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Synthesis of 6-substituted 1-phenylbenzazepines and their dopamine D_1 receptor activities

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ABSTRACT

A series of racemic 6-aryl substituted 1-phenylbenzazepines **7a**–**e**, and **17a**,**b** were prepared. All these compounds showed binding potencies compatible to or much higher than that of the prototypic (±)-SKF-38393 ((±)-**1**) and (±)-SKF-83959 (**3**) for the D_1 receptor. Among analogs of (±)-SKF-38393, compounds **7b**, **7c** and **7e** possess 10-, 2- and 7-fold enhancement in binding for the D_1 receptor, respectively. Lower but compatible potency to that of (±)-**1** was observed for compounds **7a** and **7d**. The optimal 6-substituents (*m*-tolyl, and 2′-naphthyl) were applied to the skeleton of (±)-SKF-83959 (**3**). The resulting compounds **17a**,**b** displayed high affinity at the D_1 receptor, only slightly lower than that of **3**. These two compounds also showed good binding at the D_2 receptor.

1. Introduction

The D_1 receptor is the most highly expressed subtype among dopamine (DA) receptor family (D_1–D_5). It plays a crucial role in a variety of cognitive functions and is a major target for development of anti-parkinsonian agents.[1,2] SKF-38393, (1*R*)-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine-7,8-diol (*R*-(+)-**1**) (Fig. 1), is the earliest D_1 receptor agonist with high binding affinity and selectivity.[3] Although it was reported more than two decades ago, SKF-38393 still remains one of the widely used ligands for characterization of the D_1 receptor, and as the prototype for developing new D_1 receptor agonists.[1,4,5] Ironically, compared to the large number of phenylbenzazepines derived from SKF-38393, clinically useful D_1 receptor selective ligands are rare.[5] This is mostly due to the poor intrinsic activity, low metabolic stability and some unwanted side effects observed from these compounds.[1,4,5]

A comprehensive analysis[5] of the phenylbenzazepines developed by far, reveals that the catecholic-, amino-, and the 1-phenyl-fragments in phenylbenzazepines, such as SKF-38393, are the major determinants of the D_1 receptor agonism, but minor changes in the N-3, C-6, as well as substitution pattern of the 1-phenyl group also have important consequences for the D_1 receptor activity.[5,6] It has been found that H, CH_3, or allyl as the *N*-substituent, and a *meta*-tolyl, or *ortho*-tolyl as the 1-substituent, are optimal for the D_1 receptor activity.[6] It has also been reported that a small 6-substituent, such as Cl-, or Br- might further enhance the interaction between the D_1 receptor and the ligand.[5,6] However, the effect of a relatively large 6-substituent, such as ph- or substituted ph-, on the D_1 receptor binding remains largely unexplored.[7] In this report, we synthesized a small series of 6-substituted phenylbenzazepines, and evaluated their binding affinities at DA (D_1, D_2) and 5-HT (5-HT_{1A}, 5-HT_{2A}) receptors.

2. Chemistry

(±)-SKF-38393 ((±)-**1**) and its 6-Cl analog (**2**) were prepared from homoveratrylamine and styrene oxide by using a literature procedure.[8–10] The key intermediate 6-bromo-benzazepine **5** was prepared from *O*,*O*-dimethyl-protected *R*/*S*(±)SKF-38393 (**4**) in 63% yield.[10,11] Suzuki coupling[12,13] of bromide **5** with an appropri-

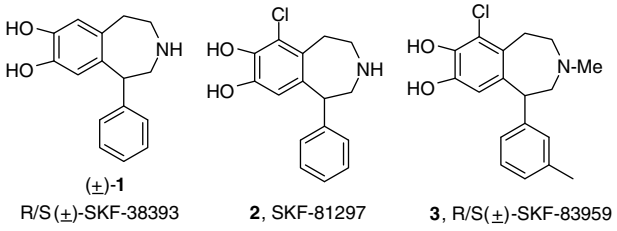

Figure 1. Representative 1-arylbenzazepines.

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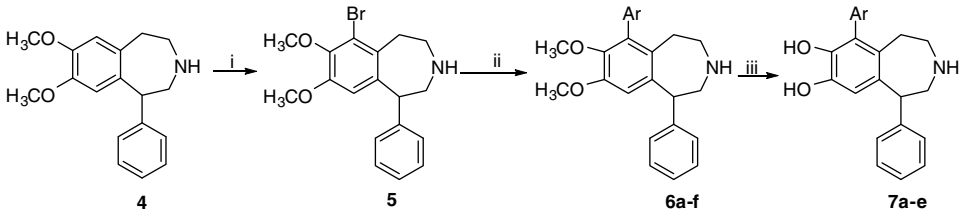
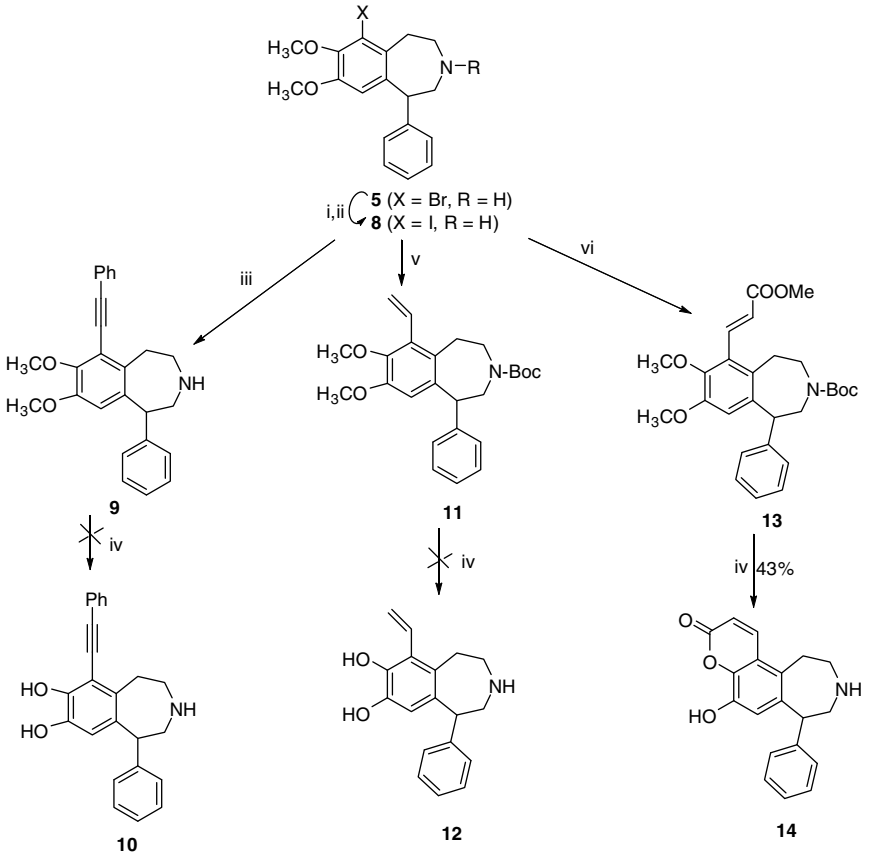


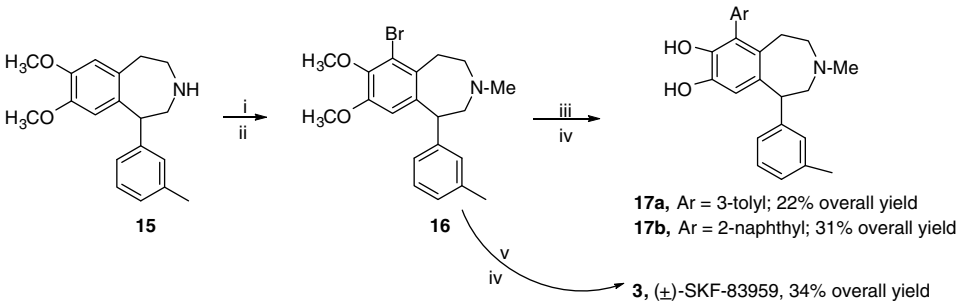
Scheme 1. Reagents and conditions: (i) Br_2, Ac_2O, 63%; (ii) $ArB(OH)_2$, $Pd(PPh_3)_4$, 2 N Na_2CO_3, LiCl, toluene/EtOH = 4:1, 90 °C, 35–78%; (iii) BBr_3, CH_2Cl_2, 35–75% for **7a**–**d**.

ate arylboronic acid provided the corresponding 6-aryl-benzazepines **6a**–**f** as racemates in 35–78% yields (Scheme 1). Demethylation of **6a**–**e** using BBr_3 (1 M) in CH_2Cl_2 generally yielded the expected catechols **7a**–**e** in moderate yields.[14] However, in the case of **6f**, similar demethylation procedure caused a dark complex and no expected product could be isolated.

Treating *N*-trifluoroacetyl protected **5** with *n*-BuLi followed by I_2 in Et_2O gave iodide **8**[10] in 56% yield (Scheme 2). Sonogashira reaction[15,13] of iodide **8** with phenylacetylene initially conducted under $Pd(PPh_3)_4$/CuI/DMF catalytic condition was found not successful, however, simply using $Pd(OAc)_2$ in acetone/H_2O readily led to 6-(phenylethynyl) benzazepine **9** in 46% yield. It was further noted that a similar demethylation of **9** using BBr_3 (1 M in CH_2Cl_2) produced a complicated mixture and failed to give the expected benzazepine **10**. Stille coupling[16] of *N*-Boc protected iodide **8** with vinyltributylstannane under the catalytic condition[13] of $Pd_2(dba)_3$ and CuI afforded 6-vinyl-1-phenylbenzazepine **11** in 37% yield. Again to our surprise, treatment of **11** with BBr_3 (1 M) at −78 °C followed by quenching with MeOH did not give the expected demethylated product. Heck reaction[17] of the *N*-Boc protected bromide **5** with methyl acrylate catalyzed by $Pd(OAc)_2$ and (*o*-tolyl)$_3$P yielded 6-methoxycarbonylvinyl benzazepine **13** in 78% yield. The *trans*-configuration of the two vinyl protons is evidenced by the coupling constant of 16.2 Hz in the 300 M H NMR of compound **13**. Treating compound **13** with BBr_3 (1 M) in CH_2Cl_2 again did not give the expected product. However, a careful chromatography process provided compound **14** containing a tetrahydrochromen moiety in 43% yield. The production of compound **14** can be rationalized by the esterification of the 6-acrylate moiety with the 7-OH during the demethylation process of compound **13**. The *cis*-configuration of the two vinyl protons is evidenced by the coupling constant of 9.9 Hz in the 300 M H NMR of compound **14**, other spectroscopic data (MS, ^{13}C NMR, HRMS) also supported the structure of **14**. On the basis of this result, it is likely that the failure to obtain compounds **10** and **12** is due to the relatively high reactivity of the vinyl or acetylenyl moiety in these compounds.



Scheme 2. Reagents and conditions: (i) $(CF_3CO)_2O$, CH_2Cl_2, quantitative; (ii) *n*-BuLi, I_2, Et_2O, −78 °C to rt, 56%; (iii) phenylacetylene, $Pd(OAc)_2$, NaOH, acetone, H_2O, 46%; (iv) BBr_3, CH_2Cl_2; (v) a—$(Boc)_2O$, Na_2CO_3, CH_2Cl_2; b—vinyl(tributyl)tin, $Pd_2(dba)_3$, CuI, tri-(*o*-tolyl)phosphine, DMF, 37%; (vi) a—$(Boc)_2O$, Na_2CO_3, CH_2Cl_2; b—methyl acrylate, $Pd(OAc)_2$, tri(*o*-tolyl)phosphine, Et_3N, DMF, 80 °C, 78%.



Scheme 3. Reagents and conditions: (i) Br_2, HOAc/HCl (10:1), rt, 56%; (ii) $(HCHO)_n$, HCOOH, 110 °C, 92%; (iii) $ArB(OH)_2$, $Pd(OAc)_2$, (*o*-tolyl)$_3$P, K_3PO_4, DMF, 110 °C; (iv) BBr_3, CH_2Cl_2; (v) *n*-BuLi, C_2Cl_6, Et_2O, −78 °C, 63%.

Two analogs of *R*/*S*(±)-SKF-83959 (**3**), 6-aryl substituted 1-(*m*-tolyl)-benzazepines **17a**,**b** were also prepared in a similar manner (Scheme 3). Compound **15** was prepared according to a literature procedure in racemic form.[6a,6b] Bromination of **15** with Br_2 in a mixture of HOAc and concd HCl followed by N-methylation provided the key intermediate **16**[6b] in 51% yield. Suzuki coupling[12,13] of bromide **16** with an appropriate arylboronic acid followed by *O*-demethylation using similar procedures as described above yielded the corresponding 6-(*m*-tolyl)-, and 6-(2′-naphthyl)-substituted 1-(*m*-tolyl)benzazepines **17a**,**b** in 22% and 31% overall yield, respectively. Treating bromide **16** with *n*-BuLi in C_2Cl_6 at −78 °C, followed by *O*-demethylation afforded *R*/*S*(±)-SKF-83959 (**3**)[18] in 34% overall yield.

3. Results and discussion

All the new compounds (**7a**–**e**, and **17a**,**b**) were racemic, and were converted to their HBr salts for the bioassay. The binding affinity of these compounds were assayed at DA (D_1, D_2) and 5-HT (5-HT_{1A}, 5-HT_{2A}) receptors using membrane preparation obtained from stable transfected HEK293 or CHO cells. This procedure is similar to those reported previously[14,19] by us. [^{3}H]SCH23390, [^{3}H]Spiperone, [^{3}H]8-OH-DPAT and [^{3}H]Ketanserin were used as the standard radioligands for DA D_1, D_2 and serotonin 5-HT_{1A}, 5-HT_{2A} receptors, respectively. Racemic *R*/*S*(±)-SKF-38393 ((±)-**1**) and *R*/*S*(±)-SKF-83959 (**3**) were also tested in our assays for comparison.

Binding results were summarized in Table 1. Racemic (±)-SKF-38393 ((±)-**1**) and (±)-SKF-83959 (**3**) in our assay showed K_i values of 393 nM and 1.93 nM, respectively, which are consistent with the results reported in the literature (K_i: 190 nM and 1.18 nM, respectively).[6a,6b] 6-Aryl substituted benzazepines **7a**–**e**, which were analogs of ((±)-**1**), did not show any appreciable affinity for the D_2 receptor, but good to high affinity for the D_1 receptor was observed. The overall good affinity for the D_1 receptor further states the fact that 1-phenylbenzazepine skeleton functions as a typical D_1 receptor scaffold,[5] and a relatively larger 6-substituent is somewhat tolerated. Compared to the parent compound (±)-**1**, a 6-phenyl substituent did not cause any effect for the D_1 binding, and the corresponding compound **7a** showed a K_i value of 346 nM, statistically same as that of (±)-**1** (393 nM). Compound **7b** containing a *meta*-tolyl group as the 6-substituent displayed a 10-fold gain in binding affinity for the D_1 receptor with a K_i value of 39 nM. Similarly, the β-naphthyl moiety as the C-6 substituent (compound **7e**) caused a 7-fold enhancement in binding for the D_1 receptor binding (K_i, 56 nM). A 6-aryl substituent with a *para*-electro-withdrawing group, such as Cl-(**7c**), F-(**7d**), also showed good affinity for the D_1 receptor. Compound **7c** was 2-fold more potent (K_i, 190 nM), whereas compound **7d** was slightly less potent (K_i, 422 nM), compared to the parent compound (±)-**1**. It is of note that the tetrahydrochromenoazepinone **14** did not display appreciable binding for any of the DA and 5-HT receptors tested, indicative of the importance of 7-OH to the interaction between the benzazepine compounds and the monoamine receptors.[5,6] Some of these

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

Compound	K_i (nM)			
	D_1 ([^{3}H]SCH23390)	D_2 ([^{3}H]Spiperone)	5-HT_{1A} ([^{3}H]8-OH-DPAT)	5-HT_{2A} ([^{3}H]Ketanserin)
(±)-**1** *R*/*S*(±)-SKF-38393	393 ± 5 (190[b])	NA (720,000[c])	NT	NA
R-(+)-**1** SKF-38393	50[b] (26[c])	>10,000[c]	NA	NA
3 *R*/*S*(±)-SKF-83959	1.93 ± 0.47 (1.18[c])	NA	NT	NA
7a	346 ± 15	NA	775 ± 285	NT
7b	39 ± 4.1	NA	736 ± 321	NA
7c	190 ± 14	NA	NT	NT
7d	422 ± 10	NA	NT	NT
7e	56 ± 10	NA	1083 ± 348	375 ± 107
14	NA	NA	NA	NA
17a	6.81 ± 0.59	210 ± 26	NT	121 ± 36
17b	4.88 ± 0.12	29 ± 3.6	NT	43 ± 7.1

[a] Values are means of three to five experiments, all compounds were tested as HBr salts in racemates,[14] NA = not active (less than 80% of inhibition in radioligand binding at 10 μM), NT = not tested.
[b] Data from Ref. 6a.
[c] Data from Ref. 6b.

compounds also showed moderate affinity for the 5-HT_{1A}, or 5-HT_{2A} receptors, but good selectivity for the D_1 over D_2 and 5-HT receptors were generally retained. For example, compounds **7a** and **7b** showed K_i values of ~800 nM for the 5-HT_{1A} receptor, while compound **7e** displayed K_i value of ~400 nM for the 5-HT_{2A} receptor.

On the basis of the results from compounds derived from (±)-**1**, it can be concluded that a 6-aryl substituent is generally beneficial for the binding at the D_1 receptor, especially when the 6-aryl group contains an electron-donating substituent (*m*-tolyl in **7b**, 2′-naphthyl in **7e**). This may indicate that there is a relatively larger lipophilic pocket on the D_1 receptor around the 6-position of these benzazepines.

To examine if there is a same effect of such substitution patterns in other benzazepines on the D_1 receptor binding, 6-(*m*-tolyl)-(**17a**), and 6-(2′-naphthyl)-(**17b**) substituted analogs of **3** ((±)-SKF-83959) were prepared and evaluated. Both compounds displayed high D_1 receptor binding with K_i values of 6.8 nM and 4.9 nM, respectively. Although these affinities are 3.5-, and 2.5-fold lower than that of (±)-SKF-83959, they are statistically the same. Much surprisingly, these two compounds also showed good to moderate affinity at the D_2 receptor with K_i values of 210 nM and 29 nM, respectively. The 6-(2′-naphthyl) analog **17b** is 7-fold more potent than the 6-(*m*-tolyl)-analog **17a** at this receptor. The significant D_2 receptor binding cannot be explained by the single effect of the 6-aryl substituent, however, the interaction between the two aryl groups at C-1 and C-6 may enhance the binding of the ligand to the D_2 receptor.

4. Conclusion

In summary, a series of racemic 6-aryl substituted 1-phenylbenzazepines **7a**–**e**, and **17a**,**b** were prepared. All these compounds showed binding potencies compatible to or much higher than that of the prototypic (±)-SKF-38393 ((±)-**1**) and (±)-SKF-83959 (**3**) for the D_1 receptor. Among analogs of (±)-SKF-38393 ((±)-**1**), compounds **7b**, **7c** and **7e** possess 10-, 2- and 7-fold enhancement in binding for the D_1 receptor, respectively. Lower but comparable potency to that of (±)-**1** was observed for compounds **7a** and **7d**. Both compounds **7a** and **7b** showed moderate affinity for the 5-HT_{1A} receptor, while compound **7e** exhibited reasonable affinity for the 5-HT_{2A} receptor. The optimal 6-substituents (*m*-tolyl, and 2′-naphthyl) were applied to the skeleton of (±)-SKF-83959 (**3**). The resulting compounds **17a**,**b** displayed high affinity at the D_1 receptor, only slightly lower than that of **3**. These two compounds also showed good binding at the D_2 receptor.

Taking these findings together, the current report provides a new medicinal chemistry strategy to enhance or retain good binding of 1-arylbenzazepine analogs at the D_1 receptor, or at the D_2 receptor. However, it has to be pointed out that the D_1 receptor activity of 1-arylbenzazepines has been reported mostly residing on the *R*-isomer as in the case of (±)-SKF-38393 ((±)-1), whose *R*-isomer (*R*-(+)-1) is 3.8-fold more potent than the racemate (±)-1, while the *S*-(−)-1 is inactive.[6a,6b] Therefore, our next study will focus on the resolution of the most potent analogs **7b**, **7e** and **17a**,**b**, as well as the evaluation of their intrinsic activity.

5. Experimental

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

5.1. 6-Bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (5)

This compound[10] was prepared from homoveratrylamine in three steps using a literature procedure. ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.26 (m, 1H), 7.13 (d, J = 7.2 Hz, 2H), 6.40 (s, 1H), 4.30 (dd, J = 2.7, 7.2 Hz, 1H), 3.84 (s, 3H), 3.67 (s, 3H), 3.48 (dd, J = 7.2, 13.8 Hz, 1H), 3.38 (dd, J = 3.0, 13.8 Hz, 1H), 3.20 (m, 2H), 2.94 (m, 2H), 2.17 (br s, 1H).

5.2. General procedure for Suzuki coupling reaction

To a mixture of bromide **5** (100 mg, 0.28 mmol) and an appropriate arylboronic acid (0.45 mmol) in toluene and ethanol (toluene/ethanol = 4:1, 5 mL) was added $Pd(PPh_3)_4$ (52 mg, 0.045 mmol), 2 N aq Na_2CO_3 solution (0.5 mL) and $LiCl{\cdot}H_2O$ (17 mg, 0.28 mmol). The resulting mixture was allowed to reflux under nitrogen at 100 °C for 36 h. Then the dark mixture was poured into water and extracted with EtOAc for three times, and the combined organic phases were washed with brine and then dried ver anhydrous Na_2SO_4. After filtration and removal of solvents, the crude material was purified by chromatography (EtOAc + Et_3N) to yield benzazepines **6a**–**f**.

5.2.1. 7,8-Dimethoxy-1,6-diphenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (6a)

Yellow liquid (35.2%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H), 7.26 (m, 5H), 6.47 (s, 1H), 4.33 (d, J = 5.7 Hz, 1H), 3.70 (s, 3H), 3.51 (s, 3H), 3.43 (m, 2H), 2.81 (m, 2H), 2.59 (m, 2H), 2.26 (br s, 1H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 150.1, 144.8, 142.2, 139.6, 137.9, 137.0, 132.4, 129.9, 129.8, 128.6, 128.2, 127.8, 126.7, 126.3, 113.6, 60.4, 55.6, 53.5, 52.6, 47.6, 33.9; EI-MS m/z: 359 (M^+); HR-MS Calcd for $C_{24}H_{25}NO_2$ (M^+) 359.1885. Found: 359.1902.

5.2.2. 7,8-Dimethoxy-1-phenyl-6-*m*-tolyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (6b)

Yellow liquid (38.7%), ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.23 (m, 5H), 7.00 (m, 2H), 6.46 (d, J = 5.7 Hz, 1H), 4.33 (d, J = 5.7 Hz, 1H), 3.70 (d, J = 3.9 Hz, 3H), 3.52 (s, 3H), 3.41 (m, 2H), 2.80 (m, 2H), 2.56 (m, 2H), 2.40 (s, 3H), 2.29 (br s, 1H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 150.1, 144.9, 142.2, 139.5, 139.4, 137.9, 137.4, 137.1, 132.4, 130.6, 130.5, 128.7, 128.3, 128.2, 127.7, 127.5, 126.9, 126.8, 126.4, 113.6, 113.5, 60.5, 55.7, 53.5, 47.7, 33.8, 29.7, 21.5; EI-MS m/z: 373 (M^+).

5.2.3. 6-(4-Chlorophenyl)-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (6c)

39.0% yield, ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 4H), 7.27 (m, 1H), 7.16 (m, 4H), 6.46 (s, 1H), 4.35 (d, J = 6.6 Hz, 1H), 3.68 (s, 3H), 3.50 (s, 3H), 3.43 (m, 2H), 2.81 (m, 2H), 2.58 (m, 2H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 150.2, 144.7, 141.8, 139.7, 136.3, 135.7, 132.8, 132.0, 131.3, 131.2, 128.7, 128.1, 126.5, 113.8, 60.4, 55.6, 52.9, 52.2, 47.3, 33.4; EI-MS m/z: 393 (M^+); HR-MS Calcd for $C_{24}H_{24}ClNO_2$ (M^+) 393.1496. Found: 393.1487.

5.2.4. 6-(4-Fluorophenyl)-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (6d)

78.5% yield, ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.18 (m, 7H), 6.47 (s, 1H), 4.33 (d, J = 5.7 Hz, 1H), 3.66 (s, 3H), 3.50 (s, 3H), 3.38 (m, 2H), 2.79 (m, 2H), 2.55 (m, 2H), 2.24 (br s, 1H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 163.0, 160.5, 150.1, 144.8, 142.1, 139.7, 135.8, 133.7, 133.7, 132.4, 131.5, 131.4, 131.3, 128.6, 128.2, 126.3, 114.9,

114.7, 113.7, 60.3, 55.6, 53.5, 52.6, 47.6, 33.9; EI-MS *m*/*z*: 377 (M^+); HR-MS Calcd for $C_{24}H_{24}FNO_2$ (M^+) 377.1791. Found: 377.1787.

5.2.5. 8-Dimethoxy-6-(naphthalen-2-yl)-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (6e)

71.4% yield, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 3H), 7.69 (d, J = 6.6 Hz, 1H), 7.51 (m, 2H), 7.39 (m, 3H), 7.28 (m, 3H), 6.50 (s, 1H), 4.37 (d, J = 5.4 Hz, 1H), 3.72 (s, 3H), 3.50 (s, 3H), 2.71 (m, 6H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 150.2, 145.0, 142.1, 139.7, 136.8, 135.5, 133.1, 132.4, 132.3, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 127.7, 127.4, 126.4, 126.0, 125.8, 113.7, 60.5, 55.7, 53.4, 52.5, 47.6, 33.8, 29.6; EI-MS *m*/*z*: 409 (M^+); HR-MS Calcd for $C_{28}H_{27}NO_2$ (M^+) 409.2042. Found: 409.2036.

5.2.6. 6-(Furan-2-yl)-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (6f)

22.7% yield, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.36 (m, 2H), 7.27 (m, 1H), 7.18 (m, 2H), 6.50 (s, 1H), 6.37 (d, J = 2.7 Hz, 1H), 4.32 (d, J = 4.5 Hz, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.46 (m, 2H), 2.91 (m, 2H), 2.66 (m, 2H), 2.46 (br s, 1H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 150.2, 149.5, 146.5, 142.0, 141.9, 139.6, 134.4, 128.7, 128.2, 126.4, 126.3, 115.4, 110.6, 110.1, 61.0, 55.8, 53.3, 52.4, 47.4, 34.1; EI-MS *m*/*z*: 349 (M^+); HR-MS Calcd for $C_{28}H_{27}NO_2$ (M^+) 349.1678. Found: 349.1681.

5.3. General procedure for demethylation of 6,7-dimethoxy-benzazepines 6a–e

A solution of compound **6a–e** (0.36 mmol) in 2 mL dry CH_2Cl_2 was stirred at −78 °C under N_2 for 30 min, a solution of BBr_3 solution (6 mL, 1 M in CH_2Cl_2) was added dropwise. The mixture was allowed to stir at −78 °C for additional 30 min, and at rt overnight. It was quenched with MeOH at −78 °C, and the mixture was concentrated under reduced pressure. The obtained residue was treated with MeOH and concentrated again. This procedure was repeated for several times. Finally the crude material was recrystallized from MeOH/Et_2O to give the corresponding demethylated products **7a–e**.

5.3.1. 1,6-Diphenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine-7,8-diol (7a)

Brown solid (30.6%), mp 198–205 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.45 (m, 4H), 7.28 (m, 6H), 6.29 (s, 1H), 4.63 (t, J = 5.4 Hz, 1H), 3.68 (m, 2H), 3.28 (m, 1H), 2.90 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 145.5, 143.5, 142.2, 139.2, 134.5, 132.1, 131.9, 131.8, 130.7, 130.0, 129.9, 129.0, 128.8, 117.0, 51.8, 47.7, 47.5, 28.6; EI-MS *m*/*z*: 331 (M^+). Anal. Calcd for $C_{22}H_{21}NO_2{\cdot}2HBr{\cdot}2H_2O$: C, 49.93; H, 5.14; N, 2.65. Found: C, 49.93; H, 5.30; N, 2.38.

5.3.2. 1-Phenyl-6-*m*-tolyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine-7,8-diol (7b)

54.5% yield, mp 180–184 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.44 (m, 2H), 7.32 (m, 4H), 7.18 (m, 1H), 7.01 (m, 2H), 6.28 (d, J = 7.2 Hz, 1H), 4.61 (t, J = 5.4 Hz, 1H), 3.66 (m, 2H), 3.25 (m, 1H), 2.93 (m, 2H), 2.77 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 145.5, 143.4, 142.3, 142.2, 139.7, 139.1, 134.5, 134.4, 132.5, 132.4, 132.2, 130.7, 129.9, 129.5, 129.0, 128.9, 128.8, 117.0, 116.9, 51.8, 51.7, 47.8, 47.7, 47.5, 28.6, 22.0; EI-MS *m*/*z*: 345 (M^+). Anal. Calcd for $C_{23}H_{23}NO_2{\cdot}0.75HBr{\cdot}2.0H_2O$: C, 62.48; H, 6.33; N, 3.17. Found: C, 62.77; H, 6.29; N, 2.95.

5.3.3. 6-(4-Chlorophenyl)-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine-7,8-diol (7c)

56.4% yield, mp 203–205 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.44 (m, 4H), 7.25 (m, 5H), 6.29 (s, 1H), 4.59 (br s, 1H), 3.64 (br s, 2H), 3.22 (m, 1H), 2.93 (m, 2H), 2.71 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 145.4, 143.5, 142.4, 138.0, 134.8, 134.6, 133.6, 133.5, 130.7, 130.0, 129.9, 129.1, 128.9, 117.2, 52.0, 48.1, 47.5, 29.0; EI-MS *m*/*z*: 365 (M^+). Anal. Calcd for $C_{22}H_{20}ClNO_2{\cdot}0.85HBr{\cdot}0.75H_2O$: C, 58.96; H, 5.03; N, 3.13. Found: C, 58.95; H, 5.07; N, 2.94.

5.3.4. 6-(4-Fluorophenyl)-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine-7,8-diol (7d)

56.0% yield, mp > 210 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.45 (m, 2H), 7.29 (m, 7H), 6.30 (s, 1H), 4.64 (br s, 1H), 3.68 (br s, 2H), 3.25 (m, 1H), 2.96 (m, 2H), 2.76 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 165.2, 162.7, 145.4, 143.6, 142.3, 135.3, 134.7, 133.8, 133.7, 133.6, 130.9, 130.7, 129.9, 129.2, 128.9, 117.1, 116.7, 116.5, 51.8, 47.8, 47.4, 28.8; EI-MS *m*/*z*: 349 (M^+). Anal. Calcd for $C_{22}H_{20}FNO_2{\cdot}1.0HBr{\cdot}0.75H_2O$: C, 59.54; H, 5.11; N, 3.16. Found: C, 59.66; H, 5.19; N, 2.98.

5.3.5. 6-(Naphthalen-2-yl)-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine-7,8-diol (7e)

37.8% yield, mp 215–217 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.81 (m, 4H), 7.46 (m, 4H), 7.33 (m, 4H), 6.33 (s, 1H), 4.64 (t, J = 5.1 Hz, 1H), 3.64 (m, 2H), 3.23 (m, 1H), 2.86 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 145.5, 143.7, 142.3, 136.8, 136.7, 135.7, 135.4, 134.6, 134.5, 133.6, 132.0, 131.2, 130.7, 130.6, 130.1, 129.9, 129.4, 129.2, 129.1, 129.0, 127.8, 127.6, 123.9, 117.1, 51.8, 47.8, 47.5, 28.8; EI-MS *m*/*z*: 381 (M^+). Anal. Calcd for $C_{26}H_{23}NO_2{\cdot}1.25HBr{\cdot}1.0H_2O$: C, 62.38; H, 5.29; N, 2.80. Found: C, 62.50; H, 5.36; N, 2.48.

5.4. 6-Iodo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (8)[10]

Trifluoroacetic anhydride (4.9 mL, 35.23 mmol) was added to a suspension of bromide **5** (1.4 g, 3.88 mmol) in 20 mL dry CH_2Cl_2, and the mixture was stirred at rt for 2.5 h. After evaporation, the residue was treated with CH_2Cl_2 and then evaporated. This procedure was repeated twice to give *N*-trifluoroacetyl protected derivative of **5** 1.90 g as a yellow liquid.

The solution of *N*-trifluoroacetyl protected derivative of **5** (2.47 g) in dry Et_2O, was added slowly to a solution of *n*-butyllithium (2.5 M in hexane, 7.0 mL, 17.5 mmol) in dry Et_2O (20 mL) at −78 °C. After stirring for 10 min, I_2 (2.74 g, 10.79 mmol) in dry Et_2O was added. The mixture was allowed to stir at −78 °C for 0.5 h, and then at rt for another 0.5 h. The mixture was poured into water, basified with $NH_3{\cdot}H_2O$, and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified by flash chromatography (EtOAc/MeOH = 40:1, 1% Et_3N) to give compound **8** (1.24 g, 56.5% for two steps) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 3H), 7.14 (d, J = 7.2 Hz, 2H), 6.37 (s, 1H), 4.44 (dd, J = 2.7, 6.7 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 3.47 (dd, J = 7.2, 13.8 Hz, 1H), 3.38 (dd, J = 3.0, 13.8 Hz, 1H), 3.23 (m, 1H), 3.15 (m, 1H), 2.74 (br s, 1H); EI-MS *m*/*z*: 409 (M^+).

5.5. 7,8-Dimethoxy-1-phenyl-6-(phenylethynyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (9)

A mixture of NaOH (14 mg, 0.35 mmol), $Pd(OAc)_2$ (0.8 mg, 0.0036 mmol) in H_2O and acetone (4 mL, 1:1) was stirred at rt for 5 min, then aryl iodide **8** (70 mg, 0.17 mmol) and phenylacetylene (60 μL, 0.53 mmol) were introduced. The mixture was stirred at 60 °C for 30 h, then concentrated. The residue was extracted with EtOAc, and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography ($CHCl_3$/MeOH = 30:1, 1% Et_3N) to give compound **9** (30 mg, 45.7%) as a yellow liquid. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.56 (m, 2H), 7.36 (m, 5H), 7.25 (m, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.47 (s, 1H), 4.27 (d, J = 6.9 Hz, 1H), 3.97 (s, 3H), 3.70 (s, 3H), 3.55 (m, 1H), 3.34 (m, 2H), 3.14 (m, 1H), 3.00 (m, 2H), 2.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 149.8, 148.4, 141.2, 139.1, 135.7, 131.1, 128.4, 128.0, 127.9, 127.8, 126.0, 123.2, 118.2, 114.9, 96.8, 84.4, 60.4, 55.6, 53.2, 52.1, 47.1, 34.9; EI-MS m/z: 383 (M^+).

5.6. *N-tert*-Butyl-7,8-dimethoxy-1-phenyl-6-vinyl-4,5-dihydro-1H-benzo[*d*]azepine- 3(2H)-carboxylate (11)

A mixture of iodide **8** (239 mg, 0.58 mmol), finely ground Na_2CO_3 (124 mg, 1.17 mmol) and $(Boc)_2O$ (255 mg, 1.17 mmol) in 20 mL dry CH_2Cl_2 was stirred at room temperature for 2 h under N_2, then the solvent was evaporated to give a yellow residue, which was quick chromatographed (EtOAc/petroleum ether = 2:1) to give *N*-Boc protected derivative of **8** (341 mg) as a yellow liquid.

Tributyl(vinyl)tin (60 μL, 0.19 mmol) was added slowly to a mixture of *N*-Boc protected **8** (80 mg), $Pd_2(dba)_3$ (12.6 mg, 0.014 mmol), CuI (11 mg, 0.058 mmol) and $(o\text{-tolyl})_3P$ (17 mg, 0.056 mmol) in dry DMF (10 mL). The mixture was allowed to react at 50 °C for 4 days. After evaporation of the solvents, the residue was subjected to column chromatography (EtOAc) to give a colorless liquid **11** (24 mg, 42.9% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 5H), 6.79 (m, 1H), 6.46 (s, 1H), 5.58 (dd, J = 2.1, 11.4 Hz, 1H), 5.42 (dd, J = 2.1, 18.0 Hz, 1H), 4.49 (m, 1H), 3.94 (m, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.53 (m, 2H), 2.96 (m, 2H), 1.31(m, 9H).

5.7. (*E*)-*tert*-Butyl 7,8-dimethoxy-6-(3-methoxy-3-oxoprop-1-enyl)-1-phenyl- 4,5-dihydro-1H-benzo[*d*]azepine-3(2H)-carboxylate (13)

N-Boc protected bromide **5** (163 mg) prepared as above, was added to a mixture of $Pd(OAc)_2$ (15 mg, 0.067 mmol), $(o\text{-tolyl})_3P$ (80 mg, 0.263 mmol), methyl acrylate (150 μL, 1.67 mmol) and 0.2 mL Et_3N in 4 mL dry DMF under N_2. The reaction mixture was allowed to stir under 80 °C overnight. After evaporation, the residue was subjected to chromatography (EtOAc/petroleum ether = 1:5) to yield compound **13** (109 mg, 74.1%) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 16.5 Hz, 1H), 7.24 (m, 2H), 6.52 (s, 1H), 6.37 (d, J = 16.2 Hz, 1H), 4.49 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.67 (m, 4H), 2.93 (m, 2H), 1.32 (m, 9H).

5.8. 7-Hydroxy-5-phenyl-2,3,4,5-tetrahydrochromeno[6,5-*d*]azepin-9(1H)-one (14)

Compound **14** was prepared from **13** in 43.1% yield using a similar procedure as preparation of compound **7a**–**e**. Mp > 220 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.32 (d, J = 10.2 Hz, 1H), 7.47 (m, 2H), 7.38 (m, 1H), 7.28 (d, J = 7.2 Hz, 2H), 6.56 (s, 1H), 6.48 (d, J = 9.6 Hz, 1H), 4.76 (t, J = 6.0 Hz, 1H), 3.76 (d, J = 6.0 Hz, 2H), 3.49 (m, 3H), 3.22 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.4, 142.8, 142.0, 141.4, 140.4, 138.8, 129.1, 128.4, 127.4, 126.5, 118.8, 117.9, 115.9, 48.7, 44.7, 44.4, 23.6; EI-MS m/z: 307 (M^+); HR-MS Calcd for $C_{19}H_{17}NO_3$ (M^+) 307.1208. Found: 307.1207.

5.9. 6-Bromo-7,8-dimethoxy-3-methyl-1-*m*-tolyl-2,3,4,5-tetrahydro-1H- benzo[*d*]azepine (16)

Compound **16** was prepared from compound **15**[18] in 51.5% yield using a literature reported procedure.[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.98 (m, 2H), 6.24 (s, 1H), 4.34 (d, J = 8.1 Hz, 1H), 3.81 (s, 3H), 3.59 (s, 3H), 3.41 (m, 1H), 3.14 (m, 2H), 2.85 (m, 2H), 2.37 (s, 3H), 2.35 (s, 3H), 2.30 (m, 1H).

5.10. 3-Methyl-1,6-di-(*m*-tolyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine-7,8-diol (17a)

A solution of bromide **16** (100 mg, 0.26 mmol), *m*-toylboronic acid (70 mg, 0.51 mmol), $Pd(OAc)_2$ (12 mg, 0.53 mmol), $(o\text{-toyl})_3P$ (60 mg, 0.20 mmol) and K_3PO_4 (544 mg, 2.56 mmol) in DMF was stirred at 110 °C overnight under N_2. After removal of the solvents, the residue was taken up in $CHCl_3$, washed with water, brine, and dried over anhydrous Na_2SO_4. After evaporation, the residue was purified by chromatography (petroleum ether/EtOAc = 1:2) to give the Suzuki coupling product (66 mg), which was treated with BBr_3 (1.0 M in CH_2Cl_2) by using a similar procedure as that of preparation of **7a**–**e** to give the title compound **17a** as a white solid (25 mg, 22% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.35 (m, 1H), 7.23 (m, 2H), 6.95 (m, 5H), 6.13 (s, 1H), 4.46 (d, J = 9.0 Hz, 1H), 3.38 (m, 1H), 2.99 (m, 3H), 2.72 (dd, J = 6.9, 15.6 Hz, 1H), 2.48 (s, 3H), 2.40 (m, 4H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 142.1, 141.9, 139.9, 138.1, 138.0, 136.5, 135.4, 130.7, 130.4, 129.1, 129.0, 128.9, 128.4, 128.3, 128.2, 127.9, 127.2, 127.1, 126.8, 125.2, 114.3, 62.2, 56.6, 46.6, 45.9, 29.4, 28.6, 21.1, 21.0; MS (m/z) 373 (M^+). Anal. Calcd for $C_{24}H_{25}NO_2{\cdot}0.65HBr{\cdot}1.5H_2O$: C, 66.27; H, 6.82; N, 3.09. Found: C, 66.32; H, 6.90; N, 3.21.

5.11. 3-Methyl-6-(naphthalen-2-yl)-1-*m*-tolyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine-7,8-diol hydrobromide (17b)

Compound **17b** was prepared from **16** in 31% overall yield using a similar procedure as preparation of compound **17a**. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.76 (m, 3H), 7.59 (s, 1H), 7.39 (dd, J = 3.0, 6.0 Hz, 2H), 7.22 (dd, J = 1.2, 8.1 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.92 (m, 3H), 6.05 (s, 1H), 4.27 (d, J = 9.3 Hz, 1H), 3.18 (d, J = 12.0 Hz, 1H), 2.65 (m, 4H), 2.27 (s, 3H), 2.19 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 142.6, 141.8, 140.0, 138.1, 136.0, 134.4, 134.2, 133.2, 132.3, 129.8, 129.0, 128.9, 128.7, 128.4, 128.1, 127.8, 127.7, 127.5, 127.4, 127.1, 126.0, 125.9, 125.8, 125.2, 114.5, 62.6, 56.7, 47.3, 46.2, 29.4, 29.2, 21.0; MS (m/z) 409 (M^+). Anal. Calcd for $C_{28}H_{27}NO_2{\cdot}0.25HBr{\cdot}1.0H_2O$: C,75.11; H, 6.58; N, 3.13. Found: C, 75.08; H, 6.42; N, 2.92.

5.12. Radioligand binding assays

The affinity of *compounds* to the D_1 and D_2 dopamine receptors, and the 5-HT_{1A} receptor was determined by competition binding assays. Membrane homogenates of 5-HT_{1A}-CHO cells, D_1- or D_2-HEK293 cells were prepared as described previously.[6a,18] Duplicated tubes were incubated at 30 °C for 50 min with increasing concentrations of respective compound and with 0.7 nM [^{3}H]8-OH-DPAT (for 5-HT_{1A} receptor), [^{3}H]SCH23390 (for D_1 dopamine receptors), or [^{3}H]Spiperone (for dopamine D_2 receptor) in a final volume of 200 μL binding buffer containing 50 mM Tris, 4 mM $MgCl_2$, pH 7.4. Nonspecific binding was determined by parallel incubations with either 10 μM WAY100635 for 5-HT_{1A}, SCH23390 for D_1 or Spiperone for D_2 dopamine receptors, respectively. The reaction was started by addition of membranes (15 ng/tube) and stopped by rapid filtration through Whatman GF/B glass fiber filter and subsequent washing with cold buffer (50 mM Tris, 5 mM EDTA, pH 7.4) using a Brandel 24-well cell harvester. Scintillation cocktail was added and the radioactivity was determined in a MicroBeta liquid scintillation counter. The IC_{50} and K_i values were calculated by nonlinear regression (PRISM, Graphpad, San Diego, CA) using a sigmoidal function.

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Supplementary data

Supplementary data associated with this article can be found in the online version: copies of ^{1}H and ^{13}C of the new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.09.049.

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