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Structural manipulation on the catecholic fragment of dopamine D_1 receptor agonist 1-phenyl-*N*-methyl-benzazepines

Jing Zhang [a, 1], Jiye Huang [b, 1], Zilan Song [a], Lin Guo [c], Wenxian Cai [b], Yun Wang [c], Xuechu Zhen [b, c, **], Ao Zhang [a, *]

[a] CAS Key Laboratory of Receptor Research, and Synthetic Organic & Medicinal Chemistry Laboratory (SOMCL), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences (CAS), Shanghai 201203, China
[b] Department of Pharmacology, Shanghai Institute of Materia Medica, CAS, China
[c] Department of Pharmacology, College of Pharmaceutical Sciences, Soochow University, Suzhou 215123, China

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ABSTRACT

A series of new benzazepines with modification on the catecholic fragment were designed. The 8-hydroxyl group, other than the 7-hydroxyl was confirmed crucial to the interaction with the dopamine D_1 receptor. Subsequent replacement of the 7-hydroxyl with benzylamino groups was found tolerable. 7-(*m*-Chlorophenyl)methylamino- and 7-(*m*- or *o*-tolyl)methylamino-substituted benzazepines **13b**–**d** displayed K_i values of 270–370 nM at the D_1 receptor, which were slightly more potent than that of parent compound **1**. In addition, 7-(arylmethyl)amino-benzazepines **13a**–**c** were found possessing high binding affinities less than 10 nM at the 5-HT_{2A} receptor. Among them, the non-substituted 7-benzylamino analogue **13a** was the most potent showing a K_i values of 4.5 nM at the 5-HT_{2A} receptor and a 5-HT_{2A}/D_1 selectivity of 147.

1. Introduction

Dopamine (DA) is one of the major cerebral neurotransmitters and plays an essential role in the pathophysiology of many neurobehavioral and neuropsychiatric disorders. DA exerts its agonistic actions primarily through its five major DA receptors (D_1–D_5), among which, D_1,–D_3 receptors are the most studied DA receptors [1–3] and are the primary targets of current clinically prescribed dopaminergic drugs [4,5]. Although the D_1 receptor was discovered very early with high abundance in the mammalian brains, clinically useful D_1 receptor agonists and antagonists are very limited [4–6]. Among the reported D_1 receptor-targeting agents, the skeleton of 1-aryl-*N*3-benzazepines remains the most reliable structural scaffold in terms of the affinity and selectivity against the D_1 receptor. Many widely used D_1 receptor tool drugs (e.g. D_1 agonist SKF-38393, D_1 antagonist SCH-23390, Fig. 1) were born from this series [6–8]. Unfortunately, most of these compounds eventually failed as drug candidates due to their limited in vivo efficacy, poor pharmacokinnetics (PK) and several other unwanted side effects [6,9,10].

Since the catechol fragment in the 1-aryl-*N*3-benzazepine framework is an essential feature for effective binding to the amino acid residues of the D_1 receptor, most of the reported structural modification is focused on other sites, especially the 1-aryl, azepine ring, and C6 [11–13]. A few early reports also discussed the possibility of replacing the catecholic component, but only lower alkyls and halogens (especially 7-Cl) were investigated as the replacement of 7-OH [14–19]. As a continuation of our structure–activity relationship (SAR) study [12,13,20–23] on the 1-aryl-*N*3-benzazepine skeleton, here we report our structural manipulation on the catecholic fragment and the binding affinity and selectivity of the new compounds at the DA (D_1–D_3) receptors.

2. Chemistry

Although the *R*-enantiomers of benzazepines 1–4 are generally more active than corresponding *S*-enantiomers, there is no significant difference between the racemates and their *R*-enantiomers at the DA receptor binding level [6,12,13]. Therefore, to quickly

* Corresponding author.
** Corresponding author.
E-mail addresses: zhenxuechu@suda.edu.cn (X. Zhen), aozhang@mail.shcnc.ac.cn (A. Zhang).
[1] These two authors contributed equally to this work.

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0223-5234/

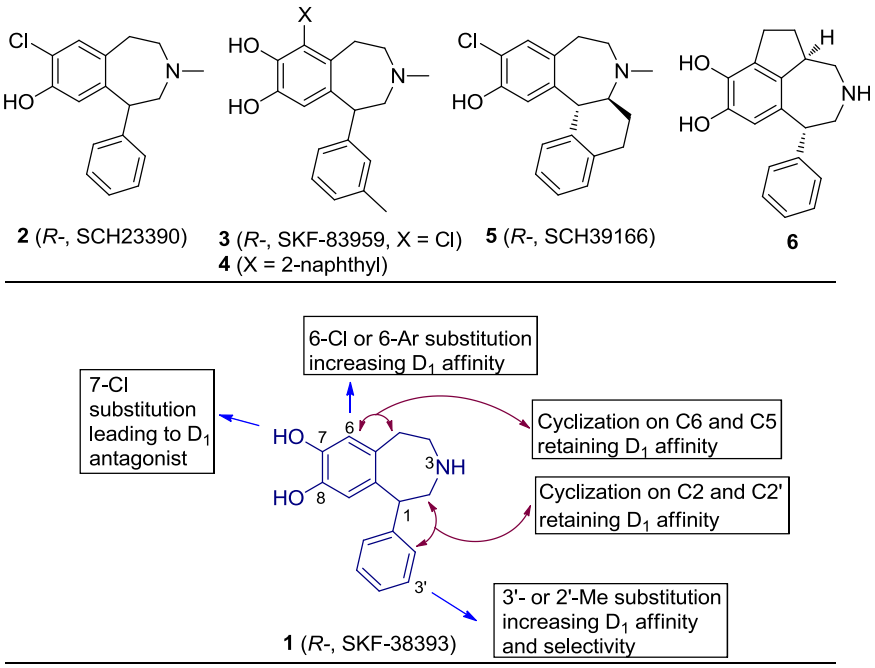
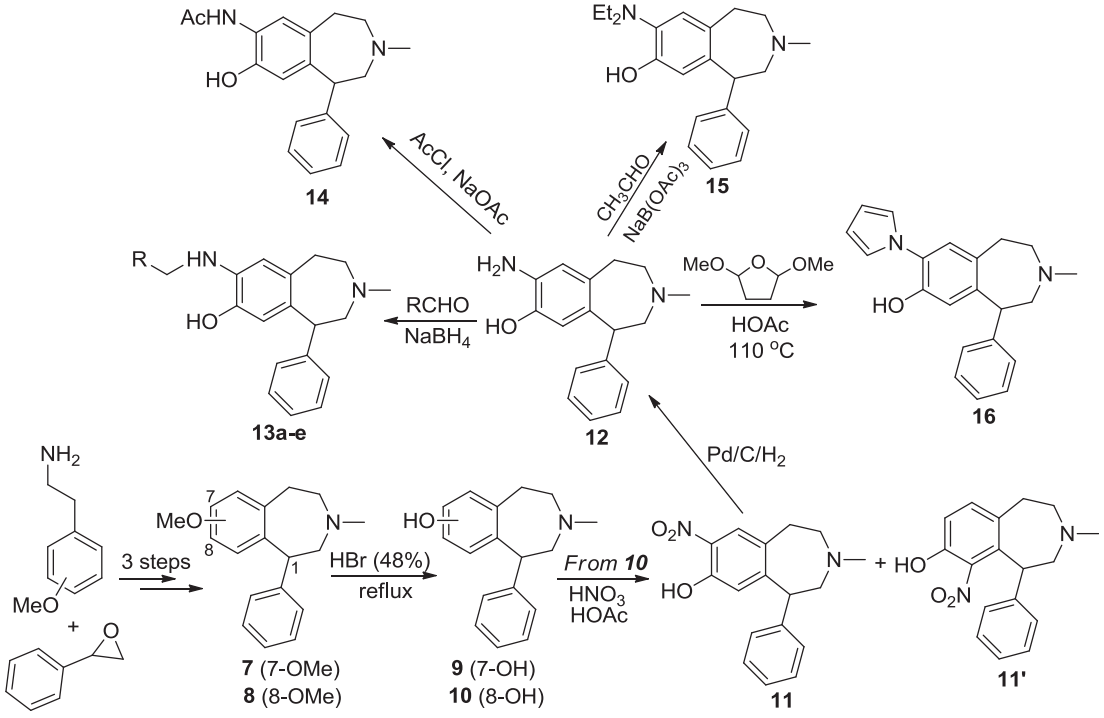
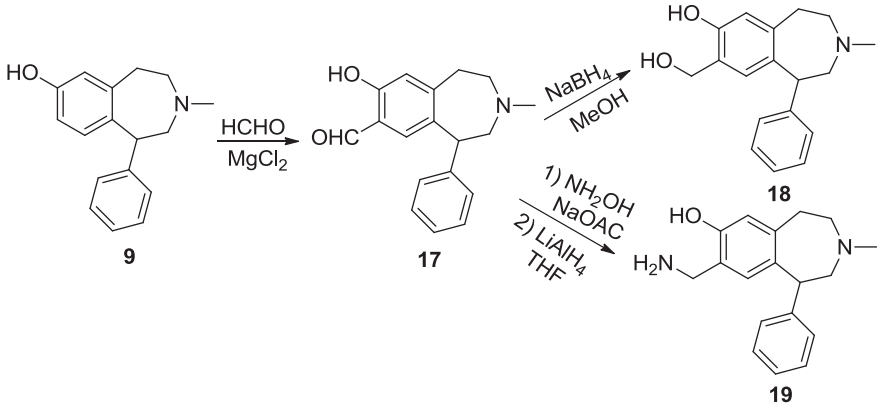


Fig. 1. Established SAR and representative 1-aryl-3-benzazepines.

identify new compounds for further study, all compounds in current report were prepared and evaluated as racemates. As shown in Scheme 1, by following a literature procedure [12,13,22,23], 7- and 8-methoxy-*N*-methyl-1-benzazepines 7 and 8 were prepared from corresponding 3- or 4-methoxyphenyl ethanamine and 2-phenyloxirane in three steps [18,19]. Removal [23] of the *O*-methyl group by refluxing in 48% HBr aqueous solution led to monohydroxyl benzazepines 9 and 10 in 90% yield. Nitration of 8-hydroxy-*N*-methyl-1-phenylbenzazepine 10 with fuming HNO_3 and HOAc provided compounds 11 and 11′ in 96% overall yield, with nearly no regioselectivity (1.1/1). Reduction of nitrobenzene 11 with Pd/C gave 7-amino-8-hydroxybenzazepine 12 in 96% yield. Reductive amination [13] of 12 by treating with aryl aldehydes followed by $NaBH_4$ yielded corresponding benzylamines 13a–e in 80–91% yields. Acylation of amine 12 led to benzazepine 14 in 41% yield, and diethylamino-substituted benzazepine 15 was prepared in 81% yield by treating 12 with acetaldehyde and $NaBH(OAc)_3$. Meanwhile, treatment [24] of 12 with 2,5-dimethoxy-



Scheme 1. Synthesis of compounds **7**–**16**.



Scheme 2. Synthesis of compounds **17**–**19**.

tetrahydrofuran in HOAc/H_2O at 110 °C afforded 7-(1H-pyrrol-1-yl)-8-hydroxy-benzazepine 16 in 81% yield.

Aryl methanol **18** was prepared [23] by treating phenol **9** with formaldehyde and anhydrous $MgCl_2$ in refluxing THF, followed by reduction with $NaBH_4$ in 45% overall yield (Scheme 2). Meanwhile, the benzaldehyde intermediate **17** was reacted with hydroxylamine hydrochloride followed by reduction with $LiAlH_4$ to afford phenylmethyl amine **19** in 58% overall yield [24].

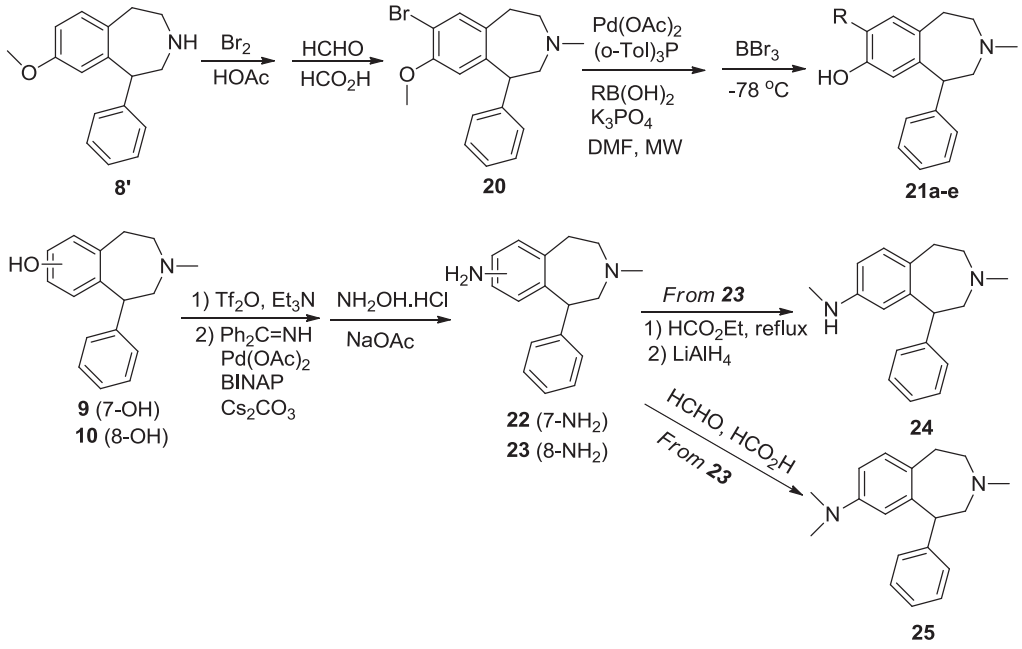
Synthesis of 7-aryl substituted benzazepine analogues **21a**–**e** was described in Scheme 3. Bromination of 8-methoxy-3-H-benzazepine **8′** followed by *N*-methylation provided bromide **20** in 40% yield, which was then subjected to palladium-catalyzed Suzuki coupling with arylboronic acids followed by *O*-demethylation [22] with BBr_3 at −78 °C to deliver target compounds **21a**–**e** in 27–73% overall yields. Meanwhile, triflation of 7- and 8-hydroxylbenzazepines **9** and **10** with Tf_2O and Et_3N, followed by $Pd(OAc)_2$-catalyzed C–N bond formation [23] and subsequent hydrolysis provided 7- and 8-aminobenzazepines **22** and **23** in 82% overall yields. *N*-Methylation was completed by treating amine **23** with ethyl formate followed by $LiAlH_4$ giving benzazepine **24** in 48% overall yield. Additionally, reacting amine **23** with formalin and formic acid at 90 °C led to dimethylamino analogue **25** (Scheme 3).

Similarly, nitration [18,19] of 7-hydroxybenzazepine **9** with fuming HNO_3 and HOAc provided 7-hydroxy-8-nitrobenzazepine **26** and 6-nitro-7-hydroxybenzazepinf **27** in 43% and 24% yields, respectively (Scheme 4). Reduction of **26** with Pd/C yielded 7-hydroxy-8-aminobenzazepine **28** in 90% yield. Treating **28** with CDI in refluxing THF provided benzoxazolone **29** in 68% yield. Acylation of **28** with 2-chloroacetyl chloride afforded benzo[b][1,4]oxazin-3-one **30** in 75% yield. Benzo[d]oxazole **31** was prepared in 93% yield by refluxing amine **28** with orthoethyl formate in EtOH. Meanwhile, reaction [25] of amine **28** with CS_2 and KOH in EtOH offered benzo[d]oxazole-2-thiol **32** in 89% yield, which was then treated with *N*-methylpiperazine under microwave irradiation at 100 °C to provide benzazepine **33** in 72% yield [26].

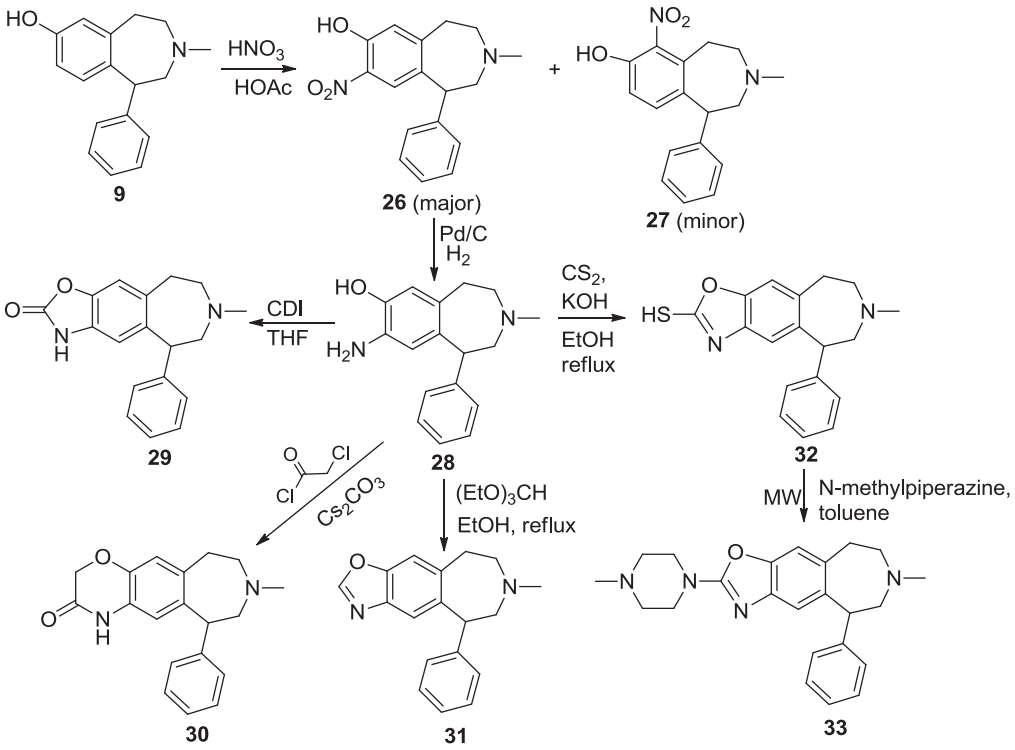
3. Results and discussion

3.1. Binding assay at the human dopamine D_1–D_3 receptors

All new compounds, together with the prototypic catecholic benzazepine **1** were bioassayed for their binding at the dopamine D_1 receptor using membrane preparation obtained from stable transfected HEK293 or CHO cells. Meanwhile, to evaluate the



Scheme 3. Synthesis of compounds **20**–**25**.



Scheme 4. Synthesis of compounds **26**–**33**.

selectivity of these compounds among the DA receptor subtypes, binding affinities at the D_2 and D_3 receptors were also tested. The procedure is similar to those reported by us previously [12,13,22,23]. As shown in Table 1, significant discrepancy in D_1 receptor binding was observed between the two mono-hydroxyl benzazepines **9** and **10**. Compared to catechol **1**, 8-hydroxyl analogue **10** is slightly more potent at the D_1 receptor showing a K_i value of 207 nM, whereas the 7-hydroxyl congener **9** is inactive (K_i > 1 μM). The result further confirms the necessity of the 8-hydroxyl group to the interactions with the D_1 receptor, as that in benzazepines **1**–**6**. Interestingly, replacing either the 7- or 8-hydroxyl of benzazepine **1** with an amino group did not impact the D_1 receptor binding at all, and both compounds **12** and **28** displayed K_i values (330–400 nM) nearly identical to that of compound **1**. It was found that variously substituted benzylamino groups were relatively tolerant as the 7-substituent, and compounds **13a**–**e** displayed K_i values in the range of 277–756 nM at the D_1 receptor. Electron-withdrawing group substituted 7-benzylamino-benzazepine **13b** showed a K_i value of 277 nM at the D_1 receptor, which is higher than that of the prototypic **1**. Compound **13b** is also slightly more potent than both non-substituted (**13a**) and electron-donating group substituted benzylamino analogues (**13c**–**e**). Among the three methyl substituted benzylamines **13c**–**e**, the *ortho*-isomer is most potent having a K_i value of 292 nM, whereas the *para*-methyl analogue is the least potent. Surprisingly, 7-acylamino-8-hydroxybenzazepine **14** lost binding affinity at the D_1 receptor, indicating that a weak H-bond donor or an H-bond acceptor at the 7-position is not beneficial to the interaction with the D_1 receptor. This was further confirmed by the inactivity of 7-dimethylamino- and 7-pyrrolinyl-substituted benzazepines **15** and **16**. Interestingly, among the 7-aryl substituted benzazepines **21a**–**e**, *m*-tolyl analog **21b** and *p*-hydroxyphenyl analog **21e** showed good binding affinities at the D_1 receptor with K_i values of 216 and 349 nM, respectively, which were even more potent than that of compound **1**. All the compounds were inactive at the D_2 and D_3 receptors, confirming the preference of 1-phenyl-*N*-methyl-benzezapine skeleton as a privileged scaffold for the D_1 receptor.

From the results above, the 7-hydroxyl group in the prototypical benzazepine **1** was confirmed replaceable by an appropriately substituted benzylamino-(e.g. **13b**) or substituted aryl moiety (e.g. **21b**, **21e**). To further explore the importance of the nearly 'ignored' 8-hydroxyl in **1**, 8-hydroxymethyl and 8-aminomethyl analogues **18** and **19** were designed first to retain the H-bonding donor property and to improve the metabolic stability. Unfortunately, both compounds did not show appreciable binding affinity at the D_1 receptor (Table 2). As to the 7- or 8-amino substituted benzazepines (**22** and **23**), only the 8-amino substituted analogue **23** retained good affinity at this receptor with a K_i value of 583 nM, which is only 1.5-fold less potent than that of **1**. Quite disappointingly, further substitutions on the 8-amino moiety, including alkylamino-(**24**, **25**), cyclic amido-(**29**, **30**), and aromatic *N*-heterocycle (**31**, **33**) led to complete loss of binding affinity at the D_1 receptor.

3.2. Binding assay of the D_1 active compounds at the rat 5-HT_{1A} and human 5-HT_{2A} receptors

In our previous studies [12,13], we found that benzazepines with substitutions at the *N*3- or C6 showed substantial binding affinities at the serotonin (5-HT) receptors, especially 5-HT_{1A} and 5-HT_{2A} subtypes. To investigate the selectivity of our newly synthesized benzazepine analogues over the 5-HT receptors, binding assays of the D_1-active compounds were further evaluated at the 5-HT_{1A} and 5-HT_{2A} receptors by using [^{3}H]8-OH-DPAT and [^{3}H]ketanserin as the respective standard radioligands [12,13,22,23]. As summarized in Table 3, most of these compounds displayed moderate to high affinities at the 5-HT_{2A} receptor, yet low or no affinities at the 5-HT_{1A} receptor. Compared to the D_1 receptor affinity, much higher affinity was observed for 8-hydroxybenzazepine **10** at the 5-HT_{2A} receptor showing a K_i value of 133 nM. Interestingly, introducing a 7-amino group to compound **10** abolished the 5-HT_{2A} binding,

Table 1
Binding affinities of phenolic benzazepines at human DA D_1–D_3 receptors.[a]

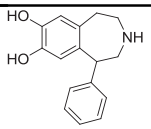
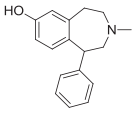
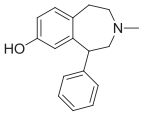
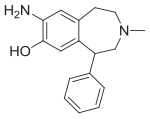
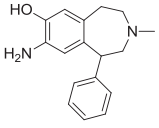
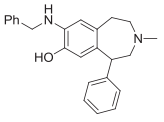
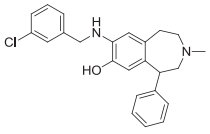
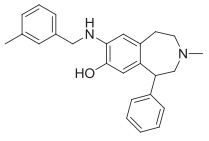
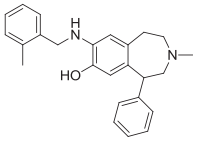
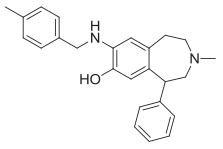
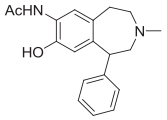
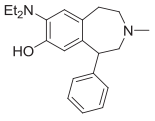
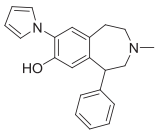
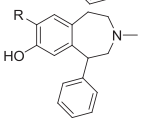
Cpd	Structure	K_i (nM)		
		hD_1	hD_2	hD_3
1		393 ± 5	NA	–
9		>1000	>1000	>1000
10		207 ± 25	>1000	>1000
12		334 ± 37	>1000	>1000
28		351 ± 67	>1000	>1000
13a		665 ± 66	>1000	>1000
13b		277 ± 32	>1000	–
13c		370 ± 40	>1000	–
13d		292 ± 16	>1000	–
13e		756 ± 162	>1000	–
14		>1000	>1000	–
15		>1000	>1000	>1000

Table 1 (*continued*)

Cpd	Structure	K_i (nM)		
		hD_1	hD_2	hD_3
16		>1000	>1000	–
				
21a	4′-Me-Ph	>1000	>1000	>1000
21b	3′-Me-Ph	216 ± 28	>1000	>1000
21c	2′-Me-Ph	912 ± 97	>1000	–
21d	2′-Napthyl	>1000	>1000	–
21e	4′-OH-Ph	349 ± 41	>1000	–

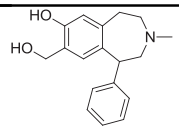
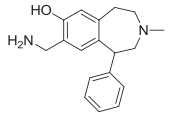
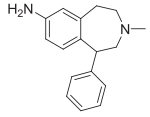
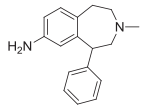
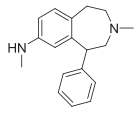
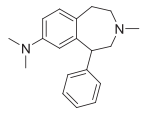
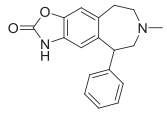
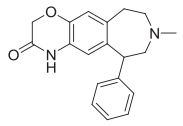
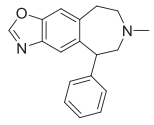
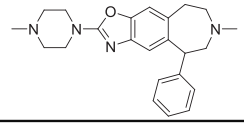
[a] Values are means of three to five experiments, and all compounds were tested in racemic form; dash line indicates that the data is not available.

whereas the D_1 receptor affinity was retained. Similar result was observed in 7-hydroxy-8-aminobenzazepine **28**, indicating that a potential interaction site of the 5-HT_{2A} receptor might exist at the C7-position of the benzazepine analogues. Significant discrepancy of the 5-HT_{2A} binding affinities was observed among the 7-(arylmethyl)amino substituted benzazepines **13a**–**e**. Compounds **13a**–**c** displayed high affinities at this receptor and showed K_i values of less than 10 nM. Non-substituted 7-benzylamino benzazepine **13a** is the most potent with a K_i value of 4.5 nM at the 5-HT_{2A} receptor and a high 5-HT_{2A}/D_1 selectivity of 147. The lower affinities of compounds **13d** and **13e** suggested that the substitution pattern other than electronic property of the arylmethylamino moiety play an important role to the interactions with the receptor. Moderate affinities at the 5-HT_{2A} receptor were observed for the 7-aryl benzazepines **21b** and **21e** showing K_i values of 163 and 826 nM, respectively. Compound **21b** with a lipophilic substituent (methyl) is 5-fold more potent than the phenol analogue **21e**.

4. Conclusion

As a part of our long-term objective of developing novel benzazepine analogues useful for the treatment of CNS diseases, we prepared a series of new benzazepines with modifications on the catecholic fragment that potentially lead to better metabolic stability. First, the importance of the 8-hydroxyl group to the interaction with the D_1 receptor was confirmed, and then several series of new analogues bearing a larger substituent at the C7 position were subsequently investigated. In comparison with the binding affinity of the prototypical **1**, non-/substituted benzylamino groups were well tolerated. 7-(*m*-Chlorophenyl)methylamino- and 7-(*m*- or *o*-tolyl)methylamino-substituted benzazepines (**13b**,**c**,**d**) displayed K_i values of 270–370 nM at the D_1 receptor, which were slightly more potent than that of **1**. Slightly higher affinities were also observed for 7-(*m*-methylphenyl)- and 7-(*p*-hydroxyphenyl)-substituted benzazepines **21b** and **21e**. Meanwhile, these D_1-active compounds were further evaluated at the 5-HT_{1A} and 5-HT_{2A} receptors. Most compounds displayed good binding affinities at the 5-HT_{2A} receptor, whereas negligible affinity at the 5-HT_{1A} receptor. 7-(Arylmethyl) amino-benzazepines **13a**–**c** displayed K_i values of less than 10 nM, with the non-substituted 7-benzylamino analogue **13a** as the most potent showing a K_i values of 4.5 nM at the 5-HT_{2A} receptor and a high 5-HT_{2A}/D_1 selectivity of 147. Moderate affinities at the 5-HT_{2A} receptor were observed for 7-aryl-benzqzepines **21b** and **21e**. They

Table 2
Binding affinities of nonphenolic benzazepines at human DA D_1–D_3 receptors.[a]

Cpd	Structure	K_i (nM)		
		hD_1	hD_2	hD_3
18		>1000	>1000	>1000
19		>1000	>1000	>1000
22		>1000	>1000	>1000
23		583 ± 25	>1000	>1000
24		>1000	>1000	–
25		>1000	>1000	–
29		>1000	>1000	–
30		>1000	>1000	–
31		>1000	>1000	–
33		>1000	>1000	–

[a] Values are means of three to five experiments, and all compounds were tested in racemic form; dash line indicates that the data is not available.

were still slightly more potency at this receptor than at the D_1 receptor. All the new synthetic benzazepines were either inactive or significantly less active at the D_2, D_3 and 5-HT_{1A} receptors.

5. Experimental

5.1. General methods

^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 column chromatography was conducted on silica gel. The column output was monitored with TLC. Yields of all the reactions were not optimized. Compounds **9** and **10** were prepared by following a literature procedure [17,18].

Table 3
In vitro binding assays of new benzazepines at rat 5-HT_{1A} and human 5-HT_{2A} receptors. [a]

Compound	K_i (nM)		
	r5-HT_{1A}	h5-HT_{2A}	hD_1
1	–	–	393 ± 5
10	>1000	133 ± 17	207 ± 25
12	>1000	>1000	334 ± 37
28	>1000	>1000	351 ± 67
13a	>1000	4.52 ± 0.07	665 ± 66
13b	479 ± 85	10.3 ± 1.8	277 ± 32
13c	>1000	9.95 ± 1.10	370 ± 40
13d	>1000	192 ± 37	292 ± 16
13e	>1000	862 ± 17	756 ± 162
21b	>1000	163 ± 9.4	216 ± 28
21e	>1000	826 ± 84	349 ± 41

[a] Values are means of three to five experiments, and all compounds were tested in racemic form; dash line indicates that the data is not available.

5.2. 7-Nitro and 9-nitro-substituted 8-hydroxy-1-phenyl-N-methyl benzazepines *11* and *11′*

To a solution of phenol **10** (990 mg, 3.91 mmol) in acetic acid (10 mL) was added foaming nitric acid (320 mg, 5.08 mmol) slowly. The reaction was allowed to stir at room temperature for 2 h before ice-water was added. The resulting mixture was basified with $NH_3 \cdot H_2O$, and extracted with $CHCl_3$. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash column chromatograph ($CHCl_3$:MeOH:$NH_3 \cdot H_2O$ = 100:1:1) to give **11** (577 mg, 50%) and **11′** (531 mg, 46%). For **11**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.33 (m, 3H), 7.16 (m, 2H), 6.43 (s, 1H), 4.35 (d, J = 8.4 Hz, 1H), 3.15 (m, 2H), 2.88 (m, 3H), 2.35 (m, 4H); for **11′**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.18 (m, 2H), 7.07 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 4.68 (m, 1H), 3.56 (dd, J = 6.0, 13.2 Hz, 1H), 2.80 (m, 3H), 2.52 (m, 1H), 2.34 (m, 4H).

5.3. 7-Amino-8-hydroxy-1-phenyl-N-methyl benzazepine *12*

A solution of compound **11** (1.5 g, 5.03 mmol) and 10% Pd/C (450 mg) in MeOH/THF (1:1, 40 mL) was stirred overnight under H_2 at room temperature. After filtration, the filtrate was concentrated to give a yellow solid **12** (1.3 g, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 3H), 7.38 (m, 2H), 6.97 (s, 1H), 6.23 (s, 1H), 4.55 (d, J = 8.7 Hz, 1H), 3.60 (m, 1H), 3.35 (m, 2H), 3.03 (m, 2H), 2.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 142.6, 135.0, 132.7, 132.1, 128.6, 128.4, 126.2, 117.5, 115.4, 63.1, 57.0, 47.4, 46.5, 34.5; EI-MS *m/z*: 268 (M^+); HR-MS calcd for $C_{17}H_{20}N_2O$ (M^+) 268.1576. Found: 268.1576.

5.4. 7-(Arylmethyl)amino-8-hydroxy-1-phenyl-N-methyl benzazepines *13a–e*

A solution of amine **12** (1.0 mmol) and an appropriate aryl aldehyde (1.3 mmol) in dry ethanol (6 mL) was stirred at room temperature for 3 h. The mixture was then cooled to 0 °C, and $NaBH_4$ (1.5 mmol) was added slowly. After stirring at room

temperature for 1 h, the reaction was quenched with water, and extracted with $CHCl_3$. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and then evaporated. The yellowish residue was subjected to column chromatograph ($CHCl_3$:MeOH = 30:1) to give corresponding benzylamines **13a**–**e**.

5.4.1. 7-(Benzylamino)-3-methyl-8-hydroxy-1-phenyl-benzazepine **13a**

White solid (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 8H), 6.84 (m, 2H), 6.40 (s, 1H), 5.74 (s, 1H), 4.34 (s, 2H), 4.05 (d, J = 9.3 Hz, 1H), 3.13 (m, 1H), 2.85 (m, 2H), 2.53 (m, 2H), 2.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 142.0, 139.9, 135.5, 132.8, 132.0, 128.6, 128.4, 128.3, 127.4, 126.9, 126.1, 114.3, 112.6, 63.1, 56.8, 48.4, 47.1, 46.3, 34.8; EI-MS m/z: 358 (M^+); HR-MS calcd for $C_{24}H_{26}N_2O$ (M^+) 358.2045. Found: 358.2046.

5.4.2. 7-(3′-Chlorobenzylamino)-3-methyl-8-hydroxy-1-phenyl-benzazepine **13b**

Colorless liquid (82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.20 (m, 6H), 6.87 (d, J = 7.2 Hz, 2H), 6.27 (s, 1H), 5.83 (s, 1H), 4.28 (s, 2H), 4.17 (d, J = 9.0 Hz, 1H), 3.09 (m, 3H), 2.61 (m, 2H), 2.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 142.4, 142.1, 135.4, 134.3, 132.1, 131.1, 129.8, 128.5, 127.3, 127.1, 126.5, 125.3, 114.4, 112.4, 62.3, 56.4, 47.7, 46.1, 45.8, 33.6; EI-MS m/z: 392 (M^+); HR-MS calcd for $C_{24}H_{25}ClN_2O$ (M^+) 392.1655. Found: 392.1647.

5.4.3. 7-((3-Methylbenzyl)amino)-3-methyl-8-hydroxy-1-phenyl-benzazepine **13c**

white solid (91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (m, 7H), 6.91 (m, 2H), 6.35 (s, 1H), 5.91 (s, 1H), 4.38 (m, 1H), 4.25 (s, 2H), 3.26 (m, 3H), 2.85 (m, 1H), 2.49 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.0, 139.7, 138.0, 135.7, 132.5, 131.9, 128.6, 128.4, 128.3, 128.2, 127.7, 126.3, 124.5, 114.4, 112.6, 62.9, 56.8, 48.5, 46.9, 46.3, 34.5, 21.4; EI-MS m/z: 372 (M^+); HR-MS calcd for $C_{25}H_{28}N_2O$ (M^+) 372.2202. Found: 372.2211.

5.4.4. 7-((2-Methylbenzyl)amino)-3-methyl-8-hydroxy-1-phenyl-benzazepine **13d**

white solid (80%). ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.15 (m, 9H), 6.30 (s, 1H), 5.89 (s, 1H), 4.38 (d, J = 9.3 Hz, 1H), 4.15 (s, 2H), 3.25 (m, 3H), 3.00 (m, 1H), 2.56 (m, 5H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 142.0, 137.5, 136.2, 135.7, 132.7, 132.0, 130.1, 128.6, 128.4, 128.1, 127.0, 126.2, 126.0, 114.3, 112.4, 63.1, 56.9, 47.1, 46.5, 46.4, 34.8, 18.9; EI-MS m/z: 372 (M^+); HR-MS calcd for $C_{25}H_{28}N_2O$ (M^+) 372.2202. Found: 372.2202.

5.4.5. 7-((4-Methylbenzyl)amino)-3-methyl-8-hydroxy-1-phenyl-benzazepine **13e**

white solid (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (brs, 1H), 7.17 (m, 7H), 6.88 (m, 2H), 6.35 (s, 1H), 5.89 (s, 1H), 4.24 (m, 3H), 3.15 (m, 3H), 2.67 (m, 2H), 2.38 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 143.3, 141.9, 136.3, 135.0, 132.6, 131.9, 128.8, 128.2, 127.2, 126.0, 114.0, 112.8, 63.1, 57.0, 48.0, 47.8, 46.6, 34.8, 20.6; EI-MS m/z: 372 (M^+); HR-MS calcd for $C_{25}H_{28}N_2O$ (M^+) 372.2202. Found: 372.2200.

5.5. 7-(Acetylamino)-8-hydroxy-3-methyl-1-phenyl-benzazepine **14**

Acetyl chloride (39 mg, 0.50 mmol) was added to a solution of compound **12** (90 mg, 0.34 mmol) and NaOAc (55 mg, 0.67 mmol) in dry THF in ice-bath. The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was taken in $CHCl_3$, washed with saturated NH_4Cl solution and brine, and then dried over anhydrous Na_2SO_4. After evaporation of the solvents, the residue was subjected to column chromatograph (EtOAc:MeOH = 15:1) to give a yellow liquid **14** (43 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.40 (s, 1H), 7.22 (m, 3H), 6.91 (m, 2H), 6.00 (s, 1H), 4.08 (d, J = 9.0 Hz, 1H), 2.84 (m, 3H), 2.61 (m, 2H), 2.20 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 145.3, 142.9, 141.6, 132.0, 128.6, 128.4, 126.6, 124.0, 121.9, 117.2, 62.9, 57.0, 48.2, 46.8, 34.7, 24.1; EI-MS m/z: 310 (M^+); HR-MS calcd for $C_{19}H_{22}N_2O_2$ (M^+) 310.1681. Found: 310.1684.

5.6. 7-(Diethylamino)-8-hydroxy-3-methyl-1-phenyl-benzazepine **15**

A solution of compound **12** (50 mg, 0.19 mmol), acetaldehyde (25 mg, 0.57 mmol) and $NaBH(OAc)_3$ (79 mg, 0.38 mmol) in 1,2-dichloroethane (7 mL) was stirred at room temperature overnight. After filtration, the filtrate was concentrated and chromatographied ($CHCl_3$:MeOH = 30:1) on neutral aluminum oxide to yield diethylamine **15** as white solid (49 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 5H), 6.86 (s, 1H), 6.24 (s, 1H), 4.28 (d, J = 8.4 Hz, 1H), 3.10 (m, 2H), 2.81 (m, 7H), 2.33 (m, 4H), 0.95 (t, J = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 143.3, 142.8, 133.5, 132.5, 128.5, 128.4, 126.3, 123.8, 113.5, 57.7, 49.9, 49.6, 47.6, 35.9, 13.0; EI-MS m/z: 324 (M^+); HR-MS calcd for $C_{21}H_{28}N_2O$ (M^+) 324.2202. Found: 324.2203.

5.7. 7-(1H-pyrrol-1-yl)-8-hydroxy-3-methyl-1-phenyl-benzazepine **16**

A mixture of amine **12** (105 mg, 0.39 mmol) and 2,5-dimethoxytetrahydrofuran (52 mg, 0.39 mmol) in HOAc/H_2O (6:1, 7 mL) was stirred at 110 °C for 1.5 h. The reaction mixture was then cooled and evaporated in vacuum. The obtained residue was dissolved in $CHCl_3$, washed with $NH_3 \cdot H_2O$ and brine, then evaporated. The crude product was further purified by column chromatograph ($CHCl_3$:MeOH = 30:1) to afford compound **16** (101 mg, 81%) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 3H), 7.00 (m, 3H), 6.90 (s, 2H), 6.28 (s, 2H), 6.10 (s, 1H), 5.53 (brs, 1H), 4.22 (d, J = 9.0 Hz, 1H), 3.07 (m, 2H), 2.75 (m, 3H), 2.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 144.3, 142.7, 132.5, 128.7, 128.5, 126.7, 126.5, 126.1, 121.6, 117.0, 109.3, 62.8, 56.9, 48.2, 46.7, 34.5; EI-MS m/z: 318 (M^+); HR-MS calcd for $C_{21}H_{22}N_2O$ (M^+) 318.1732. Found: 318.1729.

5.8. 7-Hydroxy-3-methyl-1-phenyl-benzazepine-8-carbaldehyde **17**

A mixture of phenol **9** (550 mg, 2.17 mmol), paraformaldehyde (649 mg, 21.62 mmol), anhydrous $MgCl_2$ (616 mg, 6.47 mmol) and Et_3N (660 mg, 6.52 mmol) in dry THF was refluxed under N_2 overnight. The reaction was quenched by ice-water, and extracted with $CHCl_3$. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was further purified by chromatography ($CHCl_3$:MeOH = 50:1) to give aldehyde **17** (277 mg, 45%) as a light yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.94 (brs, 1H), 9.56 (s, 1H), 7.28 (m, 5H), 6.76 (m, 2H), 4.32 (d, J = 8.7 Hz, 1H), 2.98 (m, 5H), 2.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 160.1, 151.8, 142.5, 136.4, 132.5, 128.7, 128.2, 126.6, 118.4, 118.2, 63.1, 56.4, 48.6, 47.4, 36.8; EI-MS m/z: 281 (M^+); HR-MS calcd for $C_{18}H_{19}NO_2$ (M^+) 281.1416. Found: 281.1421.

5.9. 8-(Hydroxymethyl)-3-methyl-7-hydroxy-1-phenyl-benzazepine **18**

A solution of aldehyde **17** (35 mg, 0.12 mmol) and $NaBH_4$ (9.4 mg, 0.24 mmol) in MeOH (5 mL) was stirred at room

temperature for 1 h. Water was added, and the mixture was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography ($CHCl_3$:MeOH = 15:1) to give alcohol **18** (35 mg, 99%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.26 (m, 5H), 6.64 (s, 1H), 6.31 (s, 1H), 4.53 (s, 2H), 4.27 (d, J = 8.4 Hz, 1H), 2.93 (m, 5H), 2.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 153.9, 142.8, 141.4, 134.9, 128.5, 128.2, 128.0, 126.3, 123.0, 117.0, 63.1, 62.6, 56.8, 49.2, 47.0, 35.1; EI-MS m/z: 283 (M^+); HR-MS calcd for $C_{18}H_{21}NO_2$ (M^+) 283.1572. Found: 283.1564.

5.10. 8-(Aminomethyl)-3-methyl-7-hydroxy-1-phenyl-benzazepine **19**

A mixture of aldehyde **17** (66 mg, 0.23 mmol), hydroxylamine hydrochloride (33 mg, 0.47 mmol) and NaOAc (38 mg, 0.47 mmol) in MeOH was heated to reflux for 2 h. The mixture was cooled and concentrated. The residue was basified with $NH_3 \cdot H_2O$, and extracted with $CHCl_3$. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated to give the oxime intermediate (61 mg, 88%) as a white solid. The intermediate (32 mg, 0.11 mmol) was then dissolved in dry THF (10 mL), and lithium aluminum hydride (12 mg, 0.32 mmol) was added. The mixture was heated to reflux for 3 h, then cooled and quenched with 10% NaOH aqueous solution slowly. The white suspension was filtered, and the filtrate was dried over anhydrous Na_2SO_4. After evaporation, the crude material was chromatographied ($CHCl_3$:MeOH = 5:1) to give amine **19** (20 mg, 66%) as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 6.66 (s, 1H), 6.23 (s, 1H), 4.25 (d, J = 8.1 Hz, 1H), 3.91 (brs, 2H), 2.94 (m, 5H), 2.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 143.6, 141.7, 134.7, 128.5, 128.4, 127.9, 126.2, 117.9, 63.4, 57.2, 49.0, 47.6, 45.0, 36.0; EI-MS m/z: 282 (M^+); HR-MS calcd for $C_{18}H_{22}N_2O$ (M^+) 282.1732. Found: 282.1727.

5.11. 7-Bromo-3-methyl-8-methoxy-1-phenyl-benzazepine **20**

Br_2 (0.98 mL, 19.20 mmol) was added to a mixture of compound 8-methoxy-1-phenyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine **8′** (4.3 g, 16.08 mmol) in glacial acetic acid (30 mL), then the mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled, poured into water, and then extracted with CH_2Cl_2. The combined organic phase was washed with 2 N NaOH solution, followed by water and brine. After the solvents were evaporated, the residue was purified by column chromatography ($CHCl_3$:MeOH = 12:1) to give bromide intermediate (2.6 g, 49%) as a yellow liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 4H), 7.12 (m, 2H), 6.44 (s, 1H), 4.24 (d, J = 6.3 Hz, 1H), 3.70 (s, 3H), 3.57 (m, 1H), 3.35 (m, 1H), 2.95 (m, 2H), 2.78 (m, 2H), 2.64 (brs, 1H). A mixture of the bromide intermediate (610 mg, 1.84 mmol) and 37% formaldehyde aqueous solution (7 mL) in formic acid (20 mL) was stirred under 100 °C overnight. After cooled down and concentrated, the obtained residue was taken up in H_2O and basified with 2 N NaOH aqueous solution. The suspension was extracted with EtOAc, and the organic phase was washed with H_2O and brine. After evalopated, the obtained crude product was purified by chromatography (EtOAc:MeOH = 8:1) to give the yellow liquid **20** (520 mg, 81.8%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 4H), 7.18 (m, 2H), 6.24 (s, 1H), 4.30 (d, J = 8.4 Hz, 1H), 3.60 (s, 3H), 2.90 (m, 5H), 2.39 (m, 4H).

5.12. 7-Aryl-3-methyl-8-hydroxy-1-phenyl-benzazepines **21a–e**

To a mixture of bromide **20** (1.0 mmol) in dry DMF (4 mL), an appropriate arylboronic acid (2.0 mmol), $Pd(OAc)_2$ (0.2 mmol), P(*o*-Tol)$_3$ (0.8 mmol) and K_3PO_4 (2.0 mmol) were added under N_2. The reaction was irradiated in microwave reactor at 110 °C for 1 h. After cooled to room temperature, the mixture was poured into water, and extracted with Et_2O. The combined organic phase was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was then subjected to demethylation by using a procedure previously reported to yield the desired products **21a–e**.

5.12.1. 7-(p-Tolyl)-3-methyl-1-phenyl-8-hydroxy-benzazepine **21a**

Light yellow solid (73% yield for two steps). ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 7H), 7.10 (m, 2H), 7.04 (s, 1H), 6.13 (s, 1H), 4.30 (d, J = 8.7 Hz, 1H), 3.13 (m, 2H), 2.90 (m, 1H), 2.75 (m, 2H), 2.40 (s, 3H), 2.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 145.1, 143.1, 136.9, 134.5, 132.7, 131.2, 129.4, 128.9, 128.6, 126.5, 125.6, 115.9, 63.1, 57.2, 48.7, 47.0, 35.0, 21.2; EI-MS m/z: 343 (M^+); HR-MS calcd for $C_{24}H_{25}NO$ (M^+) 343.1936. Found: 343.1933.

5.12.2. 7-(m-Tolyl)-3-methyl-1-phenyl-8-hydroxy-benzazepine **21b**

Yellow solid (60% yield for two steps). ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 6H), 7.15 (m, 3H), 7.02 (s, 1H), 6.18 (s, 1H), 4.36 (d, J = 8.7 Hz, 1H), 3.17 (m, 2H), 2.86 (m, 3H), 2.36 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 145.2, 142.8, 138.6, 137.1, 132.7, 131.2, 129.7, 128.8, 128.7, 128.5, 128.2, 126.6, 126.0, 125.8, 115.9, 63.0, 57.3, 48.7, 47.1, 34.8, 21.5; EI-MS m/z: 343 (M^+); HR-MS calcd for $C_{24}H_{25}NO$ (M^+) 343.1936. Found: 343.1936.

5.12.3. 7-(o-Tolyl)-3-methyl-1-phenyl-8-hydroxy-benzazepine **21c**

White solid (70% yield for two steps). ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 9H), 6.88 (s, 1H), 6.16 (s, 1H), 4.33 (d, J = 9.0 Hz, 1H), 3.14 (m, 2H), 2.81 (m, 3H), 2.26 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 145.3, 143.1, 137.2, 136.5, 132.4, 131.3, 130.4, 130.3, 128.6, 128.5, 127.9, 126.5, 126.0, 125.5, 115.3, 63.1, 57.4, 48.9, 47.1, 35.0, 19.9; EI-MS m/z: 343 (M^+); HR-MS calcd for $C_{24}H_{25}NO$ (M^+) 343.1936. Found: 343.1935.

5.12.4. 7-(2-Naphthyl)-3-methyl-1-phenyl-8-hydroxy-benzazepine **21d**

White solid (41% yield for two steps). ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.87 (m, 3H), 7.68 (m, 1H), 7.49 (m, 2H), 7.29 (m, 3H), 7.16 (s, 1H), 7.09 (m, 2H), 6.16 (s, 1H), 4.33 (d, J = 9.3 Hz, 1H), 3.14 (m, 2H), 2.84 (m, 3H), 2.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 145.4, 143.0, 135.2, 133.5, 132.7, 132.4, 131.5, 128.6, 128.1, 128.0, 127.7, 127.6, 127.5, 126.5, 126.1, 125.9, 125.7, 116.1, 63.0, 57.2, 48.6, 46.9, 34.8; EI-MS m/z: 379 (M^+); HR-MS calcd for $C_{27}H_{25}NO$ (M^+) 379.1936. Found: 379.1933.

5.12.5. 7-(p-Hydroxyphenyl)-3-methyl-1-phenyl-8-hydroxy-benzazepine **21e**

White solid (27% yield for two steps). ^1H NMR (300 MHz, CD_3OD) δ 7.31 (m, 7H), 7.02 (s, 1H), 6.79 (m, 2H), 6.17 (s, 1H), 4.35 (d, J = 8.7 Hz, 1H), 3.03 (m, 5H), 2.43 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.7, 153.9, 145.2, 144.6, 133.3, 133.0, 131.8, 131.5, 130.4, 130.1, 128.3, 127.9, 117.6, 116.3, 64.7, 59.2, 50.1, 48.0, 35.8; EI-MS m/z: 345 (M^+); HR-MS calcd for $C_{23}H_{23}NO_2$ (M^+) 345.1729. Found: 345.1736.

5.13. 7-Amino or 8-amino-3-methyl-1-phenyl-benzazepine **22** or **23**

Amines **22** and **23** were prepared by triflation of corresponding phenols **9** and **10** followed by a C–N coupling using a set of procedures similar to that reported by us early [22,23].

5.13.1. 7-Amino-3-methyl-1-phenyl-benzazepine ***22***

Yellow liquid (82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 6.51 (s, 1H), 6.40 (m, 2H), 4.27 (d, J = 8.1 Hz, 1H), 3.52 (brs, 2H), 3.06 (m, 2H), 2.88 (m, 2H), 2.74 (m, 1H), 2.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 143.6, 142.2, 134.4, 129.2, 128.4, 128.3, 126.1, 116.6, 112.4, 63.3, 57.1, 48.9, 47.7, 36.4; EI-MS m/z: 252 (M^+); HR-MS calcd for $C_{17}H_{20}N_2$ (M^+) 252.1626. Found: 252.1632.

5.13.2. 8-Amino-3-methyl-1-phenyl-benzazepine ***23***

Light yellow liquid (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 6.93 (d, J = 8.1 Hz, 1H), 6.45 (dd, J = 2.1, 7.5 Hz, 1H), 5.99 (s, 1H), 4.31 (d, J = 8.7 Hz, 1H), 3.51 (brs, 2H), 3.10 (m, 2H), 2.90 (m, 2H), 2.75 (m, 1H), 2.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 144.5, 143.1, 131.1, 130.3, 128.5, 126.3, 115.4, 112.5, 63.0, 57.6, 49.4, 47.5, 35.2; EI-MS m/z: 252 (M^+); HR-MS calcd for $C_{17}H_{20}N_2$ (M^+) 252.1626. Found: 252.1630.

5.14. 8-(N-methylamino)-3-methyl-1-phenyl-benzazepine ***24***

A solution of amine **23** (36 mg, 0.14 mmol) in ethyl formate (7 mL) was heated to reflux for 3 h under N_2. After cooled, the mixture was concentrated. The residue was subjected to flash chromatography to yield *N*-formyl product (32 mg, 80%) as a yellow liquid, which was then subjected to reduction with $LiAlH_4$ (15 mg, 0.39 mmol). After work-up, the crude product was purified by preparative TLC ($CHCl_3$:MeOH = 12:1) to give product **24** (17 mg, 60%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 6.98 (d, J = 7.8 Hz, 1H), 6.38 (dd, J = 2.1, 7.8 Hz, 1H), 5.89 (s, 1H), 4.50 (d, J = 9.3 Hz, 1H), 3.15 (m, 4H), 2.79 (m, 1H), 2.66 (s, 3H), 2.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 144.4, 142.2, 130.4, 128.8, 128.6, 128.5, 126.6, 113.6, 109.2, 62.6, 57.6, 48.3, 47.0, 34.1, 30.6; EI-MS m/z: 266 (M^+); HR-MS calcd for $C_{18}H_{22}N_2$ (M^+) 266.1783. Found: 266.1786.

5.15. 8-(N,N-dimethylamino)-3-methyl-1-phenyl-benzazepine ***25***

A mixture of amine **23** (40 mg, 0.16 mmol) in formalin (2 mL) and formic acid (6 mL) was stirred at 90 °C under N_2 overnight. The reaction was cooled and then concentrated. The obtained residue was basified with 2 N NaOH solution and extracted with $CHCl_3$. The combined organic phase was washed with brine, and dried over anhydrous Na_2SO_4. The crude product was then subjected to preparative TLC ($CHCl_3$:MeOH = 12:1) to give compound **25** (8 mg, 18%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 5H), 7.01 (d, J = 8.4 Hz, 1H), 6.51 (dd, J = 2.4, 8.1 Hz, 1H), 6.08 (s, 1H), 4.46 (d, J = 8.4 Hz, 1H), 3.11 (m, 4H), 2.80 (m, 1H), 2.74 (s, 6H), 2.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 144.3, 142.5, 130.2, 128.5, 128.4, 126.5, 113.6, 110.3, 62.6, 57.7, 49.2, 47.3, 40.5, 34.4; EI-MS m/z: 280 (M^+); HR-MS calcd for $C_{19}H_{24}N_2$ (M^+) 280.1939. Found: 280.1932.

5.16. 6-And 8-nitro-7-hydroxy-3-methyl-1-phenyl-benzazepines ***26*** *and* ***27***

These two compounds were prepared by nitration of phenol **8** following a similar procedure as that for preparation of **11** and **11′**.

5.16.1. 8-Nitro-7-hydroxy-3-methyl-1-phenyl-benzazepines ***26***

Yellow liquid (43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 6H), 6.93 (s, 1H), 6.87 (d, J = 8.7 Hz, 1H), 3.11 (m, 2H), 2.88 (m, 3H), 2.41 (m, 4H).

5.16.2. 6-Nitro-7-hydroxy-3-methyl-1-phenyl-benzazepines ***27***

Yellow liquid (24%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.01 (brs, 1H), 7.30 (m, 3H), 7.06 (d, J = 7.2 Hz, 2H), 6.44 (m, 2H), 4.34 (d, J = 9.0 Hz, 1H), 3.01 (m, 5H), 2.51 (m, 4H).

5.17. 8-Amino-7-hydroxy-3-methyl-1-phenyl-benzazepines ***28***

This compound was prepared as white solid (90%) from **26** by using a procedure similar to that for preparation of amine **12**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 6.40 (s, 1H), 5.94 (s, 1H), 5.10 (brs, 2H), 4.25 (d, J = 8.4 Hz, 1H), 2.96 (m, 4H), 2.44 (m, 4H), 2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.7, 136.1, 132.4, 131.6, 128.5, 128.4, 126.3, 117.0, 63.3, 57.4, 48.2, 47.2, 34.8; EI-MS m/z: 268 (M^+); HR-MS calcd for $C_{17}H_{20}N_2O$ (M^+) 268.1576. Found: 268.1578.

5.18. 7-Methyl-3,5,6,7,8,9-hexahydro-2-oxazolo[4′,5′:4,5] benzazepin-2-one ***29***

A mixture of compound **28** (43 mg, 0.16 mmol) and carbonyldiimidazole (CDI, 78 mg, 0.48 mmol) in dry THF (6 mL) was refluxed for 1 h. After cooled, the mixture was concentrated, and the residue was dissolved in $CHCl_3$. The organic phase was washed with saturated NH_4Cl solution and then dried over anhydrous Na_2SO_4. After evaporation, the crude material was subjected to chromatograph on silica gel ($CHCl_3$:MeOH = 30:1) to afford product **29** (32 mg, 68%) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 5H), 6.95 (s, 1H), 6.25 (s, 1H), 4.37 (d, J = 8.4 Hz, 1H), 2.97 (m, 5H), 2.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 142.7, 142.1, 140.4, 135.4, 128.7, 128.3, 127.8, 126.7, 110.8, 109.9, 62.7, 56.8, 49.0, 47.1, 35.8; EI-MS m/z: 294 (M^+); HR-MS calcd for $C_{18}H_{18}N_2O_2$ (M^+) 294.1368. Found: 294.1364.

5.19. 6-Phenyl-4,6,7,8,9,10-hexahydro-[1,4]oxazino[2′,3′:4,5] benzazepin-3-one ***30***

To a suspension of **28** (35 mg, 0.13 mmol) and Cs_2CO_3 (127 mg, 0.39 mmol) in CH_3CN (6 mL) in ice-bath, was added slowly a solution of chloroacetic chloride (18 mg, 0.16 mmol) in CH_3CN. The mixture was allowed to stir at room temperature overnight and concentrated. The obtained residue was dissolved in $CHCl_3$, washed with brine, dried over anhydrous Na_2SO_4 and then evaporated. The residue was further purified by column chromatography ($CHCl_3$:MeOH = 30:1) to give compound **30** (30 mg, 75%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.26 (m, 5H), 6.75 (s, 1H), 6.04 (s, 1H), 4.49 (s, 2H), 4.25 (d, J = 9.0 Hz, 1H), 2.89 (m, 5H), 2.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 142.8, 141.5, 139.0, 137.1, 128.7, 128.3, 126.6, 123.7, 117.7, 116.0, 67.3, 62.9, 57.0, 48.9, 47.4, 35.6; EI-MS m/z: 308 (M^+); HR-MS calcd for $C_{19}H_{20}N_2O_2$ (M^+) 308.1525. Found: 308.1522.

5.20. 7-Methyl-5-phenyl-6,7,8,9-tetrahydro-5H-oxazolo[4′,5′:4,5] benzazepine ***31***

A mixture of compound **28** (50 mg, 0.19 mmol) and orthoethyl formate (200 mg, 1.35 mmol) in EtOH (6 mL) was heated to reflux overnight. After cooled to room temperature, the reaction mixture was concentrated. The residue was taken-up in CH_2Cl_2, washed with 2 N NaOH solution and brine, and then evaporated. The obtained residue was subjected to column chromatograph ($CHCl_3$:MeOH = 50:1) to give compound **31** (48 mg, 93%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.24 (m, 7H), 4.46 (d, J = 8.4 Hz, 1H), 3.24 (m, 2H), 2.92 (m, 3H), 2.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 148.3, 142.9, 141.8, 139.7, 138.1, 128.6, 128.3, 126.5, 119.8, 111.1, 63.0, 57.2, 49.5, 47.4, 36.6; EI-MS $m/$

z: 278 (M^+); HR-MS calcd for $C_{18}H_{18}N_2O$ (M^+) 278.1419. Found: 278.1410.

5.21. 7-Methyl-5-phenyl-tetrahydro-5H-oxazolo[4′,5′:4,5] benzazepine-2-thiol **32**

A mixture of compound **28** (60 mg, 0.22 mmol), KOH (31 mg, 0.56 mmol) in CS_2/EtOH (CS_2:EtOH = 1:2, 9 mL) was heated to reflux for 3 h. After cooled, the mixture was concentrated, and the residue was dissolved in $CHCl_3$. The organic phase was washed with saturated NH_4Cl and brine, and then dried over anhydrous Na_2SO_4. After concentrated, the crude product was purified by column chromatograph ($CHCl_3$:MeOH = 30:1) to afford product **32** (62 mg, 89%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.24 (m, 5H), 6.99 (s, 1H), 6.25 (s, 1H), 4.56 (d, J = 8.4 Hz, 1H), 3.08 (m, 5H), 2.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 181.2, 147.8, 141.9, 140.0, 135.2, 132.0, 128.7, 128.2, 126.9, 110.9, 110.3, 61.6, 56.2, 47.8, 46.4, 34.5; EI-MS *m*/*z*: 310 (M^+); HR-MS calcd for $C_{18}H_{18}N_2OS$ (M^+) 310.1140. Found: 310.1140.

5.22. 7-Methyl-2-(4-methylpiperazinyl)-5-phenyl-oxazolo[4′,5′:4,5] benzazepine **33**

To a solution of thiol **32** (40 mg, 0.13 mmol) in dry toluene (4 mL), was added *N*-methylpiperazine (0.5 mL). The mixture was irradiated in microwave reactor at 100 °C for 50 min. After cooled, the mixture was concentrated and dissolved in $CHCl_3$. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated. The obtained residue was further purified by chromatograph ($CHCl_3$:MeOH = 30:1) to yield product **33** (35 mg, 72%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 7.03 (s, 1H), 6.67 (s, 1H), 4.37 (d, J = 8.7 Hz, 1H), 3.64 (t, J = 5.1 Hz, 4H), 3.13 (m, 2H), 2.88 (m, 3H), 2.46 (m, 4H), 2.35 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 147.0, 143.4, 140.9, 140.7, 134.3, 128.5, 128.4, 126.3, 116.2, 109.4, 63.1, 57.5, 54.1, 49.5, 47.6, 46.2, 45.5, 36.4; EI-MS *m*/*z*: 376 (M^+); HR-MS calcd for $C_{23}H_{28}N_4O$ (M^+) 376.2263. Found: 376.2272.

5.23. Established stable expression of cell lines

The rat 5-HT_{1A} receptor gene, human 5-HT_{2A} receptor gene, human D_1, D_2 and D_3 receptor genes were individually cloned into pcDNA 3.0 vector. The cell line that stable expressed respective receptor was prepared as described before [12,13,22,23]. Briefly, the 5-HT_{1A} and 5-HT_{2A} plasmid was transfected into CHO cells. The 5-HT_{2A}, D_1, D_2, D_3 receptor were transfected into HEK293 cells respectively. After 24 h, the cells were selected with antibiotic G418 at a concentration of 800 mg/L. After several rounds of selection, monoclonal transfected cells were isolated and cultured in medium containing Ham's F12 nutrient mixture for CHO cells and DMEM for HEK293 cells (Gibco), respectively, with 10% fetal bovine serum (Gibco), 100 U/mL penicillin (Sigma), 100 U/mL streptomycin (Sigma), and 200 mg/L G418 at 37 °C and 5% CO_2.

5.24. Binding assay of new compounds at the D_1–D_3 and 5-HT_{1A}, 5-HT_{2A} receptors

The affinity of compounds binding to respective dopamine (D_1–D_3) or 5-HT (5-HT_{1A}, 5-HT_{2A}) receptors was measured by competition binding assay according our published method previously [12,13,22,23]. All radioligands were purchased from PerkinElmer, USA. All compounds were dissolved in DMSO to prepare a stock solution at a concentration of 10^{-1} M. Membrane homogenates of 5-HT_{1A}-CHO cells, 5-HT_{2A}-HEK293 cells, D_1-HEK293 cells, D_2-HEK293 cells and D_3-HEK293 cells were prepared as described previously [12,13,22,23]. Binding buffer contains 50 mM Tris, 4 mM $MgCl_2$, pH7.4 in the presence of tested compound and. 0.7 nM respective radioligand ([^{3}H]8-OH-DPAT for 5-HT_{1A} receptor, [^{3}H] Ketanserin for 5-HT_{2A} receptor, [^{3}H]SCH23390 for D_1 dopamine receptor, [^{3}H]Spiperone for D_2 and D_3 dopamine receptor). Duplicated tubes were incubated at 30 °C for 50 min with increasing concentrations of respective compounds and different radioligands in a final volume of 200 μL binding buffer. Nonspecific binding was determined by parallel incubations with 10 μM WAY100635 for 5-HT_{1A} receptor, Ketanserin for 5-HT_{2A} receptor, SCH23390 for D_1 dopamine receptor, Spiperone for D_2 and D_3 dopamine receptor respectively. The competition binding reaction was started by adding membrane homogenates (15 ng/tube) and stopped by rapid filtration through Whatman GF/B glass fiber filter, and subsequently washed with cold washing buffer using a Brandel 24-well cell harvest. 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 sigmodial function.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.07.059.

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