, 1996; see also Wigerinck P et al, J Med Chem, 36() p. 538, 1993	4.6500
 Original LogP =5.628		phenyl - alkene (CHA023b)	Beard R L et al, Bioorg Med Chem Lett, 4() p. 1447, 1994; Beautement K et al, Pestic Sci, 31() p. 499, 1991; Clinch K, Bioorg Med Chem Lett, 6() p. 467, 1996; Kim B T et al, Biosci Biotechnol Biochem, 56() p. 624, 1992; Posner G H et al, J Med Chem, 38() p. 4529, 1995; Procopiou P A et al, J Med Chem, 37() p. 3274, 1994; Simoni D et al, J Med Chem, 48() p. 723, 2005; Yue X et al, Tetrahedron Lett, 37() p. 8213, 1996; see also Wigerinck P et al, J Med Chem, 36() p. 538, 1993	4.6500
 Original LogP =5.628		phenyl - bicyclopentane (PHE069)	Costantino G et al, Bioorg Med Chem, 9() p. 221, 2001; Filosa R et al, Bioorg Med Chem, 14() p. 3811, 2006; Patzel M et al, Eur J Org Chem, () p. 493, 2004; Pellicciari R et al, Chemmedchem, 1() p. 358, 2006; Pellicciari R et al, J Med Chem, 39() p. 2874, 1996; Schwab P F H et al, J Org Chem, 67() p. 5476, 2002; see also Pellicciari R et al, Bioorg Med Chem Lett, 8() p. 1569, 1998	4.6940

Input Molecule	Transformed Molecule	Bioisosteric Transformation	References	New ALogP
 Original LogP =5.628		phenyl - bicyclopentane (PHE069)	Costantino G et al, Bioorg Med Chem, 9() p. 221, 2001; Filosa R et al, Bioorg Med Chem, 14() p. 3811, 2006; Patzel M et al, Eur J Org Chem, () p. 493, 2004; Pellicciari R et al, Chemmedchem, 1() p. 35 8, 2006; Pellicciari R et al, J Med Chem, 39() p. 2874, 1996; Schwab P F H et al, J Org Chem, 67() p. 5476, 2002; see also Pellicciari R et al, Bioorg Med Chem Lett, 8() p. 1569, 1998	4.6940
 Original LogP =5.628		biphenyl - phenylpyrrole (PHE039)	Ankersen M et al, Bioorg Med Chem Lett, 7() p. 1293, 1997; Guillon J et al, Synlett, () p. 1263, 1999; Krajewska D, Rozanski A, J Antibiot, 52() p. 1140, 1999; Massa S et al, Med Chem Res, 2() p. 148, 1992; Perrone R et al, Bioorg Med Chem Lett, 7() p. 1327, 1997; Ragno R et al, Bioorg Med Chem, 8() p. 1423, 2000; Tafi A et al, J Med Chem, 39() p. 1227, 1996; Tafi A et al, J Med Chem, 45() p. 2720 , 2002; see also Di Santo R et al, Farmaco, 49() p. 229, 1994	4.7220
 Original LogP =5.628		biphenyl - phenylpyrrole (PHE039)	Ankersen M et al, Bioorg Med Chem Lett, 7() p. 1293, 1997; Guillon J et al, Synlett, () p. 1263, 1999; Krajewska D, Rozanski A, J Antibiot, 52() p. 1140, 1999; Massa S et al, Med Chem Res, 2() p. 148, 1992; Perrone R et al, Bioorg Med Chem Lett, 7() p. 1327, 1997; Ragno R et al, Bioorg Med Chem, 8() p. 1423, 2000; Tafi A et al, J Med Chem, 39() p. 1227, 1996; Tafi A et al, J Med Chem, 45() p. 2720 , 2002; see also Di Santo R et al, Farmaco, 49() p. 229, 1994	4.7220
 Original LogP =5.628		phenyl - acetylene (CHA839b)	Vernier J -M et al, J Med Chem, 42() p. 1684, 1999; see also Bergauer M et al, Bioorg Med Chem Lett, 12() p. 1937, 2002	4.9370
 Original LogP =5.628		phenyl - acetylene (CHA839b)	Vernier J -M et al, J Med Chem, 42() p. 1684, 1999; see also Bergauer M et al, Bioorg Med Chem Lett, 12() p. 1937, 2002	4.9370

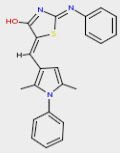
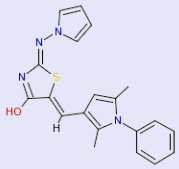
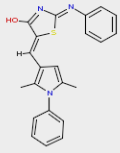
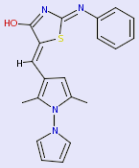
Input Molecule	Transformed Molecule	Bioisosteric Transformation	References	New ALogP
 Original LogP =5.628		biphenyl - phenylpyrrole (PHE039)	Ankersen M et al, Bioorg Med Chem Lett, 7() p. 1293, 1997; Guillon J et al, Synlett, () p. 1263, 1999; Krajewska D, Rozanski A, J Antibiot, 52() p. 1140, 1999; Massa S et al, Med Chem Res, 2() p. 148, 1992; Perrone R et al, Bioorg Med Chem Lett, 7() p. 1327, 1997; Ragno R et al, Bioorg Med Chem, 8() p. 1423, 2000; Tafi A et al, J Med Chem, 39() p. 1227, 1996; Tafi A et al, J Med Chem, 45() p. 2720 , 2002; see also Di Santo R et al, Farmaco, 49() p. 229, 1994	4.9770
 Original LogP =5.628		biphenyl - phenylpyrrole (PHE039)	Ankersen M et al, Bioorg Med Chem Lett, 7() p. 1293, 1997; Guillon J et al, Synlett, () p. 1263, 1999; Krajewska D, Rozanski A, J Antibiot, 52() p. 1140, 1999; Massa S et al, Med Chem Res, 2() p. 148, 1992; Perrone R et al, Bioorg Med Chem Lett, 7() p. 1327, 1997; Ragno R et al, Bioorg Med Chem, 8() p. 1423, 2000; Tafi A et al, J Med Chem, 39() p. 1227, 1996; Tafi A et al, J Med Chem, 45() p. 2720 , 2002; see also Di Santo R et al, Farmaco, 49() p. 229, 1994	4.9770

Fig S29. Bioisostere Map for OSM-S-35. (Related to Text S8)

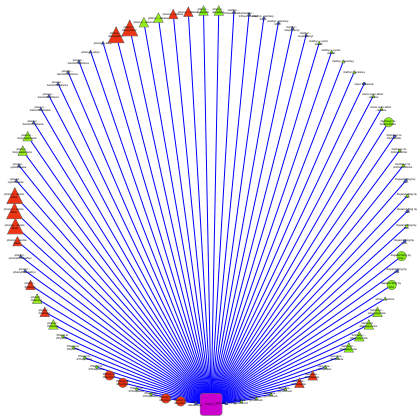


Fig S30. Screengrab of Synaptic Leap Node 400 (http://www.thesynapticleap.org/node/400), Bioisosteric Transformation Maps, Iain Wallace, 2012. (Related to Text S8)

The Synaptic Leap
Open Source Biomedical Research

Search

HOME COMMUNITIES GETTING STARTED RESOURCES NEEDED ABOUT

You are here: Home » Malaria Research Community » Current Projects for Malaria » Open Source Drug Discovery: The GSK Arylpyrrole Series » Prediction of Biological Targets of Actives

Bioisosteric transformation maps

Published by wallacei on 14 April 2012 - 3:27pm

Community
malaria research community
Subject
Request for Help

It is common in drug discovery to have a highly potent hit that has to be optimised to remove undesirable characteristics such as poor oral bioavailablity, metabolic stability or toxicity. In our case, we have a number of highly potent compounds that have quite a high LogP, which is considered a warning sign for both a promiscousity (i.e. binding to many compound targets in vitro) as well as poor oral bioavailabilty (as it breaks the Lipinski Rule of 5).

One approach to solving this issue is the concept of bioisosterism. From Wikipedia, http://en.wikipedia.org/wiki/Bioisostere "*bioisosteres are substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to a chemical compound. In drug design, the purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure.*"
One such example would be replacing a hydrogen with a flourine at a site of metabolic oxidation. "*Because the fluorine atom is similar in size to the hydrogen atom the overall topology of the molecule is not significantly affected, leaving the desired biological activity unaffected. However, with a blocked pathway for metabolism, the drug candidate may have a longer half-life.*"

To that end I have created biosteric transformations using the Pipeline Pilot software programme for the compounds synthesized as part of this project. Two different approaches are implemented to generate the transformations:
1) Classic Biosteres involve transforming the original molecule based on a set of ~200 commonly used transfomrations, such as replacing a hydroxyl with a sufonamide.
2) Database Biosteres involve transformations based on an algorithm described in this paper http://www.ncbi.nlm.nih.gov/pubmed/16562998
"M. Wagener, J.P.M. Lommerse, "The Quest for Bioisomeric Replacements", J. Chem. Info. Modeling, 2006, 46(2), 677-685"

Focusing on just ZYH-3-1, I generated two reports (one for both methods) showing about 20 compounds resulting from such transformations that would all have ALogP < 5. It would be intereting to know how easy they would be to synthesize, as well as what would make sense to make based on what we know about the SAR of these compounds.
All the reports and data are available
http://malaria.ourexperiment.org/in_silico_prediction/2954

‹ Prediction of Biological Targets of Actives up Compound Similarity Networks from Iain ›

Printer-friendly version Add new comment

User login

Username *

Password *

Create new account

Request new password

Log in

Malaria Research Community

Current Projects for Malaria
- Functional Reconstitution of the Plasmodium GPI:protein transamidase Complex
- Gene Wiki Overview
- Open Source Drug Discovery for Malaria Meeting - February 2012 - Why?
- Open Source Drug Discovery for Malaria Project Meetings
- Open Source Drug Discovery: The GSK Arylpyrrole Series
  - A list of what's needed in the OSDD Malaria project
  - Analog Synthesis - Variation of the Aryl Ring
  - Availability of TCMDC-123812 and TCMDC-123794
  - Biological Evaluation of Arylpyrrole Series
  - Druggability of the Arylpyrrole leads (TCMDC-123794 etc)
  - Known Near Neighbours of Initial Tres Cantos Leads
  - Prediction of Biological Targets of Actives
    - Bioisosteric transformation maps
    - Compound Similarity Networks from Iain
    - Purchasable compound similarity maps
  - Proposed resynthesis strategy for TCMDC-123812 and TCMDC-123794

THE SUBCELLULAR DRUG TRANSPORT LABORATORY: Cellular

pharmacokinetic analysis of antimalarials

The GSK Aminothienopyrimidine (ATP) Series

Completed Projects for Malaria

Toxoplasma Research Community

Recent posts

Biological Results for ATP Series from April 2013
1 May 2013 - 3:48am By MatTodd
Replies: 0

Biological Data
1 May 2013 - 3:39am By MatTodd
Replies: 0

The GSK Aminothienopyrimidine (ATP) Series
1 May 2013 - 3:38am By MatTodd
Replies: 0

more

Recent comments

anacardic compounds to cure TB 5 March 2014 - 12:27am

Protein available 24 September 2013 - 8:20pm

Hi there, just watched Tom's 17 May 2013 - 11:32am

Meeting Recording and Minutes 21 March 2013 - 2:57am

SOLVED-onamides - perhaps! 28 February 2013 - 5:44pm

more

IP Guidelines

TSL Privacy Policy

We respect your privacy.

Fig S31. Liver Stage Potency Curve for OSM-S-106 and OSM-S-111.

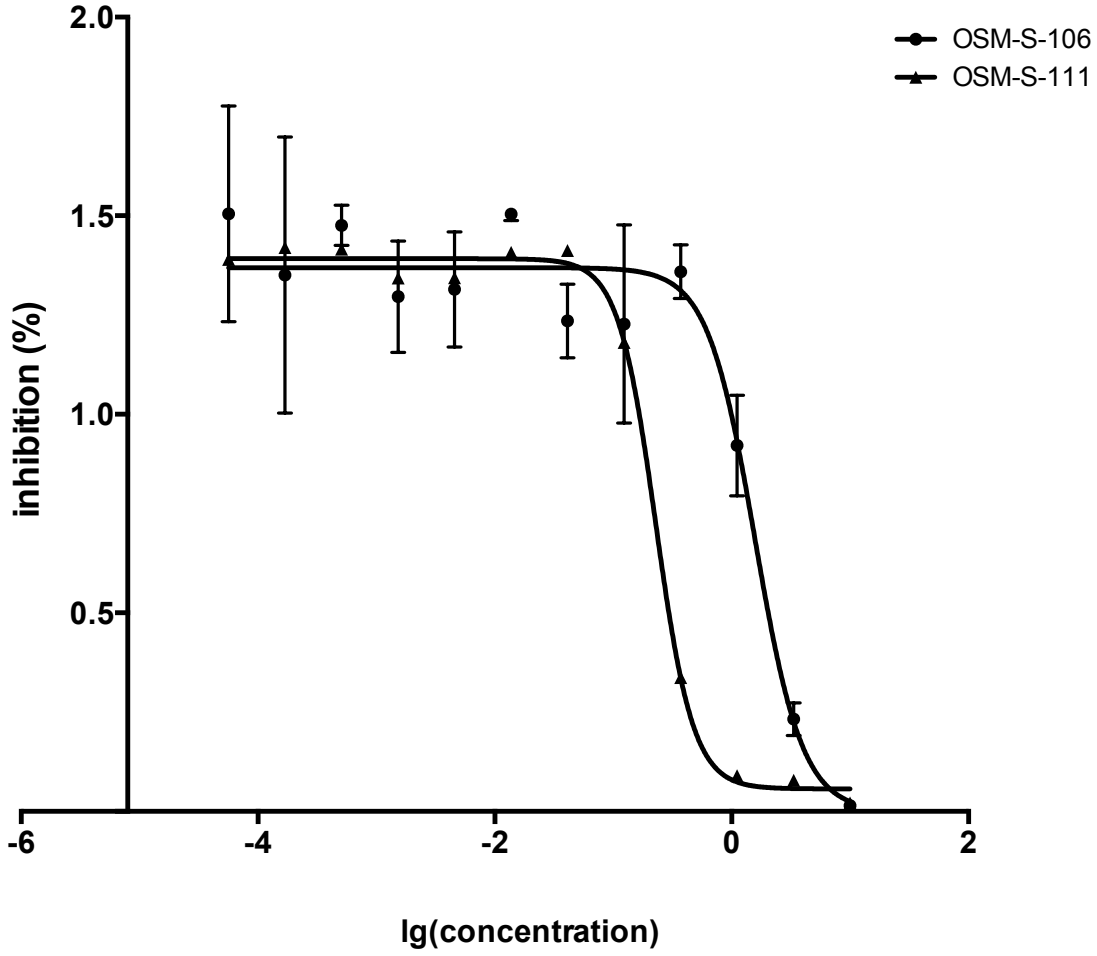


Fig S32. Gene Set Enrichment Map for OSM-S-9 (500 μM)

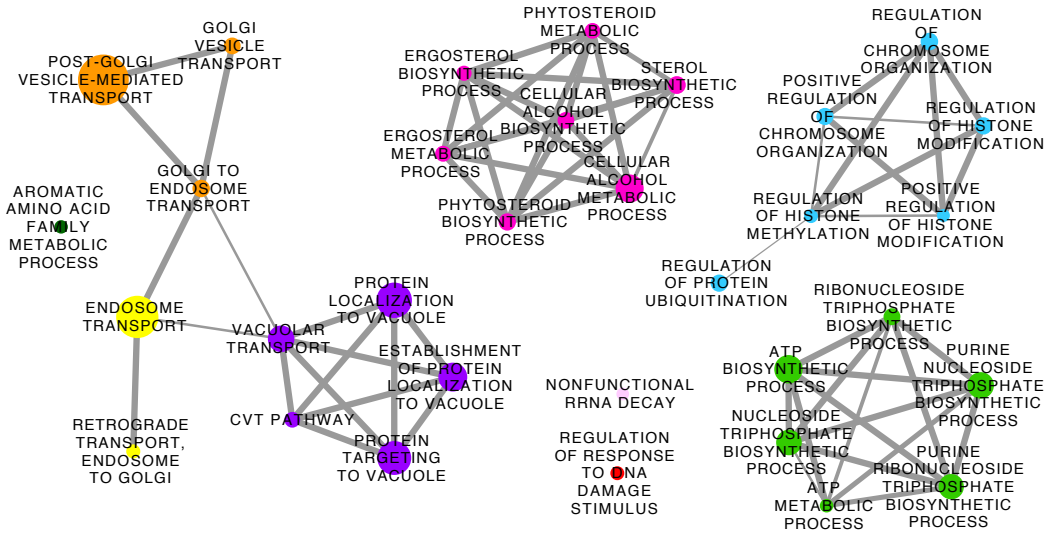


Fig S33. Gene Set Enrichment Map for OSM-S-12 (1 mM)

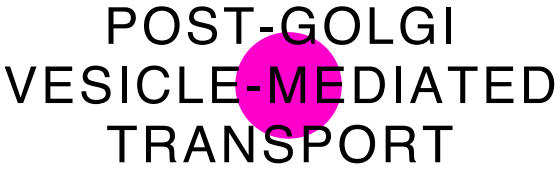


Fig S34. Gene Set Enrichment Map for OSM-S-31 (1 mM)

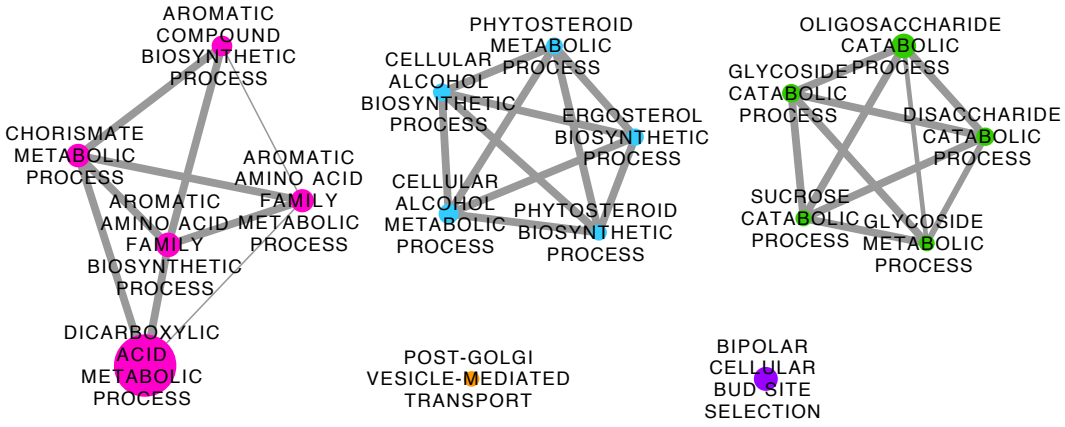


Fig S35. Gene Set Enrichment Map for OSM-S-39 (500 μM)

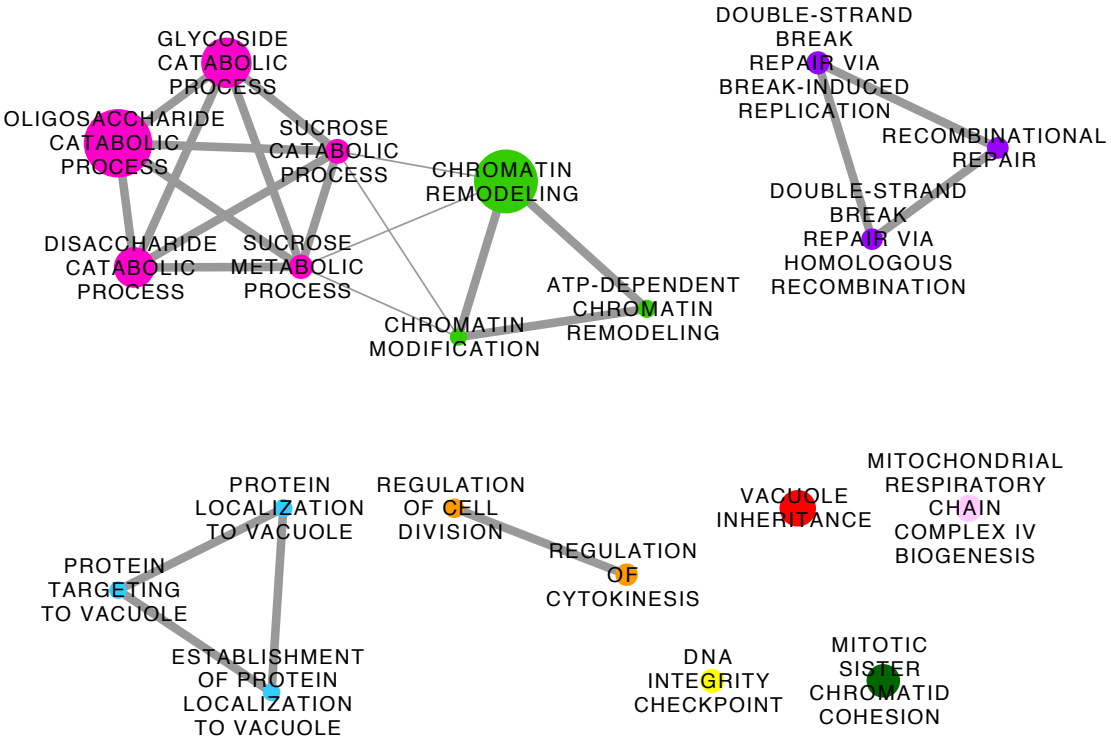


Fig S36. Gene Set Enrichment Map for OSM-S-51 (125 μM)

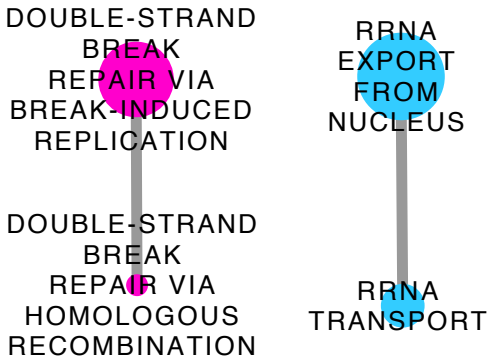
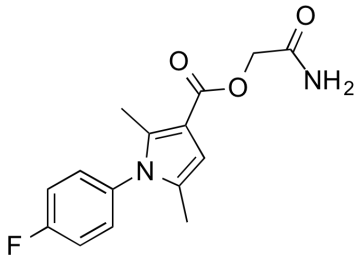
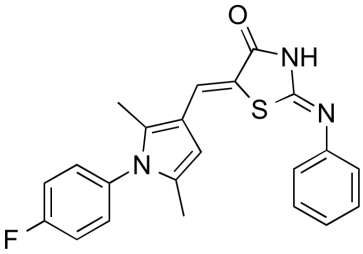


Fig S37. Composite PRR Assay Results and Potencies for Compounds OSM-S-5, -10, -35, -37, -39 and -51.

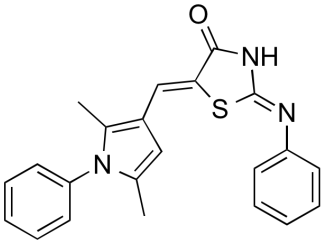
MMV code
OSM code
This assay potency vs. Previous potency (* = non-GSK data)
killing rate



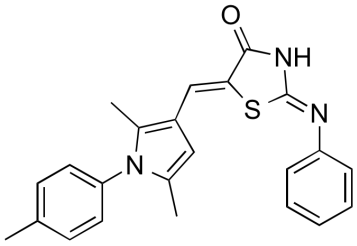
MMV**019247**
OSM-S-**5**
0.177 *vs.* 0.818
moderate-slow



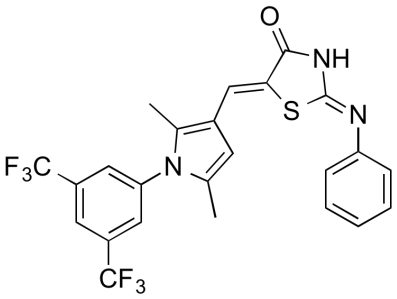
MMV**689017**
OSM-S-**10**
0.032 vs. 0.246*
slow



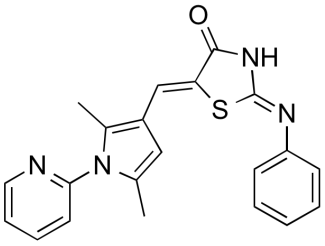
MMV**689018**
OSM-S-**35**
0.012 *vs.* 0.036
moderate-slow



MMV**689019**
OSM-S-**37**
0.015 *vs.* 0.028
moderate



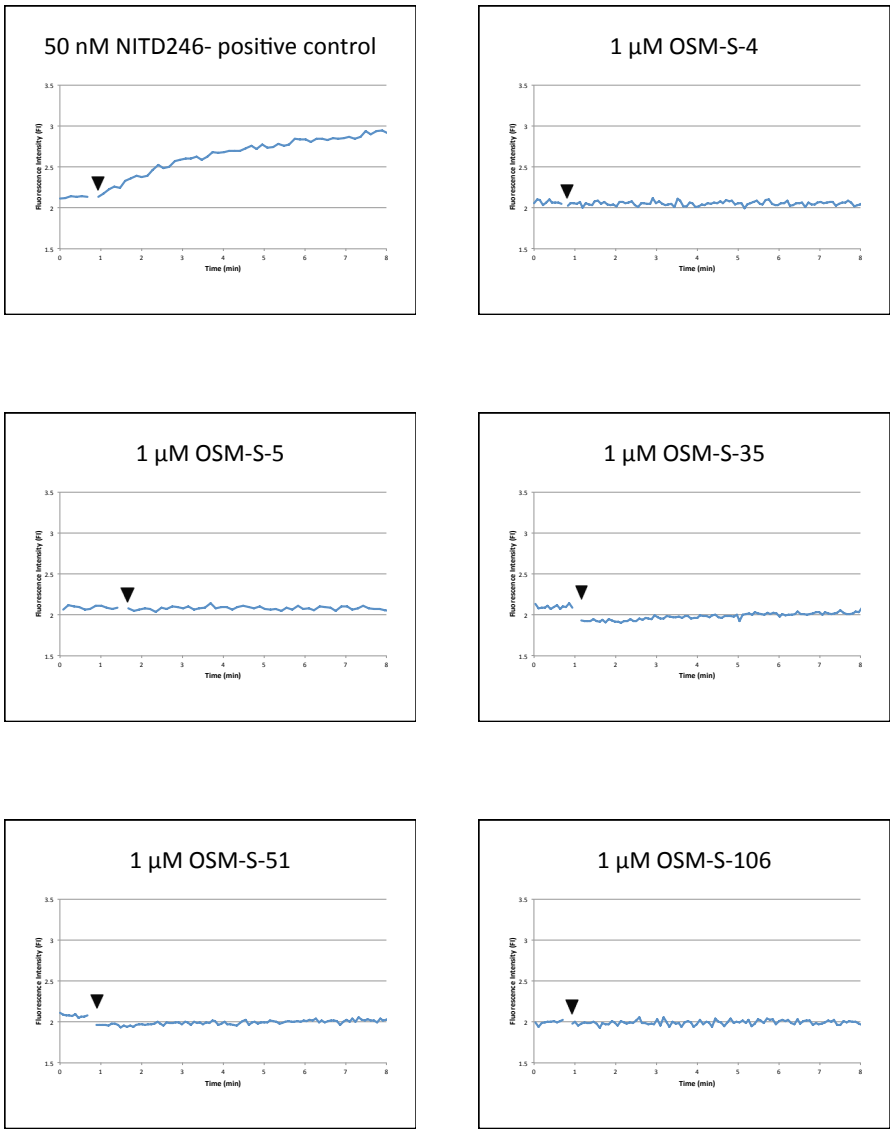
MMV**689020**
OSM-S-**39**
0.121 *vs.* 0.007
slow



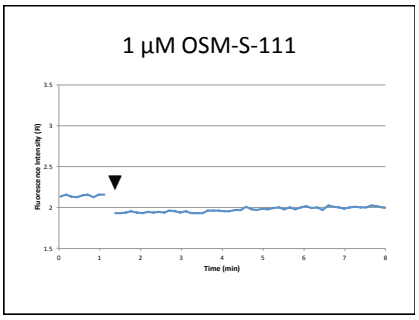
MMV**689021**
OSM-S-**51**
0.048 vs. 0.309
slow

Fig S38. Ion Regulation Assay for Compounds OSM-S-4, -5, -35, -51, -106, -111.

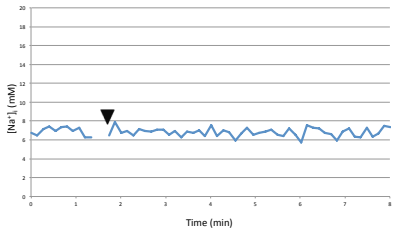
5/06/2014



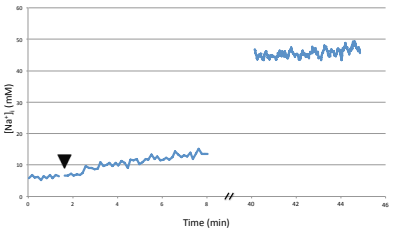
1


1 µM OSM-S-111
Fluorescence Intensity (FI)
Time (min)
3.5
3
2.5
2
1.5
0
1
2
3
4
5
6
7
8

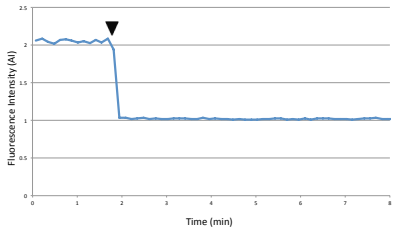
150 µM OSM-S-4 – no sodium increase



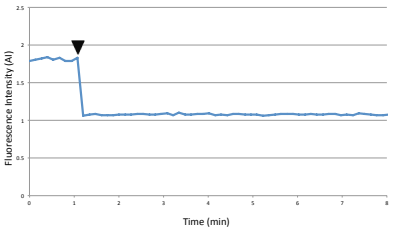
150 µM OSM-S-5 – sodium increase



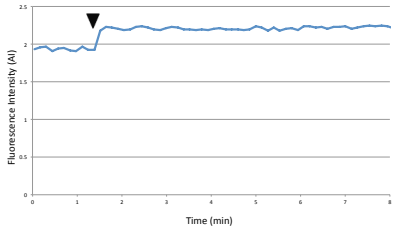
150 µM OSM-S-35 – optical effect



150 µM OSM-S-51 – optical effect



150 µM OSM-S-106 – optical effect



150 µM OSM-S-111 – optical effect

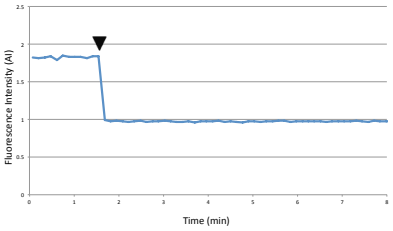
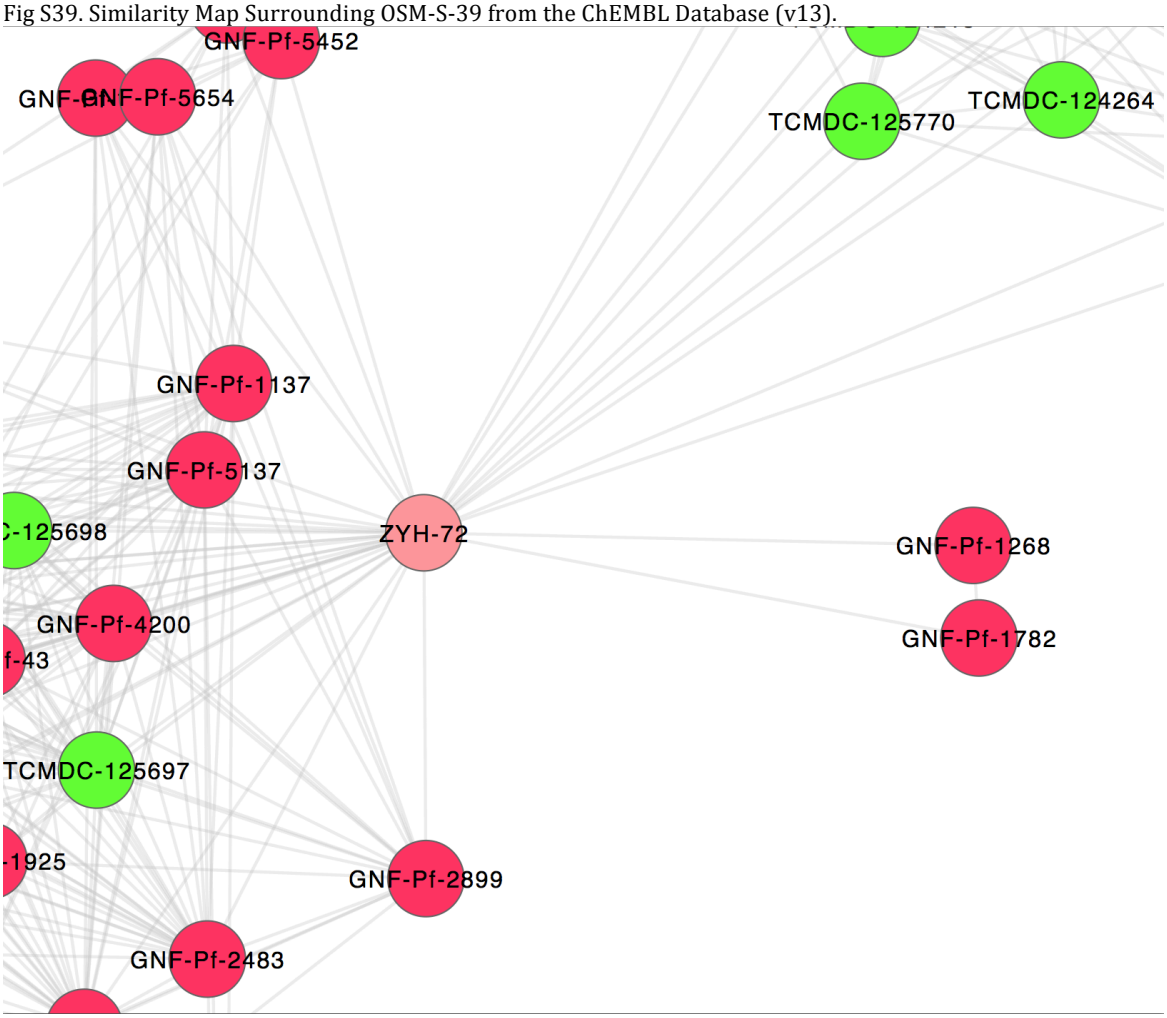


Fig S39. Similarity Map Surrounding OSM-S-39 from the ChEMBL Database (v13).



From [Company Time For Your Own Ideas, Or Not? (July 21, 2016) (http://blogs.sciencemag.org/pipeline/archives/2016/07/21/company-time-for-your-own-ideas-or-not)] Reprinted with permission from AAAS

Fig S40. Screengrab of Blog Post, In the Pipeline (http://blogs.sciencemag.org/pipeline/archives/2016/07/21/company-time-for-your-own-ideas-or-not), Company Time for Your Own Ideas, Or Not? Derek Lowe, 2016.

IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of *Science Translational Medicine*.

By Derek Lowe

Company Time For Your Own Ideas, Or Not?

By Derek Lowe | July 21, 2016

Over the years, at many R&D-driven companies, there have been official/unofficial policies that researchers could spend some percent of their time pursuing their own ideas, versus their official projects and goals. You hear different figures, especially when it comes to past glories, but there are definitely companies that have made this a stated policy: Google, for example, with 20% quoted by its founders when the company went public (which is definitely the highest I've heard). On the other hand, I don't know if the old Bell Labs had any formal percentage or not, but people sure seemed to do a lot of their own things there.

From [Company Time For Your Own Ideas, Or Not? (July 21, 2016) (http://blogs.sciencemag.org/pipeline/archives/2016/07/21/company-time-for-your-own-ideas-or-not)] Reprinted with permission from AAAS

Here's a short **article** on Google's situation – some people say that it used to be that way at the company (but isn't any more), some say it never really was that way in the first place, some say that sure, you can work on your own stuff, but only after you finish all the (long) hours of your regular work, and so on. The take I found most interesting was that the key thing was that people thought that the policy was there if they wanted it. That was what actually made a difference in the culture.

In the past, some drug companies have had similar systems (notably Upjohn, which takes us back a few years). What I'm wondering is whether any companies have a formal, stated policy like this now? People at my first company talked as if that had been a rule in the past, which had been abandoned, but I never knew if it was an official thing or not, and it was hard to tell if this was just the usual "Man, you should have been around here when things were better" sort of talk. That's not to say that in many cases things were better in the old days in the drug business – the sheer number of layoffs and amount of turmoil over the last twenty years will speak to that. But laid on top of that is a general human tendency to talk about the good old days, either last week when the fish were really biting and you shoulda been here all the way to back in the distant Golden Age past when the gods spoke directly to humankind. (A digression: if you've thought at all about that last part, which is common to a whole list of human cultures, you really should have a look at Julian Jaynes' ***The Origin of Consciousness in the Breakdown of the Bicameral Mind***, which some forty years later is still one of the great unprovable (?) hypotheses).

Back to the present. I hope to hear in the comments about any current your-own-research-time schemes that might exist, but even if some do, there are several ways that they could go. The nastiest would be a company that announces such a policy, but has no real intention of ever making good on it (and whacks anyone who tries over the head?) Then there could just be a situation where the policy exists, but no one has ever, to anyone's knowledge, taken advantage of it. That might partake of the Google effect mentioned in that above link, or might not, depending on the culture. Finally, there could be a place – although there must not be too many of them, especially on a large scale – where this is not only an official policy but has been seen in action and rewarded when it's worked out. In a related vein, I have heard of companies awarding time and funding to people for unusual projects after a more formal proposal process, and I'd be glad to hear of more examples of that sort of thing as well.

But in the end, the whole idea of working some on your own ideas isn't necessarily a matter of stated policy. That article on Google mentioned that the company had found at one point that only about ten per cent of its employees had ever done any such work, and to be honest, I think that's probably about the right percentage (even at a place like Google). Not everyone is a bubbling fountain of ideas. If you went around and proclaimed that as of Labor Day, everyone in the R&D labs would be *forced* to devote (say) ten per cent of their effort to ideas of their own, relevant to the company's general goals but having nothing to do with anyone's current project

they wouldn't be entirely unjustified in those feelings – the worst way to get ideas is to tell people that they damn well better come up with some and quotas will be enforced.

Some of the best ideas, I think, are going to come from people who are going to work on them no

matter what. And that's what I think that it's important for a company to allow and encourage – whether there's an official figure or not, and no matter how many people actually ever use it, when some people get a good business-relevant brainstorm, they should be able to mess with it some. If your company's culture allows for such, and allows for someone to go up and down the hall asking for a little of this and a little of that on the side in the service of the occasional weird idea, then I would say that's good news. On the other end of the scale, if the answer to an interesting idea is "Too bad", then pretty soon everyone will be out of practice in having any at all.

37 comments on "Company Time For Your Own Ideas, Or Not?"

dearieme
July 21, 2016 at 8:35 am

When they interviewed me decades ago, the British company Courtaulds claimed that the research lab people got Friday to pursue their own notions.

That would be less than 20%, then.

Reply

Isidore
July 21, 2016 at 8:44 am

Biogen in the 1990s has a 10% policy, I don't know if this still holds true.

Reply

BCP
July 21, 2016 at 9:13 am

I remember this concept being floated at the local level when I was at Glaxo in the early to mid '90's. Thing was that a) your day job responsibilities made it pretty hard to conjure up the required "free time" in the face of deadlines etc. and b) as a chemist, it's pretty hard to move a project forward at a reasonable pace with just an afternoon of thought/reading/experimental work each week.

Reply

Matthew Todd *in reply to BCP*
July 21, 2016 at 9:15 am

elsewhere...!

Reply

From [Company Time For Your Own Ideas, Or Not? (July 21, 2016) (http://blogs.sciencemag.org/pipeline/archives/2016/07/21/company-time-for-your-own-ideas-or-not)] Reprinted with permission from AAAS

BCP *in reply to Matthew Todd*
July 21, 2016 at 9:46 am

Theoretically yes, but at the time open source research was not "a thing" – this was 20 years ago. The message was one of individual scientific fulfillment/exploration rather than "let's collaborate in a networked manner to do something big".

Reply

These people are morons
July 21, 2016 at 9:21 am

Someone from Merck should chime in on the reqt (recently done away with?) to break down their day/week into percentage of time spent on a particular project. 5%? 2.5%? 10%?? I mean everyone knows that discovering drugs is just like making sales calls...wait, what?

Reply

FormerPdDrone
July 21, 2016 at 9:57 am

While obviously no longer involved in the pharmaceutical world, 3M has a long standing policy of "15% time." Really it is more of a 15% culture but people are generally encouraged, in corporate research anyway, to pursue their own ideas. Many times this is how blockbuster products come about and the company recognizes and rewards that.

Reply

TartanHSgrad *in reply to FormerPdDrone*
July 21, 2016 at 9:10 pm

Sounds like time have changed, even at 3M. Back in the mid-'80s I toured their labs as a high school student and the researchers there bragged about what they were able to do with their 20% creative time. 15% is better than nothing, I guess, but I wonder how much was never discovered.

Reply

I found a bigger bunch of morons
July 21, 2016 at 10:08 am

Might not be Pharma, but one of the SUNY (State University of New York) schools that shall remain unnamed has a policy that professors can spend 20% of their time on literally anything (consulting, working to commercialize tech, etc.) as long as their work gets done. Doesn't stop administration from coming after professors for trying to commercialize the technology they invented (and gave patent rights to SUNY). Then again, these are the same morons screaming

budget problems while adding vice presidents.....

Reply

Wavefunction
July 21, 2016 at 10:35 am

A few Merck veterans that I heard the other day at an event said that they could spend 15% of their time and a pretty much no-strings-attached small amount of money (10-15K) on essentially whatever they wanted. I know for a fact that my graduate school advisor who was at Merck during the same time wrote academic papers on hydrogen bonding and electrostatics.

Did I mention this was in the 80s? Don't know if it's still true.

Reply

Anon
July 21, 2016 at 10:40 am

Frankly I would think a better policy would be to allow 3-6 month periods of 50-100% paid leave to establish proof of concept for more outlandish ideas. The ideas would be selected on the basis that they:

1. Are truly radical and could have a big upside; and
2. Could be substantially de-risked within the given time and budget

Because that is how value is created with innovation, not by working on things that are already likely to work because they have *already* been proven.

Reply

exGlaxoid
July 21, 2016 at 10:43 am

When I was at Glaxo and GW, during the good days, there was a long standing, somewhat written policy that you could spend time doing side projects, whether they were having a summer intern work on something publishable, collaborating with other groups inside or outside of the company, following up on a side reaction discovered by accident, or even sometimes on completely novel work. I was able to work on several areas like that over the years, even gave a poster on a novel reaction, published a paper on a novel irreversible ligand, and worked with the HTS people to find better fluorescent tagged molecules.

Some projects were company encouraged, most not, but in most cases my manager or Dept. head agreed to the work and funded it. Some were clearly not even going to make money, some did make a lot or save money elsewhere. But when we were run like a true research facility, we were given a lot of freedom to do things right and even follow out own ideas sometimes. We did have to complete our "day job", but given that many people already worked 50-60 hours a week,

no one complained if we worked more on our own ideas. I loved that part of the job, as well as the lack of top down or micromanagement during the best years there.

Reply

Palo
July 21, 2016 at 10:46 am

At my biotech company the idea of a "10% innovation time" has been floated, but sadly, I suspect it would go in the form of either 1) there's no real intention of making good of it, or 2) you can have all the 10%, or 20% if you want, as long as you do everything else that takes 120% of your time right now. At the end, I think Derek is right and innovation will come from the ones that 'know' they're onto something and have the power to move in that direction no matter what, and that usually means that you put that 10-20% of your own time.

Reply

Dr CNS
July 21, 2016 at 11:23 am

C'mon guys... if you have an idea, and you really like it, do you need someone to tell you how much time you can spend on it?

I've been in biotech/pharma for 20+ years, and always found ways to test hypotheses that looked reasonable and intriguing, whether mine or from colleagues... A few projects were actually started this way... a couple of patents and a few papers...

I have to admit: in other groups in some of the same companies, people had to ask permission to make a certain compound that had not been discussed in a group meeting.... Unbelievable!

I say: do what you are responsible for as soon as you can, and then have fun testing your own ideas!

Reply

Isidore *in reply to Dr CNS*
July 21, 2016 at 11:42 am

I don't think it's as much an issue of time, I mean, you are right, one can find the time to test an interesting hypothesis or make a few interesting compounds. But having such activities formally sanctioned allows one to spend some money and many reagents or small pieces of equipment can run into thousands of dollars. Being able to be upfront about why you want to spend this money can save you a lot of trouble, not to mention time and effort in not having to cut corners or make do with materials that are not appropriate to the task.

Reply

Big Pharma
July 21, 2016 at 11:37 am

Novartis (NIBR) DMP has a policy in our hub of 10% tech development for associates.

Reply

Idea Pharm
July 21, 2016 at 11:52 am

Paul Reider once told me, "it's better to beg forgiveness than to ask permission." Even if you don't get an allotted amount of "innovation time" at your company, you would hope that, assuming your idea has some legs, someone up the ladder will realize that the research is worthwhile. Some really good ideas are worth putting things on the line for, and I think that more than one breakthrough has been made through this sort of career gamble.

Reply

Amnonymous *in reply to Idea Pharm*
July 23, 2016 at 1:18 pm

Paul Reider once yelled at me across a crowded cafeteria, "If cared as much about small molecules as you did cookies we'd have dozens of approved molecules". True story. Except the part about caring more about cookies. Both were a high priority with small molecules taking 80% of time and cookies only 20%.

Reply

Peter S. Shenkin
July 21, 2016 at 12:14 pm

Before retiring from Schrödinger (not a pharma company per se, but perhaps of interest), one group I was associated with decided to hold an internal hackathon between Thanksgiving and Christmas one year. Participation was voluntary. People wrote brief proposals for what they wanted to do. The proposals were passed around. Others could join a project they found exciting, work on their own projects, or just do their assigned work. A presentation session was held at the end.

Some cool things came out out of this, but I don't think anything was commercialized — though there was some exploration toward commercialization based on one project (which I had helped advise). During this time, I myself started a project, more for self-education than anything else, that I actually didn't finish until long after. For the "long-after" time, I utilized a combination of earned time off (excess vacation days) and the fact that as a Fellow, I could naturally spend some time working on stuff like this in between urgent work projects.

I can't argue that this was a great commercial success story for the company, but things that I think were good were: it was voluntary; people knew what others were working on, and could join;

and everyone got to hear what resulted.

Reply

Albert
July 21, 2016 at 1:01 pm

No official policy here, but I can still do some science not strictly project related. Usually either by doing few reactions myself during not so busy periods or using summer interns. In fact I'm just about to submit a synthetic paper which originated as a side reaction. In general as long as the actual project moves forward I can squeeze in some "unusual things".

Reply

anon
July 21, 2016 at 1:48 pm

Rohm and Haas used to encourage us to spend something like ~10-20% of our time on "scouting" work. The senior scientists always had plenty of suggestions if you didn't have any of own ideas to pursue, but even technicians were encouraged to spend some time working on their own ideas. I'm not sure if spending time on "scouting" was an official written policy or not, but it was widely encouraged. We also had some internal publications where you could write and share a short report on a small project you did on your own.

Reply

matt
July 21, 2016 at 1:51 pm

I'm surprised no one has chimed in with a mention of the Apple Fellows program. As I understand it, Apple Fellows were given carte blanche, because of their distinguished past history of not just innovation, but the ability to spot what's important in developing other people's ideas. True, that's outside the pharmaceutical industry, but perhaps the "available to select individuals" aspect applies inside the industry? Or, more generally, 100% freedom awarded rarely to extremely rare individuals, but then a range of less time and money allowed for more modest resumes (and by managers more confident they can harvest the rose among thorns).

Reply

Gene *in reply to matt*
July 21, 2016 at 7:39 pm

This is descended from the "IBM fellows" who were selected/recognized by the CEO

Wikipedia: "IBM Fellows have generated 9,307 patents, received five Nobel prizes, thousands

of government and professional citations and have a massive store of published research in scientific journals"

Reply

Gene *in reply to Gene*
July 21, 2016 at 7:46 pm

Dang. What's really sort of sobering, is I can scan the list of IBM Fellows and recognize about 20% of them and name their accomplishments off the top of my head. That's a bunch of seriously heavy hitters. Heck, one of them (E.F. Codd) is responsible for the relational database industry I'm working in.

Reply

steve
July 21, 2016 at 1:56 pm

If you have a great idea, quit and become an entrepreneur. High risk, high reward. You need the courage of your convictions, however.

Reply

CMCguy
July 21, 2016 at 2:03 pm

Except for a couple possible responses most people so far here have exemplified past rather than current citations for allotments for extracurricular research which appears to anecdotally track with trends I have experienced over last couple decades. I well could be misapplying correlations when I suggest this is a predictable consequence when R&D people are devalued a replaceable commodity where companies wish to exploit then discard such human assets to focus on quarterly bottom-lines. Even back in the old days such policies came off to me largely as attempted recruiting inducements for fresh PhDs whose training often focused on individual lone wolf approach to projects. The places I worked, both big and small, where under staffed verses workloads as it was (granted more in lean process than greater resourced medchem groups) so the ability to sustain and advance assigned projects was tough to handle where any off book side/skunk works activities undertaken typically were directly meant to address critical issues that did not fit with lab heads immediate goals. Additionally getting a academic style paper published could be rarely obtained without questions on dedication to real job, plus since the standard rewards for obtaining a patent, owed by the company of course, was $1 and a wall ornament the customary benefits one might expect from such endeavors often are lacking. Although not intended to do so certain companies inadvertently discouraged facilitation side projects such as due to legitimate safety concerns required no person working alone in lab so unless had a cohort available could not spend nights or weekends on projects, which frankly after a kid or two not too many spouses willing to tolerate anyway. Unless one could scrounge

the materials purchasing an item without a proper project code or unbudgeted can be a big barrier.

Reply

Dr CNS *in reply to CMCguy*
July 21, 2016 at 4:30 pm

That reminds me of my last employer, where *some* colleagues would agree to do exploratory work ONLY "if one was sure it would work".
Of course, the usual response was: "if I were sure it would work, why would I ask you to do it?"

Reply

Zenboy99
July 21, 2016 at 2:28 pm

I've had zero time over the last 15 years in R&D at CRO's. However I've talked to engineers at Honda in Japan who use to get free Fridays to play with things. I guess several ground breaking ideas came out of that, but they only admitted to the 3 wheeler and the Honda Rube Goldberg commercial.

Reply

Ex Schering
July 21, 2016 at 2:36 pm

A while back at Schering Plough, Ismail Kola had the policy "Better to ask for forgiveness than to ask for permission" when it came to creative/exploratory work

Reply

Chrispy
July 21, 2016 at 2:38 pm

My academic research institute allows for a 6 month sabbatical every ten years at 2/3 pay to pursue almost anything. There is an approval process but I don't think anyone has been denied. This policy applies to all full-time employees. Surprisingly, not many take advantage of it.

Reply

Dr. Manhatten
July 21, 2016 at 3:57 pm

"Frankly I would think a better policy would be to allow 3-6 month periods of 50-100% paid leave to establish proof of concept for more outlandish ideas."

Back in the 1980's, BMS had a "sabbatical" plan that allowed extended time to go to an academic institution to develop fresh ideas, approaches and new skills. One of the first research fellows to take advantage of the policy returned to find his previous job gone. Fortunately, another department picked him up, but that pretty much ended anyone else trying the plan, despite encouragement from management (it looked good for them to have a report who was part of the program). It became like the Indiana Jones Dialog:

Jones: Snakes. Why'd it have to be snakes?
Sallah: Asps... very dangerous. You go first.

Reply

Old Guy
July 21, 2016 at 6:05 pm

Four observations from a fossil:

Back in the day, at an aforementioned company that valued independent thought and a degree of entrepreneurial research, I always felt that I could take some time to pursue an idea that I found really promising, or just some interesting chemistry, even if it was not directly aligned with my formal research goals. Never got burned doing it.

However, most of us were way too wrapped up in our ongoing research projects to feel the need for many extracurricular projects, even though the company I worked for offered the time and resources. It was not a matter of not being allowed to explore something else, but a desire to push the current work forward. Mind you, that was in the day before all of the metrics on progress took much of the fun out of drug discovery. I guess part of it was that we had the freedom to pursue approaches on our programs that we felt committed to as opposed to meeting some preconceived number of analogs or unrealistic program team timelines.

At the time we were organized by therapeutic area. The chemistry head of one of the other areas decided it would be a good idea to require that everyone have an ongoing "academic" research program to keep them sharp. A total failure. A lot of time wasted on some really lame programs. You cannot force creativity, you can only nurture it.

We also had a sabbatical program that you could qualify for after a certain number of years of service. You would identify an academic lab that was willing to host you and the company would pay your salary, a stipend for expenses, and a grant to the PI you were working with. This was to provide an opportunity to update skills and develop stronger interactions with academia. To the best of my recollection, more than half of those granted the huge perk of a paid sabbatical used the time to search for another position and they resigned and moved on at the end of their freebie experience.

Reply

From [Company Time For Your Own Ideas, Or Not? (July 21, 2016) (http://blogs.sciencemag.org/pipeline/archives/2016/07/21/company-time-for-your-own-ideas-or-not)] Reprinted with permission from AAAS

Former Cube
July 21, 2016 at 8:59 pm

In the last year of the company's independence, Cubist had an "internal venture fund" that supplied $100k and 20-60% of a small team's time (with more to team leaders and less to the people just helping) to pursue a novel idea. The ideas were submitted anonymously in a two-page white paper and selected by the full discovery department in what was functionally a voting process. Although there was a declared winner, typically the next 3-5 projects were also funded to lesser amounts of money and time.

We spent a lot of time testing ways to get authentic innovation going in the Discovery arm and that was by far the most successful. I don't think it was a coincidence that it was also the most well-funded and largest profile effort. Unfortunately the company was acquired about 6 or 8 months later so we never really got to see it play out.

Reply

ADifferentFormerCube *in reply to Former Cube*
July 21, 2016 at 11:45 pm

As another former Cube I thought one of the best and most valuable things about the internal venture effort at Cubist was that we created approx. 30 new research proposals in the area anti-infectives. As a means of getting people deeply immersed in the area to think hard about opportunities in the field, write coherent proposals and bring multidisciplinary teams together this was probably one of the best $100,000 spent. If I remember correctly we had about 8 weeks to find people to form teams and were given management support to actually take time to work on the proposals.
The winning team also had the remit to get the job done and voluntarily come for feedback to the management team vs. some of the mandated program reviews to provide them more independence.
I agree, it would have been good to see where the winning and funded runner up proposals would have gone but the change of control at Cubist ended the program.

Reply

TX Raven *in reply to ADifferentFormerCube*
July 22, 2016 at 11:31 am

There's one point that I appreciate here, which is that when teams form spontaneously. People get together who like to work together, and usually that leads to high-performing teams.

I have seen management "force-feed" team members who ended up destroying the team's morale, which led to the killing of otherwise good projects.

Reply

Dilbert
July 22, 2016 at 5:58 am

Here's an 10 yr old article about Genentech's 20 % "discretionary time" – was it storytelling or for real ? http://money.cnn.com/2006/01/06/news/companies/bestcos_genentech/

Reply

anon *in reply to Dilbert*
July 22, 2016 at 12:25 pm

Was there around that time. 20% was correct.

Reply

Leave a Reply

Your email address will not be published. Required fields are marked *

Comment

Name *

Email *

Website

Solve the math problem. *

Time limit is exhausted. Please reload CAPTCHA.

+ 8 = 11

Post Comment

MORE FROM *SCIENCE TRANSLATIONAL MEDICINE*

From [Company Time For Your Own Ideas, Or Not? (July 21, 2016) (http://blogs.sciencemag.org/pipeline/archives/2016/07/21/company-time-for-your-own-ideas-or-not)] Reprinted with permission from AAAS

RECENT COMMENTS

- Joseph Hertzlinger on Label the Label Labels
- sleepingatscripps on Woodward's Prose Style
- Amnonymous on Company Time For Your Own Ideas, Or Not?
- Phil on Woodward's Prose Style
- Phil on Woodward's Prose Style

CATEGORIES

- "Me Too" Drugs (30)
- Academia (vs. Industry) (141)
- Aging and Lifespan (73)
- Alzheimer's Disease (107)

- Analytical Chemistry (100)
- Animal Testing (39)
- Autism (23)
- Biological News (266)
- Birth of an Idea (43)
- Blink &#8250 (5)
- Blog Housekeeping (258)
- Book Recommendations (31)
- Business and Markets (963)
- Cancer (328)
- Cardiovascular Disease (154)
- Chem/Bio Warfare (15)
- Chemical Biology (88)
- Chemical News (426)
- Clinical Trials (397)
- Closing Time (16)
- Current Events (145)
- Diabetes and Obesity (142)
- Drug Assays (282)
- Drug Development (497)
- Drug Industry History (360)
- Drug Prices (135)
- General Scientific News (166)
- Graduate School (63)
- How Not to Do It (39)
- How To Get a Pharma Job (32)
- In Silico (116)
- Infectious Diseases (171)
- Inorganic Chemistry (5)
- Intelligent Design (9)
- Job Postings (1)
- Life As We (Don't) Know It (24)
- Life in the Drug Labs (339)
- Lowe's Laws of the Lab (7)
- Metaphors, Good and Bad (2)
- Natural Products (30)
- Odd Elements in Drugs (12)
- Patents and IP (160)
- Pharma 101 (15)
- Pharmacokinetics (67)
- Press Coverage (97)
- Regulatory Affairs (202)
- Safety Warnings (19)
- Science Gifts (13)
- Snake Oil (94)

- The Central Nervous System (153)
- The Dark Side (205)
- The Scientific Literature (410)
- Things I Won't Work With (30)
- Things I'm Glad I Don't Do (6)
- Toxicology (169)
- Uncategorized (83)
- Who Discovers and Why (160)
- Why Everyone Loves Us (85)