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Design, synthesis, and pharmacological evaluation of novel tetrahydroprotoberberine derivatives: Selective inhibitors of dopamine D_1 receptor

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ABSTRACT

A series of new tetrahydroprotoberberine (THPB) derivatives were designed, synthesized, and tested for their binding affinity towards dopamine (D_1 and D_2) and serotonin (5-HT_{1A} and 5-HT_{2A}) receptors. Many of the THPB compounds exhibited high binding affinity and activity at the dopamine D_1 receptor, as well as high selectivity for the D_1 receptor over the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors. Among these, compound **19c** exhibited a promising D_1 receptor binding affinity (K_i = 2.53 nM) and remarkable selectivity versus D_2R (inhibition = 81.87%), 5-HT_{1A}R (inhibition = 61.70%), and 5-HT_{2A}R (inhibition = 24.96%). Compared with *l*-(*S*)-stepholidine (*l*-SPD) (D_1 K_i = 6.23 nM, D_2 K_i = 56.17 nM), compound **19c** showed better binding affinity for the D_1 receptor (2.5-fold higher) and excellent D_2/D_1 selectivity. Functional assays found compounds **18j**, **18k**, and **19c** are pure D_1 receptor antagonists. These results indicate that removing the C10 hydroxy group and introducing a methoxy group at C11 of the pharmacophore of *l*-SPD can reverse the function of THPB compounds at the D_1 receptor. These results are in accord with molecular docking studies.

1. Introduction

Abnormal dopamine (DA) transmission is associated with several neuro- and psycho-disorders, including schizophrenia,[1] depression,[2] Parkinson's disease,[3] and substance abuse, etc.[4] Five subtypes of DA receptors have been cloned, which are divided into two subfamilies: D_1-like (D_1, D_5) and D_2-like (D_2, D_3 and D_4).[5]

The D_1 receptor is the most abundant DA receptor subtype in the areas of mammalian forebrain, such as the corpus striatum, substantia nigra, nucleus accumbens, hypothalamus, thalamus, frontal cortex, and olfactory bulb.[6] In addition to the importance of D_1 receptor in psychiatric disorders such as schizophrenia,[7] recent information indicates that modulation of D_1 receptor merged as potential target for drug discovery in anti-substance abuse.[8] In addition, the discovery of the high-affinity and selective D_1 receptor antagonists **1** (SCH23390)[9] and **1a** (SCH83566)[6,10] along with the partial agonist **2** (SKF38393)[11] were major breakthroughs in the pharmacology of dopamine receptors. SCH23390 and SKF38393 have been widely used as standard pharmacological tools. These specific D_1 receptor ligands have radically changed our understanding on the functional roles of dopamine receptors. Recently, a series of phenyltetrahydrobenzazepine derivatives have been discovered to be D_1 receptor antagonists, including **3** (NNC112),[12] **4** (SCH39166),[13] **5** (BTS73947),[14] and **6** (BW737C89)[15] shown in Figure 1. After that, a chemically novel structure 7 (LE300, Fig. 1)[16] was found to exhibit excellent binding affinity for both D_1 and D_2 receptors. However, most of those D_1 receptor antagonists suffer from weak selectivity or poor pharmacokinetic profiles.*l*-(*S*)-Stepholidine (*l*-SPD, **8**, Fig. 1), a tetrahydroprotoberberine alkaloid isolated from the Chinese herb *Stephanie intermedi*,[17] has attracted a great deal of attention because its unique pharmacological profile as dual dopamine/serotonin receptor ligand.[18,19] So far, animal studies and clinical trials have confirmed that *l*-SPD is a potential candidate for the treatment of schizophrenia and drug abuse.[20,21]

In the present study, we designed and synthesized a series of novel tetrahydroprotoberberine compounds by introducing various substituents (such as methyl, methoxy, benzyloxy, and

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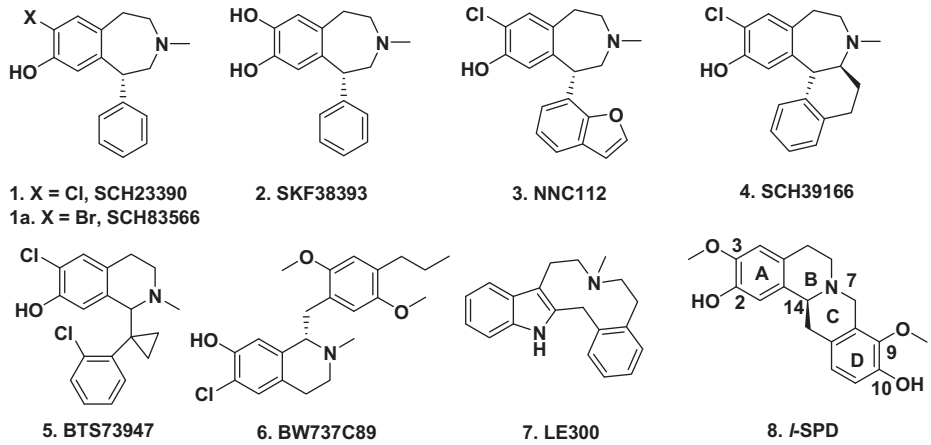
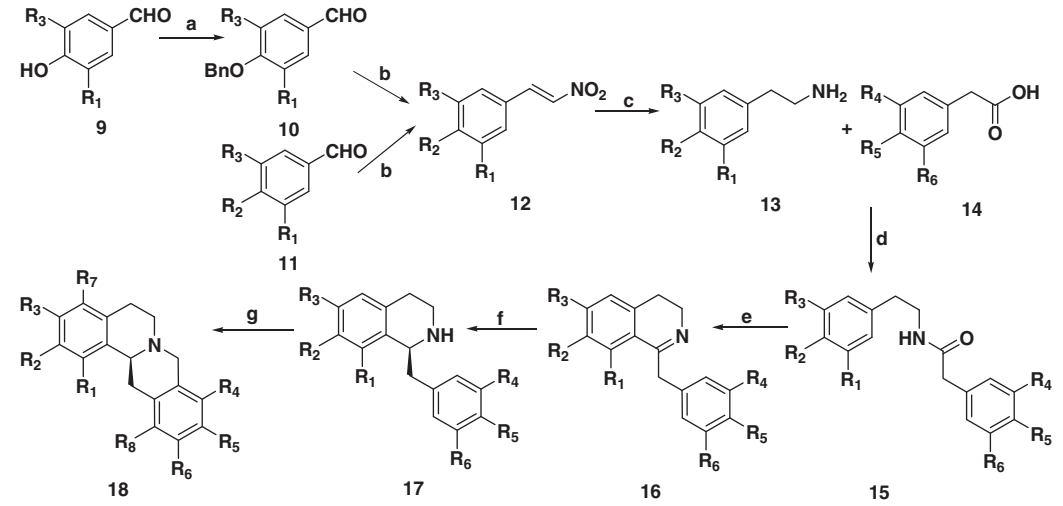


Figure 1. Representative D_1 receptor antagonists **1**–**7** and *l*-SPD.

methylenedioxy groups) at different positions on the pharmacophore of *l*-SPD. We found a few potent D_1 receptor antagonists with promising selectivity.

2. Design

With regard to the chemical structure of *l*-SPD, we presumed that its shortcomings (poor physicochemical properties and low oral bioavailability) resulted from the two phenolic hydroxy groups on the A- and D-rings. Based on this assumption, compounds **18** and **19** were designed and synthesized. To improve the pharmacokinetic properties and potency of the pharmacophore, the C2 and C10 hydroxy groups were replaced with other substituents, such as methoxy, benzyloxy, hydroxymethyl, and methylenedioxy groups, providing compounds **18a**–**h**. Compounds **18i**–**p** with substituents at C1 and C4 of the A-ring were designed to enhance potency and selectivity for the dopamine D_1 receptor. To evaluate the influence of the configuration of C14 on the binding



18a: R_1,R_4,R_5,R_7,R_8 = H; R_2 = OBn; R_3,R_6 = OCH_3
18b: R_1,R_5,R_7 = H; R_2,R_3 = OCH_2O; R_4,R_6 = OCH_3; R_8 = CH_2OH
18c: R_1,R_5,R_7,R_8 = H; R_2 = OBn; R_3,R_4,R_6 = OCH_3
18d: R_1,R_4,R_5,R_7,R_8 = H; R_2,R_3,R_6 = OCH_3
18e: R_1,R_4,R_5,R_7,R_8 = H; R_2,R_3 = OCH_2O; R_6 = OCH_3
18f: R_1,R_5,R_7,R_8 = H; R_2,R_3,R_4,R_6 = OCH_3
18g: R_1,R_5,R_7 = H; R_2,R_3,R_4,R_6 = OCH_3; R_8 = CH_2OH
18h: R_1,R_5,R_7,R_8 = H; R_2,R_3 = OCH_2O; R_4,R_6 = OCH_3
18i: R_1,R_3,R_4,R_6 = OCH_3; R_2 = OBn; R_5,R_7,R_8 = H
18j: R_1,R_3,R_4,R_6 = OCH_3; R_2,R_5,R_7,R_8 = H
18k: R_1,R_2,R_3,R_4,R_6 = OCH_3; R_5,R_7,R_8 = H
18l: R_1,R_2,R_3,R_4,R_6 = OCH_3; R_5,R_7 = H; R_8 = CH_2OH
18m: R_1,R_2,R_3 = OCH_3; R_4,R_7,R_8 = H; R_5,R_6 = OCH_2O
18n: R_1,R_3 = OCH_3; R_2,R_4,R_8 = H; R_5,R_6 = OCH_2O; R_7 = CH_2OH
18o: R_1,R_3,R_6 = OCH_3; R_2,R_4,R_5,R_8 = H; R_7 = CH_2OH
18p: R_1,R_3,R_4,R_8 = OCH_3; R_2,R_5,R_6 = H; R_7 = CH_2OH
18q: R_1,R_5,R_7,R_8 = H; R_2,R_3 = OCH_3; R_4,R_6 = CH_3

19a: R_1,R_4,R_5,R_7,R_8 = H; R_3,R_6 = OCH_3
19b: R_1,R_3,R_4,R_6 = OCH_3; R_5,R_7,R_8 = H
19c: R_1,R_5,R_7,R_8 = H; R_3,R_4,R_6 = OCH_3
19d: R_1,R_5,R_7 = H; R_3,R_4,R_6 = OCH_3; R_8 = CH_2OH
19e: R_1,R_5,R_7,R_8 = H; R_3 = OCH_3; R_4,R_6 = CH_3

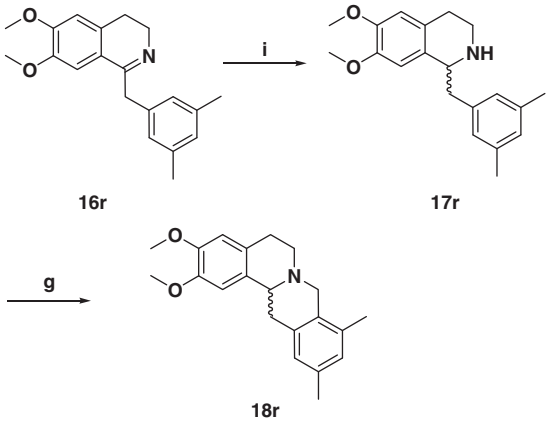
Scheme 1. Synthesis of (−)-THPB compounds. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux, 2 h; (b) CH_3NO_2, CH_3COONH_4, CH_3COOH, 90 °C, 4 h; (c) $LiAlH_4$, THF, reflux, 2 h; (d) EDCI, Et_3N, CH_2Cl_2, rt, 8 h; (e) $POCl_3$, CH_3CN, reflux, 0.5 h; (f) (*R*,*R*)-Noyori's catalyst, HCOOH/Et_3N, DMF, rt, 10 h; (g) HCOOH, 40% HCHO, 25–90 °C, 2 h; (h) 37% HCl, C_2H_5OH, reflux, 2 h.

affinity, C14-*S*-configured compound **18q** and its racemate **18r** were examined. To improve the potency at the D_1 receptor, the C2 hydroxy group and conformation of *l*-SPD were maintained while introducing various groups, such as methyl, methoxy, methylenedioxy, and hydroxymethyl groups, at different positions on the D-ring, leading to compounds **19a–e**.

3. Chemistry

The designed compounds were synthesized via the routes shown in Schemes 1 and 2. The key intermediates **13** were prepared by protection, Knoevenagel condensation, and reduction from aldehydes **9** and **11**. Condensation of intermediates **13** with commercially available 2-phenylacetic acids **14** generated amides **15** in good yields. Using the Bischler–Napieralski reaction, treatment of the amides **15** with phosphoryl trichloride ($POCl_3$) gave access to imines **16** in excellent yields. Asymmetric hydrogenation of **16** catalyzed by a chiral Ru-(II) complex (Noyori's catalyst)[18] afforded chiral amines **17**. Cyclization of amines **17** via the Pictect–Spengler reaction provided products **18a–q** in good isolated yields and excellent enantiomeric excess. Products **19a–e** were obtained by deprotection of compounds **18**.

Additionally, non-chiral compound **18r** was prepared according to the procedure outlined in Scheme 2. Reduction of imine **16r** with sodium borohydride followed by cyclization, gave **18r** in an excellent yield.



Scheme 2. Synthesis of compound **18r**. Reagents and conditions: (i) $NaBH_4$, methanol, rt, 1 h; (g) HCOOH, 40% HCHO, 25–90 °C, 2 h.

4. Results and discussion

4.1. Binding assay

All the synthesized THPB new compounds were subjected to competitive binding assays for the dopamine (D_1 and D_2) and serotonin (5-HT_{1A} and 5-HT_{2A}) receptors, using membrane preparation obtained from HEK293 cells stable transfected respective receptor. [^{3}H] SCH23390 (D_1), [^{3}H]-Spiperone (D_2), [^{3}H] 8-OH-DPAT (5-HT_{1A}), and [^{3}H]-Ketanserin (5-HT_{2A}) were used as standard radioligands. The inhibition, K_i and IC_{50} values of these original THPB compounds are reported in Table 1.

4.1.1. Structure–activity relationship: D_1 receptor affinity

Many of the synthesized THPB compounds exhibited a mild to high affinity for the dopamine D_1 receptor, especially compounds **18j** (K_i = 7.97 nM) and **19c** (K_i = 2.53 nM).

Table 1
Binding affinity of THPB compounds for D_1, D_2, 5-HT_{1A}, and 5-HT_{2A} receptors

Compound	D1		D2		5-HT1A	5-HT2A
	Inhibition (%) or K_i (±SEM, nM)[c]	IC_{50}[a] (nM)	Inhibition (%) or K_i (±SEM, nM)	IC_{50}[b] (nM)	Inhibition (%) or K_i (±SEM, nM)	Inhibition (%) or K_i (±SEM, nM)
18a	86.01%		35.99%		37.34%	13.54%
18b	182.41 ± 10.88	323.79 ± 19.30	41.75%		599.89 ± 147.71	56.23%
18d	81.88%		10.21%		57.37%	33.54%
18e	83.23%		22.71%		5.48%	20.79%
18f	106.45 ± 10.62	188.96 ± 18.84	3.48%		66.91%	17.17%
18g	64.12 ± 4.43	113.81 ± 7.86	39.50%		730.02 ± 141.78	24.07%
18h	74.51 ± 3.85	141.58 ± 7.33	1.02%		57.57%	31.26%
18i	59.30%		54.22%		43.73%	69.13%
18j	**7.97 ± 1.29**	**14.29 ± 2.12**	**81.87%**		**61.70%**	**24.96%**
18k	**23.76 ± 2.09**	**45.45 ± 3.98**	**51.68%**		**66.93%**	**48.81%**
18l	7.37%		47.18%		67.38%	59.74%
18m	43.40%		70.71%		70.27%	72.68%
18n	17.40%		−24.74%		-18.28%	16.93%
18o	55.98%		-12.59%		1.34%	21.44%
18p	48.81%		-18.17%		33.12%	25.34%
18q	337.7 ± 71.74	684.0 ± 145.2	223.61 ± 26.50	1155.3 ± 136.9	54.83%	36.54%
18r[d]	1440.62 ± 96.87	2917.2 ± 196.2	77.4%		28.42%	19.90%
19a	35.79 ± 2.60	68.89 ± 5.01	346.76 ± 30.54	873.14 ± 63.72	65.61%	68.69%
19b	52.34 ± 1.66	98.13 ± 3.11	58.82%		44.94%	51.56%
19c	**2.53 ± 0.16**	**4.86 ± 0.31**	**83.31%**		**56.87%**	**32.39%**
19d	17.29 ± 0.54	30.70 ± 0.97	146.99 ± 10.21	514.46 ± 35.74	80.92%	18.37%
19e	28.91 ± 2.73	56.37 ± 5.33	160.99 ± 21.18	456.13 ± 60.01	74.55%	27.05%
l-SPD	6.23 ± 0.51	12.29 ± 6.54	56.17 ± 4.78	105.41 ± 7.48	89.31%	45.60%
SCH23390	1.24 ± 0.37	2.52 ± 0.74				
Spiprone			0.28 ± 0.02	1.27 ± 0.08		2.24 ± 0.56
5-HT					0.62 ± 0.04	

[a] Potency of selected compound inhibits 50% of [^{3}H] SCH23390 binding with D_1 receptor.
[b] Potency of selected compound inhibits 50% of [^{3}H] Spiprone binding with D_2 receptor.
[c] Only compounds with the inhibition of radioligand binding higher than 80% were further tested for K_i values. The K_i ± SE was derived from the equation $K_i = IC_{50}/1 + [C/K_d]$.
[d] Compound **18r** is a racemate of compound **18q**.

Introducing different substituents, such as methoxy, benzyloxy groups, on the C2 of A-ring of *l*-SPD, the order of efficacy (OH > OMe > OBn) was maintained in the whole set of molecules. For example, the 2-OH derivative **19c** was 42-fold higher in terms of D_1 receptor binding affinity than the 2-OMe derivative **18f** (K_i = 106.45 nM). Besides, these two compounds were both more potent than 2-OBn derivative **18i** (**inhibition** = 59.30%). Similarly, the 2-OH derivative **19a** (K_i = 35.79 nM) was found to be more potent in binding than the corresponding 2-OMe derivative **18d** (**inhibition** = 81.88%), 2-OBn derivative **18a** (Inhibition = 86.01%), and 2,3-OCH_2O derivative **18e** (**inhibition** = 83.23%) at the D_1 receptor. Compounds **18b** and **18h** were roughly 11- and 29-fold weaker than the corresponding 2-OH-3-OMe substituted compounds **19d** and **19c**, respectively. These suggest that the 2,3-OCH_2O group is detrimental to D_1 receptor binding compared with 2-OH-3-OMe substituent. Compounds **18j** and **18k** were about 13- and 4-fold more potent than compound **18f**, which indicates that introducing a methoxy group at C1 enhances binding affinity to the D_1 receptor. The binding affinity of compounds **18n**, **18o**, and **18p** were dramatically decreased, suggesting that introducing a hydroxymethyl group at C4 impaired the binding affinity to the D_1 receptor. The highlight of the series was compound **18j**, in which two phenolic hydroxy groups on the A- and D-rings of *l*-SPD were removed. Compound **18j** (K_i = 7.97 nM) exhibited excellent D_1 receptor binding affinity.

Compared to the C14-*S*-configured compound **18q**, its racemate **18r** showed a weaker binding affinity for all tested receptors (D_1, D_2, 5-HT_{1A}, and 5-HT_{2A} receptors). This indicates that the C14-*S* configuration in THPB compounds is important for the binding affinity to those receptors.

Maintaining the 2-OH-3-OMe group on the A-ring of the pharmacophore, we obtained compounds **19a**–**d** by introducing different kinds of substituents on the D-ring. The 9,11-dimethyl substituted compound **19e** exhibited a slightly decreased D_1 receptor affinity as the lead compound **8**. This suggests that the hydroxy group at C10 may not be crucial for binding to the D_1 receptor. Compound **19c** with methoxy groups at C9 and C11 was found to be 2.5-fold more potent than the lead compound **8**, indicating that replacing the 10-OH by 11-OMe can enhance D_1 receptor binding affinity. With the methoxy group at C9 removed, compound **19a** exhibited 14-fold less potent than the corresponding 9,11-dimethoxy substituted THPB derivative **19c**. This suggests that the 9-OMe substituent is involved in binding to the D_1 receptor. Introducing a hydroxymethyl group at C12 has slightly impact on the D_1 receptor binding, as depicted in compound **19d**, which showed a weaker affinity at the D_1 receptor as compared to the corresponding C12 unsubstituted derivative **19c**. Taken together, we conclude that introducing methoxy groups at C9 and C11 boosts binding to the dopamine D_1 receptor. Among them, **19c**, has the highest affinity (K_i = 2.53 nM) for the D_1 receptor, which is 2.5-fold more potent than the parent compound **8**.

4.1.2. Selectivity for D_1R versus D_2R, 5-$HT_{1A}R$, and 5-$HT_{2A}R$

Very high level of D_1R versus D_2R selectivity was obtained with many of the synthesized THPB compounds. Among these, compounds **18j** (D_1 K_i = 7.97 nM, D_2 inhibition = 81.87%) and **19c** (D_1 K_i = 2.53 nM, D_2 inhibition = 83.31%) displayed much higher selectivity toward D_1 receptor than the lead compound **8** (D_2/D_1 = 9). Comparing the D_2/D_1 selectivity of all the tested compounds, we found that substituents on the D-ring of the pharmacophore are important for the determination of D_2/D_1 selectivity. Introducing methyl group at C9 and C11 such as compounds **18q** and **19e** resulted in a decreasing in the D_1 receptor selectivity. Whereas introducing methoxy group at C9 and C11 significantly enhanced the D_1 receptor selectivity (such as compounds **18j**, **18k**, and **19c**). Compounds **18j**, **18k**, and **19c** showed excellent selectivity for the D_1 receptor (K_i = 7.97, 23.76, and 2.53 nM, respectively) over the D_2 receptor (inhibition = 81.87%, 51.68%, and 83.31%, respectively). These results suggest that substituents at C9 and C11 are critical for the selectivity towards dopamine D_1 receptor. Besides, compared to compound **19c**, compound **19d** with a hydroxymethyl group at C12 decreased the D_1 receptor selectivity significantly.

We also tested the binging affinity of all new compounds at the 5-HT_{1A} and 5-HT_{2A} receptors, only compounds **18b** and **18g** with substituent at C12 exhibited weak binding affinity.

From the above results, compounds **18j**, **18k**, and **19c** exhibit excellent D_1 receptor affinity and remarkable selectivity over D_2, 5-HT_{1A}, and 5-HT_{2A} receptors. These three compounds were thus selected for further bioassay.

Table 2
[^{35}S] GTPγS binding assays of compounds **18j**, **18k**, **19c**, and SCH23390 for the D_1 receptor

Compound	Potency (nM) and intrinsic activity at cloned D_1 receptor			
	EC_{50} (μM)	E_{max} (%)	IC_{50} (μM)	I_{max} (%)
18j	–[a]	–	23.28 ± 1.00	94.22 ± 6.87
18k	–	–	11.84 ± 0.82	82.55 ± 8.33
19c	–	–	1.38 ± 0.24	94.27 ± 1.50
SCH23390	–	–	0.52 ± 0.04	80.05 ± 6.87
l-SPD	41.1 ± 8.6[b]	–	–	–
SKF38393	0.17 ± 0.007	100	–	–

[a] [^{35}S] GTPγS binding activity could not be detected.
[b] EC_{50} value of *l*-SPD was cited from Dong's paper.[23]

4.2. [^{35}S] GTPγS binding assays for compounds 18j, 18k, and 19c

Stably transfected D_1 cell membrane fraction was prepared. [^{35}S] GTPγS binding assays were performed as previously described.[22] Compounds **18j**, **18k**, and **19c** were diluted to different concentrations and added to the reaction tubes, respectively. The D_1 receptor selective agonist SKF38393 and antagonist SCH23390 were used for comparison.

From the results in Table 2, all three tested compounds produced antagonistic activity at D1 receptor. Among them, compound **19c** (**IC_{50}** = 1.38 μM) appears to be the most potent. To the best of our knowledge, this is the first discovery of a THPB scaffold that acts as a pure D1 receptor selective antagonist.

4.3. Molecular modeling

To evaluate the impact of introducing different substituents at different positions of the THPB scaffold on the D_1 receptor binding affinity and function, molecular docking studies of *l*-SPD, **18i**, **18k**, and **19c** in a human dopamine D_1 receptor model were carried out.[24] The docking was performed using the Glide[25] program from the Schrödinger Suite.[26] The results are shown in Fig. 2.

Compounds *l*-SPD, **19c**, **18k**, and **18i** were found to bind with the dopamine D_1 receptor in a same pocket, providing complexes A, B, C, and D, respectively. In complex A, the oxygen atoms of the 2-hydroxy-3-methoxy group, 10-hydroxy group, and the nitrogen atom in *l*-SPD formed hydrogen bonds with LYS81, SER198, and SER188, respectively. However, in complex B, the whole THPB scaffold was reversed. The oxygen atoms of the 2-hydroxy group and 11-methoxy group in compound **19c** formed two hydrogen bonds with ASN929 and LYS81, respectively. This different binding mode to that of *l*-SPD confirmed that replacing the 10-hydroxy group by 11-methoxy group reverses D_1 receptor function and enhances D_1 receptor affinity.

Compound **18k** demonstrated the same binding mode as **19c** as in complex C. This could explain that introducing a methoxy group at C1 enhanced D_1 receptor binding affinity. However, when the 2-

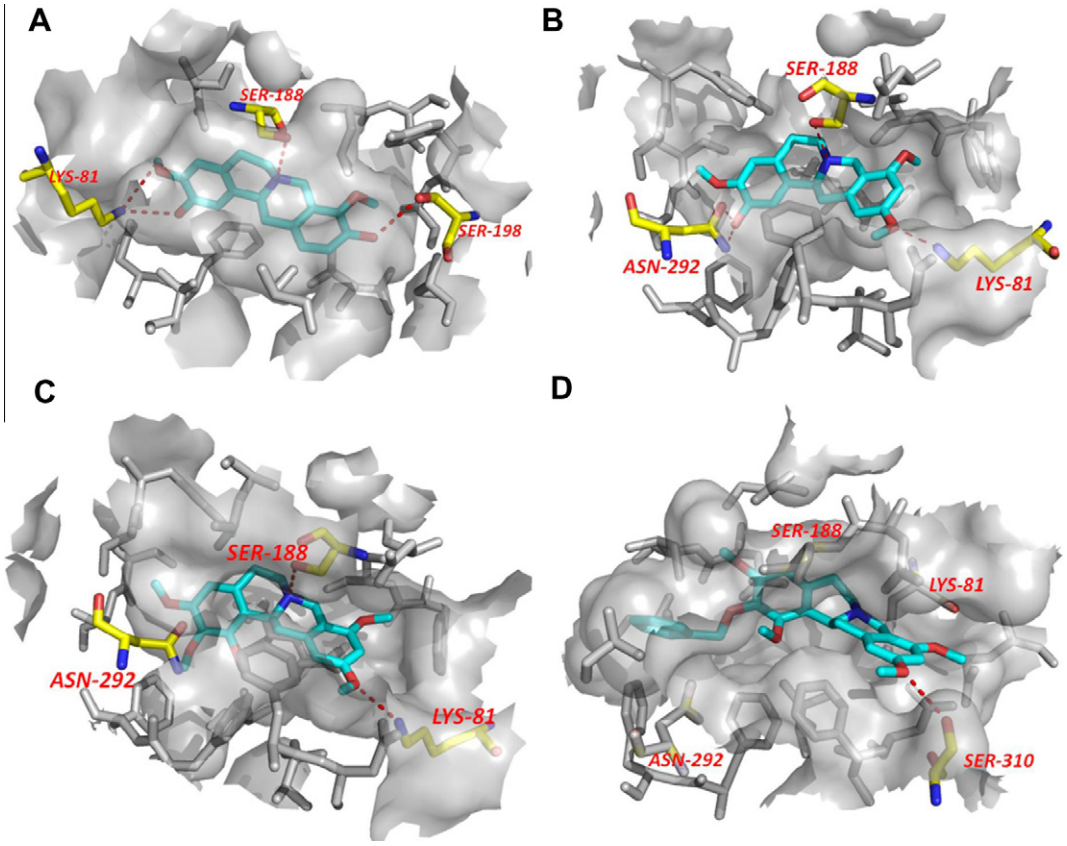


Figure 2. Docked structures of *l*-SPD, **19c**, **18k**, and **18i** (C, N, and O atoms in green, blue, and red, respectively) in a human dopamine D_1 receptor model built by homology modeling (complex A, B, C, and D, respectively).

hydroxy group was replaced by a more hindered 2-benzyloxy group, as compound **18i**, the binding affinity for the D_1 receptor was lost. This result confirmed that the order of efficacy of the function groups at C2 is OH > OMe > OBn.

5. Conclusions

In the present study, we designed a series of THPB compounds, with varieties of substituents at different positions. Binding assays revealed the position- and substituent-dependent effect for compounds **18** and **19**. Compound **19c** showed the most promising binding and selectivity profile, displaying marked low-nanomolar D_1R binding affinity (K_i = 2.53 nM) and remarkable selectivity versus D_2R (inhibition = 83.31%), 5-$HT_{1A}R$ (inhibition = 56.87%), and 5-$HT_{2A}R$ (inhibition = 32.39%). Compared with *l*-(*S*)-stepholidine (*l*-SPD) (D_1 K_i = 6.23 nM, D_2 K_i = 56.17 nM), compound **19c** showed a mild improved binding affinity for the D_1 receptor (2.5-fold higher) and excellent D_2/D_1 selectivity. Compound **18j**, in which two phenolic hydroxy groups on the A- and D-rings were removed, exhibited excellent D_1 receptor binding affinity (K_i = 7.97 nM) and selectivity. Functional assays revealed that compounds **18j**, **18k**, and **19c** were full D_1 receptor antagonists. This is the first report discovering a full D_1 receptor antagonist from THPB scaffold derivatives. We further conducted the docking studies with dopamine D_1 receptor. Compounds **18i**, **18k**, and **19c** bound to the D_1 receptor in a same pocket as *l*-SPD, however, the three new compounds reversed the molecular skeleton in binding with D_1 receptor compared with *l*-SPD. The different binding modes compared with that of *l*-SPD are in accord with the binding property and the opposite function. The novel D_1 receptor antagonists herein described are remarkable for their original structure and excellent selectivity. Given the fact that D_1 receptor blockage is promising therapeutic target in drug abuse, potential application of these new THPB compounds in drug abuse therapeutics is under investigation.

6. Experimental section

Chemicals and solvents were purchased and used without further purification. All target products were characterized by ^1H NMR and LC–MS (ESI), and some products were also characterized by ^{13}C NMR. ^1H NMR spectra were recorded on a Brucker AMX 300 or 400 MHz instrument (TMS as IS). ^{13}C NMR spectra were recorded on a Brucker AMX 100 MHz instrument (TMS as IS). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). High performance liquid chromatography (HPLC) analysis was performed on chiralpak OD column (0.46 cm × 25 cm 5 μm). Melting points are uncorrected and were measured in open capillary tubes, using a SGW X-4 melting point apparatus.

6.1. General procedures for the synthesis of compounds 10 are described as those for 10a

6.1.1. 4-(Benzyloxy)-3-methoxybenzaldehyde (10a)

To a solution of commercial available compound 3-methoxy-4-hydroxybenzaldehyde **9a** (6.08 g, 40 mmol) in dry acetone (100 mL) was added BnBr (7.18 g, 42 mmol) and K_2CO_3 (11.04 g, 80 mmol). The mixture was stirred for 2 h in reflux. Then the reaction solution was filtered after cooled to room temperature. The filtrate was concentrated, and purified by column chromatography

(PE/EA = 4/1) to give **10a** (9 g, 93%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.85 (s, 1H), 7.44–7.34 (m, 7H), 6.99 (d, J = 8.1 Hz, 1H), 5.26 (s, 2H), 3.96 (s, 3H). ESI-MS m/z 243 $[M+H]^+$.

6.1.2. 4-(Benzyloxy)-3,5-dimethoxybenzaldehyde (10b)

Yield 91%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.86 (s, 1H), 7.48–7.45 (m, 2H), 7.37–7.29 (m, 3H), 7.11 (s, 2H), 5.13 (s, 2H), 3.90 (s, 6H); ESI-MS m/z 273 $[M+H]^+$.

6.2. General procedures for the synthesis of compounds 12 are described as those for 12a

6.2.1. 1-(Benzyloxy)-2-methoxy-4-(2-nitroethenyl)benzene (12a)

To a solution of **10a** (8.5 g, 35 mmol) in glacial acetic acid (30 mL) was added CH_3NO_2 (6.4 g, 105 mmol) and ammonium acetate (2.70 g, 35 mmol), the mixture was heated to 90 °C for 4 h, then cooled to room temperature and poured to water (200 mL) to favor the precipitation as a solid, which was subsequently filtered and washed with cold water and methanol. The crude product was purified by column chromatography (PE/EA = 6/1) to yield **12a** (8.58 g, 86%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, J = 13.5 Hz, 1H), 7.52 (d, J = 13.2 Hz, 1H), 7.44–7.30 (m, 5H), 7.10 (dd, J = 8.4, 1.8 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 5.22 (s, 2H), 3.93 (s, 3H); ESI-MS m/z 284 $[M-H]^-$.

6.2.2. 1,2-Dimethoxy-4-(2-nitroethenyl)benzene (12b)

Yield 83%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, J = 13.5 Hz, 1H), 7.55–7.51 (m, 1H), 7.18 (d, J = 6.9 Hz, 1H), 7.01(s, 1H), 6.92 (d, J = 8.1 Hz, 1H), 3.95 (s, 3H), 3.93(s, 3H); ESI-MS m/z 208 $[M-H]^-$.

6.2.3. 1,3-Dimethoxy-5-(2-nitroethenyl)benzene (12c)

Yield 87%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (d, J = 13.5 Hz, 1H), 7.54 (d, J = 13.8 Hz, 1H), 6.66 (d, J = 2.1 Hz, 2H), 6.59–6.57 (m, 1H), 3.83 (s, 6H); ESI-MS m/z 208 $[M-H]^-$.

6.2.4. 1,2,3-Trimethoxy-5-(2-nitroethenyl)benzene (12d)

Yield 91%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, J = 13.5 Hz, 1H), 7.53 (d, J = 13.5 Hz, 1H), 6.76 (s, 2H), 3.91 (s, 3H), 3.90 (s, 6H); ESI-MS m/z 238 $[M-H]^-$.

6.2.5. 2-(Benzyloxy)-1,3-dimethoxy-5-(2-nitroethenyl)benzene (12e)

Yield 78%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (d, J = 13.5 Hz, 1H), 7.52 (d, J = 13.8 Hz, 1H), 7.47–7.44 (m, 2H), 7.38–7.30 (m, 3H), 6.74 (s, 2H), 5.09 (s, 2H), 3.87 (s, 6H); ESI-MS m/z 314 $[M-H]^-$.

6.3. General procedures for the synthesis of compounds 13 are described as those for 13a

6.3.1. 2-(4-(Benzyloxy)-3-methoxyphenyl)ethan-1-amine hydrochloride (13a)

A suspension of $LiAlH_4$ (3.42 g, 90 mmol) in dry THF (50 mL) was cooled in an ice-water bath, and compound **12a** (8.55 g, 30 mmol) was added by portion. The reaction was stirred at 0 °C for 0.5 h, then heated to reflux and stirred for another 2 h. After the mixture was cooled to 0 °C, water (6 mL) was added to decompose the rest $LiAlH_4$. The mixture was diluted with THF (50 mL) and filtrated. The organic layer was dried over Na_2SO_4 and concentrated to give yellow oil. Then, HCl–Et_2O solution was added to the yellow oil to yield **13a** (6.59 g, 75%) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.66 (br, 2H), 7.44–7.30 (m, 5H), 6.96 (d, J = 8 Hz, 1H), 6.88 (d, J = 2 Hz, 1H), 6.73 (dd, J = 8, 2 Hz, 1H), 5.05 (s, 2H), 3.77 (s, 3H), 3.01–2.97 (m, 2H), 2.80–2.77 (m, 2H); ESI-MS m/z 258 $[M+H]^+$.

6.3.2. 2-(3,4-Dimethoxyphenyl)ethan-1-amine (13b)

Yield 78%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.60–6.51 (m, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 2.72 (t, J = 6.9 Hz, 2H), 2.47 (t, J = 6.9 Hz, 2H), 1.20 (s, 2H); ESI-MS m/z 182 $[M+H]^+$.

6.3.3. 2-(3,5-Dimethoxyphenyl)ethan-1-amine hydrocloride (13c)

Yield 69%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.03 (br, 2H), 6.43 (s, 1H), 6.42 (s, 1H), 6.38 (s, 1H), 3.73 (s, 6H), 3.03–3.00 (m, 2H), 2.83–2.79 (m, 2H); ESI-MS m/z 182 $[M+H]^+$.

6.3.4. 2-(3,4,5-Trimethoxyphenyl)ethan-1-amine (13d)

Yield 71%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.38 (s, 2H), 3.81 (s, 6H), 3.78 (s, 3H), 2.94–2.91 (m, 2H), 2.65 (t, J = 6.8 Hz, 2H), 1.43 (s, 2H); ESI-MS m/z 212 $[M+H]^+$.

6.3.5. 2-(4-(Benzyloxy)-3,5-dimethoxyphenyl)ethan-1-amine hydrocloride (13e)

Yield 76%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.95 (br, 2H), 7.47–7.44 (m, 2H), 7.39–7.28 (m, 3H), 6.58 (s, 2H), 4.85 (s, 2H), 3.78 (s, 6H), 3.06–3.02 (m, 2H), 2.84–2.79 (m, 2H); ESI-MS m/z 288 $[M+H]^+$.

6.4. General procedures for the synthesis of compounds 15 are described as those for 15c

6.4.1. *N*-(2-(4-(Benzyloxy)-3-methoxyphenyl)ethyl)-2-(3,5-dimethoxyphenyl)acetamide (15c)

To a solution of 3,5-dimethoxyphenylacetic acid **14a** (0.98 g, 5 mmol) in CH_2Cl_2 (10 mL), EDCI (*N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimidehydrochloride) (1.15 g, 6 mmol) was added. The mixture was stirred at room temperature for 0.5 h, and 2-(4-(benzyloxy)-3-methoxyphenyl)ethan-1-amine hydrochloride **13a** (1.47 g, 5 mmol) was added. The mixture was stirred for another 8 h, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (CH_2Cl_2/MeOH = 80/1) to afford **15c** (1.76 g, 81%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.30 (m, 5H), 6.74 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 1.8 Hz, 1H), 6.48 (dd, J = 8.1, 1.8 Hz, 1H), 6.37–6.35 (m, 1H), 6.31 (s, 2H), 5.46 (br, 1H), 5.12 (s, 2H), 3.83 (s, 3H), 3.75 (s, 6H), 3.46–3.40 (m, 4H), 2.66 (t, J = 6.9 Hz, 2H); ESI-MS m/z 436 $[M+H]^+$.

6.4.2. *N*-(2-(4-(Benzyloxy)-3-methoxyphenyl)ethyl)-2-(3-methoxyphenyl)acetamide (15a)

Yield 87%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.30 (m, 5H), 7.18 (t, J = 8.1 Hz, 1H), 6.80–6.71 (m, 4H), 6.63 (d, J = 1.5 Hz, 1H), 6.48–6.45 (m, 1H), 5.45 (br, 1H), 5.12 (s, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.49–3.39 (m, 4H), 2.66 (t, J = 6.9 Hz, 2H); ESI-MS m/z 406 $[M+H]^+$.

6.4.3. *N*-(2-(3,4-Dimethoxyphenyl)ethyl)-2-(3-methoxyphenyl)-acetamide (15d)

Yield 90%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (t, J = 7.8 Hz, 1H), 6.82–6.79 (m, 1H), 6.75–6.70 (m, 3H), 6.60 (d, J = 2.1 Hz, 1H), 6.53 (dd, J = 8.4, 2.1 Hz, 1H), 5.42 (br, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.50 (s, 2H), 3.46–3.40 (m, 2H), 2.66 (t, J = 6.9 Hz, 2H); ESI-MS m/z 330 $[M+H]^+$.

6.4.4. *N*-(2-(2*H*-1,3-Benzodioxol-5-yl)ethyl)-2-(3-methoxyphenyl)acetamide (15e)

Yield 83%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, J = 7.8 Hz, 1H), 6.84–6.80 (m, 1H), 6.77–6.71 (m, 2H), 6.66 (d, J = 7.8 Hz, 1H), 6.52 (d, J = 1.8 Hz, 1H), 6.45–6.42 (m, 1H), 5.92 (s, 2H), 5.37 (br, 1H), 3.79 (s, 3H), 3.51 (s, 2H), 3.43–3.36 (m, 2H), 2.63 (t, J = 6.9 Hz, 2H); ESI-MS m/z 314 $[M+H]^+$.

6.4.5. *N*-(2-(3,4-Dimethoxyphenyl)ethyl)-2-(3,5-dimethoxyphenyl)acetamide (15f)

Yield 86%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.72 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 1.8 Hz, 1H), 6.53 (dd, J = 8.1, 1.8 Hz, 1H), 6.37–6.36 (m, 1H), 6.30 (d, J = 2.1 Hz, 2H), 5.45 (br, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.75 (s, 6H), 3.47–3.40 (m, 4H), 2.67 (t, J = 6.9 Hz, 2H); ESI-MS m/z 360 $[M+H]^+$.

6.4.6. *N*-(2-(2*H*-1,3-Benzodioxol-5-yl)ethyl)-2-(3,5-dimethoxyphenyl)acetamide (15h)

Yield 76%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.66 (d, J = 7.8 Hz, 1H), 6.54 (d, J = 1.5 Hz, 1H), 6.46–6.43 (m, 1H), 6.37 (t, J = 2.1 Hz, 1H), 6.32 (s, 1H), 6.31 (s, 1H), 5.92 (s, 2H), 5.44 (br, 1H), 3.76 (s, 6H), 3.46 (s, 2H), 3.43–3.36 (m, 2H), 2.63 (t, J = 6.9 Hz, 2H); ESI-MS m/z 344 $[M+H]^+$.

6.4.7. *N*-(2-(4-(Benzyloxy)-3,5-dimethoxyphenyl)ethyl)-2-(3,5-dimethoxyphenyl)acetamide (15i)

Yield 84%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50–7.47 (m, 2H), 7.37–7.28 (m, 3H), 6.36–6.30 (m, 5H), 5.52 (br, 1H), 4.96 (s, 2H), 3.77 (s, 6H), 3.75 (s, 6H), 3.48–3.44 (m, 4H), 2.69 (t, J = 6.9 Hz, 2H); ESI-MS m/z 466 $[M+H]^+$.

6.4.8. *N*-(2-(3,4,5-Trimethoxyphenyl)ethyl)-2-(3,5-dimethoxyphenyl)acetamide (15k)

Yield 81%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.37–6.35 (m, 1H), 6.32–6.31 (m, 4H), 5.50 (br, 1H), 3.81 (s, 3H), 3.80 (s, 6H), 3.75 (s, 6H), 3.50–3.43 (m, 4H), 2.69 (t, J = 6.9 Hz, 2H); ESI-MS m/z 390 $[M+H]^+$.

6.4.9. 2-(2*H*-1,3-Benzodioxol-5-yl)-*N*-(2-(3,4,5-trimethoxyphenyl)ethyl)acetamide (15m)

Yield 76%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.73 (d, J = 7.5 Hz, 1H), 6.64–6.59 (m, 2H), 6.30 (s, 2H), 5.95 (s, 2H), 5.43 (br, 1H), 3.81 (s, 9H), 3.50–3.44 (m, 4H), 2.69 (t, J = 6.9 Hz, 2H); ESI-MS m/z 374 $[M+H]^+$.

6.4.10. 2-(2*H*-1,3-Benzodioxol-5-yl)-*N*-(2-(3,5-dimethoxyphenyl)ethyl)acetamide (15n)

Yield 82%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.72 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 1.5 Hz, 1H), 6.60 (dd, J = 7.8, 1.8 Hz, 1H), 6.31–6.23 (m, 1H), 6.23 (s, 1H), 6.22 (s, 1H), 5.95 (s, 2H), 5.40 (br, 1H), 3.76 (s, 6H), 3.49–3.43 (m, 4H), 2.68 (t, J = 6.9 Hz, 2H); ESI-MS m/z 344 $[M+H]^+$.

6.4.11. *N*-(2-(3,5-Dimethoxyphenyl)ethyl)-2-(3-methoxyphenyl)acetamide (15o)

Yield 88%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23–7.17 (m, 1H), 6.80–6.71 (m, 3H), 6.29–6.28 (m, 1H), 6.22 (s, 2H), 5.57 (br, 1H), 3.76 (s, 3H), 3.73 (s, 6H), 3.48 (s, 2H), 3.45–3.40 (m, 2H), 2.66 (t, J = 6.9 Hz, 2H); ESI-MS m/z 330 $[M+H]^+$.

6.4.12. *N*-(2-(3,5-Dimethoxyphenyl)ethyl)-2-(2,5-dimethoxyphenyl)acetamide (15p)

Yield 82%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.77 (s, 1H), 6.76 (s, 2H), 6.31–6.29 (m, 1H), 6.24 (d, J = 2.1 Hz, 2H), 5.87 (br, 1H), 3.74 (s, 9H), 3.67 (s, 3H), 3.49–3.42 (m, 4H), 2.67 (t, J = 6.9 Hz, 2H); ESI-MS m/z 360 $[M+H]^+$.

6.5. General procedures for the synthesis of compounds 16 are described as those for 7-(benzyloxy)-1-((3,5-dimethoxyphenyl)-methyl)-6-methoxy-3,4-dihydroisoquinoline (16c)

To a solution of the amide **15c** (1.74 g, 4 mmol) in dry acetonitrile (20 mL) was added $POCl_3$ (3.06 g, 20 mmol), then the mixture was refluxed for 0.5 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to yield **16c** (1.63 g, 98%) as a yellow solid. It was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.28 (m, 5H), 7.03 (s, 1H), 6.67 (s, 1H), 6.41 (s, 2H), 6.29 (t, J = 2 Hz, 1H), 4.99 (s, 2H), 3.92 (s, 2H), 3.88 (s, 3H), 3.75–3.68 (m, 8H), 2.67 (t, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.30, 160.91 (2C), 152.14, 146.36, 139.73, 136.63, 132.48, 128.54 (2C), 127.96, 127.55, 127.24 (2C), 112.94, 110.64, 106.73 (2C), 98.39, 71.37, 56.00, 55.24 (2C), 46.29, 42.89, 25.73; ESI-MS m/z 418 $[M+H]^+$.

6.6. General procedures for the synthesis of compounds 17

6.6.1. General procedures for the synthesis of compounds 17a–q are described as those for (*S*)-7-(benzyloxy)-1-((3,5-dimethoxyphenyl)methyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (17c)

A freshly prepared imine **16c** (1.63 g, 3.9 mmol) was dissolved in anhydrous DMF (6 mL), RuCl[(*R*,*R*)-TsDPEN(P-cymene)] (27 mg, 39 μmol) was added followed by formic acid/triethylamine (v/v = 5/2, 1.2 mL), and the reaction mixture was stirred at room temperature for 10 h. Then, the pH of reaction mixture was adjusted to 8 with saturated $NaHCO_3$ (100 mL), and extracted by ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield **17c** (1.65 g, 101%) as a brown oil. It was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44–7.29 (m, 5H), 6.67 (s, 1H), 6.62 (s, 1H), 6.38 (s, 2H), 6.36 (s, 1H), 5.08 (s, 2H), 4.11–4.10 (m, 1H), 3.86 (s, 3H), 3.77 (s, 6H), 3.20–3.18 (m, 1H), 3.04 (d, J = 10 Hz, 1H), 2.94–2.89 (m, 1H), 2.81–2.69 (m, 3H), 2.20 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.79 (2C), 148.14, 145.94, 141.22, 137.16, 129.99, 128.40 (2C), 127.87, 127.71, 127.31 (2C), 112.53, 112.17, 107.19 (2C), 98.30, 71.27, 56.51, 55.86, 55.20 (2C), 42.74, 40.66, 29.27. ESI-MS m/z 420 $[M+H]^+$.

6.6.2. Procedures for the synthesis of compound (*RS*)-1-((3,5-dimethylphenyl)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (17r)

A solution of compound **16r** (0.5 g, 1.6 mmol) in methanol (10 mL) was cooled in an ice-water bath, and $NaBH_4$ (0.12 g, 3.2 mmol) was added by portion. The reaction was stirred at 0 °C for 0.5 h, then warmed to room temperature and stirred for another 1 h. After the mixture was cooled to 0 °C, saturated NH_4Cl solution (5 mL) was added to decompose the rest $NaBH_4$. The mixture was diluted with water (50 mL) and extracted by CH_2Cl_2 (50 mL × 2), washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield **17r** (0.49 g, 97%) as a white solid. It was used in the next step without further purification. ESI-MS m/z 420 $[M+H]^+$.

6.7. General procedures for the synthesis of compounds 18 are described as those for 18c

6.7.1. (*S*)-2-(Benzyloxy)-3,9,11-trimethoxytetrahydroprotoberberine (18c)

Compound 17c (0.42 g, 1 mmol) was dissolved in HCOOH/40% HCHO (v/v = 1.4/1, 10 ml) mixture solution, the reaction was stirred at 50 °C for 2 h. The reaction mixture was cooled to room temperature, and alkalified pH to 9 by K_2CO_3. The solution was extracted by CH_2Cl_2 (50 mL × 2), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography to yield **18c** (0.4 g, 92%, chiral HPLC: hexane/*i*-PrOH = 70/30, flow rate = 0.6 ml/mim, λ = 214 nm, 99% ee) as a light yellow solid: mp 84–86 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.46 (m, 5H), 6.76 (s, 1H), 6.64 (s, 1H), 6.30 (s, 1H), 6.24 (s, 1H), 5.14 (s, 2H), 4.15–4.09 (m, 1H), 3.88 (s, 3H), 3.80 (s, 6H), 3.54–3.36 (m, 2H), 3.13–3.09 (m, 3H), 2.82–2.65 (m,

3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.87, 156.78, 148.19, 146.37, 137.25 (2C), 136.13, 129.53, 128.49 (2C), 127.78, 127.44 (2C), 115.78, 111.91, 111.74, 103.84, 95.93, 71.52, 58.89, 55.91, 55.29, 53.29, 51.38, 37.12, 29.02; ESI-MS *m/z* 432 $[M+H]^+$.

6.7.2. (*S*)-2-(Benzyloxy)-3,11-dimethoxytetrahydroprotoberberine (18a)

Yield 86%; mp 107–110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, J = 7.2 Hz, 2H), 7.40–7.30 (m, 3H), 6.99 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 6.72 (dd, J = 8.4, 2.8 Hz, 1H), 6.66 (d, J = 2.4 Hz, 1H), 6.64 (s, 1H), 5.15 (s, 2H), 3.99–3.94 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.64 (d, J = 14.4 Hz, 1H), 3.55–3.51 (m, 1H), 3.16–3.11 (m, 3H), 2.78 (dd, J = 16.4, 11.2 Hz, 1H), 2.69–2.58 (m, 2H); ESI-MS *m/z* 402 $[M+H]^+$.

6.7.3. (*S*)-2,3-Methylenedioxy-9,11-dimethoxy-12-hydroxymethyltetrahydroprotoberberine (18b)

Yield 79%; mp 134 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79 (s, 1H), 6.59 (s, 1H), 6.36 (s, 1H), 5.92 (s, 2H), 4.77–4.61 (m, 2H), 4.12 (d, J = 15.3 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.54 (d, J = 11.4 Hz, 1H), 3.49–3.36 (m, 2H), 3.18–3.07 (m, 2H), 2.84–2.75 (m, 1H), 2.68–2.59 (m, 2H), 1.83 (br, 1H); NOE 6.36 (1H) connected with 3.87 (3H) and 3.85 (3H); ESI-MS *m/z* 370 $[M+H]^+$.

6.7.4. (*S*)-2,3,11-Trimethoxytetrahydroprotoberberine (18d)

Yield 87%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (d, J = 8.4 Hz, 1H), 6.74 (s, 2H), 6.71 (s, 1H), 6.62 (s, 1H), 3.96–3.94 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.69–3.58 (m, 2H), 3.30 (dd, J = 16.5, 3.6 Hz, 1H), 3.19–3.12 (m, 2H), 2.94–2.79 (m, 1H), 2.69–2.63 (m, 2H); ESI-MS *m/z* 326 $[M+H]^+$.

6.7.5. (*S*)-2,3-Methylenedioxy-11-methoxytetrahydroprotoberberine (18e)

Yield 82%; mp 114–116 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (d, J = 8.4 Hz, 1H), 6.74–6.69 (m, 3H), 6.59 (s, 1H), 5.92 (s, 2H), 3.96 (d, J = 14.4 Hz, 1H), 3.78 (s, 3H), 3.68–3.55 (m, 2H), 3.29–3.22 (m, 1H), 3.16–3.06 (m, 2H), 2.87 (dd, J = 15.9, 11.4 Hz, 1H), 2.67–2.55 (m, 2H); ESI-MS *m/z* 310 $[M+H]^+$.

6.7.6. (*S*)-2,3,9,11-Tetramethoxytetrahydroprotoberberine (18f)

Yield 85%; mp 153–156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.73 (s, 1H), 6.61 (s, 1H), 6.30 (s, 2H), 4.10 (d, J = 15.3 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.70–3.55 (m, 2H), 3.28–3.08 (m, 3H), 2.94–2.83 (m, 1H), 2.67–2.60 (m, 2H); ESI-MS *m/z* 356 $[M+H]^+$.

6.7.7. (*S*)-2,3,9,11-Tetramethoxy-12-hydroxymethyltetrahydroprotoberberine (18g)

Yield 76%; mp 132–133 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.77 (s, 1H), 6.61 (s, 1H), 6.36 (s, 1H), 4.77–4.61 (m, 2H), 4.11 (d, J = 15.3 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 6H), 3.85 (s, 3H), 3.55–3.36 (m, 3H), 3.18–3.07 (m, 2H), 2.82–2.74 (m, 1H), 2.68–2.56 (m, 2H), 2.04 (br, 1H); ESI-MS *m/z* 386 $[M+H]^+$.

6.7.8. (*S*)-2,3-Methylenedioxy-9,11-dimethoxytetrahydroprotoberberine (18h)

Yield 83%; mp 155–157 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.73 (s, 1H), 6.59 (s, 1H), 6.30 (s, 2H), 5.92 (s, 2H), 4.10 (d, J = 15.3 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.54 (d, J = 10.5 Hz, 1H), 3.38 (d, J = 15.3 Hz, 1H), 3.24–3.08 (m, 3H), 2.90–2.81 (m, 1H), 2.66–2.57 (m, 2H); ESI-MS *m/z* 340 $[M+H]^+$.

6.7.9. (*S*)-2-(Benzyloxy)-1,3,9,11-tetramethoxytetrahydroprotoberberine (18i)

Yield 85%; mp 124–125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55–7.53 (m, 2H), 7.42–7.32 (m, 3H), 6.48 (s, 1H), 6.33 (s, 1H), 6.31 (s, 1H), 5.04 (dd, J = 28.4, 10.8 Hz, 2H), 4.11–4.07 (m, 1H), 3.97–3.93 (m, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.77–3.73 (m, 1H), 3.48 (dd, J = 16.4, 3.6 Hz, 1H), 3.16–3.00 (m, 2H), 2.86–2.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.73, 156.99, 152.05, 151.18, 139.01, 137.69, 137.05, 130.82, 128.18 (2C), 128.15 (2C), 127.74, 124.23, 115.47, 107.37, 103.84, 95.86, 75.03, 60.79, 55.77, 55.21, 55.15, 55.10, 52.63, 48.13, 33.76, 30.24; ESI-MS *m/z* 462 $[M+H]^+$.

6.7.10. (*S*)-1,3,9,11-Tetramethoxytetrahydroprotoberberine (18j)

Yield 84%; mp 90–92 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.32 (d, J = 2.4 Hz, 1H), 6.29 (dd, J = 4.2, 2.1 Hz, 2H), 6.24 (d, J = 2.7 Hz, 1H), 4.15–4.01 (m, 2H), 3.90–3.82 (m, 1H), 3.79 (s, 9H), 3.78 (s, 3H), 3.48 (dd, J = 16.8, 3.3 Hz, 1H), 3.20–3.03 (m, 2H), 2.94–2.89 (m, 1H), 2.81–2.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.99 (2C), 157.48, 157.12, 136.57, 136.34, 118.84, 114.45, 104.27, 103.87, 96.59, 96.01, 55.29, 55.24 (2C), 55.16, 54.69, 52.42, 47.81, 33.08, 30.05; ESI-MS *m/z* 356 $[M+H]^+$.

6.7.11. (*S*)-1,2,3,9,11-pentamethoxytetrahydroprotoberberine (18k)

Yield 74%; mp 171–174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.46 (s, 1H), 6.33 (d, J = 1.8 Hz, 1H), 6.28 (s, 1H), 4.22–4.14 (m, 2H), 4.05–3.96 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.46 (dd, J = 17.1, 4.2 Hz, 1H), 3.26–3.19 (m, 1H), 3.09–3.05 (m, 2H), 2.96–2.79 (m, 2H); ESI-MS *m/z* 386 $[M+H]^+$.

6.7.12. (*S*)-1,2,3,9,11-Pentamethoxy-12-hydromethyltetrahydroprotoberberine (18l)

Yield 77%; mp 91–93 °C; chiral HPLC: hexane/*i*-PrOH = 70/30, flow rate = 0.6 ml/mim, λ = 214 nm, 99% ee; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.45 (s, 1H), 6.40 (s, 1H), 4.65 (s, 2H), 4.30–4.25 (m, 2H), 4.18–4.10 (m, 1H), 3.94 (d, J = 0.9 Hz, 3H), 3.88 (s, 3H), 3.86 (s, 6H), 3.84 (s, 3H), 3.68 (dd, J = 17.7, 4.2 Hz, 1H), 3.27–3.22 (m, 2H), 3.06–2.94 (m, 2H), 2.88–2.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.39, 156.72, 152.10, 150.74, 140.13, 135.52, 129.98, 123.88, 118.60, 114.66, 107.23, 92.42, 60.74, 60.65, 56.11, 55.84, 55.70, 55.31, 54.49, 52.36, 47.37, 30.15, 29.66; ESI-MS *m/z* 416 $[M+H]^+$.

6.7.13. (*S*)-1,2,3-Trimethoxy-10,11-methylenedioxytetrahydroprotoberberine (18m)

Yield 86%; mp 89–91 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.58 (s, 1H), 6.55 (s, 1H), 6.45 (s, 1H), 5.29 (s, 2H), 4.12 (d, J = 14.7 Hz, 1H), 4.07–4.01 (m, 1H), 3.95–3.91 (m, 4H), 3.87 (s, 3H), 3.84 (s, 3H), 3.36 (dd, J = 16.8, 4.2 Hz, 1H), 3.15–3.08 (m, 1H), 3.02–2.88 (m, 2H), 2.77–2.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.06, 150.53, 146.12, 145.80, 140.21, 129.63, 127.35, 125.86, 123.53, 108.46, 107.21, 106.07, 100.54, 60.80, 60.60, 57.31, 55.75, 54.81, 47.17, 32.74, 29.52; ESI-MS *m/z* 370 $[M+H]^+$.

6.7.14. (*S*)-1,3-Dimethoxy-4-hydromethyl-10,11-methylenedioxytetrahydroprotoberberine (18n)

Yield 73%; mp 164–165 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.54 (s, 2H), 6.38 (s, 1H), 5.88 (s, 2H), 4.67 (s, 2H), 4.06–3.97 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.81–3.75 (m, 1H), 3.32 (dd, J = 16.5, 3.9 Hz, 1H), 3.13–3.00 (m, 3H), 2.68–2.56 (m, 2H), 2.18 (br, 1H); ESI-MS *m/z* 370 $[M+H]^+$.

6.7.15. (*S*)-1,3,11-Trimethoxy-4-hydromethyltetrahydroprotoberberine (18o)

Yield 76%; mp 121–122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (d, J = 8.4 Hz, 1H), 6.74 (dd, J = 8.4, 2.7 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.38 (s, 1H), 4.66 (s, 2H), 4.25–4.18 (m, 2H), 3.98 (d, J = 15.6 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.48–3.41 (m, 1H),

3.19–3.05 (m, 3H), 2.85–2.81 (m, 1H), 2.78–2.69 (m, 1H); ESI-MS *m/z* 356 $[M+H]^+$.

6.7.16. (*S*)-1,3,9,12-Tetramethoxy-4-hydromethyltetrahydroprotoberberine (18p)

Yield 69%; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.66 (s, 2H), 6.38 (s, 1H), 4.68 (dd, *J* = 16.2, 12 Hz, 2H), 4.22 (d, *J* = 16.8 Hz, 2H), 4.02 (d, *J* = 14.1 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.51–3.43 (m, 1H), 3.22–3.12 (m, 3H), 2.90–2.85 (m, 1H), 2.50–2.41 (m, 1H), 2.01 (br, 1H); ESI-MS *m/z* 386 $[M+H]^+$.

6.7.17. (*S*)-2,3-Dimethyloxy-9,11-dimethyltetrahydroprotoberberine (18q)

Yield 77%; chiral HPLC: hexane/*i*-PrOH = 70/30, flow rate = 0.6 ml/mim, λ = 214 nm, 98% ee; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.86 (s, 1H), 6.84 (s, 1H), 6.75 (s, 1H), 6.63 (s, 1H), 4.02 (d, *J* = 15.2 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.58 (dd, *J* = 11.2, 3.2 Hz, 1H), 3.50 (d, *J* = 15.2 Hz, 1H), 3.28 (dd, *J* = 16, 3.6 Hz, 1H), 3.21–3.13 (m, 2H), 2.93–2.86 (m, 1H), 2.70–2.62 (m, 2H), 2.29 (s, 3H), 2.20 (s, 3H); ESI-MS *m/z* 324 $[M+H]^+$.

6.7.18. (*RS*)-2,3-Dimethyloxy-9,11-dimethyltetrahydroprotoberberine (18r)

Yield 81%; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H), 6.83 (s, 1H), 6.73 (s, 1H), 6.62 (s, 1H), 4.02 (d, *J* = 15.2 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.58 (dd, *J* = 11.2, 3.2 Hz, 1H), 3.48 (d, *J* = 15.2 Hz, 1H), 3.28 (dd, *J* = 16, 3.6 Hz, 1H), 3.22–3.12 (m, 2H), 2.93–2.86 (m, 1H), 2.70–2.60 (m, 2H), 2.27 (s, 3H), 2.19 (s, 3H); ESI-MS *m/z* 324 $[M+H]^+$.

6.8. General procedures for the synthesis of compounds 19 are described as those for 19c

6.8.1. (*S*)-2-Hydroxy-3,9,11-trimethoxytetrahydroprotoberberine (19c)

Compound **18c** (0.35 g, 0.8 mmol) was refluxed in a mixture solution of concentrated hydrochloric acid (10 mL) and EtOH (3 mL) for 2 h. Then, the reaction mixture was cooled to 0 °C, alkalified pH to 9 by K_2CO_3, and extracted with CH_2Cl_2 (30 mL × 2). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by column chromatography to yield **19c** (0.23 g, 83%, chiral HPLC: hexane/*i*-PrOH = 70/30, flow rate = 0.6 ml/mim, λ = 214 nm, 97% ee) as a light yellow solid: mp 118–120 °C;. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.78 (s, 1H), 6.58 (s, 1H), 6.30 (s, 2H), 4.12 (d, *J* = 15.2 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 6H), 3.52 (dd, *J* = 11.2, 3.2 Hz, 1H), 3.38 (d, *J* = 15.2 Hz, 1H), 3.22–3.10 (m, 3H), 2.89–2.82 (m, 1H), 2.66–2.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.85, 156.74, 145.22, 143.92, 136.29, 130.25, 125.96, 115.82, 111.56, 110.61, 103.88, 95.98, 58.94, 55.75, 55.28, 55.24, 53.37, 51.56, 37.03, 29.03; ESI-MS *m*/*z* 342 $[M+H]^+$.

6.8.2. (*S*)-2-Hydroxy-3,11-dimethoxytetrahydroprotoberberine (19a)

Yield 85%; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.04 (d, *J* = 8.1 Hz, 1H), 6.83 (s, 1H), 6.73–6.69 (m, 2H), 6.60 (s, 1H), 5.56 (br, 1H), 3.98 (d, *J* = 14.7 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.69–3.57 (m, 2H), 3.28 (dd, *J* = 15.9, 3.9 Hz, 1H), 3.19–3.11 (m, 2H), 2.93–2.83 (m, 1H), 2.70–2.58 (m, 2H); ESI-MS *m/z* 312 $[M+H]^+$.

6.8.3. (*S*)-1,3,9,11-Tetramethoxy-2-hydroxytetrahydroprotoberberine (19b)

Yield 87%; mp 153–156 °C; chiral HPLC: hexane/*i*-PrOH = 70/30, flow rate = 0.6 ml/mim, λ = 214 nm, 99% ee; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.42 (s, 1H), 6.29 (s, 1H), 6.25 (s, 1H), 4.06 (d, *J* = 16.2 Hz, 1H), 3.96–3.91 (m, 1H), 3.86 (s, 6H), 3.79 (s, 3H), 3.77 (s, 3H), 3.73–3.66 (m, 1H), 3.50–3.43 (m, 1H), 3.14–2.95 (m, 2H), 2.88–2.61 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.93, 157.12, 146.34, 144.27, 136.98, 136.62, 125.85, 124.13, 115.26, 106.55, 104.01, 96.02, 60.23, 56.10, 55.35, 55.29, 55.22, 52.68, 48.41, 33.77, 29.84; ESI-MS *m/z* 372 $[M+H]^+$.

6.8.4. (*S*)-2-Hydroxy-3,9,11-trimethoxy-12-hydroxymethyltetrahydroprotoberberine (19d)

Yield 76%; mp 133–134 °C; chiral HPLC: hexane/*i*-PrOH = 70/30, flow rate = 0.6 ml/mim, λ = 214 nm, 99% ee; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.86 (s, 1H), 6.58 (s, 1H), 6.32 (s, 1H), 4.74–4.57 (m, 2H), 4.12 (d, *J* = 15 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.47–3.33 (m, 3H), 3.19–3.16 (m, 2H), 2.81–2.56 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.37, 156.31 (2C), 145.23, 144.03, 135.30, 125.77, 118.64 (2C), 111.58, 110.65, 92.52, 58.88, 55.99, 55.89, 55.68, 55.37, 53.47, 51.44, 33.95, 28.95; ESI-MS *m/z* 372 $[M+H]^+$.

6.8.5. (*S*)-2-Hydroxy-3-methoxy-9,11-dimethyltetrahydroprotoberberine (19e)

Yield 89%; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 2H), 6.82 (s, 1H), 6.60 (s, 1H), 4.04 (d, *J* = 15 Hz, 1H), 3.85 (s, 3H), 3.59–3.47 (m, 2H), 3.26–3.18 (m, 3H), 2.93–2.89 (m, 1H), 2.70–2.63 (m, 2H), 2.28 (s, 3H), 2.20 (s, 3H); ESI-MS *m/z* 310 $[M+H]^+$.

6.9. Binding assay of new compounds at the D_1, D_2, 5-HT_{1A}, and 5-HT_{2A} receptors

All the synthesized THPB compounds were subjected to the competitive binding assays for the human cloned dopamine (D_1 and D_2) and serotonin (5-HT_{1A} and 5-HT_{2A}) receptors, which were expressed by HEK293 cells. The initial screening at a concentration of 10 μM for every compound to inhibit the binding of a tritiated labeled ligand to the corresponding receptor was tested. Compounds that inhibited binding by more than 90% for DA receptor and serotonin receptor were subjected to measure the K_i/IC_{50}. [^{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 D_1, D_2, 5-HT_{1A}, and 5-HT_{2A} receptors, respectively.

6.10. [^{35}S] GTPγS binding assays for compounds 18j, 18k, and 19c

Stably transfected D_1 cell membrane fraction was prepared, and the [^{35}S] GTPγS binding assay was performed as previously described. Compounds **18j**, **18k**, and **19c** were diluted to various concentrations and added to the reaction tubes. The D_1 receptor agonist SKF38393 (1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol) and antagonist SCH23390 (7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol) were used for comparison.

6.11. Molecular modeling

Docking study was performed using the Glide program from the Schrödinger Suite. The 3D model of the D_1 receptor was constructed using a homology-modeling approach based on the x-ray crystal structure of bovine rhodopsin (Protein Data Bank: 1F88) by our group.[24] The D_1 receptor was processed by removing all solvent, adding hydrogens and minimal minimization with the OPLS2001 force field using Protein Preparation Wizard. The grid was sized to 15 Å in each direction. All the small molecules were generated and minimized using SYBYL 7.3, Tripos.[27] In all cases, the compounds were prepared for docking using Ligprep under its default parameters. The maximum number of heavy atoms permitted per compound was 120, and the maximum number of rotatable bonds allowed per compound was 30. Docking was

performed using Glide in standard-precision mode, with up to 50 poses saved per molecule. The top scoring pose for each compound, as assessed by its Glide score, was employed for discussions.

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