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Novel indole-based sigma-2 receptor ligands: synthesis, structure–affinity relationship and antiproliferative activity†

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We report the synthesis and biological evaluation of a series of indole-based σ_2 receptor ligands derived from siramesine. *In vitro* competition binding assays showed that these analogues possessed high to moderate affinity and selectivity for σ_2 receptors. Structure–affinity relationship analyses of these indole-based σ_2 receptor ligands were performed. In the 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, **1a** and **1b** displayed significant and comparable antiproliferative activity in DU145, MCF7 and C6 cells to siramesine. In cell cycle analyses, compounds **1a**, **1b** and siramesine were found to induce a G_1 phase cell cycle arrest in DU145 cells using flow cytometry. The combination of 5,6-dimethoxy-isoindoline scaffold and *N*-(4-fluorophenyl)indole moiety was identified as a new σ_2 receptor ligand deserving further investigation as an antitumor agent.

1. Introduction

Two subtypes of sigma (σ) receptors, termed σ_1 and σ_2, have been identified.[1] Both subtypes display different distributions in the central nervous system and peripheral organs. The σ_1 receptor contains 223 amino acids with two transmembrane regions.[2,3] It functions as "ligand-operated receptor chaperone" and regulates various ion channels, G protein-coupled receptors, lipids, and other signaling proteins.[4,5] In contrast, the σ_2 receptor has not been cloned so far, and its molecular weight was estimated to be 21.5 kD. Recently, progesterone receptor membrane component 1 (PGRMC1) was reported as the putative σ_2 receptor binding site.[6]

It is interesting that both subtypes are expressed in a variety of human and rodent tumor cell lines.[7,8] However, the expression of the σ_2 receptor was found to be higher than that of the σ_1 receptor. In proliferating tumor cells, the density of the σ_2 receptor was about 8- to 10-fold higher than that in quiescent tumor cells.[9–11] Moreover, σ_2 receptor ligands can rapidly internalize into tumor cells and activate apoptosis *via* multiple pathways.[12–15] Thus, the σ_2 receptor may both serve as a receptor-based biomarker to distinguish different proliferative states of solid tumors and as a promising target for the treatment of cancer.[16]

In the past decades, morphans, indoles (siramesine analogues), granatanes, flexible benzamides and *N*-cyclohexylpiperazines have been reported to serve as selective σ_2 receptor ligands.[17] Among these ligands, siramesine (also known as Lu-28-179) and its analogues, conformationally flexible amines such as RHM-1, and PB28 analogues were more extensively investigated.[17] Their structures are presented in Fig. 1. Although clinical trials of siramesine for the treatment of depression and anxiety were paused in 2002, it proved to be non-toxic and well tolerated in humans. Most importantly, siramesine was demonstrated to induce cell death in many tumorigenic and immortalized cells *via* different apoptotic pathways.[12–14,18] To obtain selective σ_2 receptor ligands with antiproliferative activity, we used siramesine as the lead compound to design a series of novel indole-based compounds. It was reported that the indole residue and the butyl chain between the indole and the spirocyclic piperidine moieties were important to maintain the σ_2 receptor selectivity for siramesine derivatives.[17] We introduced different functional groups to develop new σ_2 receptor ligands. Moreover, we also introduced the substituents with fluorine atom to find PET radiotracers for σ_2 receptor tumor imaging. The design concept is shown in Fig. 2. First, by keeping the 4-fluorophenyl ring at the indole N-atom and the butyl chain constant,

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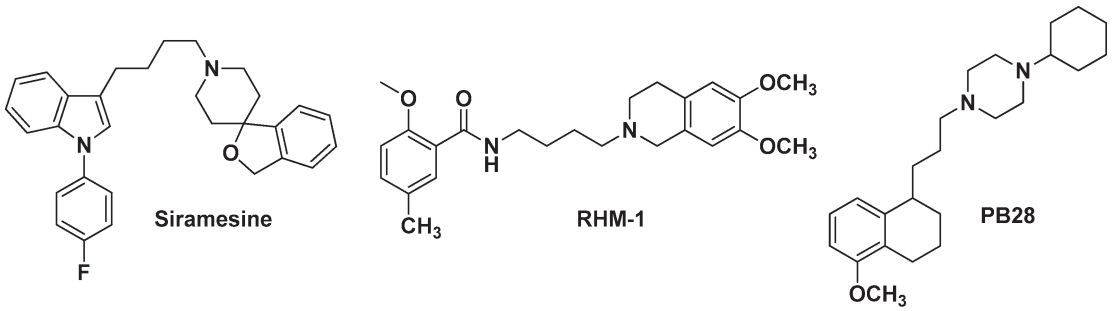


Fig. 1 The structures of siramesine, RHM-1 and PB28.

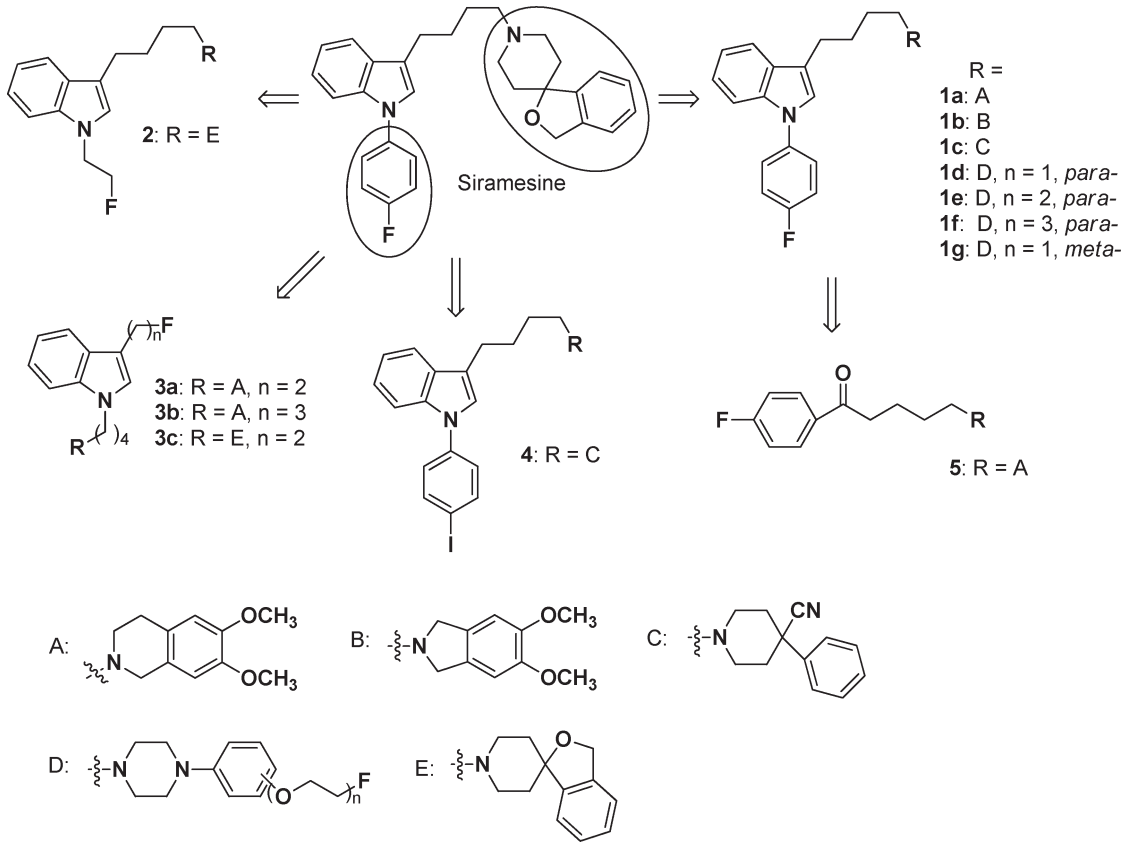


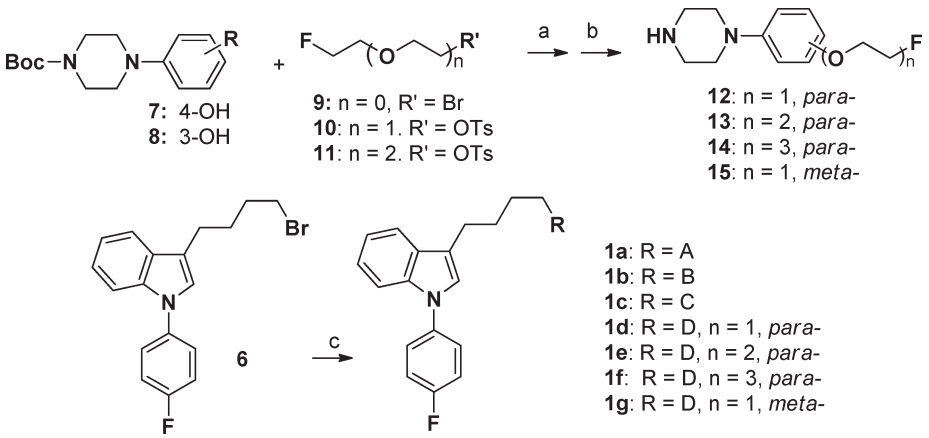
Fig. 2 Design concept of the indole-based compounds.

3*H*-spiro(2-benzofuran-1,4′-piperidinyl) moiety was replaced by different pharmacophores including σ_1 preferred group C and σ_2 preferred group A, B, or D (1). Secondly, the 4-fluorophenyl ring at the indole N-atom was replaced by a 2-fluoroalkyl group (2). As a third approach, both the 4-fluorophenyl ring at the indole N-atom and the 3*H*-spiro(2-benzofuran-1,4′-piperidinyl) moiety were modified (3). Fourth, 4-fluorophenyl was replaced by the 4-iodophenyl group, while the 3*H*-spiro(2-benzofuran-1,4′-piperidinyl) moiety was replaced by C (4). Finally, the indole core was replaced by 4-fluoro-benzophenone (5). Moreover, the structure–affinity relationships (SAR) of these analogues for σ_2 receptors were analyzed. The 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to investigate the antiproliferative activity of the most potent ligands. In order to further support this, cell cycle analysis was carried out to examine the effects of these potent compounds on the cell cycle progression using flow cytometry in DU145 cells.

2. Results and discussion

2.1 Chemistry

The synthetic routes of fluorophenylindole derivatives **1a–1g** are depicted in Scheme 1. All compounds in this series were prepared from the key bromobutyl derivative **6**. Compounds **6**,[19]



Scheme 1 Synthesis of fluorophenylindole derivatives **1a–1g**. Reagents and conditions: (a) K_2CO_3, NaI, DMF, 105 °C, overnight, 64–92%; (b) TFA, CH_2Cl_2, 0 °C, 2 h; (c) K_2CO_3, NaI, CH_3CN, 80 °C, 4 h, for **1a**, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**16**), 52%; for **1b**, 5,6-dimethoxyisoindoline (**17**), 52%; for **1c**, 4-phenylpiperidine-4-carbonitrile (**18**), 42%; for **1d–1g**, **12–15**, 16–83%.

12,[20] **15**[20] and **19**[21] were synthesized according to the method reported in the literature. Compound **7** or **8** reacted with intermediates **9–11** under basic conditions, followed by deprotection to obtain compounds **12–15** with yields of 56–95%. *N*-Alkylation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**16**), 5,6-dimethoxyisoindoline (**17**), 4-phenylpiperidine-4-carbonitrile (**18**) or **12–15** with compound **6** provided compounds **1a**, **1b**, **1c**, or **1d–1g**, respectively, with yields of 29–84%.

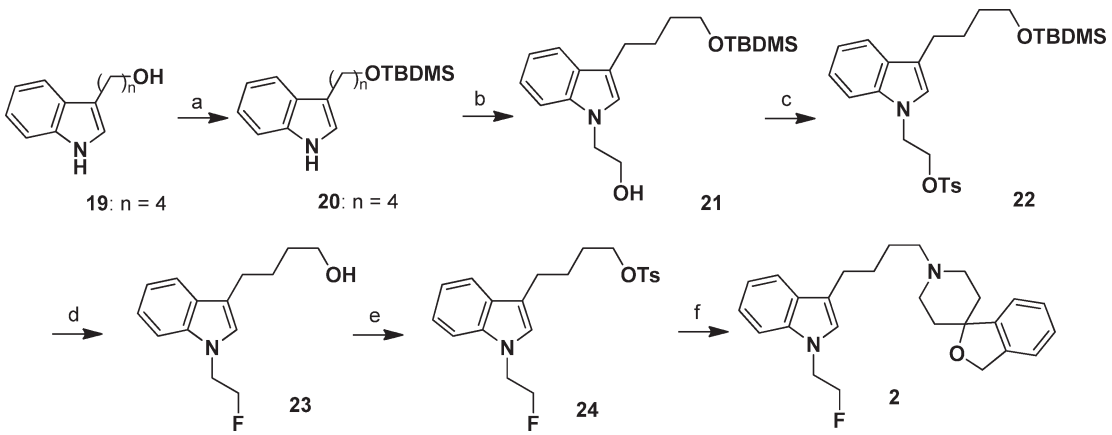
The synthetic route of compound **2** is presented in Scheme 2. Protection of compound **19** with TBDMS chloride, followed by *N*-alkylation of compound **20** with 2-bromoethanol and tosylation of compound **21** with *p*-TsCl provided compound **22**. Deprotection of TBDMS and fluorination of compound **22** with TBAF by a one-pot reaction afforded compound **23** with yield of 56%. Tosylation of compound **23** led to compound **24**, which reacted with 3*H*-spiro[2-benzofuran-1,4′-piperidine] (**25**) to obtain target compound **2**.

The synthetic routes of compounds **3a–3c** are depicted in Scheme 3. Reduction of indole-3-acetic acid (**26**) and indole-3-propanoic acid (**27**) with $LiAlH_4$ gave the corresponding alcohols **28** and **29** in 86% and 79% yield, respectively. Alkylation with 1,4-dibromobutane yielded **30** and **31**, followed by fluorination with DAST to obtain **32** and **33**. Finally, compound **32** or **33** reacted with intermediate **16** to provide **3a** and **3b**, respectively. Compound **32** reacted with **25** to obtain **3c**.

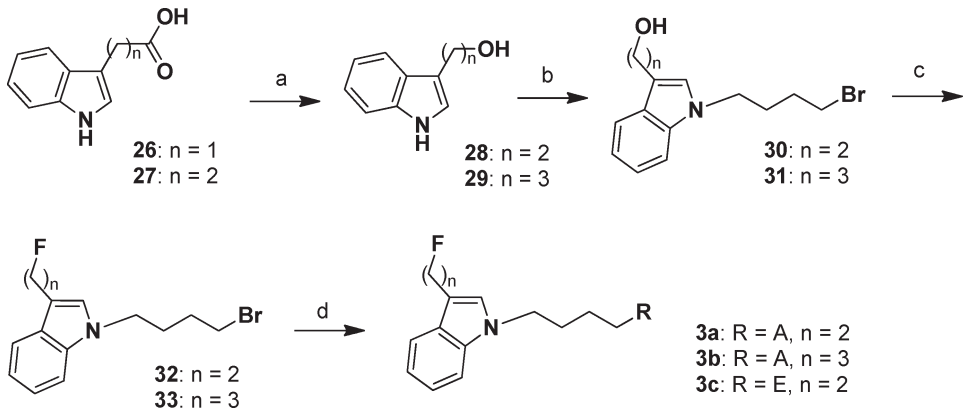
The synthetic routes of compounds **4** and **5** are depicted in Scheme 4. Synthesis of compound **4** was similar to that of compound **1c**. Ullmann reaction between compound **19** and 1,4-diiodobenzene[22] instead of the 4-fluorophenyl residue provided **34** which was subsequently treated with PBr_3 to yield **35**. Finally, reaction between **35** and intermediate **18** provided target compound **4**. *N*-Alkylation of intermediate **16** with 5-bromo-1-(4-fluorophenyl)pentan-1-one (**36**) gave compound **5** with yield of 62%.

2.2 *In vitro* radioligand competition studies and structure–affinity relationship analyses

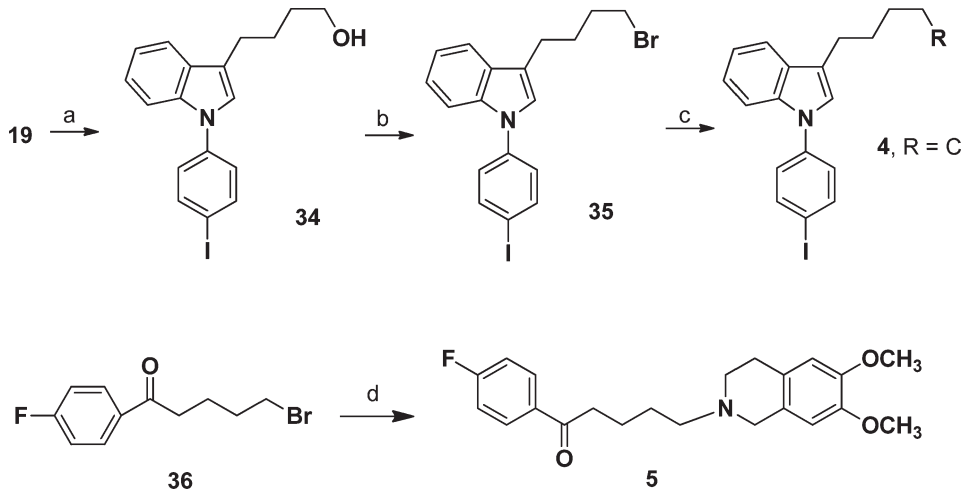
The affinities of the indole-based analogues for the σ_1 and σ_2 receptors were determined by radioligand competition binding



Scheme 2 Synthetic route of compound **2**. Reagents and conditions: (a) TBDMSCl, imidazole, CH_2Cl_2, r.t., 2 h, 84%; (b) Ar atmosphere, 110 °C, 2-bromoethanol, NaH, DMF, overnight, 37%; (c) *p*-TsCl, DIPEA, DMAP, THF, r.t., 2 h, 18%; (d) TBAF, THF, r.t., overnight, 56%; (e) *p*-TsCl, DIPEA, DMAP, THF, r.t., 2 h, 44%; (f) K_2CO_3, NaI, CH_3CN, 3*H*-spiro[2-benzofuran-1,4′-piperidine] (**25**), 80 °C, 4 h, 38%.



Scheme 3 Synthetic routes of compounds **3a**–**3c**. Reagents and conditions: (a) Ar atmosphere, 0 °C, $LiAlH_4$, anhydrous THF, 4 h, 86% for **28**, 79% for **29**; (b) Ar atmosphere, 110 °C, 1,4-dibromobutane, NaH, DMF, overnight, 19% for **30**, 34% for **31**; (c) Ar atmosphere, −78 °C, DAST, anhydrous CH_2Cl_2, 2 h, 58% for **32**, 87% for **33**; (d) K_2CO_3, NaI, CH_3CN, 80 °C, 4 h, for **3a**, **32**, **16**, 43%; for **3b**, **33**, **16**, 36%; for **3c**, **32**, **25**, 41%.



Scheme 4 Synthetic routes of compounds **4** and **5**. Reagents and conditions: (a) 1,4-diiodobenzene, K_2CO_3, copper powder, DMF, 120 °C, 5 h, 23%; (b) PBr_3, anhydrous CH_2Cl_2, 0 °C, 2 h, 58%; (c) K_2CO_3, NaI, CH_3CN, **18**, 80 °C, 4 h, 49%. (d) K_2CO_3, NaI, CH_3CN, **16**, 80 °C, 4 h, 62%.

assays as reported previously.[23] (+)-[^{3}H]Pentazocine and [^{3}H]1,3-di-*o*-tolyl-guanidine (in the presence of 10 μM dextrallorphan) were used as radioligands for the σ_1 and σ_2 receptors, respectively. The results are listed in Table 1.

It was reported that siramesine possessed a subnanomolar affinity ($IC_{50}(\sigma_2)$ = 0.12 nM) and high subtype selectivity ($IC_{50}(\sigma_1)$ = 17 nM, $IC_{50}(\sigma_1)/IC_{50}(\sigma_2)$ = 140) for σ_2 receptors.[24] More recently, Niso *et al.* revealed its high affinity ($K_i(\sigma_2)$ = 12.6 nM) and low subtype selectivity ($K_i(\sigma_1)/K_i(\sigma_2)$ = 0.83).[25] For comparison, we also synthesized this compound and our sample showed nanomolar affinity ($K_i(\sigma_2)$ = 3.08 nM) and low subtype selectivity ($K_i(\sigma_1)/K_i(\sigma_2)$ = 1.52), which is in good agreement with that reported by Niso *et al.*

Keeping the 4-fluorophenyl ring at the indole N-atom and the butyl chain constant, replacement of 3*H*-spiro(2-benzofuran-1,4′-piperidinyl) moiety with σ_1 preferred group C retained the low nanomolar affinity and non-selectivity for σ_2 receptors (**1c** *vs.* siramesine). On the other hand, replacement with σ_2 preferred group A, B, or D decreased the affinity for σ_2 receptors but increased the subtype selectivity. Compounds **1a**, **1b**, **1d** and **1g** showed moderate affinity ($K_i(\sigma_2)$ = 48.4–68 nM) and increased selectivity ($K_i(\sigma_1)/K_i(\sigma_2)$ = 4.8–10.7) compared to siramesine. Compound **1d** with substitution at the *para*-position of the phenyl ring in group D showed comparable affinity to compound **1g** with substitution at the *meta*-position but had a somewhat higher subtype selectivity. Substitution at the *para*-position with an increased length of the fluorooligoethoxylated chain (n = 2, 3) dramatically decreased the affinities for σ_1 and σ_2 receptors (**1e** and **1f**). In the literature, compound **1a** was reported to possess nanomolar affinity ($K_i(\sigma_2)$ = 5.34 nM) and high subtype selectivity ($K_i(\sigma_1)/K_i(\sigma_2)$ = 260) for σ_2 receptors.[25] However, our sample displayed only moderate affinity ($K_i(\sigma_2)$ = 49.2 nM) and selectivity ($K_i(\sigma_1)/K_i(\sigma_2)$ = 10.8). The above discrepancy may result from the different experimental conditions employed by different groups. It is interesting to note that compound **1b** with the 5,6-dimethoxyisoindoline moiety displayed comparable affinity and selectivity to compound

Table 1 Binding affinities of indole-based analogues for σ_1 and σ_2 receptors[a]

Compound	$K_i(\sigma_1)$ (nM)	$K_i(\sigma_2)$ (nM)	$K_i(\sigma_1)/K_i(\sigma_2)$
1a	530.8 ± 181.1	49.2 ± 11.7	10.8
1a[b]	1390 ± 20	5.34 ± 1.22	260
1b	255.6 ± 14.8	53.8 ± 1.4	4.8
1c	2.58 ± 0.82	3.03 ± 0.75	0.9
1d	614 ± 137	68.0 ± 0.04	9.0
1e	1110 ± 252	458 ± 51	2.4
1f	2158 ± 404	1879 ± 11	1.1
1g	257 ± 62.8	48.4 ± 2.65	5.3
2	246 ± 59.4	44.0 ± 28.1	5.6
3a	493.5 ± 84.1	27.5 ± 0.7	17.9
3b	262.5 ± 62.9	28.5 ± 4.9	9.2
3c	11.0 ± 0.5	29.8 ± 1.6	0.4
4	386 ± 94	18.5 ± 5.7	20.9
5	16.6 ± 1.1	12.4 ± 0.6	1.3
Siramesine	4.69 ± 2.36	3.08 ± 0.68	1.5
Siramesine[b]	10.5 ± 2.6	12.6 ± 0.1	0.8
Siramesine[c]	17	0.12	140
ISO-1	102.3 ± 15.1	28.2 ± 0.9	3.6
ISO-1[d]	330 ± 25	6.95 ± 1.63	47.5

[a] Values are means ± standard deviation (SD) of three experiments performed in triplicate. [b] From ref. 25. [c] IC_{50} value, from ref. 24. [d] From ref. 27.

1a. In the literature, 5-bromo-*N*-[4-(5,6-dimethoxyisoindolin-2-yl)butyl]-2,3-dimethoxybenzamide ($K_i(\sigma_2)$ = 0.82 nM) was found to possess ten-fold higher affinity for σ_2 receptors compared to 5-bromo-*N*-{4-[6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]butyl}-2,3-dimethoxybenzamide ($K_i(\sigma_2)$ = 8.2 ± 1.4 nM).[26] These data indicate that the 5,6-dimethoxyisoindoline moiety is a promising σ_2 preferred group with less lipophilicity.

To evaluate a suitable approach for future fluorine-18 radiotracer development for imaging of σ_2 receptors by positron emission tomography, a fluoroalkyl group was introduced. Replacement of the 4-fluorophenyl ring at the indole N-atom with a 2-fluoroethyl residue decreased the affinity for σ_2 receptors but slightly increased the subtype selectivity (**2** *vs.* siramesine). Compounds **3a** and **3b** with the σ_2 preferred group A displayed comparable affinity for σ_2 receptors to ISO-1.[27] However, compound **3b** with a 3-fluoropropyl group showed decreased selectivity in comparison to compound **3a** with a 2-fluoroethyl group. Replacement of σ_2 preferred group A with 3*H*-spiro(2-benzofuran-1,4′-piperidinyl) moiety increased the σ_1 affinity significantly and thus decreased the selectivity (**3c** *vs.* **3a**). Moreover, replacement of 1-(4-fluorophenyl) moiety with 1-(4-iodophenyl) group slightly decreased the affinity for σ_2 receptors but increased the selectivity (**4** *vs.* **1c**). Replacement of the whole indole moiety with 1-(4-fluorophenyl)carbonyl group dramatically increased the affinity for σ_1 receptors (**5** *vs.* **1a**, **5** *vs.* **3a**, **5** *vs.* **3b**), indicating the high importance of the indole moiety to retain the selectivity for σ_2 receptors.

2.3 Antiproliferative activity

Recently, a series of compounds with the indole moiety were reported to display antiproliferative activity in MCF7 and MCF7/adr cells.[25] In order to find new scaffolds and new σ_2 receptor ligands as potent antitumor agents, antiproliferative activity of compounds **1a** and **1b** was evaluated in MCF7 (breast cancer), DU145 (androgen-independent human prostate cancer) and C6 (rat glioma) cells using the MTT assay. Antiproliferative activity of siramesine was also determined in these cells as comparison. The effects of these compounds on cellular viability were analyzed using different concentrations between 100 nM and 100 μM. The results expressed as EC_{50} values are shown in Table 2. All EC_{50} values were found to be in the micromolar range. Compound **1a** and siramesine showed notable antiproliferative effects in MCF7 cells with EC_{50} values of 20.9 and 23.6 μM, respectively, which are consistent with that reported in the literature (with EC_{50} values of 17.8 and 12.3 μM, respectively).[25] It is interesting to note that the new compound **1b** exhibited the highest activity in MCF7 cells. Moreover, compound **1b** displayed notable and comparable antiproliferative effects to compound **1a** and siramesine in DU145 cells. However, all of the three compounds displayed a higher EC_{50} value in C6 cells than those in the human DU145 and MCF7 tumor cells. Besides compound **1a** and siramesine, the indole-based compound **1b** with the 5,6-dimethoxyisoindoline moiety seems to be promising as an anti-tumor agent and warrants further evaluation.

2.4 Cell cycle analysis

To further examine the antitumor activity of compounds **1a** and **1b**, their effects on the cell cycle progression were analyzed by flow cytometry in DU145 cells. Cell cycle phase distribution in control DU145 cells and cells treated with different concentrations of **1a**, **1b** and siramesine at 24 h time point is presented in Fig. 3. The percentages of G_1, S and G_2 phases of the untreated DU145 cells (control) are 58.2%, 38.6% and 3.25%, respectively. Treatment with compound **1a** or **1b** or siramesine increased the percentage of G_1 cells in a dose-dependent manner. After treatment with 40 μM **1a** or 30 μM **1b**, the percentages of G_1 cells increased to 84.1% and 80.5%, respectively. At the same time, the percentages of S cells decreased to 15.9% and 19.3%, respectively. The percentage of G_1 phase cells was maintained at 75.7–77.2% after treatment with 15 to 25 μM siramesine. These data suggest that compounds **1a** and **1b** and siramesine could induce cell cycle delay and arrest the cell cycle progression predominantly at the G_1 phase in DU145 cells. It was reported that σ_2

Table 2 EC_{50} values of compounds **1a** and **1b** in different tumor cells[a]

Cell lines	EC_{50} (μM)		
	1a	**1b**	Siramesine
MCF7	20.9 ± 6.3	17.0 ± 6.5	23.6 ± 7.8
MCF7[b]	17.8 ± 0.4	—	12.3 ± 0.6
DU145	28.8 ± 3.9	26.9 ± 6.9	13.9 ± 0.7
C6	76.5 ± 4.6	44.1 ± 9.9	43.1 ± 6.2

[a] Values are means ± standard deviation (SD) of two to three experiments performed in triplicate. [b] From ref. 25.

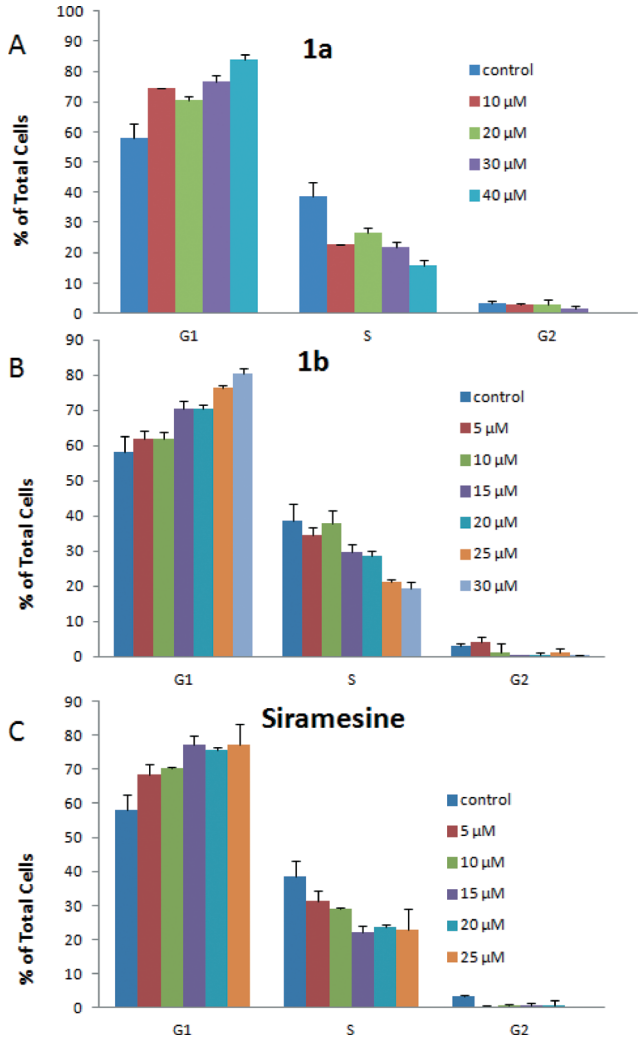


Fig. 3 Cell cycle phase distribution in control DU145 cells and cells treated with different concentrations of **1a** (A), **1b** (B) and siramesine (C) at 24 h time point.

ligands can induce the tumor cell death by multiple signaling pathways.[15] 10 μM siramesine decreased the expression levels of cyclin D1, which are responsible for progression through the G_1 phase in MDA-MB-435 cells in a time-dependent manner. Thus, siramesine may block G_1-phase progression by decreasing cyclin D1 expression. In addition, siramesine also mainly decreased cyclin B1 and pRb in MDA-MB-435 cells. The investigation of the detailed mechanism in which compounds **1a** and **1b** impair the G_1 phase of the cell cycle progression in DU145 cells is in progress.

3. Conclusion

We have developed a series of indole-based σ_2 receptor ligands derived from siramesine. Structure–affinity relationship analyses indicated the high importance of the indole moiety and σ_2 preferred group to improve the selectivity for σ_2 receptors. In the MTT experiments, compound **1b** displayed notable and comparable antiproliferative effects to compound **1a** and siramesine in DU145 cells and exhibited the highest activity in MCF7 cells. Cell cycle analysis by flow cytometry demonstrated that compounds **1a**, **1b** and siramesine impaired the cell cycle progression predominantly at the G_1 phase in DU145 cells. The indole-based compound **1b** with the 5,6-dimethoxyisoindoline moiety shows potential as an antitumor agent and warrants further evaluation.

4. Experiments

4.1. Chemistry

All the chemicals or reagents were purchased from chemical suppliers and used without further purification unless otherwise noted. NMR spectra were recorded on a Varian Inova-400 spectrometer or on a Bruker Avance III NMR spectrometer at 400 (^{1}H), 376 (^{19}F), and 100 MHz (^{13}C), respectively. The chemical shifts of the spectra were reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard, and coupling constants are reported in Hertz (Hz). MS spectra were obtained using a Xevo TQ-S spectrometer (Waters) with electrospray (ESI) as the ionization method. High-resolution mass spectrometry (HRMS) was performed on a LCT Premier XE ESI-TOF mass spectrometry instrument (Waters, USA). Chromatographic separations were carried out using Merck Silica Gel 60 (63–200 μm). TLC detections were carried out using Merck Silica Gel 60 F_{254} sheets and TLCs were developed by visualization under UV light (λ = 254 nm). Microanalyses were carried out using a Hekatech CHNS elemental analyser EuroEA 3000 or an Elementar 240C device (PerkinElmer). The HPLC analyses were performed using an AGILENT 1100 HPLC (Agilent Technologies, USA) equipped with a DAD detector. Analyses were carried out using a Nucleodur C18 ISIS column (250 × 4 mm, 5 μm, Macherey-Nagel, Germany) with an eluent of acetonitrile/H_2O (0.1% TFA) (30 : 70) at a flow rate of 0.5 mL min^{-1}. Cell cycle analysis was performed using a BD FACSCalibur flow cytometer (BD Biosciences, California, USA), and DNA distributions were analyzed using Modfit LT MacIntel (Verity Software House, Topsham, ME, USA).

4.1.1. *tert*-Butyl 4-{4-[2-(2-fluoroethoxy)ethoxy]phenyl}piperazine-1-carboxylate (Boc-13). Compounds 7 (168 mg, 0.60 mmol) and **10** (190 mg, 0.72 mmol) were dissolved in CH_3CN (25 mL), followed by addition of K_2CO_3 (124 mg, 0.90 mmol) and NaI (27 mg, 0.18 mmol). The mixture was heated under reflux and stirred overnight. After cooling and filtration, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (PE (petroleum ether) : EE (ethyl acetate) = 1 : 1) to afford **Boc-13** (203 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92–6.80 (m, 4*H*), 4.59 (dt, *J* = 47.7, 4.2 Hz, 2*H*), 4.10 (t, *J* = 5.8 Hz, 2*H*), 3.86 (t, *J* = 5.0 Hz, 2*H*), 3.82 (dt, *J* = 29.8, 4.2 Hz, 2*H*), 3.57 (t, *J* = 5.0 Hz, 4*H*), 3.00 (t, *J* = 4.8 Hz, 4*H*), 1.48 (s, 9*H*).

4.1.2. *tert*-Butyl 4-(4-{2-[2-(2-fluoroethoxy)ethoxy]ethoxy}-phenyl)piperazine-1-carboxylate (Boc-14). The procedure described for the synthesis of **Boc-13** was applied to compounds 7 (152 mg, 0.55 mmol) and **11** (188 mg, 0.61 mmol) to afford **Boc-14** (171 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91–6.80 (m, 4*H*), 4.57 (dt, *J* = 47.7, 4.2 Hz, 2*H*), 4.09 (t, *J* =

4.8 Hz, 2*H*), 3.84 (t, *J* = 4.8Hz, 2*H*), 3.81–3.70 (m, 6*H*), 3.57 (t, *J* = 5.0 Hz, 4*H*), 3.00 (t, *J* = 4.8Hz, 4*H*), 1.48 (s, 9*H*).

4.1.3. *tert*-Butyl 4-[3-(2-fluoroethoxy)phenyl]piperazine-1-carboxylate (Boc-15). The procedure described for the synthesis of **Boc-13** was applied to compounds **8** (414 mg, 1.49 mmol) and **9** (188 mg, 2.90 mmol) to afford **Boc-15** (311 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.2 Hz, 1*H*), 6.57 (d, *J* = 8.2 Hz, 1*H*), 6.51 (s, 1*H*), 6.44 (d, *J* = 8.1 Hz, 1*H*), 4.74 (dt, *J* = 47.4, 4.1 Hz, 2*H*), 4.20 (dt, *J* = 27.9, 4.1 Hz, 2*H*), 3.57 (t, *J* = 4.7 Hz, 4*H*), 3.14 (t, *J* = 4.4 Hz, 4*H*), 1.48 (s, 9*H*).

4.1.4. General procedure for the syntheses of compounds 12, 13, 14, and 15. The Boc-protected group of compound **Boc-12**, **Boc-13**, **Boc-14**, or **Boc-15** was cleaved using TFA in dichloromethane solution at 0 °C for 1 h. Compounds **12–15** were obtained in nearly quantitative yields and used for the next step without further purification.

4.2. General procedure for the syntheses of 1a–1g

3-(4-Bromobutyl)-1-(4-fluorophenyl)-1*H*-indole (**6**) and the respective amine (**12–18**) were dissolved in CH_3CN, followed by addition of K_2CO_3. The mixture was heated under reflux and stirred overnight. After cooling and filtration, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (PE : EE = 1 : 1) to afford **1a–1g.**

4.2.1. 2-{4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]butyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1a). The synthesis of **1a** was similar to that reported in the literature.[25] 3-(4-Bromobutyl)-1-(4-fluorophenyl)-1*H*-indole (**18**) (321 mg, 0.92 mmol), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**5**) (176 mg, 0.77 mmol) and K_2CO_3 (233 mg, 1.69 mmol) dissolved in CH_3CN (25 mL) afforded **1a** (185 mg, 44%) as light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.66 (m, 1*H*), 7.50–7.40 (m, 3*H*), 7.28–7.13 (m, 4*H*), 7.10 (s, 1*H*), 6.60 (s, 1*H*), 6.52 (s, 1*H*), 3.85 (s, 3*H*), 3.84 (s, 3*H*), 3.57 (s, 2*H*), 2.90–2.80 (m, 4*H*), 2.72 (t, *J* = 5.9 Hz, 2*H*), 2.62–2.54 (m, 2*H*), 1.89–1.82 (m, 2*H*), 1.82–1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 147.5, 147.2, 136.3, 136.0, 128.9, 126.1, 125.8, 125.7, 125.1, 122.4 (2C), 119.7, 119.3, 117.7, 116.3 (2C), 111.3, 110.1, 109.5, 58.1, 55.9 (2C), 55.7, 51.0, 28.5, 27.9, 27.1, 24.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ –116.0; MS (ESI^+): *m*/*z* = calcd. for $C_{29}H_{31}FN_2O_2$ $[M + H]^+$ 459.2, found 459.0; HRMS (EI): *m*/*z* calcd. for $C_{29}H_{31}FN_2O_2$ $[M + H]^+$ 459.2448, found 459.2441. Anal. calcd. for $C_{29}H_{31}FN_2O_2 \cdot 3/4H_2O$ (472.08): C 73.78, H 6.94, N 5.93; found: C 73.52, H 6.83, N 5.74.

4.2.2. 3-[4-(5,6-Dimethoxyisoindolin-2-yl)butyl]-1-(4-fluorophenyl)-1*H*-indole (1b). Compounds **6** (233 mg, 0.67 mmol) and **17** (119 mg, 0.67 mmol) and K_2CO_3 (144 mg, 1.04 mmol) in CH_3CN (25 mL) afforded **1b** as brown solid (156 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.69 (m, 1*H*), 7.49–7.41 (m, 3*H*), 7.25–7.15 (m, 4*H*), 7.11 (s, 1*H*), 6.74 (s, 2*H*), 3.91 (s, 4*H*), 3.86 (s, 6*H*), 2.87 (t, *J* = 7.4 Hz, 2*H*), 2.79 (t, *J* = 7.4 Hz, 2*H*), 1.92–1.83 (m, 2*H*), 1.78–1.67 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 148.4 (2C), 136.3, 136.0, 131.6 (2C), 128.9, 125.8, 125.1, 122.4 (2C), 119.7, 119.3, 117.8, 116.3 (2C), 110.1, 106.8 (2C), 59.2 (2C), 56.1 (2C), 28.9, 27.8 (2C), 24.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ –116.0; MS (ESI^+): *m*/*z* = calcd. for $C_{28}H_{29}FN_2O_2$ $[M + H]^+$ 445.2, found 445.2; HRMS (EI): *m*/*z* calcd. for $C_{28}H_{29}FN_2O_2$ $[M + H]^+$ 445.2291, found 445.2296. Anal. calcd. for $C_{28}H_{29}FN_2O_2$ (444.54): C 75.65, H 6.58, N 6.30; found: C 75.14, H 6.62, N 6.30.

4.2.3. 1-{4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]butyl}-4-phenylpiperdine-4-carbonitrile (1c). Compounds **6** (121 mg, 0.35 mmol) and **18** (89 mg, 0.48 mmol) and K_2CO_3 (483 mg, 3.5 mmol) in CH_3CN (25 mL) afforded **1c** as light-yellow oil (66 mg, 42%). ^{1}H NMR (400 MHz, MeOD) δ 7.52 (d, *J* = 7.7 Hz, 1*H*), 7.44–7.36 (m, 4*H*), 7.36–7.27 (m 3*H*), 7.25–7.20 (m, 1*H*), 7.19–7.10 (m, 3*H*), 7.09–7.04 (m, 1*H*), 7.03–6.98 (m, 1*H*), 2.94 (d, *J* = 12.1 Hz, 2*H*), 2.75 (t, *J* = 7.3 Hz, 2*H*), 2.39 (t, *J* = 7.7 Hz, 2*H*), 2.36–2.26 (m, 2*H*), 1.98 (t, *J* = 7.7 Hz, 4*H*), 1.75–1.65 (m, 2*H*), 1.61–1.51 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 136.4, 135.8, 129.5, 129.1, 128.5 (2C), 126.0, 125.9, 125.6 (2C), 122.7, 120.4 (2C), 120.1, 119.1. 116.6, 116.3 (2C), 110.4, 57.7, 50.4 (2C), 41.9, 33.5 (2C), 27.3, 24.5, 23.6; MS (ESI^+): *m*/*z* = calcd. for $C_{30}H_{30}FN_3$ $[M + H]^+$ 452.3, found 452.7; HRMS (EI): *m*/*z* calcd. for $C_{30}H_{30}FN_3$ $[M + H]^+$ 452.2502, found 452.2505. Anal. calcd. for $C_{30}H_{30}FN_3 \cdot HCl \cdot 1/4H_2O$: C 73.16, N 8.53, H 6.45; found: C 73.19, N 8.48, H 6.69.

4.2.4. 3-(4-{4-[4-(2-Fluoroethoxy)phenyl]piperazin-1-yl}butyl)-1-(4-fluorophenyl)-1*H*-indole (1d). Compounds **6** (180 mg, 0.52 mmol) and **12** (132 mg, 0.59 mmol) and K_2CO_3 (680 mg, 4.92 mmol) in CH_3CN (25 mL) afforded **1d** as white solid (210 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.6 Hz, 1*H*), 7.48–7.40 (m, 3*H*), 7.24–7.12 (m, 4*H*), 7.08 (s, 1*H*), 6.93–6.83 (m, 4*H*), 4.71 (dt, *J* = 47.4, 4.1 Hz, 2*H*), 4.16 (dt, *J* = 27.9, 4.2 Hz, 2*H*), 3.10 (t, *J* = 4.8 Hz, 4*H*), 2.84 (t, *J* = 7.4 Hz, 2*H*), 2.61 (t, *J* = 4.7 Hz, 4*H*), 2.46 (t, *J* = 7.6 Hz, 2*H*), 1.86–1.75 (m, 2*H*), 1.72–1.61 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 152.5, 146.3, 136.4, 136.1, 128.9, 125.9 (2C), 125.1, 122.5, 119.8, 119.4, 118.0 (2C), 117.8, 116.4 (2C), 115.5 (2C), 110.2, 82.1, 67.7, 58.6 (2C), 53.4, 50.4 (2C), 28.0, 26.9, 25.0; MS (ESI^+): *m*/*z* = calcd. for $C_{30}H_{33}F_2N_3O$ $[M + H]^+$ 490.3, found 490.6. Anal. calcd. for $C_{30}H_{33}F_2N_3O$ (489.60): C 73.60, H 6.79, N 8.58; found: C 73.99, H 7.12, N 8.26.

4.2.5 3-[4-(4-{4-[2-(2-Fluoroethoxy)ethoxy]phenyl}piperazin-1-yl)butyl]-1-(4-fluorophenyl)-1*H*-indole (1e). Compounds **6** (488 mg, 1.41 mmol) and **13** (138 mg, 0.51 mmol) and K_2CO_3 (84 mg, 0.61 mmol) in CH_3CN (25 mL) afforded **1e** as light-yellow oil (43 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (t, *J* = 7.6 Hz, 1*H*), 7.50–7.40 (m, 3*H*), 7.24–7.13 (m, 4*H*), 7.08 (s, 1*H*), 6.91–6.82 (m, 4*H*), 4.58 (dt, *J* = 47.7, 4.1 Hz, 2*H*), 4.09 (t, *J* = 4.8 Hz, 2*H*), 3.89–3.75 (m, 4*H*), 3.10 (t, *J* = 4.7 Hz, 4*H*), 2.84 (t, *J* = 7.4 Hz, 2*H*), 2.62 (t, *J* = 4.5 Hz, 4*H*), 2.46 (t, *J* = 7.6 Hz, 2*H*), 1.85–1.74 (m, 2*H*), 1.72–1.62 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 152.8, 146.0, 136.3, 136.0, 128.9, 125.8, 125.8 (2C), 125.1, 122.5, 119.6 (2C), 118.0 (2C), 117.8, 116.4, 115.4 (2C), 110.2, 83.2, 70.6, 70.1, 68.0, 58.6 (2C), 53.4, 50.5 (2C), 28.0, 26.8, 25.0. HRMS (EI): *m*/*z* calcd. for $C_{32}H_{37}F_2N_3O_2$ $[M + H]^+$ 534.2932, found 534.2916.

4.2.6. 3-{4-[4-(4-{2-[2-(2-Fluoroethoxy)ethoxy]ethoxy}-phenyl)piperazin-1-yl]butyl}-1-(4-fluorophenyl)-1*H*-indole (1f). Compounds **6** (142 mg, 0.41 mmol) and **14** (129 mg, 0.41

mmol) and K_2CO_3 (70 mg, 0.51 mmol) in CH_3CN (25 mL) afforded **1f** (68 mg, 29%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 7.6 Hz, 1*H*), 7.48–7.40 (m, 3*H*), 7.24–7.14 (m, 4*H*), 7.08 (s, 1*H*), 6.91–6.82 (m, 4*H*), 4.56 (dt, J = 47.7, 4.1 Hz, 2*H*), 4.08 (t, J = 4.8 Hz, 2*H*), 3.83 (t, J = 4.8 Hz, 2*H*), 3.80–3.68 (m, 6*H*), 3.10 (t, J = 4.7 Hz, 4*H*), 2.84 (t, J = 7.4 Hz, 2*H*), 2.61 (t, J = 4.8 Hz, 4*H*), 2.46 (t, J = 7.6 Hz, 2*H*), 1.85–1.75 (m, 2*H*), 1.74–1.63 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 152.9, 145.9, 136.3, 136.0, 128.9, 125.8, 125.7, 125.1, 122.4, 119.5 (2C), 118.0 (2C), 117.7, 116.3 (2C), 115.3 (2C), 110.1, 83.1, 70.8, 70.5, 70.3, 69.9, 67.8, 58.6, 53.4 (2C), 50.5 (2C), 27.9, 26.8, 24.9; MS (ESI$^+$): m/z = calcd. for $C_{34}H_{41}F_2N_3O_3$ $[M + H]^+$ 577.3, found 577.4. Anal. calcd. for $C_{34}H_{41}F_2N_3O_3{\cdot}2HCl{\cdot}H_2O$ (668.64): C 61.07, H 6.78, N 6.28; found: C 61.47, H 6.80, N 6.38.

4.2.7. 3-(4-{4-[3-(2-Fluoroethoxy)phenyl]piperazin-1-yl}butyl)-1-(4-fluorophenyl)-1*H*-indole (1g). Compounds **6** (259 mg, 0.75 mmol) and **15** (168 mg, 0.75 mmol) and K_2CO_3 (132 mg, 0.97 mmol) in CH_3CN (25 mL) afforded **1g** as light-yellow oil (130 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.61 (m, 1*H*), 7.47–7.39 (m, 3*H*), 7.22–7.11 (m, 5*H*), 7.07 (s, 1*H*), 6.59–6.53 (m, 1H), 6.49 (t, J = 2.3 Hz, 1H), 6.44–6.36 (m, 1*H*), 4.71 (dt, J = 47.1, 4.2 Hz, 2*H*), 4.17 (dt, J = 27.8, 4.2 Hz, 2*H*), 3.18 (t, J = 5.2 Hz, 4*H*), 2.83 (t, J = 7.4 Hz, 2*H*), 2.57 (t, J = 5.0 Hz, 4*H*), 2.43 (t, J = 7.6 Hz, 2*H*), 1.87–1.71 (m, 2*H*), 1.73–1.60 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 159.4, 152.7, 136.3, 136.0, 129.7, 128.8, 125.8 (2C), 125.1, 122.4, 119.8, 119.3, 117.7, 116.3 (2C), 110.1, 109.3, 104.6, 103.2, 82.0, 67.0, 58.6, 53.2 (2C), 48.9 (2C), 27.9, 26.8, 24.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −120.7, −228.6; MS (ESI$^+$): m/z = calcd. for $C_{30}H_{33}F_2N_3O$ $[M + H]^+$ 490.3, found 490.5; HRMS (EI): m/z calcd. for $C_{30}H_{33}F_2N_3O$ $[M + H]^+$ 490.2670, found 490.2673. Anal. calcd. for $C_{30}H_{33}F_2N_3O{\cdot}H_2O$ (507.61): C 70.98, H 6.95, N 8.28; found: C 71.18, H 6.87, N 8.01.

4.2.8. 3-{4-[(*tert*-Butyldimethylsilyl)oxy]butyl}-1*H*-indole (20). To a solution of **19** (2.10 g, 11.1 mmol) in CH_2Cl_2 (40 mL), TBDMSCl (2.06 g, 13.7 mmol) and imidazole (1.43 g, 21.0 mmol) were added. The mixture was stirred at room temperature for 2 h. After filtration, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (PE : EE = 1 : 5) to afford **20** (2.80 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.58 (d, J = 7.9 Hz, 1*H*), 7.32 (d, J = 8.1 Hz, 1*H*), 7.20–7.13 (m, 1*H*), 7.12–7.04 (m, 1*H*), 6.95 (s, 1*H*), 3.63 (t, J = 6.5 Hz, 2*H*), 2.75 (t, J = 7.5 Hz, 2*H*), 1.80–1.68 (m, 2*H*), 1.65–1.58 (m, 2*H*), 0.87 (s, 9*H*).

4.2.9. 2-(3-{4-[(*tert*-Butyldimethylsilyl)oxy]butyl}-1*H*-indol-1-yl)ethanol (21). To a solution of compound **20** (1.88 g, 6.19 mmol) in DMF, 2-bromoethanol (1.23 g, 9.92 mmol) and NaH (240 mg, 10.0 mmol) were added. The mixture was stirred at 110 °C overnight. After cooling, the crude product was extracted with ethyl acetate, dried with anhydrous $MgSO_4$, and purified by silica gel column chromatography (PE : EE = 5 : 1) to afford **21** (805 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.9 Hz, 1*H*), 7.30 (d, J = 8.2 Hz, 1*H*), 7.20–7.15 (m, 1*H*), 7.10–7.05 (m, 1*H*), 6.91 (s, 1*H*), 4.21 (t, J = 5.3 Hz, 2*H*), 3.92 (t, J = 5.3 Hz, 2*H*), 3.62 (t, J = 6.4 Hz, 2*H*), 2.73 (t, J = 7.5 Hz, 2*H*), 1.79–1.65 (m, 2*H*), 1.65–1.53 (m, 2*H*), 0.87 (s, 9*H*).

4.2.10. 2-(3-{4-[(*tert*-Butyldimethylsilyl)oxy]butyl}-1*H*-indol-1-yl)ethyl 4-methylbenzenesulfonate (22). Compound **21** (805 mg, 2.32 mmol), TsCl (661 mg, 3.48 mmol), DIPEA (450 mg, 3.48 mmol), and DMAP (425 mg, 3.48 mmol) were dissolved in 30 mL of THF. The mixture was stirred at room temperature for 2 h. After the solvent was removed under reduced pressure, the crude product was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (PE : EE = 10 : 1) to afford **22** (208 mg, 18%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.56 (m, 1*H*), 7.49 (d, J = 8.3 Hz, 2*H*), 7.17–7.04 (m, 5*H*), 6.80 (s, 1*H*), 4.36–4.24 (m, 4*H*), 3.72 (t, J = 6.3 Hz, 2*H*), 2.75 (t, J = 7.5 Hz, 2*H*), 2.36 (s, 3*H*), 1.86–1.73 (m, 2*H*), 1.73–1.64 (m, 2*H*), 0.97 (s, 9*H*).

4.2.11. 4-[1-(2-Fluoroethyl)-1*H*-indol-3-yl]butan-1-ol (23). TBAF (345 mg, 1.32mmol) and **22** (265 mg, 0.53 mmol) were added into THF (20 mL). The mixture was stirred at room temperature overnight. After the solvent was removed under reduced pressure, the crude product was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (PE : EE = 3 : 1) to afford **23** (69 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 7.9 Hz, 1*H*), 7.30 (d, J = 8.1 Hz, 1*H*), 7.43–7.21 (m, 2*H*), 7.17–7.10 (m, 1*H*), 6.95 (s, 1*H*), 4.69 (dt, J = 47.0, 5.0 Hz, 2*H*), 4.35 (dt, J = 25.7, 4.9 Hz, 2*H*), 3.68 (t, J = 6.5 Hz, 2*H*), 2.80 (t, J = 7.4 Hz, 2*H*), 1.87–1.75 (m, 2*H*), 1.75–1.63 (m, 2*H*).

4.2.12. 4-[1-(2-Fluoroethyl)-1*H*-indol-3-yl]butyl 4-methylbenzenesulfonate (24). To a solution of **23** (120 mg, 0.51 mmol) in THF (20 mL), TsCl (116 mg, 0.61 mmol), DIPEA (129 mg, 1.00 mmol), and DMAP (122 mg, 1.00 mmol) were added. The mixture was stirred at room temperature for 2 h. After the solvent was removed under reduced pressure, the crude product was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (PE : EE = 5 : 1) to afford **24** (88 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.3 Hz, 2*H*), 7.50 (d, J = 7.9 Hz, 1*H*), 7.32–7.16 (m, 4*H*), 7.11–7.05 (m, 1*H*), 6.86 (s, 1*H*), 4.66 (dt, J = 47.0, 5.0 Hz, 2*H*), 4.32 (dt, J = 25.8, 5.0 Hz, 2*H*), 4.07–3.99 (m, 2*H*), 2.68 (t, J = 6.7 Hz, 2*H*), 2.40 (s, 3*H*), 1.75–1.68 (m, 4*H*).

4.2.13. 1′-{4-[1-(2-Fluoroethyl)-1*H*-indol-3-yl]butyl}-3*H*-spiro[isobenzofuran-1,4′-piperidine] (2). To a solution of **24** (88 mg, 0.23 mmol) in 20 mL of CH_3CN, 3*H*-spiro[isobenzofuran-1,4′-piperidine] (**25**) (32 mg, 0.17 mmol) and K_2CO_3 (32 mg, 0.23 mmol) were added. The mixture was stirred at 80 °C for 4 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel chromatography (PE : EE = 1 : 1) to afford **2** (26 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.8 Hz, 1*H*), 7.31–7.25 (m, 3*H*), 7.24–7.20 (m, 2*H*), 7.18–7.09 (m, 2*H*), 6.96 (s, 1*H*), 5.08 (s, 2*H*), 4.70 (dt, J = 47.0, 5.0 Hz, 2*H*), 4.36 (dt, J = 25.5, 5.0 Hz, 2*H*), 2.90 (d, J = 11.2 Hz, 2*H*), 2.80 (t, J = 7.3 Hz, 2*H*), 2.49 (t, J = 10.0 Hz, 2*H*), 2.41 (t, J = 11.1 Hz, 2*H*), 2.07–1.97 (m, 2*H*),

1.84–1.63 (m, 6*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 139.1, 136.6, 128.5, 127.8, 127.6, 125.4, 121.9, 121.2, 121.1, 119.5, 119.1, 116.3, 109.1, 84.2, 81.8, 71.0, 59.1, 50.5 (2C), 46.5, 36.8 (2C), 28.5, 27.2, 25.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ –219.8; MS (ESI$^+$): *m*/*z* = calcd. for $C_{26}H_{31}FN_2O$ $[M + H]^+$ 407.2, found 407.2; HRMS (EI): *m*/*z* calcd. for $C_{26}H_{31}FN_2O$ $[M + H]^+$ 407.2499, found 407.2492; purity (HPLC): 95%.

4.2.14. 2-(1*H*-Indol-3-yl)ethanol (28). Under ice bath and argon atmosphere, a solution of **26** (1.00 g, 5.71 mmol) in THF (60 mL) was added to a solution of $LiAlH_4$ (642 mg, 17.1 mmol) in THF (40 mL). The mixture was stirred for 4 h at room temperature, followed by addition of ethanol until no H_2 was formed. Then 4 M hydrochloric acid was added to adjust the pH to 5. After filtration, the solution was concentrated under reduced pressure. The crude product was extracted with ethyl acetate, dried with anhydrous $MgSO_4$, and purified by silica gel column chromatography (PE : EE = 5 : 1) to afford alcohol **28** (795 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1*H*), 7.35 (d, *J* = 8.1 Hz, 1*H*), 7.21–7.16 (m, 1*H*), 7.13–7.09 (m, 1*H*), 7.06 (d, *J* = 2.1 Hz, 1*H*), 3.89 (t, *J* = 6.3 Hz, 2*H*), 3.02 (t, *J* = 6.3 Hz, 2*H*).

4.2.15. 3-(1*H*-Indol-3-yl)propan-1-ol (29). The procedure described for the synthesis of **28** was applied to **27** (3.00 g, 15.8 mmol) and $LiAlH_4$ (2.93 g, 77.2 mmol) to afford alcohol **29** (2.18 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1*H*), 7.65–7.55 (m, 1*H*), 7.37–7.30 (m, 1*H*), 7.23 (s, 1*H*), 7.19–7.14 (m, 1*H*), 7.12–7.07 (m, *J* = 8.0, 1*H*), 6.97 (s, 1*H*), 3.71 (t, *J* = 6.4 Hz, 2*H*), 2.90–2.78 (m, 2*H*), 2.04–1.93 (m, 2*H*).

4.2.16. 2-[1-(4-Bromobutyl)-1*H*-indol-3-yl]ethanol (30). Under ice bath and argon atmosphere, alcohol **28** (220 mg, 1.37 mmol), 1,4-dibromobutane (875 mg, 4.11 mmol), and NaH (98 mg, 4.11 mmol) were added into DMF (30 mL). The mixture was stirred at 110 °C overnight. After cooling and filtration, the crude product was extracted with ethyl acetate, dried with anhydrous $MgSO_4$, and purified by silica gel column chromatography (PE : EE = 3 : 1) to afford **30** (78 mg, 19%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.9 Hz, 1*H*), 7.30 (d, *J* = 8.2 Hz, 1*H*), 7.24–7.18 (m, 1*H*), 7.14–7.04 (m, 1*H*), 6.96 (s, 1*H*), 4.10 (t, *J* = 6.9 Hz, 2*H*), 3.87 (t, *J* = 6.4 Hz, 2*H*), 3.35 (t, *J* = 6.5 Hz, 2*H*), 3.00 (t, *J* = 6.4 Hz, 2*H*), 2.05–1.94 (m, 2*H*), 1.89–1.78 (m, 2*H*).

4.2.17. 3-[1-(4-Bromobutyl)-1*H*-indol-3-yl]propan-1-ol (31). The procedure described for the synthesis of **30** was applied to alcohol **29** (1.20 g, 6.86 mmol), 1,4-dibromobutane (4.38 g, 20.6 mmol), and NaH (329 mg, 13.7 mmol) to afford **31** (728 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.9 Hz, 1*H*), 7.29 (d, *J* = 8.2 Hz, 1*H*), 7.25–7.14 (m, 1*H*), 7.12–7.07 (m, 1*H*), 6.87 (s, 1*H*), 4.08 (t, *J* = 6.8 Hz, 2*H*), 3.70 (t, *J* = 6.4 Hz, 2*H*), 3.35 (t, *J* = 6.5 Hz, 2*H*), 2.84 (t, *J* = 7.5 Hz, 2*H*), 2.03–1.90 (m, 4*H*), 1.86–1.77 (m, 2*H*).

4.2.18. 1-(4-Bromobutyl)-3-(2-fluoroethyl)-1*H*-indole (32). Under argon atmosphere (–78 °C), a solution of DAST (352 mg, 2.18 mmol) in CH_2Cl_2 (20 mL) was added into a solution of **30** (538 mg, 1.82 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 2 h, followed by addition of saturated sodium hyposulfite to quench the reaction. The crude product was extracted with ethyl acetate, dried with anhydrous $MgSO_4$, and purified by silica gel column chromatography (PE : EE = 10 : 1) to afford **32** (315 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.9 Hz, 1*H*), 7.30 (d, *J* = 8.2 Hz, 1*H*), 7.23–7.18 (m, 1*H*), 7.14–7.08 (m, 1*H*), 6.96 (s, 1*H*), 4.67 (dt, *J* = 47.2, 6.7 Hz, 2*H*), 4.11 (t, *J* = 6.9 Hz, 2*H*), 3.36 (t, *J* = 6.5 Hz, 2*H*), 3.15 (dt, *J* = 22.2, 6.5 Hz, 2*H*), 2.03–1.95 (m, 2*H*), 1.90–1.79 (m, 2*H*).

4.2.19. 1-(4-Bromobutyl)-3-(3-fluoropropyl)-1*H*-indole (33). The procedure described for the synthesis of **32** was applied to DAST (205 mg, 1.28 mmol) and **31** (360 mg, 1.16 mmol) to afford **33** (315 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.9 Hz, 1*H*), 7.33 (d, *J* = 8.2 Hz, 1H), 7.28–7.22 (m, 1*H*), 7.17–7.11 (m, 1*H*), 6.92 (s, 1*H*), 4.53 (dt, *J* = 47.3, 5.9 Hz, 2*H*), 4.12 (t, *J* = 6.8 Hz, 2*H*), 3.38 (t, *J* = 6.5 Hz, 2*H*), 2.92 (t, *J* = 7.5 Hz, 2*H*), 2.19–2.05 (m, 2*H*), 2.04–1.96 (m, 2*H*), 1.90–1.81 (m, 2*H*).

4.2.20. 2-{4-[3-(2-Fluoroethyl)-1*H*-indol-1-yl]butyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3a). The procedure described for the synthesis of **3a** was applied to **32** (78 mg, 0.26 mmol), **16** (76 mg, 0.39 mmol), and K_2CO_3 (54 mg, 0.39 mmol) to afford **3a** (46 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.9 Hz, 1*H*), 7.31 (d, *J* = 8.2 Hz, 1*H*), 7.21–7.16 (m, 1*H*), 7.12–7.07 (m, 1*H*), 6.98 (s, 1*H*), 6.57 (s, 1*H*), 6.48 (s, 1*H*), 4.66 (dt, *J* = 47.2, 6.7 Hz, 2*H*), 4.11 (t, *J* = 7.0 Hz, 2*H*), 3.82 (s, 3*H*), 3.81 (s, 3*H*), 3.48 (s, 2*H*), 3.15 (dt, *J* = 22.1, 6.7 Hz, 2*H*), 2.78 (t, *J* = 5.7 Hz, 2*H*), 2.64 (t, *J* = 5.8 Hz, 2*H*), 2.48 (t, *J* = 5.8 Hz, 2*H*), 1.94–1.84 (m, 2*H*), 1.66–1.54 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 147.4, 136.4, 128.1, 126.7, 126.4, 126.3, 121.7, 119.1, 119.0, 111.6, 109.8, 109.8, 109.7, 84.1, 57.9, 56.1, 56.0, 51.3, 46.3, 28.9, 28.4, 26.9, 26.6, 24.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ –213.3. MS (ESI$^+$): *m*/*z* = calcd. for $C_{25}H_{31}FN_2O_2$ $[M + H]^+$ 411.2, found 411.1; HRMS (EI): *m*/*z* calcd. for $C_{25}H_{31}FN_2O_2$ $[M + H]^+$ 411.2448, found 411.2443; purity (HPLC): 95%.

4.2.21. 2-{4-[3-(3-Fluoropropyl)-1*H*-indol-1-yl]butyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3b). The procedure described for the synthesis of **3a** was applied to **33** (113 mg, 0.36 mmol), **16** (73 mg, 0.38 mmol), and K_2CO_3 (60 mg, 0.43 mmol) to afford **3b** (55 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.8 Hz, 1*H*), 7.33 (d, *J* = 8.2 Hz, 1*H*), 7.20 (t, *J* = 7.6 Hz, 1*H*), 7.11 (t, *J* = 7.4 Hz, 1*H*), 6.93 (s, 1*H*), 6.60 (s, 1*H*), 6.51 (s, 1*H*), 4.51 (dt, *J* = 47.4, 5.9 Hz, 2*H*), 4.13 (t, *J* = 7.0 Hz, 2*H*), 3.85 (s, 3*H*), 3.84 (s, 3*H*), 3.51 (s, 2*H*), 2.90 (t, *J* = 7.4 Hz, 2*H*), 2.81 (t, *J* = 5.6 Hz, 2*H*), 2.67 (t, *J* = 5.8 Hz, 2*H*), 2.51 (t, *J* = 7.3 Hz, 2*H*), 2.18–2.02 (m, 2*H*), 1.97–1.88 (m, 2*H*), 1.67–1.57 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 147.4, 136.6, 128.1, 126.8, 126.4, 125.6, 121.6, 119.2, 118.8, 113.9, 111.6, 109.7, 109.6, 83.7, 57.9, 56.1, 56.0, 51.3, 46.2, 31.3, 31.2, 28.9, 28.4, 24.9, 20.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ –220.5; MS (ESI$^+$): *m*/*z* = calcd. for $C_{26}H_{33}FN_2O_2$ $[M + H]^+$ 425.3, found 425.0; HRMS (EI): *m*/*z* calcd. for $C_{26}H_{33}FN_2O_2$ $[M + H]^+$ 425.2604, found 425.2601. Anal. calcd. for $C_{26}H_{33}FN_2O_2 \cdot 3/4H_2O$ (438.06): C 71.29, N 6.39, H 7.94; found: C 71.24, N 6.57, H 7.63.

4.2.22. 1′-{4-[3-(2-Fluoroethyl)-1*H*-indol-1-yl]butyl}-3*H*-spiro[isobenzofuran-1,4′-piperidine] (3c). To a solution of **32** (70 mg, 0.24 mmol) in CH_3CN (20 mL), **25** (45 mg, 0.24 mmol) and K_2CO_3 (40 mg, 0.29 mmol) were added. The mixture was stirred at 80 °C for 4 h. After cooling and filtration, the solvent

was removed under reduced pressure. The residue was purified by silica gel column chromatography (PE : EE = 1 : 5) to afford **3c** (40 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.9 Hz, 1*H*), 7.33 (d, J = 8.2 Hz, 1*H*), 7.29–7.16 (m, 4*H*), 7.15–7.07 (m, 2*H*), 6.99 (s, 1*H*), 5.06 (s, 2*H*), 4.66 (dt, J = 47.2, 6.7 Hz, 2*H*), 4.10 (t, J = 7.1 Hz, 2*H*), 3.16 (dt, J = 21.9, 6.7 Hz, 2*H*), 2.81 (d, J = 11.0 Hz, 2*H*), 2.47–2.29 (m, 4*H*), 2.03–1.81 (m, 4*H*), 1.75 (d, J = 12.5 Hz, 2*H*), 1.62–1.52 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 139.1, 136.4, 128.1, 127.8, 127.6, 126.3, 121.8, 121.3, 121.0, 119.1, 109.8, 109.8, 109.7, 84.9, 83.3, 71.0, 58.6, 50.4 (2C), 46.4, 36.8 (2C), 28.6, 26.8, 24.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ –213.2; MS (ESI$^+$): m/z = calcd. for $C_{26}H_{31}FN_2O$ $[M + H]^+$ 407.2, found 407.1; HRMS (EI): m/z calcd. for $C_{26}H_{31}FN_2O$ $[M + H]^+$ 407.2499, found 407.2501; purity (HPLC): 96%.

4.2.23. 4-[1-(4-Iodophenyl)-1*H*-indol-3-yl]butan-1-ol (34). Compound **19** (595 mg, 3.14 mmol), 1,4-diiodobenzene (780 mg, 2.36 mmol), K_2CO_3 (3.12 g, 23.6 mmol), a catalytic amount of copper powder, and 18-crown-6 were added into 25 mL of DMF. The mixture was stirred at 120 °C for 5 h. After cooling and filtration, the crude product was extracted with ethyl acetate and washed with 1 M HCl and saturated NaCl solution. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (PE : EE = 4 : 1) to afford **34** (208 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.72 (m, 2*H*), 7.57 (t, J = 7.6 Hz, 1*H*), 7.46 (t, J = 8.2 Hz, 1*H*), 7.18–7.08 (m, 4*H*), 7.03 (s, 1*H*), 3.64 (t, J = 6.5 Hz, 2*H*), 2.76 (t, J = 7.4 Hz, 2*H*), 1.80–1.73 (m, 2*H*), 1.67–1.60 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 138.6 (2C), 135.8, 129.2, 125.7, 124.6, 122.7 (2C), 120.1, 119.4, 118.3, 110.3, 90.0, 62.9, 32.6, 26.1, 24.8; MS (ESI$^+$): m/z = calcd. for $C_{18}H_{18}INO$ $[M + H]^+$ 392.0, found 392.2.

4.2.24. 3-(4-Bromobutyl)-1-(4-iodophenyl)-1*H*-indole (35). Under argon atmosphere and ice bath, PBr_3 (192 mg, 0.71 mmol) was added to a solution of **34** (550 mg, 1.41 mmol) in CH_2Cl_2. The mixture was stirred at room temperature for 2 h, followed by addition of saturated $NaHCO_3$ solution to quench the reaction. The crude product was extracted with ethyl acetate, dried with anhydrous $MgSO_4$, and purified by silica gel column chromatography (PE : EE = 4 : 1) to afford **35** (187 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (t, J = 8.2 Hz, 2*H*), 7.64 (t, J = 7.0 Hz, 1*H*), 7.52 (t, J = 8.1 Hz, 1*H*), 7.26–7.16 (m, 4*H*), 7.10 (s, 1*H*), 3.47 (t, J = 6.5 Hz, 2*H*), 2.83 (t, J = 7.24 Hz, 2*H*), 2.03–1.98 (m, 2*H*), 1.96–1.91 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 138.6 (2C), 135.8, 129.1, 125.7, 124.6, 122.7 (2C), 120.2, 119.4, 117.8, 110.4, 90.0, 33.8, 32.5, 28.4, 24.2; MS (ESI$^+$): m/z = calcd. for $C_{18}H_{17}BrIN$ $[M + H]^+$ 454.0, found 453.9.

4.2.25. 1-{4-[1-(4-Iodophenyl)-1*H*-indol-3-yl]butyl}-4-phenylpiperidine-4-carbonitrile (4). Compound **35** (163 mg, 0.36 mmol), 4-phenylpiperidine-4-carbonitrile (**18**) (147 mg, 0.72 mmol), K_2CO_3 (496 g, 3.60 mmol), and KI (64 mg, 0.39 mmol) were added into CH_3CN solution. The mixture was stirred at 80 °C for 4 h. After cooling and filtration, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (PE : EE = 2 : 1) to afford **4** (99 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.71 (m, 2*H*), 7.57 (d, J = 3.8 Hz, 1*H*), 7.46–7.41 (m, 3*H*), 7.34 (t, J = 7.2 Hz, 2*H*), 7.30–7.23 (m, 2*H*), 7.19–7.17 (m, 2*H*) 7.12–7.08 (m, 1*H*), 7.03 (s, 1*H*), 2.98 (d, J = 11.96 Hz, 2*H*), 2.76 (t, J = 7.36 Hz, 2*H*), 2.47–2.38 (m, 4*H*), 2.04 (s, 4*H*), 1.74–1.68 (m, 2*H*), 1.61–1.58 (m, 2*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 138.6 (2C), 137.6, 134.8, 128.2 (2C), 128.0, 127.1, 124.7 (2C), 124.6, 123.5, 121.7 (2C), 120.8, 119.1, 118.4, 117.3, 109.3, 88.9, 57.3, 49.8 (2C), 41.8, 35.4 (2C), 26.8, 25.7, 23.9; MS (ESI$^+$): m/z = calcd. for $C_{30}H_{30}IN_3$ $[M + H]^+$ 560.1, found 560.1. Anal. calcd. for $C_{30}H_{30}IN_3 \cdot HCl \cdot 1/2H_2O$ (604.95): C 59.56, N 6.95, H 5.33; found: C 59.76, N 6.82, H 5.17.

4.2.26. 2-{4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]butyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5). Compound **36** (279 mg, 1.08 mmol), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (153 mg, 0.67 mmol), and K_2CO_3 (220 mg, 1.59 mmol) were added into 25 mL of CH_3CN. The mixture was stirred at 80 °C for 4 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 20 : 1) to afford **5** (153 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.90 (m, 2*H*), 7.09–7.02 (m, 2*H*), 6.54 (s, 1*H*), 6.47 (s, 1*H*), 3.80 (s, 3*H*), 3.79 (s, 3*H*), 3.52 (s, 2*H*), 2.96 (t, J = 7.2 Hz, 2*H*), 2.77 (t, J = 5.8 Hz, 2*H*), 2.67 (t, J = 5.9 Hz, 2*H*), 2.52 (t, J =7.3 Hz, 2*H*), 1.82–1.71 (m, 2*H*), 1.71–1.61 (m, 2*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.6, 165.5, 147.5, 147.2, 133.3, 130.6 (2C), 126.5, 126.1, 115.6 (2C), 111.3, 109.4, 57.8, 55.9, 55.9, 55.7, 50.9, 38.2, 28.6, 26.6, 22.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ –106.7; MS (ESI$^+$): m/z = calcd. for $C_{22}H_{26}FNO_3$ $[M + H]^+$ 372.2, found 372.2; HRMS (EI): m/z calcd. for $C_{22}H_{26}FNO_3$ $[M + H]^+$ 372.1975, found 372.1972. Anal. calcd. for $C_{22}H_{26}FNO_3 \cdot 3/4H_2O$ (384.96): C 68.64, N 3.64, H 7.20; found: C 68.74, N 3.92, H 6.82.

4.3 *In vitro* radioligand competition studies

Competition assays of σ_1 and σ_2 receptors were performed as previous reported in the literature.[28,29] The detailed procedures are provided in the ESI.†

4.4 Cell culture and antiproliferative assay

The cancer cell lines MCF7 (human mammary carcinoma), DU145 (human prostate carcinoma) and C6 (rat glioma) were routinely cultured in Beijing Normal University. The MTT assay was used to determine the antiproliferative activity of compounds **1a** and **1b** and siramesine in these cell lines as described previously.[30,31] The procedures are shown in the ESI.†

4.5 Flow cytometry cell cycle analysis

1a, **1b** and siramesine were cultured in DU145 cell line for 24 h to examine cell cycle arrest as described previously.[32] The detailed procedures are shown in the ESI.†

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