

Supporting Information

Discovery and optimization of small molecule ligands for the CBP/p300 bromodomains

Duncan A. Hay^{††}, Oleg Fedorov^{‡#}, Sarah Martin^{‡#}, Dean C. Singleton^{‡#}, Cynthia Tallant^{‡#}, Christopher Wells^{‡#}, Sarah Picaud[‡], Martin Philpott^{‡#}, Octovia P. Monteiro^{‡#}, Catherine M. Rogers^{‡#}, Stuart J. Conway[†], Timothy P. C. Rooney[†], Anthony Tumber^{‡#}, Clarence Yapp^{‡#}, Panagis Filippakopoulos[‡], Mark E. Bunnage^{††}, Susanne Müller^{‡#}, Stefan Knapp^{‡#}, Christopher J. Schofield[†], Paul E. Brennan^{‡#*}.

[†]Department of Chemistry, University of Oxford, South Parks Road, Oxford OX1 3TA, UK.

[‡]Structural Genomics Consortium, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Oxford, OX3 7DQ, UK.

[#]Target Discovery Institute, University of Oxford, NDM Research Building, Roosevelt Drive, Oxford, OX3 7LD, UK.

^{††}Worldwide Medicinal Chemistry, Pfizer, Cambridge, Massachusetts, Massachusetts.

Table of Contents

Synthetic procedures	S3
General experimental for parallel synthesis compounds	S56
Protein Expression and purification	S86
Differential scanning fluorimetry	S86
AlphaScreen	S86
Isothermal Titration Calorimetry	S87
Crystallization	S87
Data Collection and Structure solution	S87
Cell culture and reagents	S88
Fluorescence Recovery After Photobleaching (FRAP) Assay	S88
Luciferase assay	S88
Cytotoxicity assay	S88
Table S1. DSF vs AlphaScreen for compounds 14-20.	S89
Table S2. SAR for additional C-2 analogues.	S90
Table S3. Dissociation constants and thermodynamic parameters from ITC assays.	S91
Table S4. DSF selectivity panel vs AlphaScreen	S92
Table S5. X-ray crystallography data collection and refinement statistics	S93

Table S6. Compound 58 ADME	S94
Table S7. Compound 58 Cerep wide ligand profiling.....	S95
FRAP with GFP-CBP N1168F mutant.....	S98
Compound 58 cytotoxicity	S98
References	S99

Synthetic procedures

List of Abbreviations

Ac – Acetate

Aq. – Aqueous

Ar – Aryl

Boc – *tert*-Butoxycarbonyl

BINAP – 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

Bn – Benzyl

CDI – 1,1'-Carbonyldiimidazole

CVs – Column volumes

DAD – Diode Array Detector

DBA – Dibenzylideneacetone

Dec – Decomposition (during melting point determination)

DMAP – 4-(Dimethylamino)pyridine

DME – 1,2-Dimethoxyethane

DMF – Dimethylformamide

DMSO – Dimethyl sulphoxide

EDCI – *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride

ELSD – Evaporative Light Scattering Detector

er – Enantiomeric ratio

ESI – Electrospray Ionisation

Et – Ethyl

EtOAc – Ethyl acetate

EtOH – Ethanol

h – hours

HBTU – *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate

LCMS – High Performance Liquid Chromatography

HRMS – High Resolution Mass Spectrometry

LRMS – Low Resolution Mass Spectrometry

Oxone – Potassium peroxymonosulfate

Ph – Phenyl

PyBOP – (Benzotriazol-1-yl-oxy)trypyrrolidinophosphonium hexafluorophosphate

MeCN – Acetonitrile

min – Minutes

mp – Melting point

MS – Mass spectrometry

NMP – 1-Methyl-2-pyrrolidinone

NMR – Nuclear Magnetic Resonance

R_f – Retardation factor

SCX – Strong cation exchange

T3P – Propane phosphonic acid anhydride

TEBAC - Benzyltriethylammonium chloride

THF – Tetrahydrofuran

TIPS – Triisopropylsilyl

TLC – Thin Layer Chromatography

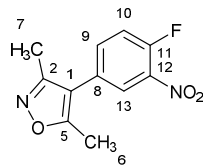
t_r – Retention time

UV – Ultraviolet

General Experimental

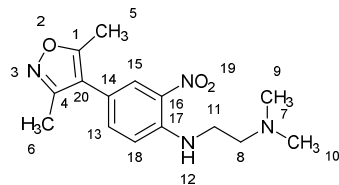
All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was oven dried and cooled under nitrogen before use. Commercial anhydrous solvents used in reactions and LCMS grade solvents were employed for work-up and chromatography. Water was purified using an Elix UV-10 system. All other reagents were used as supplied (analytical or LCMS grade) without prior purification. Parallel synthesis was carried out using a Radleys GreenHouse reactor. Parallel work-ups were carried out using a Radleys stacker and Isolute phase separation cartridges. Thin layer chromatography was performed on aluminium plates coated with 60 F₂₅₄ silica. Plates were visualised using UV light (254 nm) or 1% aq. KMnO₄. R_f values are quoted to the nearest 0.05. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column, or on a Biotage SP4 automated flash column chromatography platform. Melting points were recorded on a Gallenkamp Hot Stage apparatus. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm² g⁻¹ and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer; selected characteristic peaks are reported in cm⁻¹. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at room temperature unless otherwise stated. The field was locked by external referencing to the relevant deuterium resonance. Coupling constants (J) are quoted in Hz and are recorded to the nearest 0.5 Hz. Identical proton coupling constants are averaged in each spectrum and reported to the nearest 0.5 Hz. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. m/z values are reported in Daltons. LRMS were recorded on a Waters LCT Premier, equipped with electrospray ionisation source and TOF analyser, acquiring in positive and negative ionisation modes or on an Agilent 6100 mass spectrometer operated with an electrospray ionisation source via flow injection analysis with an Agilent 1200 isocratic pump; data acquisition and processing was performed using Waters Masslynx 4.1 software or Agilent chemstation software. HRMS were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass. Elemental analyses were recorded by the elemental analysis service of the London Metropolitan University. Microwave experiments were carried out using a Biotage Initiator 8. Flash column chromatography was carried out using a Presearch Isco Combiflash Companion using Presearch columns or on a Biotage SP4 using Biotage SNAP columns. LCMS t_r are quoted to the nearest 0.1 min. LCMS were performed on the following systems: System A: WATERS sunfire C18 column (150 mm × 4.6 mm, 5 μm) using a linear gradient of solvent A (water + 0.01% CF₃CO₂H) and solvent B (acetonitrile + 0.01% CF₃CO₂H), eluting at a flow rate of 1 mL/min and monitoring at 254 nm: 0% B over 2 min, 0% B to 100% B over 16 min and 100 % B over 2 min; System B: Merk Millipore Chromolith Performance RP-18e column (100 mm × 2 mm, 1.6 μm) using a linear gradient of solvent A (water + 0.01% CF₃CO₂H) and solvent B (acetonitrile + 0.01% CF₃CO₂H), eluting at a flow rate of 1 mL/min and monitoring at 254 nm: 2% B over 2 min, 2% B to 100% B over 8 min and 100 % B over 1 min.

4-(4-Fluoro-3-nitrophenyl)-3,5-dimethyl-1,2-oxazole (10)



Pd(dppf)Cl₂ (1.81 g, 2.47 mmol) was added to a solution of 4-bromo-1-fluoro-2-nitrobenzene (10.87 g, 49.4 mmol) and 3,5-dimethylisoxazole-4-boronic acid pinacol ester (12.68 g, 56.8 mmol) in DME (100 mL). The mixture was stirred then saturated aq. NaHCO₃ solution (100 mL) was added. The mixture was degassed by evacuating and refilling with nitrogen (×3) then heated at 80 °C for 3 h. The reaction was allowed to cool then partitioned between EtOAc (100 mL) and water (100 mL). The phases were separated then MgSO₄ and activated charcoal was added. The solid was filtered then the filtrate was evaporated. The resultant residue was re-dissolved in the minimum of methylene chloride then purified by flash column chromatography on a silica column (330 g). The column was eluted with a gradient of EtOAc:*c*-hexane, which was increased linearly from 10:90 to 30:70 over 10 CVs (some product crystallised on the column but re-dissolved as the percentage of EtOAc increased). The desired fractions were combined and evaporated. Et₂O (30 mL) was added, resulting in crystallisation of the product. The supernatant was decanted off with a pipette then the process was repeated. The solid was dried under vacuum to yield the product as a beige solid (8.57 g, 73%); *R*_f 0.25 (EtOAc:*n*-hexane, 30:70); mp 128-131 °C; *v*_{max} (neat) 3063 (C-H), 2933 (C-H), 1538 (N-O), 1354 (N-O); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.29 (s, 3 H, C(7)H₃), 2.44 (s, 3 H, C(6)H₃), 7.41 (dd, *J*=10.5, 8.5 Hz, 1 H, C(10)H), 7.54 (ddd, *J*=8.5, 4.0, 2.5 Hz, 1 H, C(9)H), 7.96 (dd, *J*=7.0, 2.5 Hz, 1 H, C(13)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(7)), 11.8 (s, 1 C, C(6)), 114.2 (s, 1 C, C(1)), 119.3 (d, *J*=21.5 Hz, 1 C, C(10)), 126.5 (d, *J*=2.5 Hz, 1 C, C(13)), 127.9 (d, *J*=5.0 Hz, 1 C, C(8)), 136.1 (d, *J*=8.0 Hz, 1 C, C(9)), 137.8 (d, *J*=6.5 Hz, 1 C, C(12)), 154.9 (d, *J*=266.0 Hz, 1 C, C(11)), 158.2 (s, 1 C, C(2)), 166.4 (s, 1 C, C(5)); ¹⁹F NMR (377 MHz, CDCl₃) δ ppm -118.5 (s, 1 F); LRMS *m/z* (ESI⁺) 237 [MH⁺]; HRMS (ESI⁺) found 259.0492, calculated for C₁₁H₉FN₂NaO₃⁺ 259.0489; LCMS (System A) *t*_r 15.1 min (99%).

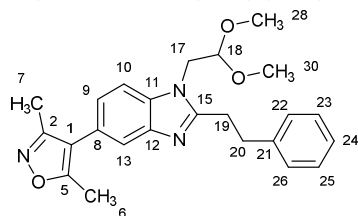
N'-[4-(3,5-Dimethyl-isoxazol-4-yl)-2-nitro-phenyl]-*N,N*-dimethylethane-1,2-diamine (11)



N,N-Dimethylenediamine (0.694 mL, 6.35 mmol) was added drop-wise to a solution of compound **10** (1.00 g, 4.23 mmol) and EtN(*i*-Pr)₂ (1.1 mL, 6.4 mmol) in THF (10 mL). The mixture was left to stir at room temperature for 16 h then partitioned between EtOAc (20 mL) and water (20 mL). The phases were separated then the organic phase was washed with water (20 mL) and brine (20 mL) then dried over MgSO₄ and evaporated to an orange solid. Ether (10 mL) was added then the resultant suspension was agitated then allowed to settle. The supernatant was decanted off with a pipette then more ether (10 mL) was added. This was again agitated, allowed to settle then decanted as before. The resultant solid was dried under vacuum to yield the product as an orange solid (1.10 g, 86%); *R*_f 0.15 (EtOAc:MeOH:NEt₃, 90:10:1); mp 118-119 °C; *v*_{max} (neat) 3355 (N-H), 2951 (C-H), 2876 (C-H), 2795 (C-H), 1554 (N-O), 1354 (N-O); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.27 (s, 3 H, C(6)H₃), 2.33 (s, 6 H, C(9)H₃+C(10)H₃), 2.41 (s, 3 H, C(5)H₃), 2.67 (t, *J*=6.0 Hz, 2 H, C(8)H₂), 3.40 (q, *J*=6.0 Hz, 2 H, C(11)H₂), 6.93 (d, *J*=9.0 Hz, 1 H, C(18)H), 7.34 (dd, *J*=9.0, 2.0 Hz, 1 H, C(13)H), 8.08 (d, *J*=2.0 Hz, 1 H, C(15)H), 8.40 (br. s., 1 H, NH); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.7 (s, 1 C,

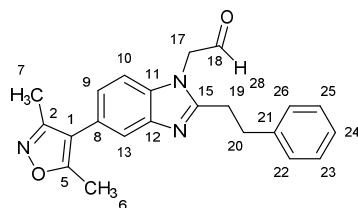
C(6)), 11.5 (s, 1 C, C(5)), 40.8 (s, 1 C, C(11)), 45.2 (s, 2 C, C(9)+C(10)), 57.3 (s, 1 C, C(8)), 114.6 (s, 1 C, C(18)), 114.9 (s, 1 C, C(20)), 117.2 (s, 1 C, C(14)), 127.0 (s, 1 C, C(15)), 131.9 (s, 1 C, C(16)), 136.7 (s, 1 C, C(13)), 144.5 (s, 1 C, C(17)), 158.6 (s, 1 C, C(4)), 165.3 (s, 1 C, C(1)); LCMS (System A) t_r 3.6 min, m/z 305 [MH⁺]; LRMS (ESI⁺) m/z 631 [(2M+Na)⁺], 609 [(2M+H)⁺], 327 [(M+Na)⁺], 305 [MH⁺]; (ESI⁻) 303 [(M-H)⁻]; HRMS (ESI⁺) found 305.1614, calculated for C₁₅H₂₁N₄O₃⁺ 305.1608.

1-(2,2-Dimethoxyethyl)-5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazole (13)



Aminoacetaldehyde dimethyl acetal (218 μ L, 2.00 mmol) was added to a solution of compound **10** (472 mg, 2.00 mmol) in DMSO (1 mL). The solution was heated at 80 °C for 2 h. The solution was removed from the heat then a solution of 3-phenylpropanal (263 μ L, 2.00 mmol) in MeOH (4 mL) was added, followed by 1 M aq. Na₂S₂O₄ (3.0 mL, 3.0 mmol). The mixture was heated at 80 °C for 4 h then allowed to cool. The mixture was partitioned between EtOAc (15 mL) and 10 % aq. ammonia solution (15 mL). The phases were separated then the organic phase was washed with water (15 mL) and brine (15 mL) then dried over MgSO₄ and evaporated. The crude material was purified by flash column chromatography on a silica column. The column was eluted with a gradient of EtOAc:c-hexane, which was increased linearly from 50:50 to 70:30 over 10 CVs. The desired fractions were combined and evaporated to yield the product as a white solid (525 mg, 65%); R_f 0.50 (EtOAc); mp 105-107 °C; ν_{max} (neat) 2396 (C-H), 2825 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.31 (s, 3 H, C(7)H₃), 2.44 (s, 3 H, C(6)H₃), 3.20 - 3.32 (m, 4 H, C(19)H₂+C(20)H₃), 3.36 (s, 6 H, C(28)H₃+C(30)H₃), 4.12 (d, J =5.0 Hz, 2 H, C(17)H₂), 4.50 (t, J =5.0 Hz, 1 H, C(18)H), 7.13 (dd, J =8.5, 1.5 Hz, 1 H, C(9)H), 7.23 - 7.35 (m, 5 H, 5 \times PhH), 7.40 (d, J =8.5 Hz, 1 H, C(10)H), 7.64 (d, J =1.5 Hz, 1 H, C(13)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(7)), 11.6 (s, 1 C, C(6)), 29.5 (s, 1 C, C(19)), 33.9 (s, 1 C, C(20)), 46.5 (s, 1 C, C(17)), 55.5 (s, 2 C, C(28)+C(30)), 103.1 (s, 1 C, C(18)), 109.6 (s, 1 C, C(10)), 117.1 (s, 1 C, C(1)), 119.8 (s, 1 C, C(13)), 123.5 (s, 1 C, C(9)), 124.3 (s, 1 C, C(8)), 126.4 (s, 1 C, C(24)), 128.4 (s, 2 C, C(22/23)+C(26/25)), 128.6 (s, 2 C, C(22/23)+C(26/25)), 134.6 (s, 1 C, C(11)), 141.0 (s, 1 C, C(21)), 142.9 (s, 1 C, C(12)), 156.0 (s, 1 C, C(15)), 159.0 (s, 1 C, C(2)), 165.0 (s, 1 C, C(5)); LRMS m/z (ESI⁺) 833 [(2M+Na)⁺], 811 [(2M+H)⁺], 428 [(M+Na)⁺], 406 [MH⁺], (ESI⁻) 404 [(M-H)⁻]; HRMS (ESI⁺) found 406.2118, calculated for C₂₄H₂₈N₃O₃⁺ 406.2125; LCMS (System A) t_r 11.8 min (99%).

[5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]acetaldehyde



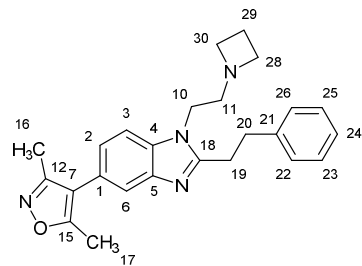
A mixture of compound **13** (1.15 g, 2.84 mmol), water (2.5 mL) CF₃CO₂H (2.5 mL) and CH₂Cl₂ (5 mL) was crimp-sealed in a microwave vial then heated under microwave irradiation for 20 min at 150 °C then for a further 30 min at 150 °C. The reaction mixture was added carefully to a conical flask containing saturated aq. NaHCO₃ solution (50 mL) then transferred to a separating funnel. The phases were separated then the

organic phase was washed with 1:1 water:brine (50 mL) then brine (50 mL) then dried over MgSO_4 and evaporated to yield the product as a cream-coloured solid (1.01 g, 99%); 75-80 °C; R_f 0.30 (EtOAc); ν_{max} (neat) 2928 (C-H), 1733 (C=O); ^1H NMR (400 MHz, CDCl_3) δ ppm 2.29 (s, 3 H, C(7) H_3), 2.43 (s, 3 H, C(6) H_3), 3.05 - 3.15 (m, 2 H, C(19) H_2), 3.21 - 3.30 (m, 2 H, C(20) H_2), 4.69 (s, 2 H, C(17) H_2), 7.07 - 7.35 (m, 7 H, 7 \times ArH), 7.67 (d, $J=1.0$ Hz, 1 H, C(13) H), 9.48 (s, 1 H, CHO); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.8 (s, 1 C, C(7)), 11.5 (s, 1 C, C(6)), 29.6 (s, 1 C, C(19)), 34.0 (s, 1 C, C(20)), 52.6 (s, 1 C, C(17)), 108.9 (s, 1 C, C(10)), 116.9 (s, 1 C, C(1)), 120.2 (s, 1 C, C(13)), 124.0 (s, 1 C, C(9)), 124.9 (s, 1 C, C(8)), 126.7 (s, 1 C, C(24)), 128.4 (s, 2 C, C(22/23)+C(26/25)), 128.8 (s, 2 C, C(22/23)+C(26/25)), 134.3 (s, 1 C, C(11)), 140.3 (s, 1 C, C(21)), 143.0 (s, 1 C, C(12)), 155.2 (s, 1 C, C(15)), 158.9 (s, 1 C, C(2)), 165.1 (s, 1 C, C(5)), 194.5 (s, 1 C, CHO); LRMS m/z (ESI $^-$) 358 [(M-H)]; HRMS (ESI $^-$) found 358.1563, calculated for $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_2^-$ 358.1561; LCMS (System A) t_r 10.6 min (38%, aldehyde/hydrate), 11.3 min (62%, MeOH hemiacetal).

General procedure A

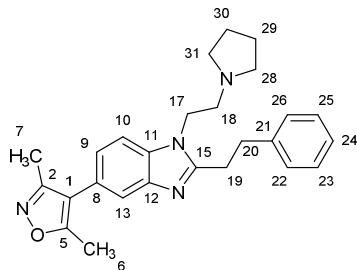
$\text{NaBH}(\text{OAc})_3$ (42 mg, 0.20 mmol) was added to a stirred solution of [5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]acetaldehyde (50 mg, 0.14 mmol), the appropriate amine (0.20 mmol) and acetic acid (10 μL) in THF (1 mL). The mixture was left to stir at room temperature for 2 h then partitioned between CH_2Cl_2 (2 mL) and 1 M NaOH (2 mL). The phases were separated using a hydrophobic frit separation cartridge then the organic phase was evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (10 g). The desired fractions were combined and evaporated to yield the product.

1-[2-(Azetidin-1-yl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazole (14)



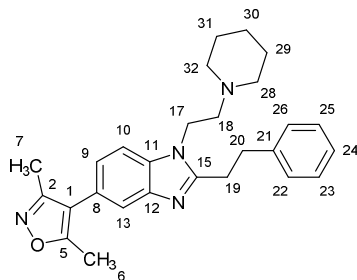
Azetidine (14 μL , 0.20 mmol) was reacted with [5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]acetaldehyde (50 mg, 0.14 mmol) according to general procedure A. Chromatography was carried out with a gradient of CH_2Cl_2 :MeOH: NH_4OH , which was increased linearly from 98:2:0.2 to 90:10:1 over 10 CVs. The product was obtained as a cream solid (48 mg, 86%); mp 163-165 °C; R_f 0.40 (CH_2Cl_2 :MeOH: NH_4OH , 90:10:1); ν_{max} 2953 (C-H), 2921 (C-H), 2857 (C-H), 2840 (C-H), 2798 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 2.07 (quin, $J=7.0$ Hz, 2 H, C(29) H_2), 2.30 (s, 3 H, C(16) H_3), 2.43 (s, 3 H, C(17) H_3), 2.68 (t, $J=7.0$ Hz, 2 H, C(11) H_2), 3.16 (t, $J=7.0$ Hz, 4 H, C(28) H_2 +C(30) H_2), 3.19 - 3.24 (m, 2 H, C(29) H_2 , C(19) H_2), 3.25 - 3.32 (m, 2 H, C(20) H_2), 3.98 (t, $J=7.0$ Hz, 2 H, C(10) H_2), 7.12 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2) H), 7.20 - 7.34 (m, 5 H, 5 \times PhH), 7.36 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.63 (d, $J=1.5$ Hz, 1 H, C(6) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.8 (s, 1 C, C(16)), 11.5 (s, 1 C, C(17)), 17.9 (s, 1 C, C(29)), 29.5 (s, 1 C, C(19)), 33.9 (s, 1 C, C(20)), 42.1 (s, 1 C, C(10)), 55.7 (s, 2 C, C(28)+C(30)), 58.2 (s, 1 C, C(11)), 109.4 (s, 1 C, C(3)), 117.1 (s, 1 C, C(7)), 119.8 (s, 1 C, C(6)), 123.3 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 126.4 (s, 1 C, C(24)), 128.4 (s, 2 C, C(22/23)+C(26/25)), 128.6 (s, 2 C, C(22/23)+C(26/25)), 134.3 (s, 1 C, C(4)), 140.8 (s, 1 C, C(21)), 143.0 (s, 1 C, C(5)), 155.3 (s, 1 C, C(18)), 159.0 (s, 1 C, C(12)), 165.0 (s, 1 C, C(15)); LRMS m/z 823 [(2M+Na) $^+$], 801 [(2M+H) $^+$], 423 [(M+Na) $^+$], 401 [MH $^+$]; HRMS found 401.2334, calculated for $\text{C}_{25}\text{H}_{29}\text{N}_4\text{O}^+$ 401.2336; LCMS (System A) t_r 9.7 min (98%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1-[2-(pyrrolidin-1-yl)ethyl]-1H-benzimidazole (15)



Pyrrolidine (16 μ L, 0.20 mmol) was reacted with [5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]acetaldehyde (50 mg, 0.14 mmol) according to general procedure A. Chromatography was carried out with a gradient of EtOAc:MeOH:NEt₃, which was increased linearly from 92:8:0.8 to 90:10:1 over 10 CVs. The product was obtained as a colourless gum (39 mg, 67%); *R_f* 0.15 (EtOAc:MeOH:NEt₃, 90:10:1); v_{\max} 2960 (C-H), 2921 (C-H), 2794 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.76 - 1.84 (m, 4 H, C(29)H₂+C(30)H₂), 2.30 (s, 3 H, C(7)H₃), 2.43 (s, 3 H, C(6)H₃), 2.53 - 2.61 (m, 4 H, C(28)H₂+C(31)H₂), 2.69 - 2.77 (m, 2 H, C(18)H₂), 3.16 - 3.23 (m, 2 H, C(19)H₂), 3.25 - 3.34 (m, 2 H, C(20)H₂), 4.11 - 4.21 (m, 2 H, C(17)H₂), 7.12 (dd, *J*=8.5, 1.5 Hz, 1 H, C(9)H), 7.20 - 7.27 (m, 3 H, 3 \times PhH), 7.28 - 7.33 (m, 2 H, 2 \times PhH), 7.37 (d, *J*=8.5 Hz, 1 H, C(10)H), 7.63 (d, *J*=1.5 Hz, 1 H, C(13)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(7)), 11.5 (s, 1 C, C(6)), 23.5 (s, 2 C, C(29)+C(30)), 29.5 (s, 1 C, C(19)), 33.9 (s, 1 C, C(20)), 43.0 (s, 1 C, C(17)), 54.5 (s, 2 C, C(28)), 55.0 (s, 1 C, C(31)), 109.4 (s, 1 C, C(10)), 117.1 (s, 1 C, C(1)), 119.8 (s, 1 C, C(13)), 123.4 (s, 1 C, C(9)), 124.1 (s, 1 C, C(8)), 126.4 (s, 1 C, C(24)), 128.3 (s, 2 C, C(22/23)+C(26/25)), 128.6 (s, 2 C, C(22/23)+C(26/25)), 134.3 (s, 1 C, C(11)), 140.8 (s, 1 C, C(21)), 143.0 (s, 1 C, C(11)), 155.2 (s, 1 C, C(15)), 159.0 (s, 1 C, C(2)), 165.0 (s, 1 C, C(5)); LRMS *m/z* (ESI⁺) 851 [(2M+Na)⁺], 829 [(2M+H)⁺], 437 [(M+Na)⁺], 415 [MH⁺]; HRMS (ESI⁺) found 415.2491, calculated for C₂₆H₃₁N₄O⁺ 415.2492; LCMS (System A) *t_r* 9.7 min (99%).

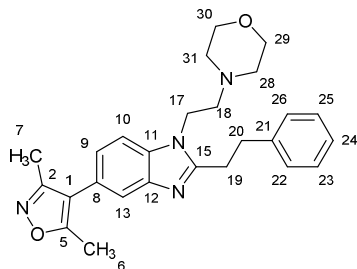
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1-[2-(piperidin-1-yl)ethyl]-1H-benzimidazole (16)



Piperidine (15 μ L, 0.20 mmol) was reacted with [5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]acetaldehyde (50 mg, 0.14 mmol) according to general procedure A. Chromatography was carried out with a gradient of EtOAc:MeOH:NEt₃, which was increased linearly from 98:2:0.2 to 92:8:0.8 over 10 CVs. The product was obtained as a colourless gum (21 mg, 49%); *R_f* 0.15 (EtOAc); v_{\max} 2933 (C-H), 2857 (C-H), 2842, (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.40 - 1.48 (m, 2 H, C(30)H₂), 1.53-1.62 (m, *J*=5.5 Hz, 4 H, C(29)H₂+C(31)H₂), 2.30 (s, 3 H, C(7)H₃), 2.42-2.45 (m, 7 H, C(6)H₃+C(28)H₂+C(32)H₂), 2.57 (t, *J*=7.0 Hz, 2 H, C(18)H₂), 3.17 - 3.26 (m, 2 H, C(19)H₂), 3.26 - 3.34 (m, 2 H, C(20)H₂), 4.14 (t, *J*=7.0 Hz, 2 H, C(17)H₂), 7.12 (dd, *J*=8.5, 1.0 Hz, 1 H, C(9)H), 7.21 - 7.35 (m, 5 H, 5 \times PhH), 7.37 (d, *J*=8.5 Hz, 1 H, C(10)H), 7.64 (d, 1 H, 1.0 Hz, C(13)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(7)), 11.5 (s, 1 C, C(6)), 24.1 (s, 1 C, C(7)), 25.9 (s, 2 C, C(29)+C(31)), 29.5 (s, 1 C, C(19)), 33.8 (s, 1 C, C(20)), 41.7 (s, 1 C, C(17)), 55.1 (s, 2 C, C(28)+C(32)), 57.9 (s, 1 C, C(18)), 109.5 (s, 1 C, C(10)), 117.1 (s, 1 C, C(1)), 119.8 (s, 1 C, C(13)), 123.3 (s, 1 C, C(9)), 124.0 (s, 1 C, C(8)),

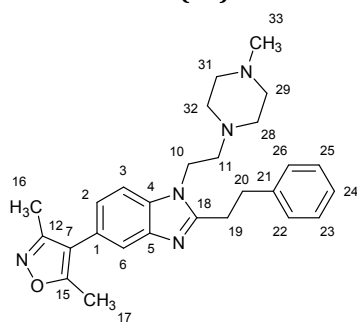
126.4 (s, 1 C, C(24)), 128.4 (s, 2 C, C(22/23)+C(26/25)), 128.6 (s, 2 C, C(22/23)+C(26/25)), 134.3 (s, 1 C, C(11)), 140.9 (s, 1 C, C(21)), 143.0 (s, 1 C, C(12)), 155.4 (s, 1 C, C(15)), 159.0 (s, 1 C, C(2)), 165.0 (s, 1 C, C(5)); LRMS m/z (ESI⁺) 879 [(2M+Na)⁺], 857 [(2M+H)⁺], 451 [(M+Na)⁺], 429 [MH⁺]; HRMS (ESI⁺) found 429.2643, calculated for C₂₇H₃₃N₄O⁺ 429.2649; LCMS (System A) t_r 9.9 min (99%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-(2-phenylethyl)-1H-benzimidazole (17)



Morpholine (18 μ L, 0.20 mmol) was reacted with [5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]acetaldehyde (50 mg, 0.14 mmol) according to general procedure A. Chromatography was carried out with a gradient of EtOAc:MeOH:NEt₃, which was increased linearly from 99:1:0.1 to 90:10:1 over 10 CVs. The product was obtained as a colourless gum (21 mg, 35%); R_f 0.40 (EtOAc:MeOH:NEt₃, 90:10:1); ν_{max} (neat) 2930 (C-H), 29 (C-H), 2855 (C-H), 2814 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(7)H₃), 2.43 (s, 3 H, C(6)H₃), 2.44 - 2.48 (m, 4 H, C(28)H₂+C(31)H₂), 2.61 (t, $J=7.0$ Hz, 2 H, C(18)H₂), 3.18 - 3.25 (m, 2 H, C(19)H₂), 3.27 - 3.34 (m, 2 H, C(20)H₂), 3.64 - 3.71 (m, 4 H, C(29)H₂+C(30)H₂), 4.12 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 7.13 (dd, $J=8.0, 1.5$ Hz, 1 H, C(9)H), 7.22 - 7.28 (m, 3 H, 3 \times PhH), 7.30 - 7.34 (m, 2 H, 2 \times PhH), 7.36 (d, $J=8.5$ Hz, 1 H, C(10)H), 7.64 (d, $J=1.0$ Hz, 1 H, C(13)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(7)), 11.6 (s, 1 C, C(6)), 29.6 (s, 1 C, C(19)), 33.8 (s, 1 C, C(20)), 41.4 (s, 1 C, C(17)), 54.0 (s, 2 C, C(28)+C(31)), 57.6 (s, 1 C, C(18)), 66.8 (s, 2 C, C(29)+C(30)), 109.4 (s, 1 C, C(10)), 117.1 (s, 1 C, C(1)), 119.9 (s, 1 C, C(13)), 123.4 (s, 1 C, C(9)), 124.2 (s, 1 C, C(8)), 126.5 (s, 1 C, C(24)), 128.4 (s, 2 C, C(22/23)+C(26/25)), 128.7 (s, 2 C, C(22/23)+C(26/25)), 134.3 (s, 1 C, C(11)), 140.9 (s, 1 C, C(21)), 143.0 (s, 1 C, C(11)), 155.3 (s, 1 C, C(15)), 159.0 (s, 1 C, C(2)), 165.0 (s, 1 C, C(5)); LRMS m/z (ESI⁺) 883 [(2M+Na)⁺], 861 [(2M+H)⁺], 453 [(M+Na)⁺], 431 [MH⁺]; HRMS (ESI⁺) found 431.2434, calculated for C₂₆H₃₁N₄O₂⁺ 431.2442; LCMS (System B) t_r 3.4 min (93%).

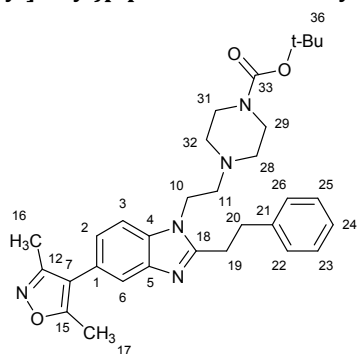
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(4-methylpiperazin-1-yl)ethyl]-2-(2-phenylethyl)-1H-benzimidazole (18)



1-Methylpiperazine (14 μ L, 0.20 mmol) was reacted with [5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]acetaldehyde (50 mg, 0.14 mmol) according to general procedure A. Chromatography was carried out with a gradient of CH₂Cl₂:MeOH:NH₄OH, which was increased linearly from 95:5:0.5 to 90:10:1 over 10 CVs. The product was obtained as a colourless gum (29 mg, 47%); R_f 0.30 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); ν_{max} (neat) 2863 (C-H), 2720 (C-H), 2625 (C-H); ¹H NMR (400 MHz, CDCl₃) δ

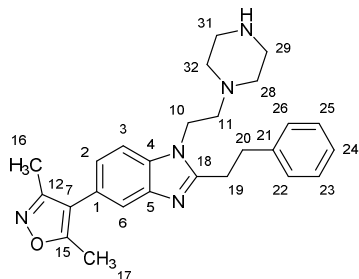
ppm 2.28 (s, 3 H, C(33)H₃), 2.30 (s, 3 H, C(16)H₃), 2.36 - 2.56 (m, 11 H, C(17)H₃+C(28)H₂+C(29)H₂+C(31)H₂+C(32)H₂), 2.61 (t, *J*=7.0 Hz, 2 H, C(11)H₂), 3.17 - 3.25 (m, 2 H, C(19)H₂), 3.26 - 3.33 (m, 2 H, C(20)H₂), 4.11 (t, *J*=7.0 Hz, 2 H, C(10)H₂), 7.12 (dd, *J*=8.0, 1.0 Hz, 1 H, C(2)H), 7.21 - 7.34 (m, 5 H, 5×PhH), 7.35 (d, *J*=8.0 Hz, 1 H, C(3)H), 7.63 (d, *J*=1.0 Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(16)), 11.5 (s, 1 C, C(15)), 29.6 (s, 1 C, C(19)), 33.8 (s, 1 C, C(20)), 41.6 (s, 1 C, C(10)), 45.9 (s, 1 C, C(33)), 53.5 (s, 2 C, C(29)+C(31)), 54.9 (s, 2 C, C(28)+C(32)), 57.1 (s, 1 C, C(11)), 109.4 (s, 1 C, C(3)), 117.1 (s, 1 C, C(7)), 119.8 (s, 1 C, C(6)), 123.4 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 126.4 (s, 1 C, C(24)), 128.4 (s, 2 C, C(22/23)+C(26/25)), 128.6 (s, 2 C, C(22/23)+C(26/25)), 134.3 (s, 1 C, C(4)), 140.9 (s, 1 C, C(21)), 143.0 (s, 1 C, C(5)), 155.4 (s, 1 C, C(18)), 159.0 (s, 1 C, C(12)), 165.0 (s, 1 C, C(15)); LRMS *m/z* (ESI⁺) 909 [(2M+Na)⁺], 887 [(2M+H)⁺], 466 [(M+Na)⁺], 444 [MH⁺]; HRMS (ESI⁺) found 444.2743, calculated for C₂₇H₃₄N₅O⁺ 444.2758; LCMS *t_r* 9.8 min (>99%); LCMS (System A) *t_r* 9.7 min (98%).

tert-Butyl 4-{2-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]ethyl}piperazine-1-carboxylate



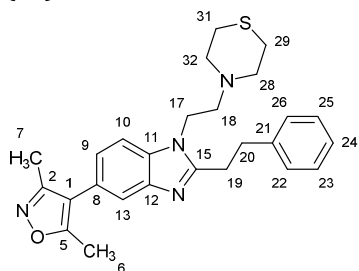
1-Boc-piperazine (37 mg, 0.20 mmol) was reacted with [5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]acetaldehyde (50 mg, 0.14 mmol) according to general procedure A. Chromatography was carried out with an isocratic gradient of EtOAc. The product was obtained as a colourless gum (52 mg, 70%); *R_f* 0.15 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); *v*_{max} (neat) 2975 (C-H), 2930 (C-H), 2917 (C-H), 1688 (C=O); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.45 (s, 9 H, C(CH₃)₃), 2.30 (s, 3 H, C(16)H₃), 2.35 - 2.45 (m, 7 H, C(17)H₃+C(28)H₂+C(32)H₂), 2.61 (t, *J*=7.0 Hz, 2 H, C(11)H₂), 3.15 - 3.24 (m, 2 H, C(19)H₂), 3.26 - 3.34 (m, 2 H, C(20)H₂), 3.35 - 3.44 (m, 4 H, C(29)H₂+C(31)H₂), 4.11 (t, *J*=7.0 Hz, 2 H, C(10)H₂), 7.12 (dd, *J*=8.5, 1.5 Hz, 1 H, C(2)H), 7.21 - 7.33 (m, 5 H, 5×PhH), 7.35 (d, *J*=8.5 Hz, 1 H, C(3)H), 7.64 (d, *J*=1.5 Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(16)), 11.6 (s, 1 C, C(17)), 28.4 (s, 3 C, C(CH₃)₃), 29.7 (s, 1 C, C(19)), 33.8 (s, 1 C, C(20)), 41.6 (s, 1 C, C(10)), 43.2 (s, 2 C, C(29)+C(31)), 53.4 (s, 2 C, C(28)+C(32)), 57.2 (s, 1 C, C(11)), 79.8 (s, 1 C, C(CH₃)₃), 109.4 (s, 1 C, C(3)), 117.1 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.4 (s, 1 C, C(2)), 124.2 (s, 1 C, C(1)), 126.5 (s, 1 C, C(24)), 128.3 (s, 2 C, C(22/23)+C(26/25)), 128.7 (s, 2 C, C(22/23)+C(26/25)), 134.2 (s, 1 C, C(4)), 140.8 (s, 1 C, C(21)), 143.0 (s, 1 C, C(5)), 154.6 (s, 1 C, C(33)), 155.3 (s, 1 C, C(18)), 159.0 (s, 1 C, C(12)), 165.0 (s, 1 C, C(15)); LRMS *m/z* (ESI⁺) 552 [(M+Na)⁺], 530 [MH⁺]; HRMS (ESI⁺) found 530.3122, calculated for C₃₁H₄₀N₅O₃⁺ 530.3126; LCMS (System B) *t_r* 4.2 min (89%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1-[2-(piperazin-1-yl)ethyl]-1H-benzimidazole (19)



tert-Butyl 4-{2-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1*H*-benzimidazol-1-yl]ethyl}piperazine-1-carboxylate (50 mg, 0.094 mmol) was dissolved in F₃CCOOH (2 mL) then stirred for 1 h. The excess F₃CCOOH was evaporated then the residue purified by flash column chromatography on a silica column (4 g). Eluted with CH₂Cl₂:MeOH:NH₄OH, which was increased linearly from 95:5:0.5 to 90:10:1 over 5 CVs. The desired fractions were combined and evaporated to a golden-yellow gum. This material was dissolved in MeOH then loaded onto a pre-wetted SCX cartridge (1 g). The cartridge was eluted with MeOH then with 10% NEt₃ in MeOH. The basic eluent was evaporated then dried under high vacuum to yield the product as a colourless gum (27 mg, 67%); *R*_f 0.20, (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); *v*_{max} (neat) 3373 (N-H), 2937 (C-H), 2811 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.29 - 2.31 (m, 3 H, C(16)H₃), 2.41 - 2.49 (m, 7 H, C(17)H₃+C(28)H₂+C(32)H₂), 2.59 (t, *J*=7.0 Hz, 2 H, C(11)H₂), 2.83 - 2.91 (m, 4 H, C(29)H₂+C(31)H₃), 3.17 - 3.25 (m, 2 H, C(19)H₂), 3.25 - 3.33 (m, 2 H, C(20)H₂), 4.11 (t, *J*=7.0 Hz, 2 H, C(10)H₂), 7.12 (dd, *J*=8.0, 1.0 Hz, 1 H, C(2)H), 7.19 - 7.34 (m, 5 H, 5×PhH), 7.35 (d, *J*=8.5 Hz, 1 H, C(3)H), 7.63 (d, *J*=1.0 Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(16)), 11.5 (s, 1 C, C(17)), 29.6 (s, 1 C, C(19)), 33.8 (s, 1 C, C(20)), 41.5 (s, 1 C, C(10)), 45.7 (s, 2 C, C(29)+C(31)), 54.5 (s, 2 C, C(28)+C(32)), 57.7 (s, 1 C, C(11)), 109.4 (s, 1 C, C(3)), 117.1 (s, 1 C, C(7)), 119.8 (s, 1 C, C(6)), 123.4 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 126.4 (s, 1 C, C(24)), 128.3 (s, 2 C, C(22/23)+C(26/25)), 128.6 (s, 2 C, C(22/23)+C(26/25)), 134.3 (s, 1 C, C(4)), 140.8 (s, 1 C, C(21)), 143.0 (s, 1 C, C(5)), 155.3 (s, 1 C, C(18)), 159.0 (s, 1 C, C(12)), 165.0 (s, 1 C, C(15)); LRMS *m/z* (ESI⁺) 859 [(2M+H)⁺], 430 [MH⁺]; HRMS (ESI⁺) found 430.2592, calculated for C₂₆H₃₂N₅O⁺ 430.2601; LCMS (System B) *t*_r 3.4 min (92%).

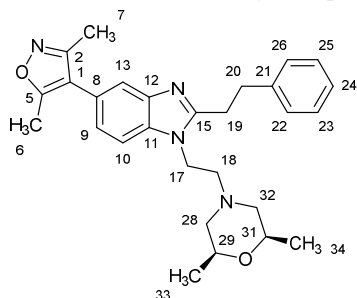
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1-[2-(thiomorpholin-4-yl)ethyl]-1H-benzimidazole (20)



Thiomorpholine (20 μL, 0.20 mmol) was reacted with [5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1*H*-benzimidazol-1-yl]acetaldehyde (50 mg, 0.14 mmol) according to general procedure A. Chromatography was carried out with a gradient of CH₂Cl₂:MeOH:NH₄OH, which was increased linearly from 99:1:0.1 to 92:8:0.8 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (37 mg, 59%); *R*_f 0.45 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); *v*_{max} (neat) 2926 (C-H), 2813 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(7)H₃), 2.43 (s, 3 H, C(6)H₃), 2.64 (s, 6 H, C(7)H₃+C(29)H₂+C(31)H₂), 2.69 - 2.75 (m, 4 H, C(28)H₂+C(32)H₂), 3.17 - 3.24 (m, 2 H, C(19)H₂), 3.26 - 3.33 (m, 2 H, C(20)H₂), 4.09 (t, *J*=7.0 Hz, 2 H, C(17)H₂), 7.12 (dd, *J*=8.0, 1.5 Hz, 1 H, C(9)H), 7.23 - 7.28 (m, 3 H, 3×PhH), 7.28 - 7.37 (m, 3 H, C(10)H+2×PhH),

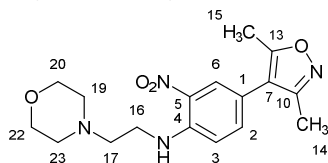
7.64 (d, $J=1.5$ Hz, 1 H, C(13) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.8 (s, 1 C, C(7)), 11.5 (s, 1 C, C(6)), 27.8 (s, 2 C, C(29)+C(31)), 29.7 (s, 1 C, C(19)), 33.8 (s, 1 C, C(20)), 41.6 (s, 1 C, C(17)), 55.4 (s, 2 C, C(28)+C(32)), 57.8 (s, 1 C, C(18)), 109.4 (s, 1 C, C(10)), 117.0 (s, 1 C, C(1)), 119.9 (s, 1 C, C(10)), 123.3 (s, 1 C, C(9)), 124.1 (s, 1 C, C(8)), 126.5 (s, 1 C, C(24)), 128.3 (s, 2 C, C(22/23)+C(26/25)), 128.7 (s, 2 C, C(22/23)+C(26/25)), 134.2 (s, 1 C, C(11)), 140.8 (s, 1 C, C(21)), 143.0 (s, 1 C, C(12)), 155.3 (s, 1 C, C(15)), 159.0 (s, 1 C, C(2)), 165.0 (s, 1 C, C(5)); LRMS m/z (ESI $^+$) 915 [(2M+Na) $^+$], 893 [(2M+H) $^+$], 447 [MH $^+$]; HRMS found 447.2204, calculated for $\text{C}_{26}\text{H}_{31}\text{N}_4\text{O}_5^+$ 447.2213; LCMS (System B) t_r 3.6 min (86%).

1-{2-[(*cis*-2,6-Dimethylmorpholin-4-yl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazolidimethylmorpholine (21)



cis-2,6-Dimethylmorpholine (25 μL , 0.20 mmol) was reacted with [5-(3,5-dimethyl-1,2-oxazol-4-yl)-2-(2-phenylethyl)-1H-benzimidazol-1-yl]acetaldehyde (50 mg, 0.14 mmol) according to general procedure A. Chromatography was carried out with a gradient of CH_2Cl_2 :MeOH: NH_4OH , which was increased linearly from 99:1:0.1 to 92:8:0.8 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (29 mg, 45%); R_f 0.45 (CH_2Cl_2 :MeOH: NH_4OH , 90:10:1); v_{max} (neat) 2973 (C-H), 2934 (C-H), 2870 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.13 (d, $J=6.5$ Hz, 6 H, C(33) H_3 +C(34) H_3), 1.83 (t, $J=10.5$ Hz, 2 H, C(28) H +C(32) H), 2.30 (s, 3 H, C(7) H_3), 2.43 (s, 3 H, C(6) H_3), 2.58 (t, $J=7.0$ Hz, 2 H, C(18) H_2), 2.65 (d, $J=10.5$ Hz, 2 H, C(28) H +C(32) H), 3.16 - 3.24 (m, 2 H, C(19) H_2), 3.26 - 3.33 (m, 2 H, C(20) H_2), 3.56 - 3.67 (m, 2 H, C(29) H +C(31) H), 4.12 (t, $J=7.0$ Hz, 2 H, C(17) H_2), 7.13 (dd, $J=8.5, 1.5$ Hz, 1 H, C(9) H), 7.22 - 7.27 (m, 3 H, 3 \times Ph H), 7.29 - 7.38 (m, 3 H, C(9) H +2 \times Ph H), 7.64 (d, $J=1.5$ Hz, 1 H, C(13) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(7)), 11.5 (s, 1 C, C(6)), 19.0 (s, 2 C, C(33)+C(34)), 29.7 (s, 1 C, C(19)), 33.7 (s, 1 C, C(20)), 41.3 (s, 1 C, C(17)), 57.2 (s, 1 C, C(18)), 59.7 (s, 2 C, C(28)+C(32)), 71.5 (s, 2 C, C(29)+C(31)), 109.4 (s, 1 C, C(10)), 117.1 (s, 1 C, C(1)), 119.9 (s, 1 C, C(13)), 123.4 (s, 1 C, C(9)), 124.1 (s, 1 C, C(8)), 126.5 (s, 1 C, C(24)), 128.3 (s, 2 C, C(22/23)+C(26/25)), 128.7 (s, 2 C, C(22/23)+C(26/25)), 134.3 (s, 1 C, C(11)), 140.9 (s, 1 C, C(21)), 143.0 (s, 1 C, C(12)), 155.3 (s, 1 C, C(15)), 159.0 (s, 1 C, C(2)), 165.0 (s, 1 C, C(5)); LRMS m/z (ESI $^+$) 939 [(2M+Na) $^+$], 917 [(2M+H) $^+$], 459 [MH $^+$]; HRMS (ESI $^+$) found 459.2756, calculated for $\text{C}_{28}\text{H}_{35}\text{N}_4\text{O}_2^+$ 459.2755; LCMS (System B) t_r 3.7 min (81%).

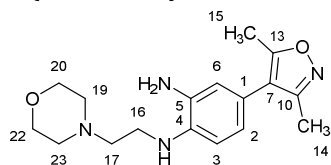
4-(3,5-Dimethyl-1,2-oxazol-4-yl)-N-[2-(morpholin-4-yl)ethyl]-2-nitroaniline



4-(2-Aminoethyl)morpholine (0.787 mL, 6.00 mmol) was added to a solution of compound **10** (1.18 g, 5.00 mmol) and $\text{EtN}(i\text{-Pr})_2$ (1.05 mL, 6.00 mmol) in THF (25 mL). The mixture was left to stir for 16 h at room temperature then more 4-(2-aminoethyl)morpholine (0.262 mL, 2.00 mmol) was added and the reaction was

left to stir for a further 5 h. The mixture was partitioned between EtOAc (20 mL) and water (20 mL). The phases were separated then the organic phase was washed with water (20 mL) and brine (20 mL) then dried over MgSO₄ and evaporated to yield the product as an orange solid (1.63 g, 94%); *R_f* 0.15 (EtOAc); mp 131-133 °C; *v*_{max} (neat) 3343 (N-H), 2967 (C-H), 2941 (C-H), 2856 (C-H), 2811 (C-H), 1526 (N-O), 1352 (N-O); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.26 (s, 3 H, C(14)H₃), 2.40 (s, 3 H, C(15)H₃), 2.50 - 2.60 (m, 4 H, C(19)H₂+C(23)H₂), 2.76 (t, *J*=6.0 Hz, 2 H, C(17)H₂), 3.35 - 3.45 (m, 2 H, C(16)H₂), 3.73 - 3.81 (m, 4 H, C(20)H₂+C(22)H₂), 6.92 (d, *J*=9.0 Hz, 1 H, C(3)H), 7.34 (dd, *J*=9.0, 2.0 Hz, 1 H, C(2)H), 8.09 (d, *J*=2.0 Hz, 1 H, C(6)H), 8.55-8.64 (m, 1 H, NH); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.7 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 39.4 (s, 1 C, C(16)), 53.1 (s, 2 C, C(19)+C(23)), 55.9 (s, 1 C, C(17)), 67.0 (s, 2 C, C(20)+C(22)), 114.7 (s, 1 C, C(3)), 114.9 (s, 1 C, C(7)), 117.2 (s, 1 C, C(1)), 127.0 (s, 1 C, C(6)), 131.9 (s, 1 C, C(5)), 136.7 (s, 1 C, C(2)), 144.4 (s, 1 C, C(4)), 158.6 (s, 1 C, C(10)), 165.3 (s, 1 C, C(13)); LRMS *m/z* (ESI⁺) 715 [(2M+Na)⁺], 693 [(2M+H)⁺], 369 [(M+Na)⁺], 347 [MH⁺]; HRMS (ESI⁺) found 347.1714, calculated for C₁₇H₂₃N₄O₄⁺ 347.1714; LCMS (System A) *t_r* 10.0 min (99%).

4-(3,5-Dimethyl-1,2-oxazol-4-yl)-N¹-[2-(morpholin-4-yl)ethyl]benzene-1,2-diamine (22)



1.0 M aq. Na₂S₂O₄ (50 mL, 50 mmol) was added to a suspension of 4-(3,5-dimethylisoxazol-4-yl)-N-(2-morpholinoethyl)-2-nitroaniline (3.43 g, 3.43 mmol) in EtOH (50 mL). The reaction was heated under reflux for 1 hour then allowed to cool. The mixture was partitioned between 10% aq. NH₃ (50 mL) and EtOAc (50 mL). The phases were separated then the aqueous phase was extracted with more EtOAc (50 mL). The combined organic phases were washed with brine (50 mL) then dried over MgSO₄ and evaporated to yield the product as a pale yellow gum (2.737 g, 87%); *R_f* 0.40 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); *v*_{max} (neat) 3339 (N-H), 2957 (C-H), 2854 (C-H), 2816 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.26 (s, 3 H, C(10)H₃), 2.39 (s, 3 H, C(13)H₃), 2.47 - 2.55 (m, 4 H, C(19)H₂+C(23)H₂), 2.72 (t, *J*=6.0 Hz, 2 H, C(17)H₂), 3.21 (t, *J*=6.0 Hz, 2 H, C(16)H₂), 3.48 (br. s., 2 H, NH₂), 3.70 - 3.78 (m, 4 H, C(20)H₂+C(22)H₂), 4.08 (br. s., 1 H, NH), 6.60 (s, 1 H, C(2)H), 6.69 (s, 2 H, C(3)H+C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 40.2 (s, 1 C, C(17)), 53.4 (s, 2 C, C(19)+C(23)), 57.2 (s, 2 C, C(20)+C(22)), 67.0 (s, 1 C, C(16)), 111.7 (s, 1 C, C(3)), 116.6 (s, 1 C, C(6)), 116.7 (s, 1 C, C(7)), 120.3 (s, 1 C, C(1)), 121.3 (s, 1 C, C(2)), 134.5 (s, 1 C, C(5)), 137.0 (s, 1 C, C(4)), 159.0 (s, 1 C, C(10)), 164.5 (s, 1 C, C(13)); LRMS *m/z* (ESI⁺) 655 [(2M+Na)⁺], 339 [(M+Na)⁺], 317 [MH⁺]; HRMS (ESI⁺) found 317.1971, calculated for C₁₇H₂₄N₄NaO₂⁺ 317.1972; LCMS (System B) *t_r* 2.6 min (97%).

General procedure B

A solution of compound **22** (50 mg, 0.16 mmol), T3P (50 wt.% in EtOAc, 0.50 mL, 0.79 mmol), EtN(*i*-Pr)₂ (31 μL, 0.18 mmol) and a carboxylic acid (0.18 mmol) in EtOAc (0.5 mL) was crimp-sealed in a microwave vial then heated under microwave irradiation for 10 min at 150 °C. The reaction mixture was basified by addition of 1 M aq. NaOH solution then extracted with EtOAc (3 mL). The organic phase was washed with water (3 mL) and brine (3 mL) then the organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on silica (10 g). The desired fractions were combined and evaporated to yield the product.

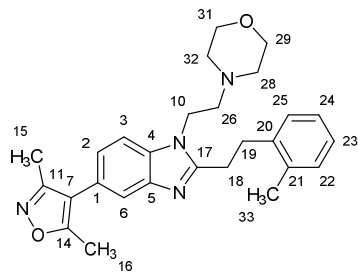
General procedure C

A solution of compound **22** in EtOAc (0.25 M, 0.50 mL, 0.13 mmol) was added to a Radley's GreenHouse tube containing the appropriate carboxylic acid (0.14 mmol). EtN(*i*-Pr)₂ (25 μ L, 0.14 mmol) was added, followed by T3P (50 wt. % in EtOAc, 0.39 mL, 0.65 mmol). The reaction tube was placed in a Radley's GreenHouse reactor with a reflux head and under a nitrogen atmosphere. The reaction was heated under reflux for 16 h then allowed to cool. The reaction mixture was partitioned between 1 M aq. NaOH (2 mL) and CH₂Cl₂ (2 mL). The phases were separated by passing the organic phase through a hydrophobic frit with a small amount of MgSO₄ on the frit. The collected organic phase was evaporated by nitrogen blow-down then the crude material was purified by flash column chromatography on silica (4 g). The column was eluted with a gradient of EtOAc:MeOH:NEt₃, which was increased linearly from 99:1:0.1 to 95:5:0.5 over 20 CVs. The desired fractions were combined and evaporated to yield the product.

General procedure D

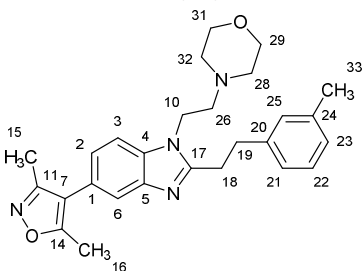
A mixture of compound **22** (40 mg, 0.13 mmol) and a carboxylic acid (0.26 mmol) in 6 M aq. HCl (0.5 mL) was crimp-sealed in a microwave vial then heated under microwave irradiation for 15 min at 210 °C. The mixture was neutralised by careful addition of saturated aq. NaHCO₃ solution then extracted with EtOAc (5 mL). The organic phase was dried by passing through a hydrophobic frit with a small amount of MgSO₄ on top. The crude material was purified by flash column chromatography on silica (4 g). The desired fractions were combined and evaporated to yield the product.

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(2-methylphenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1*H*-benzimidazole (**23**)



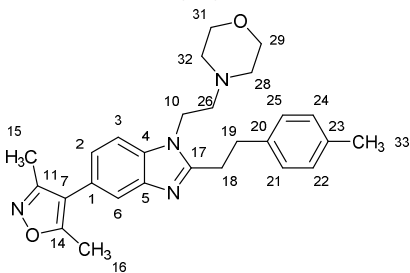
2-Methylhydrocinnamic acid (30 mg, 0.18 mmol) was reacted with compound **22** according to general procedure B. Chromatography was carried out with a gradient of CH₂Cl₂:MeOH:NH₄OH, which was increased linearly from 99:1:0.1 to 90:10:1 over 10 CVs. The product was obtained as a beige solid (44 mg, 62%); mp 121-123 °C; ν_{\max} (neat) 2956 (C-H), 2930 (C-H), 2867 (C-H), 2826 (C-H); R_f 0.40 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); ν_{\max} (neat) 2956 (C-H), 2931 (C-H), 2857 (C-H), 2826 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(15)H₃), 2.38 (s, 3 H, C(33)H₃), 2.43 (s, 3 H, C(16)H₃), 2.44 - 2.48 (m, 4 H, C(28)H₂+C(32)H₂), 2.62 (t, J =7.0 Hz, 2 H, C(26)H₂), 3.09 - 3.20 (m, 2 H, C(18)H₂), 3.25 - 3.34 (m, 2 H, C(19)H₂), 3.58 - 3.70 (m, 4 H, C(29)H₂+C(31)H₂), 4.11 (t, J =7.0 Hz, 2 H, C(10)H₂), 7.00 - 7.23 (m, 5 H, C(2)H+4 \times ArH), 7.36 (d, J =8.5 Hz, 1 H, C(3)H), 7.65 (s, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(15)), 11.5 (s, 1 C, C(16)), 19.3 (s, 1 C, C(33)), 28.3 (s, 1 C, C(18)), 31.1 (s, 1 C, C(19)), 41.4 (s, 1 C, C(10)), 54.0 (s, 2 C, C(28)+C(32)), 57.5 (s, 1 C, C(26)), 66.7 (s, 2 C, C(29)+C(31)), 109.4 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.4 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 126.3 (s, 1 C, C(23/24)), 126.6 (s, 1 C, C(23/24)), 128.8 (s, 1 C, C(25)), 130.4 (s, 1 C, C(22)), 134.2 (s, 1 C, C(4)), 135.9 (s, 1 C, C(21)), 139.0 (s, 1 C, C(20)), 143.0 (s, 1 C, C(5)), 155.4 (s, 1 C, C(17)), 158.9 (s, 1 C, C(11)), 164.9 (s, 1 C, C(14)); LRMS m/z (ESI⁺) 911 [(2M+Na)⁺], 889 [(2M+H)⁺], 467 [(M+Na)⁺], 445 [MH⁺], (ESI⁻) 443 [(M-H)⁻]; HRMS (ESI⁺) found 445.2595, calculated for C₂₇H₃₃N₄O₂⁺ 445.2598; LCMS (System B) t_r 3.7 min (96%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(3-methylphenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (24)



3-(3-Methylphenyl)propionic acid (30 mg, 0.18 mmol) was reacted with compound **22** according to general procedure B. Chromatography was carried out with a gradient of CH₂Cl₂:MeOH:NH₄OH, which was increased linearly from 99:1:0.1 to 92:8:0.8 over 10 CVs. The product was obtained as a pale brown solid (22 mg, 31%); *R_f* 0.40 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); mp 68-70 °C; *v*_{max} (neat) 2925 (C-H), 2815 (C-H), 2816 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(15)H₃), 2.34 (s, 3 H, C(33)H₃), 2.43 (s, 3 H, C(16)H₃), 2.45 - 2.51 (m, 4 H, C(28)H₂+C(32)H₂), 2.62 (t, *J*=7.0 Hz, 2 H, C(26)H₂), 3.16 - 3.24 (m, 2 H, C(18)H₂), 3.24 - 3.31 (m, 2 H, C(19)H₂), 3.63 - 3.73 (m, 4 H, C(29)H₂+C(31)H₂), 4.14 (t, *J*=7.0 Hz, 2 H, C(10)H₂), 7.00 - 7.10 (m, 3 H, C(21)H+C(23)H+C(25)H), 7.13 (dd, *J*=8.5, 1.5 Hz, 1 H, C(2)H), 7.18 - 7.24 (m, 1 H, C(22)H), 7.36 (d, *J*=8.5 Hz, 1 H, C(3)H), 7.64 (d, *J*=1.5 Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(15)), 11.5 (s, 1 C, C(16)), 21.4 (s, 1 C, C(33)), 29.7 (s, 1 C, C(18)), 33.7 (s, 1 C, C(19)), 41.4 (s, 1 C, C(10)), 54.0 (s, 2 C, C(28)+C(32)), 57.6 (s, 1 C, C(26)), 66.8 (s, 2 C, C(29)+C(31)), 109.3 (s, 1 C, C(3)), 117.1 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.4 (s, 1 C, C(2)), 124.2 (s, 1 C, C(1)), 125.3 (s, 1 C, C(21)), 127.2 (s, 1 C, C(23)), 128.6 (s, 1 C, C(22)), 129.2 (s, 1 C, C(25)), 134.3 (s, 1 C, C(4)), 138.3 (s, 1 C, C(20)), 140.8 (s, 1 C, C(24)), 143.0 (s, 1 C, C(5)), 155.4 (s, 1 C, C(17)), 159.0 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); LRMS *m/z* (ESI⁺) 911 [(2M+Na)⁺], 889 [(2M+H)⁺], 467 [(M+Na)⁺], 445 [MH⁺]; HRMS (ESI⁺) found 445.2587, calculated for C₂₇H₃₃N₄O₂⁺ 445.2598; LCMS (System B) *t_r* 3.7 min (99%).

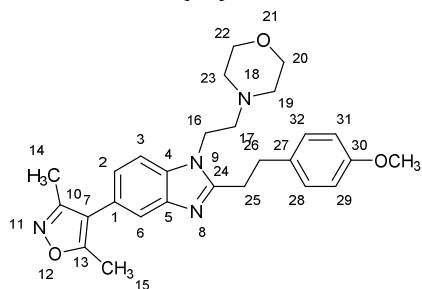
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(4-methylphenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (25)



3-(*p*-Tolyl)propionic acid (30 mg, 0.18 mmol) was reacted with compound **22** according to general procedure B. Chromatography was carried out with a gradient of CH₂Cl₂:MeOH:NH₄OH, which was increased linearly from 99:1:0.1 to 90:10:1 over 10 CVs. The product was obtained as a white solid (25 mg, 35%); *R_f* 0.40; (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); mp 131-133 °C; *v*_{max} (neat) 2962 (C-H), 2922 (C-H), 2860 (C-H), 2824 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(15)H₃), 2.34 (s, 3 H, C(33)H₃), 2.43 (s, 3 H, C(16)H₃), 2.44 - 2.49 (m, 4 H, C(28)H₂+C(32)H₂), 2.60 (t, *J*=7.0 Hz, 2 H, C(26)H₂), 3.14 - 3.22 (m, 2 H, C(18)H₂), 3.23 - 3.31 (m, 2 H, C(19)H₂), 3.65 - 3.71 (m, 4 H, C(29)H₂+C(31)H₂), 4.13 (t, *J*=7.0 Hz, 2 H, C(10)H₂), 7.10 - 7.17 (m, 5 H, C(2)H+4×ArH), 7.36 (d, *J*=8.5 Hz, 1 H, C(3)H), 7.64 (d, *J*=1.0 Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(15)), 11.5 (s, 1 C, C(16)), 21.0 (s, 1 C, C(33)), 29.8 (s, 1 C, C(18)), 33.4 (s, 1 C, C(19)), 41.4 (s, 1 C,

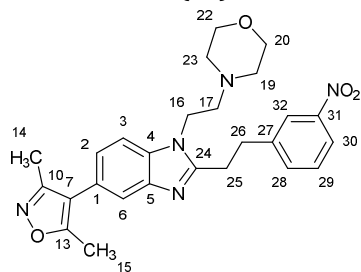
C(10)), 54.0 (s, 2 C, C(28)+C(32)), 57.5 (s, 1 C, C(26)), 66.8 (s, 2 C, C(29)+C(31)), 109.4 (s, 1 C, C(3)), 117.1 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.3 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 128.2 (s, 2 C, C(21/22)+C(25/24)), 129.3 (s, 2 C, C(21/22)+C(25/24)), 134.2 (s, 1 C, C(4)), 136.0 (s, 1 C, C(23)), 137.8 (s, 1 C, C(20)), 143.0 (s, 1 C, C(5)), 155.4 (s, 1 C, C(17)), 159.0 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); LRMS m/z (ESI⁺) 911 [(2M+Na)⁺], 889 [(2M+H)⁺], 467 [(M+Na)⁺], 445 [MH⁺], 443 [(M-H)⁻]; HRMS (ESI⁺) found 445.2590, calculated for C₂₇H₃₃N₄O₂⁺ 445.2598; LCMS (System B) t_r 3.7 min (99%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(4-methoxyphenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (26)



3-(4-Methoxyphenyl)propionic acid (32 mg, 0.18 mmol) was reacted with compound **22** according to general procedure B. Chromatography was carried out with a gradient of CH₂Cl₂:MeOH:NH₄OH, which was increased linearly from 99:1:0.1 to 92:8:0.8 over 10 CVs. The product was obtained as a pale yellow gum (27 mg, 37%); R_f 0.50 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); v_{max} (neat) 2956 (C-H), 2926 (C-H), 2854 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(15)H₃), 2.43 (s, 3 H, C(16)H₃), 2.44 - 2.49 (m, 4 H, C(19)H₂+C(23)H₂), 2.60 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 3.13 - 3.21 (m, 2 H, C(25)H₂), 3.21 - 3.28 (m, 2 H, C(26)H₂), 3.65 - 3.70 (m, 4 H, C(20)H₂+C(22)H₂), 3.79 (s, 3 H, OCH₃), 4.12 (t, $J=7.0$ Hz, 2 H, C(16)H₂), 6.81 - 6.88 (m, 2 H, C(29)H+C(31)H), 7.12 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2)H), 7.14 - 7.18 (m, 2 H, C(28)H+C(32)H), 7.35 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.63 (d, $J=1.5$ Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 29.9 (s, 1 C, C(25)), 33.0 (s, 1 C, C(26)), 41.4 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 55.2 (s, 1 C, OCH₃), 57.5 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 114.0 (s, 2 C, C(29)+C(31)), 117.1 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.3 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 129.3 (s, 2 C, C(28)+C(32)), 132.9 (s, 1 C, C(27)), 134.2 (s, 1 C, C(4)), 143.0 (s, 1 C, C(5)), 155.4 (s, 1 C, C(24)), 158.2 (s, 1 C, C(30)), 159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS m/z (ESI⁺) 943 [(2M+Na)⁺], 921 [(2M+H)⁺], 483 [(M+Na)⁺], 461 [MH⁺]; HRMS (ESI⁺) found 461.2543, calculated for C₂₇H₃₃N₄O₃⁺ 461.2547; LCMS (System B) t_r 3.5 min (91%).

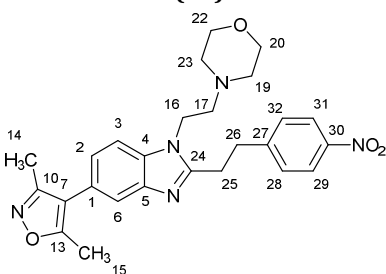
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-[2-(3-nitrophenyl)ethyl]-1H-benzimidazole (27)



3-(3-Nitrophenyl)propanoic acid (27 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a brown gum (23 mg, 37%); R_f 0.20 (EtOAc:MeOH:NEt₃, 95:5:0.5); v_{max} (neat) 2960 (C-H), 2931 (C-H), 2855 (C-H), 2816 (C-H), 1582 (N-O), 1350 (N-O); ¹H NMR (400

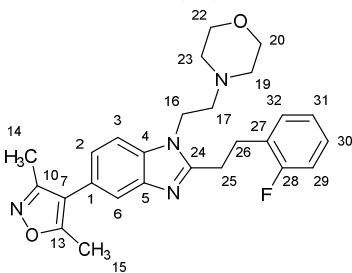
MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.43 (s, 3 H, C(15)H₃), 2.45 - 2.52 (m, 4 H, C(19)H₂+C(23)H₂), 2.68 (t, *J*=6.5 Hz, 2 H, C(17)H₂), 3.28 (t, *J*=8.5 Hz, 2 H, C(25)H₂), 3.47 (t, *J*=8.5 Hz, 2 H, C(26)H₂), 3.62 - 3.69 (m, 4 H, C(20)H₂+C(22)H₂), 4.21 (t, *J*=6.5 Hz, 2 H, C(16)H₂), 7.15 (dd, *J*=8.0, 1.0 Hz, 1 H, C(2)H), 7.38 (d, *J*=8.0 Hz, 1 H, C(3)H), 7.49 (t, *J*=8.0 Hz, 1 H, C(29)H), 7.59 - 7.67 (m, 2 H, C(4)H+C(28)H), 8.11 (d, *J*=8.0 Hz, 1 H, C(30)H), 8.17 (s, 1 H, C(32)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 28.8 (s, 1 C, C(25)), 32.7 (s, 1 C, C(26)), 41.6 (s, 1 C, C(10)), 54.1 (s, 2 C, C(19)+C(23)), 57.7 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 120.0 (s, 1 C, C(6)), 121.6 (s, 1 C, C(30)), 123.1 (s, 1 C, C(32)), 123.7 (s, 1 C, C(2)), 124.4 (s, 1 C, C(1)), 129.6 (s, 1 C, C(29)), 134.3 (s, 1 C, C(4)), 134.9 (s, 1 C, C(28)), 142.8 (s, 1 C, C(5/27)), 142.9 (s, 1 C, C(5/27)), 148.4 (s, 1 C, C(31)), 154.2 (s, 1 C, C(24)), 158.9 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS *m/z* (ESI⁺) 498 [(M+Na)⁺], 476 [MH⁺]; HRMS (ESI⁺) found 476.2277, calculated for C₂₆H₃₀N₅O₄⁺ 476.2292; LCMS (System B) *t_r* 3.8 min (95%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-[2-(4-nitrophenyl)ethyl]-1*H*-benzimidazole (28)



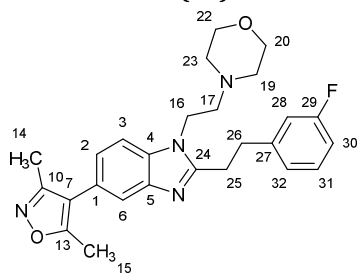
3-(4-Nitrophenyl)propanoic acid (27 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a brown/orange gum (18 mg, 29%); *R_f* 0.15 (EtOAc:MeOH:NEt₃, 95:5:0.5); *v_{max}* (neat) 2934 (C-H), 2854 (C-H), 1516 (N-O), 1344 (N-O); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.43 (s, 3 H, C(15)H₃), 2.45 - 2.53 (m, 4 H, C(19)H₂+C(23)H₂), 2.66 (t, *J*=6.5 Hz, 2 H, C(17)H₂), 3.26 (t, *J*=8.5 Hz, 2 H, C(25)H₂), 3.47 (t, *J*=8.5 Hz, 2 H, C(26)H₂), 3.62 - 3.72 (m, 4 H, C(20)H₂+C(22)H₂), 4.18 (t, *J*=6.5 Hz, 2 H, C(16)H₂), 7.15 (dd, *J*=8.0, 1.0 Hz, 1 H, C(3)H), 7.37 (d, *J*=8.0 Hz, 1 H, C(2)H), 7.45 (d, *J*=8.5 Hz, 2 H, C(28)H+C(32)H), 7.63 (s, 1 H, C(6)H), 8.18 (d, *J*=8.5 Hz, 2 H, C(29)H+C(31)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 28.7 (s, 1 C, C(25)), 33.1 (s, 1 C, C(26)), 41.6 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 57.6 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.5 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(2)), 123.7 (s, 1 C, C(6)), 123.9 (s, 2 C, C(29)+C(31)), 124.5 (s, 1 C, C(1)), 129.3 (s, 2 C, C(28)+C(32)), 134.2 (s, 1 C, C(4)), 142.8 (s, 1 C, C(5)), 146.7 (s, 1 C, C(30)), 148.5 (s, 1 C, C(27)), 154.2 (s, 1 C, C(24)), 158.9 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS *m/z* (ESI⁺) 476 [MH⁺], (ESI⁻) 474 [(M-H)⁻]; HRMS (ESI⁺) found 476.2282, calculated for C₂₆H₃₀N₅O₄⁺ 476.2292; LCMS (System B) *t_r* 3.8 min (97%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(2-fluorophenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1*H*-benzimidazole (29)



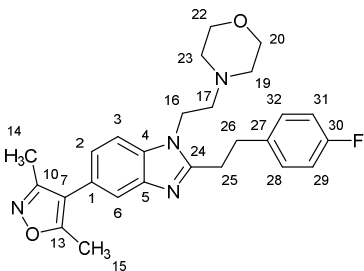
3-(2-Fluorophenyl)propanoic acid (23 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale yellow gum (11 mg, 19%); R_f 0.35 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{\max} (neat) 2933 (C-H), 2856 (C-H), 2819 (C-H); ¹H NMR (500 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.43 (s, 3 H, C(15)H₃), 2.47 - 2.53 (m, 4 H, C(19)H₂+C(23)H₂), 2.68 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 3.19 - 3.26 (m, 2 H, C(26)H₂), 3.27 - 3.34 (m, 2 H, C(25)H₂), 3.65 - 3.71 (m, 4 H, C(20)H₂+C(23)H₂), 4.21 (t, $J=7.0$ Hz, 2 H, C(16)H₂), 7.02 - 7.11 (m, 2 H, C(29)H+C(31)H), 7.14 (dd, $J=8.0, 1.5$ Hz, 1 H, C(2)H), 7.20 - 7.31 (m, 2 H, C(30)H+C(32)H), 7.38 (d, $J=8.0$ Hz, 1 H, C(3)H), 7.64 (d, $J=1.5$ Hz, 1 H C(6)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 27.9 (d, $J=1.9$ Hz, 1 C, C(26)), 28.1 (s, 1 C, C(25)), 41.5 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(22)), 57.6 (s, 1 C, C(17)), 66.7 (s, 2 C, C(20)+C(22)), 109.5 (s, 1 C, C(3)), 115.4 (d, $J=21.0$ Hz, 1 C, C(29)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.5 (s, 1 C, C(2)), 124.3 (s, 1 C, C(1)), 124.4 (d, $J=4.0$ Hz, 1 C, C(31)), 127.5 (d, $J=15.5$ Hz, 1 C, C(27)), 128.4 (d, $J=8.6$ Hz, 1 C, C(30)), 130.9 (d, $J=5.0$ Hz, 1 C, C(32)), 134.2 (s, 1 C, C(4)), 142.8 (s, 1 C, C(5)), 155.1 (s, 1 C, C(24)), 159.0 (s, 1 C, C(10)), 161.2 (d, $J=244.0$ Hz, 1 C, C(28)), 165.0 (s, 1 C, C(13)); ¹⁹F NMR (377 MHz, CDCl₃) δ ppm -118.8 (s, 1 F); LRMS m/z (ESI⁺) 449 [MH⁺]; HRMS (ESI⁺) found 449.2337, calculated for C₂₆H₃₀FN₄O₂⁺ 449.2347; LCMS (System A) t_r 9.4 min (92%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(3-fluorophenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (30)



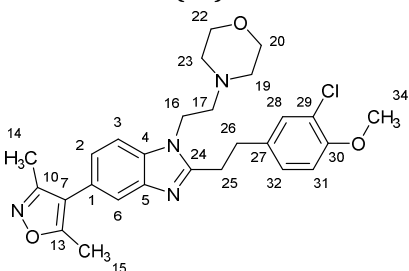
3-(3-Fluorophenyl)propanoic acid (23 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale yellow gum (21 mg, 37%); R_f 0.25 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{\max} (neat) 2962 (C-H), 2929 (C-H), 2854 (C-H), 2825 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.43 (s, 3 H, C(15)H₃), 2.44 - 2.52 (m, 4 H, C(19)H₂+C(23)H₂), 2.63 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 3.18 - 3.24 (m, 2 H, C(25)H₂), 3.29 - 3.37 (m, 2 H, C(26)H₂), 3.61 - 3.72 (m, 4 H, C(20)H₂+C(22)H₂), 4.15 (t, $J=7.0$ Hz, 2 H, C(16)H₂), 6.90 - 6.95 (m, 1 H, C(30)H), 6.95 - 7.00 (m, 1 H, C(28)H), 7.04 (d, $J=7.5$ Hz, 1 H, C(32)H), 7.13 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2)H), 7.24 - 7.31 (m, 1 H, C(23)H), 7.36 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.63 (s, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 29.2 (s, 1 C, C(25)), 33.3 (s, 1 C, C(26)), 41.5 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 57.6 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 113.4 (d, $J=21.5$ Hz, 1 C, C(30)), 115.2 (d, $J=21.0$ Hz, 1 C, C(28)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.5 (s, 1 C, C(2)), 124.0 (d, $J=3.0$ Hz, 1 C, C(32)), 124.3 (s, 1 C, C(1)), 130.1 (d, $J=8.0$ Hz, 1 C, C(31)), 134.2 (s, 1 C, C(4)), 142.9 (s, 1 C, C(5)), 143.4 (d, $J=7.0$ Hz, 1 C, C(27)), 154.8 (s, 1 C, C(24)), 159.0 (s, 1 C, C(10)), 162.9 (d, $J=246.0$ Hz, 1 C, C(29)), 165.0 (s, 1 C, C(13)); ¹⁹F NMR (377 MHz, CDCl₃) δ ppm -113.0 (s, 1 F); LRMS m/z (ESI⁺) 449 [MH⁺]; HRMS (ESI⁺) found 449.2335, calculated for C₂₆H₃₀FN₄O₂⁺ 449.2347; LCMS (System A) t_r 9.6 min (94%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(4-fluorophenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (31)



3-(4-Fluorophenyl)propanoic acid (23 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as an orange gum (22 mg, 39%); R_f 0.20 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{\max} (neat) 2926 (C-H), 2854 (C-H), 2815 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.43 (s, 3 H, C(15)H₃), 2.44 - 2.49 (m, 4 H, C(19)H₂+C(23)H₂), 2.61 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 3.15 - 3.22 (m, 2 H, C(25)H₂), 3.25 - 3.33 (m, 2 H, C(26)H₂), 3.60 - 3.71 (m, 4 H, C(20)H₂+C(22)H₂), 4.13 (t, $J=7.0$ Hz, 2 H, C(16)H₂), 6.99 (t, $J=8.5$ Hz, 2 H, C(29)H+C(31)H), 7.13 (dd, $J=8.0$, 1.5 Hz, 1 H, C(2)H), 7.20 (dd, $J=8.5$, 5.5 Hz, 2 H, C(28)H+C(32)H), 7.36 (d, $J=8.0$ Hz, 1 H, C(3)H), 7.63 (s, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1, C(14)), 11.5 (s, 1 C, C(15)), 29.7 (s, 1 C, C(25)), 32.9 (s, 1 C, C(26)), 41.4 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 57.6 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 115.4 (d, $J=21.5$ Hz, 2 C, C(29)+C(31)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.4 (s, 1 C, C(2)), 124.2 (s, 1 C, C(1)), 129.8 (d, $J=8.0$ Hz, 2 C, C(28)+C(32)), 134.2 (s, 1 C, C(4)), 136.5 (s, 1 C, C(27)), 143.0 (s, 1 C, C(5)), 155.0 (s, 1 C, C(24)), 158.9 (s, 1 C, C(10)), 161.5 (d, $J=253.0$ Hz, 1 C, C(30)), 165.0 (s, 1 C, C(13)); ¹⁹F NMR (377 MHz, CDCl₃) δ ppm -116.5 (s, 1 F); LRMS m/z (ESI⁺) 449 [MH⁺]; HRMS (ESI⁺) found 449.2334, calculated for C₂₆H₃₀FN₄O₂⁺ 449.2347; LCMS (System A) t_r 9.5 min (91%).

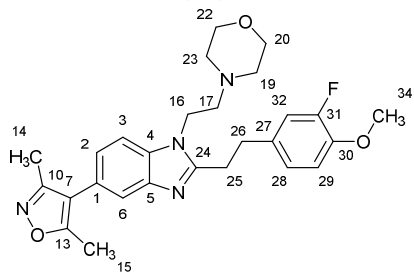
2-[2-(3-Chloro-4-methoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (32)



3-(3-Chloro-4-methoxyphenyl)propanoic acid (30 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale orange gum (27 mg, 43%); R_f 0.25 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{\max} (neat) 2955 (C-H), 2934 (C-H), 2851 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.29 (s, 3 H, C(14)H₃), 2.42 (s, 3 H, C(15)H₃), 2.44 - 2.50 (m, 4 H, C(19)H₂+C(23)H₂), 2.62 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 3.13 - 3.20 (m, 2 H, C(25)H₂), 3.20 - 3.27 (m, 2 H, C(26)H₂), 3.65 - 3.70 (m, 4 H, C(20)H₂+C(22)H₂), 3.88 (s, 3 H, C(34)H₃), 4.15 (t, $J=7.0$ Hz, 2 H, C(16)H₂), 6.86 (d, $J=8.5$ Hz, 1 H, C(31)H), 7.09 (dd, $J=8.5$, 2.0 Hz, 1 H, C(32)H), 7.13 (dd, $J=8.0$, 1.0 Hz, 1 H, C(2)H), 7.27 (d, $J=2.0$ Hz, 1 H, C(28)H), 7.36 (d, $J=8.0$ Hz, 1 H, C(3)H), 7.62 (d, $J=1.0$ Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 29.5 (s, 1 C, C(25)), 32.5 (s, 1 C, C(26)), 41.5 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 56.2 (s, 1 C, C(34)), 57.6 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 112.2 (s, 1 C, C(31)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 122.3 (s, 1 C, C(29)), 123.5 (s, 1 C, C(2)), 124.2 (s, 1 C, C(1)), 127.6 (s, 1 C, C(32)), 130.0 (s, 1 C, C(28)), 133.9 (s, 1 C, C(4/27)), 134.2 (s, 1 C, C(4/27)), 142.9 (s, 1 C, C(5)), 153.6 (s, 1 C, C(30)), 154.9 (s, 1 C, C(24)),

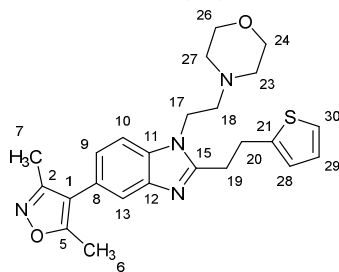
159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS (ESI⁺) *m/z* 497 [M(³⁷Cl)H⁺], 495 [M(³⁵Cl)H⁺]; HRMS (ESI⁺) found 495.2138, calculated for C₂₇H₃₂³⁵ClN₄O₃⁺ 495.2157; LCMS (System A) *t_r* 9.9 min (92%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(3-fluoro-4-methoxyphenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (33)



3-(3-Fluoro-4-methoxyphenyl)propanoic acid (28 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as an off-white solid (19 mg, 31%); *R_f* 0.25 (EtOAc:MeOH:NEt₃, 90:10:1); mp 119-122 °C; *v*_{max} (neat) 2956 (C-H), 2928 (C-H), 2856 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.43 (s, 3 H, C(15)H₃), 2.45 - 2.51 (m, 4 H, C(19)H₂+C(23)H₂), 2.63 (t, *J*=7.0 Hz, 2 H, C(17)H₂), 3.11 - 3.21 (m, 2 H, C(25)H₂), 3.21 - 3.29 (m, 2 H, C(26)H₂), 3.63 - 3.71 (m, 4 H, C(20)H₂+C(22)H₂), 3.87 (s, 3 H, C(34)H₃), 4.15 (t, *J*=7.0 Hz, 2 H, C(16)H₂), 6.85 - 7.02 (m, 3 H, 3×ArH), 7.13 (d, *J*=8.5 Hz, 1 H, C(2)H), 7.36 (d, *J*=8.5 Hz, 1 H, C(3)H), 7.63 (s, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 29.5 (s, 1 C, C(25)), 32.7 (s, 1 C, C(26)), 41.5 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 56.3 (s, 1 C, C(34)), 57.6 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 113.6 (d, *J*=2.5 Hz, 1 C, C(29)), 116.0 (d, *J*=17.5 Hz, 1 C, C(32)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.5 (s, 1 C, C(2)), 123.9 (d, *J*=3.0 Hz, 1 C, C(28)), 124.2 (s, 1 C, C(1)), 133.8 (d, *J*=5.5 Hz, 1 C, C(27)), 134.2 (s, 1 C, C(4)), 142.9 (s, 1 C, C(5)), 146.1 (d, *J*=10.5 Hz, 1 C, C(30)), 152.3 (d, *J*=246.0 Hz, 1 C, C(21)), 155.0 (s, 1 C, C(24)), 159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); ¹⁹F NMR (377 MHz, CDCl₃) δ ppm -135.0 (s, 1 F); LRMS *m/z* (ESI⁺) 479 [MH⁺]; HRMS (ESI⁺) found 479.2445, calculated for C₂₇H₃₂FN₄O₃⁺ 479.2453; LCMS (System A) *t_r* 9.5 min (96%).

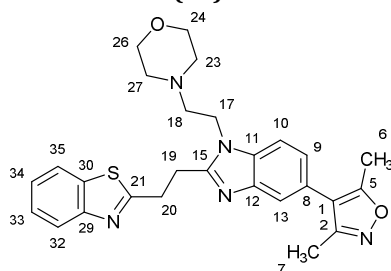
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-[2-(thiophen-2-yl)ethyl]-1H-benzimidazole (34)



2-Thiophenepropionic acid (28 mg, 0.18 mmol) was reacted with compound **22** (50 mg, 0.16 mmol) according to general procedure B. Chromatography was carried out with a gradient of CH₂Cl₂:MeOH:NH₄OH, which was increased linearly from 99:1:0.1 to 92:8:0.8 over 30 CVs. The product was obtained as a colourless gum (31 mg, 44%); *R_f* 0.45 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); *v*_{max} (neat) 2964 (C-H), 2924 (C-H), 2847, (C-H), 2817 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(7)H₃), 2.43 (s, 3 H, C(6)H₃), 2.45 - 2.51 (m, 4 H, C(23)H₂+C(37)H₂), 2.63 (t, *J*=6.5 Hz, 2 H, C(18)H₂), 3.24 - 3.33 (m, 2 H, C(19)H₂), 3.51 - 3.58 (m, 2 H, C(20)H₂), 3.64 - 3.71 (m, 4 H, C(24)H₂+C(26)H₂), 4.17 (t, *J*=6.5 Hz, 2 H, C(17)H₂), 6.86 (d, *J*=3.5 Hz, 1 H, C(28)H), 6.93 (dd,

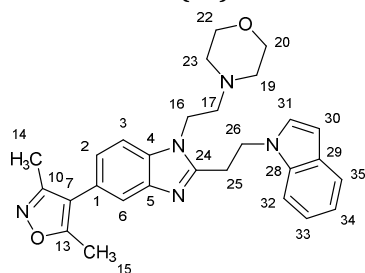
$J=5.0, 3.5$ Hz, 1 H, C(29) H), 7.10 - 7.19 (m, 2 H, C(9) H +C(30) H), 7.36 (d, $J=8.0$ Hz, 1 H, C(10) H), 7.63 (d, $J=1.0$ Hz, 1 H, C(13) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(7)), 11.5 (s, 1 C, C(6)), 27.8 (s, 1 C, C(20)), 29.9 (s, 1 C, C(19)), 41.4 (s, 1 C, C(17)), 54.0 (s, 2 C, C(23)+C(27)), 57.6 (s, 1 C) 66.8 (s, 2 C, C(24)+C(26)), 109.4 (s, 1 C, C(10)), 117.0 (s, 1 C, C(1)), 119.9 (s, 1 C, C(13)), 123.5 (s, 1 C, C(9)), 123.6 (s, 1 C, C(28)), 124.2 (s, 1 C, C(8)), 124.9 (s, 1 C, C(30)), 127.0 (s, 1 C, C(29)), 134.2 (s, 1 C, C(11)), 143.0 (s, 1 C, C(12/21)), 143.2 (s, 1 C, C(12/21)), 154.7 (s, 1 C, C(15)), 159.0 (s, 1 C, C(2)), 165.0 (s, 1 C, C(5)); LRMS m/z (ESI^+) 895 [(2M+Na) $^+$], 873 [(2M+H) $^+$], 459 [(M+Na) $^+$], 437 [MH $^+$]; HRMS (ESI^+) found 437.2011, calculated for $\text{C}_{24}\text{H}_{29}\text{N}_4\text{O}_2\text{S}^+$ 437.2006; LCMS (System B) t_r 3.4 min (94%).

2-(2-{5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazol-2-yl}ethyl)-1,3-benzothiazole (35)



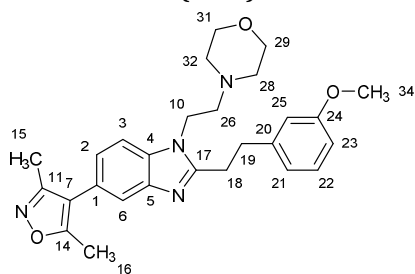
3-(1,3-Benzothiazol-2-yl)propanoic acid (37 mg, 0.14 mmol) was reacted with compound **22** (50 mg, 0.16 mmol) according to general procedure B. Chromatography was carried out with a gradient of CH_2Cl_2 :MeOH: NH_4OH , which was increased linearly from 99:1:0.1 to 92:8:0.8 over 30 CVs. The product was obtained as a light brown gum (30 mg, 38%); R_f 0.40 (CH_2Cl_2 :MeOH: NH_4OH , 90:10:1); v_{max} (neat) 2926 (C-H), 2854 (C-H), 2816 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 2.30 (s, 3 H, C(7) H_3), 2.43 (s, 3 H, C(6) H_3), 2.46 - 2.54 (m, 4 H, C(23) H_2 +C(27) H_2), 2.71 (t, $J=6.5$ Hz, 2 H, C(18) H_2), 3.52 - 3.62 (m, 2 H, C(19) H_2), 3.63 - 3.73 (m, 4 H, C(24) H_2 +C(26) H_2), 3.82 - 3.93 (m, 2 H, C(20) H_2), 4.30 (t, $J=6.5$ Hz, 2 H, C(17) H_2), 7.13 (d, $J=8.5$ Hz, 1 H, C(9) H), 7.33 - 7.40 (m, 2 H, C(10) H +C(33/34) H), 7.47 (t, $J=8.0$ Hz, 1 H, C(33/34) H), 7.63 (s, 1 H, C(13) H), 7.84 (d, $J=8.0$ Hz, 1 H, C(32/35) H), 7.97 (d, $J=8.0$ Hz, 1 H, C(32/35) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.8 (s, 1 C, C(7)), 11.5 (s, 1 C, C(6)), 26.3 (s, 1 C, C(19)), 31.5 (s, 1 C, C(20)), 41.5 (s, 1 C, C(17)), 54.0 (s, 2 C, C(23)+C(27)), 57.8 (s, 1 C, C(18)), 66.8 (s, 2 C, C(24)+C(26)), 109.4 (s, 1 C, C(10)), 117.0 (s, 1 C, C(1)), 119.9 (s, 1 C, C(10)), 121.6 (s, 1 C, C(32/35)), 122.5 (s, 1 C, C(32/35)), 123.5 (s, 1 C, C(9)), 124.3 (s, 1 C, C(8)), 124.9 (s, 1 C, C(33/34)), 126.0 (s, 1 C, C(33/34)), 134.4 (s, 1 C, C(11)), 135.2 (s, 1 C, C(30)), 142.9 (s, 1 C, C(12)), 153.1 (s, 1 C, C(29)), 154.3 (s, 1 C, C(15)), 159.0 (s, 1 C, C(7)), 165.0 (s, 1 C, C(6)), 169.7 (s, 1 C, C(21)); LRMS m/z (ESI^+) 997 [(2M+Na) $^+$], 975 [(2M+H) $^+$], 510 [(M+Na) $^+$], 488 [MH $^+$]; HRMS (ESI^+) found 488.2103, calculated for $\text{C}_{27}\text{H}_{30}\text{N}_5\text{O}_2\text{S}^+$ 488.2115; LCMS (System B) t_r 3.7 min (93%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(1H-indol-1-yl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (36)



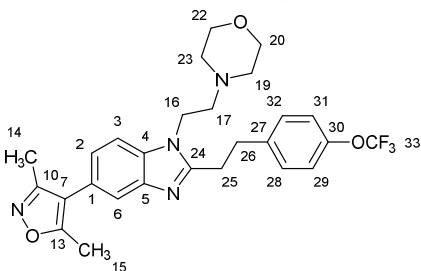
3-(1*H*-Indol-1-yl)propanoic acid (26 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale brown gum (25 mg, 41%); R_f 0.20 (EtOAc:MeOH:NEt₃, 90:10:1); ν_{\max} (neat) 2965 (C-H), 2846 (C-H), 2813 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.14 - 2.18 (m, 4 H, C(19)H₂+C(23)H₂), 2.26 - 2.34 (m, 5 H, C(17)H₂+C(14)H₃), 2.44 (s, 3 H, C(15)H₃), 3.40 (t, $J=6.5$ Hz, 2 H, C(25)H₂), 3.53 - 3.58 (m, 4 H, C(20)H₂+C(22)H₂), 3.61 (t, $J=7.0$ Hz, 2 H, C(16)H₂), 4.80 (t, $J=6.5$ Hz, 2 H, C(26)H₂), 6.43 (d, $J=3.0$ Hz, 1 H, C(30)H), 6.91 (d, $J=3.0$ Hz, 1 H, C(31)H), 7.08 - 7.15 (m, 2 H, C(2)H+C(34)H), 7.19 (t, $J=7.5$ Hz, 1 H, C(33)H), 7.26 - 7.31 (m, 1 H, C(2)H), 7.36 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.56 - 7.66 (m, 2 H, C(6)H+C(35)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 28.4 (s, 1 C, C(25)), 40.9 (s, 1 C, C(16)), 45.0 (s, 1 C, C(26)), 53.6 (s, 2 C, C(19)+C(23)), 57.2 (s, 1 C, C(17)), 66.7 (s, 2 C, C(20)+C(22)), 101.8 (s, 1 C, C(30)), 108.9 (s, 1 C, C(32)), 109.6 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 119.7 (s, 1 C, C(6/34)), 119.8 (s, 1 C, C(6/34)), 121.3 (s, 1 C, C(35)), 121.8 (s, 1 C, C(33)), 123.7 (s, 1 C, C(2)), 124.5 (s, 1 C, C(1)), 127.9 (s, 1 C, C(31)), 128.8 (s, 1 C, C(29)), 134.1 (s, 1 C, C(4)), 135.4 (s, 1 C, C(28)), 142.9 (s, 1 C, C(5)), 153.2 (s, 1 C, C(24)), 158.9 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS m/z (ESI⁺) 492 [(M+Na)⁺], 470 [MH⁺]; HRMS (ESI⁺) found 470.2540, calculated for C₂₇H₃₂N₄O₃⁺ 470.2551; LCMS (System A) t_r 10.1 min (93%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(3-methoxyphenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1*H*-benzimidazole (s101)



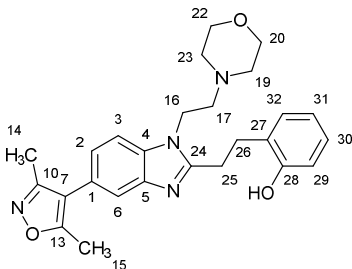
3-(Methoxyphenyl)propionic acid (32 mg, 0.18 mmol) was reacted with compound **22** according to general procedure B. Chromatography was carried out with a gradient of CH₂Cl₂:MeOH:NH₄OH, which was increased linearly from 99:1:0.1 to 90:10:1 over 10 CVs. The product was obtained as a pale yellow gum (38 mg, 52%); R_f 0.40 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); ν_{\max} (neat) 2957 (C-H), 2931 (C-H), 2854 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(15)H₃), 2.43 (s, 3 H, C(16)H₃), 2.44 - 2.49 (m, 4 H, C(28)H₂+C(32)H₂), 2.60 (t, $J=7.0$ Hz, 2 H, C(26)H₂), 3.17 - 3.24 (m, 2 H, C(18)H₂), 3.25 - 3.33 (m, 2 H, C(19)H₂), 3.64 - 3.70 (m, 4 H, C(29)H₂+C(31)H₂), 3.74 (s, 3 H, C(34)H₃), 4.12 (t, $J=7.0$ Hz, 2 H, C(10)H₂), 6.75 - 6.81 (m, 2 H, C(23)H+C(25)H), 6.85 (d, $J=7.5$ Hz, 1 H, C(21)H), 7.13 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2)H), 7.20 - 7.26 (m, 1 H, C(22)H), 7.35 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.63 (d, $J=1.5$ Hz, 1 H, C(2)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(15)), 11.5 (s, 1 C, C(16)), 29.5 (s, 1 C, C(18)), 33.9 (s, 1 C, C(19)), 41.4 (s, 1 C, C(10)), 54.0 (s, 2 C, C(28)+C(32)), 55.1 (s, 1 C, C(34)), 57.5 (s, 1 C, C(26)), 66.8 (s, 2 C, C(29)+C(31)), 109.4 (s, 1 C, C(3)), 111.7 (s, 1 C, C(23)), 114.2 (s, 1 C, C(25)), 117.1 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 120.6 (s, 1 C, C(21)), 123.4 (s, 1 C, C(2)), 124.2 (s, 1 C, C(1)), 129.7 (s, 1 C, C(22)), 134.3 (s, 1 C, C(4)), 142.4 (s, 1 C, C(20)), 143.0 (s, 1 C, C(5)), 155.3 (s, 1 C, C(17)), 159.0 (s, 1 C, C(11)), 159.8 (s, 1 C, C(34)), 165.0 (s, 1 C, C(14)); LRMS m/z (ESI⁺) 943 [(2M+Na)⁺], 921 [(2M+H)⁺], 483 [(M+Na)⁺], 461 [MH⁺]; HRMS (ESI⁺) found 461.2550, calculated for C₂₇H₃₃N₄O₃⁺ 461.2547; LCMS (System B) t_r 3.5 min (99%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-[2-[4-(trifluoromethoxy)phenyl]ethyl]-1H-benzimidazole (s102)



3-[4-(Trifluoromethoxy)phenyl]propanoic acid (33 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale orange resin (32 mg, 51%); R_f 0.15 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{\max} (neat) 2926 (C-H), 2854 (C-H), 2815 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.43 (s, 3 H, C(15)H₃), 2.44 - 2.49 (m, 4 H, C(19)H₂+C(23)H₃), 2.62 (t, $J=7.0$ Hz, 2 H, C(25)H₂), 3.17 - 3.24 (m, 2 H, C(26)H₂), 3.29 - 3.37 (m, 2 H, C(17)H₂), 3.63 - 3.70 (m, 4 H, C(20)H₂+C(22)H₂), 4.13 (t, $J=7.0$ Hz, 2 H, C(16)H₂), 7.10 - 7.19 (m, 3 H, C(3)H+C(29)H+C(31)H), 7.24 - 7.31 (m, 2 H, C(28)H+C(32)H), 7.36 (d, $J=8.0$ Hz, 1 H, C(2)H), 7.63 (s, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 29.4 (s, 1 C, C(25)), 32.9 (s, 1 C, C(26)), 41.5 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 57.6 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 120.4 (q, $J=257.0$ Hz, 1 C, CF₃) 121.2 (s, 2 C, C(29)+C(31)), 123.5 (s, 1 C, C(2)), 124.3 (s, 1 C, C(1)), 129.7 (s, 2 C, C(28)+C(32)), 134.2 (s, 1 C, C(4)), 139.6 (s, 1 C, C(27)), 142.9 (s, 1 C, C(5)), 147.8 (d, $J=1.5$ Hz, 1 C, C(30)), 154.8 (s, 1 C, C(24)), 158.9 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); ¹⁹F NMR (377 MHz, CDCl₃) δ ppm -57.9 (s, 3 F); LRMS (ESI⁺) m/z 515 [MH⁺]; HRMS (ESI⁺) found 515.2251, calculated for C₂₇H₃₀F₃N₄O₃⁺ 515.2265 LCMS (System A) t_r 10.7 min (94%).

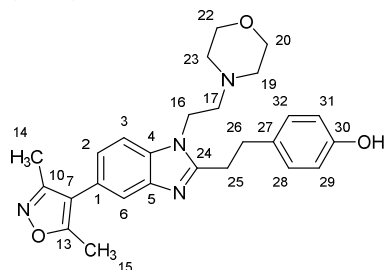
2-(2-{5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazol-2-yl}ethyl)phenol (s103)



3-(2-Hydroxyphenyl)propionic acid (44 mg, 0.26 mmol) was reacted with compound **22** (40 mg, 0.13 mmol) according to general procedure D. Chromatography was carried out with a gradient of EtOAc:MeOH:NEt₃, which was increased linearly from 99:1:0.1 to 90:10:1 over 20 CVs. The product was obtained as a pale orange solid (32 mg, 55%); R_f 0.45 (EtOAc:MeOH:NEt₃, 90:10:1); mp 172-174 °C; ν_{\max} (neat) 3198 (O-H), 2954 (C-H), 2859 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.28 (s, 3 H, C(14)H₃), 2.41 (s, 3 H, C(15)H₃), 2.44 - 2.51 (m, 4 H, C(19)H₂+C(23)H₂), 2.69 (t, $J=6.5$ Hz, 2 H, C(17)H₂), 3.34 (s, 4 H, C(25)H₂+C(26)H₂), 3.59 - 3.69 (m, 4 H, C(20)H₂+C(22)H₂), 4.20 (t, $J=6.5$ Hz, 2 H, C(16)H₂), 6.86 (td, $J=7.5, 1.0$ Hz, 1 H, C(31)H), 6.94 (dd, $J=8.0, 1.0$ Hz, 1 H, C(29)H), 7.07 - 7.16 (m, 2 H, C(2)H+C(30)H), 7.20 (dd, $J=7.5, 1.5$ Hz, 1 H, C(32)H), 7.35 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.64 (d, $J=1.0$ Hz, 1 H, C(6)H) 11.59 (br. s., 1 H, OH); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 25.5 (s, 1 C, C(26)), 29.9 (s, 1 C, C(25)), 41.6 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 57.3 (s, 1 C, C(17)), 66.7 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 116.8 (s, 1 C, C(7)), 119.1 (s, 1

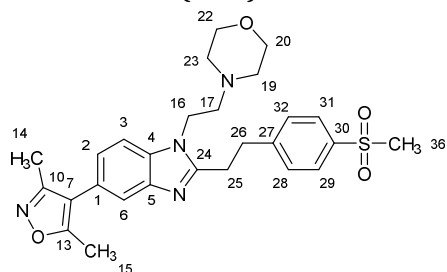
C, C(29)), 119.5 (s, 1 C, C(6)), 120.2 (s, 1 C, C(31)), 124.1 (s, 1 C, C(2)), 124.8 (s, 1 C, C(1)), 128.0 (s, 1 C, C(30)), 128.7 (s, 1 C, C(27)), 130.5 (s, 1 C, C(32)), 134.3 (s, 1 C, C(4)), 140.9 (s, 1 C, C(5)), 155.4 (s, 1 C, C(24/28)), 155.7 (s, 1 C, C(24/28)), 158.8 (s, 1 C, C(10)), 165.1 (s, 1 C, C(13)); LRMS m/z (ESI⁺) 447 [MH⁺], 445 [(M-H)⁻]; HRMS (ESI⁺) found 447.2387, calculated for C₂₆H₃₁N₄O₃⁺ 447.2391; LCMS t_r 3.3 min (System B) (96%).

4-(2-{5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazol-2-yl}ethyl)phenol (s104)



3-(2-Hydroxyphenyl)propionic acid (44 mg, 0.26 mmol) was reacted with compound **22** (40 mg, 0.13 mmol) according to general procedure D. Chromatography was carried out with a gradient of EtOAc:MeOH:NEt₃, which was increased linearly from 99:1:0.1 to 90:10:1 over 30 CVs. The product was obtained as a brown gum (26 mg, 45%); R_f 0.35 (EtOAc:MeOH:NEt₃, 90:10:1); ν_{max} (neat) 3438 (O-H), 2952 (C-H), 2929 (C-H), 2850 (C-H); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.23 (s, 3 H, C(14)H₃), 2.40 (s, 7 H, C(15)H₃+C(19)H₂+C(23)H₂), 2.53 (t, $J=6.5$ Hz, 2 H, C(17)H₂), 3.00 - 3.09 (m, 2 H, C(26)H₂), 3.10 - 3.18 (m, 2 H, C(25)H₂), 3.47 - 3.57 (m, 4 H, C(20)H₂+C(22)H₂), 4.25 (t, $J=6.5$ Hz, 2 H, C(16)H₂), 6.68 (d, $J=8.5$ Hz, 2 H, C(29)H+C(31)H), 7.08 (d, $J=8.5$ Hz, 2 H, C(28)H+C(32)H), 7.16 (dd, $J=8.0, 1.5$ Hz, 1 H, C(2)H), 7.51 - 7.61 (m, 2 H, C(3)H+C(6)H), 9.23 (s, 1 H, OH); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 10.6 (s, 1 C, C(14)), 11.4 (s, 1 C, C(15)), 28.8 (s, 1 C, C(25)), 32.0 (s, 1 C, C(26)), 40.5 (s, 1 C, C(16)), 53.6 (s, 2 C, C(19)+C(23)), 57.5 (s, 1 C, C(17)), 66.2 (s, 2 C, C(20)+C(22)), 110.4 (s, 1 C, C(3)), 115.2 (s, 2 C, C(29)+C(31)), 116.8 (s, 1 C, C(7)), 118.9 (s, 1 C, C(6)), 122.7 (s, 1 C, C(1/2)), 122.8 (s, 1 C, C(1/2)), 129.3 (s, 2 C, C(28)+C(32)), 131.3 (s, 1 C, C(27)), 134.5 (s, 1 C, C(4)), 142.6 (s, 1 C, C(5)), 155.7 (s, 1 C, C(24/30)), 155.7 (s, 1 C, C(24/30)), 158.5 (s, 1 C, C(10)), 164.6 (s, 1 C, C(13)); LRMS m/z (ESI⁺) 445 [(M-H)⁻]; HRMS (ESI⁺) found 447.2397, calculated for C₂₆H₃₁N₄O₃⁺ 447.2391; LCMS (System A) t_r 8.5 min (96%).

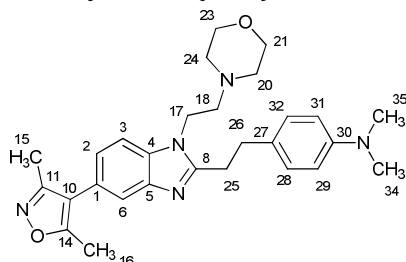
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-{2-[4-(methylsulfonyl)phenyl]ethyl}-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (s105)



3-[4-(Methylsulfonyl)phenyl]propanoic acid (32 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale-orange gum (19 mg, 29%); R_f 0.05 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{max} (neat) 2918 (C-H), 2850 (C-H), 1301 (S=O), 1147 (S=O); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.43 (s, 3 H, C(15)H₃), 2.45 - 2.50 (m, 4 H, C(19)H₂+C(23)H₂), 2.65 (t, $J=6.5$ Hz, 2 H, C(17)H₂), 3.05 (s, 3 H, C(36)H₃), 3.25 (t, $J=8.5$ Hz, 2 H, C(25)H₂), 3.45 (t, $J=8.5$ Hz, 2 H, C(26)H₂), 3.63 - 3.70 (m, 4 H, C(20)H₂+C(22)H₂), 4.17 (t, $J=6.5$ Hz, 2 H, C(16)H₂), 7.15 (dd, $J=8.5, 1.0$ Hz, 1 H, C(2)H), 7.37 (d,

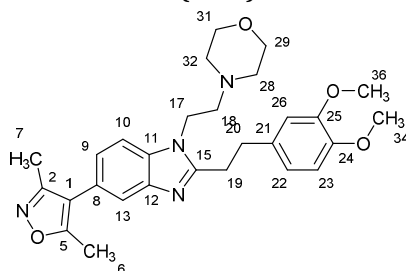
$J=8.5$ Hz, 1 H, C(3) H), 7.48 (d, $J=8.0$ Hz, 2 H, C(28) H +C(32) H), 7.64 (s, 1 H, C(6) H), 7.89 (d, $J=8.0$ Hz, 2 H, C(29) H +C(31) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 28.8 (s, 1 C, C(25)), 33.2 (s, 1 C, C(26)), 41.5 (s, 1 C, C(16)), 44.5 (s, 1 C, C(36)), 54.0 (s, 2 C, C(19)+C(23)), 57.6 (s, 1 C, C(17)), 66.7 (s, 2 C, C(20)+C(22)), 109.5 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.7 (s, 1 C, C(2)), 124.4 (s, 1 C, C(1)), 127.8 (s, 2 C, C(29)+C(31)), 129.4 (s, 2 C, C(28)+C(32)), 134.2 (s, 1 C, C(4)), 138.8 (s, 1 C, C(30)), 142.8 (s, 1 C, C(5)), 147.4 (s, 1 C, C(27)), 154.3 (s, 1 C, C(24)), 158.9 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS m/z (ESI $^+$) 531 [(M+Na) $^+$], 509 [MH $^+$]; HRMS (ESI $^+$) found 509.2205, calculated for $\text{C}_{27}\text{H}_{33}\text{N}_4\text{O}_4\text{S}^+$ 509.2217; LCMS (System B) t_r 3.4 min (92%).

4-(2-{5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazol-2-yl}ethyl)-N,N-dimethylaniline (s106)



3-[4-(Dimethylamino)phenyl]propanoic acid (27 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a colourless gum (29 mg, 47%); R_f 0.40 (EtOAc:MeOH:NEt $_3$, 90:10:1); ν_{max} (neat) 2962 (C-H), 2851 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 2.30 (s, 3 H, C(15) H_3), 2.43 (s, 3 H, C(16) H_3), 2.45 - 2.52 (m, 4 H, C(20) H_2 +C(24) H_2), 2.58 (t, $J=7.0$ Hz, 2 H, C(18) H_2), 2.93 (s, 6 H, C(34) H_3 +C(35) H_3), 3.05 - 3.27 (m, 4 H, C(25) H_2 +C(26) H_2), 3.63 - 3.80 (m, 4 H, C(21) H_2 +C(23) H_2), 4.14 (t, $J=7.0$ Hz, 2 H, C(17) H_2), 6.62 - 6.77 (m, 2 H, C(29) H +C(31) H), 7.02 - 7.17 (m, 3 H, C(2) H +C(28) H +C(32) H), 7.38 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.64 (d, $J=1.0$ Hz, 1 H, C(6) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(15)), 11.5 (s, 1 C, C(16)), 30.0 (s, 1 C, C(25)), 33.1 (s, 1 C, C(26)), 40.7 (s, 2 C, C(34)+C(35)), 41.2 (s, 1 C, C(17)), 53.9 (s, 2 C, C(20)+C(24)), 57.3 (s, 1 C, C(18)), 66.6 (s, 2 C, C(21)+C(23)), 109.4 (s, 1 C, C(3)), 113.0 (s, 2 C, C(29)+C(31)), 117.0 (s, 1 C, C(10)), 119.7 (s, 1 C, C(6)), 123.4 (s, 1 C, C(2)), 124.3 (s, 1 C, C(1)), 128.7 (s, 1 C, C(27)), 129.0 (s, 2 C, C(28)+C(32)), 134.1 (s, 1 C, C(4)), 142.7 (s, 1 C, C(5)), 149.4 (s, 1 C, C(30)), 155.6 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); LRMS m/z (ESI $^+$), 474 [MH $^+$]; HRMS (ESI $^+$) found 474.2851, calculated for $\text{C}_{28}\text{H}_{36}\text{N}_5\text{O}_2^+$ 474.2864; LCMS (System A) t_r 8.3 min (99%).

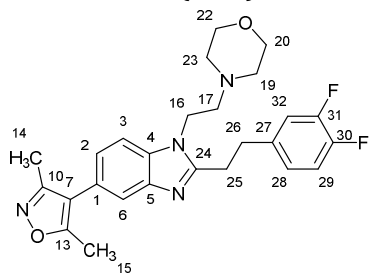
2-[2-(3,4-Dimethoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (s107)



3-(3,4-Dimethoxyphenyl)propionic acid (38 mg, 0.18 mmol) was reacted with compound **22** according to general procedure B. Chromatography was carried out with a gradient of CH_2Cl_2 :MeOH:NH $_4\text{OH}$, which was increased linearly from 99:1:0.1 to 92:8:0.8 over 30 CVs. The product was obtained as a pale yellow gum (45 mg, 57%); R_f 0.35 (CH_2Cl_2 :MeOH:NH $_4\text{OH}$, 90:10:1); ν_{max} (neat) 2958 (C-H), 2934 (C-H), 2855 (C-H), 2834 (C-H);

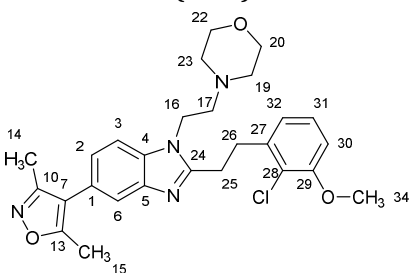
^1H NMR (400 MHz, CDCl_3) δ ppm 2.29 (s, 3 H, C(7) H_3), 2.42 (s, 3 H, C(6) H_3), 2.43 - 2.48 (m, 4 H, C(28) H_2 +C(32) H_2), 2.57 (t, $J=7.0$ Hz, 2 H, C(18) H_2), 3.14 - 3.28 (m, 4 H, C(19) H_2 +C(20) H_2), 3.64 - 3.69 (m, 4 H, C(29) H_2 +C(31) H_2), 3.72 (s, 3 H, C(34/36) H_3), 3.86 (s, 3 H, C(34/36) H_3), 4.08 (t, $J=7.0$ Hz, 2 H, C(17) H_2), 6.67 (d, $J=2.0$ Hz, 1 H, C(26) H), 7.78 (dd, $J=8.0, 2.0$ Hz, 1 H, C(22) H), 6.81 (d, $J=8.0$ Hz, 1 H, C(23) H), 7.12 (dd, $J=8.0, 1.5$ Hz, 1 H, C(9) H), 7.34 (d, $J=8.0$ Hz, 1 H, C(10) H), 7.63 (d, $J=1.5$ Hz, 1 H, C(13) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.8 (s, 1 C, C(7)), 11.5 (s, 1 C, C(6)), 29.9 (s, 1 C, C(19)), 33.6 (s, 1 C, C(20)), 41.4 (s, 1 C, C(17)), 54.0 (s, 2 C, C(28)+C(32)), 55.6 (s, 1 C, C(34/36)), 55.9 (s, 1 C, C(34/36)), 57.5 (s, 1 C, C(18)), 66.8 (s, 2 C, C(29)+C(31)), 109.4 (s, 1 C, C(10)), 111.3 (s, 1 C, C(23)), 111.7 (s, 1 C, C(26)), 117.1 (s, 1 C, C(8)), 119.8 (s, 1 C, C(13)), 120.1 (s, 1 C, C(22)), 123.4 (s, 1 C, C(9)), 124.2 (s, 1 C, C(8)), 133.4 (s, 1 C, C(21)), 134.2 (s, 1 C, C(11)), 143.0 (s, 1 C, C(12)), 147.6 (s, 1 C, C(24/25)), 148.9 (s, 1 C, C(24/25)), 155.3 (s, 1 C, C(15)), 158.9 (s, 1 C, C(2)), 165.0 (s, 1 C, C(5)); LRMS m/z (ESI^+) 981 [(2M+Na) $^+$], 513 [(M+Na) $^+$], 491 [MH^+]; HRMS (ESI^+) found 491.2648, calculated for $\text{C}_{28}\text{H}_{35}\text{N}_4\text{O}_4^+$ 491.2653; LCMS (System B) t_r 3.3 min (88%).

2-[2-(3,4-Difluorophenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (s108)



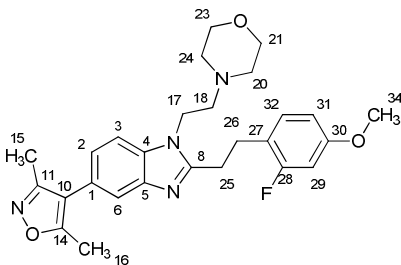
3-(3,4-Difluorophenyl)propanoic acid (26 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale pink solid (24 mg, 41%); R_f 0.20 (EtOAc:MeOH:NEt $_3$, 95:5:0.5); mp 77-80 °C; ν_{max} (neat) 2941 (C-H), 2829 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 2.30 (s, 3 H, C(14) H_3), 2.43 (s, 3 H, C(15) H_3), 2.44 - 2.50 (m, 4 H, C(19) H_2 +C(23) H_2), 2.64 (t, $J=7.0$ Hz, 2 H, C(17) H_2), 3.14 - 3.22 (m, 2 H, C(25)), 3.24 - 3.33 (m, 2 H, C(26) H_2), 3.63 - 3.71 (m, 4 H, C(20) H_2 +C(22) H_2), 4.17 (t, $J=7.0$ Hz, 2 H, C(16) H_2), 6.93 - 6.99 (m, 1 H, C(28) H), 7.03 - 7.11 (m, 2 H, C(29) H +C(32) H), 7.14 (dd, $J=8.0, 1.5$ Hz, 1 H, C(2) H), 7.37 (d, $J=8.0$ Hz, 1 H, C(3) H), 7.62 (s, 1 H, C(6) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(13)), 29.2 (s, 1 C, C(25)), 32.6 (s, 1 C, C(26)), 41.5 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 57.6 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 117.2 (t, $J=17.0$ Hz, 2 C, C(29)+C(32)), 119.9 (s, 1 C, C(6)), 123.6 (s, 1 C, C(2)), 124.2 - 124.3 (m, 1 C, C(28)), 124.3 (s, 1 C, C(1)), 134.2 (s, 1 C, C(4)), 137.7 - 137.8 (m, 1 C, C(27)), 142.9 (s, 1 C, C(5)), 147.6 - 149.2 (m, 2 C, C(30)+C(31)), 154.6 (s, 1 C, C(24)), 158.9 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); ^{19}F NMR (377 MHz, CDCl_3) δ ppm -141.1 (d, $J=21.5$ Hz, 1 F) -137.62 (d, $J=21.5$ Hz, 1 F); LRMS m/z (ESI^+) 467 [MH^+], 465 [(M-H)]; HRMS (ESI^+) found 467.2235, calculated for $\text{C}_{26}\text{H}_{29}\text{F}_2\text{N}_4\text{O}_2^+$ 467.2253; LCMS (System A) t_r 9.9 min (91%).

1-[2-(2-Chloro-3-methoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (s109)



3-(2-Chloro-3-methoxyphenyl)propanoic acid (30 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale yellow gum (22 mg, 35%); R_f 0.25 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{\max} (neat) 2936 (C-H), 2854 (C-H), 2815 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.43 (s, 3 H, C(15)H₃), 2.45 - 2.53 (m, 4 H, C(19)H₂+C(23)H₂), 2.64 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 3.20 - 3.28 (m, 2 H, C(25)H₂), 3.35 - 3.42 (m, 2 H, C(26)H₂), 3.64 - 3.69 (m, 4 H, C(20)H₂+C(22)H₂), 3.92 (s, 3 H, C(34)H₃), 4.19 (t, $J=7.0$ Hz, 2 H, C(16)H₂), 6.86 (d, $J=8.0$ Hz, 1 H, C(30)H), 6.91 (d, $J=8.0$ Hz, 1 H, C(32)H), 7.13 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2)H), 7.17 (t, $J=8.0$ Hz, 1 H, C(31)H), 7.37 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.63 (s, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 27.6 (s, 1 C, C(25)), 32.5 (s, 1 C, C(26)), 41.5 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 56.2 (s, 1 C, C(34)), 57.5 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 110.3 (s, 1 C, C(30)), 117.1 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 122.0 (s, 1 C, C(28)), 122.5 (s, 1 C, C(32)), 123.4 (s, 1 C, C(2)), 124.2 (s, 1 C, C(1)), 127.4 (s, 1 C, C(31)), 134.2 (s, 1 C, C(4)), 139.9 (s, 1 C, C(27)), 143.0 (s, 1 C, C(5)), 155.1 (s, 1 C, C(24/29)), 155.3 (s, 1 C, C(24/29)), 159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS m/z (ESI⁺) 497 [M(³⁷Cl)H⁺] 495 [M(³⁵Cl)H⁺]; HRMS (ESI⁺) found 495.2147, calculated for C₂₇H₃₂³⁵ClN₄O₃⁺ 495.2157; LCMS (System A) t_r 9.7 min (95%).

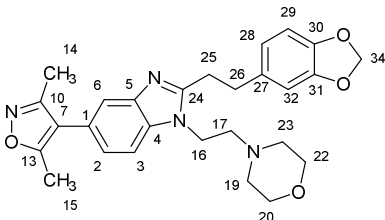
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(2-fluoro-4-methoxyphenyl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (s110)



3-(2-Fluoro-4-methoxyphenyl)propanoic acid (28 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a colourless gum (39 mg, 63%); R_f 0.50 (EtOAc:MeOH:NEt₃, 90:10:1); ν_{\max} (neat) 2943 (C-H), 1739; ¹H NMR (400 MHz, CDCl₃) δ ppm 2.29 (s, 3 H, C(15)H₃), 2.43 (s, 3 H, C(16)H₃), 2.48 - 2.59 (m, 4 H, C(20)H₂+C(24)H₂), 2.68 (t, $J=7.0$ Hz, 2 H, C(18)H₂), 3.14 - 3.34 (m, 4 H, C(25)H₂+C(26)H₂), 3.57 - 3.75 (m, 4 H, C(21)H₂+C(23)H₂), 3.79 (s, 3 H, C(34)H₃), 4.22 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 6.59 - 6.70 (m, 2 H, C(29)H+C(31)H), 7.11 - 7.20 (m, 2 H, C(2)H+C(32)H), 7.40 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.64 (d, $J=1.0$ Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(16)), 27.3 (s, 1 C, C(26)), 28.3 (s, 1 C, C(25)), 41.3 (s, 1 C, C(17)), 53.9 (s, 2 C, C(20)+C(24)), 55.5 (s, 1 C, C(34)), 57.4 (s, 1 C, C(18)), 66.6 (s, 2 C, C(21)+C(23)), 101.8 (d, $J=25.5$ Hz, 1 C, C(29)), 109.5 (s, 1 C, C(3)), 109.8 (d, $J=3.0$ Hz, 1 C, C(31)), 116.9 (s, 1 C, C(10)), 119.1 (d, $J=16.0$ Hz, 1 C, C(27)), 119.7 (s, 1 C, C(6)), 123.7 (s, 1 C, C(2)), 124.5 (s, 1 C, C(1)), 131.1 (d, $J=7.0$ Hz, 1 C, C(32)), 134.0 (s, 1 C, C(4)), 142.3 (s, 1 C, C(5)), 155.1 (s, 1 C, C(8)),

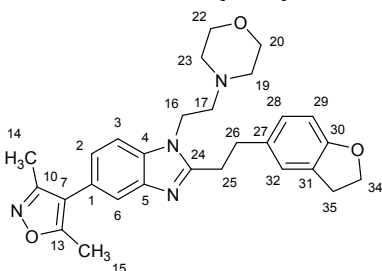
158.9 (s, 1 C, C(11)), 159.7 (d, $J=11.0$ Hz, 1 C, C(30)), 161.5 (d, $J=244.0$ Hz, 1 C, C(28)), 165.0 (s, 1 C, C(14)); ^{19}F NMR (377 MHz, CDCl_3) δ ppm -116.8 (s, 1 F); LRMS m/z (ESI^+) 501 [(M+Na) $^+$], 479 [MH $^+$]; HRMS (ESI^+) found 479.2442, calculated for $\text{C}_{27}\text{H}_{32}\text{FN}_4\text{O}_3^+$ 479.2453; LCMS (System A) t_r 9.8 min (>99%).

2-[2-(1,3-Benzodioxol-5-yl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (s111)



3-(1,3-Benzodioxol-5-yl)propanoic acid (27 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale-yellow gum (9 mg, 15%); R_f 0.25 (EtOAc:MeOH:NEt $_3$, 95:5:0.5); ν_{max} (neat) 2922 (C-H), 2852 (C-H); ^1H NMR (500 MHz, CDCl_3) δ ppm 2.31 (s, 3 H, C(14)H $_3$), 2.44 (s, 3 H, C(15)H $_3$), 2.46 - 2.54 (m, 4 H, C(19)H $_2$ +C(23)H $_2$), 2.63 (t, $J=7.0$ Hz, 2 H, C(17)H $_2$), 3.14 - 3.20 (m, 2 H, C(25)H $_2$), 3.20 - 3.28 (m, 2 H, C(26)H $_2$), 3.65 - 3.75 (m, 4 H, C(20)H $_2$ +C(22)H $_2$), 4.16 (t, $J=7.0$ Hz, 2 H, C(16)H $_2$), 5.94 (s, 2 H, C(34)H $_2$), 6.70 (dd, $J=8.0, 1.5$ Hz, 1 H, C(28)H), 6.73 - 6.78 (m, 2 H, C(29)H+C(32)H), 7.14 (dd, $J=8.0, 1.5$ Hz, 1 H, C(2)H), 7.37 (d, $J=8.0$ Hz, 1 H, C(3)H), 7.64 (d, $J=1.5$ Hz, 1 H, C(6)H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 29.9 (s, 1 C, C(25)), 33.6 (s, 1 C, C(26)), 41.5 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 57.6 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 100.9 (s, 1 C, C(34)), 108.4 (s, 1 C, C(32)), 108.8 (s, 1 C, C(29)), 109.4 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 121.2 (s, 1 C, C(28)), 123.5 (s, 1 C, C(2)), 124.3 (s, 1 C, C(1)), 134.2 (s, 1 C, C(4)), 134.6 (s, 1 C, C(27)), 142.9 (s, 1 C, C(5)), 146.1 (s, 1 C, C(30)), 147.8 (s, 1 C, C(31)), 155.2 (s, 1 C, C(24)), 159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); R_f 0.25 (EtOAc:MeOH:NEt $_3$, 95:5:0.5); LRMS m/z (ESI^+) 475 [MH $^+$]; HRMS (ESI^+) found 475.2325, calculated for $\text{C}_{27}\text{H}_{31}\text{N}_4\text{O}_4^+$ 475.2340; LCMS (System B) t_r 3.6 min (88%).

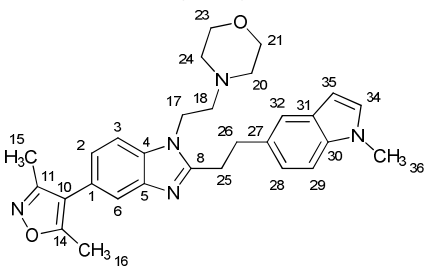
2-[2-(2,3-Dihydro-1-benzofuran-5-yl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (s112)



3-(2,3-Dihydro-1-benzofuran-5-yl)propanoic acid (27 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as an orange/brown gum (17 mg, 28%); R_f 0.25 (EtOAc:MeOH:NEt $_3$, 95:5:0.5); ν_{max} (neat) 2926 (C-H), 2855 (C-H), 2817 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 2.30 (s, 3 H, C(14)H $_3$), 2.43 (s, 3 H, C(15)H $_3$), 2.49 (m, $J=4.0$ Hz, 4 H, C(19)H $_2$ +C(23)H $_2$), 2.63 (t, $J=7.0$ Hz, 2 H, C(17)H $_2$), 3.13 - 3.27 (m, 6 H, C(25)H $_2$ +C(26)H $_2$ +C(33)H $_2$), 3.65 - 3.73 (m, 4 H, C(20)H $_2$ +C(22)H $_2$), 4.15 (t, $J=7.0$ Hz, 2 H, C(16)H $_2$), 4.56 (t, $J=8.5$ Hz, 2 H, C(34)H $_2$), 6.73 (d, $J=8.0$ Hz, 1 H, C(29)H), 6.97 (d, $J=8.0$ Hz, 1 H, C(28)H), 7.09 (s, 1 H, C(32)H), 7.13 (d, $J=8.5$ Hz, 1 H, C(2)H), 7.37 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.64 (s, 1 H, C(6)H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 29.7 (s, 1 C, C(35)), 30.2 (s, 1 C, C(25)), 33.3 (s, 1 C, C(26)), 41.4 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 57.5 (s, 1 C, C(17)), 66.8 (s, 2 C,

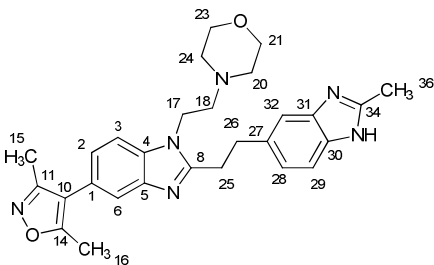
C(20)+C(22)), 71.2 (s, 1 C, C(34)), 109.3 (s, 1 C, C(3/29)), 109.4 (s, 1 C, C(3/29)), 117.0 (s, 1 C, C(7)), 119.8 (s, 1 C, C(6)), 123.4 (s, 1 C, C(2)), 124.3 (s, 1 C, C(1)), 125.0 (s, 1 C, C(32)), 127.4 (s, 1 C, C(31)), 127.7 (s, 1 C, C(28)), 132.8 (s, 1 C, C(27)), 134.2 (s, 1 C, C(4)), 142.9 (s, 1 C, C(5)), 155.4 (s, 1 C, C(24)), 158.7 (s, 1 C, C(30)), 159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS m/z (ESI⁺) 473 [MH⁺]; HRMS (ESI⁺) found 473.2535, calculated for C₂₈H₃₃N₄O₃⁺ 473.2547; LCMS (System B) t_r 3.6 min (87%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(1-methyl-1H-indol-5-yl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (s113)



3-(1-Methyl-1H-indol-5-yl)propanoic acid (28 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a colourless gum (35 mg, 56%); R_f 0.45 (EtOAc:MeOH:NEt₃, 90:10:1); ν_{max} (neat) 2930 (C-H), 2856 (C-H), 2818 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.31 (s, 3 H, C(15)H₃), 2.38 - 2.42 (m, 4 H, C(20)H₂+C(24)H₂), 2.44 (s, 3 H, C(16)H₃), 2.51 (t, $J=7.0$ Hz, 2 H, C(18)H₂), 3.20 - 3.33 (m, 2 H, C(25)H₂), 3.33 - 3.49 (m, 2 H, C(26)H₂), 3.61 - 3.74 (m, 4 H, C(21)H₂+C(23)H₂), 3.79 (s, 3 H, C(36)H₃), 4.11 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 6.43 (dd, $J=3.0, 0.8$ Hz, 1 H, C(35)H), 7.06 (d, $J=3.0$ Hz, 1 H, C(34)H), 7.09 (dd, $J=8.5, 1.5$ Hz, 1 H, C(28)H), 7.13 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2)H), 7.26 (d, $J=8.5$ Hz, 1 H, C(29)H), 7.38 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.50 (d, $J=1.5$ Hz, 1 H, C(32)H), 7.66 (d, $J=1.5$ Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 30.6 (s, 1 C, C(25)), 32.9 (s, 1 C, C(36)), 34.2 (s, 1 C, C(26)), 41.2 (s, 1 C, C(17)), 53.7 (s, 2 C, C(20)+C(24)), 57.2 (s, 1 C, C(18)), 66.6 (s, 2 C, C(21)+C(23)), 100.5 (s, 1 C, C(35)), 109.4 (s, 1 C, C(3/29)), 109.5 (s, 1 C, C(3/29)), 117.0 (s, 1 C, C(10)), 119.7 (s, 1 C, C(6)), 120.1 (s, 1 C, C(32)), 122.2 (s, 1 C, C(28)), 123.4 (s, 1 C, C(2)), 124.3 (s, 1 C, C(1)), 128.8 (s, 1 C, C(31)), 129.3 (s, 1 C, C(34)), 131.6 (s, 1 C, C(27)), 134.1 (s, 1 C, C(4)), 135.6 (s, 1 C, C(30)), 142.7 (s, 1 C, C(5)), 155.7 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); LRMS m/z (ESI⁺) 506 [(M+Na)⁺], 484 [MH⁺]; HRMS (ESI⁺) found 484.2699, calculated for C₂₉H₃₄N₅O₂⁺ 484.2707; LCMS (System A) t_r 9.5 min (>99%).

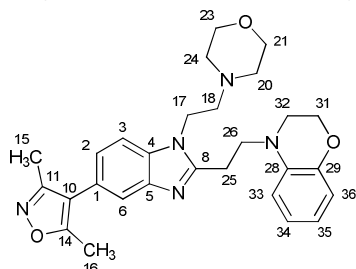
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(2-methyl-1H-benzimidazol-5-yl)ethyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (s114)



3-(2-methyl-1H-benzimidazol-5-yl)propanoic acid (53 mg, 0.26 mmol) was reacted with compound **22** (40mg, 0.13 mmol) according to general procedure D. Chromatography was carried out with a gradient of CH₂Cl₂:MeOH:NH₄OH which was increased linearly from 99:1:0.1 to 90:10:1 over 20 CVs. The product was obtained as a brown gum (39 mg, 62%); R_f 0.35 (EtOAc:MeOH:NEt₃, 90:10:1); ν_{max} (neat) 2927 (C-H), 2855 (C-H), 2814 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.27 (s, 3 H, C(15)H₃), 2.41 (s, 3 H, C(16)H₃), 2.43 - 2.48 (m, 4

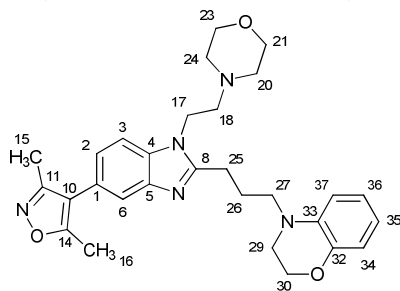
H, C(20)H₂+C(24)H₂), 2.58 - 2.66 (m, 5 H, C(18)H₂+C(36)H₃), 3.24 - 3.32 (m, 2 H, C(25)H₂), 3.33 - 3.41 (m, 2 H, C(26)H₂), 3.63 - 3.70 (m, 4 H, C(21)H₂+C(23)H₂), 4.16 (t, *J*=6.5 Hz, 2 H, C(17)H₂), 5.43 (br. s, 1 H, NH), 7.06 (dd, *J*=8.5, 1.5 Hz, 1 H, C(28)H), 7.14 (dd, *J*=8.0, 1.5 Hz, 1 H, C(2)H), 7.35 - 7.41 (m, 3 H, C(3)H+C(29)H+C(32)H), 7.57 (d, *J*=1.5 Hz, 1 H, C(6)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(15)), 11.5 (s, 1 C, C(16)), 14.9 (s, 1 C, C(36)), 30.2 (s, 1 C, C(25)), 34.1 (s, 1 C, C(26)), 41.5 (s, 1 C, C(17)), 54.0 (s, 2 C, C(20)+C(24)), 57.6 (s, 1 C, C(18)), 66.8 (s, 2 C, C(21)+C(23)), 109.5 (s, 1 C, C(3)), 114.0 (s, 1 C, C(29/32)), 114.4 (s, 1 C, C(29/32)), 117.0 (s, 1 C, C(10)), 119.7 (s, 1 C, C(6)), 122.8 (s, 1 C, C(28)), 123.5 (s, 1 C, C(2)), 124.3 (s, 1 C, C(1)), 134.2 (s, 1 C, C(4)), 134.9 (s, 1 C, C(27)), 137.0 (s, 1 C, C(30/31)), 138.7 (s, 1 C, C(30/31)), 142.8 (s, 1 C, C(5)), 151.1 (s, 1 C, C(34)), 155.4 (s, 1 C, C(8)), 158.9 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); LRMS *m/z* (ESI⁺) 485 [MH⁺], 483 [(M-H)]; HRMS (ESI⁺) found 485.2653, calculated for C₂₈H₃₃N₆O₂⁺ 485.2660; LCMS (System B) *t*_r 2.9 min (93%).

4-(2-{5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-benzimidazol-2-yl}ethyl)-3,4-dihydro-2*H*-1,4-benzoxazine (s115)



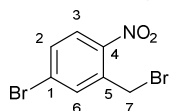
3-(2,3-Dihydro-4*H*-1,4-benzoxazin-4-yl)propanoic acid (29 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale-yellow gum (17 mg, 43%); *R*_f 0.45 (EtOAc:MeOH:NEt₃, 90:10:1); *v*_{max} (neat) 2950 (C-H), 2853 (C-H), 1502; ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(15)H₃), 2.43 (s, 7 H, C(16)H₃+C(20)H₂+C(24)H₂), 2.67 (t, *J*=6.5 Hz, 2 H, C(18)H₂), 3.24 (t, *J*=7.0 Hz, 2 H, C(25)H₂), 3.27 - 3.33 (m, 2 H, C(32)H₂), 3.58 - 3.78 (m, 4 H, C(21)H₂+C(23)H₂), 3.99 (t, *J*=7.0 Hz, 2 H, C(26)H₂), 4.11 - 4.18 (m, 2 H, C(31)H₂), 4.18 - 4.30 (m, 2 H, C(17)H₂), 6.61 - 6.69 (m, 1 H, C(34/35)H), 6.76 (dd, *J*=8.0, 1.5 Hz, 1 H, C(33/36)H), 6.82 (dd, *J*=8.0, 1.5 Hz, 1 H, C(33/36)H), 6.84 - 6.89 (m, 1 H, C(34/35)H), 7.16 (dd, *J*=8.5, 1.5 Hz, 1 H, C(2)H), 7.38 - 7.48 (m, 1 H, C(3)H), 7.63 (d, *J*=1.5 Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 23.7 (s, 1 C, C(25)), 41.2 (s, 1 C, C(17)), 47.8 (s, 1 C, C(20)), 49.4 (s, 1 C, C(18)), 53.7 (s, 2 C, C(20)+C(24)), 57.3 (s, 1 C, C(18)), 64.4 (s, 1 C, C(31)), 66.4 (s, 2 C, C(21)+C(23)), 109.6 (s, 1 C, C(3)), 111.6 (s, 1 C, C(36)), 116.8 (s, 1 C, C(33)), 116.9 (s, 1 C, C(10)), 117.9 (s, 1 C, C(34/35)), 119.7 (s, 1 C, C(6)), 121.8 (s, 1 C, C(34/37)), 123.8 (s, 1 C, C(2)), 124.7 (s, 1 C, C(1)), 133.9 (s, 1 C, C(4/5)), 134.1 (s, 1 C, C(4/5)), 144.2 (s, 1 C, C(4/5)), 153.9 (s, 1 C, C(8)), 158.9 (s, 1 C, C(11)), 165.1 (s, 1 C, C(14)); LRMS *m/z* (ESI⁺) 510 [(M+Na)⁺], 488 [MH⁺]; HRMS (ESI⁺) found 488.2637, calculated for C₂₈H₃₄N₅O₃⁺ 488.2656; LCMS (System A) *t*_r 9.9 min (92%).

4-(3-{5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazol-2-yl}propyl)-3,4-dihydro-2H-1,4-benzoxazine (s116)



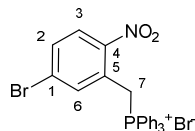
4-(2,3-Dihydro-4H-1,4-benzoxazin-4-yl)butanoic acid (31 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale-brown gum (18 mg, 28%); R_f 0.40 (EtOAc:MeOH:NEt₃, 90:10:1); ν_{\max} (neat) 2932 (C-H), 2855 (C-H); ¹H NMR (500 MHz, CDCl₃) δ ppm 2.25 - 2.36 (m, 5 H, C(15)H₃+C(26)H₂), 2.41 - 2.44 (m, 3 H, C(16)H₃), 2.46 - 2.54 (m, 4 H, C(20)H₂+C(24)H₂), 2.71 (t, $J=6.5$ Hz, 2 H, C(18)H₂), 3.01 (t, $J=7.5$ Hz, 2 H, C(25)H₂), 3.36 - 3.41 (m, 2 H, C(29)H₂), 3.48 (t, $J=7.0$ Hz, 2 H, C(27)H₂), 3.66 - 3.75 (m, 4 H, C(21)H₂+C(23)H₂), 4.19 - 4.23 (m, 2 H, C(30)H₂), 4.26 (t, $J=6.5$ Hz, 2 H, C(17)H₂), 6.60 (td, $J=7.5, 1.5$ Hz, 1 H, C(35)H), 6.63 (dd, $J=8.0, 1.5$ Hz, 1 H, C(37)H), 6.73 - 6.79 (m, 2 H, C(34)H+C(36)H), 7.15 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2)H), 7.40 (d, $J=8.5$ Hz, 1 H, C(3)H), 7.63 (d, $J=1.5$ Hz, 1 H, C(6)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(15)), 11.5 (s, 1 C, C(16)), 24.3 (s, 1 C, C(26)), 24.5 (s, 1 C, C(25)), 41.2 (s, 1 C, C(17)), 47.1 (s, 1 C, C(29)), 50.0 (s, 1 C, C(27)), 53.8 (s, 2 C, C(20)+C(24)), 57.3 (s, 1 C, C(18)), 64.4 (s, 1 C, C(30)), 66.5 (s, 2 C, C(21)+C(23)), 109.5 (s, 1 C, C(3)), 112.0 (s, 1 C, C(34/37)), 116.5 (s, 1 C, C(35/36)), 116.9 (s, 1 C, C(10)), 117.6 (s, 1 C, C(35/36)), 119.7 (s, 1 C, C(6)), 121.5 (s, 1 C, C(34/37)), 123.8 (s, 1 C, C(2)), 124.6 (s, 1 C, C(1)), 134.0 (s, 1 C, C(4)), 135.2 (s, 1 C, C(33)), 144.0 (s, 1 C, C(32)), 155.1 (s, 1 C, C(8)), 158.9 (s, 1 C, C(11)), 165.1 (s, 1 C, C(14)); LRMS m/z (ESI⁺) 524 [(M+Na)⁺], 502 [MH⁺]; HRMS (ESI⁺) found 502.2806, calculated for C₂₉H₃₆N₅O₃⁺ 502.2813; LCMS (System A) t_r 10.0 min (99%).

4-Bromo-2-(bromomethyl)-1-nitrobenzene



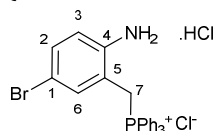
3-Bromobenzyl bromide (5.00 g, 20.0 mmol) was added portion-wise to cooled (-10 °C) c.H₂SO₄ (20 mL). c.HNO₃ (4 mL) was added drop-wise at a rate which maintained the temperature below 0 °C. The mixture was allowed to warm to room temperature over 2 h then poured onto crushed ice (50 mL). Once all the ice had melted, the resultant mixture was extracted with EtOAc (20 mL). The phases were separated then the organic phase was washed with water (3×20 mL) and brine (20 mL) then dried over MgSO₄ and evaporated directly onto silica. The crude material was purified by flash column chromatography on a silica column (330 g). The column was eluted with a gradient of EtOAc:c-hexane which was increased linearly from 2:98 to 20:80 over 10 CVs. The desired fractions were combined and evaporated to yield the product as a pale-yellow solid (2.27 g, 39%); mp 75-78 °C {lit.¹ mp 77-78 °C}; R_f 0.35 (EtOAc:c-hexane, 10:90); ¹H NMR (500 MHz, CDCl₃) δ ppm 4.79 (s, 2 H, C(7)H₂), 7.63 (dd, $J=8.5, 2.0$ Hz, 1 H, C(2)H), 7.75 (d, $J=2.0$ Hz, 1 H, C(6)H), 7.95 (d, $J=8.5$ Hz, 1 H, C(3)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 27.9 (s, 1 C, C(10)), 127.0 (s, 1 C, C(3)), 128.4 (s, 1 C, C(1)), 132.7 (s, 1 C, C(2)), 134.7 (s, 1 C, C(5)), 135.4 (s, 1 C, C(6)), 146.6 (s, 1 C, C(4)); HRMS (FI⁺) found 294.8723, calculated for C₇H₅Br₂NO₂⁺ 294.8667; LCMS (System B) t_r 5.8 min (>99%).

(5-Bromo-2-nitrobenzyl)(triphenyl)phosphonium bromide



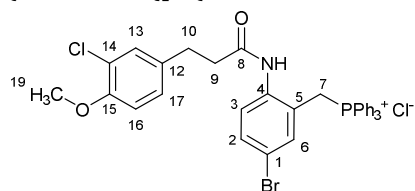
Triphenyl phosphine (1.95 g, 7.46 mmol) was added to a stirred solution of 4-bromo-2-(bromomethyl)-1-nitrobenzene (2.20 g, 7.45 mmol) in CHCl_3 (15 mL). The mixture was stirred for 64 h at room temperature then concentrate *in vacuo*. CHCl_3 (15 mL) and Et_2O (15 mL) were added then the solid was collected by filtration. The solid was dried under vacuum to yield the product as a pale yellow solid (4.15 g, quant.); mp 269-271 °C {lit.¹ mp 256-258 °C}; ^1H NMR (400 MHz, CDCl_3) δ ppm 6.23 (d, $J=15.0$ Hz, 2 H, C(7) H_2), 7.61 (dt, $J=9.0$, 2.5 Hz, 1 H, C(2) H), 7.63 - 7.70 (m, 6 H, 6 \times Ph H), 7.70 - 7.78 (m, 6 H, 6 \times Ph H), 7.78 - 7.85 (m, 4 H, 3 \times Ph H +C(3) H), 8.16 (t, $J=2.5$ Hz, 1 H, C(6) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 28.2 (d, $J=48.5$ Hz, 1 C, C(7)), 116.9 (d, $J=86.0$ Hz, 3 C, 3 \times ArC) 126.6 (d, $J=8.5$ Hz, 1 C, C(5)) 126.9 (d, $J=2.5$ Hz, 1 C, C(3)), 129.8 (d, $J=3.0$ Hz, 1 C, C(1)), 130.4 (d, $J=12.5$ Hz, 6 C, 6 \times ArC) 133.1 (d, $J=3.0$ Hz, 1 C, C(2)), 134.2 (d, $J=10.5$ Hz, 6 C, 6 \times ArC) 135.4 (d, $J=3.0$ Hz, 3 C, 3 \times ArC) 137.6 (d, $J=5.5$ Hz, 1 C, C(6)), 147.1 (d, $J=5.5$ Hz, 1 C, C(4)); ^{31}P NMR (162 MHz, CDCl_3) δ ppm 24.8 (s, 1 P); LRMS m/z (ESI⁺) 478 [$\text{M}^{(81}\text{Br})^+$], 476 [$\text{M}^{(79}\text{Br})^+$]; LCMS (System B) t_r 4.7 min (93%).

(2-Amino-5-bromobenzyl)(triphenyl)phosphonium chloride hydrochloride (38)



Zinc dust (2.96 g, 45.3 mmol) was added portion-wise to a solution of (5-bromo-2-nitrobenzyl)(triphenyl)phosphonium bromide (5.05 g, 9.06 mmol) in AcOH (90 mL). The resultant suspension was stirred at room temperature for 1 h then filtered through Celite. The filter cake was washed with MeCN then the filtrate was concentrated *in vacuo*. The residue was azeotroped with toluene (2 \times 50 mL) then dried under high vacuum to yield the desired product as a beige foam (4.67 g, 99%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 4.94 (d, $J=15.0$ Hz, 2 H, C(7) H_2), 6.54 (d, $J=8.5$ Hz, 1 H, C(2) H), 6.60 (t, $J=2.5$ Hz, 1 H, C(3) H), 7.13 (dt, $J=9.0$, 2.0 Hz, 1 H, C(6) H), 7.62 - 7.80 (m, 12 H, 12 \times Ph H), 7.85 - 8.01 (m, 3 H, 3 \times Ph H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 24.3 (d, $J=47.5$ Hz, 1 C, C(7)), 106.6 (d, $J=4.0$ Hz, 1 C, C(1)), 112.4 (d, $J=8.0$ Hz, 1 C, C(5)), 117.9 (d, $J=85.0$ Hz, 3 C, 3 \times PhC) 118.0 (d, $J=3.0$ Hz, 1 C, C(2)), 130.1 (d, $J=12.0$ Hz, 6 C, 6 \times PhC) 131.8 (d, $J=3.0$ Hz, 1 C, C(6)), 133.6 (d, $J=5.0$ Hz, 1 C, C(3)), 134.1 (d, $J=9.5$ Hz, 6 C, 6 \times PhC) 135.2 (d, $J=2.5$ Hz, 3 C, 3 \times PhC) 146.9 (d, $J=5.5$ Hz, 1 C, C(4)); ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$) δ ppm 21.5 (s, 1 P); LRMS m/z (ESI⁺) 448 [$\text{M}^{(81}\text{Br})^+$], 446 [$\text{M}^{(79}\text{Br})^+$]; LCMS (System B) t_r 4.7 min (99%).

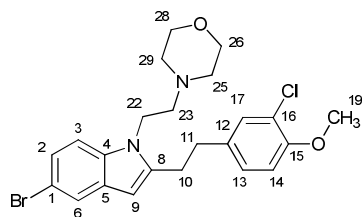
(5-Bromo-2-[[3-(3-chloro-4-methoxyphenyl)propanoyl]amino]benzyl)(triphenyl)phosphonium chloride



Oxalyl chloride (239 μL , 2.83 mmol) was added to a solution of 3-(3-chloro-4-methoxyphenyl)propanoic acid (202 mg, 0.94 mmol) in CH_2Cl_2 (5 mL). DMF (1 drop) was added then the resultant solution was stirred at room temperature for 1 h. The solvent was evaporated by nitrogen blow-down. The residue was re-dissolved in CH_2Cl_2 (5 mL) then evaporated by blow-down. The residue was dissolved in CH_2Cl_2 (1 mL) then added drop-

wise to a cooled (0 °C) solution of compound **38** (202 mg, 0.94 mmol) in DMF (1.5 mL) and pyridine (0.5 mL). The mixture was allowed to warm to room temperature then stirred for 16 h. The solvent was evaporated by nitrogen blow-down then the residue was partitioned between EtOAc (5 mL) and 1 M aq. HCl solution (5 mL). The phases were separated then the organic phase was washed with brine (5 mL) then dried over MgSO₄ and evaporated. The crude material was suspended in Et₂O (5 mL) then the supernatant was decanted off with a pipette. The solid material was dried under vacuum to yield the product as a yellow solid (243 mg, 56%); mp 169-171 °C; ν_{\max} (neat) 3064 (C-H), 2909 (C-H), 1687 (C=O) ; ¹H NMR (400 MHz, CDCl₃) δ ppm 2.41 - 2.49 (m, 2 H, C(10)H₂), 2.56 - 2.64 (m, 2 H, C(9)H₂), 3.76 (s, 3 H, C(19)H₃), 5.61 (d, *J*=14.5 Hz, 2 H, C(7)H₂), 6.69 - 6.79 (m, 2 H, C(6)H+C(16)H), 7.06 - 7.19 (m, 3 H, C(2)H+C(13)H+C(17)H), 7.44 - 7.56 (m, 7 H, C(3)H+6×PhH), 7.56 - 7.71 (m, 9 H, 9×PhH), 10.28 (br. s., 1 H, NH); ¹³C NMR (101 MHz, CDCl₃) δ ppm 27.5 (d, *J*=46.0 Hz, 1 C, C(7)), 30.1 (s, 1 C, C(10)), 37.6 (s, 1 C, C(9)), 56.1 (s, 1 C, C(19)), 112.1 (s, 1 C, C(16)), 116.9 (d, *J*=4.0 Hz, 1 C, C(1)), 117.6 (d, *J*=86.0 Hz, 3 C, 3×PhC) 121.6 (s, 1 C, C(14)), 121.9 (d, *J*=8.5 Hz, 1 C, C(5)), 127.5 (s, 1 C, C(12)), 127.7 (d, *J*=4.0 Hz, 1 C, C(3)), 128.0 (s, 1 C, C(17)), 130.1 (d, *J*=12.0 Hz, 6 C, 6×PhC) 130.3 (s, 1 C, C(13)), 131.7 (d, *J*=4.0 Hz, 1 C, C(2)), 134.3 (d, *J*=9.5 Hz, 6 C, 6×PhC) 134.5 (d, *J*=18.5 Hz, 1 C, C(6)), 134.9 (d, *J*=3.0 Hz, 3 C, 3×PhC) 137.4 (d, *J*=5.5 Hz, 1 C, C(4)), 153.0 (s, 1 C, C(15)), 171.9 (s, 1 C, C(8)); LRMS *m/z* (ESI⁺) 645 [M(⁸¹Br)⁺], 643 [M(⁷⁹Br)⁺]; HRMS found 644.0943, calculated for C₃₅H₃₁(⁸¹Br)ClNO₂P⁺ 644.0939, found 642.0959, calculated for C₃₅H₃₁(⁷⁹Br)ClNO₂P⁺ 642.0959; LCMS (System B) *t_r* 6.2 min (85%).

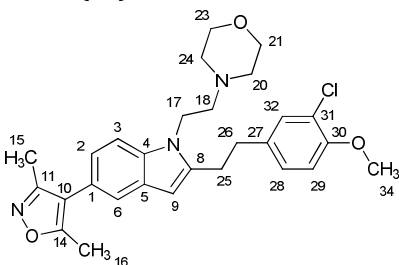
2-[2-(3-Chloro-4-methoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1H-indole



A suspension of (5-bromo-2-[[3-(3-chloro-4-methoxyphenyl)propanoyl]amino}benzyl)(triphenyl)phosphonium chloride (318 mg, 0.46 mmol) and KO^t-Bu (63 mg, 0.57 mmol) in anhydrous toluene (4 mL) was crimp-sealed in a microwave vial then heated under microwave irradiation for 15 minutes at 130 °C. The resultant mixture was partitioned between EtOAc (5 mL) and 1 M aq. HCl (5 mL). The phases were separated then the organic phase was washed with water (5 mL) and brine (5 mL) then dried over MgSO₄ and evaporated directly onto silica. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:c-hexane which was increased linearly from 10:90 to 30:70 over 12 CVs. The desired fractions were combined and evaporated to yield the intermediate bromoindole **39** as an off-white solid (94 mg, 56%). The bromoindole was dissolved in DMF (1 mL) then 4-(2-chloroethyl)morpholine hydrochloride (53 mg, 0.28 mmol), and K₂CO₃ (108 mg, 0.78 mmol) were added. The mixture was heated at 80 °C for 2 h then potassium iodide (46 mg, 0.28 mmol) was added. The mixture was heated at 80 °C for 16 h then allowed to cool. The solids were removed by filtration then NaH (60% dispersion in mineral oil, 11 mg, 0.28 mmol) was added. The mixture was heated at 80 °C for 3 h then more 4-(2-chloroethyl)morpholine hydrochloride (53 mg, 0.28 mmol) and NaH (60% dispersion in mineral oil, 11 mg, 0.28 mmol) were added. The mixture was heated at 80 °C for a further 24 h then allowed to cool. The mixture was partitioned between EtOAc (5 mL) and water (5 mL). The phases were separated then the organic phase was washed with water (5 mL) and brine (5 mL) then dried over MgSO₄ and evaporated. The crude material was purified by flash column chromatography on a silica column (4 g) which was eluted with EtOAc. The desired fractions were combined and evaporated to

yield the product as a yellow/brown gum (30 mg, 24% from bromoindole); R_f 0.30 (EtOAc); mp 157-160 °C; ^1H NMR (400 MHz, CDCl_3) δ ppm 2.31 - 2.42 (m, 4 H, $\text{C}(25)\text{H}_2+\text{C}(29)\text{H}_2$), 2.50 (t, $J=7.0$ Hz, 2 H, $\text{C}(23)\text{H}_2$), 2.93 (s, 4 H, $\text{C}(10)\text{H}_2+\text{C}(11)\text{H}_2$), 3.56 - 3.68 (m, 4 H, $\text{C}(26)\text{H}_2+\text{C}(28)\text{H}_2$), 3.81 (s, 3 H, $\text{C}(19)\text{H}_3$), 4.05 (t, $J=7.0$ Hz, 2 H, $\text{C}(22)\text{H}_2$), 6.15 (s, 1 H, $\text{C}(9)\text{H}$), 6.78 (d, $J=8.5$ Hz, 1 H, $\text{C}(14)\text{H}$), 6.97 (dd, $J=8.5, 2.0$ Hz, 1 H, $\text{C}(13)\text{H}$), 7.07 (d, $J=8.5$ Hz, 1 H, $\text{C}(3)\text{H}$), 7.15 (dd, $J=8.5, 2.0$ Hz, 1 H, $\text{C}(2)\text{H}$), 7.18 (d, $J=2.0$ Hz, 1 H, $\text{C}(17)\text{H}$), 7.57 (d, $J=2.0$ Hz, 1 H, $\text{C}(6)\text{H}$); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 28.6 (s, 1 C, $\text{C}(10)$), 33.4 (s, 1 C, $\text{C}(11)$), 41.0 (s, 1 C, $\text{C}(22)$), 54.0 (s, 2 C, $\text{C}(25)+\text{C}(29)$), 56.2 (s, 1 C, $\text{C}(19)$), 57.7 (s, 1 C, $\text{C}(23)$), 66.7 (s, 2 C, $\text{C}(26)+\text{C}(28)$), 98.9 (s, 1 C, $\text{C}(9)$), 110.3 (s, 1 C, $\text{C}(3)$), 112.1 (s, 1 C, $\text{C}(14)$), 112.7 (s, 1 C, $\text{C}(1)$), 122.3 (s, 1 C, $\text{C}(16)$), 122.5 (s, 1 C, $\text{C}(6)$), 123.5 (s, 1 C, $\text{C}(2)$), 127.5 (s, 1 C, $\text{C}(13)$), 129.7 (s, 1 C, $\text{C}(5)$), 130.0 (s, 1 C, $\text{C}(17)$), 134.1 (s, 1 C, $\text{C}(12)$), 135.1 (s, 1 C, $\text{C}(4)$), 141.1 (s, 1 C, $\text{C}(8)$), 153.5 (s, 1 C, $\text{C}(15)$); LRMS m/z (ESI^+) 479 [$\text{M}^{(81}\text{Br})\text{H}^+$], 477 [$\text{M}^{(79}\text{Br})\text{H}^+$]; HRMS (ESI^+) found 479.0902, calculated for $\text{C}_{23}\text{H}_{27}^{(81}\text{Br})\text{ClN}_2\text{O}_2^+$ 479.0918, found 477.0926, calculated for $\text{C}_{23}\text{H}_{27}^{(79}\text{Br})\text{ClN}_2\text{O}_2^+$ 477.0939; LCMS (System B) t_r 6.5 min (72%).

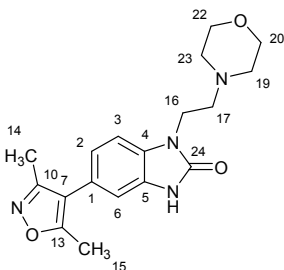
2-[2-(3-Chloro-4-methoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-indole (40)



$\text{Pd}(\text{dppf})\text{Cl}_2$ (5 mg, 0.0063 mmol) was added to a solution of 2-[2-(3-Chloro-4-methoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1H-indole (30 mg, 0.063 mmol) and 3,5-dimethylisoxazole-4-boronic acid pinacol ester (17 mg, 0.075 mmol) in DME (0.5 mL). The mixture was stirred then saturated aq. NaHCO_3 solution (0.2 mL) was added. The mixture was degassed by evacuating and refilling with nitrogen ($\times 3$) then heated at 80 °C for 2 h. The reaction was allowed to cool then partitioned between EtOAc (1 mL) and water (1 mL). The phases were separated then organic phase was passed through a hydrophobic frit then evaporated. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:*c*-hexane, which was increased linearly from 80:20 to 100:0 over 30 column volumes (CVs). The desired fractions were combined and evaporated then then the material was dissolved in MeOH and loaded onto a pre-wetted SCX-cartridge (1 g). Non-basic components were eluted with MeOH then the captured product was released by elution with methanolic ammonia solution (7 M). The basic eluent was evaporate to yield the product as a yellow gum (13 mg, 42%); R_f 0.45 (EtOAc); v_{max} (neat) 2958 (C-H), 2854 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 2.29 (s, 3 H, $\text{C}(15)\text{H}_3$), 2.42 (s, 3 H, $\text{C}(16)\text{H}_3$), 2.46 - 2.57 (m, 4 H, $\text{C}(20)\text{H}_2+\text{C}(24)\text{H}_2$), 2.66 (t, $J=6.5$ Hz, 2 H, $\text{C}(18)\text{H}_2$), 2.97 - 3.15 (m, 4 H, $\text{C}(25)\text{H}_2+\text{C}(26)\text{H}_2$), 3.64 - 3.78 (m, 4 H, $\text{C}(21)\text{H}_2+\text{C}(23)\text{H}_2$), 3.91 (s, 3 H, $\text{C}(34)\text{H}_3$), 4.16 - 4.28 (m, 2 H, $\text{C}(17)\text{H}_2$), 6.33 (s, 1 H, $\text{C}(9)\text{H}$), 6.88 (d, $J=8.5$ Hz, 1 H, $\text{C}(29)\text{H}$), 7.04 (dd, $J=8.5, 1.5$ Hz, 1 H, $\text{C}(2)\text{H}$), 7.10 (dd, $J=8.5, 2.0$ Hz, 1 H, $\text{C}(28)\text{H}$), 7.30 (d, $J=2.0$ Hz, 1 H, $\text{C}(32)\text{H}$), 7.35 (d, $J=8.5$ Hz, 1 H, $\text{C}(3)\text{H}$), 7.41 (d, $J=1.5$ Hz, 1 H, $\text{C}(6)\text{H}$); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, $\text{C}(15)$), 11.5 (s, 1 C, $\text{C}(16)$), 28.6 (s, 1 C, $\text{C}(25)$), 33.6 (s, 1 C, $\text{C}(26)$), 40.8 (s, 1 C, $\text{C}(17)$), 53.9 (s, 2 C, $\text{C}(20)+\text{C}(24)$), 56.2 (s, 1 C, $\text{C}(34)$), 57.7 (s, 1 C, $\text{C}(18)$), 66.7 (s, 2 C, $\text{C}(21)+\text{C}(23)$), 99.5 (s, 1 C, $\text{C}(9)$), 109.2 (s, 1 C, $\text{C}(3)$), 112.2 (s, 1 C, $\text{C}(29)$), 117.5 (s, 1 C, $\text{C}(10)$), 120.7 (s, 1 C, $\text{C}(6)$), 121.6 (s, 1 C, $\text{C}(1)$), 122.3 (s, 2 C, $\text{C}(2)+\text{C}(31)$), 127.6 (s, 1 C, $\text{C}(28)$), 128.3 (s, 1 C, $\text{C}(5)$), 130.0 (s, 1 C, $\text{C}(32)$), 134.2 (s, 1 C, $\text{C}(27)$), 135.7 (s, 1 C, $\text{C}(4)$), 140.7 (s, 1 C, $\text{C}(8)$), 153.5 (s, 1 C, $\text{C}(30)$), 159.2 (s, 1 C, $\text{C}(11)$), 164.7 (s, 1 C, $\text{C}(14)$); LRMS m/z (ESI^+) 496

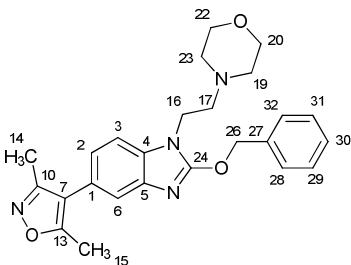
[M(³⁷Cl)H⁺], 494[M(³⁵Cl)H⁺]; HRMS (ESI⁺) found 494.2191, calculated for C₂₈H₃₃(³⁵Cl)N₃O₃⁺ 494.2205, found 496.2182, calculated for C₂₈H₃₃(³⁷Cl)N₃O₃⁺ 496.2178; LCMS (System B) t_r 5.0 min (94%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1,3-dihydro-2H-benzimidazol-2-one



A solution of compound **22** (1.00 g, 3.16 mmol) and CDI (1.02 g, 6.32 mmol) in THF (10 mL) was heated under reflux for 16 h. The reaction mixture was allowed to cool then partitioned between EtOAc (20 mL) and water (20 mL). The phases were separated then the organic phase was washed with water (20 mL) and brine (20 mL) then dried over MgSO₄ and evaporated. The crude material was purified by flash column chromatography on silica (80 g). The column was eluted with a gradient of EtOAc:MeOH, which was increased linearly from 100:0 to 80:20 over 11 CVs. The desired fractions were combined and evaporated then the resultant material re-dissolved in EtOAc (20 mL). The solution was washed with water (2×20 mL) and brine (20 mL) then dried over MgSO₄ to yield the product as an off-white solid (0.78 g, 78%); R_f 0.25 (EtOAc:MeOH:NEt₃, 90:10:1); mp 180-183 °C; v_{max} (neat) 2930 (C-H), 2857 (C-H), 2828 (C-H), 1703 (C=O); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.26 (s, 3 H, C(14)H₃), 2.40 (s, 3 H, C(15)H₃), 2.52 - 2.64 (m, 4 H, C(19)H₂+C(23)H₂), 2.75 (t, J=7.0 Hz, 2 H, C(17)H₂), 3.61 - 3.75 (m, 4 H, C(20)H₂+C(22)H₂), 4.06 (t, J=7.0 Hz, 2 H, C(16)H₂), 6.96 (dd, J=8.0, 1.5 Hz, 1 H, C(2)H), 7.00 (s, 1 H, C(6)H), 7.10 (d, J=8.0 Hz, 1 H, C(3)H), 10.29 (s, 1 H, NH); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 38.4 (s, 1 C, C(16)), 53.7 (s, 2 C, C(19)+C(23)), 56.2 (s, 1 C, C(17)), 66.9 (s, 2 C, C(20)+C(22)), 108.1 (s, 1 C, C(3)), 110.3 (s, 1 C, C(6)), 116.7 (s, 1 C, C(7)), 122.5 (s, 1 C, C(2)), 123.8 (s, 1 C, C(1)), 128.4 (s, 1 C, C(5)), 129.8 (s, 1 C, C(4)), 155.7 (s, 1 C, C(24)), 158.8 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS (System B) m/z (ESI⁺) 365 [(M+Na)⁺], 343 [MH⁺], (ESI⁻) 341 [(M-H)⁻]; HRMS (ESI⁺) found 343.1752, calculated for C₁₈H₂₃N₄O₃⁺ 343.1765; LCMS (System B) t_r 3.0 min (99%).

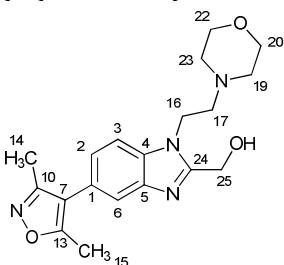
2-(Benzyloxy)-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (41)



Benzyl bromide (59 μL, 0.50 mmol) was added to a suspension of 5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1,3-dihydro-2H-benzimidazol-2-one (100 mg, 0.33 mmol) and Ag₂CO₃ (182 mg, 0.66 mmol) in toluene (2 mL). The resultant suspension was heated at 80 °C for 16 h then allowed to cool. The mixture was evaporated directly onto silica then purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH:NEt₃ which was increased linearly from 99:1:0.1 to 90:10:1 over 30 CVs. The desired fractions were combined and evaporated then the material was

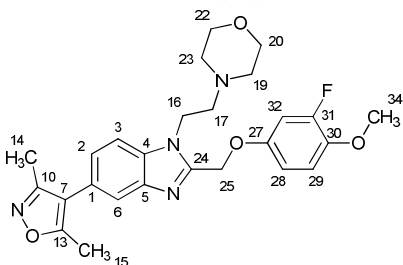
re-purified on silica (4 g). Eluted with a gradient of CH₂Cl₂:MeOH:NH₄OH which was increased linearly from 99:1:0.1 to 94:6:0.6 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (33 mg, 23%); *R_f* 0.50 (EtOAc:MeOH:NEt₃, 90:10:1); *v*_{max} (neat) 2970 (C-H), 1739; ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3 H, C(14)H₃), 2.42 (s, 3 H, C(15)H₃), 2.44 - 2.53 (m, 4 H, C(19)H₂+C(23)H₂), 2.71 (t, *J*=6.5 Hz, 2 H, C(17)H₂), 3.55 - 3.64 (m, 4 H, C(20)H₂+C(22)H₂), 4.15 (t, *J*=6.5 Hz, 2 H, C(16)H₂), 5.61 (s, 2 H, C(26)H₂), 7.04 (dd, *J*=8.0, 1.5 Hz, 1 H, C(2)H), 7.25 (d, *J*=8.0 Hz, 1 H, C(3)H), 7.37 - 7.52 (m, 6 H, C(6)H+5×PhH); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 39.5 (s, 1 C, C(16)), 53.7 (s, 2 C, C(19)+C(23)), 56.9 (s, 1 C, C(17)), 66.7 (s, 2 C, C(20)+C(22)), 72.0 (s, 1 C, C(26)), 108.4 (s, 1 C, C(3)), 117.2 (s, 1 C, C(7)), 118.4 (s, 1 C, C(6)), 122.1 (s, 1 C, C(2)), 123.7 (s, 1 C, C(1)), 128.2 (s, 2 C, 2×ArC) 128.7 (s, 3 C, 3×ArC) 133.0 (s, 1 C, C(4)), 135.4 (s, 1 C, C(27)), 140.4 (s, 1 C, C(5)), 157.8 (s, 1 C, C(24)), 159.0 (s, 1 C, C(10)), 164.9 (s, 1 C, C(13)); LRMS *m/z* (ESI⁺) 455 [(M+Na)⁺], 433 [MH⁺]; HRMS (ESI⁺) found 433.2218, calculated for C₂₅H₂₉N₄O₃⁺ 433.2234; LCMS (System B) *t_r* 4.0 min (91%).

{5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazol-2-yl}methanol



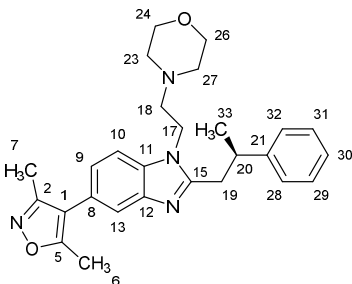
A mixture of compound **22** (316 mg, 1.00 mmol) and glycolic acid (114 mg, 1.50 mmol) in 6 M aq. HCl (5 mL) was heated under microwave irradiation for 20 minutes at 180 °C. The pH of the resultant solution was made basic by drop-wise addition of 20% aq. NaOH solution. The mixture was extracted with EtOAc (10 mL). The phases were separated then the organic phase was washed with water (10 mL) and brine (10 mL) then dried over MgSO₄ and evaporated. The crude material was purified by flash column chromatography on a silica column (24 g). The column was eluted with a gradient of CH₂Cl₂:MeOH:NH₄OH which was increased linearly from 99:1:0.1 to 90:10:1 over 12 CVs. The desired fractions were combined and evaporated to yield the product as a pale-orange solid (221 mg, 62%); *R_f* 0.35 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); mp 154-158 °C; *v*_{max} (neat) 3122 (O-H), 2842 (C-H), 2813 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.28 (s, 3 H, C(14)H₃), 2.41 (s, 3 H, C(15)H₃), 2.49 - 2.70 (m, 4 H, C(19)H₂+C(23)H₂), 2.88 (t, *J*=5.5 Hz, 2 H, C(17)H₂), 3.66 - 3.83 (m, 4 H, C(20)H₂+C(22)H₂), 4.43 (t, *J*=5.5 Hz, 2 H, C(16)H₂), 4.91 (s, 2 H, C(25)H₂), 7.18 (dd, *J*=8.5, 1.5 Hz, 1 H, C(2)H), 7.41 (d, *J*=8.5 Hz, 1 H, C(3)H), 7.64 (d, *J*=1.5 Hz, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 42.0 (s, 1 C, C(16)), 54.3 (s, 2 C, C(19)+C(23)), 56.8 (s, 1 C, C(25)), 57.8 (s, 1 C, C(17)), 66.1 (s, 2 C, C(20)+C(22)), 109.6 (s, 1 C, C(6)), 116.8 (s, 1 C, C(7)), 120.6 (s, 1 C, C(3)), 124.4 (s, 1 C, C(2)), 125.0 (s, 1 C, C(1)), 134.1 (s, 1 C, C(5)), 142.3 (s, 1 C, C(4)), 154.7 (s, 1 C, C(24)), 158.8 (s, 1 C, C(10)), 165.1 (s, 1 C, C(13)); LRMS *m/z* (ESI⁺) 379 [(M+Na)⁺], 357 [MH⁺], (ESI⁻) 355 [(M-H)⁻]; HRMS (ESI⁺) found 357.1914, calculated for C₁₉H₂₅N₄O₃⁺ 357.1921; LCMS (System B) *t_r* 2.7 min (>99%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[(3-fluoro-4-methoxyphenoxy)methyl]-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (42)



Tri-*n*-butylphosphine (165 μ L, 0.66 mmol) was added to a solution of {5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazol-2-yl}methanol (120 mg, 0.33 mmol), 3-fluoro-4-methoxyphenol (72 mg, 0.51 mmol) and azodicarbonyldipiperidide (168 mg, 0.66 mmol) in CH_2Cl_2 (2 mL). The solution was stirred at room temperature for 16 h then diluted with methanol (3 mL) and loaded onto a pre-wetted SCX cartridge (2 g). Eluted with MeOH then the captured basic components were eluted with CH_2Cl_2 :MeOH: NH_4OH (90:10:1). The basic eluent was evaporated then the crude material was purified by flash column chromatography on a silica column (12 g). The column was eluted with a gradient of EtOAc:MeOH: NEt_3 which was increased linearly from 100:0:0 to 98:2:0.2 over 20 CVs. The desired fractions were combined and evaporated to yield the product as a yellow gum (107 mg, 67%); R_f 0.15 (EtOAc); v_{max} (neat) 2953 (C-H), 2836 (C-H), 2800 (C-H), 1512; ^1H NMR (400 MHz, CDCl_3) δ ppm 2.29 (s, 3 H, C(14) H_3), 2.42 (s, 3 H, C(15) H_3), 2.48 - 2.71 (m, 4 H, C(19) H_2 +C(23) H_2), 2.75 - 2.96 (m, 2 H, C(17) H_2), 3.67 - 3.81 (m, 4 H, C(20) H_2 +C(22) H_2), 3.84 (s, 3 H, C(34) H_3), 4.42 - 4.61 (m, 2 H, C(16) H_2), 5.41 (s, 2 H, C(25) H_2), 6.80 - 6.93 (m, 3 H, C(28) H +C(29) H +C(32) H), 7.21 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2) H), 7.46 - 7.59 (m, 1 H, C(2) H), 7.66 (d, $J=1.5$ Hz, 1 H, C(6) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 41.5 (s, 1 C, C(16)), 53.8 (s, 2 C, C(19)+C(23)), 56.9 (s, 1 C, C(34)), 57.6 (s, 1 C, C(17)), 64.3 (s, 1 C, C(25)), 66.4 (s, 2 C, C(20)+C(22)), 104.6 (d, $J=22.5$ Hz, 1 C, C(32)), 109.3 (d, $J=3.0$ Hz, 1 C, C(29)), 110.0 (s, 1 C, C(3)), 114.4 (d, $J=2.5$ Hz, 1 C, C(28)), 116.8 (s, 1 C, C(7)), 120.8 (s, 1 C, C(6)), 124.8 (s, 1 C, C(2)), 124.9 (s, 1 C, C(1)), 134.7 (s, 1 C, C(4)), 142.5 (s, 1 C, C(5)), 142.7 (d, $J=11.0$ Hz, 1 C, C(24)), 150.0 (s, 1 C, C(24)), 152.7 (d, $J=247.0$ Hz, 1 C, C(31)), 151.8 (d, $J=9.5$ Hz, 1 C, C(27)), 158.9 (s, 1 C, C(10)), 165.1 (s, 1 C, C(13)); ^{19}F NMR (377 MHz, CDCl_3) δ ppm -131.4 (s, 1 F); LRMS m/z (ESI $^+$) 503 [(M+Na) $^+$], 481 [MH $^+$]; HRMS (ESI $^+$) found 481.2240, calculated for $\text{C}_{26}\text{H}_{30}\text{FN}_4\text{O}_4^+$ 481.2246; LCMS (System A) t_r 10.5 min (98%).

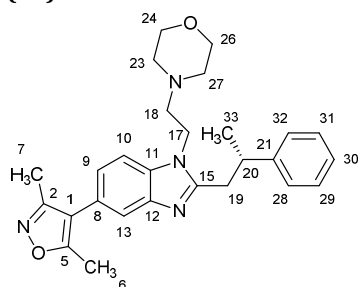
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-[(2R)-2-phenylpropyl]-1H-benzimidazole (43)



(*R*)-3-Phenylbutyric acid (28 μ L, 0.18 mmol) was reacted with compound **22** (50 mg, 0.16 mmol) according to general procedure B. Chromatography was carried out with a gradient of CH_2Cl_2 :MeOH: NH_4OH , which was increased linearly from 99:1:0.1 to 92:8:0.8 over 30 CVs. The product was obtained as a pale yellow gum (34 mg, 48%); R_f 0.45 (CH_2Cl_2 :MeOH: NH_4OH , 90:10:1); $[\alpha]_D^{22}$ -91.4 (c 2.8 in CHCl_3); v_{max} (neat) 2961 (C-H), 2931

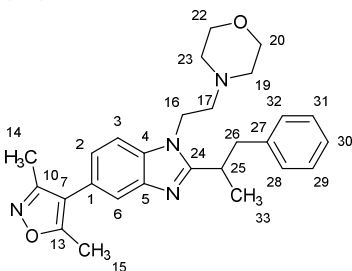
(C-H), 2855 (C-H), 2815 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.46 (d, $J=7.0$ Hz, 3 H, C(33) H_3), 2.31 (s, 3 H, C(7) H_3), 2.37 - 2.62 (m, 9 H, C(6) H_3 +C(18) H_2 +C(23) H_2 +C(27) H_2), 3.16 (d, $J=7.0$ Hz, 2 H, C(19) H_2), 3.53 - 3.64 (m, 1 H, C(20) H), 3.64-3.71 (m, 4 H, C(24) H_2 +C(26) H_2), 3.92 - 4.07 (m, 2 H, C(17) H_2), 7.11 (dd, $J=8.0, 1.5$ Hz, 1 H, C(9) H), 7.19 - 7.26 (m, 3 H, 3 \times Ph H), 7.28 - 7.35 (m, 3 H, C(10) H +2 \times Ph H), 7.63 (d, $J=1.5$ Hz, 1 H, C(13) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(7)), 11.6 (s, 1 C, C(6)), 21.2 (s, 1 C, C(33)), 36.6 (s, 1 C, C(19)), 39.0 (s, 1 C, C(20)), 41.2 (s, 1 C, C(17)), 53.9 (s, 2 C, C(23)+C(27)), 57.5 (s, 1 C, C(18)), 66.7 (s, 2 C, C(24)+C(26)), 109.4 (s, 1 C, C(10)), 117.0 (s, 1 C, C(1)), 119.8 (s, 1 C, C(13)), 123.2 (s, 1 C, C(9)), 124.1 (s, 1 C, C(8)), 126.6 (s, 1 C, C(30)), 126.7 (s, 2 C, C(28/29)+C(32/31)), 128.6 (s, 2 C, C(28/29)+C(32/31)), 134.1 (s, 1 C, C(11)), 143.1 (s, 1 C, C(12)), 145.9 (s, 1 C, C(21)), 154.7 (s, 1 C, C(15)), 159.0 (s, 1 C, C(2)), 165.0 (s, 1 C, C(5)); LRMS m/z (ESI $^+$) 911 [(2M+Na) $^+$], 889 [(2M+H) $^+$], 467 [(M+Na) $^+$], 445 [MH $^+$]; HRMS (ESI $^+$) found 445.2596, calculated for $\text{C}_{27}\text{H}_{33}\text{N}_4\text{O}_2^+$ 445.2598; LCMS (System B) t_r 3.5 min (90%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-[(2S)-2-phenylpropyl]-1H-benzimidazole (44)



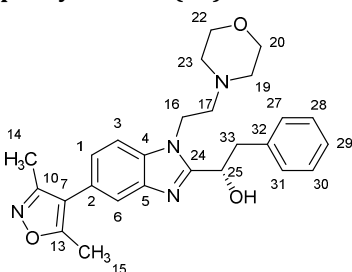
(S)-3-Phenylbutyric acid (28 μL , 0.18 mmol) was reacted with compound **22** (50 mg, 0.16 mmol) according to general procedure B. Chromatography was carried out with a gradient of EtOAc:MeOH:NEt $_3$, which was increased linearly from 99:1:0.1 to 95:5:0.5 over 20 CVs. The product was obtained as a colourless gum (26 mg, 36%); R_f 0.25 (EtOAc:MeOH:NEt $_3$, 90:10:1); $[\alpha]_D^{20}$ +99.6 (c 2.8 in CHCl_3); ν_{max} (neat) 2960 (C-H), 2929 (C-H), 2854 (C-H), 2815 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.46 (d, $J=7.0$ Hz, 3 H, C(33) H_3), 2.30 (s, 3 H, C(14) H_3), 2.41 - 2.52 (m, 8 H, C(15) H_3 +C(17) H_AH_B +C(19) H_2 +C(23) H_2), 2.53 - 2.62 (m, 1 H, C(17) H_AH_B), 3.09 - 3.22 (m, 2 H, C(25) H_2), 3.52 - 3.64 (m, 1 H, C(26) H), 3.65 - 3.71 (m, 4 H, C(20) H_2 +C(22) H_2), 3.92 - 4.11 (m, 2 H, C(16) H_2), 7.11 (dd, $J=8.5, 1.5$ Hz, 1 H, C(3) H), 7.18 - 7.26 (m, 3 H, 3 \times Ph H), 7.28 - 7.36 (m, 3 H, C(3) H +2 \times Ph H), 7.63 (s, 1 H, C(6) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 21.2 (s, 1 C, C(33)), 36.6 (s, 1 C, C(25)), 39.1 (s, 1 C, C(26)), 41.2 (s, 1 C, C(16)), 53.9 (s, 2 C, C(19)+C(23)), 57.4 (s, 1 C, C(17)), 66.7 (s, 2 C, C(20)+C(22)), 109.5 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 119.8 (s, 1 C, C(6)), 123.3 (s, 1 C, C(2)), 124.2 (s, 1 C, C(1)), 126.6 (s, 1 C, C(30)), 126.7 (s, 2 C, C(28/29)+C(32/31)), 128.7 (s, 2 C, C(28/29)+C(32/31)), 134.0 (s, 1 C, C(4)), 142.9 (s, 1 C, C(27)), 145.9 (s, 1 C, C(5)), 154.7 (s, 1 C, C(24)), 159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS m/z (ESI $^+$) 911 [(2M+Na) $^+$], 889 [(2M+H) $^+$], 467 [(M+Na) $^+$], 445 [MH $^+$], (ESI $^-$) 443 [(M-H) $^-$]; HRMS (ESI $^+$) found 445.2580, calculated for $\text{C}_{29}\text{H}_{31}\text{N}_4\text{O}_2^+$ 445.2598; LCMS (System B) t_r 3.6 min (93%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-(1-phenylpropan-2-yl)-1H-benzimidazole (45)



2-Methyl-3-phenylpropanoic acid (30 mg, 0.18 mmol) was reacted with compound **22** (50 mg, 0.16 mmol) according to general procedure B. Chromatography was carried out with a gradient of EtOAc:MeOH:NEt₃, which was increased linearly from 99:1:0.1 to 95:5:0.5 over 20 CVs. The product was obtained as a colourless gum (26 mg, 36%); *R_f* 0.30 (EtOAc:MeOH:NEt₃, 90:10:1); *v*_{max} (neat) 2966 (C-H), 2923 (C-H), 2857 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.53 (d, *J*=6.5 Hz, 3 H, C(33)H₃), 2.22 - 2.35 (m, 4 H, C(14)H₃+C(17)H_AH_B), 2.35 - 2.55 (m, 8 H, C(15)H₃+C(17)H_AH_B+C(19)H₂+C(23)H₂), 2.95 - 3.12 (m, 1 H, C(26)H_AH_B), 3.21 - 3.37 (m, 2 H, C(25)H+C(26)H_AH_B), 3.63 - 3.72 (t, *J*=4.5 Hz, 4 H, C(20)H₂+C(22)H₂), 3.83 - 4.03 (m, 2 H, C(16)H₂), 7.03 - 7.13 (m, 3 H, C(2)H+2×PhH), 7.14 - 7.25 (m, 3 H, 3×PhH), 7.31 (d, *J*=8.5 Hz, 1 H, C(3)H), 7.67 (s, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 20.5 (s, 1 C, C(33)), 34.7 (s, 1 C, C(25)), 40.9 (s, 1 C, C(16)), 43.1 (s, 1 C, C(26)), 53.9 (s, 2 C, C(19)+C(23)), 57.5 (s, 1 C, C(17)), 66.7 (s, 2 C, C(20)+C(22)), 109.4 (s, 1 C, C(3)), 117.1 (s, 1 C, C(7)), 119.9 (s, 1 C, C(6)), 123.2 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 126.4 (s, 1 C, C(30)), 128.5 (s, 2 C, C(28/29)+C(32/31)), 128.9 (s, 2 C, C(28/29)+C(32/31)), 133.8 (s, 1 C, C(4)), 140.0 (s, 1 C, C(27)), 143.0 (s, 1 C, C(5)), 159.0 (s, 1 C, C(24)), 159.5 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS *m/z* (ESI⁺) 911 [(2M+Na)⁺], 889 [(2M+H)⁺], 467 [(M+Na)⁺], 445 [MH⁺]; HRMS (ESI⁺) found 445.2580, calculated for C₂₉H₃₁N₄O₂⁺ 445.2598; LCMS (System B) *t_r* 3.6 min (90%).

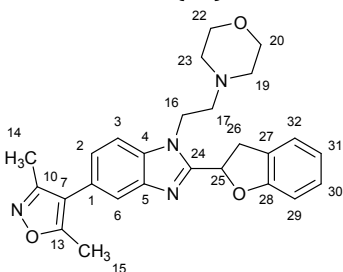
(1S)-1-[5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazol-2-yl]-2-phenylethanol (46)



L-(-)-phenyllactic acid (43 mg, 0.26 mmol) was reacted with compound **22** (40 mg, 0.13 mmol) according to general procedure D. Chromatography was carried out with a gradient of EtOAc:MeOH:NEt₃, which was increased linearly from 99:1:0.1 to 90:10:1 over 20 CVs. The desired fractions were combined and evaporated to yield the product as a brown gum (9 mg, 16%); *R_f* 0.40 (EtOAc:MeOH:NEt₃, 90:10:1); [*α*]_D²⁰ +24.9 (c 0.5 in CHCl₃); *v*_{max} (neat) 3252 (O-H), 2923 (C-H), 2853 (C-H); ¹H NMR (500 MHz, CDCl₃) δ ppm 2.31 (s, 3 H, C(14)H₃), 2.40 - 2.46 (m, 5 H, C(15)H₃+C(19)H_AH_B+C(23)H_AH_B), 2.51 - 2.60 (m, 2 H, C(19)H_AH_B+C(23)H_AH_B), 2.70 - 2.87 (m, 2 H, C(17)H₂), 3.43 (dd, *J*=14.0, 7.5 Hz, 1 H, C(33)H_AH_B), 3.58 (dd, *J*=14.0, 5.5 Hz, 1 H, C(33)H_AH_B), 3.67 - 3.73 (m, 4 H, C(20)H₂+C(22)H₂), 4.23 - 4.35 (m, 2 H, C(16)H₂), 5.20 (dd, *J*=7.5, 5.5 Hz, 1 H, C(25)H), 7.18 (dd, *J*=8.0, 1.5 Hz, 1 H, C(1)H), 7.21 - 7.33 (m, 5 H, 5×PhH), 7.39 (d, *J*=8.0 Hz, 1 H, C(3)H), 7.70 (d, *J*=1.5 Hz, 1 H, C(6)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 41.5 (s, 2 C,

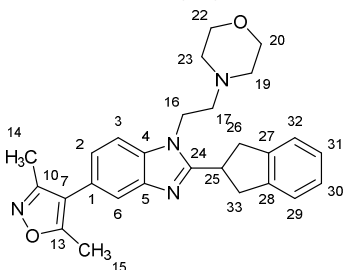
C(16)+C(33)), 54.3 (s, 2 C, C(19)+C(23)), 57.4 (s, 1 C, C(17)), 66.0 (s, 2 C, C(20)+C(22)), 67.5 (s, 1 C, C(25)), 109.6 (s, 1 C, C(3)), 116.9 (s, 1 C, C(7)), 120.7 (s, 1 C, C(6)), 124.3 (s, 1 C, C(1)), 125.0 (s, 1 C, C(2)), 126.7 (s, 1 C, C(29)), 128.4 (s, 2 C, C(27/28)+C(31/30)), 129.7 (s, 2 C, C(27/28)+C(31/30)), 134.0 (s, 1 C, C(4)), 137.8 (s, 1 C, C(32)), 142.4 (s, 1 C, C(5)), 156.3 (s, 1 C, C(24)), 158.9 (s, 1 C, C(10)), 165.1 (s, 1 C, C(13)); LRMS m/z (ESI⁺) 447 [MH⁺]; HRMS (ESI⁺) found 447.2395, calculated for C₂₆H₃₁N₄O₃⁺ 447.2391; LCMS (System B) t_r 3.6 min (79%).

(2,3-Dihydro-1-benzofuran-2-yl)-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (47)



3-(2,3-Dihydro-1-benzofuran-5-yl)propanoic acid (27 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale yellow gum (27 mg, 48%); R_f 0.35 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{\max} (neat) 2927 (C-H), 2854 (C-H), 2814 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.27 (s, 3 H, C(14)H₃), 2.40 (s, 3 H, C(15)H₃), 2.45 - 2.54 (m, 2 H, C(19)H_AH_B+C(23)H_AH_B), 2.58 - 2.67 (m, 2 H, C(19)H_AH_B+C(23)H_AH_B), 2.86 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 3.64 - 3.75 (m, 5 H, C(20)H₂+C(22)H₂+C(26)H_AH_B), 4.30 (dd, $J=15.5, 7.5$ Hz, 1 H, C(26)H_AH_B), 4.39 - 4.48 (m, 1 H, C(16)H_AH_B), 4.54 - 4.65 (m, 1 H, C(16)H_AH_B), 6.15 (dd, $J=9.5, 7.5$ Hz, 1 H, C(25)H), 6.80 (d, $J=8.0$ Hz, 1 H, C(3)H), 6.93 (t, $J=7.5$ Hz, 1 H, C(31)H), 7.15 (t, $J=7.5$ Hz, 1 H, C(30)H), 7.19 (dd, $J=8.0, 1.5$ Hz, 1 H, C(2)H), 7.31 (d, $J=7.5$ Hz, 1 H, C(32)H), 7.48 (d, $J=7.5$ Hz, 1 H, C(29)H), 7.65 (s, 1 H, C(6)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 33.5 (s, 1 C, C(26)), 42.1 (s, 1 C, C(16)), 54.0 (s, 2 C, C(19)+C(23)), 57.8 (s, 1 C, C(17)), 66.9 (s, 2 C, C(20)+C(22)), 76.8 (s, 1 C, C(25)), 109.4 (s, 1 C, C(3)), 110.0 (s, 1 C, C(29)), 116.9 (s, 1 C, C(7)), 120.9 (s, 1 C, C(6)), 121.4 (s, 1 C, C(31)), 124.5 (s, 1 C, C(2)), 124.6 (s, 1 C, C(1)), 125.1 (s, 1 C, C(32)), 126.0 (s, 1 C, C(27)), 128.2 (s, 1 C, C(30)), 135.4 (s, 1 C, C(4)), 142.3 (s, 1 C, C(5)), 152.6 (s, 1 C, C(24)), 158.2 (s, 1 C, C(28)), 158.9 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS (ESI⁺) m/z 445 [MH⁺]; HRMS (ESI⁺) found 445.2215, calculated for C₂₆H₂₉N₄O₃⁺ 445.2234; LCMS (System A) t_r 10.5 min (94%).

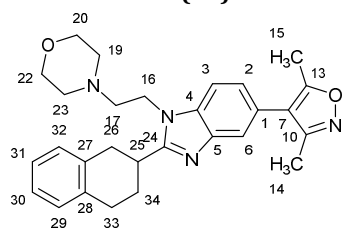
2-(2,3-Dihydro-1H-inden-2-yl)-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-benzimidazole (48)



3-(2,3-Dihydro-1H-inden-5-yl)propanoic acid (26 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale yellow gum (13 mg, 23%); R_f 0.30 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{\max} (neat) 2926 (C-H), 2853 (C-H), 2815 (C-H); ¹H NMR (500 MHz, CDCl₃) δ

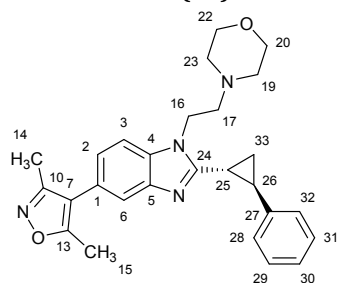
ppm 2.29 (s, 3 H, C(14)H₃), 2.42 (s, 3 H, C(15)H₃), 2.52 - 2.58 (m, 4 H, C(19)H₂+C(23)H₂), 2.80 (t, *J*=7.0 Hz, 2 H, C(17)H₂), 3.43 (dd, *J*=15.5, 9.0 Hz, 2 H, C(26)H_AH_B+C(33)H_AH_B), 3.62 (dd, *J*=15.5, 9.0 Hz, 2 H, C(26)H_AH_B+C(33)H_AH_B), 3.69 - 3.75 (m, 4 H, C(20)H₂+C(22)H₂), 4.01 (quin, *J*=9.0 Hz, 1 H, C(25)H), 4.37 (t, *J*=7.0 Hz, 2 H, C(16)H₂), 7.15 (dd, *J*=8.0, 1.5 Hz, 1 H, C(2)H), 7.20 - 7.23 (m, 2 H, C(30)H+C(31)H), 7.27 - 7.30 (m, 2 H, C(29)H+C(32)H), 7.43 (d, *J*=8.0 Hz, 1 H, C(3)H), 7.63 (d, *J*=1.5 Hz, 1 H, C(6)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 37.5 (s, 1 C, C(25)), 38.9 (s, 2 C, C(26)+C(33)), 41.7 (s, 1 C, C(16)), 54.1 (s, 2 C, C(19)+C(23)), 57.8 (s, 1 C, C(17)), 66.8 (s, 2 C, C(20)+C(22)), 109.5 (s, 1 C, C(3)), 117.1 (s, 1 C, C(7)), 120.1 (s, 1 C, C(6)), 123.6 (s, 1 C, C(2)), 124.3 (s, 3 C, C(1)+C(29)+C(32)), 126.8 (s, 2 C, C(30)+C(31)), 134.6 (s, 1 C, C(4)), 141.5 (s, 2 C, C(28)+C(27)), 142.8 (s, 1 C, C(5)), 158.2 (s, 1 C, C(24)), 159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS *m/z* (ESI⁺) 443 [MH⁺]; HRMS (ESI⁺) found 443.2435, calculated for C₂₇H₃₁N₄O₂⁺ 443.2442; LCMS (System A) *t_r* 9.6min (94%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-benzimidazole (49)



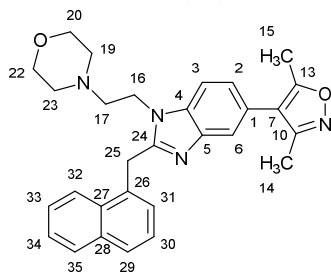
1,2,3,4-Tetrahydronaphthalene-2-carboxylic acid (26 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale orange solid (11 mg, 19%); *R_f* 0.30 (EtOAc:MeOH:NEt₃, 95:5:0.5); mp 87-90 °C; *v*_{max} (neat) 2921 (C-H), 2851 (C-H), ¹H NMR (500 MHz, CDCl₃) δ ppm 2.26 - 2.34 (m, 5 H, C(14)H₃+C(34)H₂), 2.42 - 2.44 (m, 3 H, C(15)H₃), 2.48 - 2.61 (m, 4 H, C(19)H₂+C(23)H₂), 2.74 - 2.86 (m, 2 H, C(17)H₂), 2.98 - 3.18 (m, 3 H, C(26)H_AH_B+C(33)H₂), 3.29 - 3.38 (m, 1 H, C(25)H), 3.42 - 3.51 (m, 1 H, C(26)H_AH_B), 3.65 - 3.75 (m, 4 H, C(20)H₂+C(22)H₂), 4.30 - 4.41 (m, 2 H, C(16)H₂), 7.12 - 7.22 (m, 5 H, C(2)H+4×ArH), 7.44 (d, *J*=8.0 Hz, 1 H, C(3)H), 7.68 (s, 1 H, C(6)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.6 (s, 1 C, C(15)), 29.0 (s, 1 C, C(34)), 29.4 (s, 1 C, C(33)), 33.3 (s, 1 C, C(25)), 35.1 (s, 1 C, C(26)), 41.5 (s, 1 C, C(16)), 54.1 (s, 2 C, C(19)+C(23)), 57.8 (s, 1 C, C(17)), 66.7 (s, 2 C, C(20)+C(22)), 109.6 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 120.1 (s, 1 C, C(6)), 123.7 (s, 1 C, C(2)), 124.5 (s, 1 C, C(1)), 126.0 (s, 1 C, C(30/32)), 126.2 (s, 1 C, C(30/32)), 129.0 (s, 2 C, C(29)+C(31)), 134.1 (s, 1 C, C(4)), 135.2 (s, 1 C, C(27/28)), 135.4 (s, 1 C, C(27/28)), 143.3 (s, 1 C, C(5)), 159.0 (s, 2 C, C(10)+C(24)), 165.1 (s, 1 C, C(13)); LRMS *m/z* (ESI⁺) 457 [MH⁺]; HRMS (ESI⁺) found 457.2581, calculated for C₂₈H₃₃N₄O₂⁺ 457.2598; LCMS (System A) *t_r* 10.0 min (91 %).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-[*trans*-2-phenylcyclopropyl]-1H-benzimidazole (50)



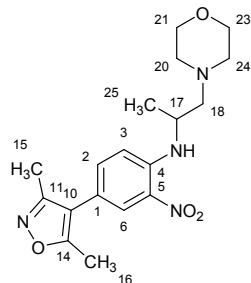
(*trans*)-2-Phenylcyclopropanecarboxylic acid (26 mg, 0.14 mmol) was reacted with compound **22** (0.13 mmol) according to general procedure C. The product was obtained as a pale orange gum (14 mg, 25%); R_f 0.35 (EtOAc:MeOH:NEt₃, 95:5:0.5); ν_{\max} (neat) 2958 (C-H), 2924 (C-H), 2854 (C-H), 2814 (C-H); ¹H NMR (500 MHz, CDCl₃) δ ppm 1.70 (dt, $J=8.5, 5.5$ Hz, 1 H, C(33)H_AH_B), 2.10 (dt, $J=8.5, 5.5$ Hz, 1 H, C(33)H_AH_B), 2.27 - 2.34 (m, 4 H, C(14)H₃+C(25)H), 2.34 - 2.44 (m, 7 H, C(14)H₃+C(19)H₂+C(23)H₂), 2.61 - 2.68 (m, 1 H, C(26)H), 2.69 - 2.80 (m, 2 H, C(17)H₂), 3.53 - 3.68 (m, 4 H, C(20)H₂+C(22)H₂), 4.27 - 4.41 (m, 2 H, C(16)H₂), 7.12 (dd, $J=8.0, 1.5$ Hz, 1 H, C(2)H), 7.18 - 7.21 (m, 2 H, C(28)H+C(32)H), 7.22 - 7.27 (m, 1 H, C(30)H), 7.31 - 7.42 (m, 3 H, C(29)H+C(31)H), 7.59 (d, $J=1.5$ Hz, 1 H, C(6)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 10.8 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 17.1 (s, 1 C, C(33)), 20.0 (s, 1 C, C(25)), 27.4 (s, 1 C, C(26)), 41.4 (s, 1 C, C(16)), 53.8 (s, 2 C, C(19)+C(23)), 57.6 (s, 1 C, C(17)), 66.6 (s, 2 C, C(20)+C(22)), 109.1 (s, 1 C, C(3)), 117.1 (s, 1 C, C(7)), 119.7 (s, 1 C, C(3)), 123.4 (s, 1 C, C(2)), 124.4 (s, 1 C, C(1)), 125.7 (s, 2 C, C(28)+C(32)), 126.5 (s, 1 C, C(30)), 128.7 (s, 2 C, C(29)+C(31)), 134.6 (s, 1 C, C(4)), 140.6 (s, 1 C, C(27)), 142.5 (s, 1 C, C(5)), 156.1 (s, 1 C, C(24)), 159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS m/z (ESI⁺) 443 [MH⁺]; HRMS (ESI⁺) found 443.2432, calculated for C₂₇H₃₁N₄O₂⁺ 443.2442; LCMS (System A) t_r 9.7 min (96%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-2-(naphthalen-1-ylmethyl)-1H-benzimidazole (51)



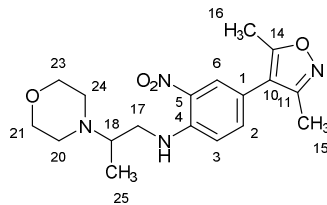
Naphthalen-1-ylacetic acid was reacted with compound **22** according to general procedure B. Chromatography was carried out with a gradient of EtOAc:MeOH:NEt₃, which was increased linearly from 99:1:0.1 to 95:5:0.5 over 20 CVs. The product was obtained as a colourless gum (27 mg, 45%); R_f 0.30 (EtOAc:MeOH:NEt₃, 90:10:1); ν_{\max} (neat) 2959 (C-H), 2855 (C-H), 2816 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 2.22 - 2.28 (m, 4 H, C(19)H₂+C(23)H₂), 2.31 (s, 3 H, C(14)H₃), 2.37 (t, $J=7.0$ Hz, 2 H, C(17)H₂), 2.44 (s, 3 H, C(15)H₃), 3.58-3.68 (m, 4 H, C(20)H₂+C(22)H₂), 4.14 (t, $J=7.0$ Hz, 2 H, C(16)H₂), 4.86 (s, 2 H, C(25)H₂), 7.15 (dd, $J=8.0, 1.5$ Hz, 1 H, C(2)H), 7.23 (d, $J=7.0$ Hz, 1 H, C(31)H), 7.35 - 7.42 (m, 2 H, C(3)H+C(30)H), 7.50 - 7.61 (m, 2 H, C(33)H+C(34)H), 7.67 (s, 1 H, C(6)H), 7.81 (d, $J=8.5$ Hz, 1 H, C(29)H), 7.91 (d, $J=7.5$ Hz, 1 H, C(29)H), 8.25 (d, $J=8.0$ Hz, 1 H, C(32)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(14)), 11.5 (s, 1 C, C(15)), 32.0 (s, 1 C, C(25)), 41.9 (s, 1 C, C(16)), 53.7 (s, 2 C, C(19)+C(23)), 57.1 (s, 1 C, C(17)), 66.6 (s, 2 C, C(20)+C(22)), 109.5 (s, 1 C, C(3)), 117.0 (s, 1 C, C(7)), 120.2 (s, 1 C, C(6)), 123.4 (s, 1 C, C(32)), 123.7 (s, 1 C, C(2)), 124.3 (s, 1 C, C(1)), 125.5 (s, 1 C, C(30)), 126.0 (s, 1 C, C(31)), 126.5 (s, 1 C, C(33/34)), 126.6 (s, 1 C, C(33/34)), 128.0 (s, 1 C, C(29)), 128.9 (s, 1 C, C(35)), 131.7 (s, 1 C, C(28)), 132.1 (s, 1 C, C(27)), 133.9 (s, 1 C, C(26)), 134.7 (s, 1 C, C(4)), 143.0 (s, 1 C, C(5)), 154.1 (s, 1 C, C(24)), 159.0 (s, 1 C, C(10)), 165.0 (s, 1 C, C(13)); LRMS m/z (ESI⁺) 955 [(2M+Na)⁺], 933 [(2M+H)⁺], 489 [(M+Na)⁺], 467 [MH⁺], (ESI⁻) 465 [(M-H)⁻]; HRMS (ESI⁺) found 467.2428, calculated for C₂₉H₃₁N₄O₂⁺ 467.2442; LCMS (System B) t_r 3.8 min (87%).

4-(3,5-Dimethyl-1,2-oxazol-4-yl)-N-[1-(morpholin-4-yl)propan-2-yl]-2-nitroaniline



1-(Morpholin-4-yl)propan-2-amine (37 mg, 0.26 mmol) was added to a solution of compound **10** (60 mg, 0.25 mmol) and $\text{EtN}(i\text{-Pr})_2$ (35 μL , 0.30 mmol) in THF (2 mL) in a sealable vial. The vial was sealed then the solution was heated at 80 °C for 16 h. The resultant mixture was partitioned between CH_2Cl_2 (3 mL) and water (3 mL). The organic phase was collected by passing it through a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:c-hexane which was increased linearly from 10:90 to 100:0 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a bright-orange solid (61 mg, 68%); R_f (0.30); mp 214-217°C; ν_{max} (neat) 3362 (N-H), 2934 (C-H), 2929 (C-H), 2850 (C-H), 2809 (C-H), 1561 (N-O), 1355 (N-O); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.35 (d, $J=6.5$ Hz, 3 H, C(25) H_3), 2.27 (s, 3 H, C(15) H_3), 2.41 (s, 3 H, C(16) H_3), 2.46 - 2.67 (m, 6 H, C(18) H_2 +C(20) H_2 +C(24) H_2), 3.64 - 3.76 (m, 4 H, C(21) H_2 +C(23) H_2), 3.79 - 3.89 (m, 1 H, C(17) H), 6.97 (d, $J=9.0$ Hz, 1 H, C(3) H), 7.33 (dd, $J=9.0, 2.0$ Hz, 1 H, C(2) H), 8.08 (d, $J=2.0$ Hz, 1 H, C(6) H), 8.28 - 8.50 (m, 1 H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.8 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 19.3 (s, 1 C, C(25)), 45.8 (s, 1 C, C(17)), 53.9 (s, 2 C, C(20)+C(24)), 63.7 (s, 1 C, C(18)), 66.9 (s, 2 C, C(21)+C(23)), 114.7 - 114.9 (m, 2 C, C(3)+C(10)), 117.1 (s, 1 C, C(1)), 127.2 (s, 1 C, C(6)), 132.0 (s, 1 C, C(5)), 136.6 (s, 1 C, C(2)), 144.0 (s, 1 C, C(4)), 158.6 (s, 1 C, C(11)), 165.3 (s, 1 C, C(14)); LRMS m/z (ESI^+) 383 [(M+Na) $^+$], 361 [MH^+], 359 [(M-H) $^-$]; HRMS (ESI^+) found 361.1858, calculated for $\text{C}_{18}\text{H}_{25}\text{N}_4\text{O}_4^+$ 361.1870; LCMS (System B) t_r 3.6 min (99%).

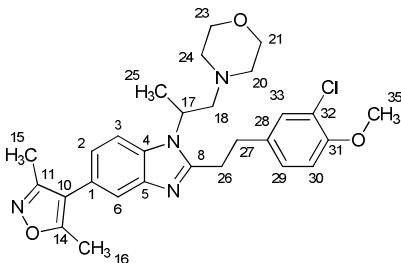
4-(3,5-Dimethyl-1,2-oxazol-4-yl)-N-[2-(morpholin-4-yl)propyl]-2-nitroaniline



2-(Morpholin-4-yl)propan-1-amine (37 mg, 0.26 mmol) was added to a solution of compound **10** (60 mg, 0.25 mmol) and $\text{EtN}(i\text{-Pr})_2$ (35 μL , 0.30 mmol) in THF (2 mL) in a sealable vial. The vial was sealed then the solution was heated at 80 °C for 16 h. The resultant mixture was partitioned between CH_2Cl_2 (3 mL) and water (3 mL). The organic phase was collected by passing it through a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:c-hexane which was increased linearly from 10:90 to 100:0 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a bright-orange solid (73 mg, 81%); R_f 0.35 (EtOAc:c-hexane, 80:20); mp 184-187 °C; ν_{max} (neat) 3321 (N-H), 2970 (C-H), 2857 (C-H), 2815 (C-H), 1352 (N-O), 1556 (N-O); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.13 (d, $J=6.5$ Hz, 3 H, C(25) H_3), 2.26 (s, 3 H, C(15) H_3), 2.40 (s, 3 H, C(16) H_3), 2.45 - 2.57 (m, 2 H, C(20) H_AH_B +C(24) H_AH_B), 2.59 - 2.74 (m, 2 H, C(20) H_AH_B +C(24) H_AH_B), 2.97 - 3.07 (m, 1 H, C(18) H), 3.07 - 3.18 (m, 1 H, C(17) H_AH_B), 3.27 - 3.37 (m, 1

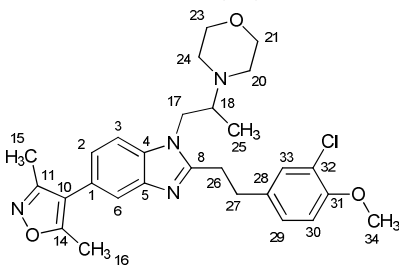
H, C(17) H_AH_B), 3.71 - 3.87 (m, 4 H, C(21) H_2 +C(23) H_2), 6.89 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.33 (dd, $J=8.5$, 2.0 Hz, 1 H, C(2) H), 8.09 (d, $J=2.0$ Hz, 1 H, C(6) H), 8.80 - 8.93 (m, 1 H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.7 (s, 1 C, C(15)), 11.3 (s, 1 C, C(16/25)), 11.5 (s, 1 C, C(16/25)), 45.3 (s, 1 C, C(17)), 48.0 (s, 2 C, C(20)+C(24)), 57.4 (s, 1 C, C(18)), 67.2 (s, 2 C, C(21)+C(23)), 114.9 (s, 1 C, C(3)), 114.9 (s, 1 C, C(10)), 116.9 (s, 1 C, C(1)), 127.0 (s, 1 C, C(6)), 131.7 (s, 1 C, C(5)), 136.6 (s, 1 C, C(2)), 144.2 (s, 1 C, C(4)), 158.6 (s, 1 C, C(2)), 165.2 (s, 1 C, C(6)); LRMS m/z (ESI $^+$) 383 [(M+Na) $^+$], 361 [MH $^+$]; HRMS (ESI $^+$) found 361.1859, calculated for $\text{C}_{18}\text{H}_{25}\text{N}_4\text{O}_4^+$ 361.1870; LCMS (System B) t_r 3.6 min (>99%).

2-[2-(3-Chloro-4-methoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[1-(morpholin-4-yl)propan-2-yl]-1H-benzimidazole (52)



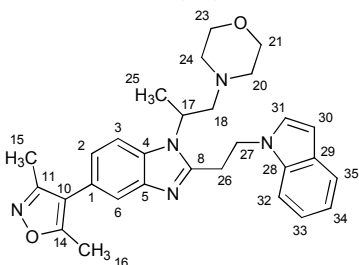
Freshly prepared 1 M aq. $\text{Na}_2\text{S}_2\text{O}_4$ (0.4 mL, 0.4 mmol) was added to a suspension of 4-(3,5-dimethyl-1,2-oxazol-4-yl)-*N*-[1-(morpholin-4-yl)propan-2-yl]-2-nitroaniline (28 mg, 0.078 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 2 h then more 1 M aq. $\text{Na}_2\text{S}_2\text{O}_4$ (0.4 mL, 0.4 mmol) was added. The mixture was heated for a further 2 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH_3 (1.5 mL) and EtOAc (1.5 mL). The organic phase was passed through MgSO_4 on a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (2 mL) then 3-(3-chloro-4-methoxyphenyl)propanoic acid (14 mg, 0.065 mmol), DIPEA (15 μL , 0.086 mmol) and T3P (50 wt.% in EtOAc, 0.2 mL, 0.31 mmol) were added. The solution was heated under reflux for 18 h then allowed to cool. The resultant solution was partitioned between EtOAc (3 mL) and 1 M aq. NaOH (3 mL). The organic phase was passed through a little MgSO_4 on a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH: NEt_3 which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (9 mg, 23%); R_f 0.50 (EtOAc:MeOH: NEt_3 , 90:10:1); v_{max} (neat) 2957 (C-H), 2923 (C-H), 2857 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.60 (d, $J=7.0$ Hz, 3 H, C(25) H_3), 2.24 - 2.35 (m, 5 H, C(15) H_3 +C(20) H_AH_B +C(24) H_AH_B), 2.41 - 2.52 (m, 5 H, C(16) H_3 +C(20) H_AH_B +C(24) H_AH_B), 2.78 (dd, $J=13.5$, 5.5 Hz, 1 H, C(18) H_AH_B), 2.96 (dd, $J=13.5$, 8.5 Hz, 1 H, C(18) H_AH_B), 3.08 - 3.30 (m, 4 H, C(26) H_2 +C(27) H_2), 3.55 - 3.64 (m, 4 H, C(21) H_2 +C(23) H_2), 3.90 (s, 3 H, C(35) H_3), 4.53 - 4.67 (m, 1 H, C(17) H), 6.88 (d, $J=8.5$ Hz, 1 H, C(30) H), 7.09 (dd, $J=8.5$, 1.5 Hz, 1 H, C(2) H), 7.13 (dd, $J=8.5$, 2.0 Hz, 1 H, C(29) H), 7.29 (d, $J=2.0$ Hz, 1 H, C(33) H), 7.49 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.64 (d, $J=1.5$ Hz, 1 H, C(6) H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 18.0 (s, 1 C, C(25)), 30.2 (s, 1 C, C(26)), 32.7 (s, 1 C, C(26)), 50.8 (s, 1 C, C(27)), 54.1 (s, 2 C, C(20)+C(24)), 56.2 (s, 1 C, C(35)), 62.2 (s, 1 C, C(18)), 66.9 (s, 2 C, C(21)+C(23)), 111.5 (s, 1 C, C(3)), 112.3 (s, 1 C, C(30)), 116.9 (s, 1 C, C(10)), 120.1 (s, 1 C, C(6)), 122.4 (s, 1 C, C(32)), 123.2 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 127.6 (s, 1 C, C(29)), 130.0 (s, 1 C, C(33)), 132.6 (s, 1 C, C(28)), 133.9 (s, 1 C, C(4)), 143.2 (s, 1 C, C(5)), 153.6 (s, 1 C, C(31)), 155.0 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.1 (s, 1 C, C(14)); LRMS m/z (ESI $^+$) 509 [MH $^+$]; HRMS (ESI $^+$) found 509.2305, calculated for $\text{C}_{28}\text{H}_{34}\text{ClN}_4\text{O}_3^+$ 509.2314; LCMS (System B) t_r 5.8 min (86%).

2-[2-(3-Chloro-4-methoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[2-(morpholin-4-yl)propyl]-1H-benzimidazole (53)



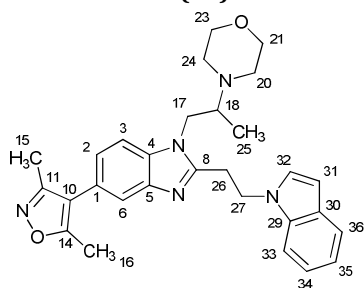
Freshly prepared 1 M aq. $\text{Na}_2\text{S}_2\text{O}_4$ (0.5 mL, 0.5 mmol) was added to a suspension of 4-(3,5-dimethyl-1,2-oxazol-4-yl)-*N*-[2-(morpholin-4-yl)propyl]-2-nitroaniline (35 mg, 0.096 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 2 h then more 1 M aq. $\text{Na}_2\text{S}_2\text{O}_4$ (0.5 mL, 0.5 mmol) was added. The mixture was heated for a further 2 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH_3 (1.5 mL) and EtOAc (1.5 mL). The organic phase was passed through MgSO_4 on a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (2 mL) then 3-(3-chloro-4-methoxyphenyl)propanoic acid (16 mg, 0.075 mmol), DIPEA (15 μL , 0.086 mmol) and T3P (50 wt.% in EtOAc, 0.2 mL, 0.31 mmol) were added. The solution was heated under reflux for 18 h then allowed to cool. The resultant solution was partitioned between EtOAc (3 mL) and 1 M aq. NaOH (3 mL). The organic phase was passed through a little MgSO_4 on a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH: NEt_3 which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (19 mg, 39%); R_f 0.45 (EtOAc:MeOH: NEt_3 , 90:10:1); v_{max} (neat) 2968 (C-H), 2855 (C-H) 1503 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.04 (d, $J=6.5$ Hz, 3 H, C(25) H_3), 2.32 (s, 3 H, C(15) H_3), 2.45 (s, 3 H, C(16) H_3), 2.50 - 2.66 (m, 2 H, C(20) H_AH_B +C(24) H_AH_B), 2.64 - 2.79 (m, 2 H, C(20) H_AH_B +C(24) H_AH_B), 2.95 - 3.06 (m, 1 H, C(18) H), 3.13 - 3.33 (m, 4 H, C(26) H_2 +C(27) H_2), 3.63 - 3.82 (m, 4 H, C(17) H_AH_B +C(34) H_3), 3.83 - 3.99 (m, 4 H, C(21) H_2 +C(23) H_2), 4.18 - 4.37 (m, 1 H, C(17) H_AH_B), 6.88 (d, $J=8.5$ Hz, 1 H, C(30) H), 7.07 - 7.20 (m, 2 H, C(2) H +C(29) H), 7.29 (d, $J=2.0$ Hz, 1 H, C(33) H), 7.40 (d, $J=7.0$ Hz, 1 H, C(3) H), 7.67 (d, $J=1.0$ Hz, 1 H, C(6) H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 12.0 (s, 1 C, C(25)), 29.6 (s, 1 C, C(26)), 32.5 (s, 1 C, C(27)), 46.5 (s, 1 C, C(17)), 49.3 (s, 2 C, C(20)+C(24)), 56.2 (s, 1 C, C(34)), 59.5 (s, 1 C, C(18)), 66.6 (s, 1 C, C(21)+C(23)), 109.9 (s, 1 C, C(3)), 112.3 (s, 1 C, C(30)), 116.9 (s, 1 C, C(10)), 119.7 (s, 1 C, C(6)), 122.4 (s, 1 C, C(32)), 123.7 (s, 1 C, C(2)), 124.6 (s, 1 C, C(1)), 127.7 (s, 1 C, C(29)), 130.0 (s, 1 C, C(33)), 133.8 (s, 1 C, C(28)), 134.3 (s, 1 C, C(4)), 142.2 (s, 1 C, C(5)), 153.6 (s, 1 C, C(31)), 155.0 (s, 1 C, C(8)), 158.9 (s, 1 C, C(11)), 165.1 (s, 1 C, C(14)); LRMS m/z (ESI $^+$) 509 [MH $^+$]; HRMS (ESI $^+$) found 509.2314, calculated for $\text{C}_{28}\text{H}_{34}\text{ClN}_4\text{O}_3$ $^+$ 509.2314; LCMS (System B) t_r 5.6 min (96%).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(1H-indol-1-yl)ethyl]-1-[1-(morpholin-4-yl)propan-2-yl]-1H-benzimidazole (54)



Freshly prepared 1 M aq. Na₂S₂O₄ (0.4 mL, 0.4 mmol) was added to a suspension of 4-(3,5-dimethyl-1,2-oxazol-4-yl)-*N*-[1-(morpholin-4-yl)propan-2-yl]-2-nitroaniline (28 mg, 0.078 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 2 h then more 1 M aq. Na₂S₂O₄ (0.4 mL, 0.4 mmol) was added. The mixture was heated for a further 2 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH₃ (1.5 mL) and EtOAc (1.5 mL). The organic phase was passed through MgSO₄ on a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (2 mL) then 3-(1*H*-indol-1-yl)propanoic acid (12 mg, 0.063 mmol), DIPEA (15 μL, 0.086 mmol) and T3P (50 wt.% in EtOAc, 0.2 mL, 0.31 mmol) were added. The solution was heated under reflux for 18 h then allowed to cool. The resultant solution was partitioned between EtOAc (3 mL) and 1 M aq. NaOH (3 mL). The organic phase was passed through a little MgSO₄ on a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH:NEt₃ which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (11 mg, 29%); *R*_f 0.45 (EtOAc:MeOH:NEt₃, 90:10:1); *v*_{max} (neat) 2927 (C-H), 2853 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.37 (d, *J*=7.0 Hz, 3 H, C(25)H₃), 2.06 - 2.16 (m, 2 H, C(20)H_AH_B+C(24)H_AH_B), 2.22 - 2.36 (m, 5 H, C(15)H₃+C(20)H_AH_B+C(24)H_AH_B), 2.46 (s, 3 H, C(16)H₃), 2.60 (dd, *J*=13.0, 6.0 Hz, 1 H, C(18)H_AH_B), 2.72 (dd, *J*=13.0, 8.0 Hz, 1 H, C(18)H_AH_B), 3.35 - 3.45 (m, 2 H, C(26)H₂), 3.46 - 3.55 (m, 4 H, C(21)H₂+C(23)H₂), 4.15 - 4.28 (m, 1 H, C(17)H), 4.76 - 4.95 (m, 2 H, C(27)H₂), 6.47 (dd, *J*=3.0, 0.5 Hz, 1 H, C(30)H), 7.04 - 7.16 (m, 3 H, C(2)H+C(31)H+C(34)H), 7.21 (td, *J*=7.5, 1.0 Hz, 1 H, C(33)H), 7.39 (d, *J*=8.0 Hz, 1 H, C(3)H), 7.45 (d, *J*=8.5 Hz, 1 H, C(32)H), 7.62 - 7.69 (m, 2 H, C(6)H+C(35)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 17.6 (s, 1 C, C(25)), 28.9 (s, 1 C, C(26)), 44.7 (s, 1 C, C(27)), 50.8 (s, 1 C, C(17)), 54.0 (s, 2 C, C(20)+C(24)), 62.2 (s, 1 C, C(18)), 66.8 (s, 2 C, C(21)+C(23)), 101.8 (s, 1 C, C(30)), 108.9 (s, 1 C, C(3)), 111.6 (s, 1 C, C(32)), 116.9 (s, 1 C, C(10)), 119.7 (s, 1 C, C(34)), 120.1 (s, 1 C, C(6)), 121.3 (s, 1 C, C(35)), 121.8 (s, 1 C, C(33)), 123.3 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 127.9 (s, 1 C, C(31)), 128.9 (s, 1 C, C(29)), 132.7 (s, 1 C, C(4)), 135.5 (s, 1 C, C(28)), 143.5 (s, 1 C, C(5)), 153.1 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.1 (s, 1 C, C(14)); LRMS *m/z* (ESI⁺) 484 [MH⁺]; HRMS (ESI⁺) found 484.2698, calculated for C₂₉H₃₄N₅O₂⁺ 484.2707; LCMS (System B) *t*_r 6.0 min (90%).

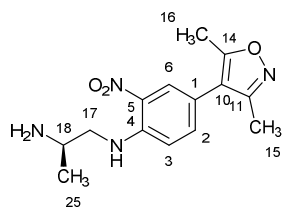
5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(1*H*-indol-1-yl)ethyl]-1-[2-(morpholin-4-yl)propyl]-1*H*-benzimidazole (55)



Freshly prepared 1 M aq. Na₂S₂O₄ (0.5 mL, 0.5 mmol) was added to a suspension of 4-(3,5-dimethyl-1,2-oxazol-4-yl)-*N*-[2-(morpholin-4-yl)propyl]-2-nitroaniline (35 mg, 0.096 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 2 h then more 1 M aq. Na₂S₂O₄ (0.5 mL, 0.5 mmol) was added. The mixture was heated for a further 2 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH₃ (1.5 mL) and EtOAc (1.5 mL). The organic phase was passed through MgSO₄ on a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (2 mL) then 3-(1*H*-indol-1-yl)propanoic acid (14 mg, 0.085 mmol), DIPEA (15 μL, 0.086 mmol) and T3P (50 wt.% in EtOAc,

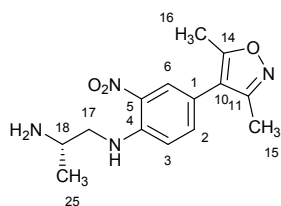
0.2 mL, 0.31 mmol) were added. The solution was heated under reflux for 18 h then allowed to cool. The resultant solution was partitioned between EtOAc (3 mL) and 1 M aq. NaOH (3 mL). The organic phase was passed through a little MgSO₄ on a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH:NEt₃ which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (12 mg, 26%); *R_f* 0.35 (EtOAc:MeOH:NEt₃, 90:10:1); *v*_{max} (neat) 2963 (C-H), 2855 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.74 (d, *J*=6.5 Hz, 3 H, C(25)H₃), 1.60 - 2.81 (m, 12 H, C(15)H₃+C(16)H₃+C(18)H+C(20)H₂+C(24)H₂), 3.10 - 3.91 (m, 7 H, C(17)H₂+C(21)H₂+C(23)H₂+ C(27)H₂), 4.81 (t, *J*=6.0 Hz, 2 H, C(26)H₂), 6.41 (d, *J*=2.5 Hz, 1 H, 1 H, C(31)H), 6.87 (d, *J*=2.5 Hz, 1 H, 1 H, C(32)H), 7.05 - 7.16 (m, 2 H, C(2)H+C(34)H), 7.20 (t, *J*=7.5 Hz, 1 H, 1 H, C(35)H), 7.27 - 7.33 (m, 1 H, C(3)H), 7.38 (d, *J*=7.5 Hz, 1 H, C(33)H), 7.61 - 7.70 (m, 2 H, C(6)H+C(36)H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 2 C, C(16)+C(25)), 28.6 (s, 1 C, C(26)), 45.4 (s, 2 C, C(17)+C(27)), 48.9 (s, 2 C, C(20)+C(24)), 59.4 (s, 1 C, C(18)), 66.5 (s, 2 C, C(21)+C(23)), 101.8 (s, 1 C, C(31)), 109.2 (s, 1 C, C(33)), 110.0 (s, 1 C, C(3)), 116.9 (s, 1 C, C(10)), 119.8 (s, 1 C, C(34)), 119.8 (s, 1 C, C(6)), 121.3 (s, 1 C, C(36)), 121.9 (s, 1 C, C(35)), 123.9 (s, 1 C, C(2)), 124.8 (s, 1 C, C(1)), 128.1 (s, 1 C, C(32)), 128.8 (s, 1 C, C(30)), 134.4 (s, 1 C, C(4)), 135.3 (s, 1 C, C(29)), 142.7 (s, 1 C, C(5)), 153.5 (s, 1 C, C(8)), 158.9 (s, 1 C, C(11)), 165.1 (s, 1 C, C(14)); LRMS *m/z* (ESI⁺) 484 [MH⁺]; HRMS (ESI⁺) found 484.2698, calculated for C₂₉H₃₄N₅O₂⁺ 484.2707; LCMS (System B) *t_r* 3.9 min (98%).

(2*R*)-*N*¹-[4-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-nitrophenyl]propane-1,2-diamine



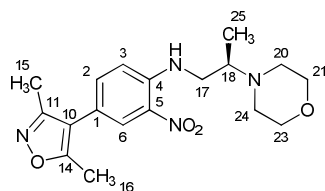
EtN(*i*-Pr)₂ (1.29 mL, 7.40 mmol) was added to a suspension of (*R*)-propane-1,2-diamine dihydrochloride (374 mg, 2.54 mmol) and compound **10** (500 mg, 2.12 mmol) and in THF (20 mL). The mixture was stirred at room temperature for 16 h then at reflux for 2 h then allowed to cool. K₂CO₃ (1.02 g, 7.40 mmol) and DMF (5 mL) were added then the mixture was heated under reflux for 4 h then allowed to cool. The resultant mixture was partitioned between EtOAc (10 mL) and water (10 mL). The phases were separated then the organic phase was washed with water (10 mL) and brine (10 mL) then dried over MgSO₄ and evaporated. The crude material was purified by flash column chromatography on a silica column (40 g). The column was eluted with a gradient of CH₂Cl₂:MeOH:NH₄OH which was increased linearly from 99:1:0.1 to 90:10:1 over 12 CVs. The desired fractions were combined and evaporated to yield the product (4:1 ratio of regioisomers in favour of desired) as a bright-orange solid (233 mg, 38%); *R_f* 0.15 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); mp 124-127 °C; [α]_D²⁰ -20.4 (c 0.44 in CHCl₃); *v*_{max} (neat) 3372 (N-H), 2964 (C-H), 2928 (C-H), 2869 (C-H), 1528 (N-O), 1353 (N-O); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.24 (d, *J*=6.0 Hz, 3 H, C(15)H₃), 2.26 (s, 3 H), 2.40 (s, 3 H, C(16)H₃), 3.11 - 3.24 (m, 1 H, C(17)H_AH_B), 3.25 - 3.41 (m, 2 H, C(17)H_AH_B+C(18)H), 6.96 (d, *J*=9.0 Hz, 1 H, C(3)H), 7.33 (dd, *J*=9.0, 2.0 Hz, 1 H, C(2)H), 8.08 (d, *J*=2.0 Hz, 1 H, C(6)H), 8.41 (br. s., 1 H, NH); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.7 (s, 1 C, C(15)), 11.5 (s, 1 C, C(16)), 22.1 (s, 1 C, C(20)), 46.0 (s, 1 C, C(18)), 50.9 (s, 1 C, C(17)), 114.6 (s, 1 C, C(3)), 114.8 (s, 1 C, C(10)), 117.4 (s, 1 C, C(1)), 127.0 (s, 1 C, C(6)), 131.9 (s, 1 C, C(5)), 136.7 (s, 1 C, C(2)), 144.7 (s, 1 C, C(4)), 158.5 (s, 1 C, C(11)), 165.3 (s, 1 C, C(14)); LRMS *m/z* (ESI⁺) 313 [(M+Na)⁺], 291 [MH⁺]; HRMS (ESI⁺) found 291.1444, calculated for C₁₄H₁₉N₄O₃⁺ 291.1452; LCMS (System B) *t_r* 3.6 min (81%).

(2S)-N¹-[4-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-nitrophenyl]propane-1,2-diamine



EtN(*i*-Pr)₂ (1.29 mL, 7.40 mmol) was added to a suspension of (*R*)-propane-1,2-diamine dihydrochloride (374 mg, 2.54 mmol) and compound **10** (500 mg, 2.12 mmol) and in THF (20 mL). The mixture was stirred at room temperature for 16 h then at reflux for 2 h then allowed to cool. K₂CO₃ (1.02 g, 7.40 mmol) and DMF (5 mL) were added then the mixture was heated under reflux for 4 h then allowed to cool. The resultant mixture was partitioned between EtOAc (10 mL) and water (10 mL). The phases were separated then the organic phase was washed with water (10 mL) and brine (10 mL) then dried over MgSO₄ and evaporated. The crude material was purified by flash column chromatography on a silica column (40 g). The column was eluted with a gradient of CH₂Cl₂:MeOH:NH₄OH which was increased linearly from 99:1:0.1 to 90:10:1 over 12 CVs. The desired fractions were combined and evaporated to yield the product (4:1 ratio of regioisomers in favour of desired) as a bright-orange solid (254 mg, 41%); *R*_f 0.15 (CH₂Cl₂:MeOH:NH₄OH, 90:10:1); mp 126-129 °C; [α]_D²⁰ +17.7 (c 1.4 in CHCl₃); ν_{max} (neat) 3369 (N-H), 2964 (C-H), 2928 (C-H), 2871 (C-H), 1526 (N-O), 1352 (N-O); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.24 (d, *J*=6.0 Hz, 3 H, C(15)H₃), 2.26 (s, 3 H), 2.40 (s, 3 H, C(16)H₃), 3.11 - 3.24 (m, 1 H, C(17)H_AH_B), 3.25 - 3.41 (m, 2 H, C(17)H_AH_B+C(18)H), 6.96 (d, *J*=9.0 Hz, 1 H, C(3)H), 7.33 (dd, *J*=9.0, 2.0 Hz, 1 H, C(2)H), 8.08 (d, *J*=2.0 Hz, 1 H, C(6)H), 8.41 (br. s., 1 H, NH); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.7 (s, 1 C, C(15)), 11.5 (s, 1 C, C(16)), 22.1 (s, 1 C, C(20)), 46.0 (s, 1 C, C(18)), 50.9 (s, 1 C, C(17)), 114.6 (s, 1 C, C(3)), 114.8 (s, 1 C, C(10)), 117.4 (s, 1 C, C(1)), 127.0 (s, 1 C, C(6)), 131.9 (s, 1 C, C(5)), 136.7 (s, 1 C, C(2)), 144.7 (s, 1 C, C(4)), 158.5 (s, 1 C, C(11)), 165.3 (s, 1 C, C(14)); LRMS *m/z* (ESI⁺) 313 [(M+Na)⁺], 291 [MH⁺]; HRMS (ESI⁺) found 291.1446, calculated for C₁₄H₁₉N₄O₃⁺ 291.1452; LCMS (System B) *t*_r 3.6 min (87%).

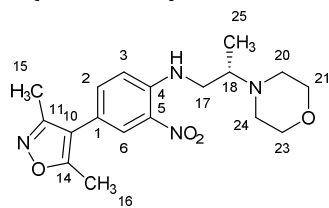
4-(3,5-Dimethyl-1,2-oxazol-4-yl)-N¹-[(2*R*)-2-(morpholin-4-yl)propyl]-2-nitroaniline (56)



2-Bromoethyl ether (100 μL, 0.79 mmol) was added to a suspension of (*2R*)-N¹-[4-(3,5-dimethyl-1,2-oxazol-4-yl)-2-nitrophenyl]propane-1,2-diamine (210 mg, 0.72 mmol) and K₂CO₃ (299 mg, 2.16 mmol) in DMF (5 mL). The mixture was heated in a sealed vial at 70 °C for 16 h then allowed to cool. The resultant mixture was partitioned between water (5 mL) and EtOAc (5 mL). The phases were separated then the aqueous phase was extracted with more EtOAc (5 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL) then dried over MgSO₄ and evaporated directly onto silica. The crude material was purified by flash column chromatography on a silica column (24 g). The column was eluted with a gradient of acetone:CH₂Cl₂ which was increased linearly from 0:100 to 6:94 over 6 CVs then isocratic at 6:94 for 10 CVs. The desired fractions were combined and evaporated then the resultant material was purified again by flash column chromatography on a silica column (12 g). The column was eluted with acetone:*c*-hexane (1:9). The desired fractions were combined and evaporated to yield the product as a pale orange solid (71 mg, 27%); *R*_f

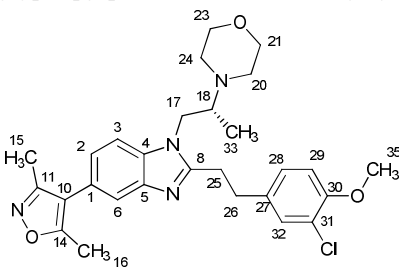
0.20 (acetone:c-hexane, 20:80); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.13 (d, $J=6.5$ Hz, 3 H, C(25) H_3), 2.26 (s, 3 H, C(15) H_3), 2.40 (s, 3 H, C(16) H_3), 2.45 - 2.57 (m, 2 H, C(20) H_AH_B +C(24) H_AH_B), 2.59 - 2.74 (m, 2 H, C(20) H_AH_B +C(24) H_AH_B), 2.97 - 3.07 (m, 1 H, C(18) H), 3.07 - 3.18 (m, 1 H, C(17) H_AH_B), 3.27 - 3.37 (m, 1 H, C(17) H_AH_B), 3.71 - 3.87 (m, 4 H, C(21) H_2 +C(23) H_2), 6.89 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.33 (dd, $J=8.5, 2.0$ Hz, 1 H, C(2) H), 8.09 (d, $J=2.0$ Hz, 1 H, C(6) H), 8.80 - 8.93 (m, 1 H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.7 (s, 1 C, C(15)), 11.3 (s, 1 C, C(16/25)), 11.5 (s, 1 C, C(16/25)), 45.3 (s, 1 C, C(17)), 48.0 (s, 2 C, C(20)+C(24)), 57.4 (s, 1 C, C(18)), 67.2 (s, 2 C, C(21)+C(23)), 114.9 (s, 1 C, C(3)), 114.9 (s, 1 C, C(10)), 116.9 (s, 1 C, C(1)), 127.0 (s, 1 C, C(6)), 131.7 (s, 1 C, C(5)), 136.6 (s, 1 C, C(2)), 144.2 (s, 1 C, C(4)), 158.6 (s, 1 C, C(2)), 165.2 (s, 1 C, C(6)); LRMS m/z (ESI $^+$) 361 [MH $^+$]; HRMS (ESI $^+$) found 361.1858, calculated for $\text{C}_{18}\text{H}_{25}\text{N}_4\text{O}_4^+$ 361.1870.

4-(3,5-Dimethyl-1,2-oxazol-4-yl)- N^1 -[(2S)-2-(morpholin-4-yl)propyl]-2-nitroaniline (57)



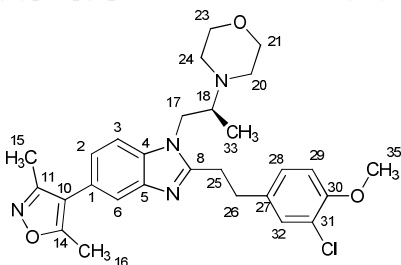
2-Bromoethyl ether (0.68 mL, 5.4 mmol) was added to a suspension of (2S)- N^1 -[4-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-nitrophenyl]propane-1,2-diamine (1.43 g, 4.92 mmol) and K_2CO_3 (2.04 g, 14.8 mmol) in DMF (50 mL). The mixture was heated at 70 °C for 16 h then allowed to cool and partitioned between EtOAc (50 mL) and water (50 mL). The phases were separated then the organic phase was extracted with more EtOAc (50 mL). The combined organic phases were washed with 1:1 brine:water (3×50 mL) then brine (50 mL) then dried over MgSO_4 and evaporated. The crude material was purified by flash column chromatography on a silica column (80 g). The column was eluted with a gradient of acetone: CH_2Cl_2 , which was increased linearly from 0:100 to 10:90 over 10 CVs. The desired fractions were combined and evaporated. The resultant material was purified further by flash column chromatography on a silica column (80 g). The column was eluted with a gradient of acetone:c-hexane, which was increased linearly from 10:90 to 20:80 over 20 CVs. The desired fractions were combined and evaporated to yield the product as an orange solid (620 mg, 35%); R_f 0.20 (acetone:c-hexane, 20:80); mp 182-185 °C; ν_{max} (neat) 3321 (N-H), 2964 (C-H), 2858 (C-H), 2815 (C-H), 1525 (N-O), 1353 (N-O); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.13 (d, $J=6.5$ Hz, 3 H, C(25) H_3), 2.26 (s, 3 H, C(15) H_3), 2.40 (s, 3 H, C(16) H_3), 2.45 - 2.57 (m, 2 H, C(20) H_AH_B +C(24) H_AH_B), 2.59 - 2.74 (m, 2 H, C(20) H_AH_B +C(24) H_AH_B), 2.97 - 3.07 (m, 1 H, C(18) H), 3.07 - 3.18 (m, 1 H, C(17) H_AH_B), 3.27 - 3.37 (m, 1 H, C(17) H_AH_B), 3.71 - 3.87 (m, 4 H, C(21) H_2 +C(23) H_2), 6.89 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.33 (dd, $J=8.5, 2.0$ Hz, 1 H, C(2) H), 8.09 (d, $J=2.0$ Hz, 1 H, C(6) H), 8.80 - 8.93 (m, 1 H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.7 (s, 1 C, C(15)), 11.3 (s, 1 C, C(16/25)), 11.5 (s, 1 C, C(16/25)), 45.3 (s, 1 C, C(17)), 48.0 (s, 2 C, C(20)+C(24)), 57.4 (s, 1 C, C(18)), 67.2 (s, 2 C, C(21)+C(23)), 114.9 (s, 1 C, C(3)), 114.9 (s, 1 C, C(10)), 116.9 (s, 1 C, C(1)), 127.0 (s, 1 C, C(6)), 131.7 (s, 1 C, C(5)), 136.6 (s, 1 C, C(2)), 144.2 (s, 1 C, C(4)), 158.6 (s, 1 C, C(2)), 165.2 (s, 1 C, C(6)); LRMS m/z (ESI $^+$) 383 [(M+Na) $^+$], 361 [MH $^+$]; HRMS (ESI $^+$) found 361.1856, calculated for $\text{C}_{18}\text{H}_{25}\text{N}_4\text{O}_4^+$ 361.1870; LCMS (System B) t_r 3.7 min (>99%).

2-[2-(3-Chloro-4-methoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[(2R)-2-(morpholin-4-yl)propyl]-1H-benzimidazole (58)



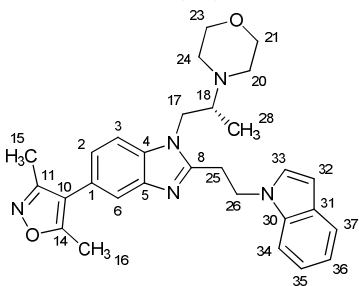
Freshly prepared 1 M aq. $\text{Na}_2\text{S}_2\text{O}_4$ (0.32 mL, 0.32 mmol) was added to a suspension of compound **56** (23 mg, 0.065 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 1 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH_3 (1 mL) and EtOAc (1 mL). The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (2 mL) then added to a vial containing 3-(3-chloro-4-methoxyphenyl)propanoic acid (13 mg, 0.061 mmol). DIPEA (23 μL , 0.13 mmol) and T3P (50 wt.% in EtOAc, 0.2 mL, 0.31 mmol) were added then the solution was heated at 80°C for 16 h then allowed to cool. 1 M aq. NaOH solution (1 mL) was added and the phases were mixed then allowed to separate. The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH: NEt_3 which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (15 mg, 46%); R_f 0.50 (EtOAc:MeOH: NEt_3 , 90:10:1); $[\alpha]_D^{20}$ -3.8 (c 0.6 in CHCl_3); ν_{max} (neat) 2964 (C-H), 2933 (C-H), 2854 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.93 (d, $J=7.0$ Hz, 3 H, C(33) H_3), 2.23 (s, 3 H, C(15) H_3), 2.36 (s, 3 H, C(16) H_3), 2.38 - 2.48 (m, 2 H, C(20) $\text{H}_\text{A}\text{H}_\text{B}$ +C(24) $\text{H}_\text{A}\text{H}_\text{B}$), 2.53 - 2.61 (m, 2 H, C(20) $\text{H}_\text{A}\text{H}_\text{B}$ +C(24) $\text{H}_\text{A}\text{H}_\text{B}$), 2.81 - 2.94 (m, 1 H, C(18) H), 3.00 - 3.12 (m, 2 H, C(25) H_2), 3.12 - 3.22 (m, 2 H, C(26) H_2), 3.51 - 3.65 (m, 4 H, C(21) H_2 +C(23) H_2), 3.76 - 3.84 (m, 4 H, C(17) $\text{H}_\text{A}\text{H}_\text{B}$ +C(35) H_3), 4.08 (dd, $J=14.5$, 6.5 Hz, 1 H, C(17) $\text{H}_\text{A}\text{H}_\text{B}$), 6.79 (d, $J=8.5$ Hz, 1 H, C(3) H), 6.99 - 7.07 (m, 2 H, C(2) H +C(28) H), 7.20 (d, $J=1.5$ Hz, 1 H, C(32) H), 7.26 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.56 (d, $J=1.0$ Hz, 1 H, C(6) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 12.2 (s, 1 C, C(33)), 29.7 (s, 1 C, C(25)), 32.5 (s, 1 C, C(26)), 46.6 (s, 1 C, C(17)), 49.3 (s, 2 C, C(20)+C(24)), 56.2 (s, 1 C, C(35)), 59.5 (s, 1 C, C(18)), 66.9 (s, 2 C, C(21)+C(23)), 109.8 (s, 1 C, C(3)), 112.2 (s, 1 C, C(29)), 117.0 (s, 1 C, C(10)), 119.8 (s, 1 C, C(6)), 122.4 (s, 1 C, C(31)), 123.5 (s, 1 C, C(2)), 124.3 (s, 1 C, C(1)), 127.7 (s, 1 C, C(28)), 130.0 (s, 1 C, C(32)), 133.9 (s, 1 C, C(27)), 134.5 (s, 1 C, C(4)), 142.7 (s, 1 C, C(5)), 153.6 (s, 1 C, C(30)), 155.1 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); LRMS m/z (ESI $^+$) 511 [M(^{37}Cl) H^+] 509 [M(^{35}Cl) H^+]; HRMS (ESI $^+$) found 511.2297, calculated for $\text{C}_{28}\text{H}_{34}(\text{Cl})\text{N}_4\text{O}_3^+$ 511.2287; HRMS (ESI $^+$) found 509.2312, calculated for $\text{C}_{28}\text{H}_{34}(\text{Cl})\text{N}_4\text{O}_3^+$ 509.2314; LCMS (System B) t_r 3.8 min (97%); er >99:1 (HPLC Chiralpak AD column, λ 220 nm, n -hexane/ i -PrOH (70:30), flow rate 0.9 mL/min, t_r 19.5 min (minor), 26.2 min (major)).

2-[2-(3-Chloro-4-methoxyphenyl)ethyl]-5-(3,5-dimethyl-1,2-oxazol-4-yl)-1-[(2S)-2-(morpholin-4-yl)propyl]-1H-benzimidazole (59)



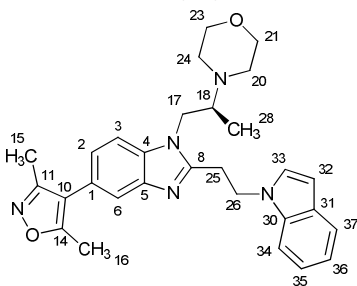
Freshly prepared 1 M aq. $\text{Na}_2\text{S}_2\text{O}_4$ (0.50 mL, 0.50 mmol) was added to a suspension of compound **57** (35 mg, 0.097 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 1 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH_3 (1 mL) and EtOAc (1 mL). The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (3 mL) then added to a vial containing 3-(3-chloro-4-methoxyphenyl)propanoic acid (19 mg, 0.089 mmol). DIPEA (34 μL , 0.19 mmol) and T3P (50 wt.% in EtOAc, 0.3 mL, 0.47 mmol) were added then the solution was heated at 80 °C for 16 h then allowed to cool. 1 M aq. NaOH solution (1 mL) was added and the phases were mixed then allowed to separate. The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH: NEt_3 which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (26 mg, 52%); R_f 0.50 (EtOAc:MeOH: NEt_3 , 90:10:1); $[\alpha]_D^{20}$ +4.0 (c 1.1 in CHCl_3); ν_{max} (neat) 2963 (C-H), 2933 (C-H), 2854 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.93 (d, $J=7.0$ Hz, 3 H, C(33) H_3), 2.23 (s, 3 H, C(15) H_3), 2.36 (s, 3 H, C(16) H_3), 2.38 - 2.48 (m, 2 H, C(20) $\text{H}_\text{A}\text{H}_\text{B}$ +C(24) $\text{H}_\text{A}\text{H}_\text{B}$), 2.53 - 2.61 (m, 2 H, C(20) $\text{H}_\text{A}\text{H}_\text{B}$ +C(24) $\text{H}_\text{A}\text{H}_\text{B}$), 2.81 - 2.94 (m, 1 H, C(18) H), 3.00 - 3.12 (m, 2 H, C(25) H_2), 3.12 - 3.22 (m, 2 H, C(26) H_2), 3.51 - 3.65 (m, 4 H, C(21) H_2 +C(23) H_2), 3.76 - 3.84 (m, 4 H, C(17) $\text{H}_\text{A}\text{H}_\text{B}$ +C(35) H_3), 4.08 (dd, $J=14.5$, 6.5 Hz, 1 H, C(17) $\text{H}_\text{A}\text{H}_\text{B}$), 6.79 (d, $J=8.5$ Hz, 1 H, C(3) H), 6.99 - 7.07 (m, 2 H, C(2) H +C(28) H), 7.20 (d, $J=1.5$ Hz, 1 H, C(32) H), 7.26 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.56 (d, $J=1.0$ Hz, 1 H, C(6) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 12.2 (s, 1 C, C(33)), 29.7 (s, 1 C, C(25)), 32.5 (s, 1 C, C(26)), 46.8 (s, 1 C, C(17)), 49.3 (s, 2 C, C(20)+C(24)), 56.2 (s, 1 C, C(35)), 59.4 (s, 1 C, C(18)), 67.1 (s, 2 C, C(21)+C(23)), 109.7 (s, 1 C, C(3)), 112.2 (s, 1 C, C(29)), 117.0 (s, 1 C, C(10)), 119.8 (s, 1 C, C(6)), 122.3 (s, 1 C, C(31)), 123.4 (s, 1 C, C(2)), 124.1 (s, 1 C, C(1)), 127.6 (s, 1 C, C(28)), 130.0 (s, 1 C, C(32)), 134.0 (s, 1 C, C(27)), 134.6 (s, 1 C, C(4)), 142.9 (s, 1 C, C(5)), 153.6 (s, 1 C, C(30)), 155.1 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); LRMS m/z (ESI $^+$) 511 [M(^{37}Cl) H^+] 509 [M(^{35}Cl) H^+]; HRMS (ESI $^+$) found 511.2290, calculated for $\text{C}_{28}\text{H}_{34}(\text{}^{37}\text{Cl})\text{N}_4\text{O}_3^+$ 511.2287; HRMS (ESI $^+$) found 509.2308, calculated for $\text{C}_{28}\text{H}_{34}(\text{}^{35}\text{Cl})\text{N}_4\text{O}_3^+$ 509.2314; LCMS (System B) t_r 3.9 min (97%); er >99:1 (HPLC Chiralpak AD column, λ 220 nm, n -hexane/ i -PrOH (70:30), flow rate 0.9 mL/min, t_r 19.7 min (major), 26.7 min (minor)).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(1*H*-indol-1-yl)ethyl]-1-[(2*R*)-2-(morpholin-4-yl)propyl]-1*H*-benzimidazole (60)



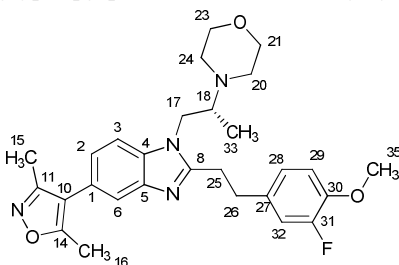
Freshly prepared 1 M aq. $\text{Na}_2\text{S}_2\text{O}_4$ (0.32 mL, 0.32 mmol) was added to a suspension of compound **56** (23 mg, 0.065 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 1 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH_3 (1 mL) and EtOAc (1 mL). The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (2 mL) then added to a vial containing 3-(1*H*-indol-1-yl)propanoic acid (11 mg, 0.058 mmol). DIPEA (23 μL , 0.13 mmol) and T3P (50 wt.% in EtOAc, 0.2 mL, 0.31 mmol) were added then the solution was heated at 80 °C for 16 h then allowed to cool. 1 M aq. NaOH solution (1 mL) was added and the phases were mixed then allowed to separate. The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH: NEt_3 which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (12 mg, 38%); R_f 0.35 (EtOAc:MeOH: NEt_3 , 90:10:1); $[\alpha]_D^{20}$ +6.4 (c 0.5 in CHCl_3); ν_{max} (neat) 2964 (C-H), 2855 (C-H), 2819 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.76 (d, $J=6.5$ Hz, 3 H, C(28) H_3), 2.12 - 2.24 (m, 2 H, C(20) H_AH_B +C(24) H_AH_B), 2.27 - 2.38 (m, 5 H, C(15) H_3 +C(20) H_AH_B +C(24) H_AH_B), 2.46 (s, 3 H, C(16) H_3), 2.53 - 2.69 (m, 1 H, C(18) H), 3.21 - 3.44 (m, 3 H, C(17) H_AH_B +C(25) H_2), 3.47 - 3.66 (m, 5 H, C(17) H_AH_B +C(21) H_2 +C(23) H_2), 4.80 (t, $J=6.5$ Hz, 2 H, C(26) H_2), 6.43 (d, $J=3.0$ Hz, 1 H, C(32) H), 6.89 (d, $J=3.0$ Hz, 1 H, C(33) H), 7.09 - 7.14 (m, 2 H, C(2) H +C(35) H), 7.16 - 7.22 (m, 1 H, C(36) H), 7.25 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.36 (d, $J=8.0$ Hz, 1 H, C(34) H), 7.57 - 7.70 (m, 2 H, C(6) H +C(37) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 11.8 (s, 1 C, C(33)), 28.6 (s, 1 C, C(25)), 45.2 (s, 1 C, C(26)), 46.2 (s, 1 C, C(17)), 49.0 (s, 2 C, C(20)+C(24)), 59.2 (s, 1 C, C(18)), 66.9 (s, 2 C, C(21)+C(23)), 101.8 (s, 1 C, C(32)), 109.0 (s, 1 C, C(34)), 109.9 (s, 1 C, C(3)), 117.0 (s, 1 C, C(10)), 119.7 (s, 1 C, C(35)), 119.8 (s, 1 C, C(6)), 121.3 (s, 1 C, C(37)), 121.8 (s, 1 C, C(36)), 123.7 (s, 1 C, C(2)), 124.5 (s, 1 C, C(1)), 128.0 (s, 1 C, C(33)), 128.9 (s, 1 C, C(31)), 134.5 (s, 1 C, C(4)), 135.4 (s, 1 C, C(30)), 142.8 (s, 1 C, C(5)), 153.5 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.1 (s, 1 C, C(14)); LRMS m/z (ESI $^+$) 484 [MH^+]; HRMS (ESI $^+$) found 484.2701, calculated for $\text{C}_{29}\text{H}_{34}\text{N}_5\text{O}_2^+$ 484.2707; LCMS (System B) t_r 3.9 min (98%); er 99:1 (HPLC Chiralpak AD column, λ 220 nm, n -hexane/ i -PrOH (80:20), flow rate 1.0 mL/min, t_r 25.1 min (minor), 27.7 min (major)).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(1*H*-indol-1-yl)ethyl]-1-[(2*S*)-2-(morpholin-4-yl)propyl]-1*H*-benzimidazole (61)



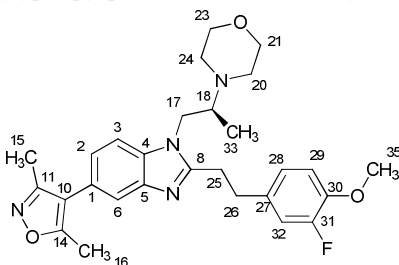
Freshly prepared 1 M aq. Na₂S₂O₄ (0.50 mL, 0.50 mmol) was added to a suspension of compound **57** (35 mg, 0.097 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 1 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH₃ (1 mL) and EtOAc (1 mL). The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (3 mL) then added to a vial containing 3-(1*H*-indol-1-yl)propanoic acid (17 mg, 0.090 mmol). DIPEA (34 μL, 0.19 mmol) and T3P (50 wt.% in EtOAc, 0.3 mL, 0.47 mmol) were added then the solution was heated at 80 °C for 16 h then allowed to cool. 1 M aq. NaOH solution (1 mL) was added and the phases were mixed then allowed to separate. The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH:NEt₃ which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (26 mg, 52%); *R*_f 0.35 (EtOAc:MeOH:NEt₃, 90:10:1); [α]_D²⁰ -5.2 (c 1.2 in CHCl₃); ν_{max} (neat) 2963 (C-H), 2955 (C-H), 2819 (C-H); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.76 (d, *J*=6.5 Hz, 3 H, C(28)H₃), 2.12 - 2.24 (m, 2 H, C(20)H_AH_B+C(24)H_AH_B), 2.27 - 2.38 (m, 5 H, C(15)H₃+C(20)H_AH_B+C(24)H_AH_B), 2.46 (s, 3 H, C(16)H₃), 2.53 - 2.69 (m, 1 H, C(18)H), 3.21 - 3.44 (m, 3 H, C(17)H_AH_B+C(25)H₂), 3.47 - 3.66 (m, 5 H, C(17)H_AH_B+C(21)H₂+C(23)H₂), 4.80 (t, *J*=6.5 Hz, 2 H, C(26)H₂), 6.43 (d, *J*=3.0 Hz, 1 H, C(32)H), 6.89 (d, *J*=3.0 Hz, 1 H, C(33)H), 7.09 - 7.14 (m, 2 H, C(2)H+C(35)H), 7.16 - 7.22 (m, 1 H, C(36)H), 7.25 (d, *J*=8.5 Hz, 1 H, C(3)H), 7.36 (d, *J*=8.0 Hz, 1 H, C(34)H), 7.57 - 7.70 (m, 2 H, C(6)H+C(37)H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 11.9 (s, 1 C, C(33)), 28.6 (s, 1 C, C(25)), 45.1 (s, 1 C, C(26)), 46.2 (s, 1 C, C(17)), 49.0 (s, 2 C, C(20)+C(24)), 59.1 (s, 1 C, C(18)), 67.0 (s, 2 C, C(21)+C(23)), 101.7 (s, 1 C, C(32)), 108.9 (s, 1 C, C(34)), 109.9 (s, 1 C, C(3)), 117.0 (s, 1 C, C(10)), 119.7 (s, 1 C, C(35)), 119.8 (s, 1 C, C(6)), 121.3 (s, 1 C, C(37)), 121.8 (s, 1 C, C(36)), 123.6 (s, 1 C, C(2)), 124.4 (s, 1 C, C(1)), 127.9 (s, 1 C, C(33)), 128.8 (s, 1 C, C(31)), 134.5 (s, 1 C, C(4)), 135.4 (s, 1 C, C(30)), 142.9 (s, 1 C, C(5)), 153.5 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); LRMS *m/z* (ESI⁺) 484 [MH⁺]; HRMS (ESI⁺) found 484.2695, calculated for C₂₉H₃₄N₅O₂⁺ 484.2707; LCMS (System B) *t*_r 3.9 min (98%); *er* >99:1 (HPLC Chiralpak AD column, λ 220 nm, *n*-hexane/*i*-PrOH (80:20), flow rate 1.0 mL/min, *t*_r 24.7 min (major), 27.6 min (minor)).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(3-fluoro-4-methoxyphenyl)ethyl]-1-[(2R)-2-(morpholin-4-yl)propyl]-1H-benzimidazole (62)



Freshly prepared 1 M aq. $\text{Na}_2\text{S}_2\text{O}_4$ (0.32 mL, 0.32 mmol) was added to a suspension of compound **56** (23 mg, 0.065 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 1 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH_3 (1 mL) and EtOAc (1 mL). The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (2 mL) then added to a vial containing 3-(3-fluoro-4-methoxyphenyl)propanoic acid (12 mg, 0.061 mmol). DIPEA (23 μL , 0.13 mmol) and T3P (50 wt.% in EtOAc, 0.2 mL, 0.31 mmol) were added then the solution was heated at 80°C for 16 h then allowed to cool. 1 M aq. NaOH solution (1 mL) was added and the phases were mixed then allowed to separate. The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH: NEt_3 which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (12 mg, 38%); R_f 0.50 (EtOAc:MeOH: NEt_3 , 90:10:1); $[\alpha]_D^{20}$ -11.5 (c 0.6 in CHCl_3); v_{max} (neat) 2963 (C-H), 2934 (C-H), 2855 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.01 (d, $J=7.0$ Hz, 3 H, C(33) H_3), 2.31 (s, 3 H, C(15) H_3), 2.44 (s, 3 H, C(16) H_3), 2.45 - 2.54 (m, 2 H, C(20) $\text{H}_\text{A}\text{H}_\text{B}$ +C(24) $\text{H}_\text{A}\text{H}_\text{B}$), 2.61 - 2.69 (m, 2 H, C(20) $\text{H}_\text{A}\text{H}_\text{B}$ +C(24) $\text{H}_\text{A}\text{H}_\text{B}$), 2.90 - 3.02 (m, 1 H, C(18) H), 3.08 - 3.20 (m, 2 H, C(25/26) H_2), 3.20 - 3.30 (m, 2 H, C(25/26) H_2), 3.60 - 3.73 (m, 4 H, C(21) H_2 +C(23) H_2), 3.81 - 3.92 (m, 4 H, C(17) $\text{H}_\text{A}\text{H}_\text{B}$ +C(35) H_3), 4.16 (dd, $J=14.5, 6.5$ Hz, 1 H, C(17) $\text{H}_\text{A}\text{H}_\text{B}$), 6.85 - 6.93 (m, 1 H, C(29) H), 6.93 - 7.02 (m, 2 H, C(28) H +C(32) H), 7.13 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2) H), 7.33 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.64 (d, $J=1.5$ Hz, 1 H, C(6) H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 12.2 (s, 1 C, C(33)), 29.7 (s, 1 C, C(25)), 32.7 (s, 1 C, C(26)), 46.6 (s, 1 C, C(17)), 49.3 (s, 2 C, C(20)+C(24)), 56.3 (s, 1 C, C(35)), 59.5 (s, 1 C, C(18)), 66.9 (s, 2 C, C(21)+C(23)), 109.8 (s, 1 C, C(3)), 113.6 (d, $J=2.0$ Hz, 1 C, C(29)), 116.0 (d, $J=17.0$ Hz, 1 C, C(32)), 117.0 (s, 1 C, C(10)), 119.8 (s, 1 C, C(6)), 123.5 (s, 1 C, C(2)), 124.0 (d, $J=3.0$ Hz, 1 C, C(28)), 124.3 (s, 1 C, C(1)), 133.8 (d, $J=6.0$ Hz, 1 C, C(27)), 134.5 (s, 1 C, C(4)), 142.6 (s, 1 C, C(5)), 146.2 (d, $J=10.5$ Hz, 1 C, C(30)), 152.3 (d, $J=245.0$ Hz, 1 C, C(31)), 155.1 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); ^{19}F NMR (377 MHz, CDCl_3) δ ppm -135.0 (s, 1 F); LRMS m/z (ESI $^+$) 493 [MH^+]; HRMS (ESI $^+$) found 493.2591, calculated for $\text{C}_{28}\text{H}_{34}\text{FN}_4\text{O}_3^+$ 493.2609; LCMS (System B) t_r 3.7 min (96%); er >99:1 (HPLC Chiralpak AD column, λ 220 nm, n -hexane/ i -PrOH (80:20), flow rate 1.0 mL/min, t_r 36.9 min (minor), 51.8 min (major)).

5-(3,5-Dimethyl-1,2-oxazol-4-yl)-2-[2-(3-fluoro-4-methoxyphenyl)ethyl]-1-[(2S)-2-(morpholin-4-yl)propyl]-1H-benzimidazole (63)



Freshly prepared 1 M aq. $\text{Na}_2\text{S}_2\text{O}_4$ (0.50 mL, 0.50 mmol) was added to a suspension of compound **57** (35 mg, 0.097 mmol) in EtOH (0.5 mL) in a sealable vial. The vial was sealed then heated at 80°C for 1 h then allowed to cool. The resultant mixture was partitioned between 10% aq. NH_3 (1 mL) and EtOAc (1 mL). The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The residue was dissolved in EtOAc (3 mL) then added to a vial containing 3-(3-fluoro-4-methoxyphenyl)propanoic acid (17 mg, 0.086 mmol). DIPEA (34 μL , 0.19 mmol) and T3P (50 wt.% in EtOAc, 0.3 mL, 0.47 mmol) were added then the solution was heated at 80°C for 16 h then allowed to cool. 1 M aq. NaOH solution (1 mL) was added and the phases were mixed then allowed to separate. The organic phase was passed through a hydrophobic frit then evaporated by nitrogen blow-down. The crude material was purified by flash column chromatography on a silica column (4 g). The column was eluted with a gradient of EtOAc:MeOH: NEt_3 which was increased linearly from 99:1:0.1 to 95:5:0.5 over 30 CVs. The desired fractions were combined and evaporated to yield the product as a colourless gum (21 mg, 43%); R_f 0.50 (EtOAc:MeOH: NEt_3 , 90:10:1); $[\alpha]_D^{20}$ +12.3 (c 1.1 in CHCl_3); v_{max} (neat) 2963 (C-H), 2934 (C-H), 2854 (C-H); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.01 (d, $J=7.0$ Hz, 3 H, C(33) H_3), 2.31 (s, 3 H, C(15) H_3), 2.44 (s, 3 H, C(16) H_3), 2.45 - 2.54 (m, 2 H, C(20) $\text{H}_\text{A}\text{H}_\text{B}$ +C(24) $\text{H}_\text{A}\text{H}_\text{B}$), 2.61 - 2.69 (m, 2 H, C(20) $\text{H}_\text{A}\text{H}_\text{B}$ +C(24) $\text{H}_\text{A}\text{H}_\text{B}$), 2.90 - 3.02 (m, 1 H, C(18) H), 3.08 - 3.20 (m, 2 H, C(25/26) H_2), 3.20 - 3.30 (m, 2 H, C(25/26) H_2), 3.60 - 3.73 (m, 4 H, C(21) H_2 +C(23) H_2), 3.81 - 3.92 (m, 4 H, C(17) $\text{H}_\text{A}\text{H}_\text{B}$ +C(35) H_3), 4.16 (dd, $J=14.5, 6.5$ Hz, 1 H, C(17) $\text{H}_\text{A}\text{H}_\text{B}$), 6.85 - 6.93 (m, 1 H, C(29) H), 6.93 - 7.02 (m, 2 H, C(28) H +C(32) H), 7.13 (dd, $J=8.5, 1.5$ Hz, 1 H, C(2) H), 7.33 (d, $J=8.5$ Hz, 1 H, C(3) H), 7.64 (d, $J=1.5$ Hz, 1 H, C(6) H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 10.9 (s, 1 C, C(15)), 11.6 (s, 1 C, C(16)), 12.2 (s, 1 C, C(33)), 29.7 (s, 1 C, C(25)), 32.6 (s, 1 C, C(26)), 46.8 (s, 1 C, C(17)), 49.3 (s, 2 C, C(20)+C(24)), 56.3 (s, 1 C, C(35)), 59.4 (s, 1 C, C(18)), 67.1 (s, 2 C, C(21)+C(23)), 109.7 (s, 1 C, C(3)), 113.6 (d, $J=1.5$ Hz, 1 C, C(29)), 116.0 (d, $J=17.5$ Hz, 1 C, C(32)), 117.0 (s, 1 C, C(10)), 119.9 (s, 1 C, C(6)), 123.4 (s, 1 C, C(2)), 123.9 (d, $J=4.0$ Hz, 1 C, C(28)), 124.2 (s, 1 C, C(1)), 133.9 (d, $J=5.5$ Hz, 1 C, C(27)), 134.6 (s, 1 C, C(4)), 142.9 (s, 1 C, C(5)), 146.1 (d, $J=10.5$ Hz, 1 C, C(30)), 152.3 (d, $J=245.5$ Hz, 1 C, C(31)), 155.2 (s, 1 C, C(8)), 159.0 (s, 1 C, C(11)), 165.0 (s, 1 C, C(14)); ^{19}F NMR (377 MHz, CDCl_3) δ ppm -135.0 (s, 1 F); LRMS m/z (ESI $^+$) 493 [MH^+]; HRMS (ESI $^+$) found 493.2603, calculated for $\text{C}_{28}\text{H}_{34}\text{FN}_4\text{O}_3^+$ 493.2609; LCMS (System B) t_r 3.7 min (97%); er >99:1 (HPLC Chiralpak AD column, λ 220 nm, n -hexane/ i -PrOH (80:20), flow rate 1.0 mL/min, t_r 36.9 min (major), 52.3 min (minor)).

General experimental for parallel synthesis compounds

All reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was oven dried and cooled under nitrogen before use. Commercial anhydrous solvents used in reactions and HPLC grade solvents were employed for work-up and chromatography. Water was purified using an Elix[®] UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Parallel synthesis was carried out using a Radleys GreenHouse reactor. Parallel work-ups were carried out using a Radleys stacker and Isolute phase separation cartridges. Parallel evaporation was carried out using a Radleys BlowDown Evaporator. NMR spectra were recorded on a Varian Mercury 400 MHz or a Bruker Avance III 400 MHz using the solvent as internal deuterium lock. Coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.5 Hz. Identical proton coupling constants are averaged in each spectrum and reported to the nearest 0.5 Hz. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Melting points were determined using a Kofler hot stage microscope and are uncorrected. *m/z* values are reported in Daltons. HRMS measurements were carried out using a Bruker MicroTOF mass spectrometer, equipped with an electrospray ionisation source acquiring in the positive ion mode (ESI⁺), using an external calibrant of sodium formate to deliver a mass accuracy of 5 ppm. Microwave experiments were carried out using a Biotage Initiator 8. Chromatography was carried out using a Presearch Isco Combiflash Companion using Presearch columns or on a Biotage SP4 using Biotage SNAP columns. LCMS *t_r* are quoted to the nearest 0.1 min. Analytical LCMS were obtained on the following systems: System A: stationary phase: Agilent SB C18 50×3 mm with 3 micron particle size, 50 °C; detection: UV: 210 nm–450 nm DAD– ELSD–MS; mobile phase: A: H₂O + 0.1% formic acid, B: MeCN + 0.1% formic acid; gradient: 95% A 1 min hold, 95-0% A over 8 min, 2.5 min hold, 0.50 min re-equilibration; flow rate: 1.2 mL/min; System B: stationary phase: Agilent SB C18 50×3 mm with 1.8 micron particle size, 50 °C; detection: UV: 200 nm–290 nm DAD–MS; mobile phase: A: H₂O + 0.05% F₃CCOOH, B: MeCN + 0.05% F₃CCOOH; gradient: 95% A 1 min hold, 95-0% A over 8 min, 2.5 min hold, 0.50 min re-equilibration; flow rate: 1.2 mL/min; System C: stationary phase: Gemini-NX 3um C18 110A, ambient temperature; detection: UV 225 nm–ELSD–MS; system/data file: CTC–MUX1; injection volume: 5 µL; flow rate: 1.5 mL/min, mobile phase (acidic conditions): A: H₂O + 0.1% formic acid, B: MeCN + 0.1% formic acid; Gradient (Time/min, %B) – (0,5), (3,95), (4,95), (4.1,5), (5,5); (basic conditions): mobile phase: A: H₂O + 0.1% ammonia, B: MeCN + 0.1% ammonia; gradient (Time/min, %B) – (0,5),(3,95),(4,95),(4.1,5),(5,5). Preparative HPLC purification was carried out using: stationary phase: Gemini NX 5um C18 100x21.2, ambient temperature; detection: ELSD–MS; injection volume: 1000 µL; flow rate: 18 mL/min. The mobile phase used was: acidic conditions: A: H₂O + 0.1% formic acid, B: MeCN + 0.1% formic acid; gradient (time/min %B) (0-1, 5),(1-7, 5-98),(7-9, 98),(9-9.1, 98-5),(9.1-10, 5); basic conditions: A: H₂O + 0.1% diethylamine, B: MeCN + 0.1% diethylamine; gradient (Time/min,%B) - (0-1, 5),(1-7, 5-98),(7-9, 98),(9-9.1, 98-5),(9.1-10, 5). Products from HPLC purification were assessed to be ≥80% peak area by UV at 225 nm, ≥90% peak area by ELSD, and ≥50% spectral purity in ES⁺ or ES⁻. LRMS were recorded on a Waters LCT Premier, equipped with electrospray ionisation source and TOF analyser, acquiring in positive and negative ionisation modes.

General procedure E

3,5-Dimethylisoxazole-4-boronic acid pinacol ester was dissolved in DME to make a 0.3 M stock solution. Aliquots (1.0 mL, 0.3 mmol) of the stock solution were added to GreenHouse reaction tubes containing the aryl bromide compounds (0.20 mmol) and Pd(dppf)Cl₂ (7 mg, 0.01 mmol). The mixtures were stirred then 1.0 M aq. NaHCO₃ solution (0.6 mL, 0.6 mmol) was added to each tube. The tubes were placed in a Radley's

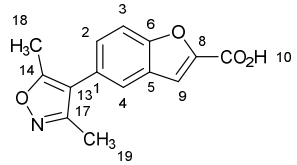
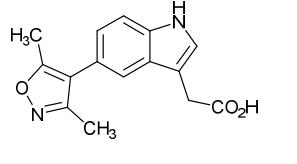
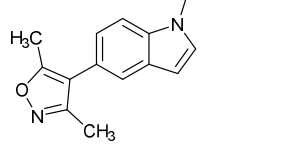
GreenHouse reactor then degassed by evacuating the apparatus then refilling with nitrogen several times. The mixtures were heated under reflux (block temperature set to 100 °C) for 24 h. Another portion of catalyst (7 mg, 0.01 mmol) was added to each tube then the mixtures were refluxed for a further 24 h. The reaction mixtures were each worked up as follows 0.5 M aq. HCl (1 mL) and EtOAc (1 mL) were added. The aqueous phase was added onto an Isolute HM-N phase-separation cartridge using a pipette then left to equilibrate on the cartridge for 5 min. The organic phase was then added onto the cartridge followed by elution with more EtOAc to extract the organics. The eluted organic phases were evaporated by blow-down under a nitrogen stream. The crude material thus obtained was purified by preparative HPLC purification.

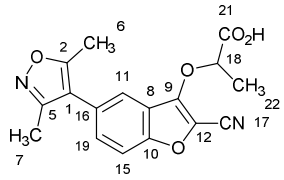
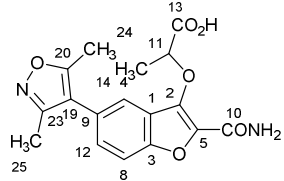
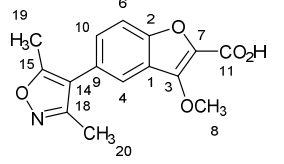
General procedure F

3,5-Dimethylisoxazole-4-boronic acid pinacol ester was dissolved in DME to make a 0.3 M stock solution. Aliquots (1.0 mL, 0.3 mmol) of the stock solution were added to GreenHouse reaction tubes containing the aryl bromide compounds (0.20 mmol) and Pd(dppf)Cl₂ (7 mg, 0.01 mmol). The mixtures were stirred then 1.0 M aq. NaHCO₃ solution (0.6 mL, 0.6 mmol) was added to each tube. The tubes were placed in a Radley's GreenHouse reactor then degassed by evacuating the apparatus then refilling with nitrogen several times. The mixtures were heated under reflux (block temperature set to 100 °C) for 24 h. The reaction mixtures were partitioned between water (3 mL) and CH₂Cl₂ (3 mL). The organic phases were separated from the aqueous by passing them through a hydrophobic frit then evaporated by blow-down using a stream of nitrogen. The crude residues were dissolved in DMSO (1 mL) then purified by preparative HPLC.

General Procedure G

Compound **9** was dissolved in DMSO to make a 0.1 M stock solution. Aliquots of this stock (1.0 mL, 0.10 mmol) were dispensed into the reaction vials. The aldehydes were dissolved in ethanol to make 0.67 M stock solutions. Portions of the aldehyde stocks (0.30 mL, 0.20 mmol) were then dispensed to the appropriate vials. 1.0 M aq. Na₂S₂O₄ solution (0.3 mL, 0.3 mmol) was added to each vial then the reactions were heated in a GreenHouse reactor at 80 °C for 18 h. The reaction mixtures were allowed to cool then analysed by LCMS. The reactions were concentrated by half under blow-down then partitioned between CH₂Cl₂ (2 mL) and 2 M aq. ammonia (2 mL). The organic phases were collected by passing through a hydrophobic frit then evaporated by blow-down. The residues were dissolved in DMSO (1 mL) then purified by preparative HPLC.

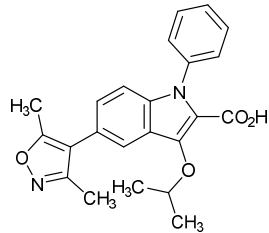
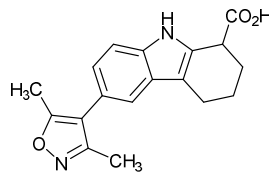
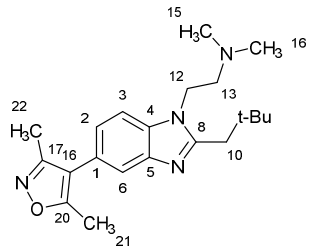
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s1	E		28	54	4.1 ^a	(ESI ⁺) 258 [MH ⁺], (ESI ⁻) 256 [(M-H) ⁻]	>99	>99	(DMSO- <i>d</i> ₆), 2.23 (s, 3 H, C(19)H ₃), 2.41 (s, 3 H, C(18)H ₃), 7.49 (dd, <i>J</i> =8.5, 2.0 Hz, 1 H, C(2)H), 7.67 (d, <i>J</i> =1.0 Hz, 1 H, C(9)H), 7.76 - 7.81 (m, 2 H, C(3)H+C(4)H) 13.66 (s, 1 H, OH)
s2	E		5	10	2.8 ^c	(ESI ⁺) 271 [MH ⁺], (ESI ⁻) 269 [(M-H) ⁻]	>99	>99	ND
s3	E		25	46	1.9 ^d	(ESI ⁺) 271 [MH ⁺], (ESI ⁻) 269 [(M-H) ⁻]	>99	>99	ND

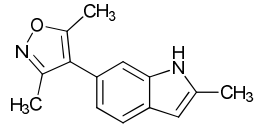
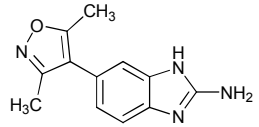
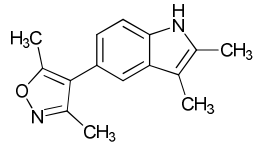
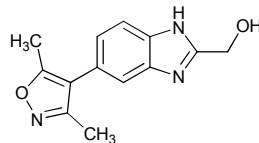
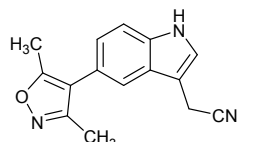
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					<i>t_r</i> (min)	<i>m/z</i>	UV purity (%)	ELSD purity (%)	
s4	E		11	17	4.9 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 325 [(M-H)]	>99	>99	(DMSO- <i>d</i> ₆) 1.65 (d, <i>J</i> =6.5 Hz, 3 H, C(22) <i>H</i> ₃), 2.22 (s, 3 H, C(7) <i>H</i> ₃), 2.40 (s, 3 H, C(6) <i>H</i> ₃), 5.36 (q, <i>J</i> =6.5 Hz, 1 H, C(18) <i>H</i>), 7.62 (dd, <i>J</i> =9.0, 2.0 Hz, 1 H, C(19) <i>H</i>), 7.74 - 7.78 (m, 2 H, C(11) <i>H</i> +C(15) <i>H</i>)
s5	E		13	19	3.8 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 345 >99 343 [(M-H)]	>99	>99	(DMSO- <i>d</i> ₆) 1.59 (d, <i>J</i> =7.0 Hz, 3 H, C(14) <i>H</i> ₃), 2.22 (s, 3 H, C(25) <i>H</i> ₃), 2.40 (s, 3 H, C(20) <i>H</i> ₃), 5.41 (q, <i>J</i> =7.0 Hz, 1 H, C(11) <i>H</i>), 7.46 (dd, <i>J</i> =8.5, 2.0 Hz, 1 H, C(12) <i>H</i>), 7.66 (dd, <i>J</i> =8.5, 0.5 Hz, 1 H, C(8) <i>H</i>), 7.71 (br. s, 2 H, NH ₂), 7.74 (dd, <i>J</i> =2.0, 0.5 Hz, 1 H, C(4) <i>H</i>), 10.88 (br. s, 1 H, OH)
s6	E		12	21	4.1 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 288 >99 286 [(M-H)]	>99	>99	(DMSO- <i>d</i> ₆) 2.24 (s, 3 H, C(20) <i>H</i> ₃), 2.42 (s, 3 H, C(19) <i>H</i> ₃), 4.19 (s, 3 H, OCH ₃), 7.51 (dd, <i>J</i> =8.5, 2.0 Hz, 1 H, C(10) <i>H</i>), 7.71 (dd, <i>J</i> =8.5, 0.5 Hz, 1 H, C(6) <i>H</i>), 7.85 (dd, <i>J</i> =2.0, 0.5 Hz, 1 H, C(4) <i>H</i>) 13.23 (br. s, 1 H, OH);

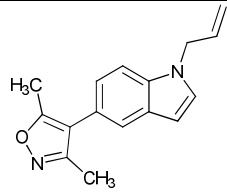
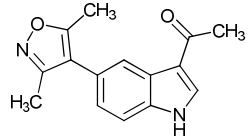
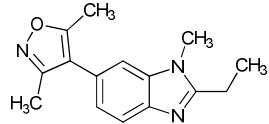
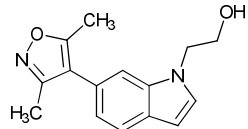
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					<i>t_r</i> (min)	<i>m/z</i>	UV purity (%)	ELSD purity (%)	
s7	E		44	55	5.0 ^a	(ESI ⁺) 403 [MH ⁺], (ESI ⁻) 401 [(M-H)]	>99	>99	(DMSO- <i>d</i> ₆) 1.99 - 2.08 (m, 2 H, C(14)H ₂), 2.22 (s, 3 H, C(25)H ₃), 2.25 (t, <i>J</i> =7.0 Hz, 2 H, C(15)H ₂), 2.40 (s, 3 H, C(24)H ₃), 4.33 (t, <i>J</i> =7.0 Hz, 2 H, C(12)H ₂), 7.30 (dd, <i>J</i> =8.5, 2.0 Hz, 1 H, C(13)H), 7.50 - 7.57 (m, 2 H, 2×PhH), 7.58 - 7.64 (m, 1 H, PhH), 7.74 (dd, <i>J</i> =8.5, 1.0 Hz, 1 H, C(8)H), 7.77 - 7.82 (m, 2 H, 2×PhH), 8.07 (s, 1 H, C(5)H), 8.18 (dd, <i>J</i> =2.0, 1.0 Hz, 1 H, C(8)H) 12.16 (br. s, 1 H, OH)
s8	E		18	20	2.3 ^d	(ESI ⁺) 451 [MH ⁺], (ESI ⁻) 449 [(M-H)]	>99	>99	ND
s9	E		21	35	3.0 ^a	(ESI ⁺) 304 [MH ⁺], (ESI ⁻) 302 [(M-H)]	>99	>99	ND

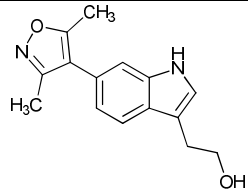
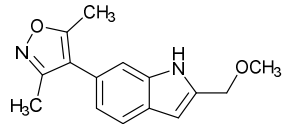
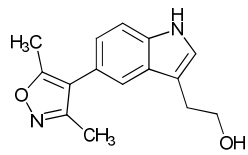
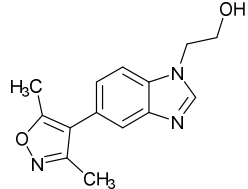
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					<i>t_r</i> (min)	<i>m/z</i>	UV purity (%)	ELSD purity (%)	
s10	E		12	24	2.8 ^c	257 [MH ⁺], (ESI ⁻) 255 [(M-H) ⁻]	>99	>99	ND
s11	E		9	16	3.0 ^c	(ESI ⁺) 272 [MH ⁺], (ESI ⁻) 270 [(M-H) ⁻]	96	89	ND
s12	E		16	28	2.1 ^d	(ESI ⁺) 285 [MH ⁺], (ESI ⁻) 283 [(M-H) ⁻]	>99	99	ND
s13	E		6	10	4.8 ^d	(ESI ⁺) 299 [MH ⁺]	>99%	ND	(CDCl ₃) 2.28 (s, 3 H, C(22)H ₃), 2.41 (s, 3 H, C(21)H ₃), 2.43 (s, 3 H, C(10)H ₃), 2.70 (t, <i>J</i> =7.5 Hz, 2 H, C(11)H ₂), 3.07 (t, <i>J</i> =7.5 Hz, 2 H, C(6)H ₂), 6.96 (dd, <i>J</i> =8.0, 1.0 Hz, 1 H, C(9)H), 7.14 (d, <i>J</i> =1.0 Hz, 1 H, C(8)H), 7.55 (d, <i>J</i> =8.0 Hz, 1 H, C(4)H), 7.90 (s, 1 H, NH)

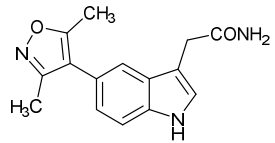
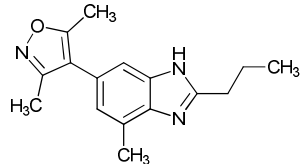
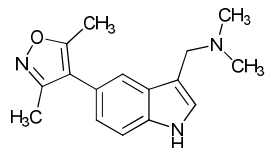
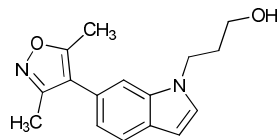
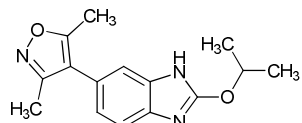
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s14	E		8	13	5.4 ^a	(ESI ⁺) [MH ⁺]	313 81	ND	(CDCl ₃) 2.01 - 2.11 (m, 2 H, C(10)H ₂), 2.31 (s, 3 H, C(23)H ₃), 2.42 - 2.49 (m, 5 H, C(22)H ₃ +C(13)H ₂), 2.81 - 2.88 (m, 2 H, C(6)H ₂), 3.80 (s, 3 H, C(11)H ₃), 6.94 (s, 1 H, C(5)H), 7.11 (dd, J=8.5, 1.5 Hz, 1 H, C(12)H), 7.36 (dd, J=8.5, 0.5 Hz, 1 H, C(8)H), 7.47 (dd, J=1.5, 0.5 Hz, 1 H, C(4)H)
s15	E		9	15	2.6 ^c	(ESI ⁺) [MH ⁺]	314 95	>99	ND
s16	E		31	45	2.6 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 340 [(M-H)]	342 >99	>99	ND

Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s17	E		24	31	2.3 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 389 [(M-H)]	391 97	98	ND
s18	E		25	41	2.3 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 309 [(M-H)]	311 95	>99	ND
10	F		37	52	2.1 ^c	353 [MH ⁺], (ESI ⁻) 351 [(M-H)]	98	>99	(CDCl ₃) 1.11 (s, 9 H, 9×t-Bu-H), 2.30 (s, 3 H, C(22)H ₃), 2.35 (s, 6 H, C(15)H ₃ +C(16)H ₃), 2.42 (s, 3 H, C(21)H ₃), 2.53 - 2.68 (m, 2 H, C(13)H ₂), 2.83 (s, 2 H, C(10)H ₂), 4.26 - 4.34 (m, 2 H, C(12)H ₂), 7.11 (dd, J=8.5, 1.5 Hz, 1 H, C(2)H), 7.38 (d, J=8.5 Hz, 1 H, C(3)H), 7.62 (d, J=1.5 Hz, 1 H, C(6)H)

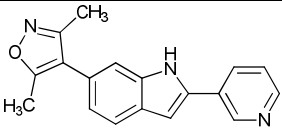
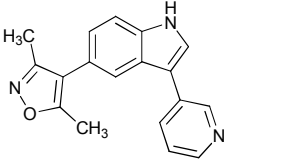
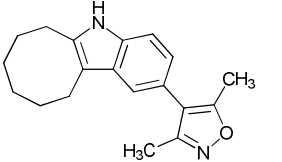
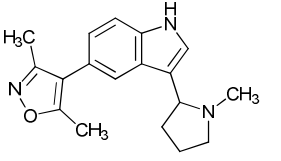
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm	
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)		
s19	F		26	58	3.4 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 225 [(M-H)]	227	97	>99	ND
s20	F		22	48	2.3 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 227 [(M-H)]	229	>99	92	ND
s21	F		24	50	3.4 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 239 [(M-H)]	241	96	>99	ND
s22	F		31	63	1.1 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 242 [(M-H)]	244	71	54	ND
s23	F		31	61	3.0 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 250 [(M-H)]	252	91	98	ND

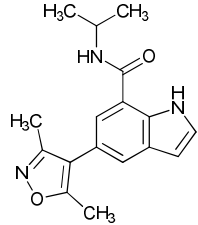
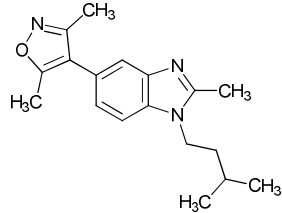
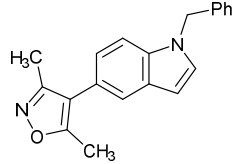
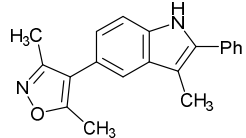
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s24	F		24	48	3.5 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 251 [(M-H)]	253 >99	>99	ND
s25	F		23	45	2.7 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 253 [(M-H)]	255 97	97	ND
s26	F		38	74	2.9 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 254 [(M-H)]	256 95	>99	ND
s27	F		12	23	2.8 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 255 [(M-H)]	257 >99	94	ND

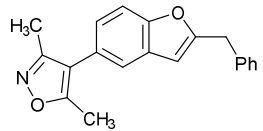
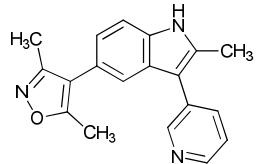
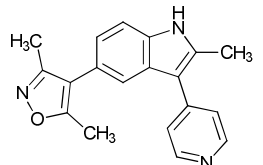
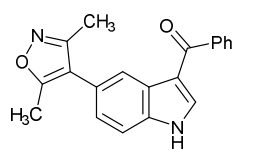
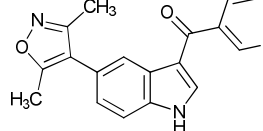
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s28	F		34	66	2.8 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 257 255 [(M-H)]	>99	>99	ND
s29	F		9	17	3.2 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 257 255 [(M-H)]	>99	>99	ND
s30	F		18	36	2.6 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 257 255 [(M-H)]	>99	95	ND
s31	F		36	70	1.9 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 258 256 [(M-H)]	98	95	ND

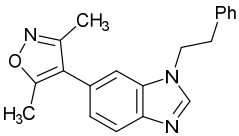
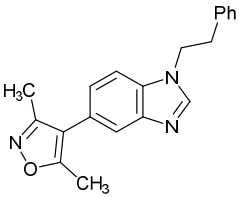
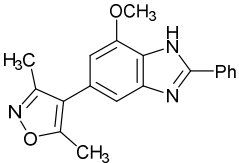
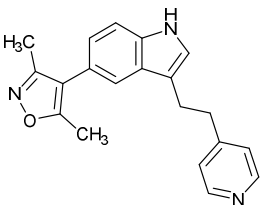
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS					¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)		
s32	F		24	44	2.6 ^c	(ESI ⁺) 270 [MH ⁺], (ESI ⁻) 268 [(M-H)]	81	93	ND	
s33	F		32	59	2.9 ^c	(ESI ⁺) 270 [MH ⁺], (ESI ⁻) 268 [(M-H)]	>99	95	ND	
s34	F		5	9	3.1 ^d	(ESI ⁺) 270 [MH ⁺], (ESI ⁻) 268 [(M-H)]	97	91	ND	
s35	F		21	39	3.1 ^c	271 [MH ⁺], (ESI ⁻) 269 [(M-H)]	93	>99	ND	
s36	F		18	33	2.6 ^c	(ESI ⁺) 272 [MH ⁺], (ESI ⁻) 270 [(M-H)]	87	>99	ND	

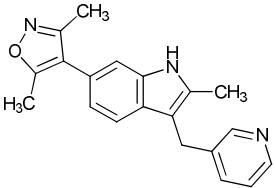
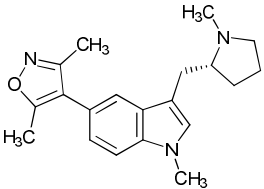
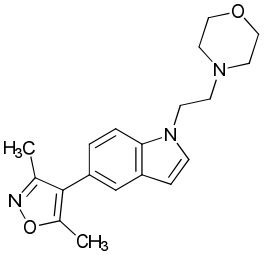
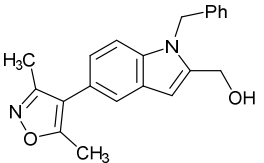
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm	
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)		
s37	F		13	23	1.9 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 283 [(M-H)]	284	>99	>99	ND
s38	F		40	70	3.5 ^d	(ESI ⁺) [MH ⁺]	285	>99	>99	ND
s39	F		53	93	3.1 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 286 [(M-H)]	288	>99	>99	ND
s40	F		13	23	2.5 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 288 [(M-H)]	290	94	>99	ND

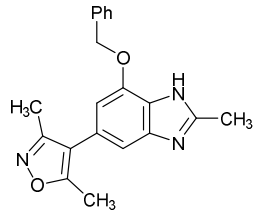
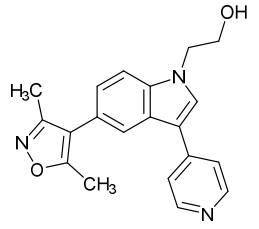
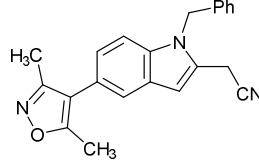
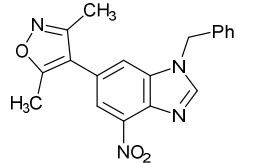
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s41	F		25	44	3.2 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 288 [(M-H) ⁻]	290 >99	>99	ND
s42	F		36	62	3.0 ^d	290 [MH ⁺], (ESI ⁻) 288 [(M-H) ⁻]	>99	>99	ND
s43	F		37	62	3.8 ^c	295 [MH ⁺], (ESI ⁻) 293 [(M-H) ⁻]	>99	>99	ND
s44	F		48	81	3.3 ^d	296 [MH ⁺], (ESI ⁻) 294 [(M-H) ⁻]	>99	>99	ND

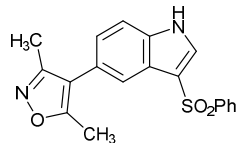
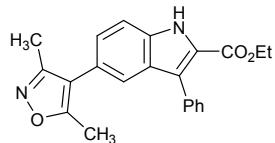
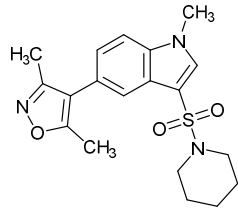
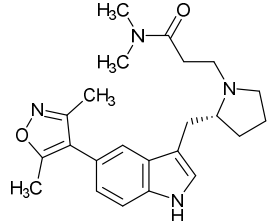
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS					¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)		
s45	F		41	70	3.3 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 296 [(M-H)]	298	95	>99	ND
s46	F		31	52	3.4 ^d	(ESI ⁺) [MH ⁺].	298	>99	>99	ND
s47	F		35	58	3.7 ^c	(ESI ⁺) [MH ⁺]	303	>99	97	ND
s48	F		24	40	3.7 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 301 [(M-H)]	303	96	97	ND

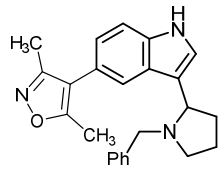
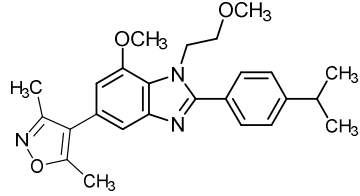
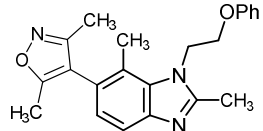
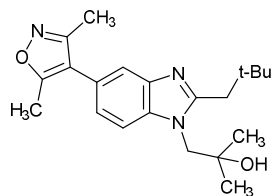
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s49	F		28	46	3.9 ^d	(ESI ⁺) 304 [MH ⁺], (ESI ⁻) 302 [(M-H) ⁻]	>99	>99	ND
s50	F		16	26	3.1 ^d	(ESI ⁺) 304 [MH ⁺], (ESI ⁻) 302 [(M-H) ⁻]	>99	>99	ND
s51	F		7	11	3.0 ^d	(ESI ⁺) 304 [MH ⁺], (ESI ⁻) 302 [(M-H) ⁻]	96	97	ND
s52	F		3	5	3.3 ^d	(ESI ⁺) 317 [MH ⁺], (ESI ⁻) 315 [(M-H) ⁻]	>99	>99	ND
s53	F		22	35	2.9 ^d	(ESI ⁺) 318 [MH ⁺]	>99	>99	ND

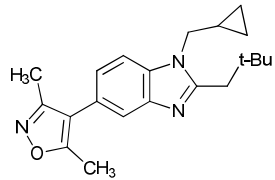
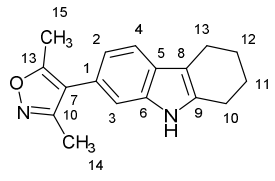
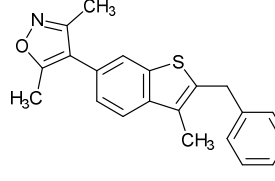
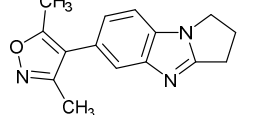
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s54	F		15	23	3.2 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻), 316 [(M-H)]	318 >99	>99	ND
s55	F		13	21	3.3 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 316 [(M-H)]	318 >99	>99	ND
s56	F		17	27	3.1 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 318 [(M-H)]	320 >99	>99	ND
s57	F		36	56	3.1 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 316 [(M-H)]	318 >99	>99	ND

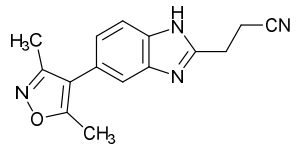
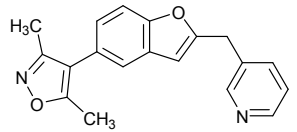
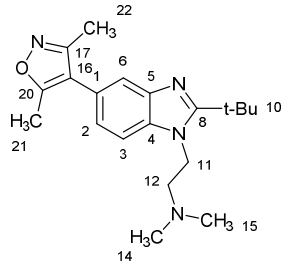
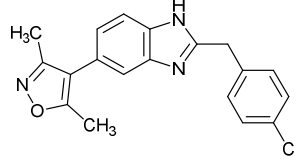
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm	
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)		
s58	F		22	34	3.2 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 316 [(M-H)]	318	>99	>99	ND
s59	F		20	31	3.7 ^d	(ESI ⁺) [MH ⁺]	324	>99	>99	ND
s60	F		51	79	3.2 ^d	(ESI ⁻) [(M-H)]	324	>99	>99	ND
s61	F		26	39	3.3 ^d	333 [MH ⁺], (ESI ⁻) 331 [(M-H)]	>99	>99	ND	

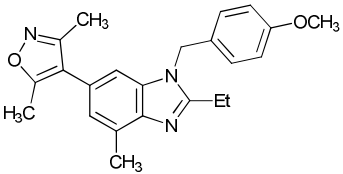
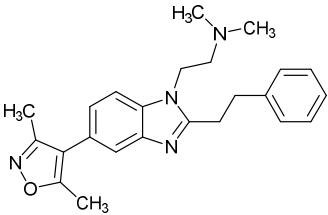
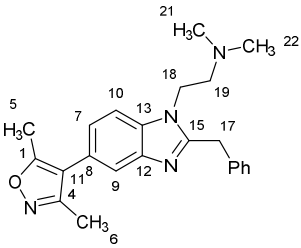
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s62	F		26	39	3.3 ^d	333 [MH ⁺], (ESI ⁻) 331 [(M-H) ⁻]	>99	>99	ND
s63	F		17	25	2.2 ^c	(ESI ⁺) 334 [MH ⁺], (ESI ⁻) 332 [(M-H) ⁻]	>99	>99	ND
s64	F		9	13	3.6 ^d	(ESI ⁺) 342 [MH ⁺], (ESI ⁻) 340 [(M-H) ⁻]	>99	>99	ND
s65	F		13	19	3.1 ^d	(ESI ⁺) 349 [MH ⁺], (ESI ⁻) 347 [(M-H) ⁻]	>99	>99	ND

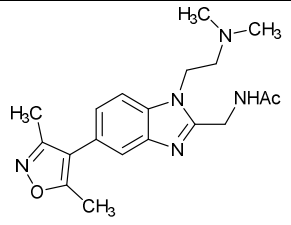
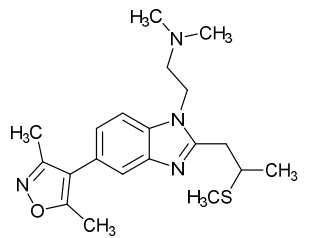
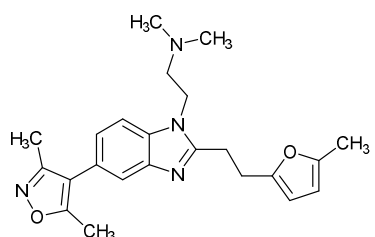
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					<i>t_r</i> (min)	<i>m/z</i>	UV purity (%)	ELSD purity (%)	
s66	F		27	38	3.1 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 351 [(M-H)]	353 >99	>99	ND
s67	F		8	11	3.6 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 359 [(M-H)]	361 >99	>99	ND
s68	F		13	18	3.4 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 372 [(M-H)]	374 >99	>99	ND
s69	F		21	27	3.0 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 393 [(M-H)]	395 96	98	ND

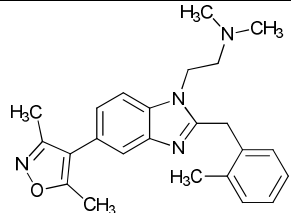
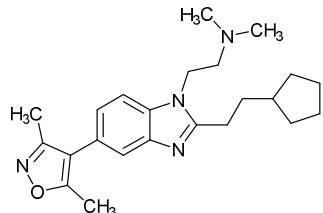
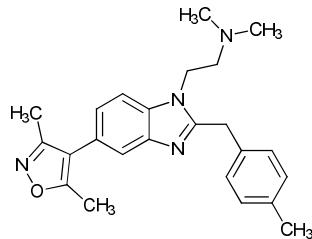
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s70	F		27	37	2.4 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 370 [(M-H)]	372 >99	>99	ND
s71	F		27	32	3.0 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 418 [(M-H)]	420 >99	>99	ND
s72	F		15	21	2.5 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 360 [(M-H)]	362 88	97	ND
s73	F		11	15	2.4 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 354 [(M-H)]	356 95	98	ND

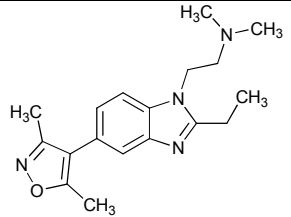
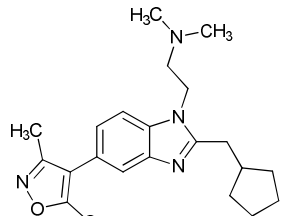
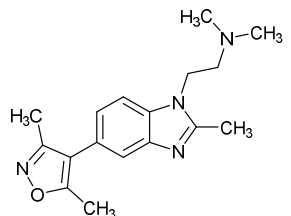
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm	
					<i>t_r</i> (min)	<i>m/z</i>	UV purity (%)	ELSD purity (%)		
s74	F		38	57	2.5 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 336 [(M-H)]	338	>99	>99	ND
s75	F		29	54	3.7 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 265 [(M-H)]	267	84	88	(CDCl ₃) 1.85 - 2.00 (m, 4 H, C(11)H ₂ +C(12)H ₂), 2.28 (s, 3 H, C(14)H ₃), 2.41 (s, 3 H, C(15)H ₃), 2.71 - 2.81 (m, 4 H, C(10)H ₂ +C(13)H ₂), 6.96 (dd, <i>J</i> =8.0, 1.0 Hz, 1 H, C(2)H), 7.15 (d, <i>J</i> =1.0 Hz, 1 H, C(3)H), 7.52 (d, <i>J</i> =8.0 Hz, 1 H, C(4)H), 7.80 (br. s., 1 H, NH)
s76	F		33	50	3.6 ^d	(ESI ⁺) [MH ⁺]	335	99	>99	ND
s77	F		15	30	2.0 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 252 [(M-H)]	254	>99	>99	ND

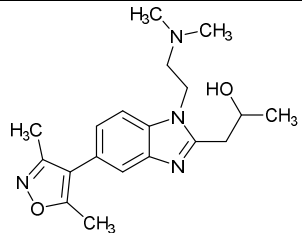
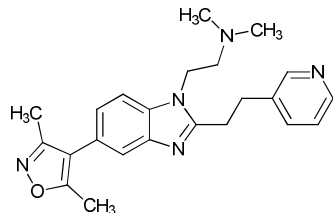
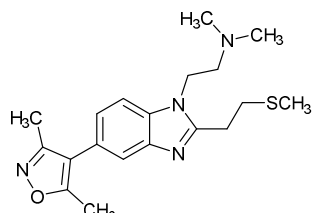
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s78	F		5	10	2.6 ^d	(ESI ⁺) 267 [MH ⁺], (ESI ⁻) 265 [(M-H)]	>99	>99	ND
s79	F		26	42	2.6 ^d	(ESI ⁺) 305 [MH ⁺], (ESI ⁻) 303 [(M-H)]	95	>99	ND
s80	F		9	13	1.2 ^c	(ESI ⁺) 341 [MH ⁺]	>99	>99	(CDCl ₃) 1.59 (s, 9 H, t-Bu), 2.28 (s, 3 H, C(22)H ₃), 2.41 (s, 9 H, C(14)H ₃ +C(15)H ₃ +C(21)H ₃), 2.72 - 2.81 (m, 2 H, C(12)H ₂), 4.43 - 4.53 (m, 2 H, C(11)H ₂), 7.13 (dd, J=8.0, 1.5 Hz, 1 H, C(2)H), 7.39 (d, J=8.0 Hz, 1 H, C(3)H), 7.64 (d, J=1.5 Hz, 1 H, C(6)H)
s81	F		61	82	3.4 ^d	(ESI ⁺) 372 [MH ⁺], (ESI ⁻) 370 [(M-H)]	97	95	ND

Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s82	F		49	68	2.5 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 374 [(M-H)]	376 >99	>99	ND
14	G		26	34	3.4 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 387 [(M-H)]	389 >99	>99	ND
s83	G		9	24	3.2 ^b	(ESI ⁺) [MH ⁺]	375 90	ND	(CDCl ₃) 2.23 (s, 6 H, C(21)H ₃ +C(22)H ₃), 2.32 (s, 3 H, C(6)H ₃), 2.38 (t, J=7.52 Hz, 2 H, C(19)H ₂), 2.45 (s, 3 H, C(5)H ₃), 4.14 (t, J=7.5 Hz, 2 H, C(18)H ₂), 4.40 (s, 2 H, CH ₂ Ph), 7.15 (dd, J=8.0, 1.5 Hz, 1 H, C(7)H), 7.27 - 7.38 (m, 6 H, C(10)H+5×PhH), 7.66 (d, J=1.5 Hz, 1 H, C(9)H)

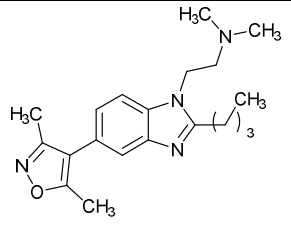
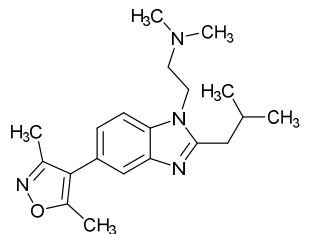
Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s84	G		19	54	2.6 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 368 [(M-H)]	370 >99	>99	ND
s85	G		4	10	3.1 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 371 [(M-H)]	373 98	>99	ND
s86	G		5	12	3.3 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 391 [(M-H)]	393 >99	>99	ND

Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s87	G		3	8	3.4 ^c	389 [MH ⁺]	95	98	ND
s88	G		3	9	3.6 ^d	(ESI ⁺) 381 [MH ⁺], (ESI ⁻) 379 [(M-H)]	99	>99	ND
s89	G		13	34	3.4 ^d	(ESI ⁺) 389 [MH ⁺], (ESI ⁻) 387 [(M-H)]	95	99	ND

Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm	
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)		
s90	G		10	31	2.9 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 311 [(M-H)]	313	98	>99	ND
s91	G		18	50	3.5 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 365 [(M-H)]	367	>99	98	ND
s92	G		16	54	2.8 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 297 [(M-H)]	299	92	>99	ND

Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s93	G		5	16	2.8 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 343 341 [(M-H)]	92	>99	ND
s94	G		13	34	2.8 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 390 388 [(M-H)]	>99	>99	ND
s95	G		4	12	2.0 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 359 357 [(M-H)]	96	>99	ND

Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS				¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)	
s96	G		10	30	1.0 ^c	(ESI ⁺) [MH ⁺]	327 >99	>99	ND
s97	G		13	36	2.1 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 367 [(M-H)]	369 >99	>99	ND
s98	G		5	13	2.9 ^d	(ESI ⁺) [MH ⁺]	384 90	>99	ND

Cmpd	General synthesis procedure	Structure	Mass obtained (mg)	Yield (%)	LCMS					¹ H NMR (400 MHz) δ ppm
					t _r (min)	m/z	UV purity (%)	ELSD purity (%)		
s99	G		6	17	1.9 ^c	(ESI ⁺) [MH ⁺], (ESI ⁻) 339 [(M-H)]	341	98	>99	ND
s100	G		17	49	3.2 ^d	(ESI ⁺) [MH ⁺], (ESI ⁻) 339 [(M-H)]	341	99	>99	ND

^a LCMS system A

^b LCMS system B

^c LCMS system C (acidic conditions)

^d LCMS system C (basic conditions)

Protein Expression and purification

cDNAs encoding human BRD4 (NCBI accession numbers NP 055114.1), human CBP (NCBI accession number 004371.1) and human EP300 (NCBI accession number 001420.2) were obtained from FivePrime and were used as template to amplify the bromodomain regions of the proteins. Proteins were cloned, expressed and purified as previously described².

Differential scanning fluorimetry

Thermal melting experiments were carried out using an Mx3005p Real Time PCR machine (Stratagene). Proteins were buffered in 10 mM HEPES pH 7.5, 500 mM NaCl and assayed in a 96 well plate at a final concentration of 2 μ M in 20 μ L volume. Compounds were added at a final concentration of 10 μ M. SYPRO Orange (Molecular Probes) was added as a fluorescence probe at a dilution of 1 in 1000. Excitation and emission filters for the SYPRO-Orange dye were set to 465 nm and 590 nm, respectively. The temperature was raised with a step of 3 $^{\circ}$ C per minute from 25 $^{\circ}$ C to 96 $^{\circ}$ C and fluorescence readings were taken at each interval. The temperature dependence of the fluorescence during the protein denaturation process was approximated by the equation

$$y(T) = y_F + \frac{y_U - y_F}{1 + e^{\Delta G(T)/RT}}$$

where ΔG is the difference in unfolding free energy between the folded and unfolded state, R is the gas constant and y_F and y_U are the fluorescence intensity of the probe in the presence of completely folded and unfolded protein respectively³. The baselines of the denatured and native state were approximated by a linear fit. The observed temperature shifts, ΔT_m^{obs} , were recorded as the difference between the transition midpoints of sample and reference wells containing protein without ligand in the same plate and determined by non linear least squares fit.

AlphaScreen

Assays were performed as described previously⁴ with minor modifications from the manufacturer's protocol (PerkinElmer, USA). All reagents were diluted in 25 mM HEPES, 100 mM NaCl, 0.1 % BSA, pH 7.4 supplemented with 0.05 % CHAPS and allowed to equilibrate to room temperature prior to addition to plates. A 11-point 1:2.5 serial dilution of the ligands was prepared over the range of 5000 – 0 μ M and 0.1 μ L transferred to low-volume 384-well plates filled with 5 μ L of the assay buffer (ProxiPlateTM-384 Plus, PerkinElmer, USA), followed by 7 μ L of 1 to 2 preparation of biotinylated peptide [H-YSGRGKacGGKacGLGKacGGAKacRHRK(Biotin)-OH for BRD4 or H-ALREIRRYQK(ac)STELLIRKLK(biotin)-OH for CBP/p300] and His-tagged protein to achieve final assay concentrations of 50 nM. Plates were sealed and incubated for a further 30 minutes, before the addition of 8 μ L of the mixture of streptavidin-coated donor beads (12.5 μ g/ml) and nickel chelate acceptor beads (12.5 μ g/ml) under low light conditions. Plates were foil-sealed to protect from light, incubated at room temperature for 60 minutes and read on a PHERAstar FS plate reader (BMG Labtech, Germany) using an AlphaScreen 680 excitation/570 emission filter set. IC50 values were calculated in Prism 5 (GraphPad Software, USA) after normalization against corresponding DMSO controls and are given as the final concentration of compound in the 20 μ L reaction volume.

Isothermal Titration Calorimetry

Experiments were carried out on a VP-ITC titration microcalorimeter from MicroCal™, LLC (Northampton, MA) with a cell volume of 1.4189 ml and a 250 µl microsyringe or a ITC200 titration microcalorimeter from GE Healthcare with a cell volume of 200 µl and a 40 µl microsyringe. Both instruments were equipped with a ThermoVac module. All experiments were carried out at 15 °C while stirring at 295 rpm, in ITC buffer (50 mM HEPES pH 7.4 (at 25 °C), 150 mM NaCl). The microsyringe was loaded with a solution of the protein sample (200-350 µM protein in ITC buffer) and was carefully inserted into the calorimetric cell which was filled with an amount of the ligand (200 µl, 20-30 µM in ITC buffer). The system was first allowed to equilibrate until the cell temperature reached 15 °C and an additional delay of 120 (VP-ITC) or 60 sec (ITC200) was applied. All titrations were conducted using an initial control injection of 2 µl (VP-ITC) or 0.3 µl followed by 34 (VP-ITC) or 38 (ITC200) identical injections of 8 µl (VP-ITC) or 1 µl (ITC200) with a duration of 4 sec (VP-ITC) or 2 sec (ITC200) per injection and a spacing of 250 sec (VP-ITC) or 120 sec (ITC200) between injections. The titration experiments were designed in such a fashion, as to ensure complete saturation of the enzymes before the final injection. The heat of dilution for the proteins were independent of their concentration and corresponded to the heat observed from the last injection, following saturation of ligand binding, thus facilitating the estimation of the baseline of each titration from the last injection. The collected data were corrected for protein heats of dilution (measured on separate experiments by titrating the proteins into ITC buffer) and deconvoluted using the MicroCal™ Origin software supplied with the instrument to yield enthalpies of binding (ΔH) and binding constants (K_B) in the same fashion to that previously described in detail by Wiseman and coworkers⁵. Thermodynamic parameters were calculated using the basic equation of thermodynamics ($\Delta G = \Delta H - T\Delta S = -RT\ln K_B$, where ΔG , ΔH and ΔS are the changes in free energy, enthalpy and entropy of binding respectively). In all cases a single binding site model was employed, supplied with the MicroCal™ Origin software package. Dissociation constants and thermodynamic parameters are listed on Table S3.

Crystallization

Aliquots of the purified proteins were set up for crystallization using a mosquito® crystallization robot (TTP Labtech, Royston UK). Coarse screens were typically setup onto Greiner 3-well plates using three different drop ratios of precipitant to protein per condition (100+50 nl, 75+75 nl and 50+100 nl). Initial hits were optimized further scaling up the drop sizes. All crystallizations were carried out using the sitting drop vapor diffusion method at 4 °C. CBP crystals with compound **6** were grown by mixing 200 nl of protein (10 mg/ml and 1 mM final ligand concentration) with 100 nl of reservoir solution containing 0.10 M MgCl₂, 0.1M TRIS pH 8.0, 20 % PEG 6K and 10 % EtGly. CBP crystals with compound **16** were grown by mixing 150 nl of the protein (9.5 mg/ml with 1 mM of final ligand concentration) with an equal volume of reservoir solution containing 0.20 M NaNO₃, 20 % PEG 3350 and 10 % EtGly. BRD4(1) crystals with compound **16** were grown by mixing 100 nl of the protein (9.0 mg/ml and 5 mM final ligand concentration) with 100 nl of reservoir solution containing 0.20 M NaI, 0.1 M BT-Propane pH 8.5, 20 % PEG3350 and 10 % ethylene glycol. CBP crystals with **58** were grown by mixing 200 nl of the protein (11.1 mg/ml with 1 mM of final ligand concentration) with 100 nl of reservoir solution containing 0.20 M NH₄Cl, 0.1 M MES pH 6.0, 20 % PEG 6K and 10 % ethylene glycol. Diffraction quality crystals grew within a few days.

Data Collection and Structure solution

All crystals were cryo-protected using the well solution supplemented with additional ethylene glycol and were flash frozen in liquid nitrogen. Data were collected in-house on a Rigaku FRE rotating anode system equipped with a RAXIS-IV detector at 1.52 Å (CBP/compound **6** and BRD4(1)/compound **16**) or at Diamond

beamline I24 at a wavelength of 0.9686 Å (CBP/compound **16**) or beamline I02 at a wavelength of 0.979 Å (CBP/compound **58**). Indexing and integration was carried out using MOSFLM⁶ or XDS^{7,8} and scaling was performed with SCALA⁹. Initial phases were calculated by molecular replacement with PHASER¹⁰ using an ensemble of known bromodomain models (PDB IDs 2OSS, 2OUO, 2GRC, 2OO1, 3DAI, 3D7C, 3DWY). Initial models were built by ARP/wARP¹¹ followed by manual building in COOT¹². Refinement was carried out in REFMAC5¹³. Thermal motions were analyzed using TLSMD¹⁴ and hydrogen atoms were included in late refinement cycles. Data collection and refinement statistics can be found in Supplemental Table S4. The model and structure factors have been deposited with PDB accession codes: 4NR4 (CBP/**6**); 4NR7 (CBP/**58**); 4NR5 (CBP/**16**) 4NR8 (BRD4(1)/**16**)

Cell culture and reagents

Human cell lines (HeLa, RKO and U2OS) were purchased from ATCC and cultivated according to the guidelines provided.

Fluorescence Recovery After Photobleaching (FRAP) Assay

FRAP studies were performed using a protocol and plasmids previously described, with the only alteration being the use of a circular bleach area of 13.5 μm^2 for GFP-CBP or 7.6 μm^2 for GFP-BRD4.^{2,15}

Luciferase assay

The p53 reporter assay (Qiagen Cignal p53 Reporter (luc)) was performed according to the instructions of the manufacturer using Dual-Glo luciferase reagents (Promega). In brief RKO cells were transfected with the plasmid mixture (p53 firefly luciferase and CMV control renilla luciferase vectors) in 96 well plate format using Fugene HD (Roche). Twelve hours after transfection cells were treated with compound for 24 h and then stimulated with 0.3 μM of doxorubicin for further 16 h. Percentage p53 activity was calculated as ratio of luminescence of the experimental reporter reading to luminescence from the control reporter, normalized to the DMSO control and multiplied by 100. IC_{50} values were calculated using GraphPad Prism v6.


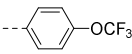

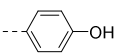
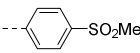
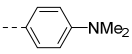
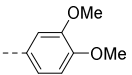
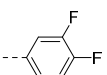
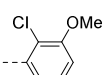
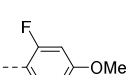
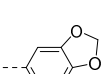
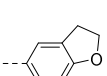
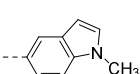
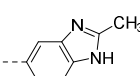

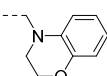
Cytotoxicity assay

U2OS cells were harvested from exponential phase cultures and plated in 96 well opaque flat-bottom plates at a cell density of 3×10^3 cells / well (100 μl). Compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 10 mM and serial dilutions performed. 5 μl of compound solution was added to each well, thoroughly mixed and incubated for 24 and 72hr at 37°C in a humidified atmosphere containing 5% CO_2 . 10 μl of WST-1 (Roche) was added to each well and after mixing plates returned to the incubator. Plates were read on a plate reader at 450 nm after 2 h for cells treated with compound for 24h or after 1 hr for cells treated with compound for 72 h. Results were plotted as % of DMSO control. CC_{50} values were calculated using GraphPad Prism v6.

Table S1. DSF vs AlphaScreen for compounds 14-20.

Cmpd	Target	DSF ΔT_m (°C)	AlphaScreen IC_{50} (μM)
13	CBP	0.27	460
14	BRD4(1)	2.6	22
	CBP	4.4	0.57
15	BRD4(1)	2.7	9.1
	BRD9	1.5	100
	CBP	5.4	0.84
16	BRD4(1)	2.7	2.4
	CECR2	1.0	12
	CBP	6.5	0.18
	p300	7.9	0.14
17	ATAD2	0.16	42
	BRD4(1)	2.1	9.8
	CBP	3.9	0.82
18	ATAD2	0.030	19
	BAZ2A	-0.52	14
	BRD4(1)	1.2	4.1
	CBP	2.0	2.0
19	BRD4(1)	4.0	7.5
	CBP	6.5	0.75
20	BRD4(1)	3.9	9.5
	CBP	6.6	0.44

Table S2. SAR for additional C-2 analgesics.

Cmpd	R	DSF ΔT_m ($^{\circ}\text{C}$)*	
		CBP	BRD4(1)
s101		5.2 \pm 0.31 (3)	2.9 \pm 0.24 (3)
s102		7.0 \pm 0.17 (4)	2.3 \pm 0.63 (3)
s103		6.0 \pm 0.70 (4)	2.1 \pm 0.39 (5)
s104		6.5 \pm 0.32 (3)	2.8 \pm 0.010 (2)
s105		2.6 \pm 0.81 (3)	1.8 \pm 0.13 (3)
s106		6.1 \pm 0.45 (3)	3.2 \pm 0.35 (3)
s107		4.5 \pm 0.54 (2)	1.9 \pm 0.32 (2)
s108		7.7 \pm 0.13 (4)	3.2 \pm 0.10 (3)
s109		7.0 \pm 0.15 (4)	2.6 \pm 0.39 (3)
s110		8.2 \pm 0.16 (3)	2.9 \pm 0.33 (3)
s111		6.6 \pm 0.22 (3)	2.2 \pm 0.25 (3)
s112		6.0 \pm 0.17 (3)	1.9 \pm 0.21 (3)
s113		7.6 \pm 0.046 (3)	3.0 \pm 0.30 (3)
s114		4.0 \pm 0.31 (6)	2.5 \pm 0.14 (4)
s115		8.4 \pm 0.49 (3)	3.0 \pm 0.24 (3)
s116		7.1 \pm 0.44 (3)	3.2 \pm 0.35 (3)

* mean ΔT_m \pm SEM (number of measurements).

Table S3. Dissociation constants and thermodynamic parameters from ITC assays.

Cmpd	BRD	N ¹	ΔH (kcal/mol)	-TΔS (kcal/mol) ²	ΔG (kcal/mol)	K _a (10 ⁶ M ⁻¹)
16	CBP	1.00 ± 0.00223	-5.76 ± 0.0184	-2.90	-8.66	3.10 ± 0.106
16	p300	1.00 ± 0.00280	-6.09 ± 0.0245	-2.51	-8.60	2.88 ± 0.122
16	BRD4(1)	1.10 ± 0.00500	-5.86 ± 0.0338	-2.15	-8.01	1.05 ± 0.0509
25	CBP	1.02 ± 0.00208	-9.70 ± 0.0399	0.0674	-9.63	20.2 ± 1.71
25	BRD4(1)	0.987 ± 0.00330	-8.74 ± 0.0402	0.501	-8.24	1.83 ± 0.0697
31	CBP	0.887 ± 0.00152	-9.63 ± 0.0319	-0.346	-9.98	36.1 ± 2.91
31	BRD4(1)	0.674 ± 0.00495	-8.02 ± 0.0815	-0.331	-8.35	2.09 ± 0.155
32	CBP	1.18 ± 0.00143	-10.8 ± 0.0290	0.760	-10.1	44.8 ± 3.12
32	BRD4(1)	0.604 ± 0.00325	-9.99 ± 0.0746	1.670	-8.32	2.26 ± 0.121
35	CBP	0.703 ± 0.00135	-9.30 ± 0.0342	-0.638	-9.94	33.1 ± 2.53
35	BRD4(1)	0.645 ± 0.00594	-9.34 ± 0.118	1.240	-8.10	1.51 ± 0.116
57	CBP	0.983 ± 0.00535	-14.0 ± 0.0994	5.72	-8.50	2.72 ± 0.178
57	BRD4(1)	1.04 ± 0.0101	-8.50 ± 0.108	0.725	-7.78	0.828 ± 0.0479
58	CBP	0.991 ± 0.00239	-10.9 ± 0.0477	0.817	-10.1	47.4 ± 4.44
58	p300	0.975 ± 0.00330	-10.5 ± 0.0565	0.638	-9.86	31.4 ± 2.49
58	BRD4(1)	1.00 ± 0.0149	-8.47 ± 0.161	0.489	-7.98	1.17 ± 0.118
60	CBP	0.88 ± 0.00202	-9.59 ± 0.0406	-0.420	-10.0	38.1 ± 3.43
60	BRD4(1)	0.84 ± 0.0113	-7.46 ± 0.127	-0.844	-8.30	1.88 ± 0.236
61	CBP	1.01 ± 0.00517	-12.5 ± 0.0855	3.94	-8.58	4.18 ± 0.297
61	BRD4(1)	0.862 ± 0.00663	-9.21 ± 0.0912	1.12	-8.09	1.46 ± 0.0973
62	CBP	1.08 ± 0.00290	-11.1 ± 0.0496	1.37	-9.71	25.4 ± 2.01
62	BRD4(1)	0.859 ± 0.00961	-9.15 ± 0.128	0.978	-8.17	1.65 ± 0.136

¹ Molar binding ratio of the ligand-protein interaction (observed stoichiometry)

² At T = 298.15 K

Table S4. DSF selectivity panel vs AlphaScreen

	<i>DSF ΔT_m (°C)*</i>		<i>AlphaScreen IC_{50} (μM)*</i>	
	Compound 16	Compound 58	Compound 16	Compound 58
BRD2(1)	2.4 ± 0.31 (4)	1.2 ± 0.21 (2)	2.3 ± 1.6 (7)	28 ± 3.0 (2)
BRD3(1)	2.6 ± 0.23 (4)	1.5 ± 0.29 (2)	<i>ND</i>	<i>ND</i>
BRD4(1)	2.6 ± 0.43 (5)	1.8 ± 0.46 (4)	<i>ND</i>	<i>ND</i>
BRD9	1.5 ± 0.32 (2)	-0.31 ± 0.19 (2)	>25	<i>ND</i>
CECR2	1.0 ± 0.49 (2)	0.87 ± 0.69 (2)	12 ± 1.7 (4)	>20
CBP	6.5 ± 0.18 (2)	9.7 ± 0.31 (4)	0.18 ± 0.041 (6)	0.069 ± 0.0080 (2)
p300	7.9 ± 0.37 (2)	9.7 ± 0.23 (3)	0.14 ± 0.029 (2)	<i>ND</i>
PB1(1)	0.34 ± 0.13 (13)	0.16 ± 0.086 (5)	<i>ND</i>	<i>ND</i>
TAF1(1)	0.28 ± 0.18 (5)	0.070 ± 0.11 (3)	<i>ND</i>	<i>ND</i>
TAF1L(1)	0.89 ± 0.19 (4)	0.53 ± 0.59 (2)	<i>ND</i>	<i>ND</i>
TIF1α	1.0 ± 0.31 (4)	0.78 ± 0.11 (2)	<i>ND</i>	<i>ND</i>
TRIM28	-0.46 ± 0.63 (2)	0.075 ± 0.42(2)	<i>ND</i>	<i>ND</i>

*Mean value ± SEM (number of measurements).

Table S5. X-ray crystallography data collection and refinement statistics.

Data Collection												
PDB ID	4NR4			4NR7			4NR5			4NR8		
Protein/Ligand	CBP/6			CBP/58			CBP/16			BRD4(1)/16		
Space group	P2 ₁ 2 ₁ 2 ₁			P2 ₁ 2 ₁ 2 ₁			P2 ₁			P2 ₁ 2 ₁ 2 ₁		
Cell dimensions:												
a, b, c (Å)	52.87	57.11	82.84	35.34	49.83	80.55	24.70	44.31	52.92	39.05	50.76	58.66
α, β, γ (deg)	90.00	90.00	90.00	90.00	90.00	90.00	90.00	95.87	90.00	90.00	90.00	90.00
Resolution* (Å)	1.69 (1.78-1.69)			1.20 (1.26-1.20)			1.66 (1.75-1.66)			1.63 (1.72-1.63)		
Unique observations*	28319 (3976)			44326 (6199)			13513 (1963)			14304 (1710)		
Completeness* (%)	98.5 (86.6)			97.9 (95.3)			99.7 (99.9)			95.5 (80.4)		
Redundancy*	3.8 (3.7)			6.5 (6.5)			3.3 (3.3)			4.0 (3.2)		
Rmerge*	0.046 (0.131)			0.032 (0.308)			0.033 (0.565)			0.110 (0.570)		
I/σI*	18.0 (7.9)			27.6 (5.5)			17.0 (2.0)			11.6 (2.0)		
Refinement												
Resolution (Å)	1.69			1.20			1.66			1.63		
R _{work} / R _{free} (%)	15.6/19.2			12.8/14.4			18.9/22.6			21.3/24.6		
Number of atoms (protein/other/water)	1874/81/286			1023/58/206			926/40/78			1046/37/121		
B-factors (Å ²) (protein/other/water)21.85	14.77/13.70/24.62			13.86/19.24/29.48			35.02/29.51/34.92			13.17/15.05/20.86		
r.m.s.d bonds (Å)	0.016			0.009			0.015			0.016		
r.m.s.d angles (°)	1.578			1.483			1.534			1.684		
Ramachadran Favoured (%)	100.00			100.00			99.10			97.52		
Allowed (%)	0.00			0.00			0.90			2.48		
Disallowed (%)	0.00			0.00			0.00			0.00		

* Values in parentheses correspond to the highest resolution shell.

Table S6. Compound 58 ADME

Solubility (PBS, pH 7.4)	38 μ M
logD (PBS, pH 7.4)	3.9
CACO-2 AB	37 10^{-6} cm/s
p-GP inhibition	21% @ 10 μ M
HLM (remaining after 60 min)	0%

Table S7. Compound 58 Cerep wide ligand profiling

Target	IC ₅₀ (μ M)
alpha 2C (h) (antagonist radioligand)	0.11
PDE5 (h) (non-selective)	0.15
PAF (h) (agonist radioligand)	0.54
alpha 2A (h) (antagonist radioligand)	0.57
5-HT1A (h) (agonist radioligand)	1.2
CB2 (h) (agonist radioligand)	1.9
Ca ²⁺ channel (L, diltiazem site) (benzothiazepines) (antagonist radioligand)	2.9
NK2 (h) (agonist radioligand)	3.9
alpha 2B (h) (antagonist radioligand)	4.2
MT1 (ML1A) (h) (agonist radioligand)	4.3
Cl ⁻ channel (GABA-gated) (antagonist radioligand)	4.6
CB1 (h) (agonist radioligand)	5.5
sigma (non-selective) (h) (agonist radioligand)	5.7
Na ⁺ channel (site 2) (antagonist radioligand)	6.6
5-HT transporter (h) (antagonist radioligand)	>10
5-HT1B (antagonist radioligand)	>10
5-HT1D (agonist radioligand)	>10
5-HT2A (h) (agonist radioligand)	>10
5-HT2B (h) (agonist radioligand)	>10
5-HT2C (h) (agonist radioligand)	>10
5-HT3 (h) (antagonist radioligand)	>10
5-HT4e (h) (antagonist radioligand)	>10
5-HT6 (h) (agonist radioligand)	>10
5-HT7 (h) (agonist radioligand)	>10
A1 (h) (agonist radioligand)	>10
A2A (h) (agonist radioligand)	>10
A2B (h) (antagonist radioligand)	>10
A3 (h) (agonist radioligand)	>10
Abl kinase (h)	>10
ACE (h)	>10
ACE-2 (h)	>10
acetylcholinesterase (h)	>10
alpha 1A (h) (antagonist radioligand)	>10
alpha 1B (h) (antagonist radioligand)	>10
AMPA (agonist radioligand)	>10
APJ (apelin) (h) (agonist radioligand)	>10
AR (h) (agonist radioligand)	>10
AT1 (h) (antagonist radioligand)	>10
AT2 (h) (agonist radioligand)	>10
ATPase (Na ⁺ /K ⁺)	>10
B2 (h) (agonist radioligand)	>10
BACE-1 (h) (beta -secretase)	>10
BB3 (h) (agonist radioligand)	>10

Target	IC ₅₀ (μ M)
beta 1 (h) (agonist radioligand)	>10
beta 2 (h) (agonist radioligand)	>10
beta 3 (h) (antagonist radioligand)	>10
BLT1 (LTB4) (h) (agonist radioligand)	>10
BZD (central) (agonist radioligand)	>10
Ca ²⁺ channel (L, dihydropyridine site) (antagonist radioligand)	>10
Ca ²⁺ channel (L, verapamil site) (phenylalkylamine) (antagonist radioligand)	>10
Ca ²⁺ channel (N) (antagonist radioligand)	>10
CaMK2alpha (h)	>10
caspase-3 (h)	>10
CCK1 (CCKA) (h) (agonist radioligand)	>10
CCK2 (CCKB) (h) (agonist radioligand)	>10
CCR2 (h) (agonist radioligand)	>10
CDK2 (h) (cycA)	>10
choline transporter (CHT1) (h) (antagonist radioligand)	>10
COMT (catechol- O-methyl transferase)	>10
COX1 (h)	>10
COX2 (h)	>10
CRF1 (h) (agonist radioligand)	>10
CysLT1 (LTD4) (h) (agonist radioligand)	>10
D1 (h) (antagonist radioligand)	>10
D2S (h) (agonist radioligand)	>10
D3 (h) (antagonist radioligand)	>10
delta 2 (DOP) (h) (agonist radioligand)	>10
dopamine transporter (h) (antagonist radioligand)	>10
EP2 (h) (agonist radioligand)	>10
ERalpha (h) (agonist fluoligand)	>10
ERK2 (h) (P42mapk)	>10
ETA (h) (agonist radioligand)	>10
ETB (h) (agonist radioligand)	>10
FLT-1 kinase (h) (VEGFR1)	>10
FP (h) (agonist radioligand)	>10
Fyn kinase (h)	>10
GABA transporter (antagonist radioligand)	>10
GABAA1 (h) (alpha 1,beta 2,gamma 2) (agonist radioligand)	>10
GABAB(1b) (h) (antagonist radioligand)	>10
glucagon (h) (agonist radioligand)	>10
glycine (strychnine-insensitive) (antagonist radioligand)	>10
GR (h) (agonist radioligand)	>10
guanylyl cyclase (h) (activator effect)	>10
H1 (h) (antagonist radioligand)	>10
H2 (h) (antagonist radioligand)	>10
H3 (h) (agonist radioligand)	>10
H4 (h) (agonist radioligand)	>10
HIV-1 protease (h)	>10
inducible NOS	>10

Target	IC ₅₀ (μ M)
IP (PGI2) (h) (agonist radioligand)	>10
IRK (h) (InsR)	>10
kainate (agonist radioligand)	>10
kappa (KOP) (agonist radioligand)	>10
LXRbeta (h) (agonist radioligand)	>10
Lyn A kinase (h)	>10
M1 (h) (antagonist radioligand)	>10
M2 (h) (antagonist radioligand)	>10
M3 (h) (antagonist radioligand)	>10
M4 (h) (antagonist radioligand)	>10
MAO-A (antagonist radioligand)	>10
MC1 (agonist radioligand)	>10
MC3 (h) (agonist radioligand)	>10
MC4 (h) (agonist radioligand)	>10
MCH1 (h) (agonist radioligand)	>10
MMP-1 (h)	>10
MMP-2 (h)	>10
MMP-9 (h)	>10
motilin (h) (agonist radioligand)	>10
MT3 (ML2) (agonist radioligand)	>10
mu (MOP) (h) (agonist radioligand)	>10
N muscle-type (h) (antagonist radioligand)	>10
N neuronal alpha 4beta 2 (h) (agonist radioligand)	>10
neutral endopeptidase (h)	>10
NK1 (h) (agonist radioligand)	>10
NMDA (antagonist radioligand)	>10
NOP (ORL1) (h) (agonist radioligand)	>10
norepinephrine transporter (h) (antagonist radioligand)	>10
p38alpha kinase (h)	>10
PCP (antagonist radioligand)	>10
PDE2A1 (h)	>10
PDE3B (h)	>10
PDE4D2 (h)	>10
PDE6 (non-selective)	>10
PPARgamma (h) (agonist radioligand)	>10
SKCa channel (antagonist radioligand)	>10
sst1 (h) (agonist radioligand)	>10
sst4 (h) (agonist radioligand)	>10
TNF-alpha (h) (agonist radioligand)	>10
TR (TH) (agonist radioligand)	>10
UT (h) (agonist radioligand)	>10
V1a (h) (agonist radioligand)	>10
V2 (h) (agonist radioligand)	>10
VPAC1 (VIP1) (h) (agonist radioligand)	>10
xanthine oxidase/ superoxide O ₂ - scavenging	>10
Y1 (h) (agonist radioligand)	>10

Target	IC ₅₀ (μ M)
ZAP70 kinase (h)	>10

FRAP with GFP-CBP N1168F mutant

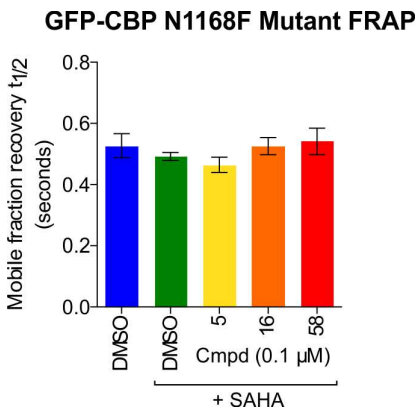


Figure S1. Time dependence of fluorescent recovery in the bleached area in Fluorescence Recovery After Photo-bleaching (FRAP) assays with GFP-tagged 3 \times CBP BRD N1168F mutant construct. Half times of fluorescence recovery ($t_{1/2}$) are shown as bars, which are colored according to DMSO control (blue), DMSO + SAHA (green), 0.1 μ M BRD4(1)-selective inhibitor 5 (yellow), 0.1 μ M compound 16 (orange), 0.1 μ M compound 58 (red).

Compound 58 cytotoxicity

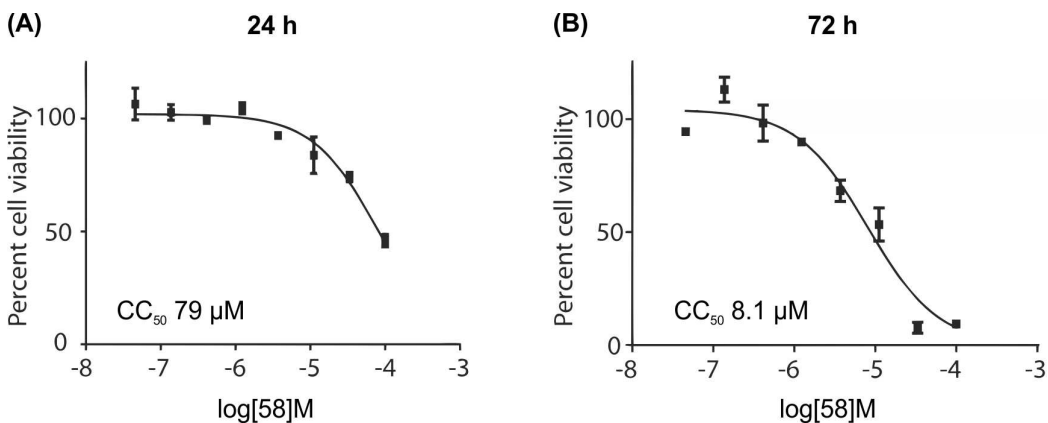


Figure S2. (A) Compound **58** in U2OS MTT cytotoxicity assays, 24 h treatment; (B) Compound **58** in U2OS MTT cytotoxicity assays, 72 h treatment.

References

- (1) Prasitpan, N.; Patel, J. N.; Decroos, P. Z.; Stockwell, B. L.; Manavalan, P.; Kar, L.; Johnson, M. E.; Currie, B. L. *J. Heterocycl. Chem.* **1992**, *29*, 335-41.
- (2) Filippakopoulos, P.; Qi, J.; Picaud, S.; Shen, Y.; Smith, W. B.; Fedorov, O.; Morse, E. M.; Keates, T.; Hickman, T. T.; Felletar, I.; Philpott, M.; Munro, S.; McKeown, M. R.; Wang, Y.; Christie, A. L.; West, N.; Cameron, M. J.; Schwartz, B.; Heightman, T. D.; La Thangue, N.; French, C. A.; Wiest, O.; Kung, A. L.; Knapp, S.; Bradner, J. E. *Nature* **2010**, *468*, 1067-73.
- (3) Matulis, D.; Kranz, J. K.; Salemme, F. R.; Todd, M. J. *Biochemistry* **2005**, *44*, 5258-66.
- (4) Philpott, M.; Yang, J.; Tumber, T.; Fedorov, O.; Uttarkar, S.; Filippakopoulos, P.; Picaud, S.; Keates, T.; Felletar, I.; Ciulli, A.; Knapp, S.; Heightman, T. D. *Mol. BioSyst.* **2011**, *7*, 2899-908.
- (5) Wiseman, T.; Williston, S.; Brandts, J. F.; Lin, L. N. *Anal. Biochem.* **1989**, *179*, 131-7.
- (6) Leslie, A. G. W.; Powell, H.; 7.01 ed.; MRC Laboratory of Molecular Biology: Cambridge, 2007.
- (7) Kabsch, W. *Journal of Applied Crystallography* **1988**, *21*, 916-24.
- (8) Kabsch, W. *Journal of Applied Crystallography* **1988**, *21*, 67-71.
- (9) Evans, P.; 3.3.0 ed.; MRC Laboratory of Molecular Biology: Cambridge, 2007.
- (10) McCoy, A. J.; Grosse-Kunstleve, R. W.; Storoni, L. C.; Read, R. J. *Acta Crystallogr D Biol Crystallogr* **2005**, *61*, 458-64.
- (11) Perrakis, A.; Morris, R.; Lamzin, V. S. *Nat Struct Biol* **1999**, *6*, 458-63.
- (12) Emsley, P.; Cowtan, K. *Acta Crystallogr D Biol Crystallogr* **2004**, *60*, 2126-32.
- (13) Murshudov, G. N.; Vagin, A. A.; Dodson, E. J. *Acta Crystallogr D Biol Crystallogr* **1997**, *53*, 240-55.
- (14) Painter, J.; Merritt, E. A. *Acta Crystallogr D Biol Crystallogr* **2006**, *62*, 439-50.
- (15) Fedorov, O.; Lingard, H.; Wells, C.; Monteiro, O. P.; Picaud, S.; Keates, T.; Yapp, C.; Philpott, M.; Martin, S. J.; Felletar, I.; Marsden, B. D.; Filippakopoulos, P.; Muller, S.; Knapp, S.; Brennan, P. E. *J. Med. Chem.* **2014**, *57*, 462-76.