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### Identification of a new selective dopamine D<sub>4</sub> receptor ligand

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### ABSTRACT

The dopamine D<sub>4</sub> receptor has been shown to play key roles in certain CNS pathologies including addiction to cigarette smoking. Thus, selective  $D_4$  ligands may be useful in treating some of these conditions. Previous studies in our laboratory have indicated that the piperazine analog of haloperidol exhibits selective and increased affinity to the DAD<sub>4</sub> receptor subtype, in comparison to its piperidine analog. This led to further exploration of the piperazine moiety to identify new agents that are selective at the D<sub>4</sub> receptor. Compound 27 ( $K_iD_4 = 0.84$  nM) was the most potent of the compounds tested. However, it only had moderate selectivity for the D<sub>4</sub> receptor. Compound **28** ( $K_iD_4$  = 3.9 nM) while not as potent, was more discriminatory for the D<sub>4</sub> receptor subtype. In fact, compound **28** has little or no binding affinity to any of the other four DA receptor subtypes. In addition, of the 23 CNS receptors evaluated, only two, 5HT<sub>1A</sub>R and  $5HT_{2B}R$ , have binding affinity constants better than 100 nM ( $K_i$  <100 nM). Compound **28** is a potentially useful D<sub>4</sub>-selective ligand for probing disease treatments involving the D<sub>4</sub> receptor, such as assisting smoking cessation, reversing cognitive deficits in schizophrenia and treating erectile dysfunction. Thus, further optimization, functional characterization and evaluation in animal models may be warranted. Published by Elsevier Ltd.

### 1. Introduction

Targeting dopamine receptors for drug development has been of interest for decades because of their potential utility in many well-known pathological conditions.<sup>1</sup> Initially, dopamine receptors were classified as D<sub>1</sub>-like and D<sub>2</sub>-like for many years until it became evident that the D<sub>1</sub>-like receptors consisted of D<sub>1</sub> and D<sub>5</sub> subtypes and the D<sub>2</sub>-like receptors consisted of D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> subtypes. By far, the D<sub>2</sub>-like receptors have been studied more because of their association with clinically relevant neuropsychiatric conditions, such as schizophrenia, mood disorders, Parkinson's disease and others. Each of these subtypes is now separately associated with certain pathophysiological conditions. For example, several D<sub>2</sub> agonists and partial agonists have shown beneficial effects in counteracting Parkinson's disease, attention-deficit hyperactivity disorder and certain mood disorders<sup>2</sup> while D<sub>2</sub> antagonism is associated with antipsychotic properties.

Since its cloning, the D<sub>4</sub> receptor has attracted considerable interest. For example, early reports indicated that D<sub>4</sub> antagonists attenuate not only the discriminative-stimulus effects of cocaine and methamphetamine<sup>3,4</sup> but also morphine-induced withdrawal signs induced by naloxone.<sup>5</sup> More recently, there was a report that the D<sub>4</sub> receptor antagonist, L-745,870 (Chart 1) but not PD 168,077, a selective D<sub>4</sub> receptor agonist, attenuated nicotine-induced reinstatement of nicotine seeking behavior.<sup>6</sup> Thus, it would appear that the pharmacological blockade of DAD<sub>4</sub> may serve as a new and potentially effective treatment against relapse to tobacco smoking. On the other hand, PD 168,077 has been shown to induce penile erection in rats when administered in vivo, and L-745,870 was able to block this action, and thus, confirming the  $D_4$  receptor mediated mechanism by which penile erection occured.<sup>7</sup> This potential could place D4 agonists in a strong position to replace the current PDE5 antagonists with a plethora of side-effects.<sup>8</sup> In addition, D4-receptor agonists may be useful in reversing cognitive deficits in schizophrenia.<sup>9</sup> These demonstrated therapeutic potentials have encouraged the search for new D<sub>4</sub> selective ligands in our laboratories.

We have previously carried out several SAR studies that sought to identify structural entities that demonstrate DA receptor subtype selectivity.<sup>10–12</sup> A frequent observation in such studies was the fact that unlike the piperidine analogs of haloperidol, the piperazine analogs demonstrated selective and significant affinities to the D<sub>4</sub> receptor subtype. Chart 1 displays common D<sub>4</sub> selective ligands with the piperazine pharmacophore. The purpose of the





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Chart 1. Known D<sub>4</sub> selective ligands with a piperazine pharmacophore

current study was to further explore the piperazine ring as a pharmacophore in a search for new entities that are selective to the  $D_4$  receptor subtype using compound **1** (Chart 1), the piperazine analog of haloperidol as the lead.

### 2. Chemistry

The syntheses of compounds **1–7** (Chart 2) have previously been reported using routine N-alkylation reactions.<sup>9</sup> Compound **8**, the cyclic analog of **1**, was synthesized as depicted in Scheme 1 below. The commercially available 4-chloro-1-(4-fluorophenyl)-butan-1-one (**29**) was converted to 4-chloro-1-(4-fluorophenyl)-2-methylenebutan-1-one (**30**) by refluxing in acetic anhydride in the presence of hexamethylenetriamine.<sup>10,13</sup> Compound **30** was cyclized by heating in concentrated sulfuric acid to produce 2-(2-chloroethyl)-5-fluoro-2,3-dihydro-1*H*-inden-1-one (**31**) which was protected by reaction with ethylene glycol to form the 1,3-dioxolane, **32**. Alkylating 4-(4-chlorophenyl)piperazine with **32** and deprotecting the dioxolane resulted in the formation of the desired target compound **8** (Scheme 1).

Compound **9** was similarly obtained using the desfluoro starting material 4-chloro-1-(phenyl)butan-1-one. To obtain compound **10**, the indanone **31** was deoxygenated (**32**) under Clemmensen reaction conditions<sup>14</sup> and then used to alkylate 4-(4-chlorophenyl)piperazine (Scheme 1).

Compounds **11–14** and **16a–c** (Chart 3) were previously synthesized as a part of a drug design effort to obtain novel antipsychotic drugs.<sup>9</sup> In general, an appropriately substituted phenol or benzenethiol (**34**) was alkylated using 3-chloropropan-1-ol (**35**) and the resulting alcohol (**36**) was either tosylated or mesylated and then utilized in alkylating the heteroaryl piperazine (**A–C**) in Scheme 2. The synthesis of compounds **15–16** followed the same procedure reported in Scheme 2.

The syntheses of compounds **17–18** (Chart 4) were also previously reported.<sup>15</sup> To obtain the benzo[*d*]oxazole analogs, **19–22** (Chart 4, Scheme 3), 2-aminophenol was reacted with chloroalkanoyl alkyl halide (**39**) to form the amide intermediate (**40**) which was then cyclized using polyphosphoric acid (PPA) to obtain

2-(2-chloroalkyl)benzo[*d*]oxazole, **41**. Compound **41** was used to alkylate 4-chlorophenyl-1-piperazine to yield the desired target compounds **19–22**.

The synthesis of benzofuran moiety in analogs **23–26** (Chart 4), followed a literature procedure.<sup>16</sup> 2-lodophenol was reacted with an appropriate alkyl-1-yn-1-ol to form the corresponding benzofuran alkanol, which was subjected to a tosylation reaction and the resulting product was used to alkylate an appropriate aryl piperazine or a related analog to form the target compounds as shown in Scheme 4.

Finally, the synthesis of compound **28** (Chart 4) followed the synthetic procedure previously utilized in obtaining compound **27** (Chart 4) as shown in Scheme 5.<sup>15</sup> Briefly, 2-aminobenzenethiol (**46**) was reacted with 4-chlorobutanoyl chloride (**47**) to form 2-(3-chloropropyl)-benzo[*d*]thiazole, **48**, which was then used to alkylate 2-(piperazin-1-yl)pyrimidine to form the desired target compound, **28**.

### 3. Results and discussion

Cigarette smoking is associated with major diseases including cardiovascular problems, stroke and cancers of several organs. In fact, according to the CDC website, cigarette smoking harms nearly every organ of the body and affects a person's overall health.<sup>17</sup> Quitting smoking cuts down on all risks including, cardiovascular risks, stroke, and cancers of the lung, mouth, throat, esophagus and bladder.<sup>18</sup> Unfortunately, smoking cessation is difficult and often requires therapeutic interventions. And yet there have been articles suggesting significant risks associated with some of the current pharmacological interventions.<sup>19</sup> Thus, a search to find new agents that could help those addicted to cigarette smoking to quit the habit is an urgent and important public health need. Similarly, the discovery of the selective D4 agonist, PD 168,077 as having the capability of reversing cognitive deficits in schizophrenia<sup>9</sup> and inducing penile erection<sup>7</sup> and hence the potential to treat erectile dysfunction is very interesting and could provide an alternative treatment option in place of the PDE5 antagonists with several known side-effects.8



Chart 2. 4-Chlorophenyl piperazine analogs.



Scheme 1. Synthesis of 4-chlorophenylpiperazine analogs, 8–10. Reagents and conditions: (i) HMTA, Ac<sub>2</sub>O, reflux; (ii) concd H<sub>2</sub>SO<sub>4</sub>, 60 °C; (iii) (a) ethylene glycol, TsOH, reflux, 48 h; (b) NaBH<sub>4</sub>, MeOH; (iv) Zn/HgCl<sub>2</sub>, concd HCl, toluene; (v) Kl, K<sub>2</sub>CO<sub>3</sub>, DME, 90 °C, 4-(4-chlorophenyl)piperazine, 12 h; (vi) TsOH, MeOH, rt.



Chart 3. Heteroaryl piperazine analogs.



Scheme 2. Synthesis of heteroaryl piperazine analogs, 11–16. Reagents and conditions: (i) KI, K<sub>2</sub>CO<sub>3</sub>, *i*PrOH or DME, reflux; (ii) MsCl/TsCl, Et<sub>3</sub>N, DCM, rt; (iii) KI, K<sub>2</sub>CO<sub>3</sub>, DME, 90 °C, heteroaryl piperazine, 12 h.



Chart 4. Benzothiazole, benzoxazole and benzofuran analogs.



Scheme 3. Synthesis of benzoxazole derivatives, 19–22. Reagents and conditions: (i) EtOAc, TEA, reflux; (ii) PPA, 110 °C; (iii) CH<sub>3</sub>CN, K<sub>2</sub>CO<sub>3</sub>, KI, reflux.



Scheme 4. Synthesis of benzofuran analogs, 23–26. Reagents and conditions: (i) An appropriate alkyl-1-yn-1-ol, Cu<sub>2</sub>O, pyridine, 100 °C, 15 h (ii) tosylCl, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, overnight; (iii) NHR<sub>2</sub> [aryl piperazine or related analog], ACN, NEt<sub>3</sub>, 60 °C, reflux.



Scheme 5. Synthesis of benzothiazole analog, 28. Reagents and conditions: (i) Toluene, rt; (ii) KI, K2CO3, CH3CN, reflux.

Our laboratory's attention has been drawn to these DAD<sub>4</sub> receptor-mediated pathologies and that has spurred us to mine our databases for new pharmacophores for the D<sub>4</sub> receptor. Previous publications from our lab have identified compounds 1-7 as having low affinities for the D<sub>2</sub> receptor while exhibiting selectivity for the D<sub>4</sub> receptor among D<sub>2</sub>-like receptors. We have now screened these compounds at the D<sub>1</sub>-like receptors (Table 1) and the results further demonstrate that their selectivity extends beyond the D<sub>2</sub>-like receptors and hence we selected compound 1 as the lead agent to conduct a structure-activity relationship (SAR) study that has led to the identification of potent and selective D<sub>4</sub> ligands. Replacing the carbonyl moiety in compound **1** with a sulfoxide (2), methylene (3), sulfur (4) or oxygen (5) group/atom resulted in increasing potency at the  $D_4$  receptor with  $K_i$  values from 17.5 to 6.9 nM, respectively while binding at other DA receptors showed no observable trends. The sulfoxide analog resulted in the lowest affinity binding at the rest of the DA receptors while its reduced counterpart, the sulfide (4) had moderate binding except at the  $D_1$  receptor where its affinity binding  $K_i$  was 52 nM.

Overall, these compounds have demonstrated better selectivity toward the  $D_4$  receptor when compared to compound **1**. In particular, compound **5**, the oxygen analog, not only had the best binding at the  $D_4$  receptor, but demonstrated the highest selectivity among compounds **1–5**. Further probing of the oxygen analog revealed that removing the *para* fluoro atom (**6**) has little or no contribution to binding to the  $D_2$ -like receptors while replacement of N-4 in the piperazine ring with CH (**7**) resulted in a very significant increase in potency for the  $D_2$  receptor with only minimal changes elsewhere. Compound **8** was designed and synthesized to explore the effect of restricting the carbonyl group in an indanone ring, on binding affinity and selectivity. Indeed, this transformation resulted in one of the highest selectivities toward the  $D_4$  receptor; the ratios for the  $D_2/D_4$  and  $D_3/D_4$  being 253 and 406, respectively. Synthesis of **9**, an analog of **8** but without the fluorine atom resulted in a significant decrease in binding at all the DA subtypes including the  $D_4$  suggesting the fluorine may have some important interaction at the binding sites for these indanones. Deoxygenation of the carbonyl to form compound **10** however, produced only minimal changes.

The next evaluations focused on the replacement of the 4-chlorophenyl moiety. Our previous work indicated that pyridine and pyrimidine rings impacted binding to CNS receptors.<sup>9–12</sup> Hence, we first explored replacing the 4-chlorophenyl moiety with the pyridine ring in compounds 3-5 to obtain compounds 11-13 (Chart 2) and the binding affinities are reported in Table 2. Compounds 11-13 bind with very high affinities at D<sub>4</sub> versus D<sub>1</sub>-D<sub>3</sub> receptors, and therefore demonstrate decreased selectivity for the D<sub>4</sub> receptor. Compound 14, an analog of 13 with the fluorine atom replaced with a trifluoromethyl group, displayed significantly lower binding affinities for all DA receptors suggesting either a steric limitation or deleterious electron withdrawing effect or both. Replacement of the pyridine ring with 5-methyl substituted pyridine for the trio (11-13) to form compounds 15a-c were also evaluated. Interestingly, compound 15a with the oxygen linker resulted in the most potent analog for the D<sub>4</sub> receptor ( $K_i = 1.1 \text{ nM}$ ) among the 17 compounds evaluated thus far. In addition, it also displayed the highest selectivity for the D<sub>4</sub> receptor when compared with the D<sub>2</sub> receptor. Not surprisingly, compounds **15b** and 15c, the sulfur and carbon analogs, respectively, have reduced binding for the D<sub>4</sub> receptor but retain similar affinities for the  $D_1 - D_3$  receptors.

Finally in this series, compounds **16a–c**, the pyrimidine analogs of **11–13** were synthesized and evaluated. Once again the oxygen analog **16a** displayed the highest potency and selectivity for the  $D_4R$  among the three analogs. The carbon analog (**16c**) had a similar binding profile at the DA subtypes as **16a** although its

Table 1

Evaluation of binding	affinities of 4-chloro	phenyl analogs	(Chart 2)	at the do	pamine rece	ptor subtypes
		F	()			F

Compd	$K_i$ (p $K_i$ ) ± SEM values in nM at the dopamine receptor subtypes									
	D <sub>1</sub>	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>	D <sub>5</sub>	$D_2/D_4$	$D_3/D_4$			
1	ND	253.3 ± 38.9	403.9 ± 66	17.5 ± 2.0	ND	14.5	23.1			
2	MT	635 (6.2 ± 0.05)	1340 (5.87 ± 0.06)	13 (7.89 ± 0.05)	MT	48.8	103			
3	589 ± 56	284 ± 21	261 ± 23	7.8 ± 0.4	1758 ± 212	36.4	33.5			
4	52 ± 3	211 ± 22	422 ± 41	8.7 ± 0.5	2808 ± 325	24.3	48.5			
5	135 ± 8	390 ± 34	885 ± 65	$6.9 \pm 0.3$	2684 ± 223	56.5	128			
6	ND	447 (6.35 ± 0.07)	726 (6.1 ± 0.1)	5.6 (8.26 ± 0.03)	ND	79.8	130			
7	126 ± 9	$41.0 \pm 4.0$	696 ± 50.0	9.5 ± 0.3	867 ± 49	4.3	73.3			
8	641 (6.19 ± 0.06)	1543 (5.81 ± 0.08)	2477 (5.6 ± 0.1)	6.1 (8.21 ± 0.05)	MT	253	406			
9	1701 (6.41 ± 0.07)	>10,000	4534 (5.34 ± 0.08)	36.0 (7.45 ± 0.04)	MT	>277	126			
10	837 ± 92	1417 ± 138	2772 ± 271	$13.0 \pm 1.0$	MT	109	213			

MT = missed primary assay threshold of 50% inhibition; ND = not determined.

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Table 2
Evaluation of the binding affinities of heteroaryl piperazine analogs (Chart 3) at the DAR subtypes

Compd	$K_i$ (pK <sub>i</sub> ) ± SEM values in nM at the dopamine receptor subtypes									
	D <sub>1</sub>	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>	D <sub>5</sub>	$D_2/D_4$	$D_3/D_4$			
11	238 ± 24.0	124 ± 10.0	86 ± 4.0	3.5 ± 0.2	1451 ± 133	35.4	24.6			
12	265 ± 24.0	183 ± 21.0	$160 \pm 16.0$	5.7 ± 0.3	3223 ± 295	32.1	28.1			
13	180 ± 14.0	186 ± 16.0	$229 \pm 20.0$	$1.8 \pm 0.1$	2392 ± 252	103	127			
14	2344 (5.63 ± 0.09)	1092 (5.96 ± 0.09)	355 (6.45 ± 0.05)	12 (7.9 ± 0.1)	>10,000	91.0	29.6			
15a	260 (6.58 ± 0.07)	1046 (5.98 ± 0.07)	$187(6.7 \pm 0.1)$	$1.1 (8.96 \pm 0.08)$	2576 (5.6 ± 0.1)	951	170			
15b	222 (6.65 ± 0.07)	$1106(6 \pm 0.1)$	$170(6.8 \pm 0.1)$	20.0 (7.71 ± 0.06)	2159 (5.7 ± 0.1)	55.3	8.5			
15c	521 (6.28 ± 0.08)	1861 (5.7 ± 0.1)	156 (6.8 ± 0.1)	23.0 (7.64 ± 0.06)	3264 (5.5 ± 0.1)	80.9	6.8			
16a	259 ± 12.0	636 ± 66.0	778 ± 63.0	$4.2 \pm 0.1$	MT	151	185			
16b	495 ± 33.0	424 ± 25.0	$68.0 \pm 10.0$	$21.0 \pm 1.0$	1370 ± 114	20.1	3.2			
16c	$134 \pm 7.0$	$269 \pm 17.0$	$262 \pm 17.0$	$6.2 \pm 0.3$	$3812 \pm 409$	43.4	42.3			

MT = missed primary assay threshold of 50% inhibition; ND = not determined.

selectivity for the D<sub>4</sub>R is much lower. Meanwhile, the sulfur analog **16b** again demonstrated a 5-fold lower affinity for the D<sub>4</sub>R compared to **16a**. These evaluations have clearly demonstrated that the oxygen analogs have the highest potencies for the D<sub>4</sub>R within each cohort evaluated. Comparing the pyridine and pyrimidine analogs in this series, the pyridine analogs overall, demonstrated moderate enhancement in binding affinity at the D<sub>4</sub>R than the pyrimidine analogs. In addition, among the twenty compounds evaluated, none has a better binding affinity for the D<sub>5</sub> receptor than compound **7** with a  $K_i$  of 867 nM. In other words, the compounds have little or no affinity for the D<sub>5</sub>R.

The last group of compounds evaluated is **17–28** (Chart 4), which may be considered as the hetero-bicyclic analogs of the compounds in Charts 2 and 3, with binding affinities reported in Table 3. Compound **17** and **18** are benzothiazole analogs which were previously synthesized and evaluated for binding to the  $D_2$ -like receptors.<sup>15</sup> In this paper, their binding affinities to the  $D_1$ -like receptors were evaluated and the results are reported. The results suggest that a chain length of 4 (**17**) produced a more potent agent at the  $D_4R$  than a chain length of 3 (**18**). The selectivities of both compounds for the  $D_4R$  were unremarkable.

Next, we synthesized and evaluated the benzoxazole analogs, **19–22**, by systematically modifying the chain length from 5 to 2, respectively. A chain length of five atoms (**19**) produced a weak binding affinity at the D<sub>4</sub>R ( $K_i$  = 240 nM) while **20**, with a chain length of 4 atoms produced an 8-fold increase in binding to the D<sub>4</sub> receptor ( $K_i$  = 30.6 nM), thus suggesting a chain length of 4 is preferred. Compound **20** however, has similar affinity for the D<sub>3</sub>R

 $(K_i = 33 \text{ nM})$  resulting in loss of selectivity. Further comparison of this benzothiazole, **20** with the benzoxazole, **17** shows over 7-fold differential, suggesting the benzothiazole ring with a 4-methylene chain is preferred at the D<sub>4</sub>R. There is however no preference at the D<sub>3</sub> receptor since they (**17** & **20**) have similar binding affinities. Compounds **21** and **22**, benzoxazoles with a chain length of 3 and 2, respectively, resulted in compounds with only moderate to very weak binding affinities at all the DA receptors.

We also synthesized and evaluated compounds obtained by replacement of the benzoxazole with a benzofuran, (Chart 4), **23–26**, of which **24** may be considered as a restricted analog of the straight chain ether analog in Chart 2. The results indicated that while somewhat selective for the  $D_4$  receptor, the 2 carbon chain analog (**23**) and the 3-chain analog (**24**) have weaker binding affinities for the  $D_4$  receptor. Replacement of the piperazine ring with its bridged counterpart (**25**) and with a homopiperazine (**26**) did not improve potency or selectivity.

Returning to the benzothiazoles, we further explored replacement of the 4-chlorophenyl moiety with 2-(piperazin-1-yl) pyrimidine to obtain the 4-chain (**27**) and 3-chain (**28**) analogs. Compound **27** was the most potent D<sub>4</sub> ligand in this study ( $K_i = 0.84 \text{ nM}$ ) as previously reported<sup>15</sup> albeit with diminished selectivity, while **28** has high potency ( $K_i = 3.9 \text{ nM}$ ) and is by far the most selective analog at the D<sub>4</sub> receptor when compared with other dopamine subtypes. Taking their binding constants at face value, compound **28** is as potent but more selective than FAUC 113, a previously reported D<sub>4</sub> ligand (Chart 1).<sup>20</sup> In addition, while not as potent as L-745,860,<sup>21</sup> compound **28** is also more selective

Table	e 3
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Evaluation of the binding affinities of benzothiazole, be	enzoxazole and benzofuran analogs (Chart 4) at the DAR subtypes
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Compd	$K_i$ (p $K_i$ ) ± SEM values in nM at the dopamine receptor subtypes						
	D <sub>1</sub>	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>	D <sub>5</sub>	$D_2/D_4$	$D_3/D_4$
17	1897 ± 364	219 ± 12.0	31 ± 4.0	$4.0 \pm 0.0$	ND	54.8	7.8
18	1273 ± 123	2321 ± 314	$214 \pm 47$	31 ± 40	>10,000	74.9	6.9
19	7939 ± 592	3108 ± 1071	119 ± 25	240 ± 36.8	>10,000	13.0	0.5
20	MT	MT	33 ± 6	30.6 ± 6.3	MT	>327	1.1
21	1172 ± 76	3962 ± 501	180 ± 31	145 ± 18	>10,000	27.3	1.5
22	MT	MT	850 ± 126	1409 ± 227	MT	>7.1	0.6
23	MT	MT	MT	282.9	MT	>35.5-	>35.5
24	$1408 \pm 242$	1979 ± 291	2290 ± 423	78.9 ± 5.7	MT	25.1	29.0
25	MT	MT	670.7 ± 118.4	2397 ± 294	MT	>4.2-	0.3
26	$274 \pm 24$	2507 ± 208	1462 ± 133	185 ± 11	1522 ± 191	13.5	7.9
27	MT	$26.5 \pm 4.5$	100 (7 ± 0.06)	$0.84 \pm 0.09$	MT	31.5	119
28	MT	MT	MT	3.9 (8.41 ± 0.04)	MT	>2564	>2564
FAC 113 <sup>a</sup>	ND	3200 ± 58	5000 ± 121	3.1 ± 0.3	ND		
L-745870 <sup>b</sup>	ND	960	2300	0.43	ND		

MT = missed primary assay threshold of 50% inhibition; ND = not determined.

<sup>a</sup> Ref. 20. <sup>b</sup> Ref. 21. for the  $D_4$  receptor among the  $D_2$ -like receptors. To determine the extent of compound **28**'s selectivity, we screened its binding affinities at several other CNS receptors and the results are reported in Table 4.

Screening experiments involving a total of 18 other receptors indicated that apart from the 5HT1A and 5HT2B receptors, where binding affinities were below 100 nM ( $K_i < 100$  nM), compound **28** exhibited significantly poorer affinities for the remainder of the assayed receptors. The above results strongly suggest that compound **28** can be a potentially useful D<sub>4</sub>-selective ligand for probing D<sub>4</sub>R related pathophysiological conditions including smoking cessation, erectile dysfunction and reversal of cognitive deficits in schizophrenia depending on the intrinsic activity.

### 3.1. Conclusions

This study was initiated to identify selective DAD<sub>4</sub> receptor ligands. The results confirm the piperazine ring as a reliable pharmacophore impacting potency and selectivity for the  $D_4$  receptor. Of the 25 piperazine derivatives evaluated, all displayed higher potencies at the D<sub>4</sub> than at the D<sub>2</sub> receptors. Compound 27  $(K_i = 0.84 \text{ nM})$  has the highest potency at the D<sub>4</sub> receptor but displays only moderate selectivity compared to the other DA subtypes. The most significant finding however is the identification of a novel benzothiazole alkyl piperazine, compound 28, with a binding affinity constant (K<sub>i</sub>) of 3.9 nM and no significant binding affinity to any of the other DA receptor subtypes (less than 50% inhibition of the appropriate radioligand at each of the other DA subtypes). In addition, compound 28 has only weak to moderate affinities for eighteen other CNS receptors. These results warrant a more elaborate pharmacological profiling, including functional characterization, which is the focus of our current ongoing studies.

### 4. Experimental

Melting points were determined on a Gallenkamp (UK) apparatus and are uncorrected. All NMR spectra were obtained on a Varian 300 MHz Mercury Spectrometer. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA, and are within 0.4% of theory unless otherwise noted. Flash chromatography was performed with Davisil grade 634 silica gel. Starting materials were obtained from Sigma–Aldrich and were used without further purification.

### 4.1. Synthetic procedure

### 4.1.1. Synthesis of 2-(2-chloroethyl)-5-fluoro-indan-1-one, 31

A mixture of 4-chloro-1-(4-fluorophenyl)-butan-1-one, **29** (10 g, 50 mmol), hexamethylenetriamine (10.5 g, 75 mmol) in Ac<sub>2</sub>O (25 mL) was refluxed under N<sub>2</sub> for 16 h. After cooling to rt, the mixture was diluted with CHCl<sub>3</sub> (500 mL) and then washed with HCl solution (10%,  $2 \times 300$  mL), H<sub>2</sub>O (300 mL), and sat NaHCO<sub>3</sub> (300 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated in vacuo, followed by column chromatography on silica gel to afford 4-chloro-1-(4-fluoro-phenyl)-2-methylene-butan-1-one, **30** (2.8 g, 26.4%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):

 $\delta$  7.82 (dd, *J* = 9.0, 5.7 Hz, 2H), 7.13 (t, *J* = 9.0 Hz, 2H), 5.99 (s, 1H), 5.73 (s, 1H), 3.72 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H).

Compound **30** (1.2 g, mmol) was dissolved in concd H<sub>2</sub>SO<sub>4</sub> (4 mL) and heated at 60 °C for 1 h. After cooling to rt, the mixture was diluted with EtOAc (200 mL) and washed with sat'd NaHCO<sub>3</sub> (2 × 200 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated under vacuum followed by column chromatography on silica gel to afford 2-(2-chloro-ethyl)-5-fluoro-indan-1-one, **31** in quantitative yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.76 (dd, *J* = 8.4, 5.4 Hz, 1H), 7.05–7.14 (m, 2H), 3.80–3.86 (m, 1H), 3.68–3.78 (m, 1H), 3.42 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.90–2.98 (m, 1H), 2.83 (dd, *J* = 17.1, 4.2 Hz, 1H), 2.38–2.49 (m, 1H), 1.86–1.98 (m, 1H).

### 4.1.2. 2'-(2-Chloroethyl)-5'-fluoro-2',3'-

### dihydrospiro[[1,3]dioxolane-2,1'-indene], 33

A solution of 2-(2-chloro-ethyl)-5-fluoro-indan-1-one (5 g. 23.5 mmol), ethylene glycol (5 mL), TsOH (100 mg) in toluene (50 mL) was refluxed under N<sub>2</sub> for 48 h. Water was removed by azeotropic distillation and the reaction was monitored by <sup>1</sup>H NMR. The reaction was quenched by addition of Et<sub>3</sub>N (1 mL), diluted with EtOAc (250 mL), washed with sat NaHCO<sub>3</sub>, (25 mL), H<sub>2</sub>O (25 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated in under vacuum to dryness yielding a mixture of 2-(2-chloro-ethyl)-5-fluoro-indan-1-one and its ethylene acetal in a ratio of 1/4. 2-(2-chloroethyl)-5-fluoro-indan-1-one was removed by reducing to its 2-(2-chloro-ethyl)-5-fluoro-indan-1-ol with NaBH<sub>4</sub> in MeOH, followed by column chromatography on silica gel which afforded 2'-(2-chloroethyl)-5'-fluoro-2',3'-dihydrospiro[[1,3]dioxolane-2,1'-indene] **33** (4.5 g, 75%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.24-7.28 (m, 1H), 6.89-6.96 (m, 2H), 4.22-4.28 (m, 1H), 4.07-4.16 (m, 3H), 3.70-3.74 (m, 1H), 3.62-3.68 (m, 1H), 3.55-3.61 (m, 1H), 3.07 (dd, J = 14.7, 6.6 Hz, 1H), 2.71–2.75 (m, 1H), 2.60– 2.68 (m, 1H), 2.11-2.20 (m, 1H), 1.91-2.00 (m, 1H).

### 4.1.3. 2-(2-(4-(4-Chlorophenyl)piperazin-1-yl)ethyl)-5-fluoroindan-1-one hydrochloride, 8

A mixture of **33** (1.2 g. 4.67 mmol), 1-(4-chlorophenyl)piperazine dihydrochloride (1.3 g, 5.6 mmol), KI (100 mg), K<sub>2</sub>CO<sub>3</sub> (1.2 g, 8.75 mmol) in DME (10 mL) was heated to reflux under N<sub>2</sub> for 12 h. The mixture was directly purified through column chromatography on silica gel to afford 2-{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethyl}-5-fluoro-indan-1-one ethylene acetal. The product was dissolved in wet MeOH and TsOH was added with stirring at rt. After stirring at rt for 12 h, the solution was diluted with EtOAc (450 mL) and washed with saturated NaHCO3 (40 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated in vacuo to dryness and column chromatographed on silica gel to give 2-{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethyl}-5-fluoro-indan-1-one, 8. The product was converted to the hydrochloride salt and further crystallization from MeOH-Et<sub>2</sub>O afforded the HCl salt (450 mg, yield 28%), mp 202-203 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.15 (br s, 1H), 7.72 (dd, J = 8.7, 4.5 Hz, 1H), 7.44 (d, J = 9.0 Hz, 1H), 7.24–7.28 (m, 3H), 7.00 (d, J = 9.0 Hz, 2H), 3.77-3.80 (m, 2H), 3.53-3.56 (m, 2H), 3.28-3.36 (m, 2H), 3.12-3.22 (m, 4H), 2.81-2.90 (m, 2H),

### Table 4

Binding affinity at other relevant CNS receptors,  $K_i$  in nM (p $K_i$ ) ± SEM

Compd	5HT <sub>1A</sub>	5HT <sub>2A</sub>	5HT <sub>2B</sub>		5HT	2C		5HT₃	5HT <sub>6</sub>	5HT <sub>7</sub>	H <sub>1</sub>
28	40.0 (7.39 ± 0.04)	283 (6.55 ± 0.03	3) 47.0 (7.33 ±	0.05)	280	(6.55±0	0.04)	MT	MT	342 (6.47 ± 0.06)	730 (6.14 ± 0.06)
Compd	$\alpha_{1A}$	$\alpha_{2A}$	$\alpha_{2C}$	$M_1$	$M_3$	DAT	NET		SERT	Sigma 1	Sigma 2
28	$259(6.59 \pm 0.08)$	844 (6.07 ± 0.04)	126 (6.9 ± 0.04)	MT	MT	MT	2773	(5.56 ± 0.06)	) MT	350 (6.46 ± 0.05)	162 (6.79 ± 0.08)

MT = missed primary assay threshold of 50% inhibition.

2.22–2.78 (m, 1H), 1.84–1.96 (m, 2H). Calcd for  $C_{21}H_{23}Cl_2FN_2O$ : C 61.62, H 5.66, N 6.84. Found: C 61.38, H 5.58, N 6.77.

### 4.1.4. 2-(2-Chloroethyl)-indan-1-one

A mixture of 4-chloro-1-phenyl-butan-1-one (10 g, 54 mmol), hexamethylene triamine (10.5 g, 75 mmol) in Ac<sub>2</sub>O (25 mL) was refluxed under N<sub>2</sub> for 18 h. After cooling to rt, the mixture was diluted with CHCl<sub>3</sub> (500 mL) and then washed with HCl solution (10%,  $2 \times 300$  mL), H<sub>2</sub>O (300 mL), and saturated aq NaHCO<sub>3</sub> (300 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford 4chloro-2-methylene-1-phenyl-butan-1-one (2.8 g, 26%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.75–7.78 (m, 2H), 7.52–7.56 (m, 1H), 7.42–7.47 (m, 2H), 6.01 (s, 1H), 5.78 (s, 1H), 3.73 (t, J=6.6 Hz, 2H), 2.95 (t, I = 6.6 Hz. 2H). The 4-chloro-2-methylene-1-phenyl-butan-1-one (1.2 g, 6.15 mmol) was dissolved in concd H<sub>2</sub>SO<sub>4</sub> (4 mL) and heated at 60 °C for 1 h. The mixture was allowed to cool to rt, diluted with EtOAc (200 mL), washed with saturated aq NaHCO<sub>3</sub> ( $2 \times 200$  mL) and dried over Na2SO4. The solution was filtered, solvent was removed in vacuo and the residue was purified by column chromatography on silica gel to afford 2-(2-chloro-ethyl)-indan-1-one in quantitative yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.75 (d, *J* = 7.5 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.45–7.48 (m, 1H,), 7.38 (t, J = 7.2 Hz, 1H), 3.75-3.86 (m, 1H), 3.68-3.74 (m, 1H), 3.39-3.47 (m, 1H), 2.89-2.94 (m, 1H), 2.80-2.88 (m, 1H), 2.38-2.47 (m, 1H), 1.88-1.96 (m, 1H).

### 4.1.5. 2-{2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-ethyl}-indan-1-one tosylate, 9

A solution of 2-(2-chloro-ethyl)-indan-1-one (5 g, 25.6 mmol), ethylene glycol (5 mL), p-toluene sulfonic acid (TsOH, 100 mg) in toluene (50 mL) was refluxed under  $N_2$  for 48 h and water was removed by azeotropic distillation. The reaction was monitored by <sup>1</sup>H NMR until a conversion of 80% was achieved. The reaction was quenched by the addition of Et<sub>3</sub>N (1 mL), diluted with EtOAc (250 mL), washed with saturated aq NaHCO<sub>3</sub>, (25 mL) and H<sub>2</sub>O (25 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated in vacuo to dryness to afford a mixture of 2-(2-chloro-ethyl)-indan-1-one and its ethylene acetal in a ratio of 1/4. 2-(2-Chloroethyl)-indan-1-one was removed by reducing to its 2-(2-chloro-ethyl)-indan-1-ol with NaBH<sub>4</sub> in MeOH, followed by column chromatography on silica gel to afford 2-(2chloro-ethyl)-indan-1-one ethylene acetal (4.4 g, 72%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.20–7.32 (m, 4H), 4.28–4.31 (m, 1H), 4.08–4.19 (m, 3H), 3.65–3.74 (m, 1H), 3.52–3.63 (m, 1H), 3.04–3.15 (m, 1H), 2.62-2.74 (m, 2H), 2.12-2.24 (m, 1H), 1.92-2.05 (m, 1H). A mixture of 2-(2-chloroethyl)indan-1-one ethylene acetal (1.0 g, 4.18 mmol), 1-(4-chlorophenyl)-piperazine dihydrochloride (1.4 g, 5.19 mmol), KI (100 mg), K<sub>2</sub>CO<sub>3</sub> (1.2 g, 8.75 mmol) in DME (10 mL) was heated to reflux under N<sub>2</sub> for 12 h. The mixture was allowed to cool to rt and then directly purified through column chromatography on silica gel to afford an oily residue. Without characterization, the product was dissolved in MeOH and p-toluene sulfonic acid (800 mg) was added with stirring at rt. After stirring for 12 h, the solution was diluted with EtOAc (450 mL) and washed with sat NaHCO3 (40 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated in vacuo to dryness. The resulting residue was purified by column chromatography on silica gel to afford 2-{2-[4-(4-chlorophenyl)-piperazin-1-yl]-ethyl}indan-1-one. The product was converted to *p*-toluenesulfonate and crystallized in MeOH-Et<sub>2</sub>O to afford the *p*-toluenesulfonate salt, 9 (610 mg, 28%). Mp 215-216 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 9.57 (br s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 9.0 Hz, 2H), 3.80–3.85 (m, 2H), 3.58–3.62 (m, 2H), 3.25–3.39 (m, 2H), 3.11–3.21 (m, 2H), 2.92–3.00 (m, 2H), 2.80–2.87 (m, 1H), 2.72–2.77 (m, 1H), 2.24 (s, 3H), 2.16–2.22 (m, 1H), 1.84–1.93 (m, 1H). Calcd for  $C_{28}H_{31}ClN_2O_4S.0.8H_2O$ : C 62.11, H 6.07, N 5.17. Found: C 62.09, H 6.06, N 5.08.

### 4.1.6. 2-(2-Chloroethyl)-5-fluoroindane, 32

Amalgamated zinc is prepared by stirring a mixture of zinc (1.2 g), HgCl<sub>2</sub> (120 mg) in H<sub>2</sub>O (5 mL) with concd HCl (0.1 mL) at rt. After stirring for 5 min, the mixture was decanted, followed by the addition of H<sub>2</sub>O (1 mL), concd HCl (1.75 mL), toluene (10 mL), and 2-(2-chloroethyl)-5-fluoro-indan-1-one, **31** (2.0 g, 9.43 mmol). The mixture was refluxed with stirring for 12 h, allowed to cool to rt and the solid was filtered off. The collected filtrate was diluted with EtOAc (200 mL), separated and the organic layer was washed with H<sub>2</sub>O (50 mL) and saturated aq NaHCO<sub>3</sub> (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated under vacuum. The resulting residue was purified by column chromatography on silica gel to afford **32** (1.68 g, 90%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.09 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.81–6.88 (m, 2H), 3.60 (t, *J* = 7.2 Hz, 2H), 3.00–3.08 (m, 2H), 2.68–2.73 (m, 1H), 2.54–2.63 (m, 2H), 1.94–2.02 (m, 2H).

## 4.1.7. 1-(4-Chlorophenyl)-4-(2-(5-fluoro-2,3-dihydro-1*H*-inden-2-yl)ethyl)piperazine dihydrochloride, 10

A mixture of **32** (0.8 g, 4.0 mmol), 1-(4-chlorophenyl)piperazine dihydrochloride (1 g, 4.3 mmol), KI (150 mg),  $K_2CO_3$  (1.2 g, 8.7 mmol) in DME (10 mL) was heated to reflux under N<sub>2</sub> for 12 h. The mixture was directly purified through column chromatography on silica gel to afford 1-(4-chloro-phenyl)-4-[2-(5-fluoro-indan-2-yl)-ethyl]-piperazine, **9**. The product was converted to the hydrochloride salt immediately and then recrystallized from MeOH–Et<sub>2</sub>O (0.78 g, 45%), mp 194–196 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 11.00 (br s, 1H), 7.26 (d, *J* = 9.0 Hz, 2H), 7.17 (dd, *J* = 5.7, 8.1 Hz, 1H), 6.99 (m, 3H), 6.90 (dt, *J* = 2.4, 8.4 Hz, 1H), 3.77 (d, *J* = 11.1 Hz, 2H), 3.53 (d, *J* = 11.1 Hz, 2H), 3.07–3.19 (m, 6H), 2.96–3.05 (m, 4H), 2.45–2.60 (m,1H), 1.88–1.96 (m, 2H). Calcd for C<sub>21-</sub>H<sub>26</sub>Cl<sub>3</sub>FN<sub>2</sub>: C 58.41, H 6.07, N 6.49. Found: C 58.56, H 6.01, N 6.49.

### 4.1.8. 3-(4-Fluorophenoxy)propan-1-ol, 36a

A mixture of 4-fluorophenol (1.12g, 10 mmol), 3-chloropropanol (1.4 g, 15 mmol), KI (50 mg),  $K_2CO_3$  (2.76 g, 20 mmol) in <sup>*i*</sup>PrOH was refluxed under N<sub>2</sub> for 1h. The mixture was diluted with EtOAc (200 mL), washed with H<sub>2</sub>O (50 mL) and then brine (50 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated in vacuo, followed by distillation in vacuo to give the intermediate, 3-(4-fluorophenoxy)propan-1-ol, **36a** (1.53 g, 90%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  6.96 (t, *J* = 8.4 Hz, 2H), 6.84 (dd, *J* = 9.0, 4.5 Hz, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.84–3.87 (m, 2H), 1.99–2.07 (m, 2H).

### 4.1.9. 3-(4-Fluorophenoxy)propyl methanesulfonate, 37a

To a solution of **36a** (1.3 g, 7.6 mmol), Et<sub>3</sub>N (3 mL) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added at rt MsCl (0.8 mL, 10.3 mmol). The mixture was stirred at rt for 12 h, solvent was removed and the residue was purified through column chromatography on silica gel, to yield 3-(4-fluorophenoxy)propyl methanesulfonate, **37a** (1.79 g, 95%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  6.97 (t, *J* = 8.1 Hz, 2H), 6.83 (dd, *J* = 9.0, 4.5 Hz, 2H), 4.44 (t, *J* = 6.0 Hz, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 2.18–2.23 (m, 2H).

### 4.1.10. 3-((4-Fluorophenyl)thio)propan-1-ol, 36b

A mixture of 4-fluorobenzenthiol (1.55 g, 12.1 mmol), 3-chloropropanol (2.26 g, 27.65 mmol), KI (100 mg),  $K_2CO_3$  (3.3 g, 23.9 mmol) in <sup>i</sup>PrOH (10 mL) was refluxed under N<sub>2</sub> for 1h. The mixture was diluted with EtOAc (200 mL), and washed with water (50 mL), brine (50 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated in vacuo, and followed by distillation in vacuo to give product 3-(4-fluorophenylthio)propan-1-ol, **36b** (1.62 g, 72%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.35 (dd, *J* = 8.4, 5.4 Hz, 2H), 6.99 (t, *J* = 8.4 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 7.2 Hz, 2H), 1.80–1.89 (m, 2H).

### 4.1.11. 3-(4-Fluorophenylthio)propyl-4methylbenzenesulfonate, 37b

To a solution of 3-(4-fluorophenyl-thio)-propan-1-ol (1 g, 5.4 mmol), Et<sub>3</sub>N (2 mL)in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added at rt TsCl (1.54 g, 8.1 mmol). The mixture was stirred at room temperature for 12 h, and then followed by directly purification through column chromatography on silica gel, and provided 3-(4-fluorophenyl-thio)propyl 4-methylbenzenesulfonate (1.72 g, 94%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.77 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.30 (dd, *J* = 5.4, 8.4 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.13 (t, *J* = 8.0 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 1.85–1.92 (m, 2H).

### 4.1.12. 3-(4-Fluorophenylthio)propyl methanesulfonate, 37c

To a solution of 3-(4-fluorophenylthio)propan-1-ol (1.2 g, 6.45 mmol), Et<sub>3</sub>N (3 mL) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added at rt MsCl (1 mL, 12.7 mmol). The mixture was stirred at room temperature for 12 h, and then followed by directly purification through column chromatography on silica gel, and provided 3-(4-fluorophenyl-thio)propyl methanesulfonate (1.60 g, 94%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.37 (dd, *J* = 9.0, 4.8 Hz, 2H), 7.00 (t, *J* = 9.0 Hz, 2H), 4.30 (t, *J* = 8.0 Hz, 2H), 3.00 (s, 3H), 2.78 (t, *J* = 7.2 Hz, 2H), 1.99–2.04 (m, 2H).

### 4.1.13. General procedure of alkylation of arylpiperazines, 15a–c

A mixture of aryl piperazines (0.4 mmol, 1 equiv) and  $K_2CO_3$  (4 mmol, 4 equiv) was stirred and refluxed for 20 min in CH<sub>3</sub>CN (10 mL). To the mixture, a solution of substituted tosylsulfonates/ mesylates/chlorides (0.53 mmol, 1.3 equiv) in CH<sub>3</sub>CN (5 mL) was added drop wise. The reaction mixture was refluxed overnight, diluted with EtOAc (100 mL), filtered and washed with brine. The organic layer was collected, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and the solvent was evaporated. The residue obtained was chromatographed on a silica gel column using hexane and EtOAc combinations as eluent. The final compounds were obtained in moderate yields, converted to HCl salts where necessary and re-crystallized using appropriate solvents.

# 4.1.14. 1-(3-(4-Fluorophenoxy)propyl)-4-(5-methylpyridin-2-yl)piperazine, 15a

Yield 30%, mp 79.6 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.02 (s, 1H), 7.32 (dd, *J* = 8.7, 2.4 Hz, 1H,), 6.99–6.93 (m, 2H), 6.85–6.81 (m, 2H), 6.59 (d, *J* = 8.7 Hz, 1H,), 4.00 (t, *J* = 6.6 Hz, 2H,), 3.52–3.48 (m, 4H), 2.61– 2.55 (m, 6H), 2.19 (s, 3H), 2.05–1.96 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$ 158.74, 158.03, 155.59, 155.07, 155.04, 147.67, 138.41, 122.45, 115.90, 115.60, 115.46, 115.35, 107.03, 66.75, 55.23, 53.04, 45.60, 26.65, 17.34. Calcd for C<sub>19</sub>H<sub>24</sub>FN<sub>3</sub>O: C 69.28, H 7.34, N 12.76. Found: C 69.47, H 7.30, N 12.50.

# 4.1.15. 1-(3-((4-Fluorophenyl)thio)propyl)-4-(5-methylpyridin-2-yl)piperazine, 15b

Yield 62%, mp 85.5 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.00 (d, J = 2.4 Hz, 1H,), 7.37–7.29 (m, 3H), 7.01–6.96 (m, 2H), 6.58 (d, J = 8.7 Hz, 1H), 3.48–3.45 (m, 4H), 2.92 (t, J = 7.5 Hz, 2H), 2.54–2.46 (m, 6H), 2.18 (s, 3H), 1.86–1.77 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  163.32, 160.06, 158.04, 147.65, 138.40, 132.20, 132.09, 122.41, 116.14, 115.85, 107.01, 105.00, 57.12, 53.01, 45.62, 32.86, 26.39, 17.34. Calcd for C<sub>19</sub>H<sub>24</sub>FN<sub>3</sub>S: C 66.05, H 7.00, N 12.16. Found: C 66.06, H 7.03, N 12.13.

### 4.1.16. 1-(4-(4-Fluorophenyl)butyl)-4-(5-methylpyridin-2-yl)piperazine, 15c

Yield 22%, mp 74 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.01 (d, *J* = 2.7 Hz, 1H,), 7.29 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.14–7.09 (m, 2H), 6.98–6.92 (m, 2H), 6.58 (d, *J* = 8.7 Hz, 1H), 3.50–3.46 (m, 4H), 2.63–2.52 (m, 6H), 2.42–2.37 (m, 2H), 2.18 (s, 3H), 1.68–1.50 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  162.78, 159.56, 158.11, 147.67, 138.39, 137.97, 137.93, 129.72, 129.62, 122.37, 115.12, 114.84, 106.99, 58.59, 53.09, 45.65, 34.98, 29.51, 26.34, 17.35. Calcd for C<sub>20</sub>H<sub>26</sub>FN<sub>3</sub>: C 73.36, H 8.00, N 12.83. Found: C 73.79, H 8.28, N 12.47.

# 4.1.17. General Procedure for the synthesis of *n*-chloro-*N*-(2-hydroxy-phenyl)alkylamide, 40, (n = 2-5)

For n = 2, a solution of 2-aminophenol (1.0 g, 9.16 mmol), 3chloropropionylchloride, (1.39 g, 11 mmol, 1.2 equiv) and Et<sub>3</sub>N (1.12 g, 11 mmol, 1.2 equiv) in EtOAc (25 mL) was heated to reflux for 6–10 h. After allowing to cool to rt, EtOAc (100 mL) was added and the solution was washed once with 10% HCl (100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic layers was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated by rotary evaporation under reduced pressure. The pure product, 3-chloro-*N*-(2-hydroxyphenyl)propanamide, **40** was obtained as a colorless solid by column chromatography using EtOAc/hexane (3:7) as eluent.

## 4.1.18. General procedure for the synthesis of (n-chloroalkyl) benzoxazole, 41, (n = 2-5)

A mixture of 3-chloro-*N*-(2-hydroxyphenyl)-propanamide (1 g, 5.01 mmol) and polyphosphoric acid (PPA, 3 g) was heated with magnetic stirring at 130 °C for 3–4 h. The reaction mixture was poured into ice-water (50 mL), neutralized with saturated aq NH<sub>3</sub>, and extracted with EtOAc ( $2 \times 50$  mL). The combined extract was washed with H<sub>2</sub>O, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give the crude product which was purified by column chromatography using EtOAc/hexane (1:9) to give 2-(2-chloroethyl)benzoxazole as a pale yellow oily liquid.

# 4.1.19. General procedure for the synthesis of 2-{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-ethyl}-benzoxazole

A mixture of 2-(2-chloroethyl)benzoxazole, (100 mg, 0.55 mmol), 4-chlorophenyl-piperazine, (108 mg, 0.55 mmol), and K<sub>2</sub>CO<sub>3</sub> (433 mg, 3.30 mmol) in CH<sub>3</sub>CN (3 mL) was heated at reflux for 12–24 h. After cooling to rt, the solvent was removed under vacuum, H<sub>2</sub>O (10 mL) was added and the solution was extracted with EtOAc ( $3 \times 50$  mL). The pooled organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated by rotary evaporation at reduced pressure. The residue was purified by column chromatography using EtOAc/hexane (9:1) as eluent to yield the pure product (2-{2-[4-(4-chlorophenyl)piperazin-1-yl]-ethyl}benzoxazole) as a colorless solid. The other benzoxazoles were similarly prepared.

### 4.1.20. 2-(5-(4-(4-Chlorophenyl)piperazin-1yl)pentyl)benzo[*d*]oxazole, 19

Yield 45%, mp 110–112 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.68–7.65 (m, 1H), 7.50–7.46 (m, 1H), 7.31–7.28 (m, 2H), 7.19 (d, *J* = 9.3 Hz, 2H), 6.82 (d, *J* = 9.3 Hz, 2H), 3.17–3.13 (m, 4H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.59–2.56 (m, 4H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.98–1.91 (m, 2H), 1.66–1.58 (m, 4H). Calcd for C<sub>22</sub>H<sub>26</sub>ClN<sub>3</sub>O: C 68.83, H 6.83, N 10.95. Found: C 69.12, H 6.86, N 10.72.

### 4.1.21. 2-(4-(4-(4-Chlorophenyl)piperazin-1yl)butyl)benzo[*d*]oxazole, 20

Yield 70%, mp 127–129 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.68–7.65 (m, 1H), 7.49–7.46 (m, 1H), 7.31–7.28 (m, 2H), 7.19 (d, *J* = 9.3 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 3.14 (t, *J* = 4.8 Hz, 4H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 4.8 Hz, 4H), 2.45 (t, *J* = 7.5 Hz, 2H),

1.98–1.93 (m, 2H), 1.72–1.62 (m, 2H). Calcd for  $C_{21}H_{24}CIN_3O$  0.18  $H_2O$ : C 67.60, H 6.48, N 11.26. Found: C 67.69, H 6.61, N 10.98.

### 4.1.22. 2-(3-(4-(4-Chlorophenyl)piperazin-1yl)propyl)benzo[*d*]oxazole, 21

Yield 37%, mp 98–99 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.68–7.65 (m, 1H), 7.49–7.46 (m, 1H), 7.30–7.28 (m, 2H), 7.18 (d, *J* = 9.3 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 3.09 (t, *J* = 5.1 Hz, 4H), 3.01 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 5.1 Hz, 4H), 2.53 (t, *J* = 6.9 Hz, 2H), 2.14–2.09 (m, 2H). Calcd for C<sub>20</sub>H<sub>22</sub>ClN<sub>3</sub>O: C 67.50, H 6.23, N 11.81. Found: C 67.28, H 6.35, N 11.56.

# 4.1.23. 2-(2-(4-(4-Chlorophenyl)piperazin-1-yl)ethyl)benzo[*d*]oxazole, 22

Yield 58%, mp 110–112 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.69–7.66 (m, 1H), 7.52–7.47 (m, 1H), 7.32–7.30 (m, 2H), 7.19 (d, *J* = 9.3 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 3.18–3.14 (m, 6H), 3.01 (t, *J* = 6.9 Hz, 2H), 2.70 (t, *J* = 5.1 Hz, 4H). Cacld for C<sub>19</sub>H<sub>20</sub>ClN<sub>3</sub>O: C 66.76, H 5.90, N 12.29. Found: C 67.06, N 5.97, H 11.90.

### 4.1.24. General method for tosylated alkyl benzofurans

The method reported in Bakunova et al.,<sup>16</sup> was followed to construct the benzofuran moiety. A mixture of 2-iodophenol (3 g, 1 equiv), alkyl-1-yn-1-ol (1.1 equiv), and copper(I) oxide (1.36 g, 0.7 equiv) in dry pyridine (15 mL) was stirred at 100–120 °C overnight. The mixture was allowed to cool to rt, diluted with EtOAc (50 mL), filtered through celite and concentrated. The residue was dissolved in EtOAc (100 mL), washed with 2 M HCl (50 mL) and brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was, then, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and TsCl (1.1 equiv) and Et<sub>3</sub>N (1.4 equiv) were added at rt while stirring overnight. The solution was diluted with EtOAc (50 mL), washed with H<sub>2</sub>O (3 × 50 mL) and brine (50 mL). The pooled organic solvent was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated under reduced pressure and purified using column chromatography with hexane/EtOAc (7:3) as the eluent.

#### 4.1.25. General procedure for benzofuran coupling

To a stirred solution of  $CH_3CN$  (10 mL) and  $Et_3N$  (2 equiv), the appropriate haloalkylbenzofuran (1 equiv) and an arylcycloalkylamine (1.1 equiv) were added and refluxed overnight. The solution was allowed to cool to rt, diluted with EtOAc (50 mL) and washed with  $H_2O$  and brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The residue was purified using column chromatography with hexane/EtOAc (6:4) as the eluent to afford an orange-yellow solid.

### 4.1.26. 1-(2-(Benzofuran-2-yl)ethyl)-4-(4chlorophenyl)piperazine, 23

Yield 93%, mp 166.6–168.2 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.49 (dd, *J* = 4.5, 4.5 Hz, 1H), 7.42 (d, *J* = 12.0 Hz, 1H), 7.24 (m, 4H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.46 (s, 1H), 3.19 (t, *J* = 15 Hz, 4H), 3.03 (t, *J* = 9.0 Hz, 2H), 3.85 (t, *J* = 9.0 Hz, 2H), 2.70 (t, *J* = 15 Hz, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  157.4, 154.3, 149.98, 128.98, 124.3, 123.2, 122.2, 120.2, 117.3, 110.07, 102.3, 56.1, 52.8, 49.3, 26.2. Calcd for C<sub>20</sub>H<sub>21</sub>-ClN<sub>2</sub>O: C 70.48, H 6.21, N 8.22. Found: C 70.63, H 6.30, N 8.25.

### 4.1.27. 1-(3-(Benzofuran-2-yl)propyl)-4-(4chlorophenyl)piperazine, 24

Yield 90%, mp 84.8–85.9 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.49 (dd, *J* = 6.0, 6.0 Hz, 1H), 7.41 (d, *J* = 12.0 Hz, 1H), 7.19 (m, 4H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.41 (s, 1H), 3.15 (t, *J* = 15 Hz, 4H), 2.83 (t, *J* = 9.0 Hz, 2H), 2.62 (t, *J* = 12.0 Hz, 2H), 2.49 (t, *J* = 9 Hz, 4H), 1.97 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  158.5, 154.5, 149.98, 128.94, 124.25, 123.21, 122.47, 120.24, 117.22, 110.75, 102.1, 57.66, 53.05, 49.11,

26.32, 24.88. Calcd for  $C_{21}H_{23}CIN_2O \cdot 0.3H_2O$ : C 70.01, H 6.43, N 7.78. Found: C 69.9, H 6.41, N 7.42.

### 4.1.28. 2-(3-(Benzofuran-2-yl)propyl)-5-(4-chlorophenyl)-2,5diazabicyclo[2.2.1]heptane, 25

Yield 70%, mp 88.1–89.5 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.46 (dd, *J* = 5.4, 4.5 Hz,1H), 7.19 (m, 1H), 7.17 (m, 1H), 7.13 (d, *J* = 9.6 Hz, 2H), 6.45 (d, *J* = 12.0 Hz, 2H), 6.35 (s, 1H), 4.18 (br s, 1H), 3.57 (br s, 1H), 3.35 (dd, *J* = 4.5, 3.3 Hz, 1H), 3.22 (d, *J* = 9 Hz, 1H), 2.99 (dd, *J* = 4.5, 4.5 Hz, 1H), 2.78 (t, *J* = 9.0 Hz, 2H), 2.55 (m, 4H), 1.94 (t, *J* = 9 Hz, 2H), 1.84 (t, *J* = 9 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  158.9, 154.2, 145.7, 128.9, 123.3, 122.2, 120.9, 120.05, 113.8, 110.6, 102.1, 61.7, 57.7, 56.9, 52.05, 36.3, 27.1, 26.01. Calcd for C<sub>22</sub>H<sub>23</sub>ClN<sub>2</sub>O: C 72.02, H 6.32, N 7.64. Found: C 71.75, H 6.38, N 7.51.

### 4.1.29. 1-(3-(Benzofuran-2-yl)propyl)-4-(4-chlorophenyl)-1,4diazepane dihydrochloride, 26

Yield 89%, mp 138.1–139.9 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.46 (dd, J = 6.0, 4.8 Hz, 1H), 7.39 (dd, J = 6.0Hz, 3.3 Hz, 1H), 7.14–7.22 (m, 2H), 7.12 (d, J = 7.2 Hz, 2H), 6.57 (d, J = 6.0 Hz, 2H), 6.35 (s, 1H), 3.53 (t, J = 6.0 Hz, 2H), 3.44 (t, J = 9.0 Hz, 2H), 2.73–2.81 (m, 4H), 2.66 (t, J = 6.0 Hz, 2H), 2.58 (t, J = 6.0 Hz, 2H), 1.91–2.00 (m, 4H). Calcd for C<sub>22</sub>H<sub>27</sub>Cl<sub>3</sub>N<sub>2</sub>O·0.5H<sub>2</sub>O: C 63.77, H 6.32, N 6.76. Found: C 63.78, H 6.35, N 6.61.

#### 4.1.30. 2-(3-Chloropropyl)benzo[d]thiazole, 48

A mixture of 2-aminobenzenethiol (10 g, 80 mmol) and 4-chlorobutyl chloride (14 g, 99 mmol) in toluene (100 mL) was stirred for 48 h at rt. The mixture was diluted with EtOAc (300 mL) and washed with saturated aq NaHCO<sub>3</sub> (2 × 100 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated in vacuo, followed by chromatography on silica gel to afford 2-(3-chloropropyl)benzo[*d*]thiazole (13.5 g, 80%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.98 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.47 (t, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 1H), 3.69 (t, *J* = 6.6 Hz, 2H), 3.30 (t, *J* = 7.5 Hz, 2H), 2.34–2.42 (m, 2H).

### 4.1.31. 2-(3-(4-(Pyrimidin-2-yl)piperazin-1yl)propyl)benzo[d]thiazole trihydrobromide, 28

A mixture of 2-(3-chloropropyl)benzothiazole (1.5 g, 7.08 mmol), 2-(piperazin-1-yl)pyrimidine dihydrochloride (1.6 g, 6.7 mmol), KI (200 mg), K<sub>2</sub>CO<sub>3</sub> (1.2 g, 8.7 mmol) in DME (10 mL) was heated to reflux under N<sub>2</sub> for 12 h. The mixture was diluted with EtOAc (400 mL) and washed with brine (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated in vacuo to dryness and the residue was column chromatographed on silica gel to afford 2-[3-(4-pyrimidin-2-yl-piperazin-1-yl) propyl]benzothiazole, 28. The product was converted into the HBr salt, and recrystallized from MeOH-Et<sub>2</sub>O (865 mg, 21%), mp >260 °C. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  12.08 (br s, 2H), 10.13 (br s, 1H), 8.45 (d, J = 4.5 Hz, 2H), 8.07 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.48 (dt, J = 1.5, 8.1 Hz, 1H), 7.40 (dt, J = 1.5, 8.1 Hz, 1H), 6.78 (t, J = 4.5 Hz, 1H), 4.68 (d, J = 14.1 Hz, 2H), 3.63 (d, J = 14.1 Hz, 2H), 3.35-3.44 (m, 2H), 3.20-3.31 (m, 4H), 3.04-3.14 (m, 2H), 2.25-2.35 (m, 2H). Calcd for C<sub>18</sub>H<sub>24</sub>Br<sub>3</sub>N<sub>5</sub>S: C 37.13, H 4.16, N 12.03. Found: C 37.22, H 4.11, N 12.01.

### 4.2. Receptor binding studies

Binding affinities ( $K_i$ , nM) reported in Tables 1–4 were conducted by the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP) unless otherwise stated. Details of the methods and the radioligands used for the binding assays at each receptor were previously reported.<sup>22</sup>

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