Bioorganic & Medicinal Chemistry 16 (2008) 8335–8338

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

N-Propylnoraporphin-11-*O*-yl carboxylic esters as potent dopamine D_2 and serotonin 5-HT_{1A} receptor dual ligands

Zhili Liu [a,†], Xuetao Chen [b,†], Peihua Sun [b], Leiping Yu [b], Xuechu Zhen [b,*], Ao Zhang [a,*]

[a] Synthetic Organic & Medicinal Chemistry Laboratory (SOMCL), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, Shanghai 201203, China
[b] Neuropharmacology Laboratory, Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, Shanghai 201203, China

ARTICLE INFO

Article history:
Received 25 June 2008
Revised 22 August 2008
Accepted 23 August 2008
Available online 28 August 2008

Keywords:
Apomorphine
Aporphine analog
Dopamine receptor
Serotonin receptor
Monoester

ABSTRACT

A small series of *N*-propylnoraporphin-11-*O*-yl carboxylic esters with variant ester lengths were synthesized and their binding potencies at dopamine receptors (D_1, D_2) and serotonin receptors (5-HT_{1A}, 5-HT_{2A}) were evaluated. Monoesters **3a–f** showed binding potency of 100 nM or less for the D_2 receptor, and potency of 10–30 nM for the 5-HT_{1A} receptor. Butyryl ester **3d** was found to be the best compound possessing the highest potency for both receptors, with K_i values of 55 and 12 nM for D_2 and 5-HT_{1A} receptors, respectively. There is no correlation between the binding potency and the length of the monoesters, but the diesters **9** and **10** were inactive for the D_2 receptor. The dual binding profile of these monoesters for the D_2 and 5-HT_{1A} receptors may be useful for the treatment of neuropsychiatric disorders.

1. Introduction

The tetracyclic skeleton of aporphine analogs is a long-standing scaffold for the dopamine (DA) receptor agonists.[1–3] The prototypic compound, *R*-(−)-Apomorphine (APO, **1**, Fig. 1), is a well-documented D_2 receptor tool drug, and has been marketed for the treatment of Parkinson's disease.[4–6] 11-Hydroxy-*N*-propylnoraporphine (**2**[7]), with deletion of the 10-OH of **1**, possesses compatible D_2 receptor activity and enhanced bioavailability.[8] The pharmacokinetic properties were further improved by esterification of the 11-OH of compound **2** without significant decrease in D_2 receptor binding, for example, 11-valeryloxynoraporphine (**3a**)[8] is only slightly less potent than **2** but has longer duration of action and better bioavailability.

Interestingly, subtle structural modifications on the aporphine core can also lead to serotonin 5-HT_{1A} receptor selective ligands.[2] In the early 1990s, Cannon et al.[9,10] reported that replacing the 10-OH moiety in **1** with Me-group resulted in compound **4** possessing extremely high potency for the 5-HT_{1A} receptor, and almost complete loss of potency for the D_2 receptor. Hedberg and co-workers[11,12] further explored the hypothesized 'methyl pocket' in the 5-HT_{1A} receptor binding site, and found that other 10-alkyl substituents, for example, Et- (**5**), were also tolerated. Furthermore, it was found that without any substitution at C-10, a single alkyl group at C-11 (compounds **7**, **8**) was sufficient for high binding potency and selectivity for the 5-HT_{1A} receptor.[13] Very recently, Si et al.[14] reported that replacing Cannon's initial 10-Me-11-OH substitution in the aporphine core with a combination of 10-$HOCH_2$-11-OH (compound **6**) retains nanomolar binding for the 5-HT_{1A} receptor but micromolar range of potency for the D_2 receptor.

Although a large number of aporphine analogs have been reported with good binding potency either for the D_2 or for the 5-HT_{1A} receptors,[1–3] ligands with dual potencies for both D_2 and 5-HT_{1A} receptors are rare. In 1996, Hedberg et al.[13] reported that compound **2** was a dual binder with potent agonism for both receptors. Its valeryl (*n*-pentanoyl) ester **3a** has been reported showing potent D_2 receptor potency in our previous report,[8] but the binding potency for the 5-HT_{1A} receptor of this compound and other ester analogs has not been explored. In this regard, we decided to resynthesize *N*-propyl-aporphin-11-*O*-yl esters **3a**[8], **3b**[8], and expand to other monoesters **3c–f** as well as diesters **9** and **10**. The binding potencies of these esters for both D_2 and 5-HT_{1A} receptors were evaluated. Such a dual pharmacological profile may have potential for the treatment of schizophrenia and Parkinson's disease.[15–17]

2. Chemistry

The synthesis of esters **3a–f** is very straightforward and demonstrated in Scheme 1. 11-Hydroxy-*N*-propylnoraporphine (**2**[7]) was prepared in six steps from morphine by using a procedure we re-

* Corresponding authors. Tel./fax: +86 21 50806750 (X.Z.); tel.: +86 21 50806035; fax: +86 21 50806600 (A.Z.).
E-mail addresses: xczhen@mail.shcnc.ac.cn (X. Zhen), aozhang@mail.shcnc.ac.cn (A. Zhang).
† These authors contributed equally to this work.

0968-0896/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2008.08.056

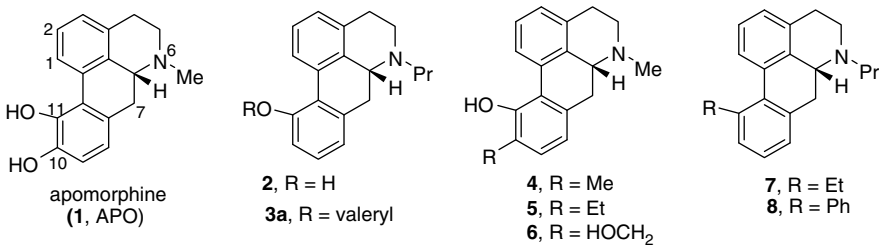
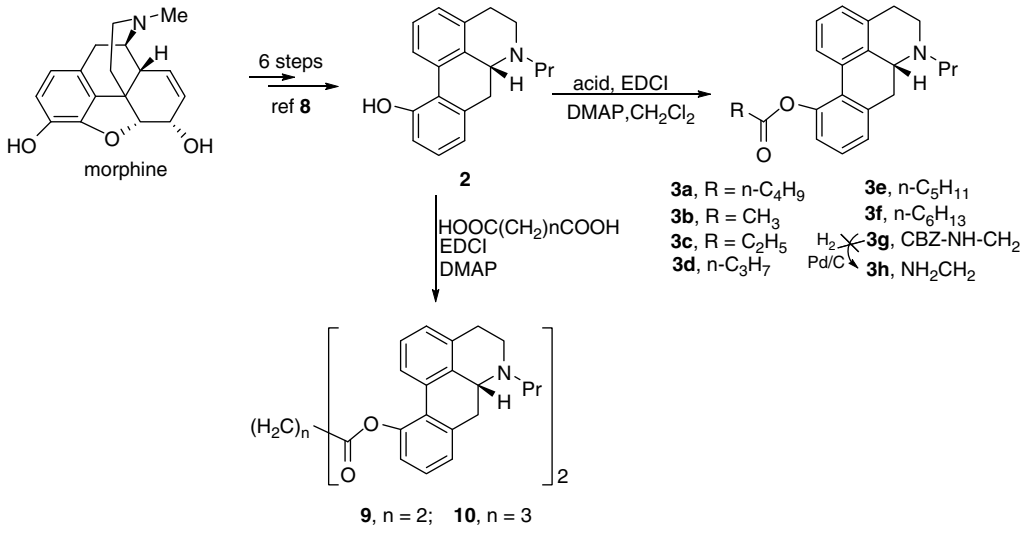


Figure 1. Apomorphine and its analogs.



Scheme 1.

ported previously.[8] Esterification of phenol **2** with an appropriate carboxylic acid under EDCI/DMAP condensation conditions[8,18] gave valeryl (*n*-pentanoyl) ester **3a**[8] (80%), acetyl ester **3b**[8] (67%), propionyl ester **3c** (88%), *n*-butyryl ester **3d** (77%), *n*-hexanoyl ester **3e** (90%), and *n*-heptanoyl ester **3f** (90%). Esterification of 11-hydroxy-aporphine **2** with *N*-CBZ-protected glycine under the same condition yielded the aminoacid ester **3g** in 70% yield (Scheme 1). However, the following hydrogenation with Pd/C did not afford the expected CBZ-removed aporphine **3h** except a complete recovery of the starting phenol **2**. Diesters **9** and **10** were synthesized in 88% and 94% yield, respectively, by reacting two equivalents of phenol **2** with one equivalent of succinic acid or glutaric acid, and a catalytic amount of DMAP in CH_2Cl_2 in the presence of EDCI as the condensation agent.[18]

3. Results and discussion

The previously reported esters **3a**[8] and **3b**,[8] together with our newly prepared monoesters **3c**–**3g** and diesters **9**, **10** were subjected to the competitive binding assays for DA receptors (D_1, D_2) and serotonin receptors (5-HT_{1A}, 5-HT_{2A}), respectively, using membrane preparations obtained from stable transfected HEK293 or CHO cells with individual receptor. These procedures are similar to those reported previously by us.[8,19] [^{3}H]SCH23390, [^{3}H]Spiperone, [^{3}H]8-OH-DPAT, and [^{3}H]Ketanserin were used as the standard radioligands for DA D_1, D_2 and serotonin 5-HT_{1A}, 5-HT_{2A} receptors, respectively. 11-Hydroxy-*N*-propylnorapophine (**2**) was also tested for comparison. Data for compound **3b** was directly taken from Ref. 8.

Table 1
Binding affinity of aporphine esters for DA (D_1, D_2) and 5-HT (5-HT_{1A}, 5-HT_{2A}) receptors from HEK293 or CHO cells[a]

Compound	K_i (nM)			
	D_1 ([^{3}H]SCH23390)	D_2 ([^{3}H]Spiperone)	5-HT_{1A} ([^{3}H]8-OH-DPAT)	5-HT_{2A} ([^{3}H]Ketanserin)
2	>10,000	114 ± 83	45 ± 28	>10,000
3a	>10,000	92 ± 18	23 ± 9	>10,000
3b[b]	>10,000	72 ± 7	ND	ND
3c	>10,000	109 ± 38	18 ± 1	>10,000
3d	>10,000	56 ± 13	12 ± 3	>10,000
3e	>10,000	109 ± 72	10 ± 4	>10,000
3f	>10,000	95 ± 85	31 ± 18	>10,000
3g	>10,000	>10,000	ND	>10,000
9	>10,000	>10,000	ND	>10,000
10	>10,000	>10,000	ND	>10,000

[a] Values are means of five to six experiments.[19] ND denotes that the activity was not determined.
[b] From Ref. 8.

As expected, compound **2** as well as most of the esters showed good binding potency for both D_2 and 5-HT_{1A} receptors (Table 1). Compound **2**, previously reported by Hedberg[13] with dual binding potentials for both D_2 and 5-HT_{1A} receptors, displayed K_i values of 114 and 45 nM for both receptors, respectively, in our current assay. In agreement with our previous report,[8] compound **3a** showed good potency for the D_2 receptor. It was four fold more potent for the 5-HT_{1A} receptor with a K_i value of 23 nM. Esters **3b–3f** with variant ester lengths displayed similarly high potency for the D_2 receptor (~100 nM) with butyryl ester **3d** possessing the highest potency (K_i, 55 nM). These esters also displayed excellent binding potency for the 5-HT_{1A} receptor with K_i values of 10–30 nM. Although there is no significant correlation between the length of the ester and the binding potency for the D_2 and 5-HT_{1A} receptors, compound **3d** was found to be the most potent compound with highest binding potency for both receptors (K_i, 55 and 12 nM for D_2 and 5-HT_{1A} receptors, respectively). It was of note that *N*-CBZ-protected aminoacetate **3g** was inactive for any of the receptors tested. It was also intriguing that diesters **9** and **10** did not show appreciable binding for the D_2 receptor, therefore their potency for the 5-HT_{1A} receptor was not tested. All these esters together with the phenol **2** did not show binding potency for D_1 and 5-HT_{2A} receptors, which is consistent with the results reported in the literature.[2]

4. Conclusions

In summary, we synthesized a small series of *N*-propylnoraporphin-11-*O*-yl carboxylic esters with variant ester lengths. Most of these compounds were potent for both D_2 and 5-HT_{1A} receptors. Compounds **3a–f** showed binding potency of 100 nM or less for the D_2 receptor, and potency of 10–30 nM for the 5-HT_{1A} receptor. Butyryl ester **3d** was found to be the most potent compound possessing the highest binding potency for both receptors, with K_i values of 55 and 12 nM for D_2 and 5-HT_{1A} receptors, respectively. There is no significant correlation between the binding potency and the length of the monoesters, but the diesters **9** and **10** were inactive for the D_2 receptors. The dual binding profile of these monoesters for the D_2 and 5-HT_{1A} receptors may be useful for the treatment of neuropsychiatric disorders.

5. Experimental

5.1. Chemistry

Melting points were determined on a Thomas–Hoover capillary tube apparatus and are reported uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Brucker AC300 spectrometer using tetramethylsilane as an internal reference. Element analyses, performed by the Analytic Laboratory, SIMM, were within ±0.4% of theoretical values. Analytical thin-layer chromatography (TLC) was carried out on 0.2-mm Kieselgel 60F_{254} silica gel plastic sheets (EM Science, Newark). Flash chromatography was used for the routine purification of reaction products. The column output was monitored with TLC. Yields of all the reactions were not optimized.

5.2. General procedure for the synthesis of 11-hydroxy-*N*-*n*-propylnoraporphine carboxylic esters (3a–g)

To a solution of 11-hydroxy-*N*-*n*-propylnoraporphine **2** (0.5 mmol), an appropriate acid (1 mmol) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (10 mL) under N_2, EDCI (1 mmol) was added at rt. The reaction mixture was stirred overnight, and then diluted with CH_2Cl_2 (30 mL) and H_2O (20 mL). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (petroleum/ethyl acetate = 3:1, 1% Et_3N) to give a pure oily product, which was then converted into the hydrochloride salt with HCl-ether (1 M). Spectroscopic data for compounds **3a** and **3b** were same as that we reported previously.[8]

5.2.1. 11-Propionyloxy-*N*-*n*-propylnoraporphine (3c)

This compound was prepared as pale solid in 88% yield from propionic acid. MS (EI-LR) 335 (M^+); ^1H NMR (300 MHz, $CDC1_3$) δ 7.75 (d, 1H, J = 7.8 Hz), 7.21 (m, 3H), 7.07 (d, 1H, J = 7.5 Hz), 7.01 (d, 1H, J = 7.2 Hz), 3.43 (dd, 1H, J = 3.0, 13.5 Hz), 3.14 (m, 3H), 2.90 (m, 1H), 2.77 (dd, 1H, J = 16.5, 4.2 Hz), 2.48 (m, 5H), 1.65 (m, 2H), 1.22 (t, 3H, J = 7.8 Hz), 0.98 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDC1_3$) δ 172.6, 147.3, 138.6, 135.8, 133.6, 130.7, 128.1, 127.7, 127.3, 125.9, 125.8, 124.7, 122.0, 59.1, 56.5, 48.8, 35.0, 29.3, 28.0, 19.5, 12.1, 8.9; Anal. ($C_{22}H_{25}N_2 \cdot 3/4HCl \cdot 3/4H_2O$) Calcd: C, 70.22; H, 7.30; N, 3.72. Found: C, 69.91; H, 7.30; N, 4.22.

5.2.2. 11-Butyryloxy-*N*-*n*-propylnoraporphine (3d)

This compound was prepared as pale solid in 77% yield from butanoic acid. MS (EI-LR) 349 (M^+); ^1H NMR (300 MHz, $CDC1_3$) δ 7.73 (d, 1H, J = 7.5 Hz), 7.21 (m, 3H), 7.06 (d, 1H, J = 7.5 Hz), 7.01 (dd, 1H, J = 8.1, 1.2 Hz), 3.42 (dd, 1H, J = 12.0, 3.6 Hz), 3.15 (m, 3H), 2.90 (m, 1H), 2.75 (dd, 1H, J = 16.2, 4.5 Hz), 2.51 (m, 5H), 1.74 (m, 2H), 1.62 (m, 2H), 0.98 (m, 6H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 171.7, 147.3, 138.6, 135.8, 133.6, 130.7, 128.1, 127.6, 127.3, 125.9, 125.8, 124.7, 122.1, 59.1, 56.5, 48.8, 36.4, 35.0, 29.3, 19.5, 18.1, 13.7, 12.0; Anal. ($C_{23}H_{27}NO_2 \cdot HCl \cdot 1/2H_2O$) Calcd: C, 69.95; H, 7.40; N, 3.55. Found: C, 69.87; H, 7.46; N, 3.55.

5.2.3. 11-Hexanoyloxy-*N*-*n*-propylnoraporphine (3e)

This compound was prepared in 90% yield from hexanoic acid. MS (EI) 377 (M^+), ^1H NMR (300 MHz, $CDC1_3$) δ 7.73 (d, 1H, J = 7.5 Hz), 7.21 (m, 3H), 7.05 (d, 1H, J = 7.5 Hz), 6.99 (d, 1H, J = 7.5 Hz), 3.42 (dd, 1H, J = 16.2, 2.7 Hz), 3.15 (m, 3H), 2.90 (m, 1H), 2.75 (dd, 1H, J = 16.2, 4.5 Hz), 2.51 (m, 5H), 1.65 (m, 4H), 1.30 (m, 4H), 0.98 (m, 6H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 172.0, 147.3, 138.6, 135.8, 133.6, 130.7, 128.1, 127.6, 127.3, 125.9, 125.8, 124.7, 122.1, 59.1, 56.5, 48.8, 35.0, 34.5, 29.3, 24.3, 22.3, 19.5, 13.9, 12.0; HR-MS Calcd for $C_{25}H_{31}NO_2$ (M^+) 377.2355. Found: 377.2348.

5.2.4. 11-Heptanoyloxy-*N*-*n*-propylnoraporphine (3f)

This compound was prepared in 90% yield as pale solid from heptanoic acid. MS (EI) 391 (M^+), ^1H NMR (300 MHz, $CDC1_3$) δ 7.73 (d, 1H, J = 7.5 Hz), 7.21 (m, 3H), 7.05 (d, 1H, J = 7.5 Hz), 6.99 (d, 1H, J = 7.5 Hz), 3.41 (dd, 1H, J = 16.2, 2.7 Hz), 3.16 (m, 3H), 2.90 (m, 1H), 2.76 (d, 1H, J = 16.2 Hz), 2.51 (m, 5H), 1.65 (m, 4H), 1.30 (m, 6H), 0.98 (m, 6H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 172.0, 147.3, 138.6, 135.8, 133.6, 130.6, 128.1, 127.6, 127.3, 125.9, 125.8, 124.7, 122.1, 59.1, 56.5, 48.8, 35.0, 34.6, 31.4, 29.3, 28.7, 24.6, 22.4, 19.5, 13.9, 12.0; HR-MS Calcd for $C_{26}H_{33}NO_2$ (M^+) 391.2511. Found: 391.2514.

5.2.5. 11-[2-(Benzyloxycarbonylamino)acetyloxy]-*N*-*n*-propylnoraporphine (3g)

This compound was prepared in 70% yield as a yellow solid from 2-(benzyloxy carbonylamino)acetic acid. MS (EI) 470 (M^+), ^1H NMR (300 MHz, $CDC1_3$) δ 7.65 (d, 1H, J = 7.8 Hz), 7.34 (m, 5H), 7.22 (m, 3H), 7.05 (m, 1H), 5.30 (br s, 1H), 5,13 (s, 2H), 4.42 (m, 2H), 3.40 (dd, 1H, J = 13.5, 3.0 Hz), 3.14 (m, 3H), 2.90 (m, 1H), 2.77 (d, 1H, J = 13.8 Hz), 2.48 (m, 3H), 1.65 (m, 2H), 0.97 (t, 3H, J = 7.2 Hz).

5.3. General procedure for the synthesis of diesters 9 and 10

To a solution of 11-hydroxy-*N*-*n*-propylnoraporphine **2** (0.5 mmol), succinic acid or glutaric acid (0.24 mmol) and a cata-

lytic amount of DMAP in anhydrous CH_2Cl_2 (10 mL) under N_2, EDCI (0.6 mmol) was added at rt. The reaction mixture was stirred overnight, and diluted with CH_2Cl_2 (30 mL) and H_2O (20 mL). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was subjected to silica gel chromatography (petroleum/ethyl acetate = 2:1, 1% Et_3N) to yield the pure products.

5.3.1. Bis[*N*-propylnoraporphin-11-*O*-yl]succinate (9)

This compound was prepared as green solid in 94% yield from succinic acid. MS (EI) 640 (M^+), ^1H NMR (300 MHz, $CDC1_3$) δ 7.71 (d, 2H, J = 7.5 Hz), 7.17 (m, 6H), 7.04 (d, 2H, J = 7.8 Hz), 6.97 (m, 2H), 3.42 (dd, 2H, J = 13.2, 2.4 Hz), 2.95 (m, 12H), 2.74 (d, 2H, J = 16.2 Hz), 2.51 (m, 6H), 1.62 (m, 4H), 0.98 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDC1_3$) δ 170.3, 147.1, 138.6, 135.9, 133.7, 130.6, 128.2, 127.7, 127.2, 126.1, 124.6, 122.0, 59.2, 56.5, 48.8, 35.0, 29.4, 29.3, 19.6, 12.1; HR-MS Calcd for $C_{42}H_{44}N_2O_4$ (M^+) 640.3301. Found: 640.3278.

5.3.2. Bis(*N*-propylnoraporphin-11-*O*-yl) glutamate (10)

This compound was prepared in 88% yield as a yellow solid from glutaric acid. MS (EI) 654 (M^+), ^1H NMR (300 MHz, $CDC1_3$) δ 7.71 (d, 2H, J = 8.1 Hz), 7.20 (m, 6H), 7.06 (d, 2H, J = 7.2 Hz), 7.00 (d, 2H, J = 7.2 Hz), 3.42 (d, 2H, J = 15.3 Hz), 3.14 (m, 6H), 2.90 (m, 2H), 2.60 (m, 12H), 2.10 (m, 2H), 1.60 (m, 4H), 0.98 (t, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDC1_3$) δ 171.1, 147.1, 138.6, 135.7, 133.7, 130.6, 128.2, 127.7, 127.3, 126.0, 124.6, 122.0, 59.1, 56.5, 48.8, 34.9, 33.5, 29.2, 19.6, 19.4, 12.1; HR-MS Calcd for $C_{43}H_{46}N_2O_4$ (M^+) 654.3458; Found: 654.3448.

5.4. Established stable expression of cell lines

The rat 5-HT1A receptor gene, human 5-HT_{2A} receptor gene, human D_1 and human D_2 receptor genes were individually cloned into pcDNA3.0 vector. The 5-HT_{1A} and 5-HT_{2A} construct was then transfected into CHO cells. The 5-HT_{2A} receptor, D_1 and D_2 receptors were transfected to HEK293 cells, respectively. G418 at 800 μg/ml was used for selection. Monoclonal transfected cells were isolated and maintained in medium containing Ham's F12 nutrient mixture (for 5-HT_{1A}-CHO) or DMEM (for 5-HT_{2A}-, D_1- or D_2-HEK293) (Gibco), 10% fetal bovine serum, 100 U/ml penicillin, 100 U/ml streptomycin, and 200 μg/ml G418 at 37 °C and 5% CO_2.

To confirm the success of transfection, the saturation binding experiment that the expression of 5-HT_{1A} receptor in the CHO cell line is 1.5531 ± 0.2803 nmol/g protein with a K_d value of 1.2058 nM, the K_d for 5-HT_{2A} is 0.80 nM. The expression for the D_1 receptor is 10.67 nmol/g protein with a K_d value of 1.31 ± 0.16 nM. The K_d for the D_2 receptor is 0.06 nM.

5.5. Radioligand binding assays

The affinity of the aporphine compounds to the D_1 and D_2 dopamine receptors, and the 5-HT_{1A}, 5-HT_{2A} receptor was determined by competition binding assays. Membrane homogenates of 5-HT_{1A}-CHO, 5-HT_{2A}-293, cells, D_1- or D_2-HEK293 cells were prepared as described previously.[8,19] Duplicated tubes were incubated at 30 °C for 50 min with increasing concentrations of respective compound and with 0.7 nM [^{3}H]8-OH-DPAT (for 5-HT_{1A} receptor), [^{3}H]Ketanserin (for 5-HT_{2A} receptor), [^{3}H]SCH23390 (for D_1 dopamine receptors), or [^{3}H]Spiperone (for dopamine D_2 receptor) in a final volume of 200 μL binding buffer containing 50 mM Tris, 4 mM $MgCl_2$, pH 7.4. Nonspecific binding was determined by parallel incubations with either 10 μM WAY100635 for 5-HT_{1A}, Ketanserin for 5-HT_{2A}, SCH23390 for D_1 or Spiperone for D_2 dopamine receptors, respectively. The reaction was started by addition of membranes (15 ng/tube) and stopped by rapid filtration through Whatman GF/B glass fiber filter and subsequent washing with cold buffer (50 mM Tris, 5 mM EDTA, pH 7.4) using a Brandel 24-well cell harvester. Scintillation cocktail was added and the radioactivity was determined in a MicroBeta liquid scintillation counter. The IC_{50} and K_i values were calculated by nonlinear regression (PRISM, Graphpad, San Diego, CA) using a sigmoidal function.

Acknowledgments

This work was financially supported by grants from Chinese National Science Foundation (30672517 to A.Z.), Shanghai Commission of Science and Technology (07pj14104 to A.Z. and X.Z.), and grant from Ministry of Science and Technology (2007AA022163 to X.Z.). Support from Chinese Academy of Sciences, and Shanghai Institute of Materia Medica was also appreciated. We also thank Professors John L. Neumeyer and Ross J. Baldessarini for their instructive discussion during this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.08.056.

References and notes

1. Neumeyer, J. L. In *The Chemistry and Biology of Isoquinoline Alkaloids*; Phillipson, J. D., Roberts, M. F., Zenk, M. H., Eds.; Springer-Verlag: Berlin, Germany, 1985; p 146.
2. Zhang, A.; Zhang, Y.; Branfman, A. R.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **2007**, *50*, 171.
3. Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274.
4. Neumeyer, J. L.; Baldessarini, R. J.; Booth, R. G. In *Burger's Medicinal Chemistry and Drug Discovery*, 6th ed.; Abraham, D. J., Ed.; John Wiley & Sons: New York, 2003; Vol. 6, Chapter 12, pp 711–714.
5. Kolls, B. J.; Stacy, M. *Clin. Neuropharmacol.* **2006**, *29*, 292.
6. Subramony, J. A. *Mol. Pharm.* **2006**, *3*, 380.
7. Gao, Y.; Zong, R.; Campbell, A.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J . L. *J. Med. Chem.* **1988**, *31*, 1392.
8. Csutoras, C.; Zhang, A.; Zhang, K.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem.* **2004**, *12*, 3553.
9. Cannon, J. G.; Mohan, P.; Bojarski, J.; Long, J. P.; Bhatnagar, R. K.; Leonard, P. A.; Flynn, J. R.; Chatterjee, T. K. *J. Med. Chem.* **1988**, *31*, 313.
10. Cannon, J. G.; Moe, S. T.; Long, J. P. *Chirality* **1991**, *3*, 19.
11. Hedberg, M. H.; Johansson, A. M.; Hacksell, U. *J. Chem. Soc., Chem. Commun.* **1992**, 845.
12. Hedberg, M. H.; Johansson, A. M.; Nordvall, G.; Yliniemela, A.; Li, H.-B.; Martin, A. R.; Hjorth, S.; Unelius, L.; Sundell, S.; Hacksell, U. *J. Med. Chem.* **1995**, *38*, 647.
13. Hedberg, M. H.; Jansen, J. M.; Nordvall, G.; Hjorth, S.; Unelius, L.; Johansson, A. M. *J. Med. Chem.* **1996**, *39*, 3491.
14. Si, Y.-G.; Gardner, M. P.; Tarazi, F. I.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4128.
15. Lacivita, E.; Leopoldo, M. *J. Med. Chem.* **2008**, *51*, 1492.
16. Newman-Tancredi, A.; Cussac, D.; Depoortere, R. *Curr. Opin. Invest. Drugs* **2007**, *8*, 539.
17. Wolf, W. A. *Solvay. Curr. Opin. Invest. Drugs* **2003**, *4*, 878.
18. Neumeyer, J. L.; Zhang, A.; Xiong, W.; Gu, X.-H.; Hilbert, J. E.; Knapp, B. I.; Negus, S. S.; Mello, N. K.; Bidlack, J. M. *J. Med. Chem.* **2003**, *46*, 5162.
19. Liu, Z.; Chen, X.; Yu, L.; Zhen, X.; Zhang, A. *Bioorg. Med. Chem.* **2008**, *16*, 6675.