

Supporting information

Rigidified A₃ Adenosine Receptor Agonists: 1-Deaza-adenine Modification Maintains High in vivo Efficacy

Dilip K. Tosh, Steven Crane, Zhoumou Chen, Silvia Paoletta, Zhan-Guo Gao, Elizabeth Gizewski, John A. Auchampach, Daniela Salvemini, and Kenneth A. Jacobson

Contents

Molecular Modeling Methods	S1-S2
Assay of adenylate cyclase at A₃AR and assays at A_{2B}AR	S3
CCI data calculations for in vivo assay of A₃AR agonists.	S4
Table of physicochemical properties	S7
Off-target interactions for compounds 11, 12, 16-20, 24 and 25	S8-S9
Synthetic Methods	S10-S23
Representative NMR and Mass Spectra	S24-S35
Representative HPLC Results	S36-S38

Molecular Modeling Methods

A₃AR 3D Structure

To perform docking studies, we used a previously reported^{1,2} homology model of the hA₃AR built, based on a hybrid template, using the alignment and the homology modeling tools implemented in the MOE suite.³ To build this model, an agonist-bound hA_{2A}AR crystal structure (PDB ID: 3QAK)⁴ was used as a template for the entire A₃AR structure except for the extracellular terminus of TM2 and EL1. The X-ray structure of the β₂ adrenergic receptor in complex with the Gs protein (PDB ID: 3SN6),⁵ after superimposition with the hA_{2A}AR crystal structure, was used as template to build the extracellular terminus of TM2. No structural template was used for the modeling of EL1. Methodological details have been previously reported.^{1,2}

Molecular Docking

Structures of potential A₃AR ligands were built and prepared for docking using the Builder and the LigPrep tools implemented in the Schrödinger suite.⁶ In particular, possible ionization states at pH 7±1 were generated using Epik, tautomers were generated and geometries were optimized using the OPLS_2005 force field.

Molecular docking of ligands at the hA₃AR model was performed by means of the Glide⁷ package from the Schrödinger suite.⁶ In particular, a Glide Grid was centered on the centroid of some key residues of the binding pocket of adenosine receptors, namely Phe (EL2), Asn (6.55), Trp (6.48) and His (7.43). The Glide Grid was built using an inner box (ligand diameter midpoint box) of 10 Å x 10 Å x 10 Å and an outer box (box within which all the ligand atoms must be contained) that extended 20 Å in each direction from the inner one. Docking of ligands was performed in the rigid binding site using the XP (extra precision) procedure. The top scoring docking conformations for each ligand were subjected to visual inspection and analysis of protein-ligand interactions to select the proposed binding conformations in agreement with the experimental data.

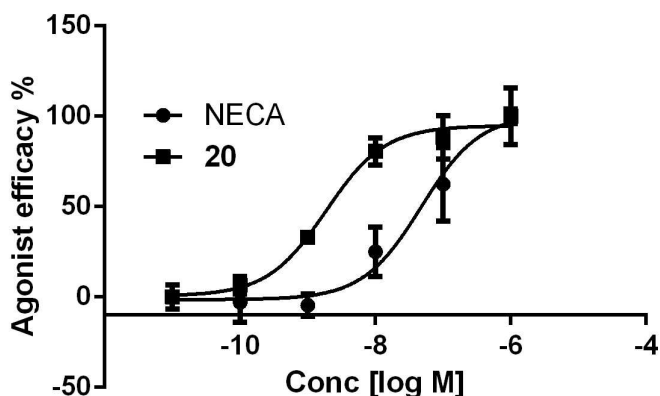
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- ¹ Tosh, D. K.; Deflorian, F.; Phan, K.; Gao, Z. G.; Wan, T. C.; Gizewski, E.; Auchampach, J. A.; Jacobson, K. A. *J. Med. Chem.* 2012, **55**, 4847.
- ² Paoletta, S.; Tosh, D. K.; Finley, A.; Gizewski, E.; Moss, S. M.; Gao, Z. G.; Auchampach, J. A.; Salvemini, D.; Jacobson, K. A. *J. Med. Chem.* 2013, **56**, 5949.
- ³ Molecular Operating Environment (MOE), version 2012.10, Chemical Computing Group Inc.; 1255 University St.; Suite 1600, Montreal, QC, H3B 3X3 (Canada).
- ⁴ Xu, F.; Wu, H.; Katritch, V.; Han, G. W.; Jacobson, K. A.; Gao, Z. G.; Cherezov, V.; Stevens, R. *Science* 2011, **332**, 322.
- ⁵ Rasmussen, S. G. F.; DeVree, B. T.; Zou, Y.; Kruse, A. C.; Chung, K. Y.; Kobilka, T. S.; Thian, F. S.; Chae, P. S.; Pardon, E.; Calinski, D.; Mathiesen, J. M.; Shah, S. T. A.; Lyons, J. A.; Caffrey, M.; Gellman, S. H.; Steyaert, J.; Skiniotis, G.; Weis, W. I.; Sunahara, R. K.; Kobilka, B. K. *Nature* 2011, **477**, 549.
- ⁶ Schrödinger Suite 2014. Schrödinger, LLC, New York, NY.
- ⁷ Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shaw, D. E.; Shelley, M.; Perry, J. K.; Francis, P.; Shenkin, P. S. *J. Med. Chem.* 2004, **47**, 1739.

Assay of adenylate cyclase at the hA₃AR.

hA₃AR-induced inhibition of the production of cyclic AMP in membranes of hA₃AR-expressing CHO cells was measured as reported.^{1,2}

Compound **20** (MRS7144) was shown to be a full agonist (mean ± SEM, n=3) with EC₅₀ of 1.5 ± 0.3 nM (cf. 38 ± 16 nM for adenosine 5'-N-ethyluronamide, NECA **44**). The maximal efficacy of **20** was 95.5 ± 2.3%, compared to **44** set at 100%.



Inactivity of **12** and **20** at the hA_{2B}AR.

An assay of stimulation of cAMP generation at the hA_{2B}AR expressed in CHO cells at a single concentration of 10 μM.^{1,2} Compound **20** (MRS7144): 8 ± 2% stimulation; Compound **12** (MRS7154): 12 ± 3%, compared with the maximum effect of **44** at 10 μM (full agonist control, 100%).

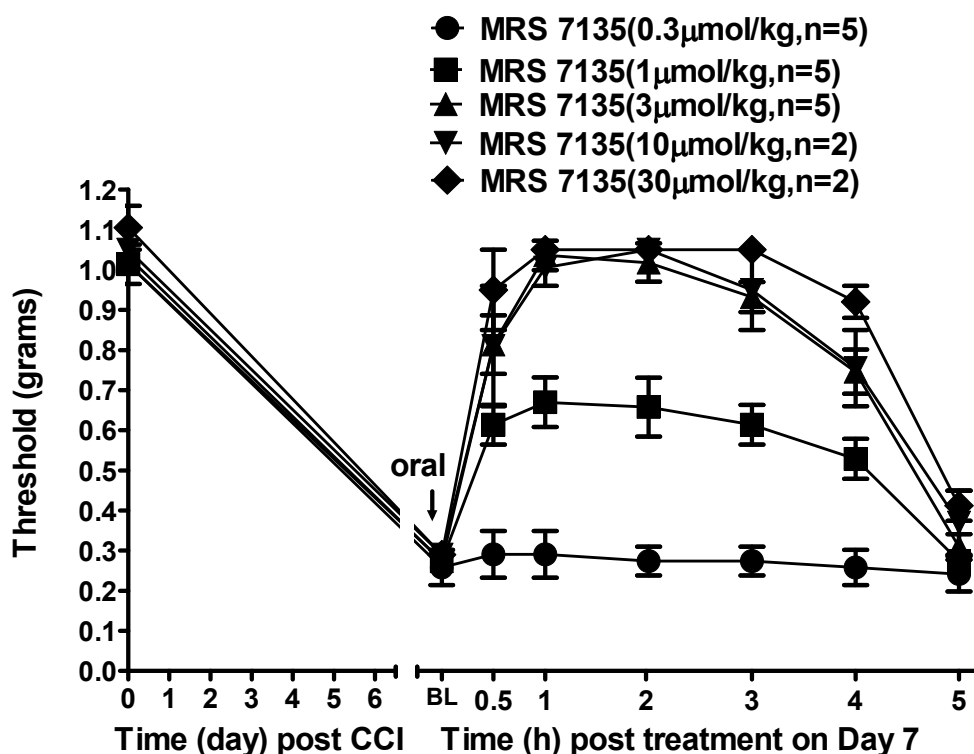
In inhibition of binding of [³H]8-[4-[[4-cyano)phenylcarbamoylmethyl]oxy]phenyl]-1,3-di-(n-propyl)xanthine ([³H]MRS1754) (2 nM) binding to membranes from HEK293 cells expressing the hA_{2B}AR: Compound **20** (MRS7144, 10 μM): 17% displacement; Compound **12** (MRS7154, 10 μM): 34% displacement.³

References

- ¹ Tosh, D. K.; Deflorian, F.; Phan, K.; Gao, Z. G.; Wan, T. C.; Gizewski, E.; Auchampach, J. A.; Jacobson, K. A. *J. Med. Chem.* **2012**, *55*, 4847.
- ² Paoletta, S.; Tosh, D. K.; Finley, A.; Gizewski, E.; Moss, S. M.; Gao, Z. G.; Auchampach, J. A.; Salvemini, D.; Jacobson, K. A. *J. Med. Chem.* **2013**, *56*, 5949.
- ³ Ji, X.-d.; Kim, Y.C.; Ahern, D.G.; Linden, J.; Jacobson, K.A. [³H]MRS 1754, a selective antagonist radioligand for A_{2B} adenosine receptors. *Biochem. Pharmacol.* **2001**, *61*, 657-663.

CCI calculations for *in vivo* assay of A₃AR agonists.

Figure S1. Dose escalation of Compound 11 (MRS7135).



All *in vivo* experiments were performed by methods described¹ and in accordance with the International Association for the Study of Pain and the National Institutes of Health guidelines on laboratory animal welfare and the recommendations by Saint Louis University Institutional Animal Care and Use Committee. All experiments were conducted with the experimenters blinded to treatment conditions.

¹ Tosh, D. K.; Finley, A.; Paoletta, S.; Moss, S. M.; Gao, Z. G.; Gizewski, E.; Auchampach, J.; Salvemini, D.; Jacobson, K. A. *J. Med. Chem.* **2014**, *57*, 9901.

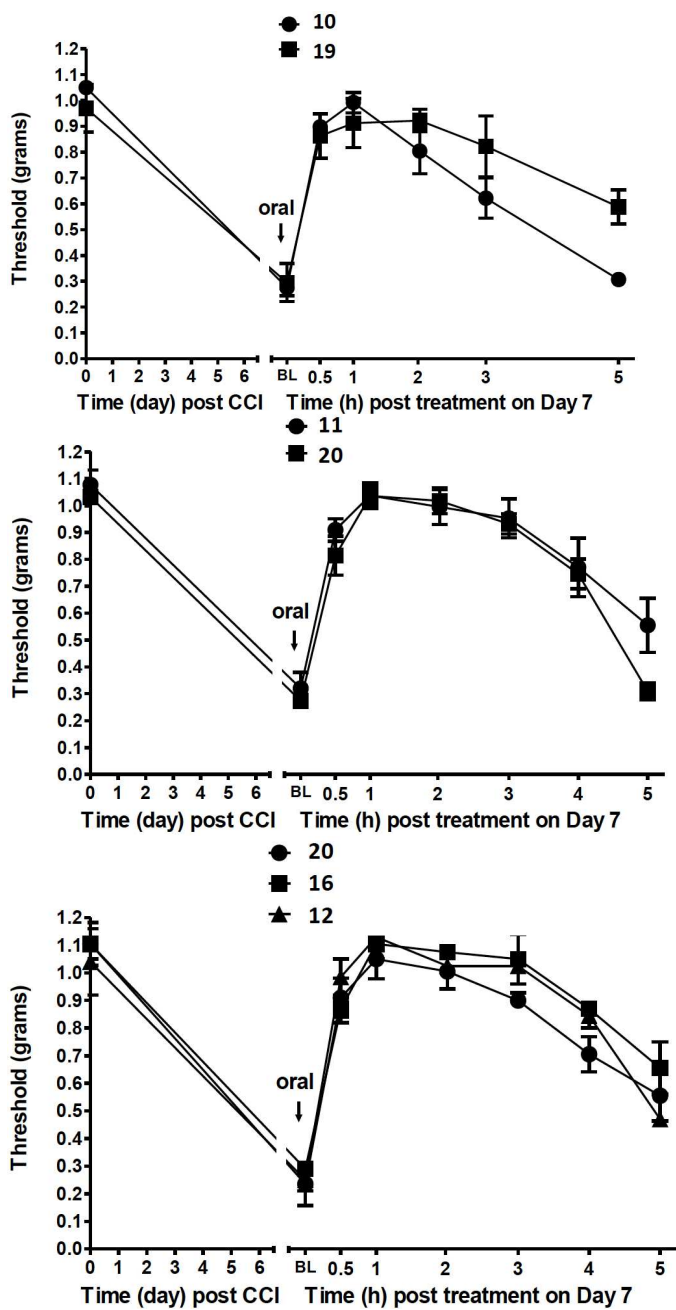
%Analgesic effect was calculated by the following equation:

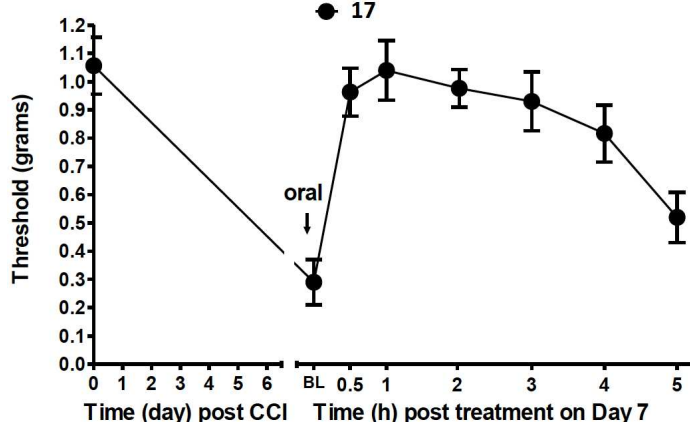
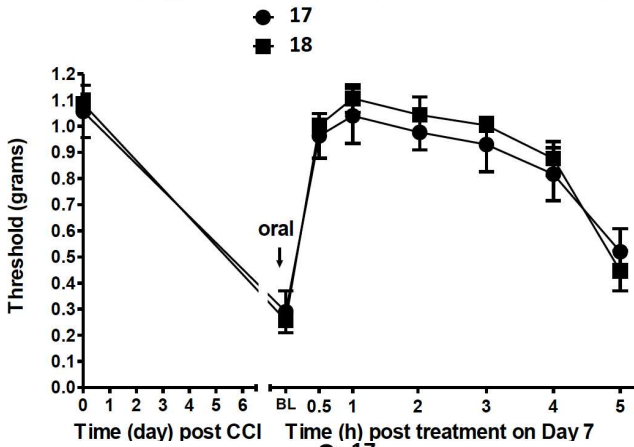
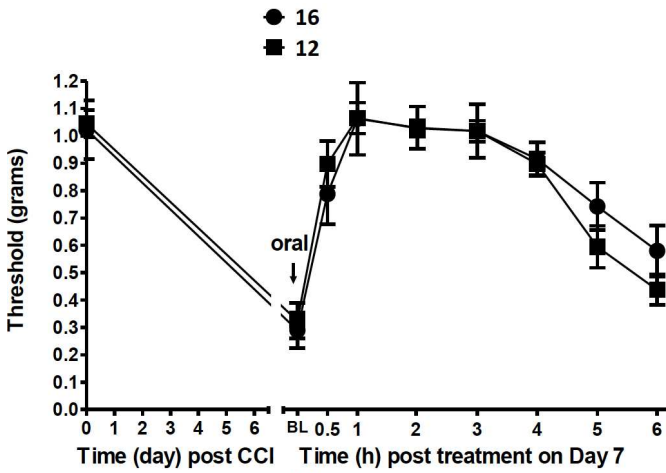
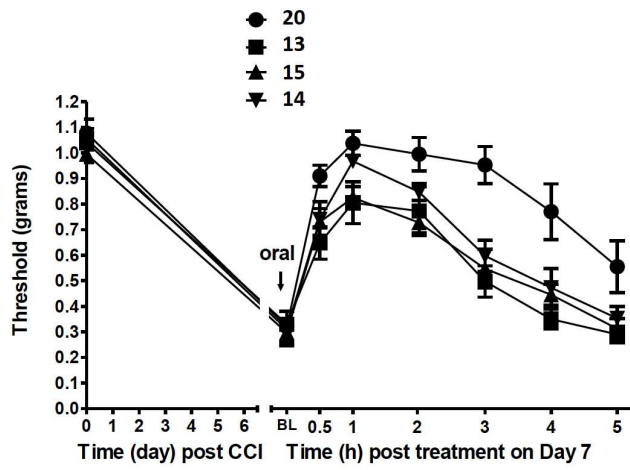
$$\% \text{Effect} = [\text{PWT (g)} t_h - \text{PWT (g)} t_{D7/BL}] / [\text{PWT (g)} t_{D0} - \text{PWT (g)} t_{D7/BL}] \times 100;$$

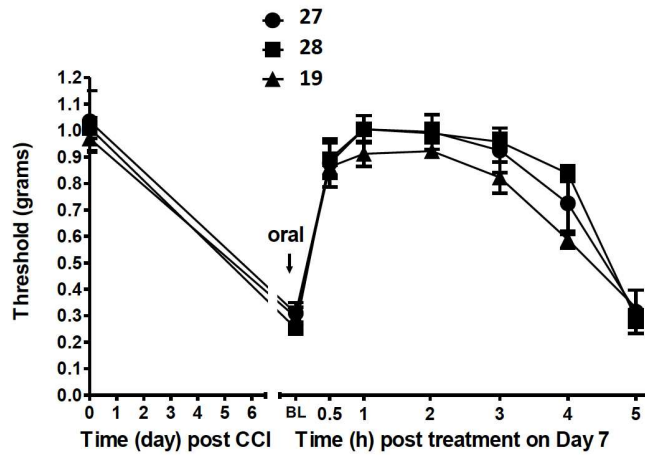
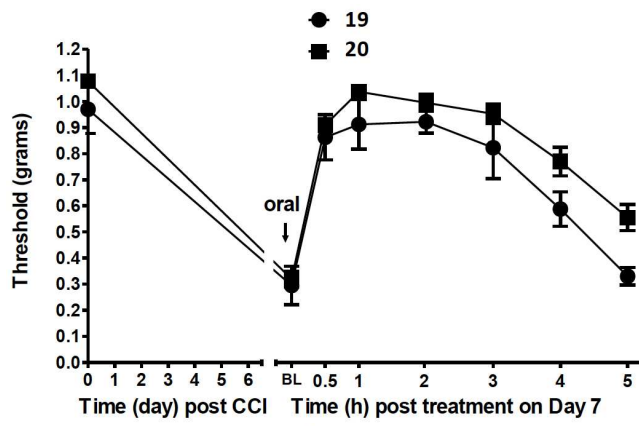
where, PWT (g) t_h = PWT (g) at 1 h (max) or 3 h post treatment; PWT (g) $t_{D7/BL}$ = PWT (g) at D7/BL; and PWT (g) t_{D0} = PWT (g) at D0.

Statistical Analysis. Data are expressed as mean \pm SEM for N animals. Differences in behavioral data from the full time course studies were analyzed by two-way ANOVA with Bonferroni comparisons using GraphPad Prism version 5.04 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com". Significant differences were defined at $P < 0.05$.

Plots of in vivo data (ipsilateral paw, each compound administered p.o., 3 $\mu\text{mol/kg}$, $n = 3$). There is no effect on the contralateral paw.







Off-target interactions for compounds 11, 12, 16-20, 24 and 25

Off-target interactions (from PDSP, protocols are available at <https://pdspdb.unc.edu/html/tutorials/UNC-CH%20Protocol%20Book.pdf>). This screening is described in Besnard et al.¹ Also, for activity of related compounds see Paoletta et al.² for systematic modeling of off-target effects.

Compounds were tested at the following sites: 5HT_{1A}, 5HT_{1B}, 5HT_{1D}, 5HT_{1E}, 5HT_{2A}, 5HT_{2B}, 5HT_{2C}, 5HT₃, 5HT_{5A}, 5HT₆, 5HT₇, α_{1A} , α_{1B} , α_{1D} , α_{2A} , α_{2B} , α_{2C} , β_1 , β_2 , β_3 , BZP rat brain site, D₁, D₂, D₃, D₄, D₅, delta opioid receptor (DOR), GABA_A, H₁, H₂, H₃, H₄, kappa opioid receptor (KOR), M₁, M₂, M₃, M₄, M₅, mu opioid receptor (MOR), peripheral benzodiazepine receptor (PBR), Sigma-1, and Sigma-2. No significant interaction was concluded when there was <50% inhibition at 10 μ M for each compound. Only significant interactions (>50% inhibition) are listed below. If a receptor is not listed, assume that there were no significant interactions. The interactions with neurotransmitter transport proteins will be reported elsewhere. Activity at biogenic amine transporters was not included.

We thank Dr. Bryan L. Roth (Univ. North Carolina at Chapel Hill) and National Institute of Mental Health's Psychoactive Drug Screening Program (Contract # HHSN-271-2008-00025-C) for screening data.

For comparison, off-target interactions of earlier reported compounds are listed here.^{1,2}

11, MRS7135 (PDSP 34074)

No significant interactions found.

12, MRS7154 (PDSP 37182)

No significant interactions found.

16, MRS7153 (PDSP 37181)

No significant interactions found.

17, MRS7146 (PDSP 34389)

5HT₆ (>10 μ M), H₂ (4.17 μ M), PBR (2.05 μ M), β_3 (6.52 μ M).

18, MRS7147 (PDSP 34390)

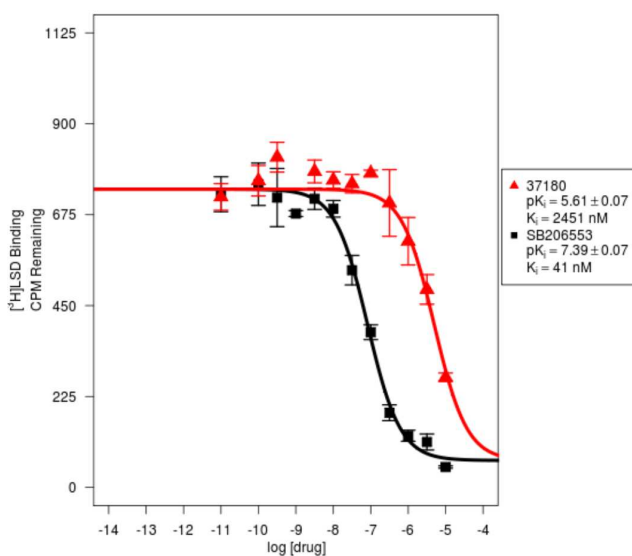
5HT_{5A} (>10 μ M), PBR (1.57 μ M), β_3 (2.14 μ M).

19, MRS7140 (PDSP 34334)

σ_2 (3.12 μ M), D₃ (>10 μ M).

20, MRS7144 (PDSP 37180)

5HT_{2B} (K_i = 2.45 μ M)



25, MRS7162 (PDSP 37183)

No significant interactions found.

26, MRS7163 (PDSP 37184)

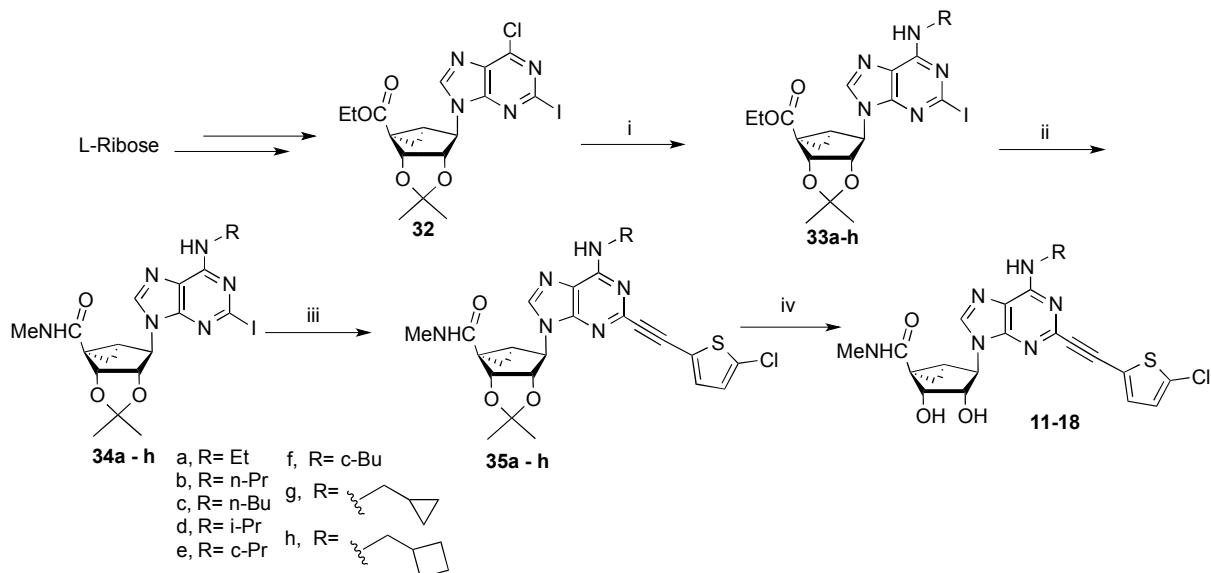
No significant interactions found.

¹Besnard, J.; Ruda, G. F.; Setola, V.; Abecassis, K.; Rodriguiz, R. M.; Huang, X. P.; Norval, S.; Sassano, M. F.; Shin, A. I.; Webster, L. A.; Simeons, F. R.; Stojanovski, L.; Prat, A.; Seidah, N. G.; Constan, D. B.; Bickerton, G. R.; Read, K. D.; Wetsel, W. C.; Gilbert, I. H.; Roth, B. L.; Hopkins, A. L. Automated design of ligands to polypharmacological profiles. *Nature* **2012**, *492*, 215–220.

²Paoletta, S.; Tosh, D. K.; Salvemini, D.; Jacobson, K. A. Structural probing of off-target G protein-coupled receptor activities within a series of adenosine/adenine congeners. *PLoS ONE* **2014**, *9*, e97858.

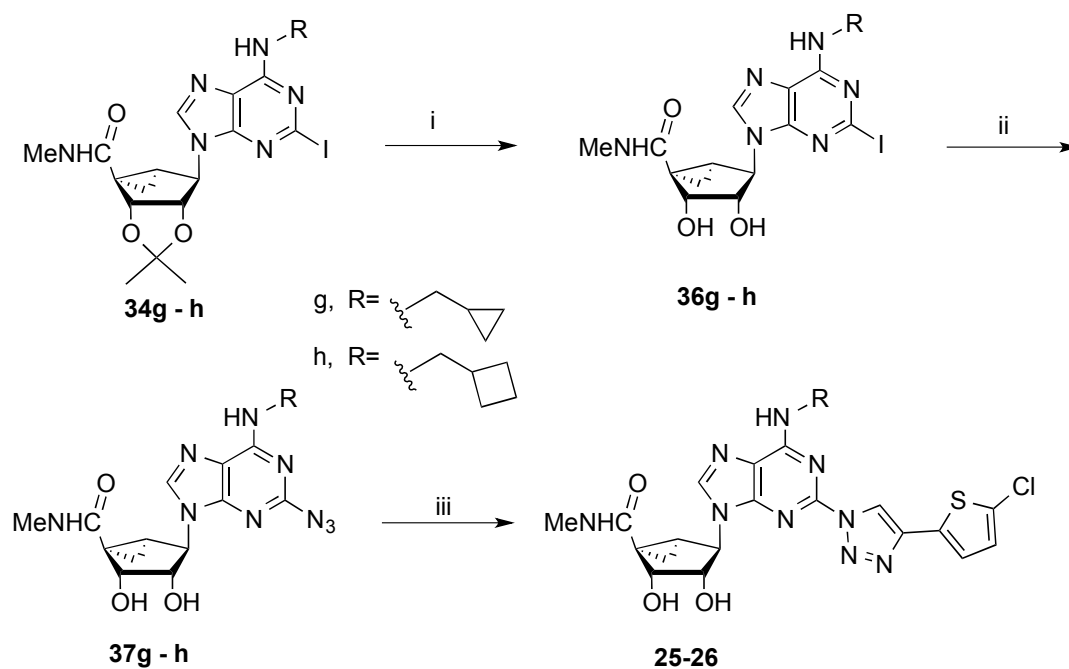
Chemical synthesis

Scheme S1



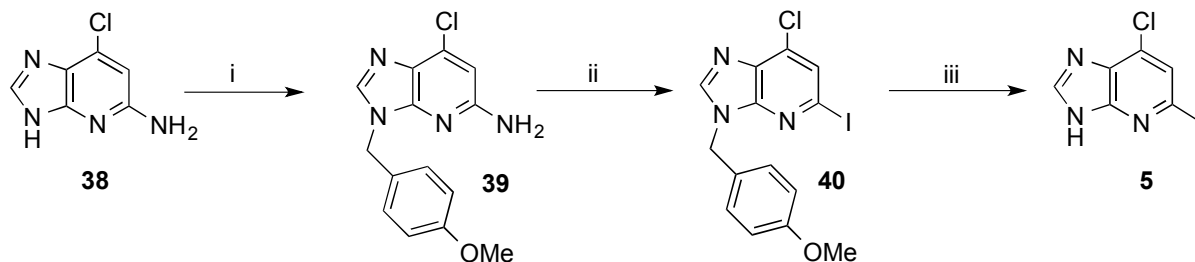
Reagents and Condition: (i) RNH₂, Et₃N, MeOH, rt, 73-90%; (ii) 40% MeNH₂, MeOH, rt, 68-76%; (iii) 2-chloro-5-ethynylthiophene, Pd(PPh₃)₂Cl₂, CuI, Et₃N, DMF, rt, 73-97%; (iv) 10%TFA, MeOH, 70 °C, 80-85%.

Scheme S2



Reagents and Condition: (i) 10%TFA, MeOH, 70 °C, 91-93%; (ii) NaN₃, sodium ascorbate, CuSO₄.5H₂O, L-proline, Na₂CO₃, ^tBuOH-H₂O, 65 °C, 78-81%; (ii) 2-chloro-5-ethynylthiophene, sodium ascorbate, CuSO₄.5H₂O, ^tBuOH-H₂O, rt, 89-91%.

Scheme S3



Reagents and Condition: i) PMBCl, TBAF, DMF, rt, 51%; ii) isoamyl nitrite, CH₂I₂, I₂, CuI, THF, reflux, 96%; iii) TFA, reflux, 94%.

Materials and instrumentation

All reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO). ¹H NMR spectra were obtained with a Bruker 400 spectrometer using CDCl₃ and CD₃OD as solvents. Chemical shifts are expressed in δ values (ppm) with tetramethylsilane (δ 0.00) for CDCl₃ and water (δ 3.30) for CD₃OD. TLC analysis was carried out on glass sheets precoated with silica gel F254 (0.2 mm) from Aldrich. The purity of final nucleoside derivatives was checked using a Hewlett–Packard 1100 HPLC equipped with a Zorbax SB-Aq 5 μm analytical column (50 × 4.6 mm; Agilent Technologies Inc., Palo Alto, CA). Mobile phase: linear gradient solvent system, 5 mM TBAP (tetrabutylammonium dihydrogenphosphate)–CH₃CN from 80:20 to 0:100 in 13 min; the flow rate was 0.5 mL/min. Peaks were detected by UV absorption with a diode array detector at 230, 254, and 280 nm. All derivatives tested for biological activity showed >95% purity by HPLC analysis (detection at 254 nm). Low-resolution mass spectrometry was performed with a JEOL SX102 spectrometer with 6-kV Xe atoms following desorption from a glycerol matrix or on an Agilent LC/MS 1100 MSD, with a Waters (Milford, MA) Atlantis C18 column. High resolution mass spectroscopic (HRMS) measurements were performed on a proteomics optimized Q-TOF-2 (Micromass-Waters) using external calibration with polyalanine, unless noted. Observed mass accuracies are those expected based on known performance of the instrument as well as trends in masses of standard compounds observed at intervals during the series of measurements. Reported masses are observed masses uncorrected for this time-dependent drift in mass accuracy. All of the monosubstituted alkyne intermediates were purchased from Sigma-Aldrich (St. Louis, MO), Small Molecules, Inc. (Hoboken, NJ), Anichem (North Brunswick, NJ), PharmaBlock, Inc. (Sunnyvale, CA), Frontier Scientific (Logan, UT) and Tractus (Perrineville, NJ).

7-Chloro-5-iodo-3*H*-imidazo[4,5-*b*]pyridine (5)

A solution of compound **40** (378, 0.94 mmol) in TFA (10 mL) was refluxed at 85 °C overnight. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 20:1) to give compound **5** (248 mg, 94%) as a colorless powder. ¹H NMR (CD₃OD, 400 MHz) δ 8.40 (s, 1H), 7.79 (s, 1H). HRMS calculated for C₆H₄N₃ClI (M + H)⁺: 279.9139; found 279.9137.

Ethyl (3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-5-(7-chloro-5-iodo-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3*b*(3*aH*)-carboxylate (6)

DIAD (0.24 mL, 1.242 mmol) was added to a solution of triphenylphosphine (0.326 g, 1.242 mmol) and 1-deaza- 2-iodo-6-chloropurine **5** (0.259 g, 0.926 mmol) in dry THF (3 mL) and the mixture stirred at room temperature for 10 min. A solution of compound **4** (0.150 g, 0.621 mmol) in THF (2 mL) was added to the reaction mixture, and the mixture stirred overnight at room temperature.

Solvent was evaporated and the residue was purified on flash silica gel column chromatography (hexane:ethyl acetate=4:1) to give compound **6** (0.160 g, 51%) as a colorless foam. ¹H NMR (CDCl₃, 400 MHz) δ 7.99 (s, 1H), 7.71 (s, 1H), 5.87 (d, *J* = 6.4 Hz, 1H), 4.94 (s, 1H), 4.81 (d, *J* = 6.0 Hz, 1H), 4.33-4.25 (m, 2H), 2.28-2.23 (m, 1H), 1.76-1.72 (1H), 1.59 (s, 3H), 1.55 (t, *J* = 5.6 Hz, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.31 (s, 3H). HRMS calculated for C₁₈H₂₀IClN₃O₄ (M + H)⁺: 504.0187; found 504.0192.

(3aR,3bS,4aS,5R,5aS)-5-(7-chloro-5-iodo-3H-imidazo[4,5-b]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (7)

40% Methylamine solution (2.5 mL) was added to a solution of compound **6** (0.160, 0.318 mmol) in methanol (3 mL) and the mixture stirred at room temperature for 24 h. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH=40:1) to give compound **7** (0.111g, 72%) as a colorless foam. ¹H NMR (CD₃OD, 400 MHz) δ 8.44 (s, 1H), 7.82 (s, 1H), 5.75 (d, *J* = 6.4 Hz, 1H), 5.07 (s, 1H), 4.91 (d, *J* = 5.6 Hz, 1H), 2.89 (s, 3H), 2.23-2.19 (m, 1H), 1.56 (s, 3H), 1.54-1.50 (m, 1H), 1.44 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H). HRMS calculated for C₁₇H₁₈IClN₄O₃Na (M + Na)⁺: 511.0004; found 511.0007.

(3aR,3bS,4aS,5R,5aS)-5-(5-iodo-7-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (8a)

MeNH₂.HCl (36.6 mg, 0.542 mmol) and DIPEA (0.18 mL, 1.08 mmol) were added to a solution of compound **7** (53 mg, 0.108 mmol) in isopropanol (1.5 mL) in a sealed tube and heated at 150 °C under microwave condition for 3 h. The reaction mixture was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 40:1) to give compound **8a** (42 mg, 81%) as a glassy syrup. ¹H NMR (CD₃OD, 400 MHz) δ 7.99 (s, 1H), 6.73 (s, 1H), 5.75 (d, *J* = 7.2 Hz, 1H), 4.95 (s, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 2.96 (s, 3H), 2.89 (s, 3H), 2.15-2.11 (m, 1H), 1.54 (s, 3H), 1.52-1.49 (m, 1H), 1.40 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H). HRMS calculated for C₁₈H₂₃IN₅O₃ (M + H)⁺: 484.0840; found 484.0840.

(3aR,3bS,4aS,5R,5aS)-5-(7-(ethylamino)-5-iodo-3H-imidazo[4,5-b]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (8b)

Compound **8b** (77%) was prepared from compound **7** following the same method for compound **8a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.99 (s, 1H), 6.75 (s, 1H), 5.75 (d, *J* = 6.8 Hz, 1H), 4.95 (s, 1H), 4.92 (d, *J* = 7.2 Hz, 1H), 3.39-3.34 (m, 2H), 2.89 (s, 3H), 2.15-2.12 (m, 1H), 1.54-1.49 (m, 4H), 1.39 (t, *J* = 5.2 Hz, 1H), 1.31-1.29 (m, 6H). HRMS calculated for C₁₉H₂₅IN₅O₃ (M + H)⁺: 498.0924; found 498.0913.

(3aR,3bS,4aS,5R,5aS)-5-(5-iodo-7-(propylamino)-3H-imidazo[4,5-b]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (8c)

Compound **8c** (84%) was prepared from compound **7** following the same method for compound **8a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.99 (s, 1H), 6.75 (s, 1H), 5.74 (d, *J* = 6.0 Hz, 1H), 4.95 (s, 1H), 4.85 (d, *J* = 5.6 Hz, 1H), 3.28 (t, *J* = 6.8 Hz, 2H), 2.88 (s, 3H), 2.15-2.11 (m, 1H), 1.74-1.67 (m, 2H), 1.55 (s, 3H), 1.54-1.49 (m, 1H), 1.39 (t, *J* = 5.2 Hz, 1H), 1.29 (s, 3H), 1.04 (t, *J* = 7.2 Hz, 3H). HRMS calculated for C₂₀H₂₇IN₅O₃ (M + H)⁺: 512.1159; found 512.1161.

(3aR,3bS,4aS,5R,5aS)-5-(7-(cyclopropylamino)-5-iodo-3H-imidazo[4,5-b]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (8d)

Compound **8d** (74%) was prepared from compound **7** following the same method for compound **8a**. ¹H NMR (CD₃OD, 400 MHz) δ 8.00 (s, 1H), 7.08 (s, 1H), 5.75 (d, *J* = 6.4 Hz, 1H), 4.95 (s, 1H),

4.88 (d, $J = 5.6$ Hz, 1H), 2.89 (s, 3H), 2.62-2.57 (m, 1H), 2.15-2.11 (m, 1H), 1.54 (s, 3H), 1.52-1.50 (m, 1H), 1.40 (t, $J = 5.2$ Hz, 1H), 1.30 (s, 3H), 0.90-0.86 (m, 2H), 0.62-0.58 (m, 2H). HRMS calculated for $C_{20}H_{25}IN_5O_3$ ($M + H$)⁺: 510.1002; found 510.0997.

(3aR,3bS,4aS,5R,5aS)-5-(5-((5-chlorothiophen-2-yl)ethynyl)-7-(methylamino)-3H-imidazo[4,5-b]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (9a)

$PdCl_2(PPh_3)_2$ (7.7 mg, 0.01 mmol), CuI (1.0 mg, 0.005 mmol), 2-chloro-5-ethynylthiophene (47 mg, 0.329 mmol) and triethylamine (0.07 mL, 0.54 mmol) were added to a solution of compound **8a** (26.5 mg, 0.05 mmol) in anhydrous DMF (1.2 mL), and the mixture stirred at room temperature overnight. Solvent was evaporated under vacuum and the residue purified on flash silica gel column chromatography ($CH_2Cl_2:MeOH = 35:1$) to give compound **9a** (26 mg, 95%) as a yellow syrup. ¹H NMR (CD_3OD , 400 MHz) δ 8.15 (s, 1H), 7.29 (d, $J = 3.6$ Hz, 1H), 7.01 (d, $J = 3.6$ Hz, 1H), 6.69 (s, 1H), 5.77 (d, $J = 7.2$ Hz, 1H), 5.05 (s, 1H), 3.03 (s, 3H), 2.81 (s, 3H), 2.15-2.12 (m, 1H), 1.55-1.53 (m, 4H), 1.42 (t, $J = 5.2$ Hz, 1H), 1.29 (s, 3H). HRMS calculated for $C_{24}H_{25}ClN_5O_3S$ ($M + H$)⁺: 498.1361; found 498.1358.

(3aR,3bS,4aS,5R,5aS)-5-(5-((5-chlorothiophen-2-yl)ethynyl)-7-(ethylamino)-3H-imidazo[4,5-b]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (9b)

Compound **9b** (84%) was prepared from compound **8b** following the same method for compound **9a**. ¹H NMR (CD_3OD , 400 MHz) δ 8.15 (s, 1H), 7.29 (d, $J = 4.0$ Hz, 1H), 7.01 (d, $J = 3.6$ Hz, 1H), 6.69 (s, 1H), 5.77 (d, $J = 7.2$ Hz, 1H), 5.05 (s, 1H), 4.88 (d, $J = 6.8$ Hz, 1H), 3.28-3.17 (m, 2H), 2.81 (s, 3H), 2.16-2.12 (m, 1H), 1.57-1.53 (m, 4H), 1.42 (t, $J = 5.2$ Hz, 1H), 1.36-1.33 (m, 6H). HRMS calculated for $C_{25}H_{27}ClN_5O_3S$ ($M + H$)⁺: 512.1518; found 512.1520.

(3aR,3bS,4aS,5R,5aS)-5-(5-((5-chlorothiophen-2-yl)ethynyl)-7-(propylamino)-3H-imidazo[4,5-b]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (9c)

Compound **9c** (89%) was prepared from compound **8c** following the same method for compound **9a**. ¹H NMR (CD_3OD , 400 MHz) δ 8.15 (s, 1H), 7.28 (d, $J = 4.0$ Hz, 1H), 7.00 (d, $J = 4.0$ Hz, 1H), 6.68 (s, 1H), 5.76 (d, $J = 6.4$ Hz, 1H), 5.05 (s, 1H), 4.85 (d, $J = 5.2$ Hz, 1H), 3.36 (t, $J = 6.8$ Hz, 2H), 2.81 (s, 3H), 2.16-2.12 (m, 1H), 1.79-1.70 (m, 2H), 1.56-1.53 (m, 4H), 1.42 (t, $J = 5.2$ Hz, 1H), 1.29 (s, 3H), 1.06 (t, $J = 7.2$ Hz, 3H). HRMS calculated for $C_{26}H_{29}ClN_5O_3$ ($M + H$)⁺: 526.1680; found 526.1677.

(3aR,3bS,4aS,5R,5aS)-5-(5-((5-chlorothiophen-2-yl)ethynyl)-7-(cyclopropylamino)-3H-imidazo[4,5-b]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (9d)

Compound **9d** (85%) was prepared from compound **8d** following the same method for compound **9a**. ¹H NMR (CD_3OD , 400 MHz) δ 8.16 (s, 1H), 7.30 (d, $J = 4.0$ Hz, 1H), 7.01 (d, $J = 3.6$ Hz, 1H), 6.99 (s, 1H), 5.77 (d, $J = 6.8$ Hz, 1H), 5.05 (s, 1H), 4.86 (d, $J = 5.2$ Hz, 1H), 2.81 (s, 3H), 2.61-2.68 (m, 1H), 2.15-2.11 (m, 1H), 1.55-1.52 (m, 4H), 1.42 (t, $J = 5.2$ Hz, 1H), 1.29 (s, 3H), 0.91-0.90 (m, 2H), 0.68-0.60 (m, 2H). HRMS calculated for $C_{26}H_{27}ClN_5O_3$ ($M + H$)⁺: 524.1523; found 524.1519.

(1S,2R,3S,4R,5S)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(ethylamino)-9H-purin-9-yl)-2,3-dihydroxy-N-methylbicyclo[3.1.0]hexane-1-carboxamide (11)

A solution of compound **35a** (25 mg, 0.048 mmol) in methanol (3 mL) and 10% trifluoromethane sulfonic acid (2 mL) was heated at 70 °C for 5 h. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 15:1) to give compound **11** (19 mg, 85%) as a light yellow powder. ¹H NMR (CD₃OD, 400 MHz) δ 8.09 (s, 1H), 7.30 (d, *J* = 4.0 Hz, 1H), 7.02 (d, *J* = 4.0 Hz, 1H), 5.03 (d, *J* = 6.4 Hz, 1H), 4.86 (s, 1H), 4.01 (d, *J* = 6.4 Hz, 1H), 3.65 (br s, 2H), 2.86 (s, 3H), 2.13-2.09 (m, 1H), 1.88 (t, *J* = 4.8 Hz, 1H), 1.41-1.37 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H). HRMS calculated for C₂₁H₂₂N₆O₃SCl (M + H)⁺: 473.1163; found 473.1166.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(propylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (12)

Compound **12** (83%) was prepared from compound **35b** following the same method for compound **11**. ¹H NMR (CD₃OD, 400 MHz) δ 8.11 (s, 1H), 7.31 (d, *J* = 4.0 Hz, 1H), 7.02 (d, *J* = 4.0 Hz, 1H), 5.03 (d, *J* = 7.2 Hz, 1H), 4.85 (s, 1H), 4.01 (d, *J* = 6.4 Hz, 1H), 3.58 (br s, 2H), 2.86 (s, 3H), 2.12-2.09 (m, 1H), 1.88 (t, *J* = 4.8 Hz, 1H), 1.75-1.70 (m, 2H), 1.41-1.37 (m, 1H), 1.04 (t, *J* = 7.6 Hz, 3H). HRMS calculated for C₂₅H₂₈N₆O₃SCl (M + H)⁺: 527.1632; found 527.1632.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-(butylamino)-2-((5-chlorothiophen-2-yl)ethynyl)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (13)

Compound **13** (86%) was prepared from compound **35c** following the same method for compound **11**. ¹H NMR (CD₃OD, 400 MHz) δ 8.11 (s, 1H), 7.31 (d, *J* = 4.0 Hz, 1H), 7.02 (d, *J* = 4.0 Hz, 1H), 5.03 (d, *J* = 6.4 Hz, 1H), 4.86 (s, 1H), 4.00 (d, *J* = 6.4 Hz, 1H), 3.61 (br s, 2H), 2.86 (s, 3H), 2.12-2.09 (m, 1H), 1.88 (t, *J* = 4.8 Hz, 1H), 1.71-1.66 (m, 2H), 1.51-1.46 (m, 2H), 1.41-1.37 (m, 1H), 1.00 (t, *J* = 7.2 Hz, 3H). HRMS calculated for C₂₃H₂₆N₆O₃SCl (M + H)⁺: 501.1476; found 501.1477.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(isopropylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (14)

Compound **14** (80%) was prepared from compound **35d** following the same method for compound **11**. ¹H NMR (CD₃OD, 400 MHz) δ 8.12 (s, 1H), 7.31 (d, *J* = 4.0 Hz, 1H), 7.02 (d, *J* = 4.0 Hz, 1H), 5.05 (d, *J* = 6.4 Hz, 1H), 4.88 (s, 1H), 4.51 (br s, 1H), 4.01 (d, *J* = 6.4 Hz, 1H), 2.86 (s, 3H), 2.12-2.09 (m, 1H), 1.88 (t, *J* = 5.2 Hz, 1H), 1.41-1.37 (m, 1H), 1.33 (d, *J* = 6.4 Hz, 6H). HRMS calculated for C₂₂H₂₄N₆O₃SCl (M + H)⁺: 487.1319; found 487.1313.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(cyclopropylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (15)

Compound **15** (83%) was prepared from compound **35e** following the same method for compound **11**. ¹H NMR (CD₃OD, 400 MHz) δ 8.12 (s, 1H), 7.32 (d, *J* = 4.0 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 5.04 (d, *J* = 6.4 Hz, 1H), 4.85 (s, 1H), 4.01 (d, *J* = 6.4 Hz, 1H), 3.07 (br s, 1H), 2.86 (s, 3H), 2.12-2.09 (m, 1H), 1.88 (t, *J* = 5.2 Hz, 1H), 1.41-1.37 (m, 1H), 0.94-0.89 (m, 2H), 0.71-0.67 (m, 2H). HRMS calculated for C₂₂H₂₂N₆O₃SCl (M + H)⁺: 485.1163; found 485.1163.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(cyclobutylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (16)

Compound **16** (85%) was prepared from compound **35f** following the same method for compound **11**. ¹H NMR (CD₃OD, 400 MHz) δ 8.11 (s, 1H), 7.31 (d, *J* = 4.0 Hz, 1H), 7.02 (d, *J* = 4.0 Hz, 1H),

5.03 (d, $J = 6.4$ Hz, 1H), 4.85 (s, 1H), 4.81 (br s, 1H), 4.00 (d, $J = 6.8$ Hz, 1H), 2.86 (s, 3H), 2.52-2.43 (m, 2H), 2.12-2.09 (m, 3H), 1.89-1.82 (m, 3H), 1.40-1.37 (m, 1H). HRMS calculated for $C_{23}H_{24}N_6O_3S$ Cl (M + H)⁺: 499.1319; found 499.1322.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-6-((cyclopropylmethyl)amino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (17)

Compound **17** (87%) was prepared from compound **35g** following the same method for compound **11**. ¹H NMR (CD₃OD, 400 MHz) δ 8.12 (s, 1H), 7.31 (d, $J = 4.0$ Hz, 1H), 7.01 (d, $J = 4.0$ Hz, 1H), 5.03 (d, $J = 6.4$ Hz, 1H), 4.85 (s, 1H), 4.01 (d, $J = 6.0$ Hz, 1H), 3.48 (br s, 2H), 2.86 (s, 3H), 2.13-2.09 (m, 1H), 1.88 (t, $J = 4.8$ Hz, 1H), 1.41-1.37 (m, 1H), 1.24-1.14 (m, 1H), 0.60-0.56 (m, 2H), 0.37-0.33 (m, 2H). HRMS calculated for $C_{23}H_{24}N_6O_3S$ Cl (M + H)⁺: 499.1319; found 499.1315.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-6-((cyclobutylmethyl)amino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (18)

Compound **18** (88%) was prepared from compound **35h** following the same method for compound **11**. ¹H NMR (CD₃OD, 400 MHz) δ 8.12 (s, 1H), 7.31 (d, $J = 4.0$ Hz, 1H), 7.02 (d, $J = 4.0$ Hz, 1H), 5.03 (d, $J = 6.4$ Hz, 1H), 4.86 (s, 1H), 4.01 (d, $J = 6.0$ Hz, 1H), 3.64 (br s, 2H), 2.86 (s, 3H), 2.75-2.67 (m, 1H), 2.18-2.09 (m, 3H), 1.99-1.91 (m, 2H), 1.89-1.83 (m, 3H), 1.41-1.37 (m, 1H). HRMS calculated for $C_{24}H_{26}N_6O_3S$ Cl (M + H)⁺: 513.1476; found 513.1470.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(5-((5-chlorothiophen-2-yl)ethynyl)-7-(methylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (19)

A solution of compound **9a** (26 mg, 0.05 mmol) in methanol (2 mL) and 10% trifluoromethane sulfonic acid (2 mL) was heated at 70 °C for 5 h. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 15:1) to give compound **19** (21 mg, 88%) as a light yellow powder. ¹H NMR (CD₃OD, 400 MHz) δ 8.09 (s, 1H), 7.23 (d, $J = 4.0$ Hz, 1H), 7.00 (d, $J = 4.0$ Hz, 1H), 6.66 (s, 1H), 4.99 (d, $J = 5.6$ Hz, 1H), 4.90 (s, 1H), 3.98 (d, $J = 6.0$ Hz, 1H), 3.03 (s, 3H), 2.86 (s, 3H), 2.15-2.11 (m, 1H), 1.92 (t, $J = 5.2$ Hz, 1H), 1.41-1.37 (m, 1H). HRMS calculated for $C_{21}H_{21}ClN_5O_3S$ (M + H)⁺: 458.1054; found 458.1055.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(5-((5-chlorothiophen-2-yl)ethynyl)-7-(ethylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (20)

Compound **20** (91%) was prepared from compound **9b** following the same method for compound **19**. ¹H NMR (CD₃OD, 400 MHz) δ 8.18 (s, 1H), 7.24 (d, $J = 4.0$ Hz, 1H), 7.00 (d, $J = 4.0$ Hz, 1H), 6.72 (s, 1H), 4.97 (d, $J = 6.8$ Hz, 1H), 4.91 (s, 1H), 4.01 (d, $J = 6.8$ Hz, 1H), 3.49-3.43 (m, 2H), 2.86 (s, 3H), 2.15-2.12 (m, 1H), 1.92 (t, $J = 5.2$ Hz, 1H), 1.41-1.38 (m, 1H), 1.37 (t, $J = 7.2$ Hz, 3H). HRMS calculated for $C_{22}H_{23}ClN_5O_3S$ (M + H)⁺: 472.1210; found 472.1214.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(5-((5-chlorothiophen-2-yl)ethynyl)-7-(propylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (21)

Compound **21** (87%) was prepared from compound **9c** following the same method for compound **19**. ¹H NMR (CD₃OD, 400 MHz) δ 8.11 (s, 1H), 7.22 (d, $J = 4.0$ Hz, 1H), 7.00 (d, $J = 4.0$ Hz, 1H), 6.68 (s, 1H), 4.98 (d, $J = 5.6$ Hz, 1H), 4.90 (s, 1H), 3.99 (d, $J = 6.0$ Hz, 1H), 3.36 (t, $J = 6.8$ Hz, 2H), 2.86 (s, 3H), 2.15-2.11 (m, 1H), 1.92 (t, $J = 5.2$ Hz, 1H), 1.77-1.70 (m, 2H), 1.41-1.37 (m, 1H), 1.06 (t, $J = 7.2$ Hz, 3H). HRMS calculated for $C_{23}H_{25}ClN_5O_3$ (M + H)⁺: 486.1367; found 486.1375.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(5-((5-chlorothiophen-2-yl)ethynyl)-7-(cyclopropylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (22)

Compound **22** (86%) was prepared from compound **9d** following the same method for compound **19**. ¹H NMR (CD₃OD, 400 MHz) δ 8.13 (s, 1H), 7.25 (d, *J* = 3.6 Hz, 1H), 7.01-6.99 (m, 2H), 4.98 (d, *J* = 6.4 Hz, 1H), 4.91 (s, 1H), 3.98 (d, *J* = 6.4 Hz, 1H), 2.86 (s, 3H), 2.71-2.62 (m, 1H), 2.13-2.11 (m, 1H), 1.92 (t, *J* = 5.2 Hz, 1H), 1.41-1.37 (m, 1H), 0.92-0.89 (m, 2H), 0.68-0.61 (m, 2H). HRMS calculated for C₂₃H₂₃ClSN₅O₃ (M + H)⁺: 484.1210; found 484.1216.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(5-chlorothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(cyclopropylmethyl)amino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (25)

2-Chloro-5-ethynylthiophene (11.5 mg, 0.08 mmol) and TBTA (1 mg, 0.001 mmol) were added to a solution of compound **37g** (23 mg, 0.057 mmol) in a mixture of *t*-butanol (1 mL) and water (1 mL). Subsequently freshly prepared 1M sodium ascorbate solution (58 μL, 0.05 mmol) followed by a 7.5% solution of copper sulfate (96 μL, 0.02 mmol) were added to the reaction mixture and the mixture stirred at room temperature overnight. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 25:1) to give compound **25** (28 mg, 91%) as a light yellow powder. ¹H NMR (DMSO, 400 MHz) δ 9.23 (s, 1H), 8.55 (t, *J* = 5.6, 1H), 8.20 (s, 1H), 7.61-7.60 (m, 2H), 7.23 (d, *J* = 3.6 Hz, 1H), 5.38 (d, *J* = 4.4 Hz, 1H), 5.16 (t, *J* = 7.2 Hz, 1H), 4.89 (d, *J* = 8.0 Hz, 1H), 4.80 (s, 1H), 4.04 (d, *J* = 5.2 Hz, 1H), 3.46 (s, 2H), 2.60 (d, *J* = 4.4 Hz, 3H), 1.89-1.86 (m, 1H), 1.56 (t, *J* = 4.8 Hz, 1H), 1.37-1.34 (m, 1H), 1.23-1.16 (m, 1H), 0.47-0.43 (m, 2H), 0.36-0.33 (m, 2H). HRMS calculated for C₂₃H₂₄N₉O₃SClNa (M + Na)⁺: 564.1309; found 564.1316.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(5-chlorothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(cyclobutylmethyl)amino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (26)

Compound **26** (89%) was prepared from compound **37h** following the same method for compound **25**. ¹H NMR (DMSO, 400 MHz) δ 9.21 (s, 1H), 8.46 (t, *J* = 5.6 Hz, 1H), 8.19 (s, 1H), 7.60-7.59 (m, 2H), 7.22 (d, *J* = 4.0 Hz, 1H), 5.38 (d, *J* = 4.4 Hz, 1H), 5.15 (t, *J* = 6.8 Hz, 1H), 4.89 (d, *J* = 3.6 Hz, 1H), 4.80 (s, 1H), 4.03 (t, *J* = 5.6 Hz, 1H), 3.63 (t, *J* = 5.2, 2H), 2.73-2.66 (m, 1H), 2.61 (d, *J* = 4.8 Hz, 3H), 2.02-1.97 (m, 2H), 1.89-1.77 (m, 5H), 1.56 (t, *J* = 4.8 Hz, 1H), 1.37-1.34 (m, 1H). HRMS calculated for C₂₄H₂₆N₉O₃SClNa (M + Na)⁺: 578.1466; found 578.1461.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(5-(4-(5-chlorothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-7-(propylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (29)

A solution of compound **31** (15 mg, 0.026 mmol) in methanol (2 mL) and 10% trifluoromethane sulfonic acid (2 mL) was heated at 70 °C for 5 h. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 20:1) to give compound **29** (11 mg, 78%) as a light yellow powder. ¹H NMR (CD₃OD, 400 MHz) δ 9.03 (s, 1H), 8.11 (s, 1H), 7.44 (d, *J* = 4.0 Hz, 1H), 7.20 (s, 1H), 7.04 (d, *J* = 4.0 Hz, 1H), 5.07 (d, *J* = 5.6 Hz, 1H), 4.93 (s, 1H), 4.15 (d, *J* = 6.4 Hz, 1H), 3.46-3.44 (m, 2H), 2.78 (s, 3H), 2.27-2.23 (m, 1H), 1.89-1.76 (m, 3H), 1.45-1.41 (m, 1H), 1.00 (t, *J* = 7.6 Hz, 3H). HRMS calculated for C₂₃H₂₆N₈O₃SCl (M + H)⁺: 529.1537; found 529.1545.

(3*aR*,3*bS*,4*aS*,5*R*,5*aS*)-5-(5-azido-7-(propylamino)-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-*N*,2,2-trimethyltetrahydrocyclopropano[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3*b*(3*aH*)-carboxamide (30)

Sodium ascorbate (1.2 mg, 0.006 mmol) and CuSO₄·5H₂O (1 mg, 0.004 mmol) were added to a mixture of compound **8c** (16 mg, 0.031 mmol), NaN₃ (4 mg, 0.061 mmol), L-Proline (1 mg, 0.006 mmol), Na₂CO₃ (1 mg, 0.006 mmol) in ^tBuOH (0.5 mL)-H₂O (0.5 mL) and heated at 100 °C for 1.5 h under microwave condition. The reaction mixture was quenched by addition of dilute ammonium hydroxide solution and was extracted with ethylacetate. Combined organic layer was washed with brine. The solution was dried (sodium sulfate), filtered and concentrated under vacuum. The crude mixture was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 35:1) to give the azido derivative **30** (12.3 mg, 92%) as a glassy syrup. ¹H NMR (CD₃OD, 400 MHz) δ 8.01 (s, 1H), 5.90 (s, 1H), 5.73 (d, *J* = 6.0 Hz, 1H), 4.99 (s, 1H), 4.86 (d, *J* = 5.6 Hz, 1H), 3.27 (t, *J* = 6.8 Hz, 2H), 2.80 (d, *J* = 4.4 Hz, 3H), 2.24-2.20 (m, 1H), 1.74-1.69 (m, 2H), 1.57-1.53 (m, 4H), 1.43 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H), 1.04 (t, *J* = 7.2 Hz, 3H). HRMS calculated for C₂₀H₂₇N₈O₃ (M + H)⁺: 427.2206; found 427.2207.

(3aR,3bS,4aS,5R,5aS)-5-(5-(4-(5-chlorothiophen-2-yl)-1H-1,2,3-triazol-1-yl)-7-(propylamino)-3H-imidazo[4,5-*b*]pyridin-3-yl)-N,2,2-trimethyltetrahydrocyclopropa [3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3aH)-carboxamide (31)

2-chloro-5-ethynylthiophene (6 mg, 0.042 mmol) and TBTA (1 mg, 0.001 mmol) were added to a solution of compound **30** (13mg, 0.03 mmol) in a mixture of *t*-butanol (1 mL) and water (1 mL). Subsequently freshly prepared 1M sodium ascorbate solution (31 μL, 0.03 mmol) followed by 7.5% solution of copper sulfate (51 μL, 0.015 mmol) were added to the reaction mixture and the mixture stirred at room temperature overnight. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 35:1) to give compound **31** (15.4 mg, 89%) as a light yellow powder. ¹H NMR (CD₃OD, 400 MHz) δ 9.01 (s, 1H), 8.14 (s, 1H), 7.60 (d, *J* = 4.0 Hz, 1H), 7.22 (s, 1H), 7.05 (d, *J* = 4.0 Hz, 1H), 5.89 (d, *J* = 7.6 Hz, 1H), 5.07 (s, 1H), 4.91 (d, *J* = 7.2 Hz, 1H), 3.44 (t, *J* = 6.8 Hz, 2H), 2.64 (s, 3H), 2.36-2.33 (m, 1H), 1.82-1.77 (m, 2H), 1.57-1.54 (m, 4H), 1.51 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H), 1.09 (t, *J* = 7.6 Hz, 3H). HRMS calculated for C₂₆H₂₉N₈O₃SClNa (M + Na)⁺: 591.1670; found 591.1675.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(6-(ethylamino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3aH)-carboxylate (33a)

Ethyl amine hydrochloride (0.122g, 1.5 mmol) and triethyl amine (0.5 mL, 2.99 mmol) were added to a solution of compound **32** (0.151g, 0.299 mmol) in anhydrous methanol (5 mL) and the mixture stirred at room temperature overnight. Solvent was evaporated under vacuum and residue was purified on flash silica gel column chromatography (hexane:ethylacetate=1:1) to give compound **33a** (0.135g, 88%) as colorless foamy solid. ¹H NMR (CD₃OD, 400 MHz) δ 7.94 (s, 1H), 5.82 (d, *J* = 7.2 Hz, 1H), 4.94 (s, 1H), 4.81 (d, *J* = 7.2 Hz, 1H), 4.33-4.24 (m, 2H), 3.56 (br s, 2H), 2.25-2.21 (m, 1H), 1.64-1.60 (m, 1H), 1.53 (s, 3H), 1.50 (t, *J* = 5.6 Hz, 1H), 1.29-1.23 (m, 6H). HRMS calculated for C₁₉H₂₅N₅O₄I (M + H)⁺: 514.0948; found 514.0948.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(2-iodo-6-(propylamino)-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3aH)-carboxylate (33b)

Compound **33b** (73%) was prepared from compound **32** following the same method for compound **33a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.94 (s, 1H), 5.82 (d, *J* = 7.2 Hz, 1H), 4.94 (s, 1H), 4.80 (d, *J* = 7.2 Hz, 1H), 4.33-4.22 (m, 2H), 3.49 (br s, 2H), 2.25-2.21 (m, 1H), 1.71-1.61 (m, 3H), 1.53-1.50 (m, 4H), 1.34 (t, *J* = 6.8 Hz, 3H), 1.29 (s, 3H), 1.00 (t, *J* = 7.6 Hz, 3H). HRMS calculated for C₂₀H₂₇N₅O₄I (M + H)⁺: 528.1108; found 528.1104.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(6-(butylamino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (33c)

Compound **33c** (90%) was prepared from compound **32** following the same method for compound **33a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.94 (s, 1H), 5.82 (d, *J* = 6.8 Hz, 1H), 4.94 (s, 1H), 4.80 (d, *J* = 7.2 Hz, 1H), 4.32-4.25 (m, 2H), 3.53 (br s, 2H), 2.25-2.21 (m, 1H), 1.67-1.61 (m, 3H), 1.53-1.49 (m, 4H), 1.47-1.42 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H). HRMS calculated for C₂₁H₂₉N₅O₄I (M + H)⁺: 542.1264; found 542.1267.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(2-iodo-6-(isopropylamino)-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (33d)

Compound **33d** (87%) was prepared from compound **32** following the same method for compound **33a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.94 (s, 1H), 5.82 (d, *J* = 7.2 Hz, 1H), 4.94 (s, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.43-4.25 (m, 2H), 3.48 (br s, 1H), 2.25-2.21 (m, 1H), 1.64-1.61 (m, 1H), 1.53-1.49 (m, 4H), 1.34 (t, *J* = 6.8 Hz, 3H), 1.30-1.28 (m, 9H). HRMS calculated for C₂₀H₂₇N₅O₄I (M + H)⁺: 528.1108; found 528.1102.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(6-(cyclopropylamino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (33e)

Compound **33e** (82%) was prepared from compound **32** following the same method for compound **33a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.95 (s, 1H), 5.83 (d, *J* = 6.8 Hz, 1H), 4.94 (s, 1H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.33-4.25 (m, 2H), 3.05 (br s, 1H), 2.25-2.21 (m, 1H), 1.65-1.61 (m, 1H), 1.53-1.50 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 0.89-0.86 (m, 2H), 0.67-0.62 (m, 2H). HRMS calculated for C₂₀H₂₅N₅O₄I (M + H)⁺: 526.0951; found 526.0952.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(6-(cyclobutylamino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (33f)

Compound **33f** (84%) was prepared from compound **32** following the same method for compound **33a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.95 (s, 1H), 5.82 (d, *J* = 6.4 Hz, 1H), 4.93 (s, 1H), 4.80 (d, *J* = 6.0 Hz, 1H), 4.67 (br s, 1H), 4.33-4.26 (m, 2H), 2.46-2.38 (m, 2H), 2.25-2.20 (m, 1H), 2.10-2.02 (m, 2H), 1.83-1.80 (m, 2H), 1.65-1.61 (m, 1H), 1.53-1.49 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H). HRMS calculated for C₂₁H₂₇N₅O₄I (M + H)⁺: 540.1108; found 540.1099.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(6-((cyclopropylmethyl)amino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (33g)

Compound **33g** (83%) was prepared from compound **32** following the same method for compound **33a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.95 (s, 1H), 5.82 (d, *J* = 6.4 Hz, 1H), 4.94 (s, 1H), 4.80 (d, *J* = 7.2 Hz, 1H), 4.31-4.22 (m, 2H), 3.39 (br s, 2H), 2.26-2.21 (m, 1H), 1.65-1.61 (m, 1H), 1.53-1.50 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 0.98-0.90 (m, 1H), 0.57-0.52 (m, 2H), 0.35-0.32 (m, 2H). HRMS calculated for C₂₁H₂₇N₅O₄I (M + H)⁺: 540.1108; found 540.1116.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(6-((cyclobutylmethyl)amino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (33h)

Compound **33h** (81%) was prepared from compound **32** following the same method for compound **33a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.94 (s, 1H), 5.82 (d, *J* = 7.2 Hz, 1H), 4.93 (s, 1H), 4.80 (d, *J* = 6.4 Hz, 1H), 4.32-4.22 (m, 2H), 3.55 (br s, 2H), 2.25-2.21 (m, 1H), 2.15-2.07 (m, 2H), 1.96-1.80 (m, 4H), 1.72-1.61 (m, 2H), 1.53-1.48 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H). HRMS calculated for C₂₂H₂₉N₅O₄I (M + H)⁺: 554.1264; found 554.1259.

(3aR,3bS,4aS,5R,5aS)-5-(6-(ethylamino)-2-iodo-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (34a)
 40% Methyl amine solution (3 mL) was added to a solution of compound **33a** (0.130, 0.25 mmol) in methanol (3 mL) and the mixture stirred at room temperature for 24 h. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH=35:1) to give compound **34a** (0.101g, 80%) as a white powder. ¹H NMR (CD₃OD, 400 MHz) δ 7.96(s, 1H), 5.72 (d, *J* = 6.0 Hz, 1H), 4.92 (s, 1H), 4.83 (d, *J* = 5.6 Hz, 1H), 3.56 (br s, 2H), 2.90 (s, 3H), 2.15-2.11 (m, 1H), 1.53-1.49 (m, 4H), 1.38 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). HRMS calculated for C₁₈H₂₄N₆O₃I (M + H)⁺: 499.0949; found 499.0952.

(3aR,3bS,4aS,5R,5aS)-5-(2-iodo-6-(propylamino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (34b)

Compound **34b** (75%) was prepared from compound **33b** following the same method for compound **34a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.96 (s, 1H), 5.73 (d, *J* = 6.0 Hz, 1H), 4.93 (s, 1H), 4.84 (d, *J* = 6.0 Hz, 1H), 3.49 (br s, 2H), 2.90 (s, 3H), 2.15-2.11 (m, 1H), 1.73-1.66 (m, 2H), 1.54-1.49 (m, 4H), 1.39 (t, *J* = 5.6 Hz, 1H), 1.30 (s, 3H), 1.00 (t, *J* = 7.6 Hz, 3H). HRMS calculated for C₁₉H₂₆N₆O₃I (M + H)⁺: 513.1111; found 513.1114.

(3aR,3bS,4aS,5R,5aS)-5-(6-(butylamino)-2-iodo-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (34c)

Compound **34c** (68%) was prepared from compound **33c** following the same method for compound **34a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.96 (s, 1H), 5.72 (d, *J* = 7.2 Hz, 1H), 4.92 (s, 1H), 4.84 (d, *J* = 7.6 Hz, 1H), 3.53 (br s, 2H), 2.90 (s, 3H), 2.14-2.11 (m, 1H), 1.66-1.61 (m, 2H), 1.54-1.47 (m, 4H), 1.45-1.38 (m, 3H), 1.30 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H). HRMS calculated for C₂₀H₂₈N₆O₃I (M + H)⁺: 527.1268; found 527.1277.

(3aR,3bS,4aS,5R,5aS)-5-(2-iodo-6-(isopropylamino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (34d)

Compound **34d** (76%) was prepared from compound **33d** following the same method for compound **34a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.96 (s, 1H), 5.71 (d, *J* = 6.8 Hz, 1H), 4.92 (s, 1H), 4.80 (d, *J* = 5.2 Hz, 1H), 4.37 (br s, 1H), 2.90 (s, 3H), 2.14-2.10 (m, 1H), 1.54-1.49 (m, 4H), 1.39 (t, *J* = 5.2 Hz, 1H), 1.30-1.28 (m, 9H). HRMS calculated for C₁₉H₂₆N₆O₃I (M + H)⁺: 513.1111; found 513.1118.

(3aR,3bS,4aS,5R,5aS)-5-(6-(cyclopropylamino)-2-iodo-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (34e)

Compound **34e** (74%) was prepared from compound **33e** following the same method for compound **34a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.97 (s, 1H), 5.72 (d, *J* = 7.2 Hz, 1H), 4.93 (s, 1H), 4.84 (d, *J* = 7.2 Hz, 1H), 3.05 (br s, 1H), 2.90 (s, 3H), 2.14-2.11 (m, 1H), 1.54-1.49 (m, 4H), 1.39 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H), 0.89-0.84 (m, 2H), 0.68-0.59 (m, 2H). HRMS calculated for C₁₉H₂₄N₆O₃I (M + H)⁺: 511.0955; found 511.0956.

(3aR,3bS,4aS,5R,5aS)-5-(6-(cyclobutylamino)-2-iodo-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (34f)

Compound **34f** (72%) was prepared from compound **33f** following the same method for compound **34a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.97 (s, 1H), 5.71 (d, *J* = 6.4 Hz, 1H), 4.92 (s, 1H), 4.83 (d, *J*

= 6.0 Hz, 1H), 4.66 (br s, 1H), 2.89 (s, 3H), 2.45-2.38 (m, 2H), 2.14-2.02 (m, 3H), 1.82-1.78 (m, 2H), 1.53-1.48 (m, 4H), 1.38 (t, $J = 5.2$ Hz, 1H), 1.30 (s, 3H). HRMS calculated for $C_{20}H_{26}N_6O_3I$ ($M + H$)⁺: 525.1111; found 525.1101.

(3aR,3bS,4aS,5R,5aS)-5-(6-((cyclopropylmethyl)amino)-2-iodo-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (34g)

Compound **34g** (74%) was prepared from compound **33g** following the same method for compound **34a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.97 (s, 1H), 5.72 (d, $J = 6.8$ Hz, 1H), 4.93 (s, 1H), 4.84 (d, $J = 7.2$ Hz, 1H), 3.38 (br s, 2H), 2.90 (s, 3H), 2.15-2.11 (m, 1H), 1.54-1.49 (m, 4H), 1.39 (t, $J = 5.2$ Hz, 1H), 1.30 (s, 3H), 1.18-1.10 (m, 1H), 0.57-0.52 (m, 2H), 0.35-0.31 (m, 2H). HRMS calculated for $C_{20}H_{26}N_6O_3I$ ($M + H$)⁺: 525.1111; found 525.1107.

(3aR,3bS,4aS,5R,5aS)-5-(6-((cyclobutylmethyl)amino)-2-iodo-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (34h)

Compound **34h** (76%) was prepared from compound **33h** following the same method for compound **34a**. ¹H NMR (CD₃OD, 400 MHz) δ 7.96 (s, 1H), 5.72 (d, $J = 6.4$ Hz, 1H), 4.92 (s, 1H), 4.83 (d, $J = 6.0$ Hz, 1H), 3.55 (br s, 2H), 2.90 (s, 3H), 2.70-2.62 (m, 1H), 2.15-2.11 (m, 3H), 1.96-1.90 (m, 2H), 1.87-1.80 (m, 2H), 1.54-1.49 (m, 4H), 1.39 (t, $J = 5.2$ Hz, 1H), 1.30 (s, 3H). HRMS calculated for $C_{21}H_{28}N_6O_3I$ ($M + H$)⁺: 539.12621; found 539.12628.

(3aR,3bS,4aS,5R,5aS)-5-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(ethylamino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (35a)

PdCl₂(PPh₃)₂ (9.3 mg, 0.013 mmol), CuI (1.27 mg, 0.006 mmol), 2-chloro-5-ethynylthiophene (57 mg, 0.399 mmol) and triethylamine (0.09 mL, 0.66 mmol) were added to a solution of compound **34a** (33.2 mg, 0.066 mmol) in anhydrous DMF (1.2 mL), and the mixture stirred at room temperature overnight. Solvent was evaporated under vacuum and the residue purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 35:1) to give compound **35a** (25 mg, 73%) as a yellow syrup. ¹H NMR (CD₃OD, 400 MHz) δ 8.14 (s, 1H), 7.37 (d, $J = 4.0$ Hz, 1H), 7.03 (d, $J = 4.0$ Hz, 1H), 5.79 (d, $J = 6.0$ Hz, 1H), 5.01 (s, 1H), 4.85 (d, $J = 5.6$ Hz, 1H), 3.65 (br s, 2H), 2.82 (s, 3H), 2.15-2.13 (m, 1H), 1.57-1.53 (m, 4H), 1.42 (t, $J = 5.2$ Hz, 1H), 1.33-1.29 (m, 6H). HRMS calculated for $C_{24}H_{26}N_6O_3SCl$ ($M + H$)⁺: 513.1476; found 513.1476.

(3aR,3bS,4aS,5R,5aS)-5-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(propylamino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (35b)

Compound **35b** (90%) was prepared from compound **34b** following the same method for compound **35a**. ¹H NMR (CD₃OD, 400 MHz) δ 8.15 (s, 1H), 7.38 (d, $J = 4.0$ Hz, 1H), 7.03 (d, $J = 4.0$ Hz, 1H), 5.78 (d, $J = 7.2$ Hz, 1H), 5.02 (s, 1H), 4.85 (d, $J = 6.0$ Hz, 1H), 3.58 (br s, 2H), 2.82 (s, 3H), 2.17-2.13 (m, 1H), 1.75-1.70 (m, 2H), 1.57-1.53 (m, 4H), 1.42 (t, $J = 5.2$ Hz, 1H), 1.30 (s, 3H), 1.03 (t, $J = 7.6$ Hz, 3H). HRMS calculated for $C_{25}H_{28}N_6O_3SCl$ ($M + H$)⁺: 527.1632; found 527.1632.

(3aR,3bS,4aS,5R,5aS)-5-(6-(butylamino)-2-((5-chlorothiophen-2-yl)ethynyl)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (35c)

Compound **35c** (93%) was prepared from compound **34c** following the same method for compound **35a**. ¹H NMR (CD₃OD, 400 MHz) δ 8.14 (s, 1H), 7.38 (d, *J* = 4.0 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 5.78 (d, *J* = 6.8 Hz, 1H), 5.02 (s, 1H), 4.85 (d, *J* = 7.2 Hz, 1H), 3.61 (br s, 2H), 2.82 (s, 3H), 2.17-2.13 (m, 1H), 1.71-1.67 (m, 2H), 1.55-1.47 (m, 4H), 1.45-1.41 (m, 3H), 1.30 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H). HRMS calculated for C₂₆H₃₀N₆O₃SCI (M + H)⁺: 541.1789; found 541.1796.

(3aR,3bS,4aS,5R,5aS)-5-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(isopropylamino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3aH)-carboxamide (35d)

Compound **35d** (95%) was prepared from compound **34d** following the same method for compound **35a**. ¹H NMR (CD₃OD, 400 MHz) δ 8.15 (s, 1H), 7.37 (d, *J* = 4.0 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 5.78 (d, *J* = 6.0 Hz, 1H), 5.02 (s, 1H), 4.85 (d, *J* = 5.2 Hz, 1H), 4.52 (br s, 1H), 2.82 (s, 3H), 2.17-2.12 (m, 1H), 1.57-1.53 (m, 4H), 1.42 (t, *J* = 5.2 Hz, 1H), 1.33 (s, 3H), 1.30 (d, *J* = 2.4 Hz, 6H). HRMS calculated for C₂₅H₂₈N₆O₃SCI (M + H)⁺: 527.1632; found 527.1636.

(3aR,3bS,4aS,5R,5aS)-5-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(cyclopropylamino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3aH)-carboxamide (35e)

Compound **35e** (96%) was prepared from compound **34e** following the same method for compound **35a**. ¹H NMR (CD₃OD, 400 MHz) δ 8.16 (s, 1H), 7.39 (d, *J* = 4.0 Hz, 1H), 7.04 (d, *J* = 4.0 Hz, 1H), 5.79 (d, *J* = 7.6 Hz, 1H), 5.02 (s, 1H), 4.86 (d, *J* = 7.2 Hz, 1H), 3.06 (br s, 1H), 2.82 (s, 3H), 2.17-2.13 (m, 1H), 1.58-1.52 (m, 4H), 1.43 (t, *J* = 5.2 Hz, 1H), 1.31 (s, 3H), 0.96-0.89 (m, 2H), 0.69-0.64 (m, 2H). HRMS calculated for C₂₅H₂₆N₆O₃SCI (M + H)⁺: 525.1476; found 525.1481.

(3aR,3bS,4aS,5R,5aS)-5-(2-((5-chlorothiophen-2-yl)ethynyl)-6-(cyclobutylamino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3aH)-carboxamide (35f)

Compound **35f** (83%) was prepared from compound **34f** following the same method for compound **35a**. ¹H NMR (CD₃OD, 400 MHz) δ 8.14 (s, 1H), 7.38 (d, *J* = 4.0 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 5.78 (d, *J* = 7.2 Hz, 1H), 5.01 (s, 1H), 4.84 (d, *J* = 6.0 Hz, 1H), 4.79 (br s, 1H), 2.82 (s, 3H), 2.49-2.44 (m, 2H), 2.16-2.08 (m, 3H), 1.86-1.80 (m, 2H), 1.57-1.53 (m, 4H), 1.42 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H). HRMS calculated for C₂₆H₂₈N₆O₃SCI (M + H)⁺: 539.1632; found 539.1622.

(3aR,3bS,4aS,5R,5aS)-5-(2-((5-chlorothiophen-2-yl)ethynyl)-6-((cyclopropylmethyl)amino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3aH)-carboxamide (35g)

Compound **35g** (81%) was prepared from compound **34g** following the same method for compound **35a**. ¹H NMR (CD₃OD, 400 MHz) δ 8.16 (s, 1H), 7.37 (d, *J* = 4.0 Hz, 1H), 7.02 (d, *J* = 4.0 Hz, 1H), 5.78 (d, *J* = 6.8 Hz, 1H), 5.02 (s, 1H), 4.88 (d, *J* = 7.2 Hz, 1H), 3.47 (br s, 2H), 2.82 (s, 3H), 2.17-2.13 (m, 1H), 1.57-1.53 (m, 4H), 1.42 (t, *J* = 5.2 Hz, 1H), 1.31 (s, 3H), 1.21-1.14 (m, 1H), 0.59-0.54 (m, 2H), 0.36-0.32 (m, 2H). HRMS calculated for C₂₆H₂₈N₆O₃SCI (M + H)⁺: 539.1632; found 539.1625.

(3aR,3bS,4aS,5R,5aS)-5-(2-((5-chlorothiophen-2-yl)ethynyl)-6-((cyclobutylmethyl)amino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3aH)-carboxamide (35h)

Compound **35h** (97%) was prepared from compound **34h** following the same method for compound **35a**. ¹H NMR (CD₃OD, 400 MHz) δ 8.13 (s, 1H), 7.38 (d, *J* = 4.0 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 5.78 (d, *J* = 6.8 Hz, 1H), 5.01 (s, 1H), 4.85 (d, *J* = 6.0 Hz, 1H), 3.64 (br s, 2H), 2.82 (s, 3H), 2.75-2.67 (m, 1H), 2.16-2.11 (m, 3H), 1.99-1.92 (m, 2H), 1.89-1.83 (m, 2H), 1.56-1.53 (m, 4H), 1.42 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H). HRMS calculated for C₂₇H₃₀N₆O₃SCl (M + H)⁺: 553.1789; found 553.1795.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-((cyclopropylmethyl)amino)-2-iodo-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (36g)

Compound **36g** (91%) was prepared from compound **34g** following the same method for compound **11**. ¹H NMR (CD₃OD, 400 MHz) δ 7.97 (s, 1H), 5.11 (d, *J* = 6.8 Hz, 1H), 4.80 (s, 1H), 4.00 (d, *J* = 5.2 Hz, 1H), 3.40 (br s, 2H), 2.90 (s, 3H), 2.06-2.02 (m, 1H), 1.80 (t, *J* = 5.2 Hz, 1H), 1.38-1.34 (m, 1H), 1.18-1.10 (m, 1H), 0.56-0.53 (m, 2H), 0.35-0.32 (m, 2H). HRMS calculated for C₁₇H₂₂N₆O₃I (M + H)⁺: 485.0798; found 485.0793.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-((cyclobutylmethyl)amino)-2-iodo-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (36h)

Compound **36h** (93%) was prepared from compound **34h** following the same method for compound **11**. ¹H NMR (CD₃OD, 400 MHz) δ 7.97 (s, 1H), 5.11 (d, *J* = 6.8 Hz, 1H), 4.80 (s, 1H), 4.00 (d, *J* = 6.4 Hz, 1H), 3.56 (br s, 2H), 2.90 (s, 3H), 2.70-2.65 (m, 1H), 2.13-2.07 (m, 2H), 2.05-2.02 (m, 1H), 1.97-1.91 (m, 2H), 1.87-1.79 (m, 3H), 1.38-1.34 (m, 1H). HRMS calculated for C₁₈H₂₄N₆O₃I (M + H)⁺: 499.0955; found 499.0948.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-azido-6-((cyclopropylmethyl)amino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (37g)

Sodium ascorbate (6.5 mg, 0.032 mmol) and CuSO₄·5H₂O (4.1 mg, 0.016 mmol) were added to a mixture of compound **36g** (80 mg, 0.165 mmol), NaN₃ (21.5 mg, 0.33 mmol), L-Proline (3.8 mg, 0.033 mmol), Na₂CO₃ (3.5 mg, 0.033 mmol) in ^tBuOH (1.2 mL)-H₂O (1.2 mL) and heated at 65 °C overnight. The reaction mixture was quenched by addition of dilute ammonium hydroxide solution and was extracted with ethylacetate (5 times). Combined organic layer was washed with brine. The solution was dried (sodium sulfate), filtered and concentrated under vacuum. The crude mixture was purified on flash silica gel column chromatography (CH₂Cl₂:MeOH = 25:1) to give the azido derivative **37g** (51 mg, 78%) as a syrup. ¹H NMR (CD₃OD, 400 MHz) δ 7.97 (s, 1H), 5.03 (d, *J* = 6.8 Hz, 1H), 4.76 (s, 1H), 4.01 (d, *J* = 5.6 Hz, 1H), 3.44 (d, *J* = 5.6 Hz, 2H), 2.86 (s, 3H), 2.07-2.04 (m, 1H), 1.81 (t, *J* = 5.2 Hz, 1H), 1.38-1.34 (m, 1H), 1.20-1.15 (m, 1H), 0.59-0.54 (m, 2H), 0.36-0.32 (m, 2H). HRMS calculated for C₁₇H₂₂N₉O₃ (M + H)⁺: 400.1846; found 400.1844.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-azido-6-((cyclobutylmethyl)amino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (37h)

Compound **37h** (81%) was prepared from compound **36h** following the same method for compound **37g**. ¹H NMR (CD₃OD, 400 MHz) δ 7.96 (s, 1H), 5.03 (d, *J* = 6.8 Hz, 1H), 4.76 (s, 1H), 4.00 (d, *J* = 5.2 Hz, 1H), 3.61 (d, *J* = 6.4, 2H), 2.86 (s, 3H), 2.73-2.66 (m, 1H), 2.14-2.10 (m, 2H), 2.07-2.04 (m, 1H), 1.97-1.91 (m, 2H), 1.88-1.79 (m, 3H), 1.38-1.34 (m, 1H). HRMS calculated for C₁₈H₂₄N₉O₃ (M + H)⁺: 414.2002; found 414.2003.

7-Chloro-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridin-5-amine (39)

PMBCl (0.56 mL, 4.15 mmol) and TBAF (4.15 ml of 1M solution in THF, 4.15 mmol) were added to a solution of compound **38** (350 mg, 2.07, mmol) in DMF (10 mL) and the mixture stirred for 1hr at room temperature. After completion of reaction, water was added into it, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried (sodium sulfate), filtered and concentrated under vacuum. The residue was purified on flash silica gel column chromatography (hexane:ethyl acetate = 1:2) to give compound **39** (306 mg, 51%) as a syrup. ¹H NMR (CD₃OD, 400 MHz) δ 7.97 (s, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 5.28 (s, 2H), 3.76 (s, 3H). HRMS calculated for C₁₄H₁₃N₄OCl (M + H)⁺: 288.7350; found 288.7346.

7-Chloro-5-iodo-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridine (**40**)

CuI (221 mg, 1.16 mmol), iodine (268 mg, 1.05 mmol), CH₂I₂ (0.85 mL, 10.5 mmol) and isoamyl nitrite (0.42 mL, 3.17 mmol) were added to a solution of compound **39** (306 mg, 1.05 mmol) in dry THF (15 mL) and the mixture refluxed at 80 °C for 1 h. Water was added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated sodium bisulfite solution followed by brine. The solution was dried (sodium sulfate), filtered and evaporated under vacuum. The residue was purified on flash silica gel column chromatography (hexane:ethyl acetate = 1:1) to give compound **40** (407 mg, 96%) as a colorless powder. ¹H NMR (CD₃OD, 500 MHz) δ 8.41 (s, 1H), 7.80 (s, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.43 (s, 2H), 2.85 (s, 3H). HRMS calculated for C₁₄H₁₂N₃OClI (M + H)⁺: 399.9714; found 399.9713.

Table of physicochemical properties.

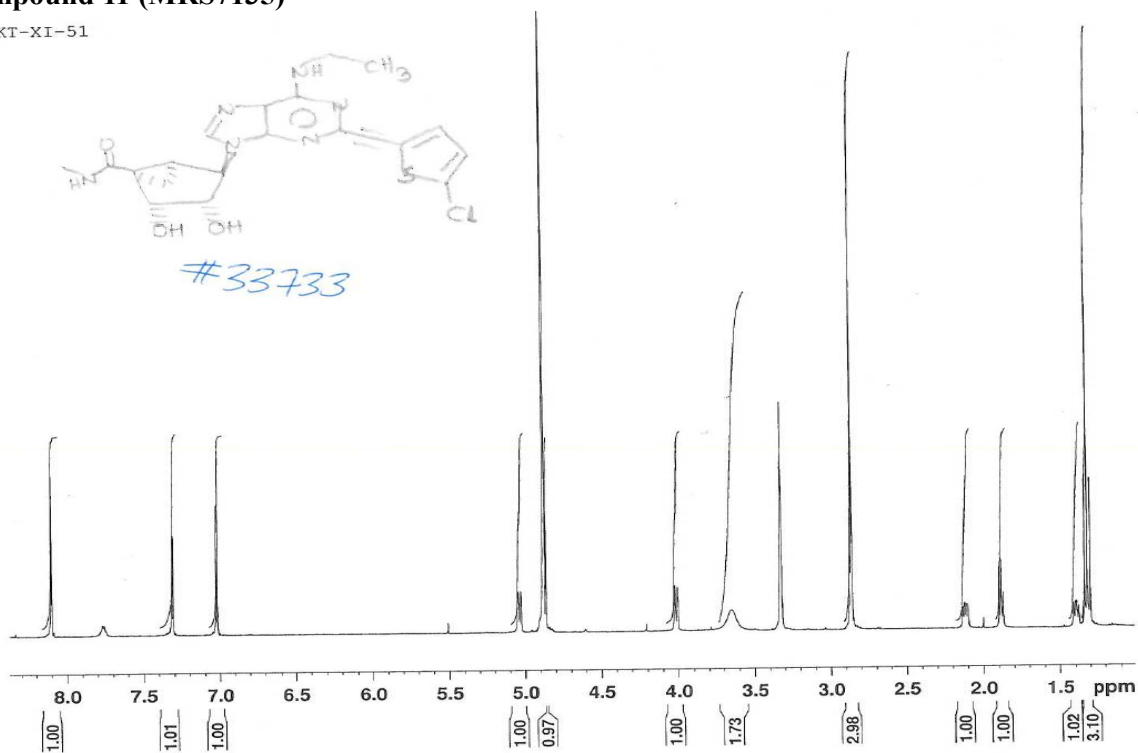
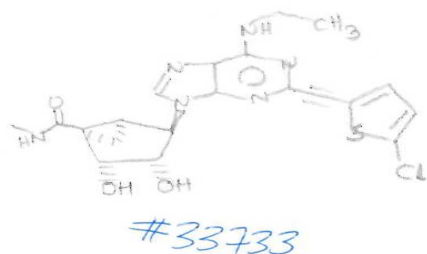
Compound	MW (D)	cLogP ^a	tPSA ^a (Å ²)
10 ^b	459	2.17	122
11 ^b	473	2.71	122
12	487	3.23	122
13	501	3.76	122
14	487	3.01	122
15	485	2.76	122
16	499	3.09	122
17	499	3.15	122
18	513	3.71	122
19	458	2.96	110
20	472	3.49	110
27 ^b	542	3.10	150
28	612	4.35	150

^aCalculated using ChemBioDraw, v. 14.0.

^bData from Tosh et al., 2014, 2015.^{5,6}

Representative ¹H-NMR and Mass Spectra Compound 11 (MRS7135)

DKT-XI-51



Elemental Composition Report

Single Mass Analysis

Tolerance = 10.0 mDa / DBE: min = -50.0, max = 500.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

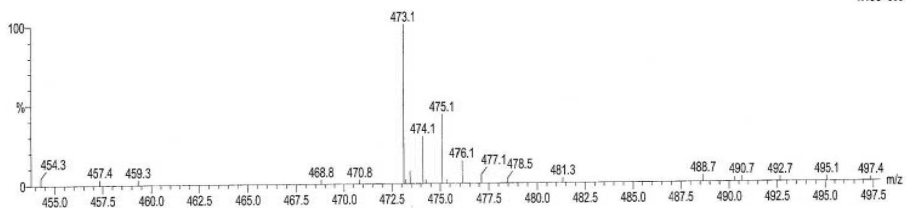
149 formula(e) evaluated with 4 results within limits (up to 50 closest results for each mass)

Elements Used:

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21-Aug-2014

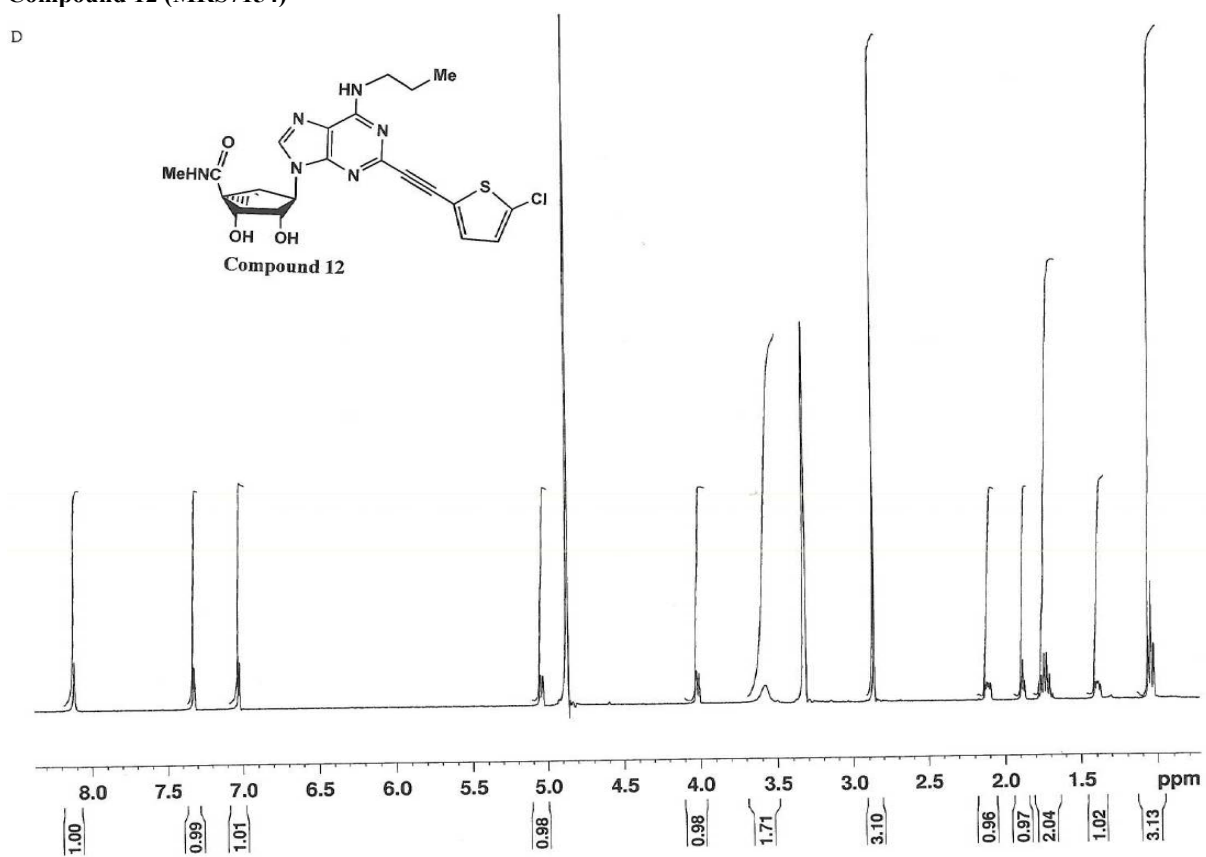
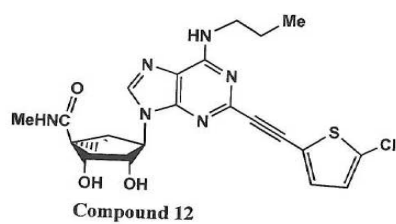
dkt-21aug14-xi-51 88 (1.627) Cn (Cen,11, 50.00, Ar); Sm (SG, 3x5.00); Sb (12.5.00); Cm (88-104x3.000)

TOF MS ES+
1.19e+003

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
473.1166	473.1163	0.3	0.6	13.5	1.5	C21 H22 N6 O3 S Cl ✓
	473.1128	3.8	8.0	-8.5	97.1	C3 H30 N6 O16 S Cl
	473.1221	-5.5	-11.6	4.5	19.8	C14 H26 N6 O8 S Cl
	473.1069	9.7	20.5	0.5	41.8	C10 H26 N6 O11 S Cl

Compound 12 (MRS7154)

D



Single Mass Analysis

Tolerance = 10.0 mDa / DBE: min = -50.0, max = 500.0
 Element prediction: Off
 Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

199 formula(e) evaluated with 4 results within limits (up to 50 closest results for each mass)

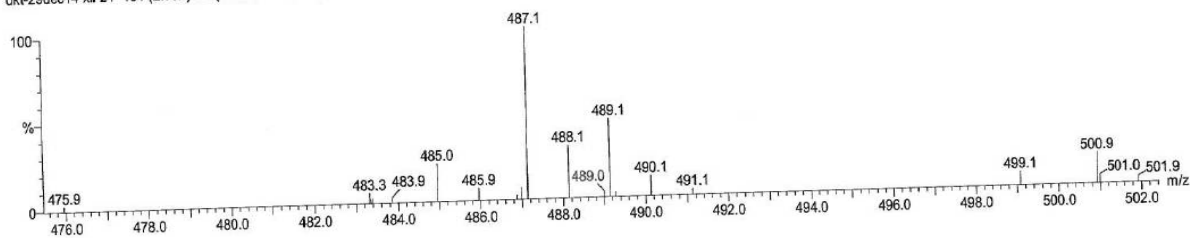
Elements Used:

C: 0-100 H: 0-200 N: 6-6 O: 0-30 S: 1-1 Cl: 1-1

29-Dec-2014

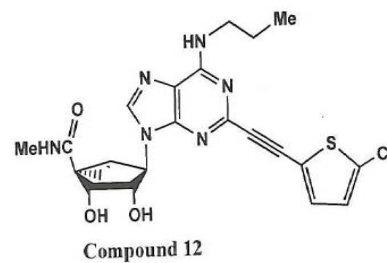
dkt-29dec14-xii-21 151 (2.792) Cn (Cen,5, 50.00, Ar); Sm (SG, 2x3.00); Sb (12,5.00)

TOF MS ES+
1.45e+003



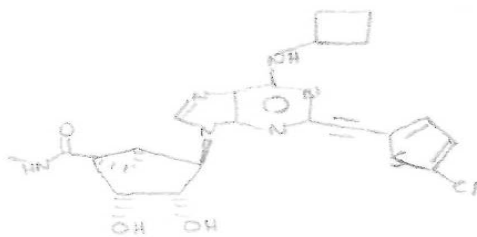
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	487.1284	2.8	5.7	-8.5	113.1	C4 H32 N6 O16 S Cl
	487.1378	-6.6	-13.5	4.5	23.9	C15 H28 N6 O8 S Cl
	487.1225	8.7	17.9	0.5	48.5	C11 H28 N6 O11 S Cl

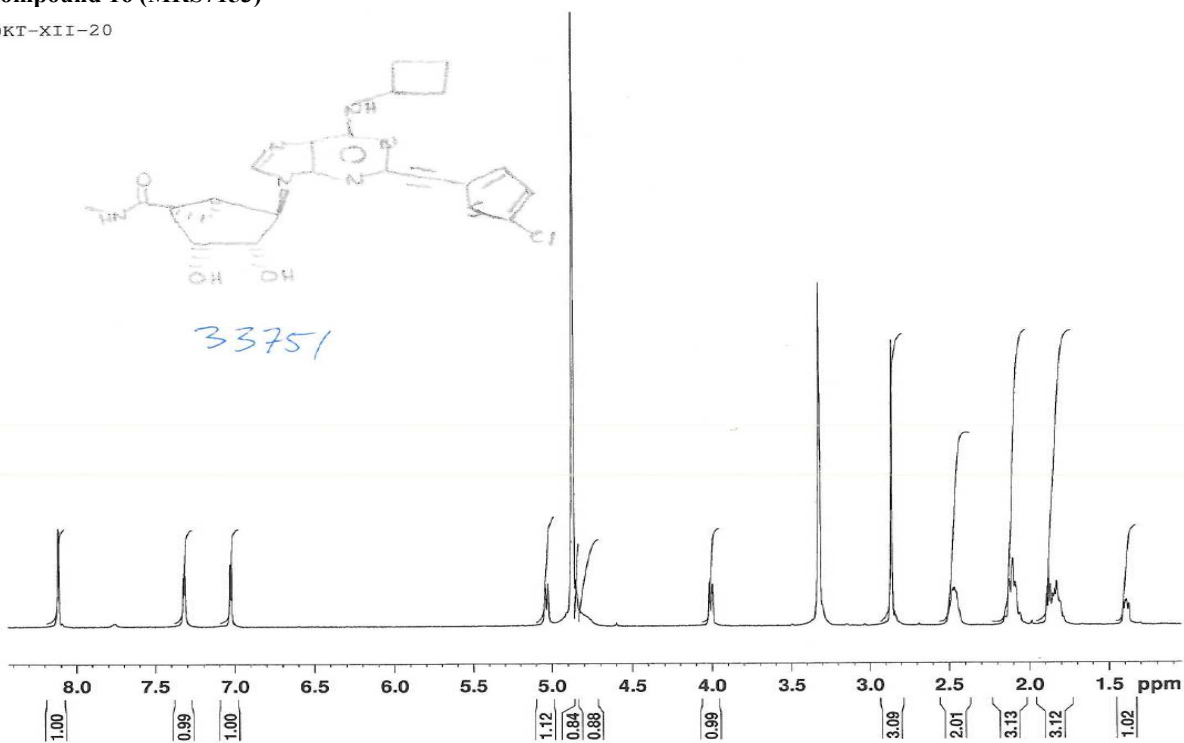


Compound 16 (MRS7153)

DKT-XII-20



33751



Monoisotopic Mass, Even Electron Ions

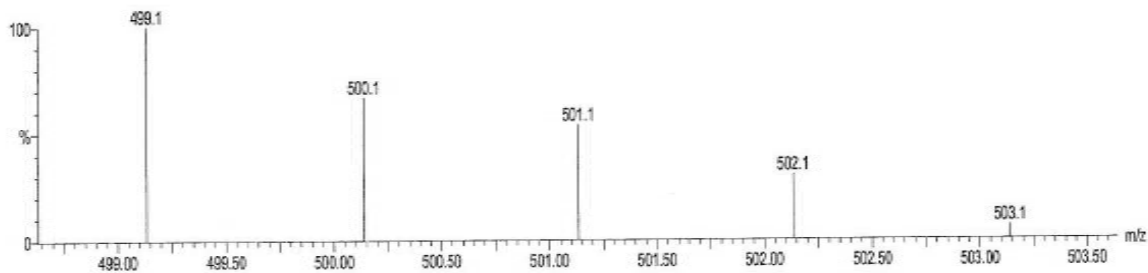
208 formula(e) evaluated with 4 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-100 H: 0-200 N: 6-6 O: 0-30 S: 1-1 Cl: 1-1

29-Dec-2014

dkt-29dec14-xii-20 38 (0.703) Cn (Cen, 5, 50.0), Ar; Sm (SG, 2x3.00); Sb (12, 5.00); Sm (SG, 3x5.00); Cm (38-85x3.000)

TOF MS ES+
2.16e+003

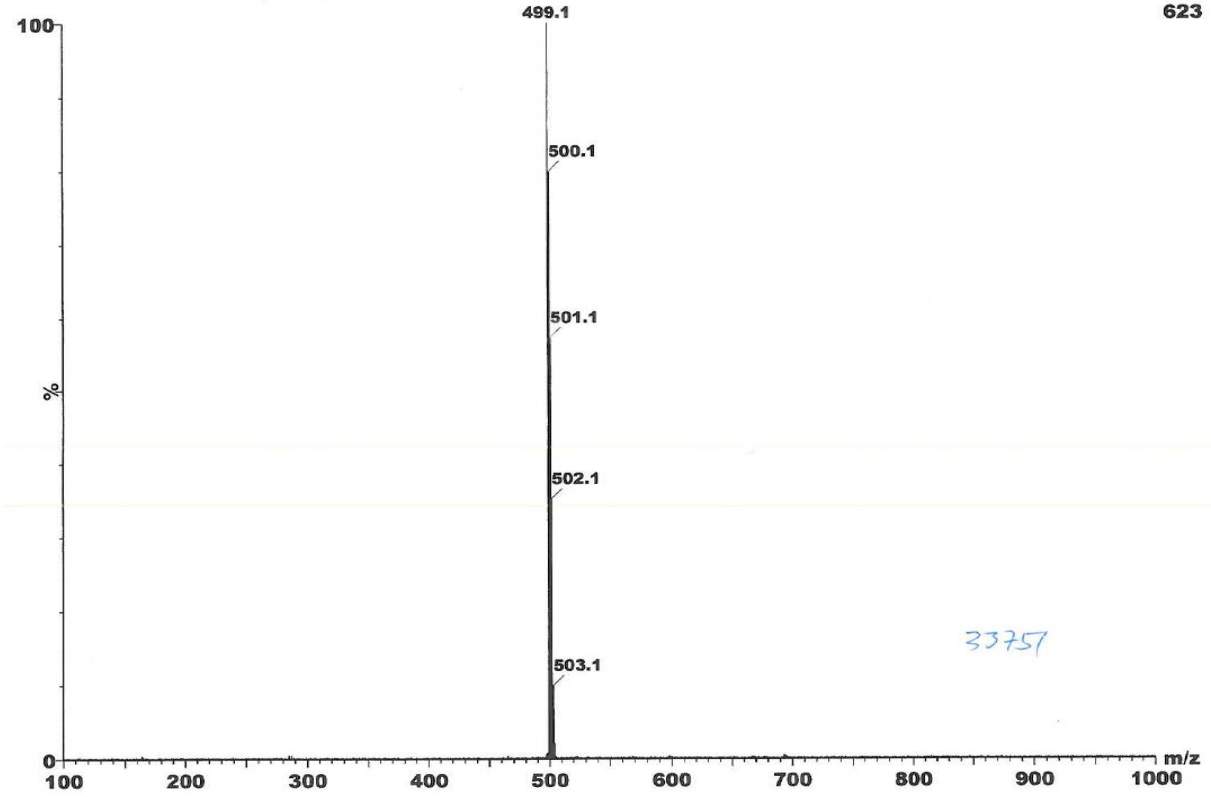
Minimum: -50.0
 Maximum: 10.0 10.0 500.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
499.1322	499.1319	0.3	0.6	14.5	210.5	C23 H24 N6 O3 S Cl ✓
	499.1284	3.8	7.6	-7.5	537.3	C5 H32 N6 O16 S Cl
	499.1378	-5.6	-11.2	5.5	319.6	C16 H28 N6 O8 S Cl
	499.1225	9.7	19.4	1.5	398.1	C12 H28 N6 O11 S Cl

29-Dec-2014

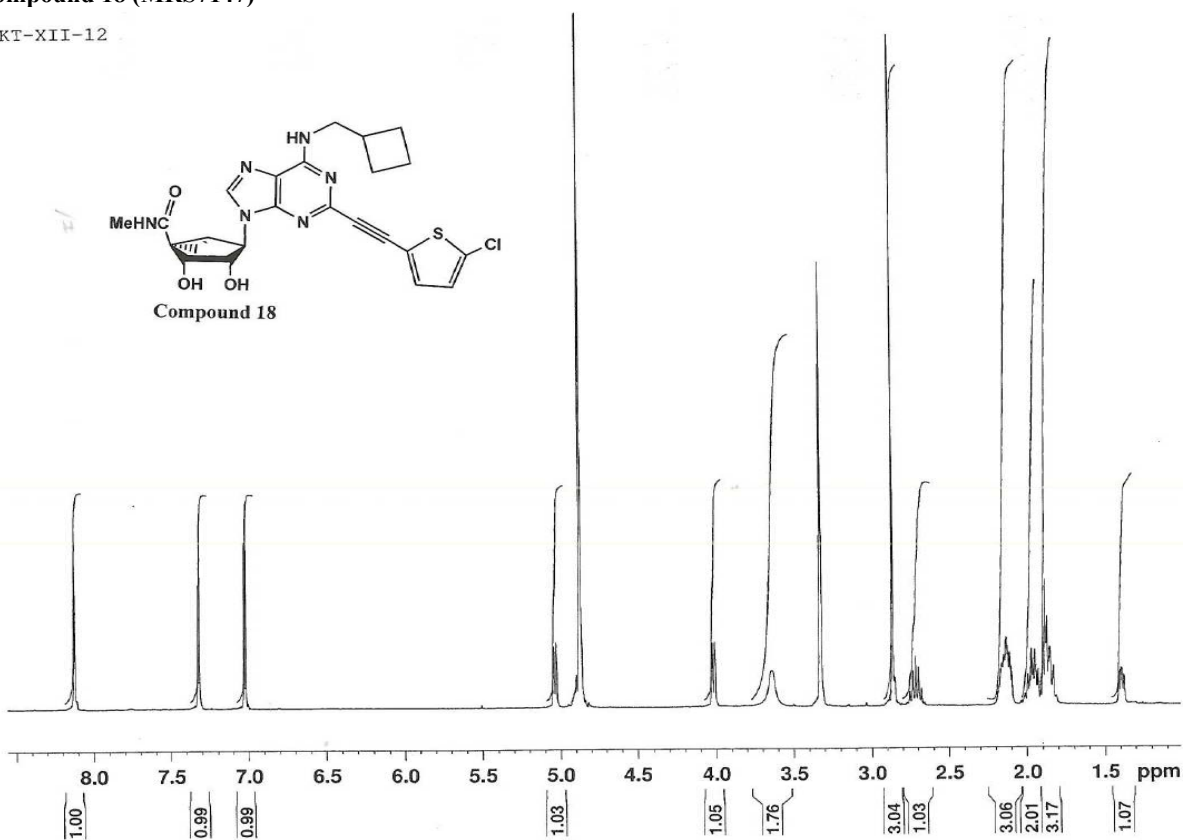
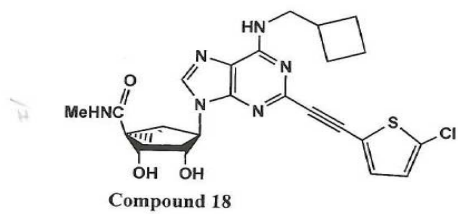
dkf-29dec14-xii-20 37 (0.684) Sm (SG, 3x5.00); Cm (37-82x3.000)

TOF MS ES+
623



Compound 18 (MRS7147)

DKT-XII-12



Single Mass Analysis

Tolerance = 25.0 mDa / DBE: min = -50.0, max = 500.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

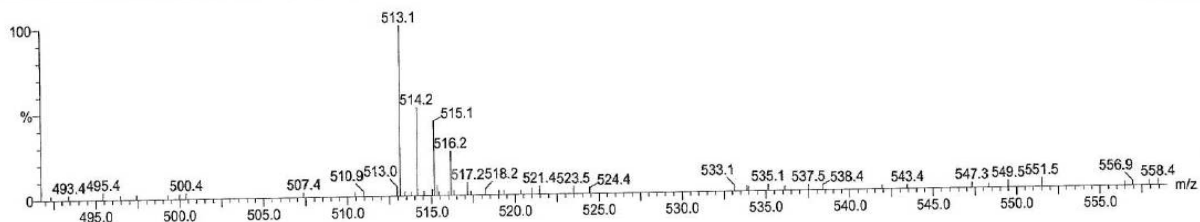
148 formula(e) evaluated with 7 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-100 H: 0-200 N: 6-6 O: 0-12 S: 1-1 Cl: 1-1

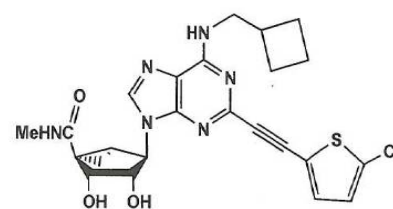
16-Dec-2014

dkt-16dec14-xii-12 79 (1.461) Cn (Cen,5, 50.00, Ar); Sm (SG, 3x5.00); Sb (12.5.00)

TOF MS ES+
1.14e+003

Minimum: -50.0
Maximum: 500.0

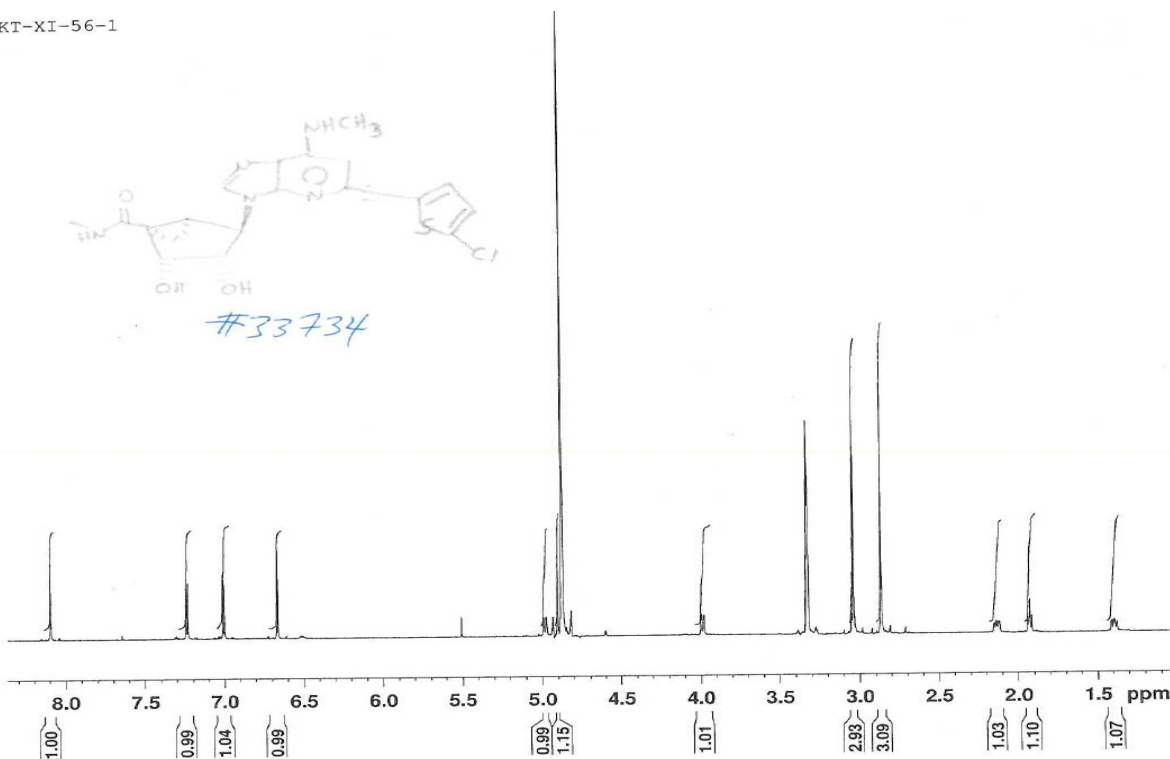
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
513.1470	513.1476	-0.6	-1.2	14.5	44.3	C24 H26 N6 O3 S Cl
	513.1534	-6.4	-12.5	5.5	86.2	C17 H30 N6 O8 S Cl
	513.1382	8.8	17.1	1.5	118.5	C13 H30 N6 O11 S Cl
	513.1323	14.7	28.6	10.5	72.0	C20 H26 N6 O6 S Cl
	513.1628	-15.8	-30.8	18.5	32.6	C28 H26 N6 S Cl
	513.1264	20.6	40.1	19.5	42.4	C27 H22 N6 O S Cl
	513.1687	-21.7	-42.3	9.5	69.8	C21 H30 N6 O5 S Cl



Compound 18

Compound 19 (MRS7140)

DKT-XI-56-1



Elemental Composition Report

Single Mass Analysis

Tolerance = 20.0 mDa / DBE min = -50.0, max = 500.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

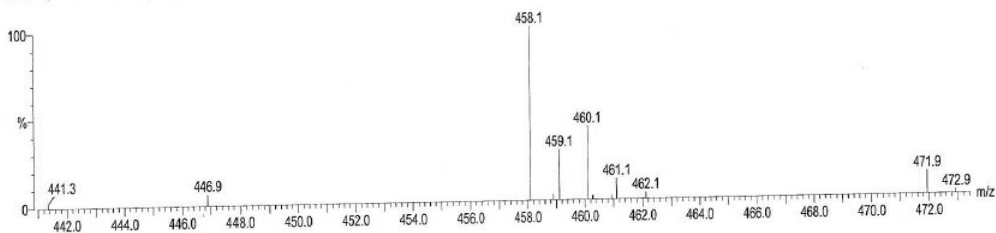
178 formula(e) evaluated with 8 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-100 H: 0-125 N: 5-5 O: 0-24 S: 1-1 Cl: 1-1

03-Sep-2014

dkT-03sep14-xi-56 89 (1.645) Cn (Cen,11, 50.00, Ar); Sm (SG, 3x5.00); Sb (12.5.00)

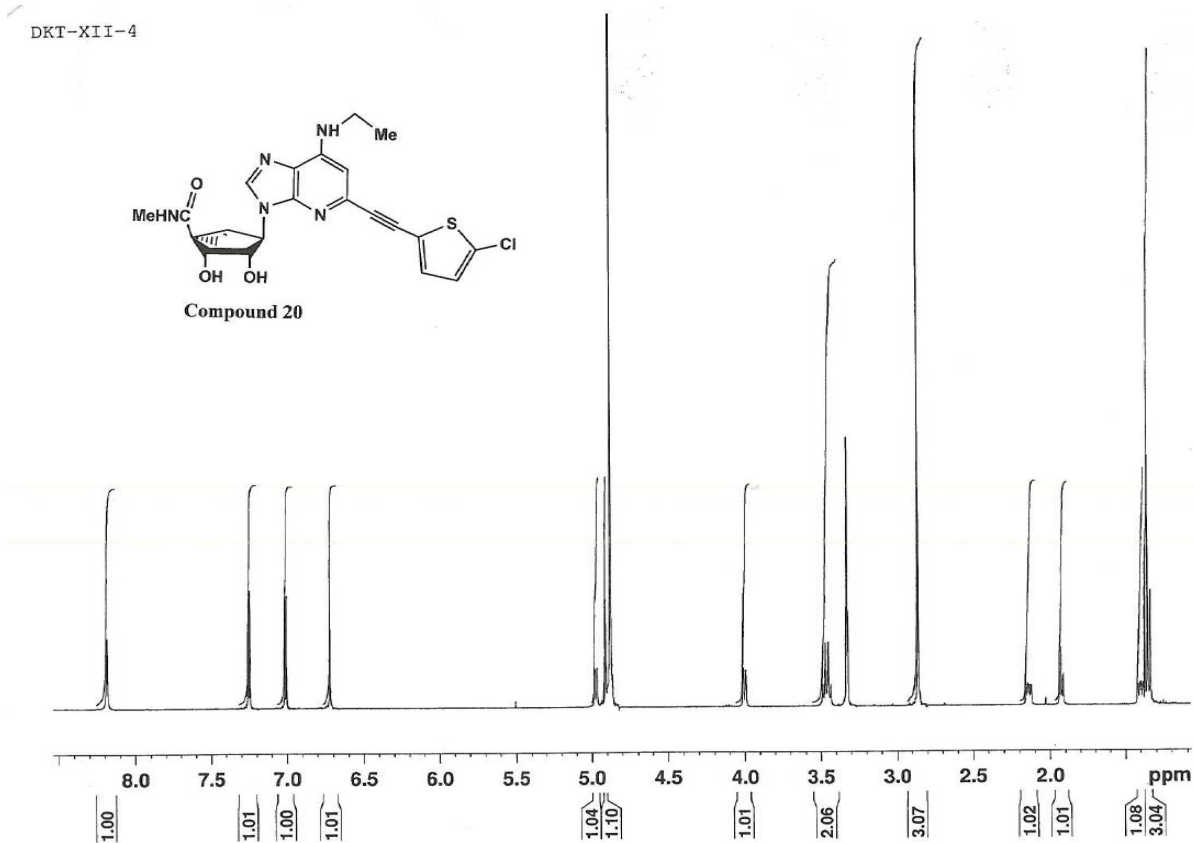
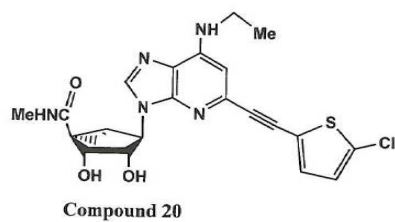
TOF MS ES+
2.08e+003

Minimum: -50.0
Maximum: 20.0 10.0 500.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
458.1055	458.1054	0.1	0.2	13.5	1.7	C21 H21 N5 O3 S Cl
	458.1019	3.6	7.9	-8.5	168.1	C3 H29 N5 O16 S Cl
	458.1112	-5.7	-12.4	4.5	32.5	C14 H25 N5 O8 S Cl
	458.0960	9.5	20.7	0.5	72.0	C10 H25 N5 O11 S Cl
	458.1171	-11.6	-25.3	-4.5	110.2	C7 H29 N5 O13 S Cl
	458.1206	-15.1	-33.0	17.5	12.1	C25 H21 N5 S Cl
	458.0901	15.4	33.6	9.5	24.9	C17 H21 N5 O6 S Cl
	458.1230	-17.5	-38.2	-13.5	236.3	H33 N5 O18 S Cl

Compound 20 (MRS7144)

DKT-XII-4



Single Mass Analysis

Tolerance = 10.0 mDa / DBE: min = -50.0, max = 500.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

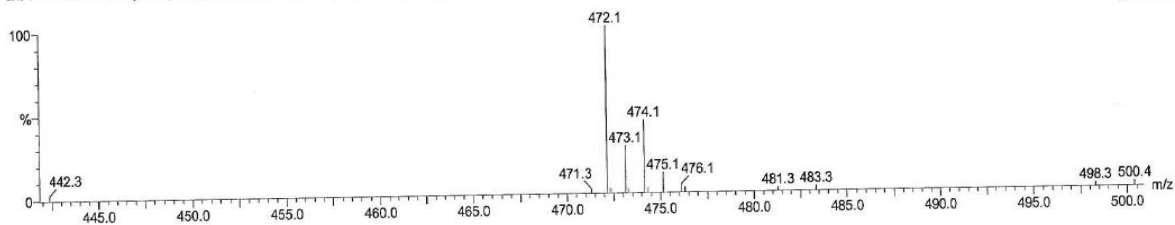
198 formula(e) evaluated with 4 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-100 H: 0-200 N: 5-5 O: 0-30 S: 1-1 Cl: 1-1

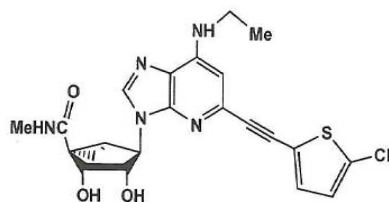
04-Dec-2014

dkt-04dec14-xii-4 53 (0.980) Cn (Cen,5, 50.00, Ar); Sm (SG, 3x5.00); Sb (12,5.00)

TOF MS ES+
1.73e+003

Minimum: -50.0
Maximum: 10.0 10.0 500.0

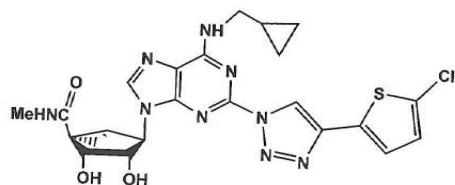
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
472.1214	472.1210	0.4	0.8	13.5	1.3	C22 H23 N5 O3 S Cl
	472.1175	3.9	8.3	-8.5	122.0	C4 H31 N5 O16 S Cl
	472.1269	-5.5	-11.6	4.5	19.2	C15 H27 N5 O8 S Cl
	472.1116	9.8	20.8	0.5	49.3	C11 H27 N5 O11 S Cl



Compound 20

Compound 25 (MRS7162)

DKT-XII-63



Compound 25

```

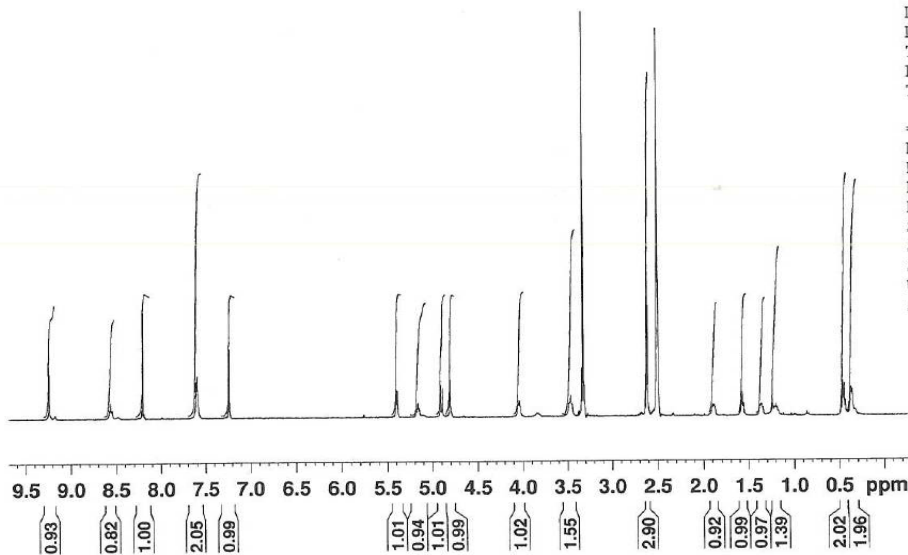
NAME          DKT-XII-6
EXPNO
PROCNO
Date_         2015031
Time         16.5
INSTRUM      spec
PROBHD       5 mm PABBO BE
PULPROG      zg3
TD           6553
SOLVENT      DMS
NS           1
DS
SWH          8223.68
FIDRES      0.12548
AQ          3.984638
RG           25
DW          60.80
DE           6.5
TE          298.
D1          1.000000
TD0

```

```

===== CHANNEL f1 ==
NUC1         1
P1           14.0
PL1          0.0
PL1W        11.7556285
SFO1        400.160471
SI          3276
SF          400.158000
WDW
SSB

```



Single Mass Analysis

Tolerance = 10.0 mDa / DBE: min = -50.0, max = 500.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

210 formula(e) evaluated with 3 results within limits (up to 19 closest results for each mass)

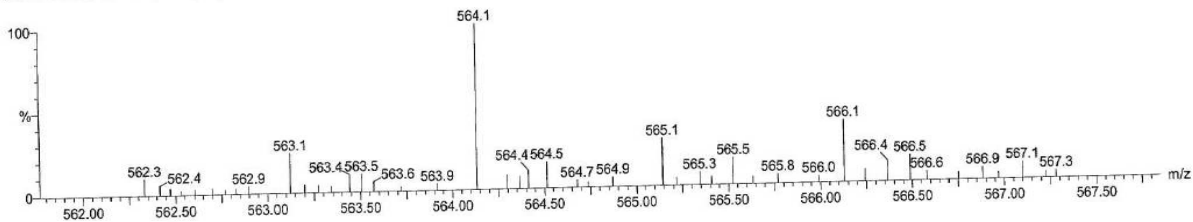
Elements Used:

C: 0-100 H: 0-200 N: 9-9 O: 0-30 Na: 1-1 32S: 1-1 35Cl: 1-1

+ NaTFA

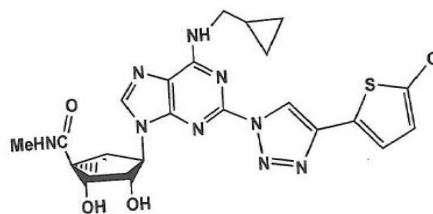
12-Mar-2015

dkt-12mar15-xii-63 384 (7.101) Cn (Cen,5, 50.00, Ar); Sm (SG, 3x5.00); Sb (12,5.00)

TOF MS ES+
2.04e+002

Minimum: -50.0
Maximum: 10.0 10.0 500.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
564.1316	564.1309	0.7	1.2	15.5	29.0	C23 H24 N9 O3 Na 32S 35Cl ✓
	564.1274	4.2	7.4	-6.5	42.4	C5 H32 N9 O16 Na 32S 35Cl
	564.1368	-5.2	-9.2	6.5	31.6	C16 H28 N9 O8 Na 32S 35Cl



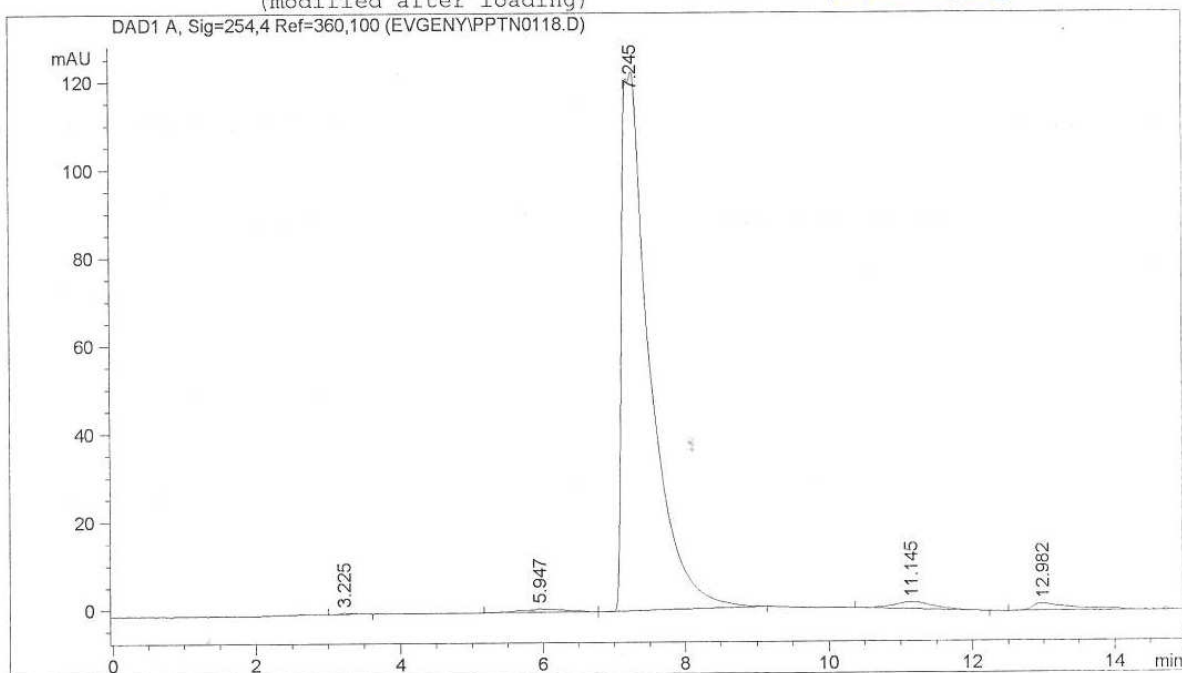
Compound 25

HPLC: Analytical purity checked using a Hewlett–Packard 1100 HPLC equipped with Zorbax SB-Aq 5 μm analytical column (150 \times 4.6 mm; Agilent Technologies, Inc., Palo Alto, CA). Mobile phase: linear gradient solvent system: 0.1% TFA (trifluoroacetic acid)- CH_3CN from 90:10 to 10:90 in 15 min; the flow rate was 1.0 mL/min. Peaks were detected by UV absorption with a diode array detector at 254, 275, and 280 nm. Purity of compounds tested for biological activity was at least 95% by HPLC.

Compound 11

Acq. Operator : evgeny
 Method : C:\HPCHEM\1\METHODS\SAIBAL.M
 Last changed : 11/18/2014 11:58:14 AM by evgeny
 (modified after loading)

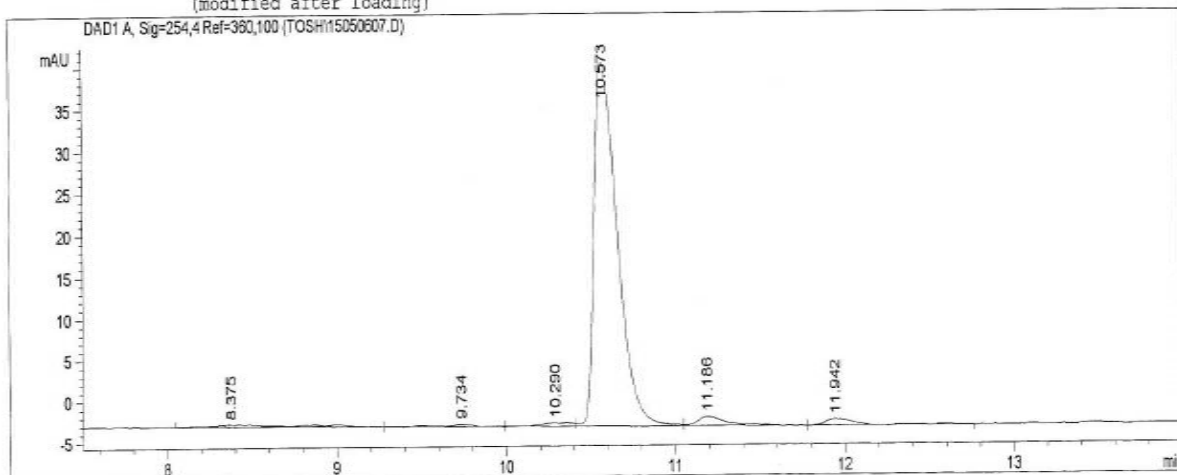
MRS 7135



Data File C:\HPCHEM\1\DATA\TOSH\15050607.D

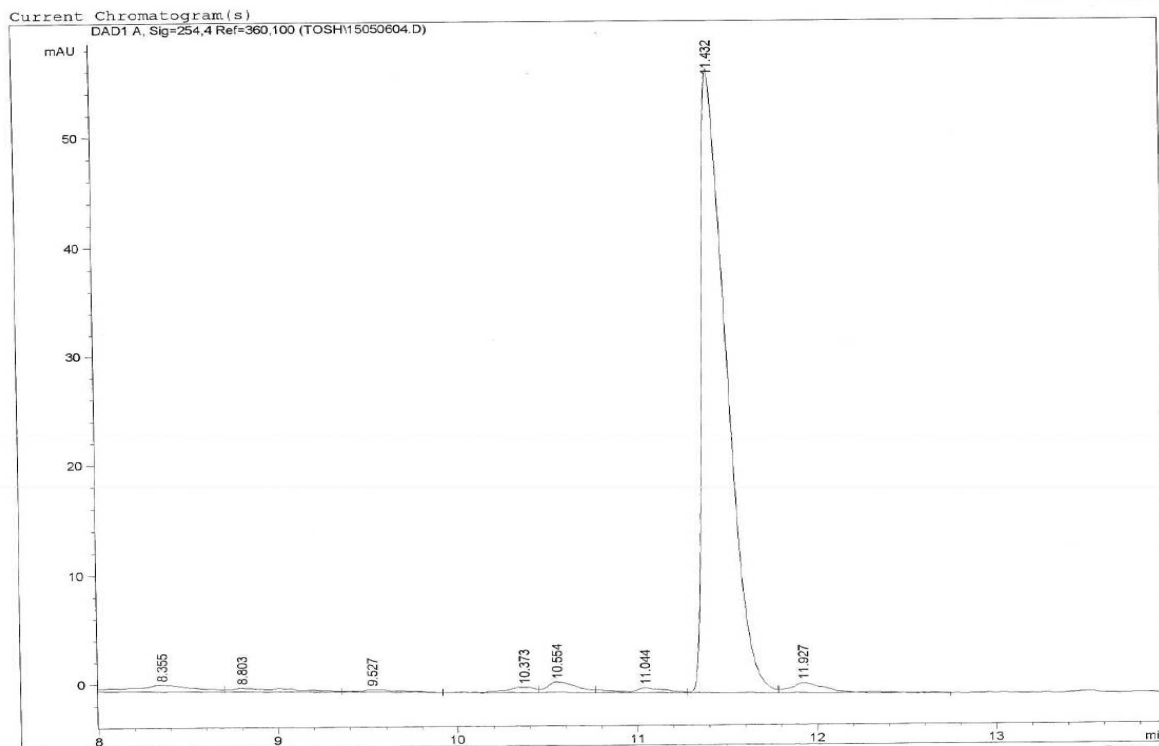
Compound 12

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 Injection Date : 5/6/2015 12:22:06 PM
 Sample Name : 7154 Location : -
 Acq. Operator : dilip
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 Last changed : 5/6/2015 11:34:21 AM by dilip
 (modified after loading)



of window 38: Current Chromatogram(s)

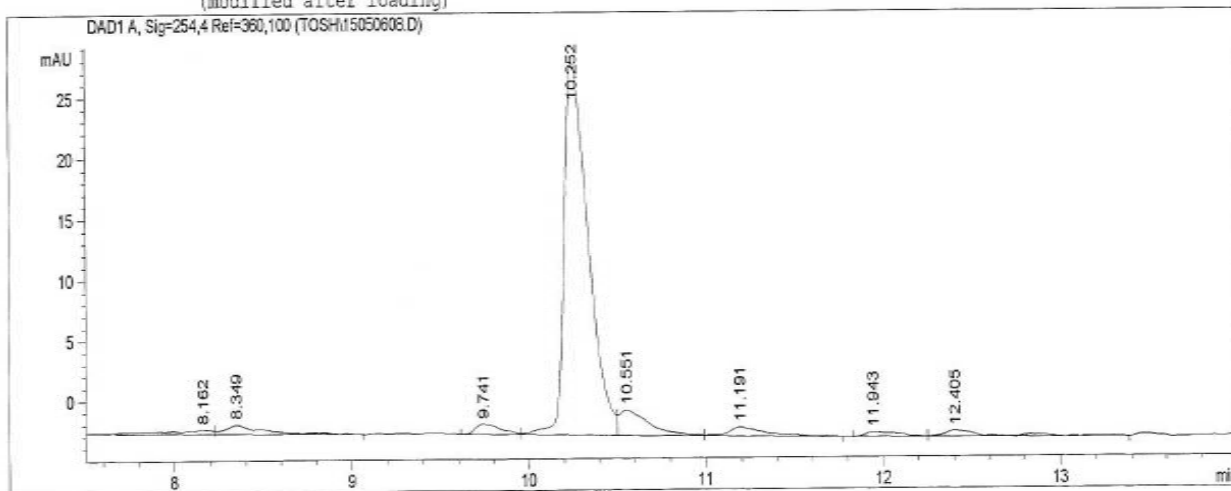
Compound 18



Data File C:\HPCHEM\1\DATA\TOSH\15050608.D

Compound 20

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Sample Name : 7144 Location : -
Acq. Operator : dilip
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Last changed : 5/6/2015 11:34:21 AM by dilip
(modified after loading)



Compound 25

File C:\HPCHEM\1\DATA\TOSH\15050605.D

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Injection Date : 5/6/2015 11:34:59 AM
Sample Name : 7162 Location : -
Acq. Operator : dilip
Method : C:\HPCHEM\1\METHODS\TOSH.M
Last changed : 5/6/2015 11:34:21 AM by dilip
(modified after loading)

