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Original article

Synthesis and pharmacological evaluation of indole-based sigma receptor ligands

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ABSTRACT

A series of novel indole-based analogs were prepared and their affinities for sigma receptors were determined using in vitro radioligand binding assays. The results of this study identified several compounds with nanomolar sigma-2 affinity and significant selectivity over sigma-1 receptors. In particular, 2-(4-(3-(4-fluorophenyl)indol-1-yl)butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**9f**) was found to display high affinity at sigma-2 receptors with good selectivity (σ-1/σ-2 = 395). The pharmacological binding profile for this compound was established with other relevant non-sigma sites.
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1. Introduction

Sigma receptors are classified into two subtypes denoted sigma-1 and sigma-2 [1]. The sigma-1 receptor has been purified and cloned in several species and is well characterized at the functional and structural level [2,3]. It is expressed in the central nervous system and is also widely distributed in peripheral organs and tissues such as heart and spleen [4]. The sigma-2 receptor suffers from a lower degree of knowledge, in part because this protein has not yet been cloned. These receptors are associated with functions and disorders such as inflammation [5], depression [6,7], anxiety [8], Alzheimer's disease [9], epilepsy and drug abuse [10–12]. Cancer diagnosis and treatment is also an area of great interest in current sigma receptor research. Indeed sigma receptor over-expression in malignant tissues suggest that tumors may be visualized by SPECT or PET imaging using radiolabeled sigma ligands [13–16]. The sigma-2 subtype is upregulated in proliferative cells where the density of sigma-2 receptors was found to be 10-fold higher than in quiescent cells [17]. Additional studies have shown that sigma ligands, especially sigma-2 agonists, can inhibit proliferation and induce apoptosis in tumor cells which give sigma ligands possible application as agents for the treatment of cancer [18,19]. Therefore, the finding of selective sigma-2 receptor ligands may aid in the isolation and characterization of this receptor, but also could lead to the development of new therapeutics, particularly in oncology.

Several classes of structurally diverse compounds have been shown to possess a high affinity for sigma receptors (for a review see Narayanan et al. [20]). While several selective, high-affinity sigma-1 ligands are available [21–25], potent sigma-2 receptor selective ligands are less common. Siramesine (**Lu28-179**, σ-1 = 17 nM, σ-2 = 0.12 nM) and 5-bromo-*N*-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)butyl)-2,3-dimethoxybenzamide (σ-1 = 12,900 nM, σ-2 = 8.2 nM) are two of the most highly selective sigma-2 ligands identified to date [26,27].

In our previous work we reported the synthesis and biological evaluation of a series of benzoazoles with high, mixed affinity for sigma-1 and sigma-2 receptors [28]. Among the compounds described in this early study, 3-(4-(4-cyclohexylpiperazin-1-yl) butyl)benzo[d]thiazol-2(3*H*)-one (**1**) exhibited a subnanomolar sigma-2 affinity and a modest preference for sigma-2 versus sigma-1 with a selectivity ratio of 11 (Fig. 1). The goal of the present study was to prepare novel sigma ligands with selectivity for sigma-2 and we decided to use this compound as our lead structure.

2. Results and discussion

2.1. Chemistry

The strategy we chose involved the replacement of the benzothiazole heterocycle of **1** by the more stable and versatile indole ring (Fig. 1). Several parts of the new molecule **4a** were then

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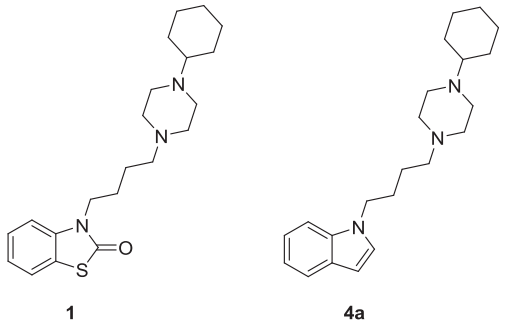
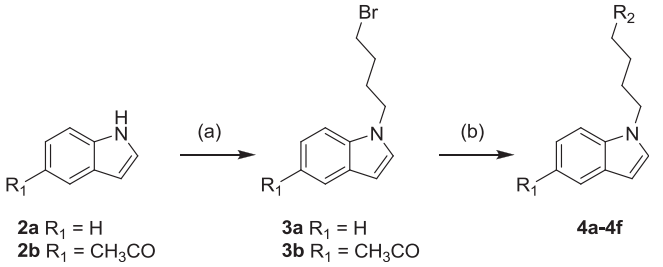


Fig. 1. Structures of **1** and its indole analog **4a**.



Scheme 1. Synthesis of indole derivatives **4a**–**4f**. Reagents and conditions: (a) 1,4-dibromobutane, KOH, TBAI, DMF, 0 °C → rt, 2 h; (b) Cyclic amine, K_2CO_3, DMF, 60 °C, 2 h.

modified to develop new indole-based sigma receptor ligands. These modifications were made at three different positions: an acetyl group was introduced at the 5 position of the indole ring, the 1-cyclohexylpiperazine (**A**-ring, Fig. 2) was replaced by other cyclic amines (**B**- and **C**-ring) and finally different aryl groups (**D**-, **E**- and **F**-rings) were introduced at the 3 position of the heterocycle.

The introduction of an acetyl group on the 5 position of the indole was motivated by previous work in our laboratory in the benzoazole series (data not shown) which hinted at this group giving better sigma-2 selectivity. Similarly, we decided to replace the piperazine group of **4a** by two cyclic amines that were described in the literature as potentially sigma-2 preferring and gave good results selectivity-wise in the benzoazole series: 1-(4-fluorophenyl)piperazine (**B**-ring) and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**C**-ring) [27]. Furthermore, the decision to introduce an aryl group in the C-3 indole position was inspired by the work of Perregaard who successfully converted a 3-(aminobutyl)indole with mixed affinity for sigma receptors to the sigma-2 selective ligand siramesine by adding a 4-fluorophenyl ring in the NH position of the indole [26]. The aryl groups we chose were the unsubstituted phenyl group (**D**-ring), the metabolically more stable 4-fluorophenyl ring (**E**-ring), and the H-bond acceptor and phenyl-bioisostere furan ring (**F**-ring).

The preparation of compounds **4a**–**4f** is outlined in Scheme 1. Treatment of indole (**2a**) or 5-acetyl-indole (**2b**) with 1,4-dibromobutane in the presence of potassium hydroxide in DMF gave the bromo derivatives **3a**–**3b**. These were then coupled with 1-cyclohexylpiperazine (**A**-ring, Fig. 2), 1-(4-fluorophenyl)piperazine (**B**-ring) or 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**C**-ring) in the presence of potassium carbonate in DMF to afford target compounds **4a**–**4f**.

The synthesis of final compounds **9a**–**9i** is described in Scheme 2. Intermediates **6a**–**6c** were prepared with excellent yields by reaction of commercially available 3-bromo-1-(phenylsulfonyl) indole (**5**) with the appropriate boronic acid under Suzuki conditions [29]. Indoles **6a**–**6c** underwent an easy and clean deprotection with magnesium and ammonium chloride in methanol to give the corresponding derivatives **7a**–**7c**. N-alkylation of the heterocycles with 1,4-dibromobutane gave the bromo intermediates **8a**–**8c** which were then reacted with **A**-, **B**- and **C**-ring to give 3-substituted-indole derivatives **9a**–**9i**.

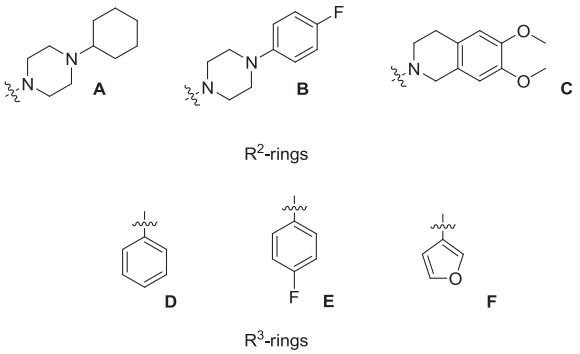
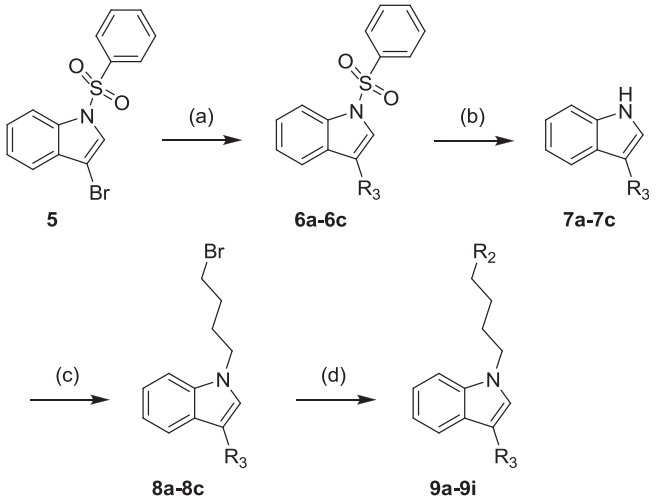


Fig. 2. R^2- and R^3-rings.

2.2. Pharmacology

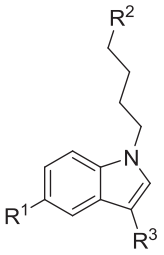
All final compounds were tested for in vitro affinity at sigma-1 and sigma-2 receptors using well-established assay conditions [30–34]. The sigma-1 receptors were labeled with 5 nM [^{3}H](+)-pentazocine and the sigma-2 receptors were labeled with 3 nM [^{3}H]di-o-tolylguanidine (DTG) in the presence of 300 nM (+)-pentazocine to block sigma-1 receptors. Non-specific binding was determined in the presence of 10 μM haloperidol. Ten concentrations of each sigma compound (0.1–1000 nM) were used in the assays. The chemical structures, sigma binding affinities and selectivity ratios of the new compounds are summarized in Table 1. In addition, the affinity of **9f** for monoamine transporters and several serotonin and dopamine receptors was determined. A binding profile of the compound was also prepared by NovaScreen/Caliper Life Sciences (Hanover, MD). The results of these experiments are summarized in Tables 2 and 3.

As shown in Table 1, the lead compound **1** had a high affinity for sigma-1 and sigma-2 receptors (4.17 and 0.39 nM, respectively) and



Scheme 2. Synthesis of 3-substituted-indole derivatives. Reagents and conditions: (a) Arylboronic acid, K_2CO_3, $Pd(P\phi_3)_4$, benzene/EtOH, reflux, 16 h; (b) Mg, NH_4Cl, MeOH/THF, rt, 2 h; (c) 1,4-dibromobutane, KOH, TBAI, DMF, 0 °C → rt, 2 h; (d) Cyclic amine, K_2CO_3, DMF, 60 °C, 2 h.

Table 1
Sigma receptor binding affinities and selectivity ratios of **1**, **4a**–**4f**, **9a**–**9i** and haloperidol.[a]



Compd	R^1	R^2	R^3	σ-1 (K_i, nM)	σ-2 (K_i, nM)	σ-1/σ-2
1	–	–	–	4.17 ± 0.62	0.39 ± 0.06	10.7
4a	H	A-ring	H	3.28 ± 0.32	1.90 ± 0.16	1.7
4b	H	B-ring	H	71.50 ± 1.53	13.32 ± 0.61	5.4
4c	H	C-ring	H	140.7 ± 5.7	3.66 ± 0.83	38.4
4d	CH_3CO	A-ring	H	5.33 ± 2.12	2.31 ± 0.02	2.3
4e	CH_3CO	B-ring	H	2.13 ± 0.31	3.30 ± 0.30	0.6
4f	CH_3CO	C-ring	H	14.55 ± 1.42	1.42 ± 0.10	10.2
9a	H	A-ring	D-ring	92.43 ± 1.90	12.30 ± 2.34	7.5
9b	H	B-ring	D-ring	222.33 ± 22.41	9.96 ± 1.19	22.3
9c	H	C-ring	D-ring	713.5 ± 163.5	46.29 ± 7.18	15.4
9d	H	A-ring	E-ring	90.87 ± 12.30	22.55 ± 1.10	4.0
9e	H	B-ring	E-ring	1202 ± 73.89	83.33 ± 3.90	14.4
9f	H	C-ring	E-ring	2948.4 ± 374.4	7.45 ± 0.71	395.8
9g	H	A-ring	F-ring	34.50 ± 4.84	10.07 ± 2.01	3.4
9h	H	B-ring	F-ring	279.0 ± 40.5	157.0 ± 1.6	1.8
9i	H	C-ring	F-ring	613.66 ± 38.29	12.02 ± 1.15	51.1
Haloperidol				3.35 ± 0.80	80.60 ± 14.10	0.042

[a] Affinities (K_i in nM) were determined in rat brain homogenates. Sigma-1 receptors were labeled with [^{3}H](+)-pentazocine. Sigma-2 receptors were labeled with [^{3}H]DTG in the presence of (+)-pentazocine to block sigma-1 receptors. Nonspecific binding was determined in the presence of haloperidol. The values in this table represent the mean ± SEM from replicate assays.

a small selectivity for sigma-2 versus sigma-1 receptors (σ-1/σ-2 = 10.7). The replacement of the benzothiazolone core by an indole core resulted in no change in affinity for sigma-1 receptors and a slight decrease in affinity for sigma-2. As a result, **4a** does not exhibit a preference for sigma-2 receptors, but this decrease in selectivity is not significant, while the change of the central template gives us access to a whole new class of potent sigma ligands. The next step was the replacement of the piperazine moiety with two different putative sigma-2 preferring elements (**B**- and **C**-ring). The 1-(4-fluorophenyl)piperazine compound **4b** showed only a slight selectivity (σ-1/σ-2 ratio of 5) while the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivative **4c** exhibited an interesting selectivity of 38 along with a high affinity for the sigma-2 receptor (K_i = 3.66 nM). Introduction of an acetyl group in the C-5 position of the indole provided compounds (**4d**–**4f**) with high affinities for both sigma receptors, but no meaningful selectivity. Compounds **9a**–**9i** were subsequently prepared to examine the influence of various aryl cycles attached in position 3 of the indole and, as depicted in Table 1, these pharmacomodulations gave mixed results. Generally most of the compounds displayed decreased affinities for both sigma receptors and a small selectivity. However 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **9f** and **9i** proved to be potent and selective sigma-2 selective ligands. In particular, compound **9f** with a 4-fluorophenyl ring in the C-3 position of its core ring presented a high affinity for the sigma-2 receptor (7.45 nM) and a weak affinity of 2948 nM for the sigma-

Table 2
Nonsigma protein binding affinities of compound **9f**.[a]

	Radioligand	Nonspecific binding	K_i (nM)
Monoamine transporters			
Dopamine[b]	40–80 pM [^{125}I]RTI-55	5 μM mazindol	5000 ± 1000
Serotonin[b]	40–80 pM [^{125}I]RTI-55	5 μM imipramine	295 ± 82
Norepinephrine[b]	40–80 pM [^{125}I]RTI-55	5 μM mazindol	1350 ± 110
Other Receptors			
Dopamine D_1[c]	0.18 nM [^{3}H]SCH-23390	1 μM SCH-23390	>10000
Dopamine D_2[d]	0.2–0.5 nM [^{3}H]YM-09151-2	1 μM chlorpromazine	870 ± 260
Dopamine D_3[d]	0.2–0.5 nM [^{3}H]YM-09151-2	1 μM chlorpromazine	544 ± 90
Serotonin 5-HT_{1A}[e]	0.5 nM [^{3}H]8–OH–DPAT	1 μM dihydroerotamine	1510 ± 410
Serotonin 5-HT_{2A}[e]	0.1 nM [^{125}I]DOI	10 μM 5-HT	1270 ± 310

[a] Affinities (K_i in nM) were determined using standard assays conditions. The values in this table represent the mean ± SEM from replicate assays. Values of >10000 nM signify that there was less than 30% displacement of the radioligand at that concentration.
[b] HEK293 cells expressing hBAT, hSERT or hNERT.
[c] LhD1 cells.
[d] CHOp-D_2 or CHOp-D_3 cells.
[e] HEK-h5-HT_{1A} or HEK-h5-HT_{2A} cells.

Table 3
Summary of binding profile of **9f** in 64 radioligand/enzyme assays at 10^{-5} M and 10^{-7} M.[a]

Assay name	50% Inhibition (10^{-7} M)	50% Inhibition (10^{-5} M)
Adrenergic, α1	No	Yes
Adrenergic, α2	No	Yes
Adrenergic, β1	No	Yes
Cannabinoid, CB_1	No	Yes
Cannabinoid, CB_2	No	Yes
Dopamine $D_{4.2}$	No	Yes
Glycine, Strychnine	Yes	Yes
Histamine, H_1	No	Yes
Histamine, H_2	No	Yes
Muscarinic, M1	No	Yes
Muscarinic, M2	No	Yes
Muscarinic, central	No	Yes
Opioid, μ	No	Yes
Calcium channel, type L (BZT)	No	Yes
Sodium, Site 2	No	Yes
Neurokinin, NK2 (NKA)	No	Yes

[a] Details of each assay condition can be accessed through Caliper's web site at www.caliperls.com.

1 receptor, giving this indole one of the best sigma-1/sigma-2 selectivity ratios (σ-1/σ-2 = 395) described so far. Because many ligands for sigma receptors also bind to non-sigma sites, we decided to submit **9f** to an extensive selectivity profile characterization. As can be seen from Table 2, compound **9f** had essentially no affinity for dopamine and norepinephrine transporters and a low affinity for serotonin transporters. It also showed no measurable affinity for the D_1 receptor and very low affinities for dopaminergic receptors D_2 and D_3 and serotoninergic receptors 5-HT_{1A} and 5-HT_{2A}. The compound was then tested by NovaScreen in 64 radioligand/enzyme assays (neurotransmitter related, steroids, ion channels, second messengers, prostaglandins, growth factors/hormones, brain/gut peptides, enzymes) at two concentrations of 10^{-5} M and 10^{-7} M. The summary of this "profiling" is presented in Table 3. A radioligand displacement of more than 50% was observed in 16 assays at the concentration of 10^{-5} M and in only the glycine, strychnine-sensitive assay at the concentration of 10^{-7} M. This compound seems to be a reasonably clean sigma-2 selective ligand and therefore could be of great interest as a lead for further development or as a pharmacological tool.

3. Conclusion

We synthesized a series of 4-(indol-1-yl)butan-1-amines and evaluated their binding affinity for sigma receptors. Several high-affinity sigma-2 receptor ligands with significant selectivity for sigma-2 versus sigma-1 were identified. The best result was obtained with the ligand bearing a 4-fluorophenyl ring in the C-3 position of its indole core and a 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline as the distal cyclic amine. This compound, which displayed a high affinity for the sigma-2 receptor (7.45 nM) and a weak affinity for the sigma-1 receptor (2948 nM), was also submitted to an extensive selectivity profile characterization and only exhibited moderate affinity for the glycine, strychnine-sensitive assay at the 10^{-7} M concentration.

4. Experimental protocols

4.1. Chemistry

Reagents and starting materials were obtained from commercial suppliers and were used without purification. Precoated silica gel GF Uniplates from Analtech were used for thin-layer chromatography (TLC). Column chromatography was performed on silica gel 60 (Sorbent Technologies). Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 500 MHz, 400 MHz, or Bruker 400 MHz Ultra Shield. The high resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-Tof Micromass spectrometer with a lock spray source. The mass spectra (MS) were recorded on a WATERS ACQUITY Ultra Performance LC with ZQ detector in ESI or APCI mode. Elemental analysis (C, H, N) were recorded on an elemental analyzer, Perkin–Elmer CHN/SO Series II Analyzer. Chemical names were generated using ChemDraw Ultra (CambridgeSoft, version 10.0). Except where otherwise noted, ^{1}H and ^{13}C NMR data for final compounds are given for materials in their salt form.

4.1.1. General procedure for the synthesis of 1-(4-bromobutyl)indole and derivatives (**3a**, **3b** and **8a–8c**)

The method adopted for the synthesis of 1-(4-bromobutyl) indole (**3a**) is described. Potassium hydroxide (3.83 g, 68.3 mmol) and tetrabutylammonium iodide (0.2 g, 0.54 mmol) were added, under mechanical stirring, to a solution of indole (**2a**) (2 g, 17.1 mmol) in anhydrous DMF (25 mL). The reaction mixture was stirred at room temperature for 45 min and cooled to 0 °C. 1,4-Dibromobutane was then added and the mixture was stirred for 15 min at 0 °C and for 1 h at room temperature. The mixture was poured into 70 mL of water, extracted with methylene chloride (3 × 50 mL), and the combined organic layers were washed with brine and dried. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel column using a gradient of hexanes/ethyl acetate (10:0 to 9:1) as the eluent to give 2.92 g (68%) of 1-(4-bromobutyl)indole as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 3.0 Hz, 1H), 6.58 (d, J = 2.9 Hz, 1H), 4.15 (t, J = 6.8 Hz, 2H), 3.38 (t, J = 6.5 Hz, 2H), 2.02 (quint, J = 7.3 Hz, 2H), 1.86 (quint, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.75, 127.69, 121.63, 121.15, 119.47, 109.39, 101.43, 101.37, 45.54, 33.20, 30.06, 28.91. MS (ESI) m/z 252 $[M + H]^+$ for ^{79}Br, 254 $[M + H]^+$ for ^{81}Br.

4.1.2. 1-[1-(4-Bromobutyl)indol-5-yl]-ethanone (**3b**)

This compound was prepared from 5-acetylindole (**2b**) as described for **3a**. 67% yield, white solid. mp 67–68 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.90 (d, J = 8.7, 1H), 7.35 (d, J = 8.7, 1H), 7.16 (d, J = 3.0, 1H), 6.63 (d, J = 3.1, 1H), 4.18 (t, J = 5.3, 2H), 3.38 (t, J = 6.4, 2H), 2.67 (s, 3H), 2.05–2.00 (m, 2H), 1.87–1.80 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.21, 138.44, 129.59, 129.20, 128.06, 123.39, 121.89, 109.13, 103.41, 45.72, 32.79, 29.84, 28.83, 26.61. MS (ESI) m/z 316 $[M + Na]^+$ for ^{79}Br, 318 $[M + Na]^+$ for ^{81}Br.

4.1.3. General procedure for the synthesis of 1-(4-(4-cyclohexylpiperazin-1-yl)butyl)indole and other final products (**4a–4f**, **9a–9i**)

The method adopted for the synthesis of 1-(4-(4-cyclohexylpiperazin-1-yl)butyl)indole dioxalate (**4a**) is described. K_2CO_3 (0.2 g, 1.43 mmol) and 1-cyclohexylpiperazine (0.081 g, 0.47 mmol) were added, under mechanical stirring, to a solution of **3a** (0.12 g, 0.47 mmol) in anhydrous DMF (4 mL). The reaction mixture was heated at 60 °C for 2 h. After cooling, the mixture was poured into 20 mL of water, extracted with ethyl acetate (3 × 30 mL), and the combined organic layers were washed with saturated aqueous NaCl and dried. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel column using methylene chloride/methanol (97:3) as the eluent. 1-(4-(4-Cyclohexylpiperazin-1-yl) butyl)indole was isolated as a dioxalate salt (white solid, 0.073 g, 30%). mp 230–233 °C ^{1}H NMR (400 MHz, DMSO-d_6, 60 °C): δ 7.55

(br s, 4H), 7.53 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 3.0 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 6.42 (d, J = 2.8 Hz, 1H), 4.18 (t, J = 6.9 Hz, 2H), 3.00 (s, 4H), 2.83–2.77 (m, 5H), 2.57 (t, J = 7.3 Hz, 2H), 1.95–1.93 (m, 2H), 1.83–1.78 (m, 4H), 1.61–1.58 (m, 1H), 1.52–1.47 (m, 2H), 1.35–1.19 (m, 4H), 1.13–1.07 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 60 °C): δ 162.58, 135.49, 128.16, 127.95, 120.64, 120.14, 118.54, 109.42, 100.22, 63.20, 55.54, 49.78, 46.85, 44.91, 27.00, 26.65, 24.2, 24.38, 22.23. Anal. calcd for $C_{26}H_{37}N_3O_8$: C, 60.10; H, 7.18; N, 8.09. Found: C, 60.58; H, 6.80; N, 8.09. HRMS (TOF ES+) calcd for $C_{22}H_{34}N_3$ $[M + H]^+$ 340.2753, found 340.2759.

4.1.4. 1-(4-(4-(4-Fluorophenyl)piperazin-1-yl)butyl)indole oxalate (**4b**)

This compound was prepared from **3a** and 1-(4-fluorophenyl) piperazine as described for **4a**. 25% yield, white solid. mp 160–162 °C ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.13–6.98 (m, 6H), 6.42 (s, 1H), 4.21–4.18 (m, 2H), 3.27–2.95 (m, 10H), 1.78–1.63 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.38, 156.47 (J = 236.0 Hz), 146.73, 135.58, 128.59, 128.15, 118.91, 117.67 (J = 7.1 Hz), 115.43 (J = 22.0 Hz), 109.75, 100.54, 55.29, 50.97, 46.67, 44.94, 27.09, 21.16. Anal. calcd for $C_{24}H_{28}FN_3O_4 \cdot ¼H_2O$: C, 64.63; H, 6.44; N, 9.42. Found: C, 64.60; H, 6.05; N, 9.32. HRMS (TOF ES+) calcd for $C_{22}H_{27}N_3F$ $[M + H]^+$ 352.2189, found 352.2206.

4.1.5. 2-(4-(Indol-1-yl)butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline oxalate (**4c**)

This compound was prepared from **3a** and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline as described for **4a**. 51% yield, white solid. mp 186–187 °C ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.57 (br s, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 3.0 Hz, 1H), 7.13 (t, J = 7.3 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.76 (s, 1H), 6.73 (s, 1H), 6.43 (d, J = 2.8 Hz, 1H), 4.20 (t, J = 6.6 Hz, 2H), 4.13 (s, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 3.31–3.29 (m, 2H), 3.10–3.06 (m, 2H), 2.93–2.91 (m, 2H), 1.83–1.71 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.62, 148.16, 147.57, 135.57, 128.60, 128.15, 123.55, 120.99, 120.66, 120.44, 118.91, 111.49, 109.77, 109.76, 100.53, 55.55, 55.48, 54.48, 51.61, 48.83, 44.93, 27.03, 24.65, 21.21. HRMS (TOF ES+) calcd for $C_{23}H_{29}N_2O_2$ $[M + H]^+$ 365.2229, found 365.2242.

4.1.6. 1-{1-[4-(4-Cyclohexyl-piperazin-1-yl)-butyl]indol-5-yl}-ethanone dioxalate (**4d**)

This compound was prepared from **3b** and 1-cyclohexyl-piperazine as described for **4a**. 31% yield, white solid. mp 224–227 °C ^{1}H NMR (free amine, 400 MHz, $CDCl_3$): δ 8.16 (d, J = 7.3 Hz, 1H), 7.74 (t, J = 8.1 Hz, 1H), 7.23 (t, J = 8.5 Hz, 1H), 7.06–7.03 (m, 1H), 6.48–6.45 (m, 1H), 4.04–3.99 (m, 2H), 2.63 (s, 4H), 2.53–2.51 (m, 3H), 2.45 (s, 4H), 2.45 (s, 1H), 2.26–2.21 (m, 2H), 1.85 (s, 2H), 1.73–1.70 (m, 4H), 1.52 (d, J = 10.0 Hz, 1H), 1.37–1.35 (m, 2H), 1.14–1.13 (m, 4H), 1.03–0.99 (s, 1H). ^{13}C NMR (100 MHz, free amine, $CDCl_3$) δ 198.09, 138.33, 129.46, 129.27, 127.94, 123.23, 121.53, 109.25, 103.00, 64.08, 57.19, 51.83, 48.37, 46.29, 27.96, 27.79, 26.56, 25.69, 25.43, 23.74. Anal. calcd for $C_{28}H_{39}N_3O_9$: C, 59.88; H, 7.00; N, 7.48. Found: C, 59.54; H, 6.83; N, 7.60. HRMS (TOF ES+) calcd for $C_{24}H_{36}N_3O$ $[M + H]^+$ 382.2858, found 382.2875.

4.1.7. 1-(1-{4-[4-(4-Fluorophenyl)-piperazin-1-yl]-butyl}indol-5-yl)-ethanone dioxalate (**4e**)

This compound was prepared from **3b** and 1-(4-fluorophenyl) piperazine as described for **4a**. 37% yield, white solid. mp 140–142 °C ^{1}H NMR (free amine, 400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 3.0 Hz, 1H), 7.00 (t, J = 8.9 Hz, 2H), 6.87 (dd, J = 8.3, 5.4 Hz, 2H), 6.61 (d, J = 2.5 Hz, 1H), 4.21 (t, J = 6.9 Hz, 2H), 2.98 (s, 4H), 2.58 (s, 3H), 2.39 (s, 4H), 2.26 (t, J = 7.1 Hz, 2H), 1.87–1.64 (m, 2H), 1.39 (d, J = 7.0 Hz, 2H). ^{13}C NMR (free amine, 100 MHz, DMSO-d_6) δ 197.82, 156.39 (J = 234.0 Hz), 148.37, 138.57, 130.92, 129.29, 128.01, 123.30, 121.38, 117.41 (d, J = 7.6 Hz), 115.64 (d, J = 21.8 Hz), 110.22, 102.98, 57.46, 53.05, 49.40, 46.03, 40.42, 40.21, 40.00, 39.59, 28.13, 27.02, 23.84. Anal. calcd for $C_{28}H_{32}FN_3O_9 \cdot 5/4H_2O$: C, 56.42; H, 5.79; N, 7.10. Found: C, 56.41; H, 5.83; N, 7.05. HRMS (TOF ES+) calcd for $C_{24}H_{29}N_3OF$ $[M + H]^+$ 394.2295, found 394.2290.

4.1.8. 1-{1-[4-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-butyl]indol-5-yl}-ethanone oxalate (**4f**)

This compound was prepared from **3b** and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline as described for **4a**. 41% yield, white solid. mp 170–171 °C ^{1}H NMR (free amine, 400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.17 (s, 1H), 6.59 (d, J = 10.8 Hz, 2H), 6.48 (s, 1H), 4.19–4.15 (m, 3H), 3.82–3.81 (m, 6H), 3.48 (s, 2H), 2.79–2.76 (m, 2H), 2.64 (s, 3H), 2.50–2.47 (m, 2H), 1.94–1.90 (m, 2H), 1.61–1.59 (m, 3H), 1.28–1.25 (m, 2H). ^{13}C NMR (free amine, 100 MHz, $CDCl_3$) δ 198.20, 162.50, 147.42, 138.47, 129.40, 128.00, 126.00, 123.28, 121.66, 111.37, 109.47, 109.26, 103.07, 57.26, 55.90, 55.44, 50.79, 46.40, 36.42, 31.37, 28.09, 26.56, 24.28. Anal. calcd for $C_{27}H_{32}N_2O_7 \cdot H_2O$: C, 63.02; H, 6.66; N, 5.44. Found: C, 63.26; H, 6.15; N, 5.46. HRMS (TOF ES+) calcd for $C_{25}H_{31}N_2O_3$ $[M + H]^+$ 407.2335, found 407.2343.

4.1.9. General procedure for the synthesis of 3-aryl-1-(phenylsulfonyl)indoles **6a**–**6c**

The method adopted for the synthesis of 3-phenyl-1-(phenylsulfonyl)indole (**6a**) is described. To a solution of phenylboronic acid (0.49 g, 4.1 mmol) in benzene (21 mL) and ethanol (10 mL) were added potassium carbonate (0.680 g, 4.4 mmol) and 3-bromo-1-(phenylsulfonyl)indole (**5**) (1.2 g, 3.4 mmol). The reaction mixture was stirred at room temperature and deoxygenated by passing through it a steam of argon for 15 min. Palladium triphenylphosphine tetrakis (0.039 mg, 0.034 mmol) was added and the solution was refluxed for 16 h. After cooling, the mixture was poured into 25 mL of water, extracted with ethyl acetate (3 × 30 mL), washed with saturated aqueous NaCl and dried. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel column using hexane/ethyl acetate (9:1) to give 0.955 g (84%) of 3-phenyl-1-(phenylsulfonyl)indole as a white solid. mp 144–146 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 7.3 Hz, 2H), 7.81 (d, J = 7.9 Hz, 1H), 7.73 (s, 1H), 7.63 (d, J = 7.4 Hz, 2H), 7.57–7.27 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.07, 135.34, 134.00, 130.37, 129.52, 127.30, 126.59, 126.08, 124.79, 120.13, 113.85, 99.44. MS (APCI) m/z 334.9 $[M + H]^+$.

4.1.10. 3-(4-Fluorophenyl)-1-(phenylsulfonyl)indole (**6b**)

This compound was prepared from 3-bromo-1-(phenylsulfonyl) indole (**5**) and 4-fluorophenylboronic acid as described for **6a**. 91% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.65 (s, 1H), 7.55–7.50 (m, 3H), 7.43 (t, J = 7.9 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 7.14 (t, J = 8.6 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.56 (d, J = 245.5 Hz), 138.38, 135.67, 134.11, 129.73 (d, J = 7.9 Hz), 129.54, 129.45, 129.20 (d, J = 3.3 Hz), 127.03, 125.29, 123.92, 123.40, 122.99, 120.43, 116.09 (d, J = 21.4 Hz), 114.07. MS (EI) m/z 374 $[M + Na]^+$.

4.1.11. 3-(Furan-3-yl)-1-(phenylsulfonyl)-1H-indole (**6c**)

This compound was prepared from 3-bromo-1-(phenylsulfonyl) indole (**5**) and furan-3-boronic acid as described for **6a**. 97% yield, yellow solid. mp 88–91 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3 Hz, 1H), 8.03–7.88 (m, 2H), 7.83 (s, 1H), 7.78–7.63 (m, 2H), 7.56–7.49 (m, 2H), 7.47–7.35 (m, 3H), 7.33–7.27 (m, 1H), 6.71

(s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.45, 139.07, 138.10, 135.46, 133.90, 129.32, 129.14, 126.79, 125.13, 123.70, 122.44, 120.48, 117.67, 115.41, 113.85, 109.66. MS (APCI) m/z 323.9 $[M]^+$.

*4.1.12. General procedure for the synthesis of 3-arylindoles **7a–7c***

The method adopted for the synthesis of 3-phenylindole (**7a**) is described. Mg (2.12 g, 875 mmol) and ammonium chloride (0.04 g, 0.8 mmol) were added to a stirred solution of **6a** (0.85 g, 2.5 mmol) in methanol (80 mL) and THF (20 mL). The exothermic mixture was stirred for 2 h at room temperature and was concentrated under reduced pressure. A saturated solution of ammonium chloride (30 mL) was then added and the mixture was extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with water and brine, dried and evaporated. The residue was chromatographed on a silica gel column using hexane/ethyl acetate (8:2) to give 0.28 g (60%) of 3-phenyl-1*H*-indole as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.4 Hz, 1H), 7.96 (s, 1H), 7.83 (d, J = 7.1 Hz, 2H), 7.61 (t, J = 7.7 Hz, 2H), 7.55–7.34 (m, 3H), 7.31 (d, J = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.77, 135.74, 129.02, 127.62, 126.19, 125.80, 122.55, 122.12, 120.51, 119.94, 118.20, 111.69. MS (APCI) m/z 193.1 $[M]^+$.

*4.1.13. 3-(4-Fluorophenyl)indole (**7b**)*

This compound was prepared from **6b** as described for **7a**. 80% yield, white solid. mp 105–107 °C ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.73–7.67 (m, 3H), 7.51 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 8.8 Hz, 2H), 7.19 (t, J = 7.2 Hz, 2H), 7.12 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.47, 159.07, 136.78, 132.21, 128.09, 128.01, 124.84, 123.22, 121.37, 119.54, 118.70, 115.47, 115.26, 114.67, 111.88. MS (ESI) m/z 210 $[M - H]^+$.

*4.1.14. 3-(Furan-3-yl)indole (**7c**)*

This compound was prepared from **6c** as described for **7a**. 89% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.98–7.81 (m, 2H), 7.60 (s, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.37–7.21 (m, 2H), 6.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.06, 137.74, 136.57, 125.74, 122.55, 121.57, 120.30, 119.88, 119.72, 111.52, 109.92, 109.06. MS (APCI) m/z 184.0 $[M]^+$.

*4.1.15. 1-(4-Bromobutyl)-3-phenylindole (**8a**)*

This compound was prepared from 3-phenylindole (**7a**) as described for **3a**. 77% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.03 (m, 1H), 7.74 (d, J = 7.0 Hz, 2H), 7.52 (t, J = 7.7 Hz, 2H), 7.43 (d, J = 8.2 Hz, 1H), 7.40–7.22 (m, 4H), 4.32–4.11 (m, 2H), 3.48–3.33 (m, 2H), 2.18–2.00 (m, 2H), 1.95–1.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.80, 135.62, 128.85, 127.40, 126.38, 125.88, 125.39, 122.11, 120.18, 120.08, 117.09, 109.68, 45.57, 33.05, 30.0, 28.85. MS (APCI) m/z 327 $[M]^+$ for ^{79}Br, 329 $[M]^+$ for ^{81}Br.

*4.1.16. 1-(4-Bromobutyl)-3-(4-fluorophenyl)indole (**8b**)*

This compound was prepared from **7b** as described for **3a**. 83% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.9 Hz, 1H), 7.60–7.56 (m, 2H), 7.37 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 7.20–7.16 (m, 2H), 7.12 (t, J = 8.7 Hz, 2H), 4.18 (t, J = 6.8 Hz, 2H), 3.38 (t, J = 6.5 Hz, 2H), 2.08–2.01 (m, 2H), 1.92–1.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.60 (d, J = 243.0 Hz), 136.87, 131.75 (d, J = 3.3 Hz), 128.99 (d, J = 7.6 Hz), 126.50, 125.28, 122.35, 120.27, 120.03, 116.41, 115.79 (d, J = 21.1 Hz), 109.82, 45.77, 33.08, 30.19, 29.03. MS (ESI) m/z 346 $[M + H]^+$ for ^{79}Br, 348 $[M + H]^+$ for ^{81}Br.

*4.1.17. 1-(4-Bromobutyl)-3-furan-3-ylindole (**8c**)*

This compound was prepared from **7c** as described for **3a**. 75% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.76 (m, 2H), 7.54 (t, J = 1.6 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.34–7.26 (m, 1H), 7.25–7.15 (m, 2H), 6.80–6.64 (m, 1H), 4.15–4.09 (m, 2H), 3.45 (t, J = 6.5 Hz, 2H), 2.06–2.00 (m, 2H), 1.91–1.78 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.96, 137.49, 136.62, 126.30, 124.88, 122.11, 120.13, 119.85, 119.62, 109.79, 109.59, 107.87, 45.47, 33.03, 29.96, 28.84. MS (APCI) m/z 327 $[M]^+$ for ^{79}Br, 329 $[M]^+$ for ^{81}Br.

*4.1.18. 1-[4-(4-Cyclohexyl-piperazin-1-yl)-butyl]-3-phenylindole dioxalate (**9a**)*

This compound was prepared from **8a** and 1-cyclohexylpiperazine as described for **4a**. 21% yield, white solid. mp 242–244 °C ^{1}H NMR (free amine, 400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.7 Hz, 2H), 7.39 (d, J = 8.2 Hz, 1H), 7.32–7.23 (m, 3H), 7.19 (t, J = 7.4 Hz, 1H), 4.18 (t, J = 7.0 Hz, 2H), 2.70 (s, 4H), 2.55 (s, 4H), 2.47–2.30 (m, 2H), 2.03–1.86 (m, 4H), 1.81 (s, 2H), 1.75–1.63 (m, 1H), 1.60–1.55 (m, 2H), 1.37–1.17 (m, 5H), 1.12 (s, 1H). ^{13}C NMR (free amine, 100 MHz, $CDCl_3$) δ 136.74, 135.66, 128.76, 127.29, 126.26, 125.71, 125.51, 121.86, 120.04, 119.86, 116.74, 109.73, 63.99, 57.62, 52.52, 48.60, 46.26, 28.35, 28.01, 25.97, 25.66, 24.13. HRMS (TOF ES+) calcd for $C_{28}H_{38}N_3$ $[M + H]^+$ 416.3066, found 416.3081.

*4.1.19. 1-{4-[4-(4-Fluorophenyl)-piperazin-1-yl]-butyl}-3-phenylindole oxalate (**9b**)*

This compound was prepared from **8a** and 1-(4-fluorophenyl) piperazine as described for **4a**. 28% yield, white solid. mp 195–197 °C ^{1}H NMR (free amine, 400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.5 Hz, 2H), 7.55–7.38 (m, 3H), 7.31 (d, J = 5.6 Hz, 3H), 7.23 (d, J = 7.4 Hz, 1H), 6.98 (t, J = 8.5 Hz, 2H), 6.88 (s, 2H), 4.21 (t, J = 6.9 Hz, 2H), 3.12 (s, 4H), 2.58 (s, 4H), 2.52–2.36 (m, 2H), 1.97 (m, 2H), 1.62 (m, 2H). ^{13}C NMR (free amine, 100 MHz, $CDCl_3$) δ 158.39, 156.02, 147.94, 136.82, 135.71, 128.78, 127.33, 126.33, 125.62 (d, J = 23.6 Hz), 121.99, 120.00 (d, J = 17.7 Hz), 117.83 (d, J = 7.6 Hz), 115.50 (d, J = 22.0 Hz), 109.73, 77.40, 77.08, 76.76, 57.82, 53.16, 50.03, 46.29, 28.07, 24.18. Anal. calcd for $C_{30}H_{32}FN_3O_4 \cdot {}^1/_3\ H_2O$: C, 68.82; H, 6.29; N, 8.03. Found: C, 68.95; H, 6.03; N, 8.01. HRMS (TOF ES+) calcd for $C_{28}H_{31}N_3F$ $[M + H]^+$ 428.2502, found 428.2516.

*4.1.20. 6,7-Dimethoxy-2-(4-(3-phenylindol-1-yl)butyl)-1,2,3,4-tetrahydroisoquinoline oxalate (**9c**)*

This compound was prepared from **8a** and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline as described for **4a**. 30% yield, white solid. mp 189–190 °C ^{1}H NMR (free amine, 400 MHz, CDCl3) δ 7.98–7.96 (m, 2H), 7.68 (d, J = 7.2 Hz, 2H), 7.53–7.36 (m, 3H), 7.31 (s, 1H), 7.29–7.24 (m, 2H), 7.19 (t, J = 7.3 Hz, 1H), 6.59 (s, 1H), 6.49 (s, 1H), 4.22–4.19 (m, 2H), 3.83 (m, 6H), 3.51 (s, 2H), 2.81–2.79 (m, 2H), 2.70–2.68 (m, 2H), 2.53–2.50 (m, 2H), 1.97–1.95 (m, 2H), 1.66–1.64 (m, 2H). ^{13}C NMR (free amine, 100 MHz, $CDCl_3$) δ 162.56, 147.59, 147.28, 136.83, 136.83, 135.73, 135.73, 128.74, 127.28, 126.32 (d, J = 6.9 Hz), 126.09, 125.67, 125.56, 121.86, 119.93 (d, J = 14.3 Hz), 116.71, 111.46, 109.68 (d, J = 19.9 Hz), 57.51, 55.93, 55.57, 50.94, 46.27, 36.42, 28.48, 28.10, 24.49. Anal. calcd for $C_{31}H_{34}N_2O_6 \cdot ½H_2O$: C, 69.00; H, 6.54; N, 5.19. Found: C, 68.60; H, 6.11; N, 5.12. HRMS (TOF ES+) calcd for $C_{29}H_{33}N_2O_2$ $[M + H]^+$ 441.2542, found 441.2521.

*4.1.21. 1-(4-(4-Cyclohexylpiperazin-1-yl)butyl)-3-(4-fluorophenyl) indole dioxalate (**9d**)*

This compound was prepared from **8b** and 1-cyclohexylpiperazine as described for **4a**. 28% yield, white solid. mp 248–249 °C ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (br s, 4H), 7.81 (d, J = 7.6 Hz, 1H), 7.70–7.65 (m, 3H), 7.53 (d, J = 7.8 Hz, 1H), 7.26–7.09 (m, 4H), 4.20 (s, 2H), 2.98–2.47 (m, 11H), 1.88–1.75 (m, 6H), 1.56–1.47 (m, 3H), 1.23–1.04 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.73, 163.36, (d, J = 241.0 Hz), 136.53, 131.91, 128.18 (d, J = 7.6 Hz), 126.72, 125.28, 121.61, 119.86, 119.18, 115.64 (d, J = 20.8 Hz), 114.01, 110.44, 63.11, 56.27, 51.13, 47.54, 45.33, 27.33,

26.32, 25.30, 24.89, 22.86. Anal. calcd for $C_{32}H_{40}FN_3O_8$: C, 62.63; H, 6.57; N, 6.85. Found: C, 62.48; H, 6.25; N, 6.76. HRMS (TOF ES+) calcd for $C_{28}H_{37}N_3F$ $[M + H]^+$ 434.2972, found 434.2987.

4.1.22. 3-(4-Fluorophenyl)-1-(4-(4-(4-fluorophenyl)piperazin-1-yl) butyl)indole oxalate (**9e**)

This compound was prepared from **8b** and 1-(4-fluorophenyl) piperazine as described for **4a**. 54% yield, white solid. mp 214–216 °C ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.40 (br s, 2H), 7.84 (d, J = 7.9 Hz, 1H), 7.76 (s, 1H), 7.70–7.67 (m, 2H), 7.58 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 8.6 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 8.7 Hz, 2H), 6.99–6.96 (m, 2H), 4.25 (t, J = 6.7 Hz, 2H), 3.26 (br s, 4H), 3.10 (br s, 4H), 2.97 (br s, 2H), 1.85–1.83 (m, 2H), 1.66 (br s, 2H). ^{13}C NMR (125, MHz, DMSO-d_6): δ 164.05, 160.38 (d, J = 240.4 Hz), 156.43 (d, J = 235.1 Hz), 146.76, 136.44, 131.86 (d, J = 3.0 Hz), 128.18 (d, J = 7.7 Hz), 126.70, 125.29, 121.63, 119.88, 119.16, 117.62 (d, J = 7.7 Hz), 115.61 (d, J = 21.0 Hz), 115.43 (d, J = 21.8 Hz), 114.08, 110.37, 55.31, 51.01, 46.72, 45.07, 27.04, 21.29. Anal. calcd for $C_{30}H_{31}F_2N_3O_4$: C, 67.28; H, 5.83; N, 7.85. Found: C, 67.08; H, 5.80; N, 7.73. HRMS (TOF ES+) calcd for $C_{28}H_{30}N_3F_2$ $[M + H]^+$ 446.2408, found 446.2391.

4.1.23. 2-(4-(3-(4-Fluorophenyl)indol-1-yl)butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline oxalate (**9f**)

This compound was prepared from **8b** and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline as described for **4a**. 53% yield, white solid. mp 182–184 °C ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.52 (br s, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 7.70–7.67 (m, 2H), 7.58 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 8.8 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 4.26 (t, J = 6.8 Hz, 2H), 4.15 (br s, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.32 (br s, 2H), 3.13–3.09 (m, 2H), 2.92 (br s, 2H), 1.90–1.85 (m, 2H), 1.75 (br s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.34, 160.39 (d, J = 240.4 Hz), 148.15, 147.55, 136.45, 131.85, 128.20 (d, J = 7.7 Hz), 126.69, 125.32, 123.50, 121.64, 120.61, 119.90, 119.17, 115.61 (d, J = 21.0 Hz), 114.11, 111.46, 110.40, 109.67, 55.53, 55.48, 54.51, 51.70, 48.90, 45.05, 26.92, 24.68, 21.29. HRMS (TOF ES+) calcd for $C_{29}H_{32}N_2O_2F$ $[M + H]^+$ 459.2448, found 459.2456.

4.1.24. 1-[4-(4-Cyclohexyl-piperazin-1-yl)-butyl]-3-furan-3-ylindole dioxalate (**9g**)

This compound was prepared from **8c** and 1-cyclohexyl-piperazine as described for **4a**. 21% yield, white solid. mp 240–243 °C ^{1}H NMR (free amine, 400 MHz, $CDCl_3$) δ 7.85–7.69 (m, 2H), 7.49 (s, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.27–7.20 (m, 2H), 7.16 (t, J = 7.4 Hz, 1H), 6.69 (s, 1H), 4.11 (t, J = 6.8 Hz, 2H), 2.72 (s, 4H), 2.54 (s, 4H), 2.45 (s, 1H), 2.40–2.27 (m, 2H), 1.94 (s, 2H), 1.87–1.81 (m, 4H), 1.61 (m, 2H), 1.55–1.48 (m, 2H), 1.28–1.22 (m, 3H), 1.15–1.08 (s, 1H). ^{13}C NMR (free amine, 100 MHz, $CDCl_3$) δ 142.90, 137.34, 136.57, 126.20, 125.09, 121.91, 120.03, 119.69, 119.67, 109.74, 109.69, 107.53, 64.17, 57.43, 52.06, 48.47, 46.14, 28.10, 27.92, 25.81, 25.54, 23.98. Anal. calcd for $C_{30}H_{39}N_3O_9 \cdot ½H_2O$: C, 60.59; H, 6.79; N, 7.07. Found: C, 60.20; H, 6.39; N, 7.01. HRMS (TOF ES+) calcd for $C_{26}H_{36}N_3O$ $[M + H]^+$ 406.2858, found 406.2874.

4.1.25. 1-{4-[4-(4-Fluorophenyl)-piperazin-1-yl]-butyl}-3-furan-3-ylindole dioxalate (**9h**)

This compound was prepared from **8c** and 1-(4-fluorophenyl) piperazine as described for **4a**. 46% yield, white solid. mp 172–174 °C ^{1}H NMR (free amine, 400 MHz, $CDCl_3$) δ 7.93–7.75 (m, 2H), 7.55–7.54 (m, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.31–7.20 (m, 3H), 7.01–6.96 (m, 2H), 6.89–6.86 (m, 2H), 6.73 (s, 1H), 4.18 (t, J = 7.0 Hz, 2H), 3.11 (t, J = 4 Hz, 4H), 2.56 (t, J = 4 Hz, 4H), 2.44–2.40 (m, 2H), 2.03–1.85 (m, 2H), 1.63–1.59 (m, 2H). ^{13}C NMR (free amine, 100 MHz, $CDCl_3$) δ 158.35, 154.92 (d, J = 212.2 Hz), 147.98 (d, J = 2.2 Hz), 142.94, 137.45, 136.64, 126.29, 125.06, 121.96, 119.92 (d, J = 36.5 Hz), 117.78 (d, J = 7.6 Hz), 115.62, 115.40, 109.81, 109.70, 107.62, 57.90, 53.22, 50.11, 46.26, 28.14, 24.28. Anal. calcd for $C_{30}H_{32}FN_3O_9 \cdot ½H_2O$: C, 59.40; H, 5.48; N, 6.93. Found: C, 59.47; H, 5.15; N, 6.92. HRMS (TOF ES+) calcd for $C_{26}H_{29}N_3OF$ $[M + H]^+$ 418.2295, found 418.2298.

4.1.26. 2-(4-(3-(Furan-3-yl)indol-1-yl)butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline oxalate (**9i**)

This compound was prepared from **8c** and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline as described for **4a**. 42% yield, white solid. mp 156 °C ^{1}H NMR (free amine, 400 MHz, $CDCl_3$) δ 7.90–7.78 (m, 2H), 7.52 (s, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.30–7.24 (m, 2H), 7.21 (t, J = 7.4 Hz, 1H), 6.72 (s, 1H), 6.61 (s, 1H), 6.51 (s, 1H), 4.18 (t, J = 6.9 Hz, 3H), 3.86–6.84 (m, 6H), 3.52 (s, 2H), 2.84–2.80 (m, 2H), 2.69 (t, J = 5.7 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2H), 2.05–1.84 (m, 2H), 1.72–1.60 (m, 2H). ^{13}C NMR (free amine, 100 MHz, $CDCl_3$) δ 147.56, 147.24, 142.89, 137.40, 136.68, 126.48, 126.27, 126.14, 125.10, 121.93, 120.05, 119.76, 119.70, 111.39, 109.80, 109.75, 109.51, 107.55, 57.65, 55.94, 55.91, 55.72, 51.06, 46.23, 28.64, 28.14, 24.58. HRMS (TOF ES+) calcd for $C_{27}H_{31}N_2O_3$ $[M + H]^+$ 431.2335, found 431.2356.

4.2. Pharmacology

In vitro competition binding assays were performed as follows. Preparation of rat brain membrane and binding assays for the σ_1 and σ_2 receptor were performed using methods published previously in detail [30–34]. In brief, homogenates of whole rat brain excluding the cerebellum (400–500 μg) were taken in test tubes and incubated with 5 nM [^{3}H](+)-pentazocine to label σ-1 receptors, or 3 nM [^{3}H]-DTG in the presence of 300 nM (+)-pentazocine to label σ-2 receptors. Non-specific binding was determined in the presence of 10 μM haloperidol. Ten concentrations of each sigma compound ranging from 0.1 to 1000 nM were incubated for 120 min at 25 °C in 50 mM Tris–HCl, pH 8.0 to measure their ability to displace the radioligands from their binding sites. The total reaction volume was 500 μl. The assay was terminated by the addition of 5 mL ice-cold 10 mM Tris–HCl, pH 8.0, followed by two washes through glass fiber filters presoaked in 1% polyethyleneimine for at least 45 min to minimize non-specific binding. Both these assays were run in duplicate. Counts were extracted from the filters using Ecoscint (National Diagnostics, Manville, NJ) for at least 8 h prior to counting. K_i values were calculated using the Cheng–Prusoff equation [35].

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References

[1] R. Quirion, W.D. Bowen, Y. Itzhak, J.L. Jumien, J.M. Musacchio, R.B. Rothman, T.P. Su, S.W. Tam, D.P. Taylor, Trends Pharmacol. Exp. Ther. 13 (1992) 85–86.
[2] M. Hanner, F.F. Moebius, A. Flandorfer, H.G. Knaus, J. Striessnig, E. Kempner, H. Glossmann, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 8072–8077.
[3] P. Seth, Y.J. Fei, H.W. Li, W. Huang, F.H. Leibach, V. Ganapathy, J. Neurochem. 70 (1998) 922–931.
[4] R.R. Matsumoto, Sigma receptors: historical perspective and background. in: R.R. Matsumoto, W.D. Bowen, T.P. Su (Eds.), Sigma Receptors: Chemistry, Cell Biology and Clinical Implications. Springer, New York, 2007, pp. 1–23.
[5] B. Bourrie, E. Bribes, J.M. Derocq, H. Vidal, P. Casellas, Curr. Opin. Invest. Drugs 5 (2004) 1158–1163.
[6] H.P. Volz, K.D. Stoll, Pharmacopsychiatry 37 (2004) S214–S220.
[7] T. Maurice, T.P. Su, Pharmacol. Ther. 124 (2009) 195–206.

[8] C. Sanchez, J. Arnt, B. Costall, M.E. Kelly, E. Meier, R.J. Naylor, J. Perregaard, J. Pharmacol. Exp. Ther. 283 (1997) 1323–1332.
[9] V. Villard, J. Espallergues, E. Keller, T. Alkam, A. Nitta, K. Yamada, T. Nabeshima, A. Vamvakides, T. Maurice, Neuropsychopharmacology 34 (2009) 1552–1566.
[10] X. Guitart, X. Codony, X. Monroy, Psychopharmacology 174 (2004) 301–319.
[11] R.R. Matsumoto, Y. Liu, M. Lerner, E.W. Howard, D.J. Brackett, Eur. J. Pharmacol. 469 (2003) 1–12.
[12] T. Maurice, R. Martin-Fardon, P. Romieu, R.R. Matsumoto, Neurosci. Biobehav. Rev. 26 (2002) 499–527.
[13] S.R. Choi, B. Yang, K. Plossl, S. Chumpradit, S.P. Wey, P.D. Acton, K. Wheeler, R.H. Mach, H.F. Kung, Nucl. Med. Biol. 28 (2001) 657–666.
[14] B.J. Vilner, C.S. John, W.D. Bowen, Cancer Res. 55 (1995) 408–413.
[15] D.J. Rowland, Z. Tu, J. Xu, D. Ponde, R.H. Mach, M.J. Welch, J. Nucl. Med. 47 (2006) 1041–1048.
[16] Z. Tu, J. Xu, L.A. Jones, S. Li, C. Dumstorff, S. Vangveravong, D.L. Chen, K.T. Wheeler, M.J. Welch, R.H. Mach, J. Med. Chem. 50 (2007) 3194–3204.
[17] R.H. Mach, C.R. Smith, I. al-Nabulsi, B.R. Whirett, S.R. Childers, K.T. Wheeler, Cancer Res. 57 (1997) 156–161.
[18] M.S. Ostenfeld, N. Fehrenbacher, M. Hoyer-Hansen, C. Thomsen, T. Farkas, M. Jaattela, Cancer Res. 65 (2005) 8975–8983.
[19] K.W. Crawford, W.D. Bowen, Cancer Res. 62 (2002) 313–322.
[20] S. Narayanan, R. Bhat, C. Mesangeau, J.H. Poupaert, C.R. McCurdy, Future Med. Chem. 3 (2011) 79–94.
[21] D.Y. Maeda, W. Williams, W.D. Bowen, A. Coop, Bioorg. Med. Chem. Lett. 10 (2000) 17–18.
[22] C.A. Maier, B. Wunsch, J. Med. Chem. 45 (2002) 4923–4930.
[23] S. Yous, W. Wallez, M. Belloir, D.H. Caignard, C.R. McCurdy, J.H. Poupaert, Med. Chem. Res. 14 (2005) 158–168.
[24] A.C. Gassiot, J. Charton, S. Girault-Mizi, P. Gilleron, M.A. Debreu-Fontaine, C. Sergheraert, P. Melnyk, Bioorg. Med. Chem. Lett. 15 (2005) 4828–4832.
[25] A.R. Hajipour, D. Fontanilla, U.B. Chu, M. Arbabian, A.E. Ruoho, Bioorg. Med. Chem. 18 (2010) 4397–4404.
[26] J. Perregaard, E.K. Moltzen, E. Meier, C. Sanchez, J. Med. Chem. 38 (1995) 1998–2008.
[27] R.H. Mach, Y. Huang, R.A. Freeman, L. Wu, S. Vangveravong, R.R. Luedtke, Bioorg. Med. Chem. Lett. 14 (2004) 195–202.
[28] C. Mesangeau, S. Narayanan, A.M. Green, J. Shaikh, N. Kaushal, E. Viard, Y.T. Xu, J.A. Fishback, J.H. Poupaert, R.R. Matsumoto, C.R. McCurdy, J. Med. Chem. 51 (2008) 1482–1486.
[29] Standard conditions for Suzuki were followed; see for example U. Jacquemard, S. Routier, N. Dias, A. Lansiaux, J.F. Goossens, C. Bailly, J.Y. Merour, Eur. J. Med. Chem. 40 (2005) 1087–1095.
[30] E.C. Nguyen, K.A. McCracken, Y. Liu, B. Pouw, R.R. Matsumoto, Neuropharmacology 49 (2005) 638–645.
[31] R.R. Matsumoto, W.D. Bowen, M.A. Tom, V.N. Vo, D.D. Truong, B.R. De Costa, Eur. J. Pharmacol. 280 (1995) 301–310.
[32] R.R. Matsumoto, J. Shaikh, L.L. Wilson, S. Vedam, A. Coop, Eur. Neuropsychopharmacol. 18 (2008) 871–881.
[33] R.R. Matsumoto, B. Pouw, Eur. J. Pharmacol. 401 (2000) 155–160.
[34] J.A. Fishback, C. Mesangeau, J.H. Poupaert, C.R. McCurdy, R.R. Matsumoto, Eur. J. Pharmacol. 653 (2011) 1–7.
[35] Y. Cheng, W.H. Prusoff, Biochem. Pharmacol. 22 (1973) 3099–3108.