Journal of Medicinal Chemistry

ARTICLE

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Identification of *N*-Propylnoraporphin-11-yl 5-(1,2-Dithiolan-3-yl)pentanoate as a New Anti-Parkinson's Agent Possessing a Dopamine D_2 and Serotonin 5-HT_{1A} Dual-Agonist Profile

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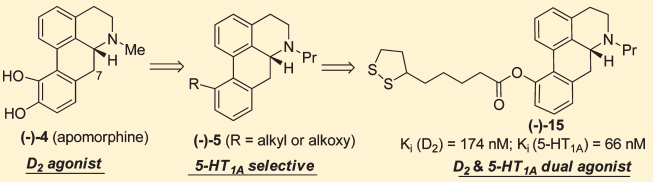
Supporting Information

ABSTRACT: A series of new aporphine analogues (aporlogues) were synthesized bearing a C-, N-, or O-linkage at the C11 position. Lipoic ester (−)-**15** was identified as a full agonist at the dopamine D_2 and serotonin 5-HT_{1A} receptors with K_i values of 174 and 66 nM, respectively. It elicited antiparkinsonian action on Parkinsin's disease (PD) rats with minor dyskinesia. Chronic use of (−)-**15** reduced L-DOPA-induced dyskinesia (LID) without attenuating the antiparkinsonian effect. These results suggest that 5-HT_{1A} and D_2 dual-receptor agonist (−)-**15** may present a novel candidate drug in the treatment of PD and LID.



INTRODUCTION

Parkinson's disease (PD) is an age-related progressive neurodegenerative disorder and is the second most common debilitating neurodegenerative disease that affects as much as 2% of the population that is ≥60 years old.[1] The clinical symptoms of PD result from progressive loss of dopamine (DA)-secreting neurons in the pars compacta of the substantia nigra and the accumulation of α-synuclein-enriched intraneuronal aggregates known as Lewy bodies.[2,3] In spite of the improved understanding of the molecular pathogenesis of PD, current anti-PD therapy is still based on exogenous replacement of DA within the striatum with levodopa (L-DOPA), the precursor of DA.[4−7] A large number of selective DA receptor agonists were developed later to replace L-DOPA either as monotherapy or as joint therapy with L-DOPA;[8−10] however, long-term use of these drugs also causes motor fluctuations and dyskinesias, possibly because of the pulsatile stimulation of DA receptors.[11−13]

To find safer anti-PD therapies, several new pharmacologic approaches involving other neurotransmitter systems are currently being investigated on the basis of PD's multifactorial pathogenic mechanisms.[4,14] Among these, dual agonists targeting serotonin 1A (5-HT_{1A}) and DA D_2 receptors have attracted extensive attention, with several drugs recently progressing to the clinic.[15] The 5-HT_{1A} receptor plays crucial roles in regulating psychoemotional, cognitive, and motor functions in the central nervous system.[16,17] It has been found that stimulation of the 5-HT_{1A} receptor can improve core motor symptoms caused by degeneration or lesions of DA neurons.[18] In patients with advanced PD, striatal serotoninergic terminals serve as important sites for the decarboxylation of exogenous L-DOPA to DA. In addition, 5-HT_{1A} receptor agonists have been shown to alleviate L-DOPA-induced dyskinesia (LID).[19−21] Sarizotan (**1**),[22] bifeprunox (**2**),[23] and pardoprunox (**3**)[24] (Figure 1) are the most studied D_2 and 5-HT_{1A} receptor dual agonists. **1** displayed full agonistic properties at the 5-HT_{1A} receptor but weak partial agonist activity at the D_2 receptor.[25] It reduced the level of LID in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced PD monkeys by up to 90% without altering the antiparkinsonian effect of L-DOPA.[26] In a "proof-of-concept" study in patients with moderate to advanced PD, **1** significantly reduced the level of LID in a within-patient comparison.[25,27,28] **2** is a partial agonist at both D_2 and 5-HT_{1A} receptors, a pharmacological profile similar to that of the antipsychotic aripiprazole. Accordingly, **2** was found to effectively improve the cognitive and negative symptoms of schizophrenia and to reduce the extrapyramidal effects of typical antipsychotics; therefore, it represented a new atypical antipsychotic in clinical evaluation.[23] Similar to **1**, **3** is also a D_2 partial agonist with full 5-HT_{1A} agonistic activity.[29] A long-lasting anti-PD effect, along with antidepressant and anxiolytic efficacy, was observed in animals treated with this compound. In a double-blind study, **3** significantly improved motor function in patients with early PD. This compound currently has progressed to phase III clinical trials as a new anti-PD treatment by Solvay Pharmaceuticals.[24,29] Although the final fate of **3** was not determined at this stage, the D_2 and 5-HT_{1A} receptor dual-agonist profile has attracted more interest in terms of the

Received: October 26, 2010
Published: May 18, 2011

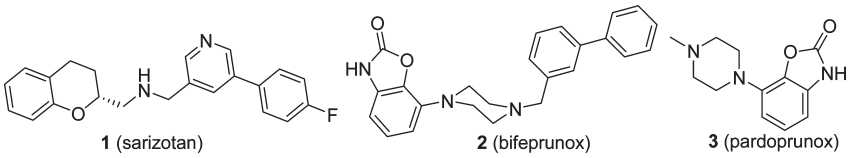


Figure 1. Representative D_2 and 5-HT_{1A} receptor agonists **1**−**3**.

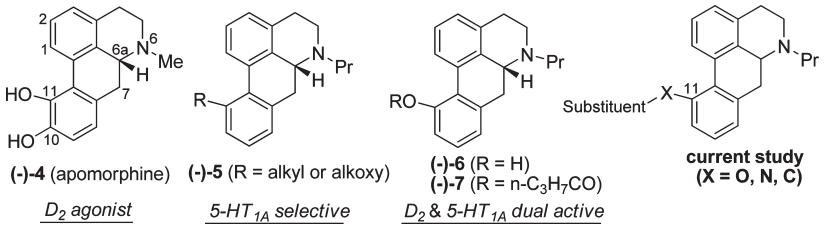
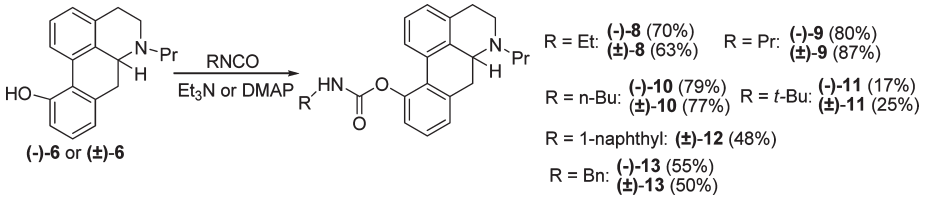


Figure 2. Reported and proposed aporlogues.

Scheme 1. Preparation of Aporphin-11-yl Carbamates



paradigm of developing new anti-PD therapeutics with less troublesome motor fluctuations and dyskinesias.

The tetracyclic skeleton of aporphine analogues (aporlogues), represented by the prototypic compound (*R*)-(−)-apomorphine [(−)-**4** (Figure 2)], is a long-standing scaffold for the D_2 receptor agonists.[30−32] We[33] and others[34−38] have reported that introducing a more lipophilic group at C10, C11, or both led to compounds like (−)-**5** with a complete loss of affinity for the D_2 receptor, but with high potency and selectivity toward the 5-HT_{1A} receptors, indicating a 5-HT_{1A} binding site existing in the D_2 agonist scaffold. Further, D_2 and 5-HT_{1A} dual-receptor activity was observed in the ester derivatives [e.g., (−)-**7**[39]] of (*R*)-(−)-11-hydroxy-*N*-propylnoraporphine[40] [(−)-**6**]. In our preliminary study, compound (−)-**7** had a significant antiparkinsonian effect; however, it suffered from a short half-life and exerted an only moderate effect on LID in rats (data not shown). With these results, we decided to further explore the structural modification on the 11-hydroxy group of aporphine (−)-**6** by synthesizing a series of new aporlogues with diversified functional groups attached to C11 through an O-, N-, or C-linkage (Figure 2). This led to the identification of lipoic ester (−)-**15**, (6α*R*)-(−)-*N*-propylnoraporphin-11-yl 5-(1,2-dithiolan-3-yl)pentanoate, as a new anti-PD agent with a D_2 and 5-HT_{1A} receptor dual-agonist profile. Herein, we report our synthesis, characterization, and biological evaluation of this compound.

RESULTS AND DISCUSSION

Synthesis. (6α*R*)-(−)-11-Hydroxy-*N*-propylnoraporphine (−)-**6** and its racemate, (±)-**6**, were used as the key intermediates. The optically pure aporphine (−)-**6**[33,39,40] was prepared from natural alkaloid morphine in six steps as described previously by us. The racemate (±)-**6**[41] was prepared by total synthesis from Reissert salt and arylmethyl bromide in eight steps according to a literature procedure. In several cases, the racemic analogues were inactive at both receptors; therefore, the corresponding (6α*R*)-(−)-isomers were not prepared because of the limited supply of the starting material, morphine.

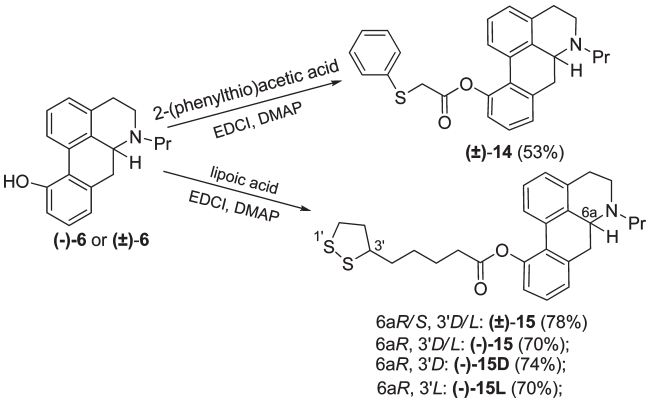
First, a series of carbamates (−)-**8**−(−)-**13** were prepared[42] by treating aporphine (−)-**6** with the corresponding isocyanates and triethylamine (Et_3N) or (dimethylamino)pyridine (DMAP) (Scheme 1). As a comparison, the racemic carbamates (±)-**8**−(±)-**13** were also prepared from (±)-**6** under the same conditions. The yields of these aporlogues were generally moderate to good. In the case of the bulky isocyanates (±)-**11** and (±)-**12**, the corresponding condensation reactions were very sluggish and lower yields were obtained. These compounds can be viewed as metabolically more stable bioisosteric congeners of the corresponding carboxylic acid esters [e.g., (−)-**7**[39]]. We must mention that these carbamates were proposed previously by us[43] and others[44] as the D_2 receptor agonists; however, neither analytic nor pharmacological data were disclosed. Esters (±)-**14** and (±)-**15** or (−)-**15** were prepared[39] via the treatment of aporphine (±)-**6** or (−)-**6** with 2-phenylthioacetic acid and lipoic acid (thioctic acid, racemic) in the presence of EDCI in 53−70% yields (Scheme 2). Similarly, (−)-**15D** and (−)-**15L** were prepared by condensation of (−)-**6** with D- and L-lipoic acid, respectively, in 70% yields.

Further, 11-carboxamides (−)-**18** and (−)-**19** were prepared by condensation[45] of 11-aminoaporphine (−)-**17** with corresponding acids in 56 and 37% yield, respectively (Scheme 3). Amine (−)-**17** was prepared from phenolic aporphine (−)-**6** through triflation followed by palladium-catalyzed C−N coupling in 46% overall yield by using a pair of procedures similar to ones that we have previously reported.[40]

dx.doi.org/10.1021/jm200347t |*J. Med. Chem.* 2011, 54, 4324–4338

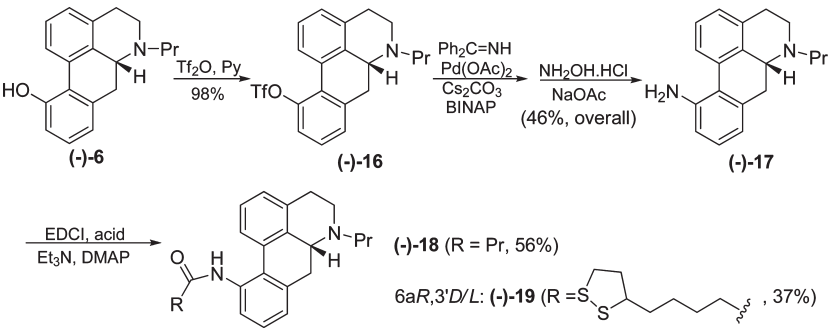
Amides (±)-**22** and (±)-**23**, urea (±)-**24**, and oxadiazole (±)-**25** were prepared as a small series of novel aporlogues bearing a C11 C-linkage (Scheme 4). Microwave heating[46] of the mixture of triflate (±)-**16**, $Zn(CN)_2$, and $Pd(PPh_3)_4$ provided 11-cyanoaporphine (±)-**20** in 97% yield. Reduction[47] of nitrile (±)-**20** with Raney nickel and ammonia at room temperature (rt) afforded 11-aminomethylaporphine (±)-**21** in 86% yield. Condensation[45] of amine (±)-**21** with racemic lipoic acid, EDCI, and HOBt yielded (±)-**22** in 76% yield, which was then converted to its thioamide (±)-**23** in 41% yield upon treatment with Lawesson's reagent[48] at 70 °C. Ureido aporphine (±)-**24** was obtained in 77% yield by reaction of amine (±)-**21** with ethyl isocyanate at rt.[49] Treating nitrile (±)-**20** with hydroxylamine hydrochloride in ethanol at reflux and condensation with lipoic acid (DCC, rt) followed by treatment with tetrabutylammonium fluoride provided oxadiazole (±)-**25** in 26% overall yield.[50]

Scheme 2. Preparation of Aporphines with Functionalized Carboxylic Acid Ester Moieties as C11 Substituents

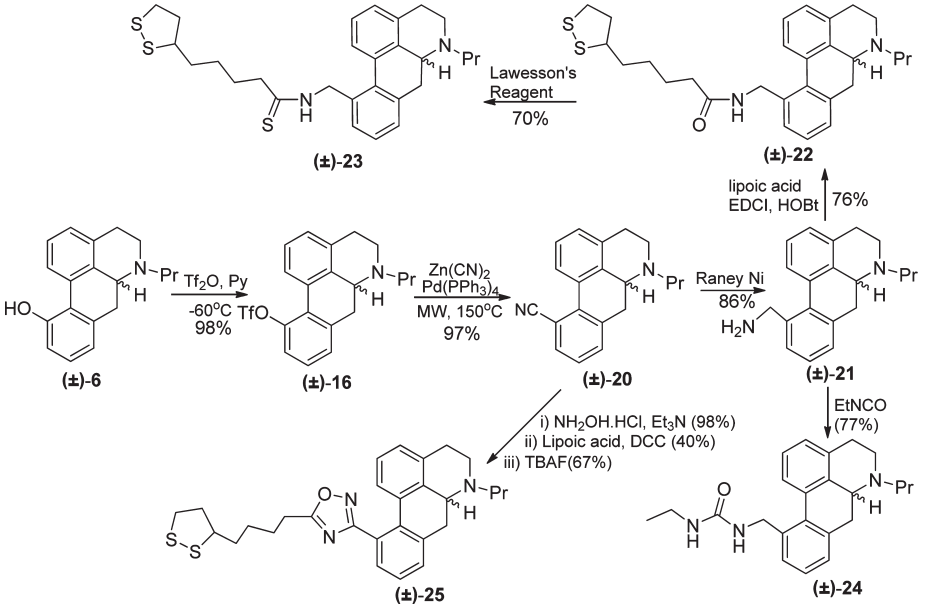


Biological Activity. *DA (D_1 and D_2), 5-HT_{1A}, and 5-HT_{2A} Receptor Binding Assays.* All the new C11 C-, N-, and O-linked aporlogues were subjected to the competitive binding assays for DA (D_1 and D_2) and serotonin (5-HT_{1A} and 5-HT_{2A}) receptors using a membrane preparation obtained from stably transfected HEK293 (for D_1 and D_2) or CHO (for 5-HT_{1A} and 5-HT_{2A}) cells. First, the ability at a concentration of 10 μM to inhibit the binding of a tritiated radioligand to the corresponding receptor was tested. Compounds that inhibited binding by more than 80% were further assayed at six or more concentrations, ranging above and below IC_{50}. The K_i ± the standard error (SE) was then

Scheme 3. Synthesis of Amide Analogues

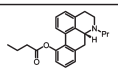
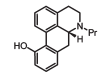
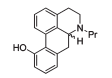
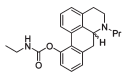
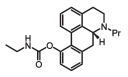
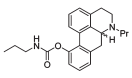
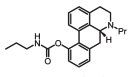
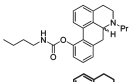
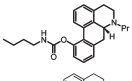
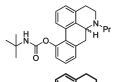
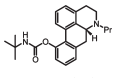
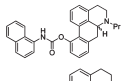
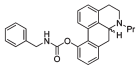


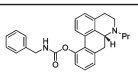
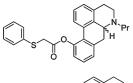
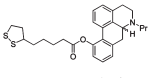
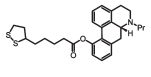
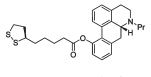
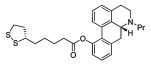
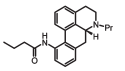
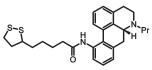
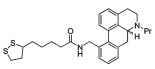
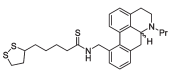
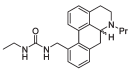
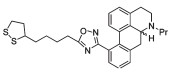
Scheme 4. Synthesis of C11-Linked Aporphines



dx.doi.org/10.1021/jm200347t | J. Med. Chem. 2011, 54, 4324–4338

Table 1. Binding Affinities of Aporphines at the D_1, D_2, 5-HT_{1A}, and 5-HT_{2A} Receptors

Compound	Structure	Inhibition (%) or K_i (±SEM, nM)[a]			
		D_1	D_2	5-HT_{1A}	5-HT_{2A}
(-)-7[b]		63.2%	55.5±13.1	11.9±2.5	68.0%
(-)-6[b]		63.2%	114±83	45±28	63.0%
(±)-6		55.9%	854±79	66±6.3	14.1%
(±)-8		46.1%	56.7%	218±23	19.8%
(-)-8		54.6%	44.3%	94±4.9	14.5%
(±)-9		26.2%	52.7%	258±16	30.1%
(-)-9		56.3%	50.9%	87±13.0	16.0%
(±)-10		36.5%	53.2%	385±10.5	37.4%
(-)-10		53.6%	40.9%	89±20.9	34.9%
(±)-11		44.2%	2800±814	217±8.1	20.0%
(-)-11		70.2%	871±71	96±9.2	29.2%
(±)-12		48.0%	2005±380	124±22.1	21.7%
(±)-13		4200±480	4300±760	259±45	2000±76

Compound	Structure	Inhibition (%) or K_i (±SEM, nM)[a]			
		D_1	D_2	5-HT_{1A}	5-HT_{2A}
(-)-13		2400±31	2200±110	90±10	76.6%
(±)-14		67.1%	851±43	-	-
(±)-15		62.7%	55.2%	137±14.3	14.7%
(-)-15		55.7%	174±17.2	66±10.5	48.0%
(-)-15D		69.6%	296±38	45±1.0	-
(-)-15L		64.8%	342±47	35±6.0	-
(-)-17		57.1%	352±80	276±30	49.4%
(-)-18		16.1%	13.5%	380±35	16.6%
(-)-19		27.2%	33.1%	249±12	36.9%
(±)-22		32.4%	9.6%	-	-
(±)-23		11.4%	3.1%	-	-
(±)-24		35.4%	15.7%	-	-
(±)-25		57.0%	19.5%	-	-

[a] Values are means of five to six experiments. Dashes denote that no experiment was conducted. [b] Data from ref 33 or 39.

derived from the equation $K_i = IC_{50}/(1 + C/K_d)$. These procedures are similar to those reported previously by us.[33,39,40] [^{3}H]-8-Chloro-3-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*- benzo-[*d*]azepin-7-ol (SCH23390), [^{3}H]spiperone, [^{3}H]-8-OH-DPAT, and [^{3}H]Ketanserin were used as standard radioligands for DA D_1 and D_2 and serotonin 5-HT_{1A} and 5-HT_{2A} receptors, respectively. The inhibition or K_i values of the newly synthetic aporlogues are summarized in Table 1.

Similar to the reported aporphines (−)-**6**[33] and (−)-**7**,[39] all the new synthetic aporlogues exhibited weak binding to the D_1 and 5-HT_{2A} receptors, except benzyl carbamates (−)-**13** and (±)-**13**, for which K_i values of 2.4 and 4.2 μM, respectively, at the D_1 receptor were observed. Compared to the C6α-*R*-configured aporphine (−)-**6**, its racemate (±)-**6** is 7-fold less potent (114 nM) at the D_2 receptor (854 nM), while compatible affinity was observed at the 5-HT_{1A} receptor (45 and 66 nM, respectively). This result indicated that the C6α-*R* configuration in aporphines is an important determinant of D_2 receptor binding, but not for 5-HT_{1A} receptor binding. A significant discrepancy was observed among the synthetic aporphin-11-yl carbamates. In comparison to the high binding affinity of 11-carboxylic acid ester (−)-**7**, carbamates (−)-**8**−(−)-**13** and their racemates (±)-**8**−(±)-**13** all exhibited remarkably weakened binding inhibition at the D_2 receptor, indicating that most of these carbamates were inactive at this receptor, except *tert*-butyl [(−)-**11**] and benzyl [(−)-**13**] carbamates from which moderate K_i values of 871 nM and 2.4 μM were observed, respectively, for the D_2 receptor. A direct comparison between ester (−)-**7** and carbamate (−)-**8** indicated that the additional hydrogen bonding donor (NH) in the carbamate moiety is detrimental to D_2 receptor binding. To our surprise, moderate to good affinity (K_i = 90−400 nM) at the 5-HT_{1A} receptor was generally retained in the carbamate subseries. All the C6α-*R*-configured carbamates (−)-**8**−(−)-**11** and (−)-**13** exhibited statistically identical binding potencies at this receptor with K_i values of ∼90 nM (87−96 nM). Similar binding potency was also observed from racemates (±)-**8**−(±)-**13** showing K_i values of 124−385 nM at the 5-HT_{1A} receptor. These racemates were generally 2−5-fold less potent than their C6α-*R*-configured carbamates, indicating that the C6α-*R* configuration in these aporphine series is beneficial to the 5-HT_{1A} receptor. In comparison to that of ester (−)-**7**, the reduced affinity of these carbamates at the 5-HT_{1A} receptor further confirmed that the carbamate moiety hampered the interaction of the ligand with both D_2 and 5-HT_{1A} receptors.

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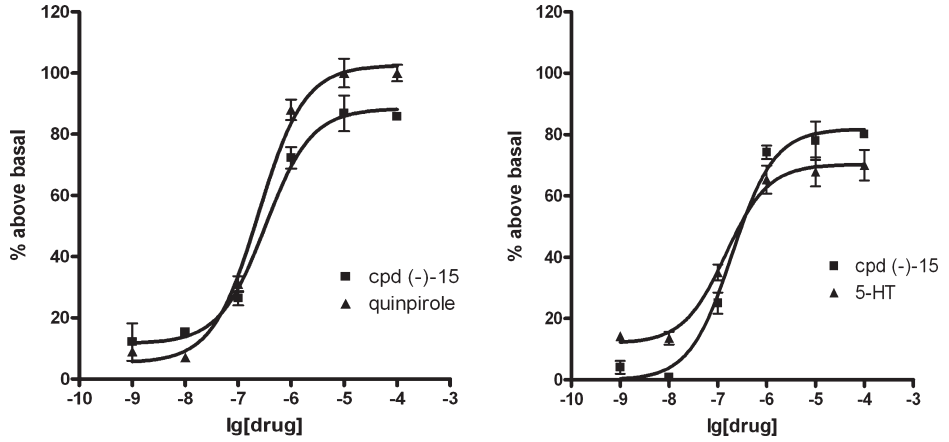

Figure 3. Agonistic effects of compound (−)-**15** on the D_2 and 5-HT_{1A} receptors. Results were calculated as the percent stimulation above basal. The data are means ± SE from at least two independent experiments.

Different from carboxylic acid ester (−)-**7**, esters (±)-**14** and (±)-**15** bearing a larger and more lipophilic esteric moiety were proposed to bring better chemostability. However, only moderate affinity was observed for (±)-**14** at the D_2 receptor (851 nM) and for (±)-**15** at the 5-HT_{1A} receptor (137 nM). Fortunately, C6α-*R*-configured (−)-**15** displayed a good affinity at the D_2 receptor and a high affinity at the 5-HT_{1A} receptor, with K_i values of 174 and 66 nM, respectively. It has to be noted that (−)-**15** was prepared from racemic lipoic acid, whereas the D- and L-lipoic esters (−)-**15D** and (−)-**15L**, respectively, exhibited somewhat lower potency at the D_2 receptor, although both isomers exhibited slightly improved affinity at the 5-HT_{1A} receptor. In addition, compared to (−)-**15**, (−)-**15D** and (−)-**15L** were found to be hardly soluble in both aqueous and organic solvents.

Aporlogues (−)-**17**−(−)-**19** represented another subseries of 11-amino-substituted aporlogues. Compared to 11-hydroxyaporphine (−)-**6**, 11-aminoaporphine (−)-**17** retained moderate affinity at the D_2 and 5-HT_{1A} receptors, with K_i values of 352 and 276 nM, respectively, which are 3- and 6-fold less potent, respectively, than that of phenol (−)-**6**. Shifting butyryl ester (−)-**7** to the corresponding amide (−)-**18** led to a complete loss of affinity at the D_2 receptor and a 32-fold reduction in affinity (380 nM) at the 5-HT_{1A} receptor. Similarly, lipoic amide (−)-**19** is also inactive at the D_2 receptor but exhibited a moderate affinity at the 5-HT_{1A} receptor (249 nM). Although amino or amido functionality has been widely used as the bioisosteric replacement[51] for the hydroxyl group, the results for compounds (−)-**17**−(−)-**19** indicated that this is not the case in our study.

Amides (±)-**22** and (±)-**23**, urea (±)-**24**, and oxadiazole (±)-**25** represented a subseries of C11-linked aporphines. Quite disappointingly, all these compounds were completely inactive at the D_2 receptor; therefore, their corresponding C6α-*R* isomers were not explored.

On the basis of the SAR of the newly synthesized aporlogues, lipoic ester (−)-**15** stands out bearing the optimal receptor binding profile. In addition, lipoic acid has been well recognized as a universal antioxidant that can readily cross the blood−brain barrier.[52−56] Therefore, lipoic ester (−)-**15** appears to have optimal pharmacokinetic properties and antioxidant benefits and was selected as a lead for further in vitro and in vivo bioassays.

*[^{35}S]GTPγS Assays of Compound (−)-**15***. Stably transfected D_2 or 5-HT_{1A} cell membrane fractions were prepared, and the GTPγS binding assay was performed as previously described.[33]

Table 2. Binding Affinities of Lipoic Ester (−)-15 at the α_{1A}, α_{1B}, α_{1D}, and β_2 Receptors

	IC_{50} (μM)			
compound	α_{1A}	α_{1B}	α_{1D}	β_2
(−)-**15**	>10	>10	>10	>10
adrenaline	1.39 (0.501[a])	0.93 (0.316[a])	0.102 (0.063[a])	0.011 (0.015[b])

[a] From ref 58. [b] From ref 59.

Compound (−)-**15** was diluted to different concentrations (1 nM to 100 μM) and added to the reaction tubes. The D_2 receptor agonist quinpirole [(4a*R*,8a*R*)-5-propyl-4,4a,5,6,7,8,8a,9-octahydro-1*H*-pyrazolo[3,4-*g*]quinoline][57] and 5-HT_{1A} receptor agonist 5-HT (5-hydroxytryptamine) were used for comparison. From the results in Figure 3, compound (−)-**15** produced compatible agonistic activity at both D_2 and 5-HT_{1A} receptors, in comparison to their respective standard agonist. Therefore, aporlogue (−)-**15** is a full agonist at both receptors, and the calculated agonistic potencies (EC_{50}) were 320 and 190 nM for the D_2 and 5-HT_{1A} receptors, respectively.

*Selectivity of Aporlogue (−)-**15** versus Adrenergic Receptors.* In addition to D_1, D_2, 5-HT_{1A}, and 5-HT_{2A} receptors, aporlogue (−)-**15** was also evaluated at the adrenergic α_{1A}, α_{1B}, α_{1D}, and β_2 receptors in cells by following literature procedures.[58,59] Adrenaline [(−)-epinephrine] was used as a standard. The results are summarized in Table 2, where no significant binding was observed for (−)-**15** at all the tested adrenergic receptors with IC_{50} values of >10 μM. The inactive property of these adrenergic receptors of (−)-**15** may provide an additional advantage in preventing a potential adverse effect on the cardiac and vascular system.

*Aporlogue (−)-**15** Elicited Potent Antiparkinsonian Actions in 6-OHDA-Lesioned Rats.* 6-OHDA-lesioned parkinsonian rats received injections of 0.5 or 1.5 mg of aporlogue (−)-**15**/kg (intraperitoneal), and contralateral rotation was recorded. As shown in Figure 4A, (−)-**15** elicited robust contralateral turning. The rotation behavior lasted for at least 6 h (Figure 4B). Pretreatment with the D_2 receptor antagonist spiperone {8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one}[60] significantly reduced (−)-**15**-induced contralateral turning. In contrast, pretreatment of 5-HT_{1A} receptors with antagonist WAY-100635

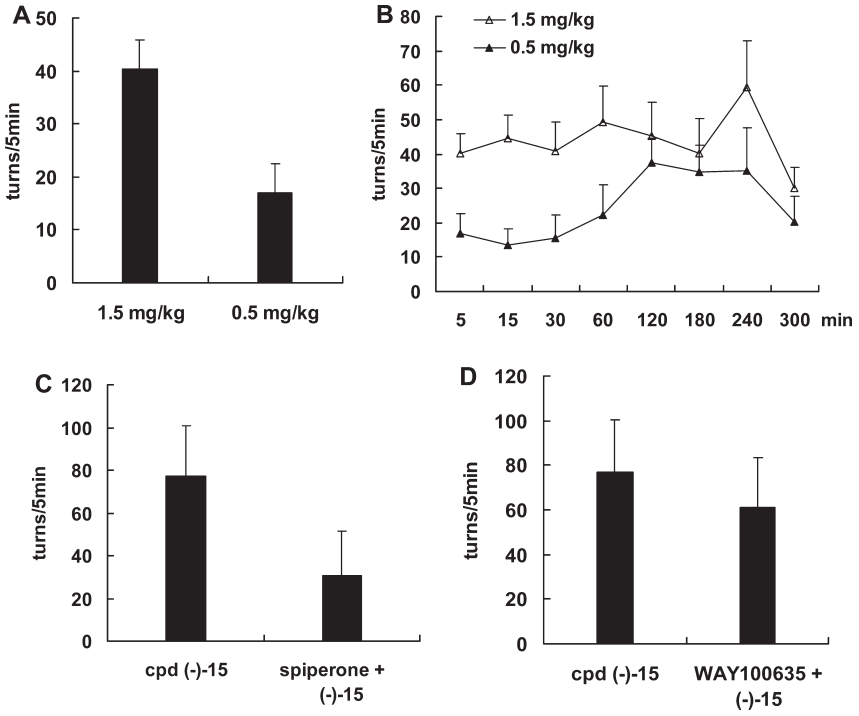

Figure 4. Compound (−)-**15** elicits a potent antiparkinsonian effect in 6-OHDA-lesioned rats. (A) 6-OHDA-lesioned rats were injected intraperitoneally (ip) with 0.5 or 1.5 mg of (−)-**15**/kg, and contralateral rotation was recorded over a period of 5 min after the injection. (B) Rats were treated as described for panel A, and contralateral rotation was monitored at the indicated time for a total of 6 h. (C) 6-OHDA-lesioned rats were pretreated with the D_2 receptor antagonist spiperone (2 mg/kg, ip) for 15 min before being challenged with 1.5 mg of (−)-**15**/kg, and contralateral turning was recorded for 5 min ($p < 0.05$). (D) 6-OHDA-lesioned rats were pretreated with the 5-HT_{1A} receptor antagonist WAY-100635 (0.1 mg/kg, ip) for 10 min before being challenged with 1.5 mg of (−)-**15**/kg. Data were summarized from six or seven animals in each group and are expressed as means ± SE.

{(*S*)-*N*-*tert*-butyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide}[61] did not significantly alter (−)-**15**-induced turning, suggesting that D_2 receptor agonistic activity contributed to the antiparkinsonian effect of (−)-**15**.

*Aporlogue (−)-**15** Reduced the Level of Development of L-DOPA-Induced Dyskinesia (LID).* PD rats were treated once daily with 6 mg of L-DOPA/kg, 0.5 or 1.5 mg of (−)-**15**/kg, or 0.5 or 1.5 mg of (−)-**15**/kg with L-DOPA and saline for 21 days. The AIM (abnormal involuntary movement) score was recorded on days 1, 4, 7, 11, 14, 17, and 21. As shown in Figure 5A, aporlogue (−)-**15** alone at both doses caused very slight dyskinesia, while L-DOPA treatment induced severe dyskinesia that reached a maximum on day 14. Treatment of rats with (−)-**15** and L-DOPA induced less dyskinesia than treatment with L-DOPA alone, and a significant difference was observed on days 14, 17, and 21. These results clearly indicate that aporlogue (−)-**15** slowed the development of LID.

To estimate the effect of aporlogue (−)-**15** on established LID, PD rats were treated with L-DOPA consecutively for 21 days to induce stable expression of LID. On day 23, rats with LID were injected with a single dose of 0.5 or 1.5 mg of (−)-**15**/kg prior to L-DOPA challenge. The AIMs were then scored. As shown in Figure 5B, acute administration of (−)-**15** did not significantly suppress established LID.

To determine if the attenuated LID development by chronic (−)-**15** treatment had any cost with respect to the antiparkinsonian potency of L-DOPA, the contralateral rotation was also recorded (Figure 6). The results indicated that there was no difference in the rotation of rats treated with L-DOPA alone and rats treated with (−)-**15** and L-DOPA, indicating that (−)-**15** attenuated the development of LID at no cost with respect to the antiparkinsonian effect of L-DOPA.

*Effects of Aporlogue (−)-**15** on G-Protein Coupling of the 5-HT_{1A} Receptor in Striatum.* A decrease in the level of 5-HT_{1A} receptor mRNA expression was reported in the LID rats, and 5-HT_{1A} receptor agonists were found to attenuate LID.[62,63] Accordingly, we explored the sensitivity of striatal 5-HT_{1A} receptor activation in LID rats in response to L-DOPA or (−)-**15** treatment. Rats were treated with saline, L-DOPA, (−)-**15** alone, or (−)-**15** with L-DOPA for 21 days and then decapitated, and the striatum was dissected for membrane preparations. The [^{35}S]GTPγS binding assay was performed to test the G-protein coupling of the 5-HT_{1A} receptor. As shown in Figure 7, 5-HT_{1A} receptor agonist 8-OH-DPAT[64] stimulated GTPγS binding of the 5-HT_{1A} receptor in lesioned striatum ($p < 0.05$, compared to intact striatum) in a saline control experiment. In agreement with our previous observation,[63] chronic L-DOPA treatment significantly reduced the level of 8-OH-DPAT-stimulated GTPγS binding in the lesioned side relative to intact striatum, indicative of the hypofunction of the striatal 5-HT_{1A} receptor in LID animals. In contrast, chronic treatment with (−)-**15** restored the sensitivity of 5-HT_{1A} receptor and G-protein coupling, suggesting that (−)-**15** improved 5-HT_{1A} receptor activation in the lesioned striatum.

*Aporlogue (−)-**15** Reduces the Level of FosB Expression in the Striatum.* In addition to receptor supersensitivity, DA depletion and chronic L-DOPA treatment were found to modify several intracellular signal pathways, in which the immediate early genes

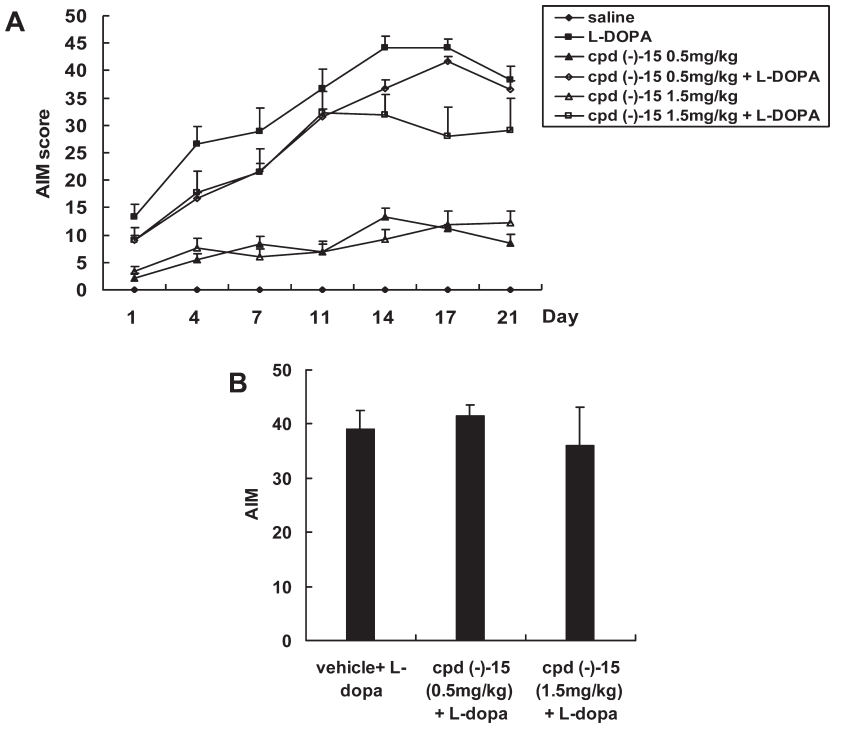

Figure 5. Effects of compound (−)-**15** on L-DOPA-induced dyskinesia (LID). (A) PD rats were treated once daily with saline, L-DOPA, compound (−)-**15** (0.5 or 1.5 mg/kg), or L-DOPA and (−)-**15** for 21 days. In the co-administration group, (−)-**15** was injected (ip) 15 min before the administration of L-DOPA. The AIM score was evaluated on the indicated days ($n = 7$; $^*p < 0.05$ compared with the L-DOPA group). (B) PD rats were treated with 6 mg L-DOPA/kg for 21 days to establish steady expression of LID. On day 23, they were treated with 0.5 or 1.5 mg of (−)-**15**/kg for 15 min before L-DOPA challenge. AIMs were scored as described ($n = 7$).

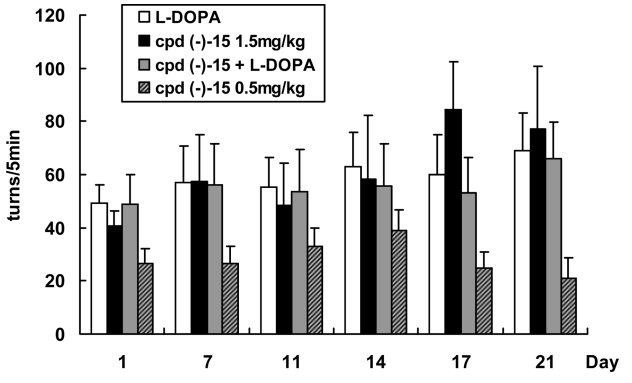

Figure 6. Rotation behavior induced by chronic drug administration. Rats were treated daily with L-DOPA, compound (−)-**15** (0.5 or 1.5 mg/kg), or (−)-**15** and L-DOPA (1.5 mg/kg) for 21 days. The contralateral rotation was recorded for 5 min on the designated days. The data are the summary obtained from at least seven animals for each group.

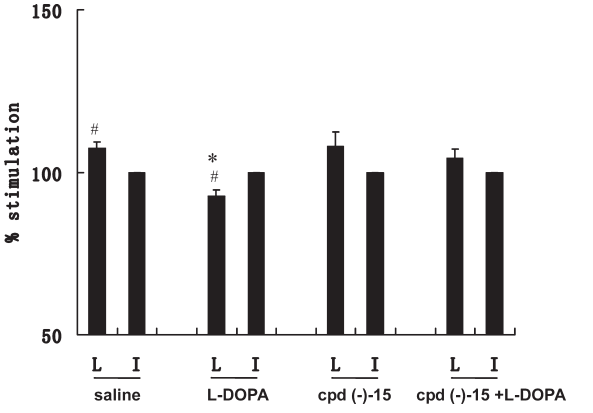

Figure 7. 8-OH-DPAT-stimulated GTPγS binding in striatum. Rats were treated with saline, L-DOPA, and 1.5 mg of (−)-**15**/kg or 1.5 mg of (−)-**15**/kg with L-DOPA for 21 days. The striatal membrane was prepared, and the [^{35}S]GTPγS binding assay was performed in the presence of 8-OH-DPAT (100 μM) as described in Experimental Section. Data are expressed as the percentage change in relation to the stimulation of [^{35}S]GTPγS binding obtained from respective intact striatum that was set to 100%. L denotes the lesion side and I the intact side. $^*p < 0.05$, compared with the lesion sides of saline control rats. $^\#p < 0.05$, compared with the intact side of the same treatment.

(IEGs) such as FosB have drawn particular attention. The expression of FosB is strongly correlated with the development of AIMs in 6-OHDA-lesioned PD rats.[65−68] In addition, L-DOPA induces a high level of expression of FosB in striatum ipsilateral to lesion that is associated with the severity of dyskinesia. We therefore determined if the (−)-**15**-attenuated LID is associated with FosB expression. As shown in Figure 8, chronic L-DOPA treatment resulted in a dramatic increase in the level of striatal FosB in lesioned striatum, while (−)-**15** treatment blocked L-DOPA-enhanced FosB expression. This result further confirmed that (−)-**15** attenuated the development of LID.

*Aporlogue (−)-**15** Acts on the Postsynaptic 5-HT$_{1A}$ Receptor.* To further explore the mechanism of action of compound (−)-**15**, we attempted to test if compound (−)-**15** acts on the pre- or postsynaptic 5-HT$_{1A}$ receptor. We sequentially elicited excitatory postsynaptic current (EPSC) pairs at an interval of

dx.doi.org/10.1021/jm200347t |J. Med. Chem. 2011, 54, 4324–4338

20 ms. The amplitude of EPSC was believed to reflect the postsynaptic response, whereas the ratio of the two pulses (paired pulse ratio, PPR) was considered to represent the presynaptic changes.[69] By comparing the EPSC amplitude and PPR prior to and during compound (−)-**15** perfusion, we were able to differentiate the pre- or postsynaptic site of drug action. As shown in Figure 9, aporlogue (−)-**15** (10 μM) decreased the EPSC amplitude to 63.8 ± 9.2% (Figure 9A,B, left panel) (n = 6; paired t test, p = 0.011). However, the drug failed to alter PPR (Figure 9A,B, right panel) (n = 6; control = 100%; compound (−)-**15** = 114.5 ± 12.2%; paired t test, p = 0.290), indicating that compound (−)-**15** has no effect on presynaptic transmission. To confirm that the effect of compound (−)-**15** was mediated by the 5-HT$_{1A}$ receptor, the 5-HT$_{1A}$ antagonist WAY-100635 (10 μM) was perfused prior to compound (−)-**15**. In this case, compound (−)-**15** produced no effect on EPSC amplitude (Figure 9C,D) (n = 6; control = 100%; compound (−)-**15** = 99.4 ± 5.8%; paired t test, p = 0.918). The results implied that compound (−)-**15** activates the postsynaptic 5-HT$_{1A}$ receptor.

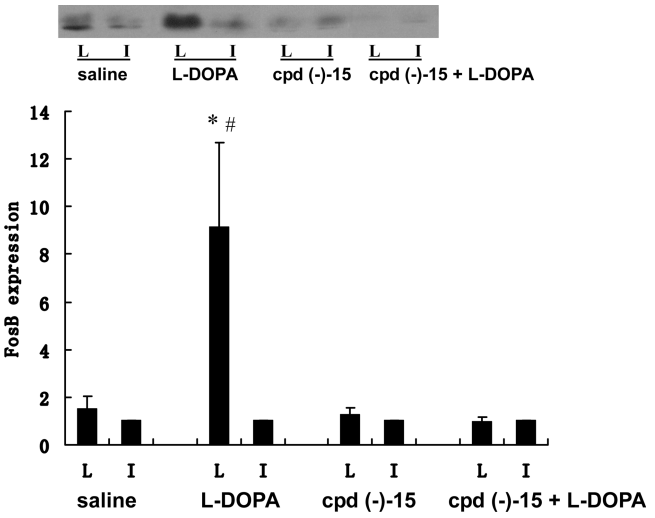

Figure 8. Compound (−)-**15** did not induce FosB expression in the striatum. PD rats were treated with saline, L-DOPA, and 1.5 mg of (−)-**15**/kg, or 1.5 mg of (−)-**15**/kg and L-DOPA for 21 days. FosB expression in the striatum of each group was detected by Western blot. The optical density of each lane was analyzed with ImageJ (National Institutes of Health). The experiment was repeated in at least three animals. Data are expressed as the percentage change in relation to the expression of respective intact striatum that was set to 1. L denotes the lesion side and I the intact side. *p < 0.05, compared with lesion sides of other three groups. #p < 0.05, compared with intact side of the same group.

CONCLUSION

This study focused on the development, characterization, and anti-PD effects of a series of new aporlogues possessing a 5-HT$_{1A}$ and D$_2$ dual-receptor agonistic profile. The rationale is based on the fact that altered 5-HT$_{1A}$ receptor function and expression were clearly documented in experimental animals with LID. Furthermore, the proof of concept of designing a dual D$_2$ and 5-HT$_{1A}$ agonist as a novel anti-PD therapy has been shown with clinical drugs sarizotan and pardoprunox.

In our previous SAR study, we found that the C11 position of the aporphine skeleton is a critical site determining different receptor binding capacities. In this regard, a series of new aporlogues were synthesized with a C-, N-, or O-linkage at the C11 position. Although a discrepancy between the C6α-*R* aporphines and their racemates existed, the 11-O- and 11-N-linked aporphines generally have moderate binding potency at the 5-HT$_{1A}$ receptor. Compared to the 11-esteric aporphines, most of the corresponding carbamates did not show appreciable binding at the D$_2$ receptor, suggesting that the additional H-bonding function (NH) in the carbamate moiety hampered the ligand−receptor interaction. Esteric aporlogues bearing a larger (or longer) and more lipophilic acid moiety retained good affinity at both D$_2$ and 5-HT$_{1A}$ receptors, with lipoic acid ester (−)-**15** displaying the optimal binding profile possessing K_i values of 174 and 66 nM at the two receptors, respectively.

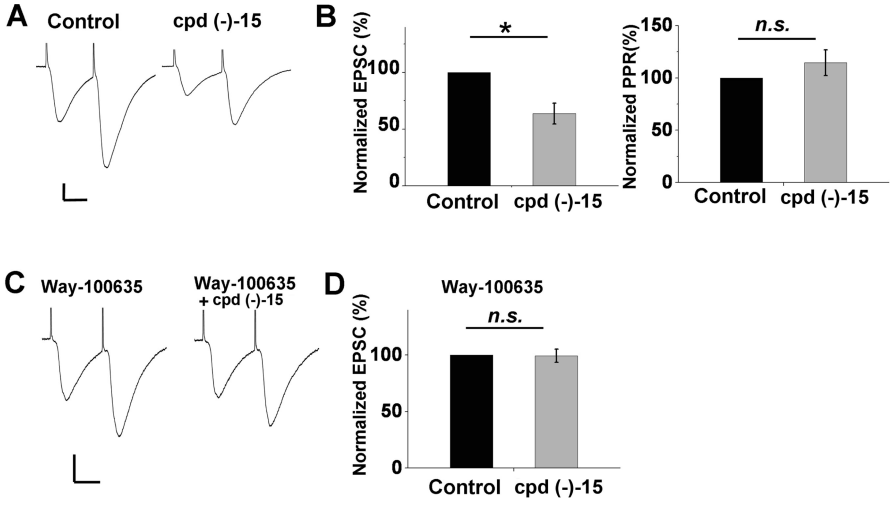

Figure 9. Compound (−)-**15** decreased the EPSC amplitude via the 5-HT$_{1A}$ receptor. (A) Sample traces of paired EPSCs (average of 10 sweeps) before and 5 min after perfusion of compound (−)-**15** (10 μM). (B) Summary of the effects of compound (−)-**15** on EPSC amplitude and PPR. (C) Sample traces of EPSC amplitude (average of 10 sweeps) before and 5 min after perfusion of compound (−)-**15** (10 μM) in the presence of WAY-100635 (10 μM). (D) WAY-100635 blocked the EPSC inhibition effect of compound (−)-**15**. The scale bar denotes 60 pA and 10 ms. *p < 0.05; n.s., no significant difference.

dx.doi.org/10.1021/jm200347t |J. Med. Chem. 2011, 54, 4324–4338

The C11-linked aporlogues showed a complete loss of affinity at the D_2 receptor. In addition, the new aporlogues did not show noticeable binding potency at either the D_1 or 5-HT_{2A} receptor.

Because lipoic ester (−)-**15** stands out as having the optimal receptor binding profile, it was elected as a lead for further in vitro and in vivo bioassays. In the [^{35}S]GTPγS assays, (−)-**15** displayed a full agonistic response at both D_2 and 5-HT_{1A} receptors. In the 6-OHDA-lesioned PD rat model, (−)-**15** elicited potent antiparkinsonian action. The contralateral rotation behavior was dose-dependent and was confirmed to be mediated by the D_2, not 5-HT_{1A}, receptor. Moreover, (−)-**15** itself induced minor dyskinesia but significantly suppressed L-DOPA-induced dyskinesia (LID) without attenuating contralateral rotation when co-administered with L-DOPA chronically. It was further found that chronic L-DOPA treatment induced 5-HT_{1A} receptor desensitization in the striatum of PD rats while (−)-**15** normalized receptor sensitivity. Meanwhile, we found that (−)-**15** did not induce significant FosB expression in the striatum, while reduction of the level of FosB expression was observed upon co-injection with L-DOPA. Furthermore, the results of electrophysiological experiments confirmed that compound (−)-**15** activates on the postsynaptic 5-HT_{1A} receptor, which further supports the importance of postsynaptic 5-HT_{1A} receptor activation in preventing the development of LID.

In conclusion, structural modification on the 11-hydroxyaporphine led to the identification of lipoic ester (−)-**15** as a full agonist at both D_2 and 5-HT_{1A} receptors. It elicited antiparkinsonian action with very slight dyskinesia in PD rats. Chronic use of (−)-**15** reduced the level of LID without attenuating the antiparkinsonian effect. These results suggest that dual-5-HT_{1A} and D_2 receptor full agonist (−)-**15** may present as a novel candidate drug in the treatment of PD and LID. The continued development of this compound will be justified by its safety and metabolic profiles, which are currently being investigated.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectral data were recorded in $CDCl_3$ on a 300 MHz NMR spectrometer, and ^{13}C NMR data were recorded in $CDCl_3$ on a 400 MHz NMR spectrometer. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded at an ionizing voltage of 70 eV. Elemental analyses were performed on an elemental analyzer. Optical rotations were determined with a digital polarimeter and were the average of three measurements. Column chromatography was conducted on silica gel (200−300 mesh). All reactions were monitored using thin-layer chromatography (TLC) on silica gel plates. Yields were of purified compounds and were not optimized. Compounds (−)-**6**,[33,39,40] (−)-**7**,[39] and (±)-**6**[41] were prepared according to corresponding literature procedures. The C6α racemic and C6α-*R* aporphine analogues were prepared from (±)-**6** and (−)-**6**, respectively, using the same procedure, and they gave nearly identical analytical data. HPLC analysis was conducted for all compounds listed in Table 1 on an Agilent 1100 series LC system (Agilent ChemStation Rev.A.10.02; ZORBAX Eclipse XDB-C8, 4.8 mm × 150 mm, 5 μm, 1.0 mL/min, uv 254 nM, room temperature) with two solvent systems (MeCN/H_2O and MeOH/H_2O). All the assayed compounds displayed purities of 95−99% in both solvent systems.

General Procedure for the Synthesis of *N-n*-Propylnoraporphin-11-yl Carbamates (±)-8−(±)-10 and (−)-8−(−)-10. To a mixture of 11-hydroxy-*N-n*-propylnoraporphine (±)-**6** or (−)-**6** (30 mg, 0.11 mmol) and a catalytic amount of Et_3N in anhydrous THF (10 mL) was added an appropriate isocyanate (0.16 mmol). The reaction mixture was refluxed for 2 days, cooled, and evaporated. The residue was subjected to column chromatography on silica gel (3:1 petroleum/ethyl acetate, 1% Et_3N) to give corresponding carbamates (±)-**8**−(±)-**10** and (−)-**8**−(−)-**10**.

*(6αR,S)-N-n-Propylnoraporphin-11-yl Ethylcarbamate (±)-**8***. Colorless oil (24 mg, 63%). ^{1}H NMR (300 MHz, $CDC1_3$): δ 7.69 (d, 1H, J = 8.1 Hz), 7.18 (m, 3H), 7.07 (t, 2H, J = 7.8, 8.7 Hz), 5.05 (s, 1H), 3.42 (dd, 1H, J = 3.3, 13.2 Hz), 3.18 (m, 5H), 2.92 (m, 1H), 2.87 (d, 1H, J = 16.2 Hz), 2.51 (m, 3H), 1.64 (m, 2H), 1.22 (t, 3H, J = 6.9, 7.5 Hz), 0.97 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 147.5, 138.4, 135.7, 133.5, 130.8, 128.0, 127.6, 127.5, 126.0, 125.5, 124.9, 122.4, 59.2, 56.5, 48.8, 36.1, 35.0, 29.3, 19.5, 15.2, 12.1. MS (ESI, $[M + H]^+$): m/z 351. HRMS (ESI) calcd for $C_{22}H_{27}N_2O_2$ 351.2073, found 351.2088.

6α*R*-(−) isomer (−)-**8**. Colorless oil (27 mg, 70%). $[\alpha]^{20}_D$ −110.3° (c 0.65, $CHCl_3$).

*(6αR,S)-N-n-Propylnoraporphin-11-yl Propylcarbamate (±)-**9***. White oil (34 mg, 87%). ^{1}H NMR (300 MHz, $CDC1_3$): δ 7.69 (d, 1H, J = 7.5 Hz), 7.14 (m, 5H), 5.12 (s, 1H), 3.43 (d, 1H, J = 13.2 Hz), 3.36 (m, 5H), 2.95 (m, 1H), 2.87 (d, 1H, J = 16.2 Hz), 2.51 (m, 3H), 1.58 (m, 4H), 0.97 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 147.4, 138.3, 135.7, 133.4, 130.8, 128.0, 127.6, 127.5, 125.9, 125.5, 124.8, 122.4, 59.1, 56.5, 48.8, 42.9, 34.9, 29.2, 23.0, 19.4, 12.1, 11.1. MS (ESI, $[M + H]^+$): m/z 365. HRMS (ESI, $[M + H]^+$) calcd for $C_{23}H_{29}N_2O_2$ 365.2229, found 365.2223.

6α*R*-(−) isomer (−)-**9**. White oil (32 mg, 80%). $[\alpha]^{20}_D$ −126.5° (c 0.65, $CHCl_3$).

*(6αR,S)-N-n-Propylnoraporphin-11-yl Butylcarbamate (±)-**10***. White oil (31 mg, 77%). ^{1}H NMR (300 MHz, $CDC1_3$): δ 7.70 (d, 1H, J = 7.5 Hz), 7.14 (m, 5H), 5.14 (s, 1H), 3.44 (d, 1H, J = 13.2 Hz), 3.19 (m, 5H), 2.92 (m, 1H), 2.75 (d, 1H, J = 15.9 Hz), 2.54 (m, 3H), 1.61 (m, 2H), 1.49 (m, 2H), 1.35 (m, 2H), 0.95 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 147.4, 138.3, 135.6, 133.3, 130.7, 128.0, 127.6, 127.4, 125.9, 125.4, 124.8, 122.4, 59.1, 56.4, 48.7, 40.9, 34.9, 31.8, 29.2, 19.7, 19.4, 13.7, 12.0. MS (ESI, $[M + H]^+$): m/z 379. HRMS (ESI) calcd for $C_{24}H_{31}N_2O_2$ 379.2386, found 379.2398.

6α*R*-(−) isomer (−)-**10**. White oil (33 mg, 79%). $[\alpha]^{20}_D$ −94.4° (c 0.90, $CHCl_3$).

*(6αR,S)-N-n-Propylnoraporphin-11-yl tert-Butylcarbamate (±)-**11***. To a mixture of 11-hydroxy-*N-n*-propylnoraporphine (±)-**6** (30 mg, 0.11 mmol) and a catalytic amount of Et_3N in anhydrous toluene (10 mL) was added 2-isocyanato-2-methylpropane (40 μL, 0.34 mmol). The reaction mixture was refluxed for 3 days, cooled, and evaporated. Purification by column chromatography on silica gel (3:1 petroleum/ethyl acetate, 1% Et_3N) provided carbamate (±)-**11** as a yellow oil (10 mg, 25%). ^{1}H NMR (300 MHz, $CDC1_3$): δ 7.67 (d, 1H, J = 7.8 Hz), 7.17 (m, 3H), 7.06 (t, 2H, J = 6.6, 7.2 Hz), 5.02 (s, 1H), 3.44 (dd, 1H, J = 3.0, 13.8 Hz), 3.13 (m, 3H), 2.92 (m, 1H), 2.75 (d, 1H, J = 15.6 Hz), 2.52 (m, 3H), 1.61 (m, 2H), 1.33 (s, 9H), 0.97 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 147.3, 138.3, 133.4, 130.9, 127.9, 127.6, 125.9, 125.3, 124.8, 122.6, 59.2, 56.5, 50.8, 48.8, 35.0, 29.2, 28.8, 19.5, 12.1. MS (ESI, $[M + H]^+$): m/z 379. HRMS (ESI) calcd for $C_{24}H_{31}N_2O_2$ 379.2386, found 379.2374.

6α*R*-(−) isomer (−)-**11**. Yellow oil (7 mg, 17%). $[\alpha]^{20}_D$ −155.2° (c 0.25, $CHCl_3$).

*N-n-Propylnoraporphin-11-yl Carbamates (±)-**12**, (−)-**13**, and (±)-**13***. To a mixture of 11-hydroxy-*N-n*-propylnoraporphine (±)-**6** or (−)-**6** (30 mg, 0.11 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (10 mL) was added naphthyl or benzyl isocyanate (0.16 mmol). The reaction mixture was reacted at room temperature for 24 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (3:1 petroleum/ethyl acetate, 1% Et_3N) to give aporphines (±)-**12**, (−)-**13**, and (±)-**13**.

*(6αR,S)-N-n-Propylnoraporphin-11-yl Naphthalen-1-ylcarbamate (±)-**12***. Colorless oil (23 mg, 48%). ^{1}H NMR (300 MHz, $CDC1_3$): δ

7.81 (m, 5H), 7.50 (m, 3H), 7.24 (m, 4H), 7.06 (d, 1H, J = 6.9 Hz), 3.44 (d, 1H, J = 11.4 Hz), 3.14 (m, 3H), 2.90 (m, 1H), 2.74 (d, 1H, J = 16.5 Hz), 2.53 (m, 3H), 1.61 (m, 2H), 0.97 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 138.6, 134.0, 133.6, 131.8, 130.6, 128.7, 128.2, 127.7, 126.4, 126.1, 125.9, 125.7, 124.8, 122.4, 59.2, 56.5, 48.8, 34.9, 29.2, 19.5, 12.1. MS (ESI, $[M + H]^+$): m/z 449. HRMS (ESI) calcd for $C_{30}H_{29}N_2O_2$ 449.2229, found 449.2226.

*(6αR,S)-N-n-Propylnoraporphin-11-yl Benzylcarbamate (±)-**13***. White oil (22 mg, 50%). ^{1}H NMR (300 MHz, $CDC1_3$): δ 7.71 (d, 1H, J = 7.5 Hz), 7.32 (m, 4H), 7.22 (d, 1H, J = 7.5 Hz), 7.17 (m, 5H), 5.41 (s, 1H), 4.40 (d, 2H, J = 5.7 Hz), 3.44 (dd, 1H, J = 2.1, 13.5 Hz), 3.16 (m, 3H), 2.91 (m, 1H), 2.76 (d, 1H, J = 15.6 Hz), 2.53 (m, 3H), 1.61 (m, 2H), 0.97 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 147.4, 138.4, 138.0, 135.7, 133.5, 130.7, 128.7, 128.1, 127.7, 127.6, 127.5, 127.3, 126.1, 125.7, 124.8, 122.4, 59.1, 56.5, 48.8, 45.2, 34.9, 29.2, 19.4, 12.1. MS (ESI, $[M^+]$): m/z 412. HRMS (ESI) calcd for $C_{27}H_{28}N_2O_2$ 412.2150, found 412.2150.

6α*R*-(−) isomer (−)-**13**. White oil (25 mg, 55%). $[\alpha]^{20}_D$ −36.5° (c 2.00, $CHCl_3$).

*N-n-Propylnoraporphin-11-yl Carboxylic Esters (±)-**14**, (±)-**15**, (−)-**15**, (−)-**15D**, and (−)-**15L***. To a solution of 11-hydroxy-*N-n*-propylnoraporphine (−)-**6** or (±)-**6** (30 mg, 0.11 mmol), an appropriate acid (0.13 mmol), and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (8 mL) under N_2 was added EDCI (42 mg, 0.22 mmol) at room temperature. The reaction mixture was stirred overnight and then diluted with CH_2Cl_2 (20 mL) and H_2O (15 mL). The organic layer was separated, washed with brine (15 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (4:1 petroleum/ethyl acetate, 1% Et_3N) to give a pure oily product, which was then converted into the hydrochloride salt with HCl ether (1 M).

*(6αR,S)-11-[2-(Phenylthio)acetyloxy]-N-n-propylnoraporphine (±)-**14***. Yellow oil (21 mg, 53%). ^{1}H NMR (300 MHz, $CDC1_3$): δ 7.68 (d, 1H, J = 7.5 Hz), 7.43 (m, 2H), 7.23 (m, 5H), 7.08 (m, 2H), 6.92 (m, 1H), 3.89 (d, 1H, J = 15.3 Hz), 3.81 (d, 1H, J = 15.3 Hz), 3.41 (dd, 1H, J = 3.3, 13.2 Hz), 3.12 (m, 3H), 2.90 (m, 1H), 2.76 (d, 1H, J = 15.6 Hz), 2.51 (m, 3H), 1.62 (m, 2H), 0.97 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDC1_3$): δ 167.9, 147.1, 138.7, 135.8, 134.6, 133.7, 130.3, 130.2, 129.1, 128.3, 127.7, 127.3, 127.2, 126. 2, 124.8, 121.7, 59.2, 56.5, 48.8, 37.1, 34.9, 29.3, 19.5, 12.0. MS (ESI, $[M^+]$): m/z 429. HRMS (ESI) calcd for $C_{27}H_{27}NSO_2$ 429.1762, found 429.1761.

*(6αR,S)-11-[5-(1,2-Dithiolan-3-yl)pentyloxy]-N-n-propylnoraporphine (±)-**15***. White oil (40 mg, 78%). ^{1}H NMR: δ 7.73 (d, 1H, J = 7.5 Hz), 7.20 (m, 3H), 7.07 (d, 1H, J = 7.5 Hz), 7.01 (d, 1H, J = 7.8 Hz), 3.54 (m, 1H), 3.43 (dd, 1H, J = 13.8, 2.7 Hz), 3.07−3.20 (m, 5H), 2.89 (m, 1H), 2.75 (d, 1H, J = 16.5 Hz), 2.38−2.62 (m, 6H), 1.89 (m, 1H), 1.69 (m, 6H), 1.49 (m, 2H), 0.98 (t, 3H, J = 7.2 Hz).

6α*R* isomer (−)-**15**. White oil (35 mg, 70%). $[\alpha]^{20}_D$ −140.2° (c 0.85, $CHCl_3$). ^{1}H NMR (600 MHz, $CDC1_3$): δ 7.71 (d, 1H, J = 7.8 Hz), 7.14−7.24 (m, 3H), 7.06 (d, 1H, J = 7.2 Hz), 6.99 (d, 1H, J = 7.8 Hz), 3.53 (m, 1H), 3.42 (d, 1H, J = 13.2 Hz), 3.06−3.18 (m, 5H), 2.89 (m, 1H), 2.74 (d, 1H, J = 16.2 Hz), 2.38−2.62 (m, 6H), 1.87 (m, 1H), 1.54−1.76 (m, 6H), 1.39−1.53 (m, 2H), 0.96 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDC1_3$): δ 171.6, 147.1, 138.6, 135.8, 133.6, 130.6, 128.1, 127.7, 127.3, 125.9, 124.6, 122.0, 59.1, 56.4, 56.2, 48.7, 40.1, 38.4, 34.9, 34.5, 34.3, 29.2, 28.7, 24.3, 19.5, 12.0. MS (ESI): m/z 467 (M^+). Anal. Calcd for $C_{24}H_{33}NO_2S_2 \cdot 0.9HCl \cdot 0.1H_2O$: C, 64.33; H, 6.86; N, 2.78. Found: C, 64.36; H, 6.86; N, 2.60. Mp: 172−174 °C (HCl salt).

*(6αR,3′D)-(−)-11-[5-(1,2-Dithiolan-3-yl)pentyloxy]-N-n-propylnoraporphine (−)-**15D***. White oil (38 mg, 74%). $[\alpha]^{20}_D$ −18.0° (c 0.07, DMSO). ^{1}H NMR (300 MHz, $CDC1_3$): δ 7.73 (d, 1H, J = 7.8 Hz), 7.19 (m, 3H), 7.07 (d, 1H, J = 7.5 Hz), 7.00 (d, 1H, J = 7.5 Hz), 3.53 (m, 1H), 3.44 (d, 1H, J = 12.3 Hz), 3.05−3.21 (m, 5H), 2.91 (m, 1H), 2.75 (d, 1H, J = 16.2 Hz), 2.38−2.65 (m, 6H), 1.89 (m, 1H), 1.70 (m, 6H), 1.48 (m, 2H), 0.97 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDC1_3$): δ 171.6, 147.1, 138.6, 135.8, 133.6, 130.6, 128.1, 127.7, 127.3, 125.9, 124.6, 122.0, 59.1, 56.4, 56.2, 48.7, 40.1, 38.4, 34.9, 34.5, 34.3, 29.2, 28.7, 24.3, 19.5, 12.0.

*(6αR,3′L)-(−)-11-[5-(1,2-Dithiolan-3-yl)pentyloxy]-N-n-propylnoraporphine (−)-**15L***. White oil (36 mg, 70%). $[\alpha]^{20}_D$ −32.0° (c 0.08, DMSO). ^{1}H NMR (300 MHz, $CDC1_3$): δ 7.72 (d, 1H, J = 7.8 Hz), 7.19 (m, 3H), 7.06 (d, 1H, J = 7.8 Hz), 7.00 (d, 1H, J = 8.1 Hz), 3.55 (m, 1H), 3.42 (dd, 1H, J = 13.5, 3.0 Hz), 3.06−3.21 (m, 5H), 2.90 (m, 1H), 2.75 (d, 1H, J = 15.9 Hz), 2.39−2.61 (m, 6H), 1.89 (m, 1H), 1.70 (m, 6H), 1.49 (m, 2H), 0.97 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDC1_3$): δ 171.6, 147.1, 138.6, 135.8, 133.6, 130.6, 128.1, 127.7, 127.3, 125.9, 124.6, 122.0, 59.1, 56.4, 56.2, 48.7, 40.1, 38.4, 34.9, 34.5, 34.3, 29.2, 28.7, 24.3, 19.5, 12.0.

*(6αR)-11-Amino-N-n-propylnoraporphine (−)-**17***. To a solution of triflate (−)-**16**[46] (0.102 g, 0.25 mmol) in THF (10 mL) were added $Pd(OAc)_2$ (20 mg), *rac*-2,2-bis(diphenylphosphino)-1,1-binaphthyl (25 mg), benzophenone imine (69 μL, 0.37 mmol), Cs_2CO_3 (122 mg), and 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (20 mg) under N_2. The mixture was heated to 65−70 °C with stirring overnight. The solvent was removed. The residue was diluted with CH_2Cl_2 (25 mL), washed with brine (15 mL), dried, and concentrated. The crude product was purified by column chromatography (3:1 petroleum/ethyl acetate, 1% of Et_3N) to yield crude imine. To a solution of the crude imine in 10 mL of methanol were added $NH_2OH \cdot HCl$ (35 mg, 0.50 mmol) and anhydrous NaOAc (61 mg, 0.75 mmol). The mixture was stirred overnight at room temperature. The solvent was removed. The residue was diluted with a 0.1 M NaOH solution (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography eluting with a 3:1 petroleum/ethyl acetate mixture (with 1% Et_3N) to give amine (−)-**17** as yellow oil (31 mg, 46% for two steps). $[\alpha]^{20}_D$ −142.0° (c 0.75, $CHCl_3$). ee 99.93%. ^{1}H NMR (300 MHz, $CDC1_3$): δ 7.89 (d, 1H, J = 7.8 Hz), 7.23 (t, 1H, J = 8.1 Hz), 7.04 (t, 2H, J = 7.8, 9.3 Hz), 6.71 (dd, 2H, J = 7.5, 10.8 Hz), 4.06 (s, 2H), 3.33 (dd, 1H, J = 2.1, 11.1 Hz), 3.18 (m, 3H), 2.91 (m, 1H), 2.77 (d, 1H, J = 17.1 Hz), 2.48 (m, 3H), 1.62 (m, 2H), 0.98 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 138.0, 136.0, 133.9, 132.7, 127.9, 127.1, 126.0, 123.0, 120.3, 118.5, 115.8, 59.8, 56.6, 48.9, 35.5, 29.3, 19.6, 12.1. MS (ESI, $[M^+]$): m/z 278. HRMS (ESI) calcd for $C_{19}H_{22}N_2$ 278.1783, found 278.1774.

*(6αR)-(−)-N-n-Propylnoraporphin-11-yl Carboxamides (−)-**18** and (−)-**19***. To a solution of 11-amino-*N-n*-propylnoraporphine (−)-**17** (29 mg, 0.1 mmol), an appropriate acid (0.12 mmol), and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (8 mL) under N_2 was added EDCI (38 mg, 0.2 mmol) at room temperature. The reaction mixture was stirred overnight and then diluted with CH_2Cl_2 (20 mL) and H_2O (10 mL). The organic layer was separated, washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (2:1 petroleum/ethyl acetate, 1% of Et_3N) to give pure oily products (−)-**18** and (−)-**19**.

*(6αR)-N-n-Propylnoraporphin-11-yl Butyramide (−)-**18***. Yellow oil (20 mg, 56%). $[\alpha]^{20}_D$ −50.2° (c 0.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDC1_3$): δ 8.08 (d, 1H, J = 8.4 Hz), 7.56 (d, 2H, J = 7.8 Hz), 7.21 (d, 1H, J = 8.4 Hz), 7.09 (t, 2H, J = 7.5, 7.8 Hz), 3.26 (dd, 1H, J = 3.0, 13.2 Hz), 3.14 (m, 3H), 2.91 (m, 1H), 2.77 (d, 1H, J = 16.2 Hz), 2.48 (m, 3H), 2.32 (m, 2H), 1.75 (m, 2H), 1.60 (m, 2H), 0.98 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 137.7, 136.9, 134.6, 133.5, 131.3, 128.1, 127.8, 126.1, 125.3, 124.3, 123.6, 122.1, 59.6, 56.5, 48.7, 39.8, 35.4, 29.3, 19.6, 18.9, 13.8, 12.0. MS (ESI, $[M^+]$): m/z 348. HRMS calcd for $C_{23}H_{28}ON_2$ 348.2202, found 348.2194.

*(6αR)-5-(1,2-Dithiolan-3-yl)-N-(N-n-propylnoraporphin-11-yl) pentanamide (−)-**19***. Yellow oil (17 mg, 37%). $[\alpha]^{20}_D$ −14.6° (c 0.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDC1_3$): δ 8.07 (d, 1H,

J = 8.1 Hz), 7.54 (d, 2H, J = 7.2 Hz), 7.23 (d, 1H, J = 8.1 Hz), 7.11 (t, 2H, J = 7.8, 8.1 Hz), 3.57 (m, 1H), 3.30 (d, 1H, J = 12.6 Hz), 3.14 (m, 5H), 2.91 (m, 1H), 2.78 (d, 1H, J = 15.9 Hz), 2.43 (m, 6H), 1.92 (m, 1H), 1.74 (m, 4H), 1.58 (m, 4H), 0.97 (t, 3H, J = 6.9, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 137.7, 134.7, 133.4, 131.3, 128.2, 127.9, 126.3, 124.4, 123.6, 122.0, 59.6, 56.5, 56.3, 48.7, 40.2, 38.5, 37.6, 35.4, 34.7, 29.3, 28.9, 28.8, 25.1, 19.7, 12.0. MS (ESI, [M$^+$]): m/z 466. HRMS calcd for $C_{27}H_{34}ON_2S_2$ 466.2112, found 466.2106.

*(6αR,S)-11-Cyano-N-n-propylnoraporphine (±)-**20***. In a 30 mL glass tube were placed triflate (±)-**16** (240 mg, 0.58 mmol), $Zn(CN)_2$ (136 mg, 1.16 mmol), $Pd(Ph_3P)_4$ (54 mg, 0.046 mmol), 15 mL of DMF, and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation (CEM Creator) was used and the temperature was kept at 150 °C for 30 min and then decreased rapidly to room temperature. The reaction vessel was opened, and the contents were poured into a separating funnel. A saturated sodium carbonate solution (15 mL) was added, and the mixture was extracted with ethyl acetate (3 × 40 mL). The extracts were combined, washed with brine (30 mL), and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (6:1 petroleum/ethyl acetate, 1% Et_3N) to yield nitrile (±)-**20** as a yellow solid (165 mg, 98%). Mp: 145−148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, 1H, J = 7.8 Hz), 7.64 (d, 1H, J = 7.8 Hz), 7.48 (d, 1H, J = 7.2 Hz), 7.29 (m, 2H), 7.17 (d, 1H, J = 7.8 Hz), 3.33 (dd, 1H, J = 3.0, 13.8 Hz), 3.14 (m, 3H), 2.82 (m, 1H), 2.50 (d, 1H, J = 17.1 Hz), 2.49 (m, 3H), 1.67 (m, 2H), 0.97 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 137.4, 135.7, 133.8, 133.7, 132.5, 130.4, 129.7, 127.1, 126.5, 124.5, 119.8, 107. 8, 58.9, 56.3, 48.8, 34.6, 29.0, 19.6, 12.0. MS (ESI, [M$^+$]): m/z 288. HRMS calcd for $C_{20}H_{20}N_2$ 288.1626, found 288.1622.

*(6αR,S)-11-Aminomethyl-N-n-propylnoraporphine (±)-**21***. Nitrile (±)-**20** (80 mg, 0.28 mmol) and ammonium hydroxide (1 mL) were dissolved in ethanol (15 mL), and catalytic Raney nickel was added. The reaction bottle was evacuated and placed under an atmosphere of hydrogen, and its contents were stirred at room temperature overnight. After filtration through Celite and concentration in vacuo, the residue was subjected to silica gel column chromatography (40:1:0.1 CH_2Cl_2/MeOH/NH_4OH) to yield white oil (±)-**21** (70 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, 1H, J = 7.8 Hz), 7.64 (d, 1H, J = 7.8 Hz), 7.48 (d, 1H, J = 7.2 Hz), 7.29 (m, 2H), 7.17 (d, 1H, J = 7.8 Hz), 4.23 (d, 1H, J = 13.8 Hz), 4.07 (d, 1H, J = 13.8 Hz), 3.33 (d, 1H, J = 13.5 Hz), 3.16 (m, 3H), 2.92 (m, 1H), 2.78 (d, 1H, J = 16.2 Hz), 2.49 (m, 3H), 1.67 (m, 2H), 0.97 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 137.4, 136.4, 133.7, 133.3, 132.9, 128.4, 127.7, 127.1, 126.5, 125.8, 125.7, 59.6, 56.5, 48.7, 44.8, 35.7, 29.3, 19.7, 12.0. MS (ESI, [M$^+$]): m/z 292. HRMS calcd for $C_{20}H_{24}N_2$ 292.1939, found 292.1939.

*(6αR,S)-5-(1,2-Dithiolan-3-yl)-N-[(N-n-propylnoraporphin-11-yl)-methyl]pentanamide (±)-**22***. 11-Aminomethyl-*N*-*n*-propylnoraporphine (±)-**21** (50 mg, 0.17 mmol), Et_3N (0.03 mL, 0.22 mmol), HOBt (33 mg, 0.24 mmol), and EDCI (94 mg, 0.49 mmol) were added successively to a solution of lipoic acid (39 mg, 0.19 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred overnight at room temperature and diluted with water (5 mL). The product was extracted with CH_2Cl_2 (2 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (40:1:0.1 CH_2Cl_2/MeOH/NH_4OH) to give aporphine (±)-**22** as a yellow solid (62 mg, 76%). Mp: 132−134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 5H), 7.09 (d, 1H, J = 6.9 Hz), 5.84 (s, 1H), 4.91 (dd, 1H, J = 6.6, 14.7 Hz), 4.52 (d, 1H, J = 14.7 Hz), 3.53 (m, 1H), 3.41 (d, 1H, J = 13.2 Hz), 3.13 (m, 5H), 2.89 (m, 1H), 2.76 (d, 1H, J = 15.6 Hz), 2.45 (m, 4H), 2.19 (m, 3H), 1.88 (m, 1H), 1.64 (m, 5H), 1.44 (m, 2H), 0.96 (dt, 3H, J = 2.1, 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 137.6, 136.4, 134.2, 134.0, 133.5, 132.2, 128.5, 127.9, 127.3, 127.1, 125.9, 125.7, 59.6, 56.5, 56.3, 48.7, 42.2, 40.1, 38.4, 36.3, 35.6, 34.5, 29.2, 28.8, 25.3, 19.6, 12.0. MS (ESI, [M$^+$]): m/z 480. HRMS calcd for $C_{28}H_{36}ON_2S_2$ 480.2269, found 480.2263.

*(6αR,S)-5-(1,2-Dithiolan-3-yl)-N-[(N-n-propylnoraporphin-11-yl)-methyl]pentanethioamide (±)-**23***. To a solution of solid (±)-**22** (118 mg, 0.25 mmol) in 8 mL of THF was added Lawesson's reagent (101 mg, 0.25 mmol), and the mixture was refluxed at 70 °C overnight. After evaporation of the solvent, the residue was purified by silica gel column chromatography (40:1:0.1 CH_2Cl_2/MeOH/NH_4OH) to give compound (±)-**23** as a yellow oil (50 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.28 (m, 3H), 7.20 (m, 2H), 7.09 (d, 1H, J = 7.2 Hz), 5.29 (dd, 1H, J = 4.8, 15.0 Hz), 4.86 (dd, 1H, J = 3.0, 15.0 Hz), 3.52 (m, 1H), 3.28 (dd, 1H, J = 3.0, 13.2 Hz), 3.01−3.22 (m, 5H), 2.89 (m, 1H), 2.77 (d, 1H, J = 16.2 Hz), 2.61 (m, 2H), 2.35−2.54 (m, 4H), 1.88 (m, 1H), 1.74 (m, 2H), 1.63 (m, 4H), 1.43 (m, 2H), 0.96 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6, 137.9, 136.3, 134.5, 133.6, 131.9, 129.1, 128.1, 127.8, 127.4, 126.1, 125.4, 59.5, 56.4, 56.2, 49.2, 48.7, 46.4, 40.1, 38.3, 35.5, 34.4, 29.2, 28.8, 28.3, 19.6, 12.0. MS (ESI, [M$^+$]): m/z 494. HRMS calcd for $C_{28}H_{36}N_2S_3$ 494.2041, found 494.2026.

*(6αR,S)-1-Ethyl-3-[(N-n-propylnoraporphin-11-yl)methyl]urea (±)-**24***. To a mixture of 11-aminomethyl-*N*-*n*-propylnoraporphine (±)-**21** (42 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (6 mL) was added ethyl isocyanate (14 μL, 0.17 mmol). The mixture was reacted at room temperature overnight. The solvent was removed, and the crude product was purified by column chromatography on silica gel (30:1:0.1 CH_2Cl_2/MeOH/NH_4OH) to give aporphine (±)-**24** as a yellow oil (40 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 1H), 7.25 (m, 4H), 7.10 (m, 1H), 6.12 (s, 1H), 5.85 (s, 1H), 5.10 (s, 1H), 4.73 (d, 1H, J = 13.8 Hz), 3.28 (m, 3H), 3.15 (m, 3H), 2.89 (m, 1H), 2.76 (d, 1H, J = 16.8 Hz), 2.34−2.61 (m, 3H), 1.60 (m, 2H), 1.10 (t, 3H, J = 7.2 Hz), 0.96 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.2, 137.7, 136.4, 134.2, 133.6, 132.0, 128.7, 128.1, 127.5, 126.1, 125.8, 59.7, 56.5, 48.7, 38.9, 35.5, 29.2, 19.6, 14.0, 12.0. MS (ESI, [M$^+$]) m/z 363. HRMS calcd for $C_{23}H_{29}ON_3$ 363.2310, found 363.2308.

*(6αR,S)-5-[4-(1,2-Dithiolan-3-yl)butyl]-3-(N-n-propylnoraporphin-11-yl)-1,2,4-oxadiazole (±)-**25***. To a solution of nitrile (±)-**20** (80 mg, 0.28 mmol) in 6 mL of absolute ethanol were added $NH_2OH\cdot HCl$ (97 mg, 1.39 mmol) and Et_3N (0.20 mL, 1.44 mmol), and the mixture was stirred at 60 °C for 3 days. After completion of the reaction, AcOEt (15 mL) and brine (10 mL) were added, and the organic layer was dried and then evaporated. The residue was purified by column chromatography (30:1 CH_2Cl_2/CH_3OH) to give a yellow solid (88 mg, 98%). To a solution of the yellow solid in CH_2Cl_2 (8 mL) were added lipoic acid (58 mg, 0.28 mmol) and DCC (68 mg, 0.33 mmol). The mixture was stirred at room temperature for 24 h and diluted with CH_2Cl_2 (15 mL) and brine (10 mL). The organic layer was dried and evaporated. The crude product was purified by column chromatography (30:1 CH_2Cl_2/CH_3OH) to afford a green-yellow solid (55 mg, 40%).

To a solution of the green-yellow solid described above (55 mg, 0.11 mmol) in 3 mL of anhydrous THF was added TBAF (29 mg, 0.11 mmol). The mixture was stirred at room temperature for 30 min and then evaporated. The residue was taken up by ethyl acetate (15 mL), washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The crude product was purified by column chromatography (50:1:0.1 CH_2Cl_2/CH_3OH/NH_4OH) to yield oxadiazole (±)-**25** as a yellow gummy solid (35 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, 1H, J = 7.8 Hz), 7.42 (d, 1H, J = 7.2 Hz), 7.31 (t, 1H, J = 7.5 Hz), 7.02 (d, 1H, J = 7.8 Hz), 6.93 (t, 1H, J = 7.8 Hz), 6.72 (d, 1H, J = 7.8 Hz), 3.54 (m, 2H), 3.14 (m, 5H), 2.91 (m, 3H), 2.77 (d, 1H, J = 16.8 Hz), 2.57 (m, 2H), 2.46 (m, 2H), 1.85 (m, 3H), 1.67 (m, 4H), 1.51 (m, 2H), 0.99 (t, 3H, J = 7.2, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 170.5, 138.0, 135.9, 134.6, 133.4, 131.8, 130.4, 130.3, 128.2, 127.1, 126.0, 125.4, 124.0, 59.0, 56.6, 56.1, 48.7, 40.1, 38.4, 35.1, 34.4, 34.3, 29.2, 28.5, 28.4, 26.4, 26.3, 19.5, 12.0. MS (ESI, [M$^+$]): m/z 491. HRMS calcd for $C_{28}H_{33}ON_3S_2$ 491.2065, found 491.2073.

Binding Assay of New Compounds at the D_1, D_2, 5-HT_{1A}, and 5-HT_{2A} Receptors. The affinities of compounds for the D_1 and D_2 dopamine receptors and the 5-HT_{1A} and 5-HT_{2A} receptors were determined by a competition binding assay. Membrane homogenates of 5-HT_{1A}- or 5-HT_{2A}-CHO cells or D_1- or D_2-HEK293 cells were prepared as described previously. Duplicate tubes were incubated at 30 °C for 50 min with increasing concentrations (1 nM to 100 μM) of each compound and with 0.7 nM [^{3}H]-8-OH-DPAT (for 5-HT_{1A}), [^{3}H]Ketanserin (for 5-HT_{2A}), [^{3}H]SCH23390 (for D_1), or [^{3}H]spiperone (for D_2) in a final volume of 200 μL of binding buffer containing 50 mM Tris and 4 mM $MgCl_2$ (pH 7.4). Nonspecific binding was assessed by parallel incubations with either 10 μM WAY-100635 for 5-HT_{1A}, Ketanserin for 5-HT_{2A}, SCH23390 for D_1, or spiperone for D_2. The reaction was started by addition of membranes (15 μg/tube) and stopped by rapid filtration through a Whatman GF/B glass fiber filter and subsequent washing with cold buffer [50 mM Tris and 5 mM ethylenediaminetetraacetic acid (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.

Effects of Compound (−)-15 on Adrenergic Receptors. Intracellular Ca^{2+} measurement was used to evaluate the compound-mediated activity on adrenergic α_{1A}, α_{1B}, α_{1D}, and β_2 receptors. CHO cells that stably express α_{1A} or α_{1B} receptors and HEK293 cells that stably express α_{1D} or β_2 receptors were cotransfected with $G_{\alpha 16}$. Cells were seeded into black-walled, clear-base 96-well plates at a density of ~30000 cells per well in Hams-F12 medium supplemented with 10% fetal bovine serum and 5 μg/mL G418. The cells were cultured overnight with a plating volume of 100 μL/well at 37 °C in a CO_2 incubator. Before the calcium assay, medium was removed, and 100 μL of Fluo4 AM calcium assay loading solution was added to each well. The plates were incubated for 30 min at 37 °C and then kept at room temperature for an additional 30 min until they were used. The assay was run on a FlexStation II plate reader. The excitation wavelength was 485 nm, and the emission wavelength was 525 nm, with an emission cutoff of 515 nm. The compounds were added in duplicate wells with concentrations from 0.01 nM to 100 μM. Antagonistic activity was measured in the presence of 23.3, 250, or 0.91 nM adrenaline for the α_{1A}, α_{1B}, or β_2 receptor, respectively. The assay was completed in 3−5 min after compound addition.

[^{35}S]GTPγS Binding Assay. For membrane preparations, cultured cells or striatum was homogenized in ice-cold buffer containing 5 mM Tris and 2 mM EDTA (pH 7.4). The homogenate was centrifugated at 1000g and 4 °C for 10 min, and the supernatant was centrifuged further at 36000g and 4 °C for 30 min. The pellet obtained was resuspended with 50 mM Tris (pH 7.5), 5 mM $MgCl_2$, 1 mM EDTA, and 100 mM NaCl. The protein concentration was determined by the BCA assay (Bio-Rad).

The [^{35}S]GTPγS binding assay was performed as previously reported.[33] The binding reaction was conducted at 30 °C for 30 min with 10 μg of membrane protein in a final volume of 100 μL of binding buffer with various concentration of **15**. The binding buffer contained 50 mM Tris (pH 7.5), 5 mM $MgCl_2$, 1 mM EDTA, 100 mM NaCl, 1 mM DL-dithiothreitol (DTT), and 40 μM guanosine triphosphate (GDP). The reaction was initiated by addition of [^{35}S]GTPγS (final concentration of 0.1 nM). For detection of 5-HT_{1A} receptor activation in striatum, the reaction was performed at 30 °C for 1 h with 10 μg of membrane protein in a final volume of 100 μL of binding buffer with 100 μM 5-HT_{1A} receptor specific agonist 8-OH-DPAT. Nonspecific binding was assessed in the presence of 100 μM 5′-guanylimidodiphosphate Gpp(NH)p. The reaction was terminated by addition of 1 mL of ice-cold washing buffer [50 mM Tris (pH 7.5), 5 mM $MgCl_2$, 1 mM EDTA, and 100 mM NaCl], and the mixture was rapidly filtered with GF/C glass fiber filters (Whatman) and washed three times. Radioactivity was determined by liquid scintillation counting.

6-OHDA Lesion Surgery. All experimental protocols were approved by the Institutional Animal Care and Use Committees and were in compliance with the Guidelines for the Care and Use of Laboratory Animals (National Research Council, People's Republic of China, 1996). Male Sprague-Dawley rats, weighing 200−250 g, were purchased from Shanghai Slac Laboratory Animal Co. Ltd. (Shanghai, China). Surgery was conducted as described previously.[56] Briefly, rats were anesthetized with sodium pentobarbital (40 mg/kg, ip) and received a single stereotactic injection of 8 μg of 6-OHDA hydrochloride in 4 μL of artificial cerebrospinal fluid containing 0.05% ascorbic acid in the medial forebrain bundle using the following coordinates (relative to bregma): anteroposterior (AP), −2.5 mm; lateral (L), +2.0 mm; dorsoventral (DV), −8.5 mm. The toxin was infused at a rate of 1 mL/min, and the cannula was left in place for 2 min before being withdrawn. To limit the damage to adrenergic neurons, desipramine hydrochloride (25 mg/kg, ip) was administered 30 min before 6-OHDA injection. Three weeks after surgery, rats were challenged with apomorphine hydrochloride (0.2 mg/kg, subcutaneously), and contralateral rotation was monitored. Animals showing fewer than 50 rotations per 5 min were excluded from further studies.

Assessment of L-DOPA-Induced Dyskinesia (LID). LID was induced with 6 mg of L-DOPA/kg and 15 mg of benzeraside/kg once daily for 21 days. Rats were monitored for abnormal involuntary movements (AIMs) using a procedure and score system described by Cenci and Lee[59] with a slight modification. On test days, rats were placed individually in cages of the same style that was used to house the animals. They were assessed every 35 min for a total of 140 min after injection of the drug or saline. Each rat was scored for exhibition of the following three categories of AIMs: (1) axial, lateral flexion and axial rotation of the neck and trunk toward the side contralateral to the lesion; (2) limb, repetitive, rhythmic jerky movements or dystonic posturing of the forelimb on the side contralateral to the lesion; and (3) orolingual, tongue protrusion without the presence of food or other objects. For each observation period of 1 min, a score of 0−4 was assigned for each category based on the following criteria: 0, absent; 1, present for less than half of the observation time; 2, present for more than half of the observation time; 3, present all the time but could be suppressed by threatening stimuli; 4, present all the time and not suppressible. For assessing rotational behavior, rats were placed in a 50 cm diameter bowl and allowed to acclimate to the environment for 10−20 min before injection. Contralateral turns were counted every 5 min after injection for a total of 30 min.

Western Blot. Rats were decapitated, and striatum was separated. Tissues were homogenized at 4 °C in 50 mM Tris (pH 7.4), 150 mM NaCl, 20 mM β-glycerophosphate, 1 mM EGTA, 20 mM NaF, 3 mM Na_3VO_4, 1 mM PMSF, 2 mg/mL aprotinin and leupeptin, and 1% NP-40. Lysates were centrifuged at 12000g for 15 min at 4 °C to precipitate the debris, and the protein content in the supernatant was determined by the BCA assay. Aliquots of supernatants were mixed with sample buffer, boiled for 5 min, and separated by 10% SDS−PAGE. The proteins were transferred to PVDF membrane and blocked with 5% fat-free milk in 0.1% Tween 20-TBS (TBST) at room temperature for 1 h. The membranes were incubated with FosB antibody (Santa Cruz, 1:1000) overnight at 4 °C, then washed with TBST, and incubated with the HRP-conjugated secondary antibody for 1 h. The membranes were washed and visualized with supersignal ECL (Pierce).

Electrophysiology Study. For slice preparation, Sprague-Dawley rats (2−3 weeks old) were anesthetized with 20% chloral hydrate and then decapitated. The brains were rapidly removed to the chilled artificial CSF (ACSF) containing 126 mM NaCl, 3 mM KCl, 1.5 mM $MgCl_2$, 2.4 mM $CaCl_2$, 1.2 mM NaH_2PO_4, 11 mM glucose, and 26 mM $NaHCO_3$. Coronal slices (300 μM) containing median prefrontal cortex (mPFC) were cut using a M752 vibroslice instrument (Campden Instruments Ltd.). Slices were incubated in the oxygenated ACSF at

37 °C for 45 min and then kept at room temperature for at least 30 min. After that, the slice was transferred to a recording chamber and perfused with warmed oxygenated ACSF (30−31 °C).

Electrophysiology Recording. Whole cell recordings were performed in layer V pyramidal neurons of mPFC under a DIC upright microscope (BX51WI, Olympus) using a MultiClamp 700A amplifier (Molecular Device). Recording electrodes (resistance of 4−6 MΩ) were pulled from borosilicate glass pipettes (Sutter Instrument) using a Flaming/Brownmicropipet puller (model P-97, Sutter Instrument) and filled with 140 mM potassium gluconate, 2 mM $MgCl_2$, 10 mM HEPES, 2 mM $ATPNa_2$, 0.1 mM $GTPNa_3$, and 0.05 mM EGTA (pH 7.25 with KOH). Data acquisition and analysis were performed by using a digitizer (DigiData 1322A, Molecular Devices) and pClamp version 9.2. Signals were filtered at 2 kHz and sampled at frequencies of 10 Hz. To record the EPSCs and paired pulse ratio, a concentric tungsten electrode (WPI) was placed in layer II/III of the mPFC and two pulses (50 Hz) with a 100 μs duration and a 50−100 pA intensity were applied at 0.033 Hz. Neurons were clamped at −65 mV during recordings. Data obtained from neurons with membrane potential below −60 mV and a series resistance (15−30 MΩ) change of <20% through the recordings were chosen for analysis.

Drug Application. Drugs were delivered through perfusion. All experiments were performed in the presence of 100 μM picrotoxin to block the GABAA receptor. Picrotoxin was purchased from Sigma.

Data Analysis. Data were presented as mean ± SE. Behavior data were evaluated by repeated measures ANOVA and *t* test. Protein blotting and receptor binding data were analyzed by one-way ANOVA. The statistical significance level was set at $p < 0.05$.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C spectra for all the final compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was financially supported by grants from the Chinese National Science Foundation (30772625, 81072528, and 30825042), National Basic Research Plan 973 of the Ministry of Science and Technology of China (2009CB522000), the Shanghai Commission of Science and Technology (10410702600, 10JC1417100, and 10dz1910104), and the National Science and Technology Major Project on "Key New Drug Creation and Manufacturing Program" (2009ZX09301-001, 2009ZX09103-062, and 2009ZX09102).

■ ABBREVIATIONS USED

5-HT, 5-hydroxytryptamine (serotonin); DA, dopamine; PD, Parkinson's disease; L-DOPA, L-3,4-dihydroxyphenylalanine (levodopa); LID, L-DOPA-induced dyskinesia; MAO-B, monoamine oxidase B; COMT, catechol-*O*-methyltransferase; HOBt, hydroxybenzotriazole; Et_3N, triethylamine; DMAP, dimethylaminopyridine; 8-OH-DPAT, 8-hydroxy-*N*,*N*-dipropylaminotetraline; EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Py, pyridine; TBAF, tetra-*n*-butylammonium fluoride; DCC, *N*,*N*′-dicyclohexylcarbodiimide; THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; MS, mass spectra; HRMS, high-resolution mass spectra; TLC, thin-layer chromatography; AIM, abnormal involuntary movement

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