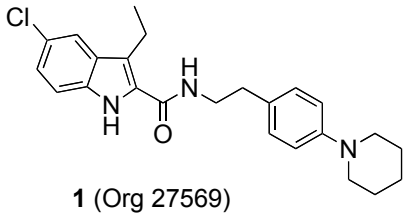
Supporting Information

Indole-2-carboxamides as Allosteric Modulators of the Cannabinoid CB_1 Receptor

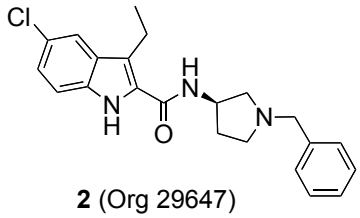
Francesco Piscitelli, Alessia Ligresti, Giuseppe La Regina, Antonio Coluccia, Ludovica Morera, Marco Allarà, Ettore Novellino, Vincenzo Di Marzo, and Romano Silvestri

Contents

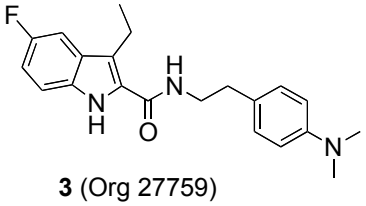
Chart 1. Structures of Reference Compounds **1-4.**



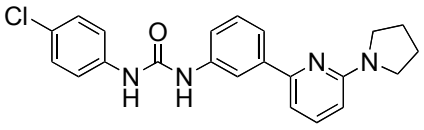
1 (Org 27569)



2 (Org 29647)



3 (Org 27759)

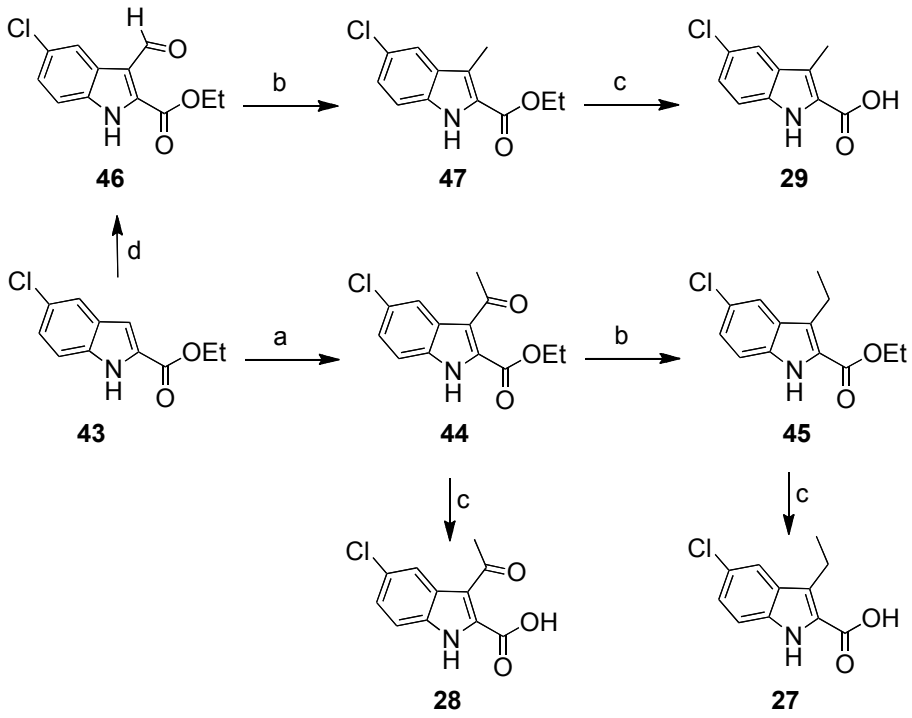


4 (PSNCBAM-1)

CHEMISTRY

5-Chloro-3-ethyl-1*H*-indole-2-carboxylic acid (**27**) and 3-acetyl-5-chloro-1*H*-indole-2-carboxylic acid (**28**) were prepared as depicted in Scheme 1S. The commercially available ester **43** was acetylated at position 3 of the indole by the Friedel-Craft reaction using acetyl chloride in the presence of the anhydrous aluminum chloride to provide **44**. The reduction of keto group of **44** to methylene was carried out using triethylsilane in trifluoroacetic acid to give **45**. Finally, the acids **27** and **28** were obtained by sodium hydroxide hydrolysis of the corresponding esters **45** and **44**, respectively. 5-Chloro-3-methyl-1*H*-indole-2-carboxylic acid **29** was prepared from ester **43**, which was formylated by Vilsmeier-Haak reaction to give **46**.[1S] Reduction of the aldehyde **46** furnished the methylindole **47** that underwent alkaline ester hydrolysis to provide the acid **29**.

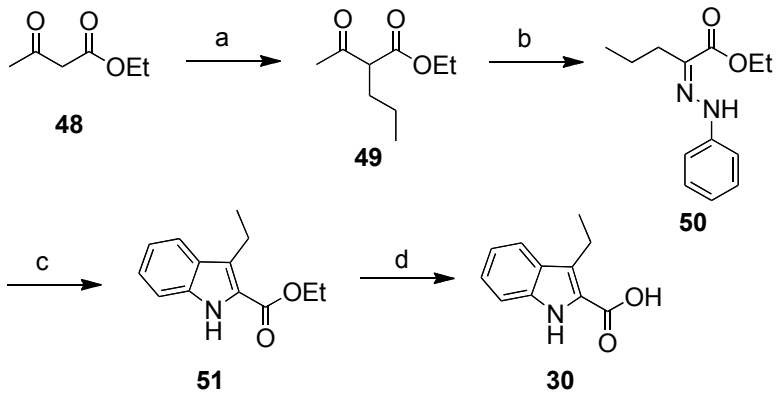
Scheme 1S. Synthesis of Carboxylic Acids **27**-**29**.[a,]



[a]*Reagents and reaction conditions:* (a) MeCOCl, anhydrous $AlCl_3$, 1,2-dichloroethane, reflux, 2 h; (b) Et_3SiH, CF_3COOH, rt, 2 h; (c) 3 N NaOH, ethanol, 60 °C, 2 h; (d) $POCl_3$, DMF, 100 °C, 3 h.

3-Ethyl-1*H*-indole-2-carboxylic acid (**30**) was prepared using the Fisher indole synthesis as strategy (Scheme 2S). The direct acetylation of the ethyl 1*H*-indole-2-carboxylate in the same conditions used to prepare **44** gave a mixture of isomers,[2S] albeit a previous paper reported methods for the selective acylation of the position 3 of the indole.[3S] The Fisher indole synthesis was investigated because such a way could allow for the preparation of 3-alkylindole-2-carboxylate not accessible by the Friedel-Craft synthesis. The alkylation of ethyl acetoacetate (**48**) with *n*-propyl iodide furnished **49** in good yield, which was converted to the hydrazone **50** by the Jaap-Klingemann reaction. The treatment of **50** with hydrochloric acid in ethanol at reflux temperature furnished the indole **51**, which was transformed into the desired acid **30** by alkaline hydrolysis.

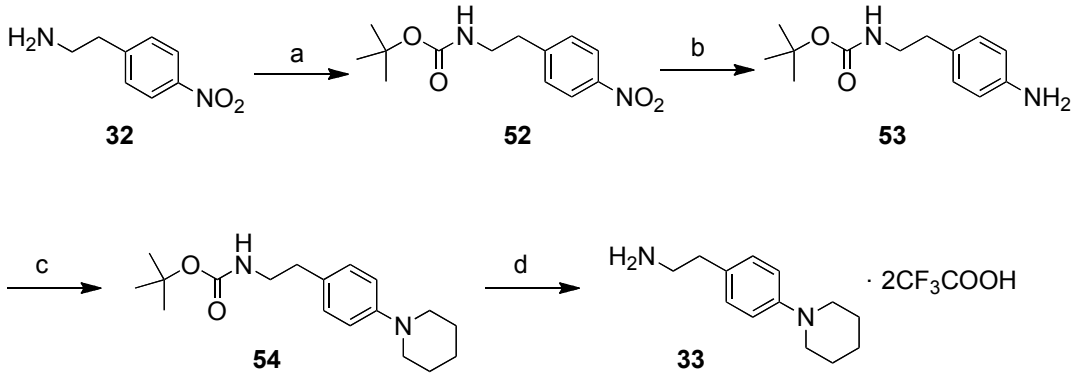
Scheme 2S. Synthesis of Carboxylic Acid **30**.[a,]



[a]*Reagents and reaction conditions:* (a) *n*-PrI, NaOEt, EtOH, reflux, 3 h; (b) (i) aniline, $NaNO_2$, 37% HCl, H_2O, 0 °C, 0.5 h; (ii) **41**, $CH_3COONa \cdot H_2O$, EtOH, H_2O, 0 °C, 3 h; (c) 37% HCl, EtOH, reflux, 2 h; (d) 3 N NaOH, ethanol, 60 °C, 2 h.

2-(4-(Piperidin-1-yl)phenyl)ethanamine bis(2,2,2-trifluoroacetate) (**33**) was prepared by protecting of 2-(4-nitrophenyl)ethanamine (**32**) with di-*tert*-butyldicarbonate in the presence of triethylamine to obtain **52**. The nitro group of **52** was reduced to amine **53** with hydrogen in the presence of palladium over carbon. The piperidine nucleus of **54** was built by heterocyclization with 1,5-dibromopentane in the presence of potassium carbonate in water, heating the reaction mixture under microwave irradiation.[4S] Attempts to carry out this reaction by heating on oil bath failed, as only the starting amine **53** was recovered. The removal of the Boc protective group with trifluoroacetic acid in dichlorometane at room temperature furnished the required amine **33** (Scheme 3S). An alternate preparation of **33** is depicted in Scheme 4S.

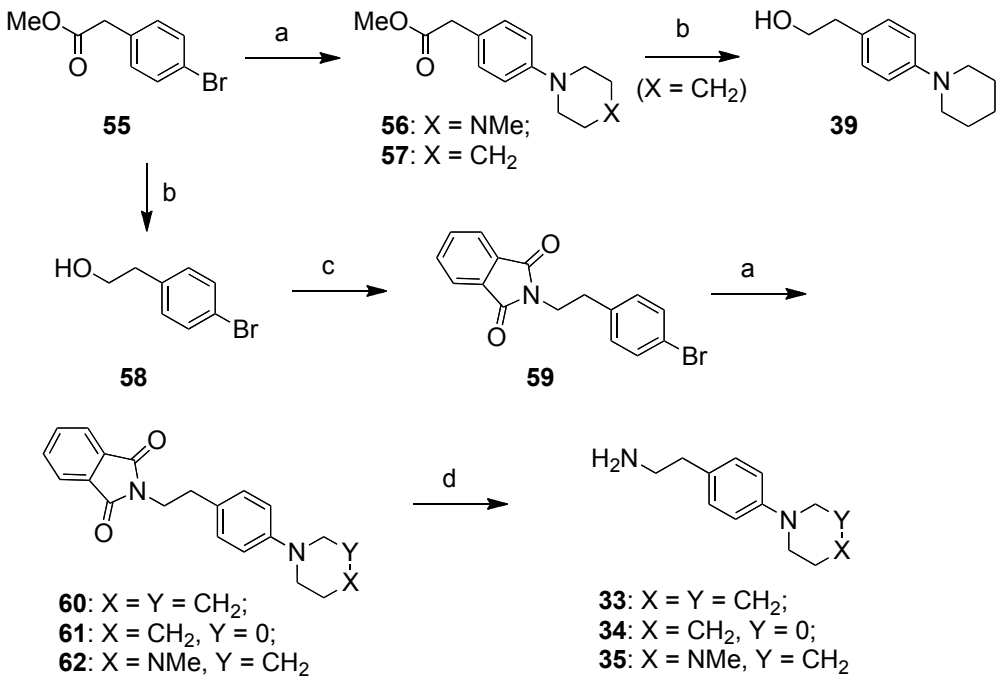
Scheme 3S. Synthesis of Amine **33**.[a,]



Reagents and reaction conditions: (a) Boc_2O, Et_3N, CH_2Cl_2, rt, 1 h; (b) H_2, Pd-C, MeOH, rt, 3 bar, 2 h; (c) 1,5-dibromopentane, K_2CO_3, H_2O, closed vessel, 150 W, 120 °C, Pmax = 250 PSI, 20 min.; (d) CF_3COOH, CH_2Cl_2, rt, 1h.

Amines **33**-**35** and alcohol **39** were prepared starting from ester **55**,[5S] which was converted in the corresponding amines **56** or **57** by the Buchwald-Hartwig amination (Scheme 4S). The reaction was optimized using *N*-methylpyperazine (2.5 eq.), 1 mol% of tris(dibenzylidene-acetone)dipalladium as source of Pd(0), 4 mol% of XPhos as ligand, 2.5 eq. of cesium carbonate in anhydrous toluene at 110 °C; after 5 h the TLC analyses showed the conversion of the starting material into **56** (yield 78%). When this reaction was carried out using either a stronger base, i.e. potassium *tert*-butoxide, or microwave irradiation, it led to a great amount of degradation. In the case of **57**, 3 mol% of catalyst and 12 mol% of ligand were required for the complete conversion of the starting material. The ester **57** was reduced to alcohol **39** using lithium aluminumhydride in anhydrous tetrahydrofuran at room temperature. Similarly, **55** was reduced to **58**, and the hydroxyl group **58** was replaced with a phtalimido group under Mitsounobu conditions to give **59**. Compound **59** was converted into the amines **60**-**62** by the Buchwald-Hartwig amination, and deprotection of the amine group using hydrazine in ethanol at reflux temperature provided the amines **33**-**35**, which were used for the next step without further purification.

Scheme 4S. Synthesis of Amines **33-35** and Alcohol **39**.[a,]



Reagents and reaction conditions: (a) 1-methylpiperazine, pyrrolidine or piperidine, Pd_2dba_3, XPhos, Cs_2CO_3, toluene, 110 °C, 5 h; (b) $LiAlH_4$, THF, rt, 3 h; (c) phthalimide, PPh_3, DEAD, THF, rt, 3 h; (d) $NH_2NH_2 \cdot H_2O$, EtOH, reflux, 1.5 h.

EXPERIMENTAL SECTION

Chemistry. All reagents and solvents were commercially available and used without further purification. Organic solutions were dried over anhydrous sodium sulfate. Evaporation of the solvents was carried out on a Büchi Rotavapor R-210 equipped with a Büchi V-850 vacuum controller and Büchi V-700 (~5 mbar) and V-710 (~2 mbar) vacuum pumps. Column chromatographies were run on glass columns packed with alumina (Merck, 70-230 mesh) or silica gel (Macherey-Nagel, 70-230 mesh) eluting with the indicated solvent. Aluminium oxide thin layer chromatography (TLC) cards from Fluka (aluminium oxide precoated aluminium cards with fluorescent indicator visualizable at 254 nm) and silica gel TLC cards from Macherey-Nagel (silica gel precoated aluminum cards with fluorescent indicator visualizable at 254 nm) were used for TLC. Developed plates were visualized by a Spectroline ENF 260C/FE UV apparatus. Melting points (mp) were determined on a SMP1 apparatus (Stuart Scientific) and are uncorrected. IR spectra were run on a SpectrumOne FT-ATR spectrophotometer (Perkin Elmer). Band position and absorption ranges are given in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a 400 MHz FT spectrometer (Bruker) in the indicated solvent. Chemical shifts are expressed in δ units (ppm) from tetramethylsilane. Mass spectral (MS) data were obtained using Agilent 1100 LC/MSD VL system (G1946C) with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methanol/

water. UV detection was monitored at 254 nm. Mass spectra were acquired either in positive or in negative mode scanning over the mass range of 105-1500. MW-assisted reactions were performed on a Discover SP (CEM) single mode reactor, controlling instrument parameters with PC-running Synergy 1.4 software. Temperature, irradiation power, maximum pressure (Pmax), PowerMAX (in situ cooling during the MW irradiation), ramp and hold times, and open and closed vessel modes were set as indicated. Reactions in a closed vessel were performed in capped MW-dedicated vials (10 mL) with cylindrical stirring bar (length 8 mm, diameter 3 mm). The temperature of the reaction was monitored by a built-in infrared (IR) sensor. After completion of the reaction, the mixture was cooled to 25 °C via air-jet cooling. Optical rotation of **18** was measured at 589 nm by a Perkin-Elmer polarimeter model 241 equipped with a Na/Hg lamp. The volume of the cell was 1 mL and the optical path was 10 cm. The system was set at a temperature of 20 °C. was measured at 589 nm by a Perkin-Elmer polarimeter model 241 equipped with a Na/Hg lamp. The volume of the cell was 1 mL and the optical path was 10 cm. The system was set at a temperature of 20 °C. Combustion analysis was used as a method for establishing compound purity. Purity of tested compounds was ≥95%. Elemental analyses of tested compounds were found within ±0.4% of the theoretical values (Table 1S). 5-Chloro-1*H*-indole-2-carboxylic acid (**31**), 2-(4-nitrophenyl)ethanamine (**32**), 2-(*p*-tolyl)ethylamine (**36**), 2-(4-fluorophenyl)ethylamine (**38**), 2-(4-nitrophenyl)ethanol (**40**), 2-(4-dimethylaminophenyl)ethanol (**41**), and ethyl 5-chloro-1*H*-indole-2-carboxylate (**43**) were purchased from Sigma-Aldrich.

Chemico-physical characterization, preparative and combustion analysis data of compounds of **6**, **7**, **9, 10, 14,-17, 19-26** and **1.**

5-Chloro-3-ethyl-*N*-(2-(4-(4-methylpiperazin-1-yl)phenyl)ethyl)-1*H*-indole-2-carboxamide (9). Compound **9** was prepared as **8** using amine **35**. Yield 47%, mp 170-172 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.33 (s, 1H), 7.94 (t, J = 5.2 Hz, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.18 (dd, J = 8.7, 1.9 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 3.54 – 3.42 (m, 2H), 3.14 – 3.04 (m, 4H), 2.96 (d, J = 7.5 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H), 2.48 – 2.39 (m, 4H), 2.22 (s, 3H), 1.13 ppm (t, J = 7.4 Hz, 3H). MS (ESI): *m/z*: 426 $[M+H]^+$. IR: ν 3285, 1602 cm^{-1}. Anal. ($C_{24}H_{29}ClN_4O$ (424.97)) C, H, N, Cl.

5-Chloro-3-ethyl-*N*-(2.(4-nitrophenyl)ethyl)-1*H*-indole-2-carboxamide (10). Compound **10** was prepared as **8** using amine **32** hydrochloride. Yield 49%, mp 198-200 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.31 (s, 1H), 8.18 (d, J = 8.7 Hz, 2H), 8.06 (t, J = 5.6 Hz, 1H), 7.65 (d, J = 1.6 Hz, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 1H), 7.18 (dd, J = 8.6, 2.0 Hz, 1H), 3.66 – 3.56 (m, 2H), 3.03 (t, J = 7.1 Hz, 2H), 2.93 (q, J = 7.5 Hz, 2H), 1.09 ppm (t, J = 7.5 Hz, 3H). MS (ESI): *m/z*: 372 $[M+H]^+$. IR: ν 3315, 1595 cm^{-1}. Anal. ($C_{19}H_{18}ClN_3O_3$ (371.82)) C, H, N, Cl.

5-Chloro-3-ethyl-*N*-(4-methylphenethyl)-1*H*-indole-2-carboxamide (14). Compound **14** was prepared as **8** using amine **36**. Yield 88%, mp 158-160 °C (from ethanol). ^{1}H NMR ($CDCl_3$): δ 9.17 (s, 1H), 7.57 (s, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.16-7.19 (m, 4H), 5.99 (s, 1H), 3.83 (q, J = 6.2 Hz, 2H), 2.96 (t, J = 6.6 Hz, 2H), 2.72 (q, J = 7.6 Hz, 2H), 2.37 (s, 3H), 1.10 ppm (t, J = 7.6 Hz, 3H). IR: ν 3298, 1684 cm^{-1}. MS (ESI): *m/z*: 341 $[M+H]^+$. Anal. ($C_{20}H_{21}ClN_2O$ (340.825)) C, H, N, Cl.

5-Chloro-*N*-(4-chlorophenethyl)-3-ethyl-1*H*-indole-2-carboxamide (15). Compound **15** was prepared as **8** using acid **28** and 2-(4-chlorophenyl)ethanamine. Yield 75%, mp 195-196 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.34 (s, 1H), 8.02 (t, J = 5.5 Hz, 1H), 7.65 (s, 1H), 7.45 – 7.26 (m, 5H), 7.18 (d, J = 8.8 Hz, 1H), 3.53 (q, J = 6.6 Hz, 2H), 2.93 (q, J = 7.6 Hz, 2H), 2.87 (t, J = 7.1 Hz, 2H), 1.10 ppm (t, J = 7.4 Hz, 3H). MS (ESI): *m/z*: 362 $[M+H]^+$. IR: ν 3468, 3364, 3334, 1630 cm^{-1}. Anal. ($C_{19}H_{18}Cl_2N_2O_2$ (361.27)) C, H, N, Cl.

5-Chloro-3-ethyl-*N*-(4-fluorophenethyl)-1*H*-indole-2-carboxamide (16). Compound **16** was prepared as **8** using amine **38**. Yield 77%, mp 161-163 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.31 (s, 1H), 7.98 (s, 1H), 7.63 (s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.35 – 7.23 (m, 2H), 7.17 (d, J = 8.8 Hz, 1H), 7.15 – 7.07 (m, 2H), 3.52 (q, J = 6.7 Hz, 2H), 2.93 (q, J = 7.5 Hz, 2H), 2.86 (t, J = 7.1 Hz, 2H), 1.10 ppm (t, J = 7.4 Hz, 3H). IR: ν 3317, 1673 cm^{-1}. MS (ESI): *m/z*: 345 [M+H]$^+$. Anal. ($C_{19}H_{18}ClFN_2O$ (344.81)) C, H, N, Cl, F.

3-Acetyl-5-chloro-*N*-(2-(4-(piperidin-1-yl)phenyl)ethyl)-1*H*-indole-2-carboxamide (17). Compound **17** was prepared as **8** using acid **28** and amine **33**. Yield 80%, mp 130-132 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 12.74 (s, 1H), 10.18 (s, 1H), 8.09 (d, J = 1.7 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.33 (dd, J = 8.7, 2.0 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.62 – 3.48 (m, 2H), 3.14 – 3.02 (m, 4H), 2.79 (t, J = 7.2 Hz, 2H), 2.59 (s, 3H), 1.67 – 1.56 (m, 4H), 1.56 – 1.46 ppm (m, 2H). MS (ESI): *m/z*: 425 [M+H]$^+$. IR: ν 3264, 1635, 1610 cm^{-1}. Anal. ($C_{24}H_{26}ClN_3O_2$ (423.94)) C, H, N, Cl.

5-Chloro-3-methyl-*N*-(2-(4-(piperidin-1-yl)phenyl)ethyl)-1*H*-indole-2-carboxamide (19). Compound **19** was prepared as **8** using acid **29** and amine **33**. Yield 69%, mp 190-192 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.36 (s, 1H), 7.90 (t, J = 5.7 Hz, 1H), 7.63 (d, J = 1.7 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.18 (dd, J = 8.9, 1.7 Hz, 1H), 7.10 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 3.54 – 3.44 (m, 2H), 3.13 – 3.03 (m, 4H), 2.77 (t, J = 7.3 Hz, 2H), 2.42 (s, 3H), 1.67 – 1.57 (m, 4H), 1.57 – 1.47 ppm (m, 2H). MS (ESI): *m/z*: 396 [M+H]$^+$. IR: ν 3249, 1627 cm^{-1}. Anal. ($C_{23}H_{26}ClN_3O$ (395.93)) C, H, N, Cl.

3-Ethyl-*N*-(2-(4-(piperidin-1-yl)phenyl)ethyl)-1*H*-indole-2-carboxamide (20). Compound **16** was prepared as **8** using acid **30** and amine **33**. Yield 59%, mp 164-167 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.37 (s, 1H), 8.15 (t, J = 5.6 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 3.91 – 3.68 (m, 2H), 3.47 – 3.37 (m, 4H), 3.32 (q, J = 7.6 Hz, 2H), 3.09 (t, J = 7.4 Hz, 2H), 2.01 – 1.88 (m, 4H), 1.88 – 1.78 (m, 2H), 1.47 ppm (t, J = 7.4 Hz, 3H). MS (ESI): *m/z*: 376 [M+H]$^+$. IR: ν 3268, 1610 cm^{-1}. Anal. ($C_{24}H_{29}N_3O$ (375.51)) C, H, N.

5-Chloro-*N*-(2-(4-(piperidin-1-yl)phenyl)ethyl)-1*H*-indole-2-carboxamide (21). Compound **21** was prepared as **8** using acid **31** and amine **33**. Yield 83%, mp 190-192 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.74 (s, 1H), 8.60 (t, J = 5.7 Hz, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.17 (dd, J = 8.7, 2.1 Hz, 1H), 7.08 (m, 3H), 6.85 (d, J = 8.6 Hz, 2H), 3.50 – 3.41 (m, 2H), 3.13 – 3.02 (m, 4H), 2.76 (t, J = 7.4 Hz, 2H), 1.66 – 1.56 (m, 4H), 1.56 – 1.47 ppm (m, 2H). MS (ESI): *m/z*: 382 [M+H]$^+$. IR: ν 3237, 1633 cm^{-1}. Anal. ($C_{22}H_{24}ClN_3O$ (381.90)) C, H, N, Cl.

5-Chloro-*N*-(4-nitrophenethyl)-1*H*-indole-2-carboxamide (22). Compound **22** was prepared as **8** using acid **31** and amine 2-(4-nitrophenyl)ethanamine hydrochloride. Yield 56%, mp 260-264 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.78 (s, 1H), 8.68 (t, J = 5.4 Hz, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.70 (s, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.5 Hz, 1H), 7.17 (dd, J = 8.6, 2.1 Hz, 1H), 7.06 (s, 1H), 3.59 (q, J = 6.4 Hz, 2H), 3.02 ppm (t, J = 6.8 Hz, 2H). MS (ESI): *m/z*: 344 [M+H]$^+$. IR: ν 3385, 3231, 1644 cm^{-1}. Anal. ($C_{17}H_{14}ClN_3O_3$ (343.76)) C, H, N, Cl.

5-Chloro-*N*-(4-chlorophenethyl)-1*H*-indole-2-carboxamide (26). Compound **26** was prepared as **8** using acid **31** and 2-(4-chlorophenyl)ethanamine (**37**). Yield 48%, mp 260-262 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.76 (s, 1H), 8.65 (t, J = 5.2 Hz, 1H), 7.69 (s, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.7 Hz, 1H), 7.06 (s, 1H), 3.52 (d, J = 6.6 Hz, 2H), 2.85 ppm (t, J = 7.1 Hz, 2H). MS (ESI): *m/z*: 334 [M+H]$^+$. IR: ν 3436, 3229, 1638 cm^{-1}. Anal. ($C_{17}H_{14}Cl_2N_2O$ (333.21)) C, H, N, Cl.

5-Chloro-3-ethyl-*N*-(2-(4-(piperidin-1-yl)phenyl)ethyl)-1*H*-indole-2-carboxamide (1). Compound **1** was prepared as **8** using amine **33**. Yield 61%, mp 178-180 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.33 (s, 1H), 7.94 (t, J = 5.5 Hz, 1H), 7.65 (d, J = 1.7 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.18 (dd, J = 8.7, 2.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 3.48 (m, 2H), 3.14 – 3.03 (m, 4H), 2.96 (q, J = 7.5 Hz, 2H), 2.76 (t, J = 7.3 Hz, 2H), 1.66 – 1.56 (m, 4H), 1.56 – 1.46 (m, 2H), 1.12 ppm (t, J = 7.4 Hz, 3H). MS (ESI): *m/z*: 411 $[M+H]^+$. IR: ν 3289, 1599 cm^{-1}.

4-Nitrophenethyl 5-chloro-3-ethyl-1*H*-indole-2-carboxylate (6). Compound **7** was prepared as **5** using alcohol **40**. Yield 39%, mp 178-181 °C (from toluene). ^{1}H NMR ($CDCl_3$): δ 8.63 (s, 1H), 8.23 (d, J = 8.5 Hz, 2H), 7.66 (s, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.34 – 7.24 (m, 2H), 4.68 (t, J = 6.7 Hz, 2H), 3.25 (t, J = 6.6 Hz, 2H), 2.99 (q, J = 7.7 Hz, 2H), 1.19 ppm (t, J = 7.5 Hz, 3H). IR: ν 3299, 1672 cm^{-1}. MS (ESI): *m/z*: 373 $[M+H]^+$. Anal. ($C_{19}H_{17}ClN_2O_4$ (372.80)) C, H, N, Cl.

4-(Dimethylamino)phenethyl 5-chloro-3-ethyl-1*H*-indole-2-carboxylate (7). Compound **7** was prepared as **5** using alcohol **41**. Yield 87%, mp 126-128 °C (from toluene). ^{1}H NMR (DMSO-d_6) δ 11.64 (s, 1H), 7.71 (s, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.24 (d, J = 7.1 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.5 Hz, 2H), 4.45 (t, J = 6.7 Hz, 2H), 3.01 – 2.88 (m, 4H), 2.83 (s, 6H), 1.10 ppm (t, J = 7.4 Hz, 3H). IR: ν 3323, 1681 cm^{-1}. MS (ESI): *m/z*: 372 $[M+H]^+$. Anal. ($C_{21}H_{23}ClN_2O_2$ (370.87)) C, H, N, Cl.

***N*-(4-Aminophenethyl)-5-chloro-1*H*-indole-2-carboxamide (23).** Compound **23** was prepared as **11** from **22**. Yield 70%, mp 245-247 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.75 (s, 1H), 8.60 (t, J = 5.6 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.16 (dd, J = 8.7, 2.0 Hz, 2H), 7.06 (s, 1H), 6.88 (d, J = 8.2 Hz, 2H), 6.48 (d, J = 8.2 Hz, 2H), 4.85 (broad s, 2H), 3.39 (q, J = 6.8 Hz, 2H), 2.66 ppm (t, J = 7.6 Hz, 2H). MS (ESI): *m/z*: 314 $[M+H]^+$. IR: ν 3305, 1602 cm^{-1}. Anal. ($C_{17}H_{16}ClN_3O$ (313.78)) C, H, N, Cl.

5-Chloro-*N*-(4-(methylamino)phenethyl)-1*H*-indole-2-carboxamide (24) and 5-chloro-*N*-(4-(dimethylamino)phenethyl)-1*H*-indole-2-carboxamide (25). Compounds **24** and **25** were prepared as **12** and **13** from **23**. Compound **24**: yield: 27%, mp 162-163 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 11.75 (s, 1H), 8.60 (t, J = 5.5 Hz, 1H), 7.68 (d, J = 1.9 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.16 (dd, J = 8.6, 1.9 Hz, 1H), 7.06 (s, 1H), 6.96 (d, J = 8.2 Hz, 2H), 6.45 (d, J = 8.3 Hz, 2H), 5.43 (q, J = 5.3 Hz, 1H), 3.41 (q, J = 6.3 Hz, 2H), 2.69 (d, J = 7.4 Hz, 2H), 2.62 ppm (d, J = 5.1 Hz, 3H). MS (ESI): *m/z*: 328 $[M+H]^+$. IR: ν 3225, 1641 cm^{-1}. Anal. ($C_{18}H_{18}ClN_3O$ (327.81)) C, H, N, Cl. Compound **25: y**ield: 32%, mp 199-201 °C (from ethanol). ^{1}H NMR ($CDCl_3$): δ 9.55 (s, 1H), 7.61 (s, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.25 (dd, J = 8.7, 1.9 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 6.65 (s, 1H), 6.21 (t, J = 5.8 Hz, 1H), 3.73 (q, J = 6.6 Hz, 2H), 2.97 (s, 6H), 2.88 ppm (t, J = 6.7 Hz, 2H). MS (ESI): *m/z*: 342 $[M+H]^+$. IR: ν 3280, 1647 cm^{-1}. Anal. ($C_{19}H_{20}ClN_3O$ (341.83)) C, H, N, Cl.

Preparation of Indole-2-carboxylic acids 27-30. General Procedure for the Hydrolysis of Esters 44, 45, 47 and 51. Example. 3-Acetyl-5-chloro-1*H*-indole-2-carboxylic acid (28). A mixture of **44** (0.59 g, 2.22 mmol), 3 N sodium hydroxide (2.22 mL) and ethanol (5 mL) was heated to 60 °C for 1.5 h. After cooling, 1 N HCl was added until pH ~ 2, and the precipitate was collected, washed with distilled water and dried under high vacuum to provide **28** as white solid. Yield 90%, mp 252-256 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 12.88 (s, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.39 (dd, J = 8.8, 2.0 Hz, 1H), 2.74 ppm (s, 3H). IR: ν 3416, 3275, 1634 cm^{-1}.

5-Chloro-3-ethyl-1*H*-indole-2-carboxylic acid (27). Compound **27** was prepared as **28** starting from **45**. Yield 96%, mp 130-132 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 13.04 (s, 1H), 11.56 (s,

1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.23 (dd, *J* = 8.7, 2.1 Hz, 1H), 3.03 (q, *J* = 7.4 Hz, 2H), 1.17 ppm (t, *J* = 7.4 Hz, 3H). IR: ν 3546, 3277, 1654 cm^{-1}.

5-Chloro-3-methyl-1*H*-indole-2-carboxylic acid (29). Compound **29** was prepared as **28** starting from **47**. Yield 96%, mp 232-234 °C. ^{1}H NMR (DMSO-d_6): δ 8.74 (s, 1H), 7.68 (s, 1H), 7.38 – 7.24 (m, 3H), 2.64 ppm (s, 3H). IR: ν 3417, 3334, 1692 cm^{-1}.

3-Ethyl-1*H*-indole-2-carboxylic acid (30). Compound **30** was prepared as **28** starting from **51**. Yield 98%, mp 159-160 °C. °C. ^{1}H NMR (DMSO-d_6): δ 12.82 (s, 1H), 11.31 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 3.06 (q, *J* = 7.5 Hz, 2H), 1.20 ppm (t, *J* = 7.4 Hz, 3H). IR: ν 3422, 3357, 1664 cm^{-1}.

Ethyl 3-acetyl-5-chloro-1*H*-indole-2-carboxylate (44). Ethyl 5-chloro-1*H*-indole-2-carboxylate (**43**) (1.0 g, 4.47 mmol) was added to a mixture of acetyl chloride (0.35 g, 0. 32 mL, 4.47 mmol) and aluminum chloride (0.60 g, 4.47 mmol) in anhydrous 1,2-dichloroethane (10 mL). The reaction mixture was heated at reflux for 2.5 h. After cooling, the reaction mixture was poured on crushed ice and made acidic using 3 N hydrochloric acid. The mixture was extracted with dichloromethane. The combined organic layers were washed with brine, dried and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate-*n*-hexane 1:1 as eluent) to provide **44** as white solid. Yield 53%, mp 142-144 °C (from aqueous ethanol). ^{1}H NMR (DMSO-d_6): δ 12.67 (s, 1H), 7.98 (dd, *J* = 2.1, 0.6 Hz, 1H), 7.54 (dd, *J* = 8.8, 0.6 Hz, 1H), 7.36 (dd, *J* = 8.8, 2.1 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 1.38 ppm (t, *J* = 7.1 Hz, 3H). IR: ν 3312, 1687, 1634 cm^{-1}.

Ethyl 5-chloro-3-ethyl-1*H*-indole-2-carboxylate (45). A mixture of **44** (0.61 mg, 2.29 mmol), triethylsilane (1.02 g, 1.40 mL, 8.77 mmol) and 2,2,2-trifluoroacetic acid (5.94 mL) was stirred at room temperature for 5 h. After quenching with a saturated solution of sodium carbonate, the mixture was extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of sodium bicarbonate, brine, and dried. After evaporation of the solvent, the residue was triturated in *n*-hexane to give **45** as white solid. Yield 89%, mp 122-124 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 11.68 (s, 1H), 7.77 – 7.72 (m, 1H), 7.43 (dd, *J* = 8.8, 0.6 Hz, 1H), 7.26 (dd, *J* = 8.8, 2.1 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.03 (q, *J* = 7.5 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.18 ppm (t, *J* = 7.5 Hz, 3H). IR: ν 3298, 1626 cm^{-1}.

Ethyl 5-chloro-3-formyl-1*H*-indole-2-carboxylate (46). A solution of **43** (0.5 g, 2.2 mmol) in anhydrous *N*,*N*-dimethylformamide (3 mL) was added dropwise onto an ice-cooled solution of phosphorus oxychloride (3.84 g, 2.3 mL, 2.5 mmol) in the same solvent (5 mL). The reaction mixture was heated at 110 °C for 2.5 h. After cooling, the reaction was quenched with ice-water and made alkaline with 2% sodium hydroxide. The precipitate was collected and recrystallized in ethanol to give **46** as yellowish solid. Yield 81%, mp 218-222 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 13.02 (s, 1H), 10.57 (s, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.43 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.41 ppm (t, *J* = 7.1 Hz, 3H). IR: ν 3324, 1664, 1634 cm^{-1}.

Ethyl 5-chloro-3-methyl-1*H*-indole-2-carboxylate (47). Compound **47** was prepared as **45** starting from **46**. Yield 85%, mp 152-154 °C. ^{1}H NMR ($CDCl_3$): δ 8.72 (s, 1H), 7.73 – 7.60 (m, 1H), 7.38 – 7.22 (m, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 2.59 (s, 3H), 1.45 ppm (t, *J* = 7.1 Hz, 3H). IR: ν 3308, 1634 cm^{-1}.

Ethyl 2-*n*-propylacetoacetate (49). Sodium (0.87 g, 0.038 ga) was dissolved in absolute ethanol (50 mL), and ethyl acetoacetate (5.0 g, 4.86 mL, 38 mmol) was added while the mixture was stirred at room temperature for 10 minutes. *n*-Propyl iodide (4.3 g, 2.47 mL, 25 mmol) was added dropwise and the reaction was heated to reflux temperature for 3 h. After cooling the solvent was

evaporated and the residue dissolved in water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate-*n*-hexane 1:9 as eluent) to provide **49** as colorless oil. Yield 70%. ^{1}H NMR ($CDCl_3$): δ 4.21 (q, *J* = 7.1 Hz, 2H), 3.42 (t, *J* = 7.4 Hz, 1H), 2.23 (s, 3H), 1.95 – 1.73 (m, 2H), 1.38 – 1.23 (m, 5H), 0.94 ppm (t, *J* = 7.3 Hz, 3H). IR: ν 1737, 1713 cm^{-1}.

Ethyl 3-ethyl-1*H*-indole-2-carboxylate (51). A solution of aniline (1.35 g, 14.5 mmol), 37% HCl (3.69 mL), water (1.85 mL) and ethanol (1.85 mL) was treated dropwise at 0 °C with a solution of sodium nitrite (1.10 g, 16 mmol) in water (5 mL). After stirring at 0 °C for 15 minutes, a solution of **49** (2.5 g, 14.5 mmol), sodium acetate trihydrate (2.96 g, 22 mmol) in water (3.95 mL) and ethanol (35 mL) was added while keeping the temperature below the 10 °C. The reaction mixture was stirred for 2 h at 0 °C, and then it was extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated to furnish **50**. The residue was dissolved in ethanol (43 mL) and 37% hydrochloric acid (7 mL) and heated at reflux temperature for 2 h. After cooling, the reaction mixture was extracted with dichloromethane, and the combined organic layers were washed with brine, dried and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate-*n*-hexane 1:3 as eluent) to provide **51** as white solid. Yield 30%, mp 112-114 °C. ^{1}H NMR (DMSO-d_6): δ 11.42 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.07 (q, *J* = 7.4 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.21 ppm (t, *J* = 7.5 Hz, 3H). IR: ν 3277, 1670 cm^{-1}.

Preparation of Amines 32-35, 37 and 39. *tert*-Butyl *N*-(2-(4-nitrophenyl)ethyl)carbamate (52). Triethylamine (1.10 g, 1.51 mL, 10.84 mmol) was added dropwise to a mixture of **32** hydrochloride (1.00 g, 4.93 mmol) and di-*tert*-butyl dicarbonate (1.18 g, 5.42 mmol) in anhydrous dichlorometane (20 mL) cooled at 0-5 °C over an ice-water bath. After stirring at room temperature for 2 h, water was added and the phases were separated. The mixture was extracted again with fresh dichloromethane and the combined organic extracts were washed with 1 N HCl, brine, and dried. Evaporation of the solvent gave a residue that was purified by crystallization in *n*-hexane to furnish **52** as white solid. Yield 99%, mp 78-80 °C (from *n*-hexane). ^{1}H NMR ($CDCl_3$): δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 4.60 (s, 1H), 3.43 (m, 2H), 2.94 (t, *J* = 7.0 Hz, 2H), 1.45 ppm (s, 9H). IR: ν 3361, 1680 cm^{-1}.

***tert*-Butyl *N*-(2-(4-aminophenyl)ethyl)carbamate (53)**. A mixture of **52** (0.90 g, 3.38 mmol), palladium over carbon (10 wt%, 0.09 g) and methanol (30 mL) was hydrogenated at room temperature under 3 psi for 2 h. The reaction mixture was filtered through a pad of celite, and the solvent was evaporated to provide **53** as white solid. Yield 95%, mp 50-55 °C (from hexane). ^{1}H NMR (DMSO-d_6): δ 6.82 (d, *J* = 8.1 Hz, 2H), 6.77 (s, 1H), 6.47 (d, *J* = 8.1 Hz, 2H), 4.83 (s, 2H), 3.02 (m, 2H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.37 ppm (s, 9H). IR: ν 3376, 1684 cm^{-1}.

***tert*-Butyl *N*-(2-(4-(piperidin-1-yl)phenyl)ethyl)carbamate (54).** A mixture of **53** (0.5 g, 2.11 mmol), 1,5-dibromopentane (0.54 g, 0.32 mL, 2.35 mmol), sodium carbonate (0.32 g, 2.33 mmol) and deionized water (2 mL) was placed into microwave cavity. Microwave irradiation of 150W was used, the temperature being ramped from rt to 120 °C. Once 120 °C was reached, taking about 1 minute, the reaction mixture was held there for 20 minutes and cooled. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated. The residue was triturated in *n*-hexane to provide **54)** as white solid. Yield: 74%, mp 78-82 °C (from hexane). ^{1}H NMR ($CDCl_3$): δ 7.08 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 4.51 (s, 1H), 3.35 (d, *J* = 5.9 Hz, 2H), 3.22 – 3.04 (m, 4H), 2.71 (t, *J* = 6.8 Hz, 2H), 1.80 – 1.67 (m, 4H), 1.66 – 1.52 (m, 2H), 1.44 ppm (s, 9H). IR: ν 3375, 1685 cm^{-1}.

2-(4-(Piperidin-1-yl)phenyl)ethanamine (33). From **54**. A mixture of **54** (0.3 g, 0.98 mmol) and trifluoroacetic acid (1 mL) in dichlorometane (1 mL) was stirred at room temperature for 1 h. The solvent was evaporated and the residue was dried in high vacuo to provide crude **33** as bis-2,2,2-trifluoroacetate which was used without further purification. Yield: 99%. ^{1}H NMR (DMSO-d_6): δ 7.86 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 5.76 (broad s, 3H), 3.41 – 3.37 (m, 4H), 3.02 – 3.06 (m, 2H), 2.85 (t, J = 6.8 Hz, 2H), 1.82 – 1.78 (m, 4H), 1.66 – 1.57 ppm (m, 2H). IR: ν 3402, 3375, 3207 cm^{-1}.

Methyl 2-(4-(piperidin-1-yl)phenyl)acetate (57). A mixture of **55** (0.20 g, 0.6 mmol), tris(dibenzylideneacetone)dipalladium(0) (3 mol%, 0.016 g, 0.018 mmol), XPhos (0.034 g, 0.072 mmol), cesium carbonate (0.45 g, 1.5 mmol) and piperidine (0.13 g, 0.15 mL, 1.5 mmol) in degassed anhydrous toluene (5 mL) was heated at 110 °C for 12 h. After cooling, water and diethyl ether were added while shaking. The organic phase was extracted with 3 N HCl (5 x 20 mL) and discarded. The acidic solution was neutralized with sodium carbonate (caution: CO_2 evolution), and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated to provide **57** as colorless oil. Yield 82%. ^{1}H NMR (DMSO-d_6): δ 7.08 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.60 (s, 3H), 3.53 (s, 2H), 3.15 – 3.05 (m, 4H), 1.68 – 1.57 (m, 4H), 1.57 – 1.48 ppm (m, 2H). IR: ν 3228, 1690 cm^{-1}.

2-(4-Bromophenyl)ethanol (58). A solution of **55** (2.00 g, 8.7 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise onto an ice-water cooled suspension of lithium aluminumhydride (0.82 g, 21.64 mmol) in the same solvent (20 mL). The reaction was stirred at room temperature for 3 h and then cooled over an ice-water bath. The excess of lithium aluminumhydride was carefully destroyed by water drops and then with a solution of Rochelle's salt. The resulting mixture was stirred at room temperature for 1 h and extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated. The residue was purified by a short silica gel column chromatography (ethyl acetate-*n*-hexane 1:1 as eluent) to provide **58** as colorless oil. Yield 87%. ^{1}H NMR (DMSO-d_6): δ 7.79 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 4.96 (s, 1H), 4.00 – 3.86 (m, 2H), 3.03 ppm (t, J = 6.8 Hz, 2H). IR: ν 3338 cm^{-1}.

2-(4-(Piperidin-1-yl)phenyl)ethanol (39). Compound **39** was prepared as **58** starting from **57**. Colorless oil. Yield: 93%. ^{1}H NMR (DMSO-d_6): δ 7.03 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.53 (t, J = 5.1 Hz, 1H), 3.60 – 3.48 (m, 2H), 3.12 – 3.01 (m, 4H), 2.61 (t, J = 7.3 Hz, 2H), 1.68 – 1.57 (m, 4H), 1.57-1.46 ppm (m, 2H). IR: ν 3342 cm^{-1}.

2-(2-(4-Bromophenyl)ethyl)isoindolin-1,3-dione (59). To a solution of phtalimide (0.33 g, 2.27 mmol) in anhydrous tetrahydrofuran (7.5 mL) cooled at 0 °C over an ice-water bath were added triphenylphosphine (0.59 g, 2.27 mmol) and **58** (0.38 g, 1.89 mmol), followed by the dropwise addition of diethyl azodicarboxylate (40 wt% in toluene, 0.99 g, 1.03 mL, 2.27 mmol). The reaction was warmed at room temperature and stirred for 3 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (gradient of ethyl acetate in *n*-hexane from 17% to 25% as eluent) to provide **59** as white solid. Yield 69%, mp 140-144 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 7.93 – 7.75 (m, 4H), 7.44 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 3.82 (t, J = 7.1 Hz, 2H), 2.91 ppm (t, J = 7.2 Hz, 2H). IR: ν 1694 cm^{-1}.

2-(4-(Piperidin-1-yl)phenethyl)isoindoline-1,3-dione (60). Compound **60** was prepared as **57** starting from **59**. Yield 78%, mp 129-131 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 7.94 – 7.76 (m, 4H), 7.02 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 3.76 (d, J = 7.4 Hz, 2H), 3.13 – 2.98 (m, 4H), 2.81 (t, J = 7.4 Hz, 2H), 1.65 – 1.55 (m, 4H), 1.48 – 1.54 ppm (m, 2H). IR: ν 1702 cm^{-1}.

2-(2-(4-(Pyrrolidin-1-yl)phenyl)ethyl)isoindoline-1,3-dione (61). Compound **61** was prepared as **57** using **59** and pyrrolidine. Yield 78%, mp 138-140 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ

7.90 – 7.75 (m, 4H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.43 (d, *J* = 8.5 Hz, 2H), 3.74 (t, *J* = 7.3 Hz, 2H), 3.16 (t, *J* = 6.4 Hz, 4H), 2.79 (t, *J* = 7.4 Hz, 2H), 1.98 – 1.86 ppm (m, 4H). IR: ν 1705 cm^{-1}.

2-(2-(4-(4-Methylpiperazin-1-yl)phenyl)ethyl)isoindoline-1,3-dione (61). Compound **61** was prepared as **57** using **59** and 1-methylpiperazine. Yield 81%, mp: 152 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 7.91 – 7.77 (m, 4H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.76 (t, *J* = 7.4 Hz, 2H), 3.11 – 3.01 (m, 4H), 2.82 (t, *J* = 7.4 Hz, 2H), 2.45 – 2.37 (m, 4H), 2.21 ppm (s, 3H). IR: ν 1694 cm^{-1}.

2-(4-(Piperidin-1-yl)phenyl)ethanamine (33). From **60**. A mixture of **60** (0.1 g, 0.3 mmol) and hydrazine monohydrate (0.075 g, 0.073 mL, 1.5 mmol) in ethanol (3 mL) was heated at reflux temperature for 2 h. After cooling, the reaction mixture treated with diethyl ether and 3 N HCl (5 x 20 mL) while shaking. The combined aqueous extracts were neutralized with sodium carbonate (caution: CO_2 evolution) and extracted with ethyl acetate. The organic layers were washed with brine, dried and evaporated. All spectroscopic data were in agreement to the sample obtained from **54**. Yield 73% as an oily material.

2-(4-(Pirrolidin-1-yl)phenyl)ethanamine (34). Compound **34** was prepared as **33** starting from **61**. Yield 79% as an oily material. ^{1}H NMR (DMSO-d_6): δ 7.02 (d, *J* = 8.5 Hz, 2H), 6.47 (d, *J* = 8.5 Hz, 2H), 2.82-2.77 (m, 2H), 3.22-3.15 (m, 4H), 2.62 (t, *J* = 7.4 Hz, 2H), 1.99 – 1.88 ppm (m, 4H). IR: ν 1705 cm^{-1}

2-(4-(4-Methylpiperazin-1-yl)phenyl)ethanamine (35). Compound **35** was prepared as **33** starting from **62**. Yield 68% as an oily material. ^{1}H NMR (DMSO-d_6) δ 7.06 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.16 – 3.00 (m, 4H), 2.80– 2.76 (m, 2H), 2.65 (d, *J* = 7.2 Hz, 2H), 2.47 – 2.40 (m, 4H), 2.22 ppm (s, 3H). IR: ν 3387, 3201 cm^{-1}.

Binding Assay. Membranes from HEK-293 cells stably transfected with the human recombinant CB_1 receptor (B_{max} = 2.5 pmol/mg protein) and human recombinant CB_2 receptor (B_{max} = 4.7 pmol/mg protein) were incubated with [^{3}H]CP-55,940 (0.14 nM/K_d = 0.18 nM and 0.084 nM/K_d = 0.31 nM respectively for CB_1 and CB_2 receptors) as the high affinity ligand and displaced with 10 μM WIN 55212-2 as the heterologous competitor for non specific binding (K_i values 9.2 nM and 2.1 nM respectively for CB_1 and CB_2 receptors). Concentration-response curves were generated by incubating drugs with [^{3}H]CP-55,940 for 90 minutes at 30 °C according to the procedure described by the manufacturer (Perkin Elmer, Italia). EC_{50} values were calculated from concentration-response curves by applying the non-linear regression analysis (obtained by GraphPad fitting program) of the bound radioligand enhancement exerted by increasing concentrations of test compounds. IC_{50} values were calculated from concentration-response curves by applying a linear regression model (obtained by GraphPad fitting program) of the bound radioligand displacement exerted by increasing concentrations of test compounds. Data are reported as mean of n = 2 experiments performed in triplicate.

Table 1S. Elemental Analysis of Compounds **5-26.**

5 Calcd.: C, 70.15; H, 6.62; N, 6.82; Cl, 8.63. Found: C, 69.97; H, 6.61; N, 6.69; Cl, 8.59.
6 Calcd.: C, 61.21; H, 4.60; N, 7.51; Cl, 9.51. Found: C, 60:88 ; H, 4.51 ; N, 7.37; Cl, 9.35.
7 Calcd.: C, 68.01; H, 6.25; N, 7.55; Cl, 9.56. Found: C, 67.75; H, 6.18 ; N, 7.40; Cl, 9.28.
8 Calcd.: C, 69.77; H, 6.62; N, 10.61; Cl, 8.95. Found: C, 69.54; H, 6.61; N, 10.48; Cl, 8.93.
9 Calcd.: C, 67.83; H, 6.88; N, 13.18; Cl, 8.34. Found: C, 67.62; H, 6.86; N, 12.98; Cl, 8.30.
10 Calcd.: C, 61.38; H, 4.88; N, 11.30; Cl, 9.54. Found: C, 61.09; H, 4.89; N, 11.28; Cl, 9.44.
11 Calcd.: C, 66.76; H, 5.90; N, 12.29; Cl, 10.37. Found: C, 66.58; H, 5.89; N, 12.25; Cl, 10.33

12 Calcd.: C, 67.50; H, 6.23; N, 11.81; Cl, 9.96. Found: C, 67.27; H, 6.22; N, 11.77; Cl, 9.92.
13 Calcd.: C, 68.19; H, 6.54; N, 11.36; Cl, 9.58. Found: C, 67.88; H, 6.55; N, 11.33; Cl, 9.59.
14 Calcd.: C, 70.48; H, 6.21; N, 8.22; Cl, 10.40. Found: C, 70.21; H, 6.14; N, 7.95; Cl, 8.19.
15 Calcd.: C, 63.17; H, 5.02; N, 7.75; Cl, 19.63. Found: C, 62.89; H, 4.94; N, 7.59; Cl, 19.45.
16 Calcd.: C, 66.18; H, 5.26; N, 8.12; Cl, 10.28; F, 5.51. Found: C, 65.95; H, 5.11; N, 7.95; Cl, 9.94; F, 5.32.
17 Calcd.: C, 68.00; H, 6.18; N, 9.91; Cl, 8.36. Found: C, 67.82; H, 6.17; N, 9.88; Cl, 8.23.
18 Calcd.: C, 67.67; H, 6.63; N, 9.87; Cl, 8.32. Found: C, 67.41; H, 6.62; N, 9.88; Cl, 8.30.
19 Calcd.: C, 69.77; H, 6.62; N, 10.61; Cl, 8.95. Found: C, 69.52; H, 6.63; N, 10.63; Cl, 8.91.
20 Calcd.: C, 76.76; H, 7.78; N, 11.19. Found: C, 76.52; H, 7.75; N, 11.13.
21 Calcd.: C, 69.19; H, 6.33; N, 11.00; Cl, 9.28. Found: C, 68.96; H, 6.31; N, 10.98; Cl, 9.26.
22 Calcd.: C, 59.40; H, 4.10; N, 12.22; Cl, 10.31. Found: C, 59.17; H, 4.02; N, 12.07; Cl, 10.15.
23 Calcd.: C, 65.07; H, 5.14; N, 13.39; Cl, 11.30. Found: C, 64.86; H, 5.02; N, 13.14; Cl, 11.12.
24 Calcd.: C, 65.95; H, 5.53; N, 12.82; Cl, 10.82. Found: C, 65.79; H, 5.42; N, 12.56; Cl, 10.57.
25 Calcd.: C, 66.76; H, 5.90; N, 12.29; Cl, 10.37. Found: C, 66.47; H, 5.79; N, 12.06; Cl, 10.13.
26 Calcd.: C, 61.28; H, 4.23; N, 8.41; Cl, 21.28. Found: C, 61.09; H, 4.14; N, 8.27; Cl, 20.97.

ABBREVIATIONS

BOP, benzotriazol-1-yloxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; DMAP, 4-dimethylaminopyridine; DCI, dicyclohexylcarbodiimide; Xphos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; Pd_2dba_3, tris(dibenzylideneacetone) dipalladium(0); Boc_2O, di-tert-butyl dicarbonate; DEAD, diethyl azodicarboxylate.

REFERENCES OF SUPPORTING INFORMATION

(1S) Yoshikawa, K.; Yokomizo, A.; Naito, H.; Haginoya, N.; Kobayashi, S.; Yoshino, T.; Nagata, T.; Mochizuki, A.; Osanai, K.; Watanabe, K.; Kanno, H.; Ohta, T. Design, synthesis, and SAR of cis-1,2-diaminocyclohexane derivatives as potent factor Xa inhibitors. Part I: Exploration of 5-6 fused rings as alternative S1 moieties. *Bioorg. Med. Chem.* **2009**, *17*, 8206-8220.

(2S) Laufer, S.; Lehmann, F. Investigations of SCIO-469-like compounds for the inhibition of p38 MAP kinase. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1461-1464.

(3S) Murakami, Y.; Tani, M.; Tanaka, K.; Yokoyama, Y. Synthetic studies on indoles and related compounds. XV. An unusual acylation of ethyl indole-2-carboxylate in the Friedel-Crafts acylation. *Chem. Pharm. Bull.* **1988**, *36*, 2023-2035.

(4S) Ju, Y.; Varma, R. S. An efficient and simple aqueous *N*-Heterocyclization of aniline derivatives: microwave-assisted synthesis of *N*-aryl azacycloalkanes. *Org. Lett.* **2005**, *7*, 2409-2411.

(5S) Bradley, P. A.; Carroll, R. J.; Lecouturier, Y. C.; Moore, R.; Noeureuil, P.; Patel, B.; Snow, J.; Wheeler, S. The synthesis of two potent beta-3 adrenergic receptor agonists. *Org. Process Res. Devel.* **2010**, *14*, 1326-1336.