Supporting Information

Towards Biophysical Probes for the 5-HT_3 Receptor – Structure-Activity Relationship Study of Granisetron Derivatives

Sanjeev Kumar V. Vernekar,[†] Hasan Y. Hallaq,[†] Guy Clarkson,[†] Andrew J. Thompson,[‡] Linda Silvestri,[‡] Sarah C. R. Lummis,[‡] and Martin Lochner*[,†]

[†]*Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK*
[‡]*Department of Biochemistry, University of Cambridge, Cambridge CB2 1QW, UK*

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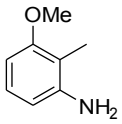
Synthesis

General

Chemicals and solvents were either purchased from commercial suppliers (Sigma-Aldrich Co. or Alfa Aesar) or purified by standard techniques. Anhydrous solvents were purchased in Sure/Seal™ bottles from Sigma-Aldrich Co. BODIPY® FL SE was purchased from Invitrogen. All experiments involving air-sensitive reagents were performed under an inert atmosphere in oven-dried glassware. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F254 plates and compounds were visualized by irradiation with UV light, by exposing to I_2 vapours and/or by staining with cerium molybdate stain (Hanessian's stain) followed by heating. Flash chromatography was carried out using Matrex silica gel 60 unless otherwise stated. Infrared spectra of the compounds were recorded neat on a Nicolet AVATAR 320 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300, 400, 500 MHz and 75, 100, 125 MHz respectively on a Bruker DPX-300, Bruker DPX-400 and DRX-500. The chemical shifts are reported in δ (ppm) and the residual signal of the solvent was used as the internal standard ($CDCl_3$ ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.0 ppm, CD_3OD ^{1}H: δ = 3.31 ppm, ^{13}C: δ = 49.05 ppm, D_2O ^{1}H: δ = 4.79 ppm). High resolution mass spectra were obtained using Electro spray ionisation mass (MS-ESI) technique on a Bruker MicroTOF instrument.

Purity was determined by elemental analysis (CE440 Elemental Analyser, Warwick Analytical Service, The Venture Centre, University of Warwick Science Park, Coventry, UK) and/or HPLC; purity of key target compounds was ≥95%.

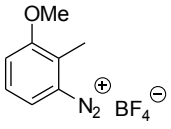
3-Methoxy-2-methylbenzenamine (17)



1-Methoxy-2-methyl-3-nitrobenzene (3.0 g, 18.0 mmol) was dissolved in EtOH (30 mL), degassed and Pd/C (10%, 0.4 g) was added. The mixture was stirred under H_2 atmosphere at room temperature. After 24 h, TLC analysis showed completion of reaction. The reaction mixture was filtered through a short pad of Celite and the residue washed with EtOH. The solvent was evaporated to yield **17** (2.5 g, 17.5 mmol, 98%) as a red oil. The product was used without any further purification in the next step: R_f = 0.29

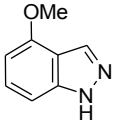
(EtOAc/hexane; 3:7); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02 (s, 3H), 3.78 (s, 3H), 6.32 (d, J = 8.1 Hz, 2H), 6.96 (t, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.8, 55.5, 101.0, 108.3, 110.3, 126.4, 145.5, 158.1; IR (neat) 3369, 2936, 2835, 1620, 1587, 1471, 1259, 1134, 1097, 766, 707 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_8H_{12}NO$ 138.0919 $[M+H]^+$, found 138.0913 $[M+H]^+$.

3-Methoxy-2-methylbenzenediazonium tetrafluoroborate (18)



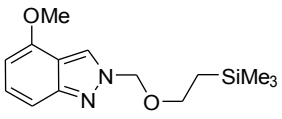
Aniline **17** (2.3 g, 16.8 mmol) was added to a 50% aqueous solution of fluoroboric acid (15 mL) at room temperature and stirred for 5 min. The mixture was cooled in an ice bath for 10 min and an aqueous solution of $NaNO_2$ (1.4 g, 20.3 mmol in 2.6 mL H_2O) was added to the mixture. The reaction mixture was stirred at 10°C for 30 min, during which the product precipitated. This increased the viscosity of the solution and the colour changed to pale yellow. The cooled reaction mixture was filtered through a Büchner funnel and the solid product washed with small amounts of H_2O, MeOH and Et_2O and dried under high vacuum to obtain **18** (3.6 g, 15.3 mmol, 91%) as a pale brown solid: ^{1}H NMR (D_2O, 400 MHz) δ 1.96 (s, 3H), 3.74 (s, 3H), 6.50 (d, J = 8.2 Hz, 1H), 6.56 (d, J = 8.3 Hz, 1H), 7.02 (t, J = 8.2 Hz, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 7.5, 56.0, 103.8, 108.7, 126.7, 126.9, 144.5, 158.2; IR (neat) 3211, 2359, 1588, 1471, 1240, 1104, 866, 703 cm^{-1}. This compound can be stored at –20°C for a limited period of time but preferably is used as soon as possible in the next step.

4-Methoxy-1*H*-indazole (8a)



In a dry flask 18-crown-6 (0.18 g, 0.68 mmol) and potassium acetate (2.9 g, 29.4 mmol) were dried under high vacuum for 1 h and anhyd. $CHCl_3$ (140 mL) was added and stirred at room temperature for 10 min. Then **18** (3.5 g, 14.9 mmol) was added to the mixture in small portions under N_2 atmosphere. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered and the residue washed with $CHCl_3$. The filtrate was washed with water (3 × 40 mL) and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give the crude product. The crude product was purified by flash column chromatography (hexane/EtOAc; 9:1) to afford **8a** (1.8 g, 12.2 mmol, 82%) as a yellow solid: mp 117-120 °C; R_f = 0.13 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (s, 3H), 6.49 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 8.19 (s, 1H), 10.80 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.4, 99.8, 102.5, 115.3, 128.1, 132.7, 142.0, 153.8; IR (neat) 3175, 2956, 2361, 2339, 1593, 1518, 1370, 1254, 1110, 983, 947, 869, 776, 734, 687 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_8H_9N_2O$ 149.0715 $[M+H]^+$, found 149.0709 $[M+H]^+$; Anal. calcd for $C_8H_8N_2O$: C 64.85%, H 5.44%, N 18.91%, found C 64.74%, H 5.50%, N 18.76%.

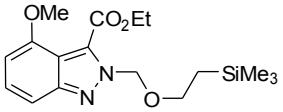
4-Methoxy-2-{[(2-trimethylsilyl)ethoxy]methyl}-2*H*-indazole (19)



To a stirred solution of compound **8a** (1.5 g, 10.1 mmol) in anhyd. THF (50 mL) was added *N,N*-dicyclohexylmethylamine (2.60 g, 13.3 mmol), followed by SEM-chloride (2.02 g, 12.2 mmol) addition and stirring at room temperature. After 12 h, TLC analysis showed presence of starting material. The reaction was continued by adding one more equivalent of *N,N*-dicyclohexylmethylamine and SEM-chloride and stirring for another 12 h. The THF was removed under reduced pressure and the crude reaction mixture was extracted with EtOAc (3 × 20 mL) and washed with 0.5 M NaOH (10 mL). The combined organic phases were washed with H_2O (10 mL),

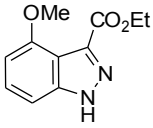
dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was further purified by flash column chromatography (hexane/EtOAc; 9:1) to afford **19** (2.3 g, 8.3 mmol, 83%) as a dark brown oil: R_f = 0.35 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H), 0.97 (t, *J* = 7.9 Hz, 2H), 3.66 (t, *J* = 8.0 Hz, 2H), 3.97 (s, 3H), 5.72 (s, 2H), 6.36 (d, *J* = 7.2 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0, 18.0, 56.6, 68.9, 83.3, 100.0, 111.8, 117.7, 122.8, 128.7, 151.9, 155.0; IR (neat) 2929, 2855, 2362, 1561, 1416, 1263, 1139, 1092, 857, 833, 766, 689 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{14}H_{22}N_2NaO_2Si$ 301.1348 $[M+Na]^+$, found 301.1343 $[M+Na]^+$. The *N*-2 substitution was confirmed by nOe difference studies.

Ethyl 4-methoxy-2-{[(2-trimethylsilyl)ethoxy]methyl}-2*H*-indazole-3-carboxylate (20)



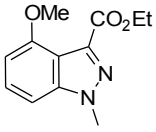
Indazole **19** (0.3 g, 1.1 mmol) was dissolved in anhyd. THF (5 mL) and stirred at –78°C for 10 min under N_2 atmosphere. Then 1.6 M solution of ^{n}BuLi in hexane (0.74 mL, 1.2 mmol) was added drop wise to the mixture at –78°C and stirred for 30 min. The reaction was briefly warmed to room temperature in 10 min, the colour changed to dark brown. The flask was re-cooled to –78°C and a solution of ethyl cyanoformate (0.13 g, 1.3 mmol) in anhyd. THF (2 mL) was added drop wise and stirred for 2 h. The reaction mixture was then slowly allowed to warm to room temperature. The reaction was stopped by adding saturated solution of NH_4Cl. The THF was removed under reduced pressure. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was further purified by flash column chromatography (hexane/EtOAc; 8:2) to afford **20** (0.27 g, 0.78 mmol, 72%) as a brown oil: R_f = 0.39 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 3H), 0.95 (t, *J* = 8.3 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H), 3.62 (t, *J* = 8.2 Hz, 2H), 3.99 (s, 3H), 4.56 (q, *J* = 7.1 Hz, 2H), 6.07 (s, 2H), 6.55 (d, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0, 15.7, 19.2, 56.8, 63.2, 68.7, 82.7, 103.2, 112.2, 116.8, 127.2, 129.0, 150.7, 154.8, 162.3; IR (neat) 2951, 2899, 1708, 1557, 1246, 1229, 1107, 1050, 833, 790, 755, 693 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{17}H_{26}N_2NaO_4Si$ 373.1560 $[M+Na]^+$, found 373.1554 $[M+Na]^+$; Anal. calcd for $C_{17}H_{26}N_2O_4Si$: C 58.26%, H 7.48%, N 7.99%, found C 57.83%, H 7.47%, N 7.82%.

Ethyl 4-methoxy-1*H*-indazole-3-carboxylate (9a)



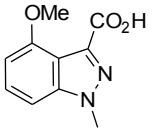
Ester **20** (0.4 g, 1.1 mmol) was dissolved in EtOH (12 mL) and 2 M HCl (10 mL) was added drop wise and stirred at room temperature for 12 h. The reaction was monitored by TLC and neutralized by adding solid Na_2CO_3, then filtered and washed with EtOH. The filtrate was concentrated under vacuo to remove EtOH and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give **9a** (0.24 g, 1.1 mmol, 96%) as a pale yellow solid: mp 109-112°C; R_f = 0.05 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (t, *J* = 7.1 Hz, 3H), 3.96 (s, 3H), 4.47 (q, *J* = 7.1 Hz, 2H), 6.59 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 12.19 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 55.7, 61.3, 102.6, 103.6, 113.4, 129.0, 136.9, 143.5, 153.9, 162.7; IR (neat) 3175, 2978, 1690, 1507, 1294, 1254, 1159, 1050, 985, 768, 732 cm^{-1}; HRMS-ESI (+) $C_{11}H_{12}N_2NaO_3$ *m/z* 243.0746 $[M+Na]^+$, found 243.0740 $[M+Na]^+$.

Ethyl 4-methoxy-1-methyl-1*H*-indazole-3-carboxylate (21)



Ester **9a** (0.2 g, 0.91 mmol) was dissolved in anhyd. THF (5 mL) and cooled to 0°C, then a solution of KO^{t}Bu (0.12 g, 0.99 mmol) in anhyd. THF (2 mL) was added drop wise and stirred for 15 min. A solution of MeI (0.15 g, 1.1 mmol) in anhyd. THF (2 mL) was added to the mixture and warmed to room temperature and stirred for 5 h. The progress of the reaction was monitored by TLC. The THF was removed in vacuo and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was further purified by flash column chromatography (hexane/EtOAc; 8:2) to afford **21** (0.19 g, 0.82 mmol, 90%) as a white solid: mp 88-90°C; R_f = 0.10 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, *J* = 7.1 Hz, 3H), 3.92 (s, 3H), 4.04 (s, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 6.55 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 36.5, 55.8, 61.3, 102.0, 102.2, 114.2, 128.3, 136.9, 143.2, 154.1, 162.7; IR (neat) 2982, 2934, 1707, 1576, 1508, 1458, 1368, 1270, 1234, 1211, 1080, 1026, 769, 747, 719 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{12}H_{14}N_2NaO_3$ 257.0902 $[M+Na]^+$, found 257.0897 $[M+Na]^+$. The *N*-1 methylation was confirmed by difference nOe studies.

4-Methoxy-1-methyl-1*H*-indazole-3-carboxylic acid (10a)



Indazole ester **21** (0.1 g, 0.43 mmol) was dissolved in MeOH (8 mL) and 2 M NaOH (2 mL) was added and stirred at room temperature for 8 h. The TLC analysis of the reaction showed disappearance of starting material, the reaction was acidified to pH 2 and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with water (5 mL), dried over Na_2SO_4, filtered and concentrated to afford **10a** (0.086 g, 0.42 mmol, 98%) as a white solid: mp 204-207°C; R_f = 0.38 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR (CD_3OD, 400 MHz) δ 4.16 (s, 3H), 4.17 (s, 3H), 6.74 (d, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 11.57 (br, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 36.7, 56.7, 102.4, 104.3, 112.8, 128.2, 143.2, 150.4, 160.4, 169.6; IR (neat) 3156, 3100, 1734, 1509, 1395, 1358, 1264, 1211, 1057, 996, 772, 698 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{10}H_{10}N_2NaO_3$ 229.0589 $[M+Na]^+$, found 229.0584 $[M+Na]^+$.

9-Methyl-9-azabicyclo[3.3.1]nonan-3-one (22)

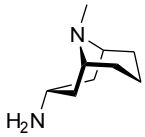
To a solution of glutaraldehyde (25.0 g, 250 mmol) in H_2O (170 mL) were added a solution of methylamine hydrochloride (25.0 g, 370 mmol) dissolved in H_2O (250 mL), acetone-1,3-dicarboxylic acid (42.0 g, 287 mmol) dissolved in H_2O (410 mL), and $Na_2HPO_4 \cdot 12\ H_2O$ (44.0 g, 123 mmol) and NaOH (3.6 g, 90 mmol) dissolved in H_2O (100 mL) at room temperature. Carbon dioxide was evolved, and the mixture was stirred for 24 h at room temperature. Then concentrated HCl (16 mL) was added and the solution was heated on a steam bath for 1 h to complete the decarboxylation. After the solution has been cooled to room temperature, NaOH (38.0 g, 950 mmol) in H_2O (50 mL) was added and the basic mixture was extracted with CH_2Cl_2 (4 × 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to half volume and filtered through a layer of alumina, then eluted with CH_2Cl_2. The eluate was concentrated under reduced pressure to yield **22** (27.0 g, 176 mmol, 71%) as a pale yellow solid: mp 63-67°C; R_f = 0.34 (CH_2Cl_2/MeOH; 8:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30-1.52 (m, 4H), 1.83-1.95 (m, 2H), 2.23 (d, *J* = 16.6 Hz, 2H), 2.56 (s, 3H), 2.70 (dd, *J* = 6.7 Hz, *J* = 16.6 Hz, 2H), 3.22-3.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 29.5, 41.1, 41.7, 55.6, 210.6; IR (neat) 2931, 2917, 2902, 1696, 1269, 1187, 1101, 1016, 841, 734 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_9H_{15}NNaO$ 176.1051

[M+Na]$^+$, found 176.1043 [M+Na]$^+$; Anal. calcd for $C_9H_{15}NO$: C 70.55%, H 9.87%, N 9.14%, found C 70.02%, H 9.77%, N 9.07%.

9-Methyl-9-azabicyclo[3.3.1]nonan-3-one oxime (23)

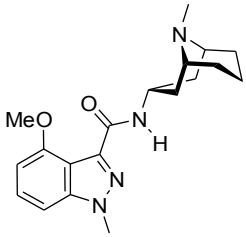
Sodium acetate (7.5 g, 91.4 mmol) and hydroxylamine hydrochloride (8.75 g, 125 mmol) were pulverized in a mortar to a thin paste and extracted with methanol, the salt was filtered off and the solution was treated with **22** (5.0 g, 32.6 mmol) and stirred for 4 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was treated with aqueous K_2CO_3 and extracted with $CHCl_3$ (5 × 50 mL) containing 5% ^{i}PrOH. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to yield **23** (5.3 g, 31.4 mmol, 96%) as a pale yellow solid: mp 126-127°C; R_f = 0.15 (CH_2Cl_2/MeOH; 8:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43-1.46 (m, 1H), 1.51-1.59 (m, 2H), 1.69-1.82 (m, 1H), 1.90-2.03 (m, 2H), 2.24 (d, *J* = 15.6 Hz, 1H), 2.40 (dd, *J* = 6.6 Hz, *J* = 16.4 Hz, 1H), 2.57 (s, 3H), 2.76 (dd, *J* = 6.0 Hz, *J* = 15.7 Hz, 1H), 3.02 (d, *J* = 16.4 Hz, 1H), 3.08-3.09 (m, 2H), 9.10 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.6, 24.8, 28.8, 29.5, 30.9, 40.9, 53.0, 53.8, 158.8; IR (neat) 3055, 2939, 2909, 1099, 959, 933, 755, 725 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_9H_{17}N_2O$ 169.1341 [M+H]$^+$, found 169.1331 [M+H]$^+$; Anal. calcd for $C_9H_{16}N_2O$: C 64.25%, H 9.59%, N 16.65%, found C 63.89%, H 9.53%, N 16.62%.

(3-*endo*)- 9-Methyl-9-azabicyclo[3.3.1]nonan-3-amine (11)



A solution of concentrated H_2SO_4 (0.75 mL) in anhyd. THF (2 mL) was added to a cooled and stirred mixture of $LiAlH_4$ (0.95 g, 25 mmol) in anhyd. THF (15 mL) at –10°C under N_2 atmosphere. The mixture was allowed to stand overnight at room temperature. A solution of **23** (1.0 g, 5.9 mmol) in anhyd. THF (10 mL) was added drop wise to the stirred mixture at 30°C and allowed to react further at 40°C for 3 h. The reaction mixture was cooled to 10°C and a solution of H_2O (0.82 mL) in THF (2 mL) was added and stirred at 30°C for 1 h. The resulting precipitate was filtered off and the residue was washed several times with CH_2Cl_2 and Et_2O. The combined organic layers were washed with sat. $NaHCO_3$ (10 mL) and dried over Na_2SO_4, filtered and concentrated to give **11** as colourless oil (0.72g, 4.7 mmol, 80%) which solidified to a waxy solid on standing: R_f = 0.05 (CH_2Cl_2/MeOH; 8:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84-0.95 (m, 2H), 0.99-1.06 (m, 2H), 1.36-1.41 (m, 1H), 1.85-1.88 (m, 3H), 2.18-2.26 (m, 2H), 2.38 (s, 3H), 2.93 (d, *J* = 10.7 Hz, 2H), 3.15 (tt, *J* = 6.4 Hz, *J* = 11.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 24.1, 37.0, 40.1, 42.2, 51.3; IR (neat) 3281, 2928, 2855, 1437, 1370, 1025, 873, 829 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_9H_{19}N_2$ 155.1548 [M+H]$^+$, found 155.1547 [M+H]$^+$.

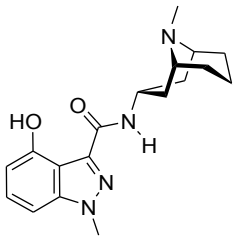
4-Methoxy-1-methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (2b)



Indazole acid **10a** (0.08 g, 0.39 mmol), DCC (0.10 g, 0.50 mmol) and HOBt (0.052 g, 0.39 mmol) were mixed together in a flask and dried under high vacuum for 1 h before dissolving in dry DMF:CH_2Cl_2 (1:4, 10 mL), and then stirring the mixture for 2 h at room temperature. A solution of amine **11** (0.066 g, 0.43 mmol) in dry CH_2Cl_2 (2 mL) was added drop wise to the mixture under N_2 atmosphere and stirred for 24 h at room temperature. The progress of the reaction was monitored by TLC. The solvents were removed in vacuo and the crude product was extracted with CH_2Cl_2 (3 × 20 mL) and washed with sat. $NaHCO_3$ (10 mL). The combined organic phases were dried over Na_2SO_4, filtered

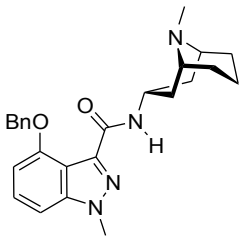
and concentrated to give the crude product. The crude product was further purified by flash column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH/Et_3N; 96:3:1) to afford **2b** (0.124 g, 0.36 mmol, 93%) as a white solid: mp 187-189°C; R_f = 0.11 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.13-1.15 (m, 2H), 1.42-1.55 (m, 3H), 1.99-2.04 (m, 3H), 2.51 (s, 3H), 2.52-2.59 (m, 2H), 3.11 (d, *J* = 10.5 Hz, 2H), 4.04 (s, 3H), 4.06 (s, 3H), 4.53 (tt, *J* = 6.8 Hz, *J* = 11.2 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.40 (t, *J* = 8.1 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 15.0, 25.8, 33.5, 36.4, 40.7, 42.1, 52.7, 56.4, 103.1, 104.5, 113.2, 129.5, 138.6, 144.7, 153.7, 163.4; IR (neat) 3340, 2924, 1635, 1612, 1541, 1264, 1025, 770, 734 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{19}H_{27}N_4O_2$ 343.2134 $[M+H]^+$, found 343.2129 $[M+H]^+$.

4-Hydroxy-1-methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (2a)



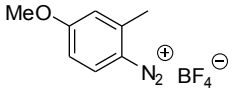
To a solution of compound **2b** (0.07 g, 0.20 mmol) in dry DMF (8 mL) was added NaSEt (0.086 g, 1.0 mmol) and heated at 110 °C for 18 h. The progress of the reaction was monitored by TLC. The reaction was cooled and stopped by adding aqueous solution of NH_4Cl. The aqueous layer was extracted several times with CH_2Cl_2, until the aqueous layer was free from the product. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was further purified by flash column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH/Et_3N; 96:3:1) to afford **2a** (0.062 g, 0.19 mmol, 93%) as a white solid: mp 104-108°C; R_f= 0.23 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.05-1.09 (m, 2H), 1.45-1.59 (m, 3H), 1.94-2.11 (m, 3H), 2.35-2.43 (m, 2H), 2.47 (s, 3H), 3.06 (d, *J* = 10.7 Hz, 2H), 4.00 (s, 3H), 4.56 (tt, *J* = 6.7 Hz, *J* = 11.6 Hz, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.9, 25.4, 33.0, 36.5, 40.4, 42.2, 52.8, 100.9, 106.7, 115.2, 130.4, 137.9, 144.8, 152.7, 164.7; IR (neat) 2916, 2858, 1583, 1555, 1268, 1050, 845, 757, 728 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{18}H_{25}N_4O_2$ 329.1978 $[M+H]^+$, found 329.1968 $[M+H]^+$.

1-Methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-4-(phenylmethoxy)-1*H*-indazole-3-carboxamide (2c)



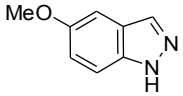
Compound **2a** (0.020 g, 0.061 mmol) was dissolved in dry acetone (2 mL) and solid Na_2CO_3 (0.017 g, 0.12 mmol) was added which was followed by drop wise addition of benzyl bromide (0.011 g, 0.067 mmol) and stirring at room temperature. The reaction was monitored by TLC and found complete in 5 h. The acetone was concentrated under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was further purified by flash column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH/Et_3N; 96:3:1) to afford **2c** (0.016 g, 0.038 mmol, 63%) as a white solid: mp 75-80°C; R_f = 0.19 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.18-1.27 (m, 4H), 1.44-1.47 (m, 1H), 1.74-1.80 (m, 1H), 1.94-2.02 (m, 2H), 2.22-2.30 (m, 2H), 2.67 (s, 3H), 3.25-3.29 (m, 2H), 4.08 (s, 3H), 4.40 (tt, *J* = 6.7 Hz, *J* = 11.7 Hz, 1H), 5.32 (s, 2H), 6.89 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.34-7.44 (m, 4H), 7.55 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 13.8, 25.0, 31.9, 36.4, 39.6, 41.2, 54.0, 72.3, 104.6, 115.2, 129.6, 129.8, 129.9, 130.0, 130.1, 137.9, 144.8, 152.7, 164.7; IR (neat) 2955, 2361, 1541, 1257, 1231, 1054, 1033, 1024, 750, 720, 696 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{25}H_{31}N_4O_2$ 419.2447 $[M+H]^+$, found 419.2448 $[M+H]^+$.

4-Methoxy-2-methylbenzenediazonium tetrafluoroborate (24)



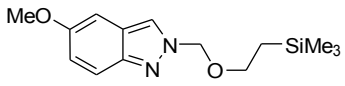
Following the procedure for **18**, 4-methoxy-2-methylbenzeneamine (1.0 g, 7.3 mmol), 50% aq. fluoroboric acid (6.5 mL) and $NaNO_2$ (0.56 g, 8.1 mmol) gave **24** as a magenta-coloured solid (1.34 g, 5.7 mmol, 78%): ^{1}H NMR (D_2O, 400 MHz) δ 2.65 (s, 3H), 4.10 (s, 3H), 7.27 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 8.05-8.09 (m, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 16.5, 56.8, 109.1, 109.2, 123.1, 142.1, 162.7, 163.9; IR (neat)) 2244, 1529, 1489, 1268, 1012, 823, 714 cm^{-1}. This compound can be stored at –20°C for a limited period of time but is preferably used as soon as possible in the next step.

5-Methoxy-1*H*-indazole (8b)



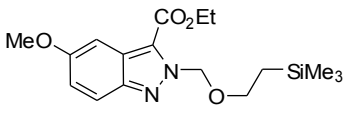
Following the procedure for **8a**, 18-crown-6 (0.06 g, 0.23 mmol), potassium acetate (0.909 g, 9.3 mmol) and **24** (1.0 g, 4.2 mmol) afforded a crude product which was purified by flash chromatography (hexane/EtOAc; 3:1) to yield **8b** (0.52 g, 3.5 mmol, 83%) as a shiny yellow solid: mp 97-99°C; R_f = 0.31 (hexane/EtOAc; 3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 3H), 7.06 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.7 Hz, 1H), 7.95 (s, 1H), 10.89 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.5, 108.9, 112.9, 121.7, 122.8, 131.2, 134.2, 146.3; IR (neat) 3133, 2902, 1602, 1513, 1265, 1156, 950, 822, 715 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_8H_9N_2O$ 149.0715 $[M+H]^+$, found 149.0710 $[M+H]^+$; Anal. calcd for $C_8H_8N_2O$: C 64.85%, H 5.44%, N 18.91%, found C 64.81%, H 5.45%, N 18.76%.

5-Methoxy-2-{[(2-trimethylsilyl)ethoxy]methyl}-2*H*-indazole (25)



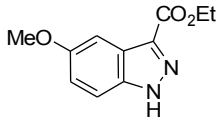
Using the procedure for **19**, **8b** (1.0 g, 6.7 mmol), *N,N*-dicyclohexylmethylamine (1.58 g, 8.1 mmol) and SEM-chloride (1.39 g, 8.3 mmol) yielded **25** (1.58 g, 5.7 mmol, 85%) as a yellow oil: R_f = 0.35 (hexane/EtOAc; 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ -0.01 (s, 9H), 0.92-0.97 (m, 2H), 3.51-3.56 (m, 2H), 3.87 (s, 3H), 5.73 (s, 2H), 7.05 (d, J = 7.7 Hz, 2H), 7.66 (d, J = 6.1 Hz, 1H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0, 18.8, 55.6, 67.9, 80.2, 108.0, 111.2, 120.2, 123.5, 126.7, 137.3, 152.6; IR (neat) 2943, 1534, 1265, 1101, 868, 832, 791, 725 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{14}H_{22}N_2NaO_2Si$ 301.1348 $[M+Na]^+$, found 301.1348 $[M+Na]^+$. The *N*-2 substitution was confirmed by nOe differences studies.

Ethyl 5-methoxy-2-{[(2-trimethylsilyl)ethoxy]methyl}-2*H*-indazole-3-carboxylate (26)



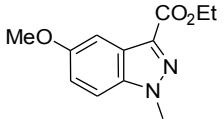
Using the procedure for **20**, indazole **25** (0.7 g, 2.5 mmol), 2.5 M solution of ^{n}BuLi in hexane (1.1 mL, 2.8 mmol) and ethyl cyanoformate (0.4 g, 4.0 mmol) afforded the crude product which was purified by flash chromatography (hexane/EtOAc; 5:1) to give **26** (0.66 g, 1.9 mmol, 75%) as a yellow oil: R_f = 0.35 (hexane/EtOAc; 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 9H), 0.92-0.96 (m, 2H), 2.10 (t, J = 7.1 Hz, 3H), 4.19-4.22 (m, 2H), 4.43 (s, 3H), 5.11 (q, J = 7.1 Hz, 2H), 6.78 (s, 2H), 7.71 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 6.0 Hz, 1H), 8.38 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.9, 16.1, 18.7, 56.8, 62.5, 68.6, 78.1, 102.2, 109.7, 121.6, 124.6, 137.1, 143.0, 151.9, 160.4; IR (neat) 2947, 2895, 1714, 1536, 1304, 1263, 1103, 1099, 844, 732 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{17}H_{26}N_2NaO_4Si$ 373.1560 $[M+Na]^+$, found 373.1561 $[M+Na]^+$; Anal. calcd for $C_{17}H_{26}N_2O_4Si$: C 58.26%, H 7.48%, N 7.99%, found C 58.41%, H 7.50%, N 7.76%.

Ethyl 5-methoxy-1*H*-indazole-3-carboxylate (9b)



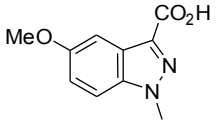
Following the procedure for **9a**, ester **26** (0.5 g, 1.4 mmol) gave **9b** (0.25 g, 1.1 mmol, 79%) as a pale yellow solid: mp 91-96°C; R_f = 0.42 (hexane/EtOAc; 3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33 (t, *J* = 7.1 Hz, 3H), 4.37 (s, 3H), 5.11 (q, *J* = 7.1 Hz, 2H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 5.1 Hz, 1H), 8.38 (d, *J* = 8.3 Hz, 1H), 10.97 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2, 57.0, 63.5, 107.9, 114.9, 125.2, 126.3, 132.2, 136.4, 146.2, 163.5; IR (neat) 3146, 2981, 1676, 1593, 1267, 1303, 1110, 1051, 799, 728 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{11}H_{12}N_2NaO_3$ 243.0746 $[M+Na]^+$, found 243.0744 $[M+Na]^+$.

Ethyl 5-methoxy-1-methyl-1*H*-indazole-3-carboxylate (27)



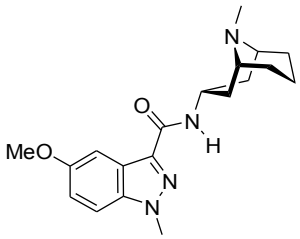
Following the procedure for **21**, ester **9b** (0.3 g, 1.4 mmol), KO^{t}Bu (0.18 g, 1.6 mmol) and MeI (0.25 g, 1.8 mmol) afforded the crude product which was purified by flash chromatography (EtOAc/hexane; 1:6) to yield **27** (0.25 g, 1.1 mmol, 77%) as a white solid: mp 122-124°C; R_f = 0.21 (hexane/EtOAc; 3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12 (t, *J* = 7.1 Hz, 3H), 3.91 (s, 3H), 4.33 (s, 3H), 5.01 (q, *J* = 7.1 Hz, 2H), 7.15 (d, *J* = 5.1 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4, 41.1, 58.1, 66.1, 109.1, 111.0, 122.5, 124.6, 131.5, 133.1, 147.2, 160.9; IR (neat) 2990, 1732, 1471, 1265, 1114, 1023, 787, 733 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{12}H_{14}N_2NaO_3$ 257.0902 $[M+Na]^+$, found 257.0898 $[M+Na]^+$; Anal. calcd for $C_{12}H_{14}N_2O_3$: C 61.53%, H 6.02%, N 11.96%, found C 61.38%, H 6.01%, N 11.97%. The *N*-1 methylation was confirmed by difference nOe studies.

5-Methoxy-1-methyl-1*H*-indazole-3-carboxylic acid (10b)



Following the procedure for **10a**, ester **27** (0.2 g, 0.85 mmol) afforded **10b** (0.17 g, 0.82 mmol, 97%) as a white solid: mp 219-221°C; R_f = 0.25 (CH_2Cl_2/MeOH; 5:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95 (s, 3H), 4.30 (s, 3H), 7.23 (d, *J* = 5.3 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H) 9.98 (s, 1H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.0, 52.0, 105.7, 112.0, 124.6, 125.8, 133.4, 137.7, 148.2, 162.6; IR (neat) 2913, 1656, 1499, 1262, 1189, 1116, 1034, 789, 734 cm^{-1}; HRMS-ESI (–) *m/z* calcd for $C_{10}H_9N_2O_3$ 205.0613 $[M-H]^-$, found 205.0614 $[M-H]^-$. Anal. calcd for $C_{10}H_{10}N_2O_3$: C 58.23%, H 4.89%, N 13.59%, found C58.23%, H 4.87%, N 13.51%.

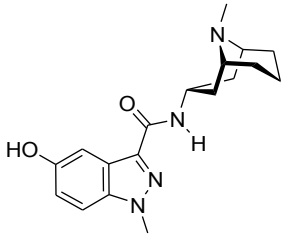
5-Methoxy-1-methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (3b)



Using the procedure for **2b**, indazole acid **10b** (0.1 g, 0.48 mmol), DCC (0.13 g, 0.63 mmol), HOBt (0.065 g, 0.48 mmol) and amine **11** (0.09 g, 0.58 mmol) yielded the crude product which was purified by flash chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH/Et_3N; 95:5:1) to give **3b** (0.139 g, 0.41 mmol, 85%) as a white solid: mp 186-190°C; R_f = 0.18 (CH_2Cl_2/MeOH; 9:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95-1.05 (m, 2H), 1.12-1.19 (m, 2H), 1.39-1.56 (m, 3H), 1.90-2.09 (m, 3H), 2.34-2.44 (m, 2H), 2.53 (s, 3H), 3.06 (d, *J* = 10.8 Hz, 2H), 3.95 (s, 3H), 4.00 (s, 3H), 4.42-4.65 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 5.0 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4, 25.8, 31.5, 35.1, 41.4, 56.5, 56.9, 103.7, 107.2, 118.2,

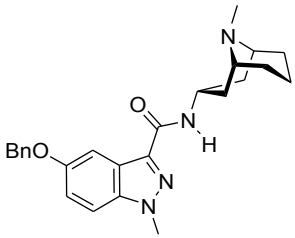
129.7, 135.5, 146.0, 155.1, 163.4; IR (neat) 3319, 2940, 2898, 1652, 1562, 1271, 1057, 883, 847, 744 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{19}H_{27}N_4O_2$ 343.2134 $[M+H]^+$, found 343.2131 $[M+H]^+$; Anal. calcd for $C_{19}H_{26}N_4O_2$: C 66.64%, H 7.65%, N 16.36%, found C 66.62%, H 7.68%, N 16.42%.

5-Hydroxy-1-methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (3a)



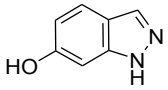
To a solution of compound **3b** (100 mg, 0.29 mmol) in dry CH_2Cl_2 (15 mL) was added a 1 M solution of BBr_3 in CH_2Cl_2 (3 mL, 3 mmol). The resulting mixture was stirred at room temperature for 24 h. The reaction was stopped with the addition of MeOH and the solvents were evaporated. H_2O (10 mL) was added and the pH adjusted to 7.5. The aqueous solution was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated to yield **3a** (81.0 mg, 0.24 mmol, 84%) as a yellow solid: mp 226-231°C; R_f = 0.22 (CH_2Cl_2/MeOH; 9:2); ^{1}H NMR (CD_3OD, 400 MHz) δ 0.99-1.07 (m, 2H), 1.11-1.17 (m, 2H), 1.42-1.58 (m, 3H), 1.91-2.10 (m, 3H), 2.34-2.44 (m, 2H), 2.51 (s, 3H), 3.05 (d, *J* = 10.8 Hz, 2H), 4.04 (s, 3H), 4.56 (tt, *J* = 6.5 Hz, *J* = 10.7 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.62 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.3, 25.9, 32.4, 35.3, 42.4, 55.1, 102.4, 106.4, 118.8, 129.5, 135.8, 145.8, 155.2, 164.3; IR (neat) 2940, 2837, 1582, 1570, 1262, 1034, 856, 845, 743, 720 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{18}H_{25}N_4O_2$ 329.1978 $[M+H]^+$, found 329.1972 $[M+H]^+$; Anal. calcd for $C_{18}H_{24}N_4O_2$: C 65.83%, H 7.37%, N 17.06%, found C 65.78%, H 7.38%, N 17.02%.

1-Methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-5-(phenylmethoxy)-1*H*-indazole-3-carboxamide (3c)



Following the procedure for **2c**, compound **3a** (0.05 g, 0.15 mmol), solid Na_2CO_3 (0.031 g, 0.29 mmol) and benzyl bromide (0.03 g, 0.18 mmol) afforded the crude product which was purified by flash chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH/Et_3N; 95:5:0.5) to give **3c** (0.061 g, 0.15 mmol, 96%) as a white solid: mp 137-140°C; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.01-1.09 (m, 2H), 1.10-1.16 (m, 2H), 1.43-1.58 (m, 3H), 1.92-2.11 (m, 3H), 2.35-2.46 (m, 2H), 2.50 (s, 3H), 3.06 (d, *J* = 10.8 Hz, 2H), 4.02 (s, 3H), 4.56 (tt, *J* = 6.5 Hz, *J* = 10.7 Hz, 1H), 5.21 (s, 2H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.35-7.43 (m, 3H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 15.0, 25.8, 32.6, 35.4, 42.8, 55.6, 72.1, 102.9, 106.1, 119.1, 129.1, 129.2, 135.3, 145.7, 155.2, 164.3; IR (neat) 3410, 2946, 2851, 1653, 1503, 1364, 1134, 1034, 978, 868, 835, 783, 724 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{25}H_{31}N_4O_2$ 419.2447 $[M+H]^+$, found 419.2448 $[M+H]^+$; Anal. calcd for $C_{25}H_{30}N_4O_2$: C 71.74%, H 7.22%, N 13.39%, found C 71.75%, H 7.29%, N 13.41%.

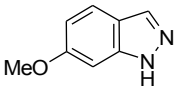
6-Hydroxy-1*H*-indazole (28)



6-Amino-1*H*-indazole (1.0 g, 7.5 mmol) was dissolved in 50% H_2SO_4 (6 ml) and stirred at 0°C for a few minutes. An aqueous solution of $NaNO_2$ (0.62 g, 9.0 mmol in 2.5 mL H_2O) was added drop wise via syringe. This was followed by the addition of conc. H_2SO_4 (1.7 mL) and boric acid (0.6 g, 9.7 mmol) at 0°C and the mixture was stirred for 15 min. The reaction mixture was heated to reflux (130°C) for 1 h and

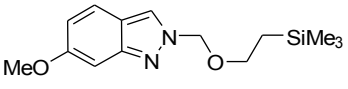
then cooled to room temperature while stirring. A 28% aqueous NH_4OH solution (2 mL) was added drop wise to the open flask. The mixture was filtered, transferred into a clean flask and more ammonia solution (7.7 mL) was added drop wise until the pH reached 8-9. The weakly alkaline mixture was filtered and the precipitate was washed with H_2O (1-5 mL) to yield **28** (0.76 g, 5.7 mmol, 76 %) as a yellow solid: mp 126-130°; R_f = 0.31 (CH_2Cl_2/MeOH; 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 4.6 Hz, 1H), 7.95 (s, 1H), 9.51 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 108.1, 122.5, 123.3, 124.7, 125.0, 126.0, 154.3; IR (neat) 3121, 2905, 1590, 1302, 1146, 950, 821, 703 cm^{-1}; Anal. calcd for $C_7H_6N_2O$: C 62.68%, H 4.51%, N 20.88%, found C 62.66%, H 4.52%, N 20.87%.

6-Methoxy-1*H*-indazole (8c)



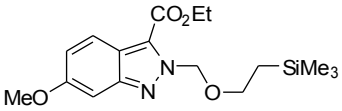
Indazole **28** (0.5 g, 3.7 mmol) was dissolved in dry acetone (10 mL), solid Na_2CO_3 (0.78 g, 7.4 mmol) was added and the mixture stirred for 5 min at room temperature. MeI (0.62 g, 4.3 mmol) in dry acetone (1 mL) was added drop wise and stirred at room temperature for 6 h. The acetone was removed in vacuo and the residue was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was further purified by flash chromatography (hexane/EtOAc; 4:1) to afford **8c** (0.43 g, 2.9 mmol, 78%) as a white solid: mp 97-99°C; R_f = 0.31 (hexane/EtOAc; 3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.97 (s, 3H), 7.01 (d, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.76 (s, 1H), 10.89 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.2, 109.7, 120.2, 121.7, 122.8, 130.7, 133.5, 146.2; IR (neat) 3108, 2941, 1637, 1569, 1263, 1089, 967, 856, 722 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_8H_9N_2O$ 149.0715 $[M+H]^+$, found 149.0711 $[M+H]^+$; Anal. calcd for $C_8H_8N_2O$: C 64.85%, H 5.44%, N 18.91%, found C 64.80%, H 5.44%, N 18.89%.

6-Methoxy-2-{[(2-trimethylsilyl)ethoxy]methyl}-2*H*-indazole (29)



Following the procedure for **19**, **8c** (1.0 g, 6.7 mmol), *N,N*-dicyclohexylmethylamine (1.58 g, 8.1 mmol) and SEM-chloride (1.39 g, 8.3 mmol) yielded **29** (1.65 g, 5.9 mmol, 88%) as a yellow oil: R_f = 0.32 (hexane/EtOAc; 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ -0.02 (s, 9H), 1.02-1.09 (m, 2H), 3.44-3.52 (m, 2H), 3.97 (s, 3H), 5.33 (s, 2H), 7.25 (d, *J* = 7.7 Hz, 2H), 7.76 (s, 1H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0, 17.6, 55.8, 68.2, 81.5, 110.0, 113.2, 120.6, 123.8, 125.2, 137.1, 153.1; IR (neat) 2909, 1536, 1264, 1155, 867, 836, 787, 714 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{14}H_{22}N_2NaO_2Si$ 301.1348 $[M+Na]^+$, found 301.1352 $[M+Na]^+$. The *N*-2 substitution was confirmed by nOe differences studies.

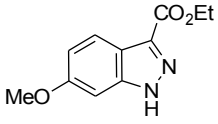
Ethyl 6-methoxy-2-{[(2-trimethylsilyl)ethoxy]methyl}-2*H*-indazole-3-carboxylate (30)



Using the procedure for **20**, indazole **29** (0.7 g, 2.5 mmol), 2.5 M solution of ^{n}BuLi in hexane (1.1 mL, 2.8 mmol) and ethyl cyanoformate (0.4 g, 4.0 mmol) afforded the crude product which was purified by flash chromatography (hexane/EtOAc; 5:1) to yield **30** (0.63 g, 1.8 mmol, 72%) as a yellow oil: R_f = 0.33 (hexane/EtOAc; 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 9H), 1.03-1.10 (m, 2H), 2.08 (t, *J* = 7.2 Hz, 3H), 4.13-4.22 (m, 2H), 4.06 (s, 3H), 5.10 (q, *J* = 7.1 Hz, 2H), 6.52 (s, 2H), 6.81 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.9, 16.8, 18.8, 55.5, 65.8, 69.7, 78.2, 108.2, 119.7, 121.5, 124.8, 134.8, 143.5, 150.7, 162.3; IR (neat) 2989, 2858, 1767, 1499, 1312, 1278, 1133, 1110, 865, 730 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{17}H_{26}N_2NaO_4Si$ 373.1560 $[M+Na]^+$, found

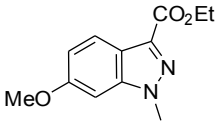
373.1560 [M+Na]$^+$; Anal. calcd for $C_{17}H_{26}N_2O_4Si$: C 58.26%, H 7.48%, N 7.99%, found C 58.39%, H 7.51%, N 7.77%.

Ethyl 6-methoxy-1*H*-indazole-3-carboxylate (9c)



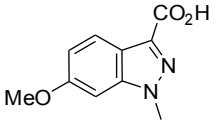
Following the procedure for **9a**, ester **30** (0.5 g, 1.4 mmol) gave **9c** (0.24 g, 1.1 mmol, 76%) as a pale yellow solid: mp 90-94°C; R_f = 0.41 (hexane/EtOAc; 3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (t, *J* = 7.1 Hz, 3H), 4.04 (s, 3H), 5.15 (q, *J* = 7.1 Hz, 2H), 6.95 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 1H), 7.89 (s, 1H), 10.97 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 58.0, 63.6, 110.0, 120.0, 123.8, 126.2, 132.7, 135.8, 146.2, 163.8; IR (neat) 3154, 2990, 1617, 1546, 1323, 1289, 1145, 1052, 854, 723 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{11}H_{12}N_2NaO_3$ 243.0746 [M+Na]$^+$, found 243.0741 [M+Na]$^+$.

Ethyl 6-methoxy-1-methyl-1*H*-indazole-3-carboxylate (31)



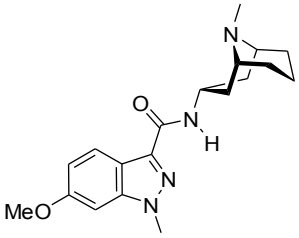
Following the procedure for **21**, ester **9c** (0.3 g, 1.4 mmol), KO^{t}Bu (0.18 g, 1.6 mmol) and MeI (0.25 g, 1.8 mmol) gave a crude product which was purified by flash chromatography (hexane/EtOAc; 6:1) to yield **31** (0.25 g, 1.1 mmol, 78%) as a white solid: mp 121-124°C; R_f = 0.23 (hexane/EtOAc; 3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (t, *J* = 7.1 Hz, 3H), 3.99 (s, 3H), 4.08 (s, 3H), 5.05 (q, *J* = 7.1 Hz, 2H), 7.01 (d, *J* = 7.1 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0, 42.1, 58.3, 67.7, 110.0, 111.6, 123.9, 124.9, 131.7, 134.3, 148.2, 161.4; IR (neat) 2890, 1767, 1473, 1287, 1125, 1057, 795, 730 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{12}H_{14}N_2NaO_3$ 257.0902 [M+Na]$^+$, found 257.0893 [M+Na]$^+$; Anal. calcd for $C_{12}H_{14}N_2O_3$: C 61.53%, H 6.02%, N 11.96%, found C 61.46%, H 6.04%, N 11.96%. The *N*-1 methylation was confirmed by difference nOe studies.

6-Methoxy-1-methyl-1*H*-indazole-3-carboxylic acid (10c)



Following the procedure for **10a**, ester **31** (0.20 g, 0.85 mmol) afforded **10c** (0.17 g, 0.82 mmol, 97%) as a white solid: mp 219-222°C; R_f = 0.27 (CH_2Cl_2/MeOH; 9:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95 (s, 3H), 4.30 (s, 3H), 6.90 (d, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 7.1 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 10.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.7, 52.1, 109.5, 118.5, 124.5, 125.6, 133.0, 136.1, 149.3, 162.6; IR (neat) 2924, 1623, 1404, 1265, 1165, 1135, 1098, 791, 730 cm^{-1}; HRMS-ESI (–) *m/z* calcd for $C_{10}H_9N_2O_3$ 205.0613 [M-H]$^-$, found 205.0624 [M-H]$^-$; Anal. calcd for $C_{10}H_{10}N_2O_3$: C 58.25%, H 4.89%, N 13.59%, found C 58.23%, H 4.87%, N 13.51%.

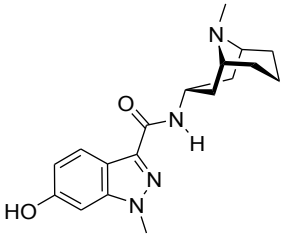
6-Methoxy-1-methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (4b)



Using the procedure for **2b**, indazole acid **10c** (0.1 g, 0.48 mmol), DCC (0.13 g, 0.63 mmol), HOBt (0.065 g, 0.48 mmol) and amine **11** (0.09 g, 0.58 mmol) afforded the crude product which was purified by flash chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH/Et_3N; 95:5:1) to yield **4b** (0.14 g, 0.41 mmol, 85%) as a white solid: mp 184-188°C; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.02-1.08 (m, 2H), 1.09-1.15 (m, 2H), 1.42-1.62 (m, 3H), 1.95-2.13 (m, 3H), 2.30-2.42 (m, 2H), 2.50 (s, 3H), 3.07 (d, *J* = 10.8 Hz, 2H), 3.89 (s, 3H), 4.02 (s, 3H), 4.45 (tt, *J* = 6.5 Hz, *J* = 10.9 Hz, 1H), 6.92 (d, *J* = 8.1

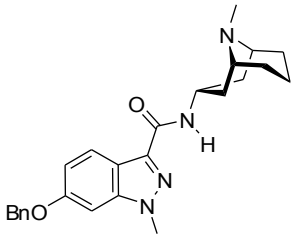
Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H,), 7.61 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 15.6, 26.4, 33.1, 36.4, 43.9, 48.8, 55.5, 101.6, 107.8, 117.9, 130.5, 135.9, 145.2, 152.2, 164.5; IR (neat) 2905, 2831, 1678, 1562, 1255, 1103, 888, 845, 723, 722 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{19}H_{27}N_4O_2$ 343.2134 $[M+H]^+$, found 343.2133 $[M+H]^+$; Anal. calcd for $C_{19}H_{26}N_4O_2$: C 66.64%, H 7.65%, N 16.36%, found C 66.63%, H 7.67%, N 16.40%. Single crystals for x-ray analysis were obtained from CD_3OD.

6-Hydroxy-1-methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (4a)



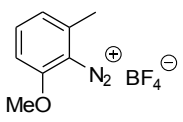
Following the procedure for **3a**, compound **4b** (100 mg, 0.29 mmol) and 1 M BBr_3 solution in CH_2Cl_2 (3 mL, 3 mmol) afforded **4a** (86 mg, 0.26 mmol, 90%) as a yellow solid: mp 224-228°C; R_f = 0.18 (CH_2Cl_2/MeOH; 9:1); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.02-1.07 (m, 2H), 1.09-1.15 (m, 2H), 1.43-1.61 (m, 3H), 1.92-2.11 (m, 3H), 2.32-2.43 (m, 2H), 2.48 (s, 3H), 3.03 (d, J = 10.8 Hz, 2H), 4.01 (s, 3H), 4.55 (tt, J = 6.5 Hz, J = 10.9 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 7.61 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 15.0, 26.1, 32.4, 36.1, 43.8, 55.2, 101.5, 107.2, 117.4, 130.4, 136.7, 145.0, 152.5, 164.3; IR (neat) 2951, 2854, 1578, 1564, 1254, 1011, 845, 812, 756, 724 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{18}H_{25}N_4O_2$ 329.1978 $[M+H]^+$, found 329.1971 $[M+H]^+$; Anal. calcd for $C_{18}H_{24}N_4O_2$: C 65.83%, H 7.37%, N 17.06%, found C 65.79%, H 7.33%, N 17.03%.

1-Methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-6-(phenylmethoxy)-1*H*-indazole-3-carboxamide (4c)



Following the procedure for **2c**, compound **4a** (0.05 g, 0.15 mmol), solid Na_2CO_3 (0.031 g, 0.29 mmol) and benzyl bromide (0.03 g, 0.18 mmol) gave the crude product which was purified by flash chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH/Et_3N; 95:5:0.5) to give **4c** (0.06 g, 0.14 mmol, 94%) as a white solid: mp 137-140°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01-1.09 (m, 2H), 1.10-1.16 (m, 2H), 1.43-1.58 (m, 3H), 1.92-2.11 (m, 3H), 2.35-2.46 (m, 2H), 2.50 (s, 3H), 3.06 (d, J = 10.8 Hz, 2H), 4.02 (s, 3H), 4.44-4.68 (m, 1H), 5.21 (s, 2H), 7.18 (d, J = 8.1 Hz, 1H), 7.35-7.43 (m, 3H), 7.52 (d, J = 7.5 Hz, 2H), 7.63 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.1, 25.4, 32.4, 35.7, 42.8, 55.8, 72.4, 102.9, 106.2, 119.1, 128.7, 129.9, 135.7, 145.7, 155.1, 163.2; IR (neat) 3412, 2960, 2889, 1693, 1523, 1369, 1167, 1056, 988, 880, 847, 793, 723 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{25}H_{31}N_4O_2$ 419.2447 $[M+H]^+$, found 419.2449 $[M+H]^+$; Anal. calcd for $C_{25}H_{30}N_4O_2$: C 71.74%, H 7.22%, N 13.39%, found C 71.71%, H 7.30%, N 13.43%.

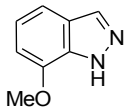
2-Methoxy-6-methylbenzenediazonium tetrafluoroborate (32)



Following the procedure for **18**, 2-methoxy-6-methylbenzeneamine (4.0 g, 29.2 mmol), 50% aq. fluoroboric acid (26.0 mL) and $NaNO_2$ (2.24 g, 32.5 mmol) gave **32** as a pale brown solid (5.3 g, 22.4 mmol, 77%): ^{1}H NMR (D_2O, 400 MHz) δ 2.69 (s, 3H), 4.21 (s, 3H), 7.27 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 8.05-8.09 (m, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 17.4, 58.4, 111.6, 124.2, 144.0, 144.5, 163.8; IR (neat) 2254, 1578, 1492, 1296, 1028, 804, 720 cm^{-1}. This compound can be stored

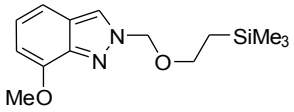
at –20°C for a limited period of time but is preferably used as soon as possible in the next step.

7-Methoxy-1*H*-indazole (8d)



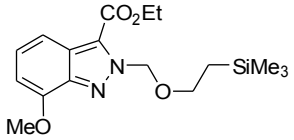
Following the procedure for **8a**, 18-crown-6 (0.240 g, 0.91 mmol), potassium acetate (4.8 g, 48.9 mmol) and **32** (5.2 g, 22.1 mmol) afforded **8d** (2.9 g, 19.6 mmol, 89%) as a pale brown solid: mp 97-99°C; R_f = 0.21 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.21 (s, 3H), 6.75 (d, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 8.09 (s, 1H), 10.89 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5, 104.9, 112.9, 121.7, 124.8, 132.3, 134.8, 145.2; IR (neat) 3115, 2906, 1589, 1518, 1258, 1101, 979, 834, 723 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_8H_9N_2O$ 149.0715 $[M+H]^+$, found 149.0711 $[M+H]^+$; Anal. calcd for $C_8H_8N_2O$: C 64.85%, H 5.44%, N 18.91%, found C 64.80%, H 5.47%, N 18.75%.

7-Methoxy-2-{[(2-trimethylsilyl)ethoxy]methyl}-2*H*-indazole (33)



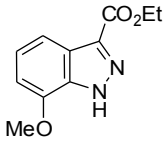
Following the procedure for **19**, **8d** (3.0 g, 20.0 mmol), *N,N*-dicyclohexylmethylamine (5.53 g, 28.3 mmol) and SEM-chloride (4.05 g, 24.3 mmol) yielded **33** (3.66 g, 13.2 mmol, 65%) as a brown oil: R_f = 0.35 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H), 0.94-0.98 (m, 2H), 3.63-3.68 (m, 2H), 4.05 (s, 3H), 5.78 (s, 2H), 6.59 (d, *J* = 7.3 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0, 18.0, 56.8, 68.9, 83.4, 104.0, 113.8, 123.8, 124.2, 125.4, 143.5, 151.9; IR (neat) 2926, 1555, 1259, 1092, 857, 833, 797, 735 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{14}H_{22}N_2NaO_2Si$ 301.1348 $[M+Na]^+$, found 301.1364 $[M+Na]^+$. The *N*-2 substitution was confirmed by nOe differences studies.

Ethyl 7-methoxy-2-{[(2-trimethylsilyl)ethoxy]methyl}-2*H*-indazole-3-carboxylate (34)



Using the procedure for **20**, indazole **33** (0.54 g, 1.9 mmol), 1.6 M solution of ^{n}BuLi in hexane (1.1 mL, 2.1 mmol) and ethyl cyanoformate (0.23 g, 2.3 mmol) afforded **34** (0.45 g, 1.3 mmol, 66%) as a brown oil: R_f = 0.41 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H), 0.94-0.98 (m, 2H), 1.55 (t, *J* = 7.1 Hz, 3H), 3.70-3.74 (m, 2H), 4.10 (s, 3H), 4.56 (q, *J* = 7.1 Hz, 2H), 6.25 (s, 2H), 6.69 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -1.4, 14.4, 17.8, 55.6, 61.2, 67.3, 81.4, 103.4, 113.5, 125.7, 126.3, 140.9, 141.8, 150.9, 159.9; IR (neat) 2950, 2892, 1706, 1525, 1315, 1246, 1088, 1062, 859, 805, 738 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{17}H_{26}N_2NaO_4Si$ 373.1560 $[M+Na]^+$, found 373.1621 $[M+Na]^+$; Anal. calcd for $C_{17}H_{26}N_2O_4Si$: C 58.26%, H 7.48%, N 7.99%, found C 58.42%, H 7.50%, N 7.75%.

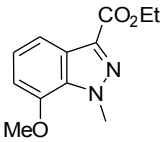
Ethyl 7-methoxy-1*H*-indazole-3-carboxylate (9d)



Following the procedure for **9a**, ester **34** (0.5 g, 1.4 mmol) gave **9d** (0.31 g, 1.4 mmol, 98%) as a pale yellow solid: mp 90-95°C; R_f = 0.11 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (t, *J* = 7.1 Hz, 3H), 3.99 (s, 3H), 4.51 (q, *J* = 7.1 Hz, 2H), 6.79 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 10.70 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 55.5, 61.0, 105.4, 113.7, 124.0, 124.3, 133.3, 137.0, 145.3, 162.7; IR (neat) 3153, 2985, 1701, 1585, 1265, 1242, 1125,

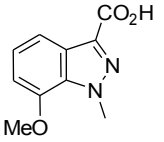
1034, 789, 734 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{11}H_{12}N_2NaO_3$ 243.0746 $[M+Na]^+$, found 243.0732 $[M+Na]^+$.

Ethyl 7-methoxy-1-methyl-1*H*-indazole-3-carboxylate (35)



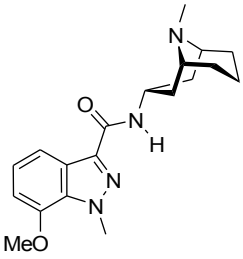
Following the procedure for **21**, ester **9d** (0.3 g, 1.3 mmol), KO^{t}Bu (0.18 g, 1.6 mmol) and MeI (0.38 g, 2.7 mmol) yielded **35** (0.30 g, 1.3 mmol, 95%) as a white solid: mp 123-124°C; R_f = 0.21 (hexane/EtOAc; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (t, *J* = 7.1 Hz, 3H), 3.97 (s, 3H), 4.39 (s, 3H), 4.50 (q, *J* = 7.1 Hz, 2H), 6.73 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 40.2, 55.6, 60.9, 105.6, 114.0, 123.9, 126.1, 132.6, 137.0, 146.5, 162.7; IR (neat) 2981, 1699, 1481, 1253, 1133, 1045, 799, 736 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{12}H_{14}N_2NaO_3$ 257.0902 $[M+Na]^+$, found 257.0891 $[M+Na]^+$; Anal. calcd for $C_{12}H_{14}N_2O_3$: C 61.53%, H 6.02%, N 11.96%, found C 61.39%, H 6.01%, N 11.96%.

7-Methoxy-1-methyl-1*H*-indazole-3-carboxylic acid (10d)



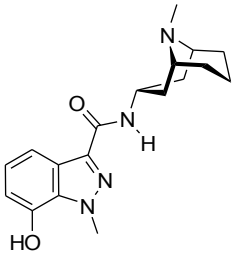
Following the procedure for **10a**, ester **35** (0.14 g, 0.6 mmol) afforded **10d** (0.12 g, 0.59 mmol, 99%) as a white solid: mp 218-220°C; R_f = 0.66 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR (CD_3OD, 400 MHz) δ 4.00 (s, 3H), 4.34 (s, 3H), 6.88 (d, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 40.5, 53.1, 106.9, 114.9, 125.5, 126.3, 134.1, 138.0, 147.9, 164.3; IR (neat) 2942, 1670, 1489, 1255, 1148, 1111, 1013, 787, 734 cm^{-1}; HRMS-ESI (–) *m/z* calcd for $C_{10}H_9N_2O_3$ 205.0613 $[M-H]^-$, found 205.0622 $[M-H]^-$.

7-Methoxy-1-methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (5b)



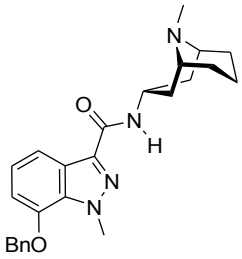
Using the procedure for **2b**, indazole acid **10d** (0.1 g, 0.48 mmol), DCC (0.13 g, 0.63 mmol), HOBt (0.065 g, 0.48 mmol) and amine **11** (0.074 g, 0.48 mmol) yielded **5b** (0.156 g, 0.46 mmol, 94%) as a white solid: mp 184-188°C (dec.); R_f = 0.23 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.63-1.70 (m, 3H), 1.94-2.01 (m, 2H), 2.16-2.28 (m, 3H), 2.58-2.66 (m, 2H), 2.97 (s, 3H), 3.73 (d, *J* = 9.9 Hz, 2H), 3.98 (s, 3H), 4.32 (s, 3H), 4.54 (tt, *J* = 6.7 Hz, *J* = 11.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 15.0, 25.7, 33.3, 40.1, 40.7, 41.5, 52.8, 56.2, 106.9, 115.0, 124.7, 126.3, 134.1, 137.2, 147.9, 164.3; IR (neat) 3315, 2926, 2902, 1637, 1542, 1252, 799, 753 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{19}H_{27}N_4O_2$ 343.2134 $[M+H]^+$, found 343.2131 $[M+H]^+$; Anal. calcd for $C_{19}H_{26}N_4O_2$: C 66.64%, H 7.65%, N 16.36%, found: C 66.59%, H 7.70%, N 16.12%. At this stage *N*-1 substitution was confirmed by nOe difference studies.

7-Hydroxy-1-methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (5a)



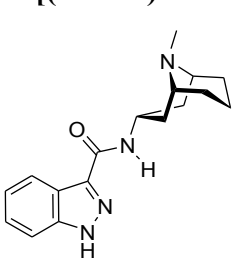
To a solution of compound **5b** (0.03 g, 0.088 mmol) in dry CH_2Cl_2 (3 mL) was added drop wise a freshly prepared solution of ionic liquid [TMAH] $[Al_2Cl_7]$ (0.093 g, 0.26 mmol) in CH_2Cl_2 (0.67 mL) under N_2 atmosphere at room temperature. The reaction mixture was heated at reflux for 24 h, TLC analysis showed presence of starting material. The reaction was continued for 48 h by adding one more equivalent of ionic liquid $[Me_3NH][Al_2Cl_7]$ in CH_2Cl_2. The reaction was cooled and neutralized by adding 1 M NaOH, and the aqueous layer was extracted several times with CH_2Cl_2, until the aqueous layer was free from the product. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was further purified by flash column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH/Et_3N; 96:3:1) to afford **5a** (0.024 g, 0.07 mmol, 86%) as a white solid: mp 225-230°C (dec.); R_f = 0.11 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.69-1.20 (m, 2H), 1.52-1.64 (m, 3H), 1.99-2.16 (m, 3H), 2.41-2.49 (m, 2H), 2.56 (s, 3H), 3.17 (d, *J* = 11.0 Hz, 2H), 4.35 (s, 3H), 4.55 (tt, *J* = 6.8 Hz, *J* = 11.5 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.5, 25.6, 32.9, 39.7, 40.3, 40.9, 53.3, 110.6, 113.5, 124.8, 126.6, 137.8, 145.4, 151.9, 164.6; IR (neat) 3420, 2931, 2867, 1640, 1491, 1392, 1265, 1112, 977, 924, 820, 796, 726 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{18}H_{25}N_4O_2$ 329.1978 $[M+H]^+$, found 329.1988 $[M+H]^+$. A small sample was recrystallized from CH_2Cl_2/MeOH which yielded single crystals for x-ray analysis.

1-Methyl-*N*-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-7-(phenylmethoxy)-1*H*-indazole-3-carboxamide (5c)



Following the procedure for **2c**, compound **5a** (0.015 g, 0.046 mmol), solid Na_2CO_3 (0.013 g, 0.091 mmol) and benzyl bromide (0.009 g, 0.05 mmol) gave **5c** (0.013 g, 0.031 mmol, 72%) as a white solid: mp 152-154°C (dec.); R_f = 0.23 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.12-1.18 (m, 2H), 1.53-1.62 (m, 3H), 1.97-2.18 (m, 3H), 2.43-2.51 (m, 2H), 2.55 (s, 3H), 3.11 (d, *J* = 10.0 Hz, 2H), 4.33 (s, 3H), 4.55 (tt, *J* = 6.7 Hz, *J* = 11.6 Hz, 1H), 5.25 (s, 2H), 6.94 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.35-7.43 (m, 3H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.9, 25.7, 33.3, 40.2, 40.6, 41.5, 52.9, 71.8, 108.4, 115.3, 124.7, 128.9, 129.3, 129.5, 129.8, 126.3, 134.1, 138.1, 147.9, 164.3; IR (neat) 2930, 2675, 1639, 1532, 1397, 1268, 1036, 733 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{25}H_{31}N_4O_2$ 419.2447 $[M+H]^+$, found 419.2449 $[M+H]^+$.

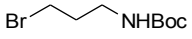
***N*-[(3-*endo*)-9-Methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (14)**



Following the procedure for **2b**, 1*H*-indazole-3-carboxylic acid (**12**, 0.4 g, 2.5 mmol), DCC (0.66 g, 3.2 mmol), HOBt (0.33 g, 2.5 mmol) and amine **11** (0.38 g, 2.5 mmol) afforded **14** (0.72 g, 2.4 mmol, 97%) as a white solid: mp 217-219°C; R_f = 0.13 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.08-1.11 (m, 2H), 1.47-1.57 (m, 3H), 1.95-2.13 (m, 3H), 2.40-2.46 (m, 2H), 2.49 (s, 3H), 3.07 (d, *J* = 10.7 Hz, 2H), 4.57 (tt, *J* = 6.8 Hz, *J* = 11.4 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 15.0, 25.7, 33.3, 40.7,

41.6, 52.8, 111.5, 122.8, 123.4, 128.0, 129.4, 134.9, 143.0, 164.7; IR (neat) 3332, 2923, 2365, 1647, 1542, 852, 753, 665 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{17}H_{23}N_4O$ 299.1872 $[M+H]^+$, found 299.1873 $[M+H]^+$; Anal. calcd for $C_{17}H_{22}N_4O$: C 68.43%, H 7.43%, N 18.78%, found C 68.25%, H 7.46%, N 18.78%.

tert-Butyl _N_-(3-bromopropyl)carbamate (36)



To a solution of 3-bromopropylamine hydrobromide (1.0 g, 4.6 mmol) in THF:H_2O (3:2, 15 mL), Et_3N (0.93 g, 9.2 mmol) was added, followed by addition of Boc anhydride (1.5 g, 6.9 mmol) and stirring at room temperature. The progress of the reaction was monitored by TLC and found to be complete in 20 h. The THF was removed in vacuo and the reaction mixture was extracted with EtOAc (3 × 20 mL), washed with 1 M HCl and then with H_2O. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was further purified by flash column chromatography (hexane/EtOAc; 97:3) to afford **36** (0.9 g, 3.8 mmol, 83%) as a white solid: mp 36-38°C; R_f = 0.47 (hexane/EtOAc; 8:2); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 2.02-2.08 (m, 2H), 3.27 (dd, *J* = 6.1 Hz, *J* = 12.4 Hz, 2H), 3.44 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4, 30.8, 32.7, 39.0, 161.5; IR (neat) 3375, 2980, 2948, 1682, 1521, 1246, 1161, 991, 847 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_8H_{16}BrNNaO_2$ 260.0262 $[M+Na]^+$, Found 260.0257 $[M+Na]^+$; Anal. calcd for $C_8H_{16}BrNO_2$: C 40.35%, H 6.77%, N 5.88%, found C 39.86%, H 6.66%, N 5.97%.

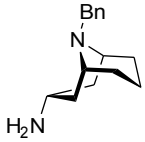
9-(Phenylmethyl)-9-azabicyclo[3.3.1]nonan-3-one (37)

Following the procedure for **22**, glutaraldehyde (4.5 g, 45 mmol), benzyl amine (5.0 g, 46 mmol) and acetone-1,3-dicarboxylic acid (7.5 g, 51 mmol) gave the crude product, which was purified by flash column chromatography (hexane/EtOAc; 3:1) to afford **37** (7.5 g, 32 mmol, 72%) as a white solid: mp 72-75°C; R_f = 0.80 (CH_2Cl_2/MeOH; 95:5); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49-1.59 (m, 4H), 1.94-2.03 (m, 2H), 2.29 (d, *J* = 16.6 Hz, 2H), 2.76 (dd, *J* = 6.7 Hz, *J* = 16.6 Hz, 2H), 3.32-3.36 (m, 2H), 3.94 (s, 2H), 7.28-7.32 (m, 1H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.6, 29.4, 42.9, 53.6, 57.1, 127.2, 128.4, 139.3, 211.6; IR (neat) 3184, 2917, 1638, 1469, 1361, 1540, 731, 697 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{15}H_{20}NO$ 230.1545 $[M+H]^+$, found 230.1539 $[M+H]^+$; Anal. calcd $C_{15}H_{19}NO$: C 78.56%, H 8.35%, N 6.11%, found C 78.09%, H 8.29%, N 6.01%.

9-(Phenylmethyl)-9-azabicyclo[3.3.1]nonan-3-one oxime (38)

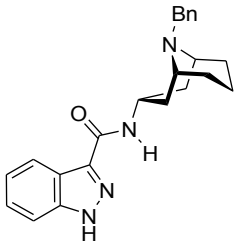
Following the procedure for **23**, **37** (2.0, 8.7 mmol) gave **38** (2.1, 8.6 mmol, 98%) as a white solid: mp 136-139°C; R_f = 0.27 (CH_2Cl_2/MeOH; 95:5); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.53-1.59 (m, 3H), 1.79-2.05 (m, 3H), 2.29 (d, *J* = 15.5 Hz, 1H), 2.44 (dd, *J* = 6.5 Hz, *J* = 16.4 Hz, 1H), 2.79 (dd, *J* = 5.7 Hz, *J* = 15.5 Hz, 1H), 3.07 (d, *J* = 16.4 Hz, 1H), 3.13-3.16 (m, 2H), 3.92 (s, 2H), 7.27-7.31 (m, 1H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 2H), 8.20 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.1, 25.8, 28.8, 29.5, 31.8, 51.1, 51.8, 56.8, 127.1, 128.4, 128.5, 139.4, 159.8; IR (neat) 2922, 1434, 1097, 930, 762, 723, 695 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{15}H_{21}N_2O$ 245.1654 $[M+H]^+$, found 245.1648 $[M+H]^+$; Anal. calcd for $C_{15}H_{20}N_2O$: C 73.74%, H 8.25%, N 11.47%, found C 72.67%, H 8.28%, N 11.26%.

(3-*endo*)- 9-(Phenylmethyl)-9-azabicyclo[3.3.1]nonan-3-amine (13)



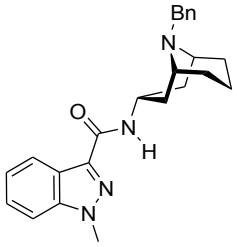
Following the procedure for **11**, **39** (1.0, 4.1 mmol) gave **13** (0.59, 2.5 mmol, 69%) as a colourless oil: R_f = 0.17 (CH_2Cl_2/MeOH; 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87-0.90 (m, 2H), 1.05-1.12 (m, 2H), 1.39-1.42 (m, 1H), 1.73-1.90 (m, 2H), 2.16-2.20 (m, 1H), 2.28 (dd, *J* = 6.6 Hz, *J* = 16.4 Hz, 1H), 2.64 (dd, *J* = 5.9 Hz, *J* = 15.4 Hz, 1H), 2.95-3.00 (m, 2H), 3.33 (tt, *J* = 5.7 Hz, *J* = 11.1 Hz, 1H), 3.77 (s, 2H), 7.27-7.31 (m, 1H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.2, 25.8, 29.8, 30.0, 32.0, 43.1, 51.2, 51.9, 56.9, 127.0, 128.3, 128.4, 139.7; IR (neat) 2921, 1434, 1359, 1095, 761, 723, 694 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{15}H_{23}N_2$ 231.1861 $[M+H]^+$, found 231.1856 $[M+H]^+$.

***N*-[(3-*endo*)-9-(Phenylmethyl)-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (15)**



Following the procedure for **2b**, indazole-3-carboxylic acid **12** (0.25 g, 1.5 mmol) and amine **13** (0.35 g, 1.5 mmol) gave **15** (0.47, 1.2 mmol, 81%) as a white solid: mp 145-149°C; R_f = 0.15 (CH_2Cl_2/MeOH; 95:5); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.07-1.11 (m, 2H), 1.53-1.60 (m, 3H), 2.00-2.21 (m, 3H), 2.37-2.45 (m, 2H), 3.16 (d, *J* = 11.2 Hz, 2H), 3.91 (s, 2H), 4.65 (tt, *J* = 6.3 Hz, *J* = 11.8 Hz, 1H), 7.22-7.34 (m, 4H), 7.42-7.44 (m, 3H), 7.59 (d, *J* = 8.5 Hz, 1H), 8.26 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 15.4, 25.5, 34.0, 42.6, 50.6, 56.8, 111.5, 122.9, 123.4, 127.8, 127.9, 129.3, 129.6, 141.7, 143.0, 164.7; IR (neat) 3184, 2915, 2849, 1638, 1540, 1469, 1146, 745, 732 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{23}H_{27}N_4O$ 375.2185 $[M+H]^+$, found 375.2184 $[M+H]^+$.

1-Methyl-*N*-[(3-*endo*)-9-(phenylmethyl)-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (6)



Following the procedure for **37**, **15** (0.1 g, 0.27 mmol) and MeI (0.045 g, 0.32 mmol) gave **6** (0.093, 2.4 mmol, 90%) as a white solid: mp 154-156°C; R_f = 0.42 (CH_2Cl_2/MeOH; 95:5); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.08-1.11 (m, 2H), 1.55-1.75 (m, 3H), 2.03-2.23 (m, 3H), 2.36-2.44 (m, 2H), 3.17 (d, *J* = 10.4 Hz, 2H), 3.92 (s, 2H), 4.15 (s, 3H), 4.65 (tt, *J* = 6.2 Hz, *J* = 11.7 Hz, 1H), 7.22-7.35 (m, 4H), 7.42-7.50 (m, 3H), 7.61 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 15.4, 25.5, 34.0, 36.3, 42.6, 50.7, 56.8, 110.8, 123.1, 123.6, 127.9, 129.2, 129.6, 141.3, 143.3, 163.9; IR (neat) 2920, 2849, 1668, 1529, 1494, 1137, 749, 738, 710 cm^{-1}; HRMS-ESI (+) *m/z* calcd for $C_{24}H_{29}N_4O$ 389.2341 $[M+H]^+$, found 389.2346 $[M+H]^+$.

Purity of tested compounds

The purity of the tested compounds was assessed by reversed-phase HPLC (ZORBAX Eclipse XDB-C18, 5 μm, 4.6 × 150 mm) using a MeOH/H_2O solvent system (Table). Compounds were eluted with a gradient of 35% MeOH/H_2O to 100% MeOH with 1% NH_4OH for 55 min at a flow rate of 1 mL/min. Purity was determined by total absorbance at 254 nm.

Table. Degree of purity for tested compounds.

compd	purity (%)	t_R (min)
2a	99	12.8
2b	98	17.8
2c	97	23.7
3a	96	14.4
3b	97	20.2
3c	95	25.6
4a	96	12.4
4b	96	20.0
4c	95	25.6
5a	98	9.3
5b	95	22.0
5c	96	27.0
6	98	27.9
7	97	23.7
16	98	24.1

Biological assay

Materials and cell culture maintenance

All cell culture reagents were obtained from Gibco BRL (Paisley, UK), except foetal calf serum which was from Labtech International (Ringmer, UK). [^{3}H]granisetron (63.5 Ci/mmol) was from PerkinElmer (Boston, Massachusetts, USA).

Human embryonic kidney (HEK)-293 cells were maintained on 90 mm tissue culture plates at 37°C and 7% CO_2 in a humidified atmosphere. Cells were cultured in DMEM:F12 (Dulbecco's modified Eagle medium/nutrient mix F12 (1:1)) with GlutaMAX™ I containing 10% foetal calf serum and passaged when 90% confluent.

Receptor expression and radioligand binding

HEK-293 cells stably expressing the human 5-HT3A subunit (accession number: P46098) were scraped into 1 mL of ice-cold HEPES buffer (10 mM, pH 7.4) and frozen at –20°C. After thawing, they were spun at 13,000 rpm for 1 min, resuspended and 50 μg of cell membranes incubated in 0.5 mL HEPES buffer containing 1 nM [^{3}H]granisetron (~K_d), in the presence or absence of synthetic granisetron derivatives **2**–**7** **(**at 10-fold dilutions). Competition binding (12 points) was performed on at least three separate plates of cells. Nonspecific binding was determined using 10 μM quipazine or other competitive antagonist. Reactions were incubated for at least 1 h at 4°C and terminated by vacuum filtration, using a Brandel cell harvester, onto GF/B filters presoaked in 0.3% polyethyleneimine. Radioactivity was determined by scintillation counting using a Beckman LS6000SC (Fullerton, CA, USA).

Competition binding data were analyzed by iterative curve fitting (GraphPad Prism v3.02, GraphPad Software, San Diego, CA, USA), according to the equation:

$$B_L = B_{\min} + \frac{B_{\max} - B_{\min}}{1 + 10^{n_H(\log IC_{50} - \log[L])}} \quad (1)$$

where $[L]$ is the concentration of ligand present, B_L is the binding in the presence of ligand concentration $[L]$, $B_{\min}$ is the binding when $[L] = 0$, $B_{\max}$ is the binding when $[L] = \infty$, IC_{50} is the concentration of L which gives a binding equal to $(B_{max} + B_{min})/2$, and n_H is the Hill coefficient. K_i values were calculated from IC_{50} values using the Cheng–Prusoff equation:

$$K_i = \frac{IC_{50}}{1 + [L]/K_d} \quad (2)$$

where K_i is the equilibrium dissociation constant for binding of the unlabelled antagonist, $[L]$ is the concentration of radioligand and K_d is the equilibrium dissociation constant of the radioligand. Values are presented as mean ± SEM.