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Synthesis and dopamine receptor pharmacological evaluations on ring C *ortho* halogenated 1-phenylbenzazepines

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ABSTRACT

A series of 1-phenylbenzazepines containing bromine or chlorine substituents at the *ortho* position of the appended phenyl ring (2′-monosubstituted or 2′,6′- disubstituted patterns) were synthesized and evaluated for affinity towards dopamine D_1R, D_2R and D_5R. As is typical of the 1-phenylbenzazepine scaffold, the compounds displayed selectivity towards D_1R and D_5R; analogs generally lacked affinity for D_2R. Interestingly, 2′,6′-dichloro substituted analogs showed modest D_5R versus D_1R selectivity whereas this selectivity was reversed in compounds with a 2′-halo substitution pattern. Compound **10a** was identified as a D_1R antagonist (K_i = 14 nM; IC_{50} = 9.4 nM).

The neurotransmitter dopamine is implicated in a number of physiological functions in both the periphery and central nervous system (CNS) such as locomotion, blood pressure regulation, cognition and emotion.[1–7] Perturbations in dopaminergic neurotransmission underlie some CNS disorders such as Parkinson's disease, schizophrenia and drug abuse.[8–11] Therefore normalization of dopaminergic neurotransmission with pharmacological agents has been explored as a means to treat these conditions.

Dopamine exerts its pharmacological actions via agonist activity at 5 dopamine receptors (D_1R – D_5R). Dopamine receptors are classified as "D_1-like" (constituted by D_1 and D_5 receptor sub-types – D_1R and D_5R) and "D_2-like" (comprising D_2R, D_3R and D_4R) based on the structure and function of the receptors and pharmacological studies.[12–15] The discovery of ligands that are highly selective for either the D_1R or D_5R sub-types has proved challenging due to the close transmembrane structural similarity between D_1R and D_5R (> 80% homology in transmembrane regions). Thus, commercially available D_1R ligands (i.e. "D_1R-like" ligands) usually display similar affinity at D_5R. It is only quite recently that D_1R subtype selective ligands have been disclosed.[16,17] The availability of highly selective ligands for either D_1R or D_5R is of current interest as such compounds would be useful tools to unravel the individual roles of D_1R and D_5R in various physiological processes and serve as lead molecules for related CNS disorders.

The 1-phenylbenzazepine framework is a classical template for D_1R-like ligands and numerous compounds along a continuum of functional activity (i.e. full agonists, partial agonists, antagonists) have been identified with this scaffold.[18–23] A number of these compounds are used as research tools in pharmacological studies. For example, SCH 23,390 (**1**, Fig. 1) is a widely used D_1R-like antagonist tool; it displays very high affinity for D_1R and D_5R (0.2 and 0.3 nM respectively).[24] SKF 38,393 (**2**) is a widely used D_1R-like agonist with strong affinity for D_1R and D_5R (1.0 and 0.5 nM respectively).[25] Fenoldopam (**3**), a peripherally restricted D_1R-like partial agonist is currently the only compound from this class that is in use clinically (it is used as a fast-acting antihypertensive drug).[26]

There have been several structure-activity relationship (SAR) studies on 1-phenylbenzazepines as D_1R-like receptor ligands and these studies have established that the aryl substituent groups as well as the nitrogen substituent can significantly impact D_1R-like affinity, D_1R-like selectivity versus "D_2-like" receptors as well as functional activity.[27–32] Although several SAR studies have been performed on the scaffold, it has not been determined how halogen substituents in the *ortho* position of ring C in the 1-phenylbenzazepine framework impacts affinity and selectivity for dopamine receptors; there is no data available concerning the D_1R versus D_5R affinity of the compounds. Given this gap in the SAR of 1-phenylbenzazepines, we set out to examine the role of ring C *ortho* halo substituents on D_1R/D_5R affinity in this scaffold. We hypothesized that such substituents might cause differences in receptor interactions with the substituents themselves and/or lead to modified conformations of the molecule as a whole that could directly influence D_1R and D_5R

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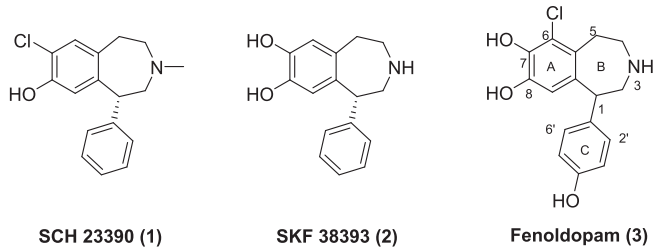


Fig. 1. Structures of typical 1-phenylbenzazepine D_1R-like ligands – Fenoldopam, SCH 23,390 and SKF 38393.

affinity and selectivity. Thus, we set out to synthesize a set of 1-phenylbenzazepine derivatives with variations in the ring A moiety (either a catechol or protected catechol motif), nitrogen alkyl group substituent and ring C *ortho* halogenated motif.

The analogs were synthesized as shown in Scheme 1. The epoxides **9** were available commercially or could be readily synthesized from the corresponding styrenes **8**. We initially attempted reaction of amine **4** and epoxides **9** to form amino alcohols **5** without the use of any additives/catalysts, as is typically done for the synthesis of 1-phenylbenzazepine syntheses,[33–35] but found the reactions to be low yielding. Presumably this less than favorable outcome was due to the steric hindrance in the epoxides used. Lewis acids or lithium salts have often been used to promote ring opening of epoxides with amine nucleophiles.[36–38] As $LiNTf_2$ was reported to provide high yields in such reactions,[39] we examined the use of this reagent and were happy to find that the reactions of **4** and **9** to form **5** proceeded in reasonable yield.

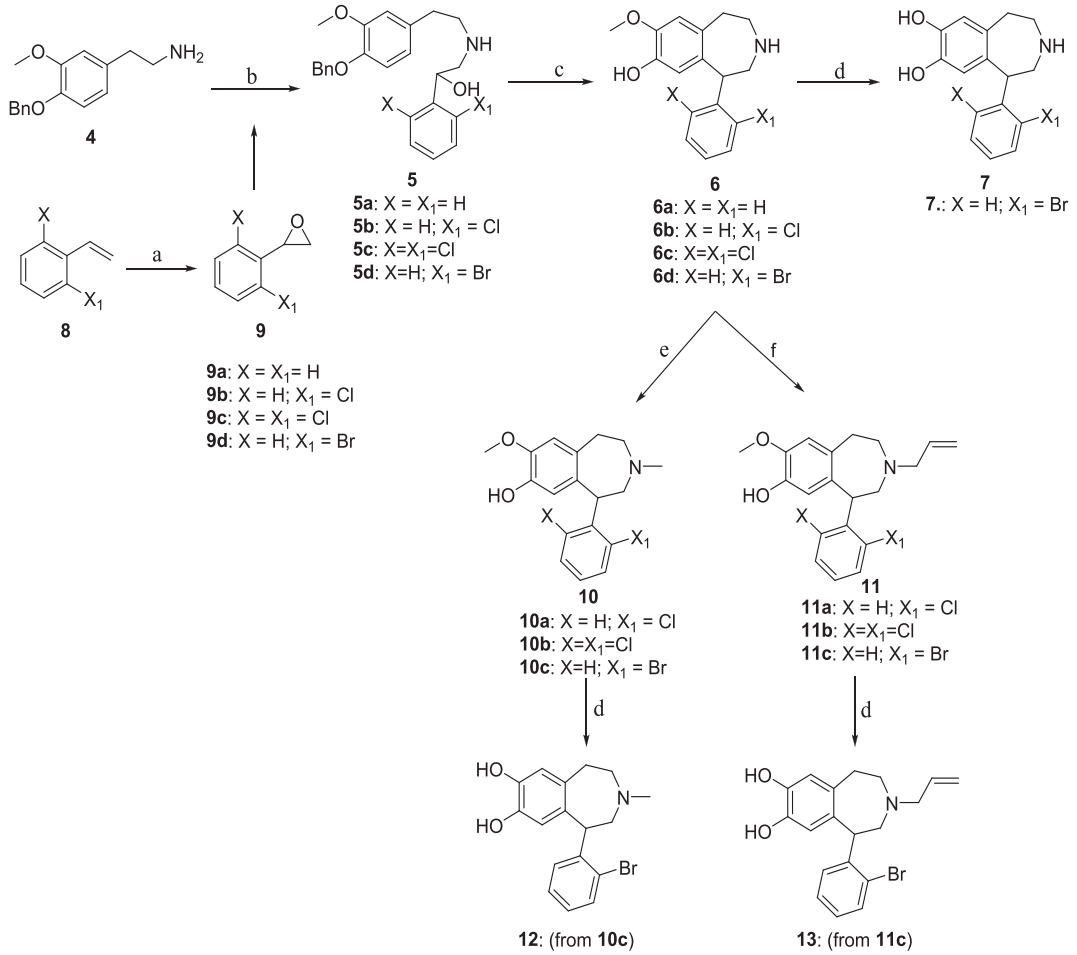
Acid-catalyzed cyclization of **5** afforded the benzazepine framework of compounds **6a-d**. Compounds **6a-d** served as key intermediates from which the synthesis diverged to prepare other analogs with variations in the phenolic moiety and/or *N*-substituent.

Thus, treatment of compounds **6b** with BBr_3 gave the catecholic compound **7**. The secondary amine in compounds **6b-d** was methylated via reductive amination to give analogs **10a-c** respectively**.** Treatment of compounds **6b-d** with allyl bromide allowed for the preparation of *N*-allylated analogs **11a-c**. Compounds **10c** and **11c** in turn were demethylated by reaction with BBr_3 affording catechols **12** and **13** respectively.

The binding affinity of compounds **6a-d**, **7**, **10a-c**, **11a-c**, **12** and **13** were assessed at dopamine D_1, D_2 and D_5 receptors. Data for these assessments are presented in Table 1 as K_i values in nM. Compounds **6a-d** had D_1R affinities ranging from 72 to 147 nM. Affinities at D_5R for this sub-group of compounds were slightly lower overall (ranging from 82 to 483 nM), so that on a whole, compounds **6a-d** were slightly more selective for D_1R over D_5R. Compound **6c** is interesting as it is the only compound of the **6a-d** subset that was D_5R selective over D_1R (3-fold). Compounds **6a**, **6b** and **6d** displayed modest selectivity for D_1R over D_5R (up to 3-fold).

Compound **7** with a bromo substituent, showed strong D_1R and D_5R affinity. In comparing phenol **7** to its C7 methoxy analog **6d**, it is apparent that the effect of cleavage of the C7 methoxy group to give the catechol **7**, results in a roughly 3-fold increase in D_1R affinity; improvement in affinity at D_5R was more modest.

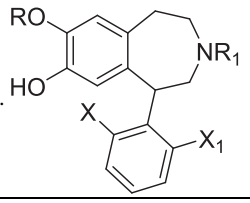
Compounds **10a-c** are the *N*-methylated analogs of **6b-d** respectively; compounds **10a-c** as a group displayed stronger D_1R affinity



Scheme 1. Reagents and Conditions: (a) 1. mCPBA, DCM, rt, 12 h; 2. NaOH, rt, (88–96%); (b) **9**, $LiNTf_2$, THF, reflux, 24 h, (56–76)%; (c) 1. TFA, H_2SO_4, rt, 5 h; 2. NaOAc, (43–54%); (d) BBr_3, DCM, 0 °C, 4 h, (56–80%); (e) HCHO, $Na(OAc)_3BH$, ACN, rt, 12 h, (23–48%); (f) Allyl Bromide, TEA, ACN, rt, 16 h, (56–64%).

Table 1

Binding affinity of analogs at D_1R, D_2R and D_5R.



Cmpd #	R	R_1	X	X_1	K_i (nM)[a]		
					D1[b]	D2[c]	D5[d]
6a	Me	H	H	H	126.4 ± 9.1	na[e]	309.9 ± 23
6b	Me	H	H	Cl	147.4 ± 4.1	na	482.8 ± 29.4
6c	Me	H	Cl	Cl	76.1 ± 3.6	na	25.4 ± 2.6
6d	Me	H	H	Br	72 ± 5.6	na	82 ± 6.2
7	H	H	H	Br	26 ± 3.1	na	67 ± 7.1
10a	Me	Me	H	Cl	14 ± 2.3	na	46.4 ± 3.8
10b	Me	Me	Cl	Cl	144.6 ± 9.0	na	49.1 ± 3.7
10c	Me	Me	H	Br	16 ± 1.4	na	47 ± 3.2
11a	Me	Allyl	H	Cl	48.3 ± 8.2	na	264.4 ± 13.6
11b	Me	Allyl	Cl	Cl	1044 ± 59.2	1507.8 ± 89.2	479.1 ± 39.2
11c	Me	Allyl	H	Br	41 ± 2.8	na	501 ± 64
12	H	Me	H	Br	59.4 ± 4.9	na	223.2 ± 18.6
13	H	Allyl	H	Br	132.9 ± 8.9	na	442.2 ± 56
(+)-Butaclamol					4.04 ± 0.2		
Haloperidol						5.58 ± 0.3	
SKF 83,566							3.95 ± 0.2

[a]Experiments carried out in triplicate; [b][3*H*]SCH23390 used as radioligand; [c][3*H*]*N*-methylspiperone used as radioligand; [d][3*H*]SCH23390 used as radioligand; [e]na – not active (< 50% inhibition in a primary assay when tested at 10 μM).

than their *N-des*-methyl counterparts. Compounds **10a** and **10c** had the strongest D_1R affinity of any compound evaluated for this study (K_i of 14 and 16 nM for **10a** and **10c** respectively). The compounds in this sub-group with mono-halogen substituents (**10a** and **10c**) showed modest D_1R selectivity over D_5R (3-fold and 4-fold respectively), but this selectivity was reversed in the dichloro substituted compound **10b**.

Similar trends as for the *N*-methylated analogs **10a-c** were seen for the *N*-allylated analogs **11a-c**. In that regard, both the mono-halo substituted analogs **11a** and **11c** were D_1R selective whereas the dichloro substituted analog was D_5R selective. In general, the *N*-allyl analogs displayed lower affinity for D_1R and D_5R than their *N*-methyl congeners.

The catecholic analogs **12** and **13** are the *O*-demethylated analogs of **10c** and **11c** respectively; both **12** and **13** showed lower D_1R and D_5R affinity than their methylated precursors and both also had modest D_1R selectivity versus D_5R (in the 3- to 4-fold range).

In analysis of the effect of monohalogenated versus dihalogenated substitutions in the pendant aryl ring, interesting observations emerge. In the case of the **6b/6c** pair, the dihalogenated compound **6c** showed higher D_1R and D_5R affinities than the monohalogenated congener **6b**. However, a similar change in the **10a/10b** pair and the **11a/11b** pair resulted in diminished D_1R and D_5R affinities for the corresponding dihalogenated analogs. This result indicates that the presence of an *N*-alkyl substituent is more favorable for binding of the monohalogenated versus their dihalogenated congeners at D_1R/D_5R, whereas absence of such a substituent leads to a stronger preference towards binding of the dihalogenated versus monohalogenated variants.

Comparison of data for the **6b/6d**, **10a/10c** and **11a/11c** compound pairs enabled an analysis of the effect of monochloro versus monobromo substitution in the analog series. In the case of the **6b/6d** pair, the bromo analog **6d** had higher D_1R and D_5R affinity than the chloro analog **6b**. However, in the case of the **10a/10c** and **11a/11c** pairs, changing from a chloro group to a bromo group did not result in a similar increase in affinity of the brominated analogs for the D_1R as was seen for **6b/6d**; affinities for the chloro and bromo variants were similar (e.g. 14 nM and 16 nM for **10a** and **10c** respectively at D_1R). Meanwhile, at the D_5R, affinities of the bromo and chloro analogs were similar (for **10a/10c**) or were worse for the bromo analog (for **11a/11c**). Therefore, it appears that in this series, the presence of an *N*-alkyl substituent group does not lead to a strong preference for binding of the monobromo versus monochloro variants at D_1R; however, the absence of an *N*-alkyl substituent leads to stronger binding of the monobromo versus monochloro congeners at D_1R.

We selected the compound with the highest D_1-like receptor affinity for further evaluation of functional activity. Thus, compound **10a** was evaluated for agonist and antagonist activity in D_1R assays that measured cAMP modulation by Eurofins Lead Hunter Discovery Services. As expected, (based on structural similarity to **3**) **10a** displayed strong antagonist activity in these assays (IC_{50} = 9.4 nM for **10a**; IC_{50} of positive control SCH 39166 = 1.5 nM). No agonist activity was detected for **10a**.

In order to provide insights into the important receptor-ligand interactions between the *ortho* halogen substituted 1-phenylbenzapines and the D_1R and D_5R, computational docking studies were conducted for the series of analogs in Table 1. In this context, we explored the docked ligand poses and identified key interactions that have a significant impact on binding to the dopamine receptors for this ligand series. These efforts focused mainly on the compounds **7**, **10a** and **10c**, which displayed the best experimental binding affinities to D_1R.

Homology models of D_1R and D_5R were generated and utilized in the docking studies. The D_1R homology model was constructed from the high-resolution crystal structure of the human β_2-adrenergic G protein-coupled receptor (GPCR) with pdb code 2RH1 followed by induced fit docking with several halogenated 1-phenylbenzazepine analogs.[40] In a similar manner, the D_5R homology model was created from the high-resolution crystal structure of the β_1-adrenergic GPCR with pdb code 6H7J followed by induced fit docking with the benzazepine analogs.[41] Models of appropriate amino acid backbone and side-chain orientations in the ligand binding site. The homology model building procedure involved application of the Schrödinger Prime Structure Prediction, Induced Fit Docking and Glide software tools in conjunction with manual intervention to support the formation of known key receptor-ligand interactions. The docking runs of the 1-phenylbenzazepine analogs into the D_1R and D_5R binding sites utilized the

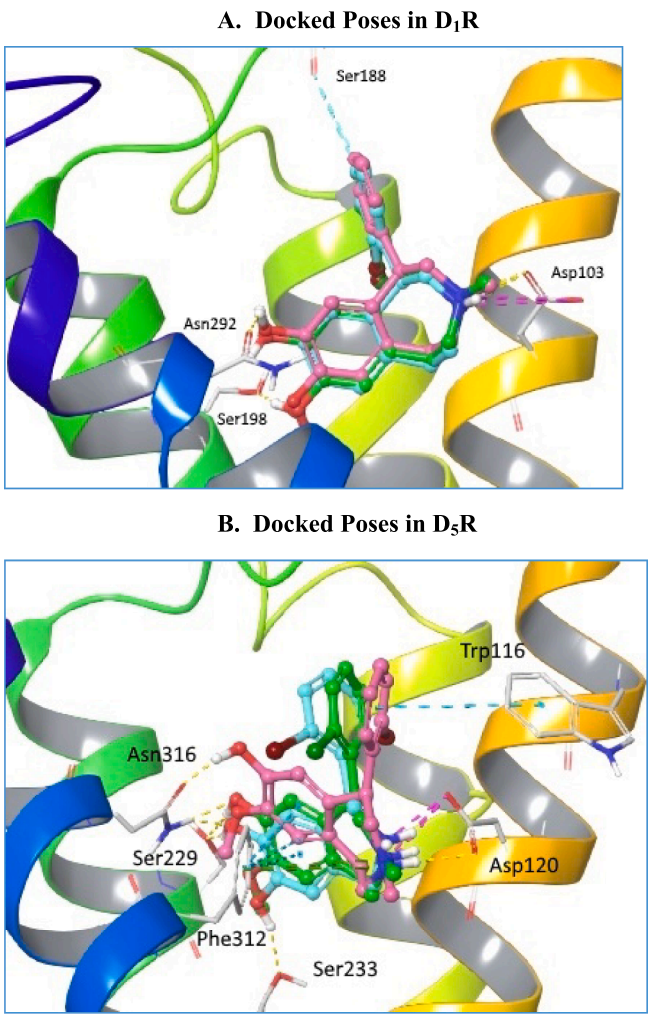


Fig. 2. Docked poses of compounds **7** (blue carbon atoms), **10a** (green carbon atoms) and **10c** (pink carbon atoms) in **A -** the D_1R target and **B -** the D_5R target. The receptor targets are depicted by secondary structure elements and grey carbon atoms for select residues. Key quaternary N – Asp salt bridges are depicted by the pink dashed lines, H-bonding interactions by the yellow dashed lines, aromatic H-bonding by the turquoise dashed lines and π-π stacking by the blue dashed lines. Docking studies were performed with the *R* enantiomers.

Schrödinger Glide methodology in Standard Precision (SP) mode. Using this approach, the Glidescore scoring function provided an estimate of the ligand binding affinities for the highest ranked poses of the ligand series in the D_1R and D_5R targets. The binding poses for the compounds **7**, **10a** and **10c** (docked as the *R* enantiomers), which gave the best D_1R experimental affinities, are depicted in Fig. 2A and 2B.

Compounds **7, 10a** and **10c** give very similar docked poses in the D_1R binding pocket as shown in Fig. 2A with binding energies in the range −7.8 kcal/mol to −8.2 kcal/mol. The docked poses display the quaternary N - Asp103 salt bridge, H-bonding interactions of the ligand hydroxyl group to the Asn292 side chain, and for compound **7** with an additional hydroxyl group in the catechol moiety there is also a H-bond to the Ser198 sidechain, as well as an aromatic H-bond involving the pendant phenyl group and Ser188.

In the D_5R binding site, the main receptor-ligand interactions for the docked poses of compounds **7, 10a** and **10c** comprise the quaternary N - Asp120 salt bridge, hydrogen bonding interactions of the ligand hydroxyl group to the Asn316 or Ser229 sidechain, and again for compound **7** there is another hydrogen bond with its second catechol hydroxyl group to Ser233, as well as π-π hydrophobic interactions involving the ligand aromatic rings with Phe312 and Trp116. Compounds **10a** and **10c** form docked poses with binding energies of −8.2 kcal/mol and −8.1 kcal/mol, respectively, which are very similar to those in the D_1R binding pocket.

Overall, the computationally predicted binding energies for the docked series of halogen substituted 1-phenylbenzapine derivatives in Table 1 are similar in both the D_1R and D_5R structures or a little better in D_5R as a consequence of the slightly stronger hydrogen bonding and π-π hydrophobic interactions. In this context, the docking scores do not align with the selectivity trends derived from the experimental binding affinities. This is at least partially attributable to the modest nature of the observed D_1R/D_5R experimental selectivities of the ring C halogenated analogs. Furthermore, D_1R and D_5R are very similar structurally in the ligand binding pocket, which provides justification for the close computational binding energies for most of the compounds in these two target sites. The docking outcomes for the compounds in Table 1 involved the *R* enantiomers whereas the affinity data were obtained with racemic mixtures and this could also have an impact on the match between the experimental and computational results. Docking simulations were investigated with the *S* enantiomers, however, they generated similar trends compared to the *R* enantiomers with, in general, slightly worse predicted binding energies in both the D_1R and D_5R targets.

In conclusion, this study extends the available SAR information on 1-phenylbenzazepines as D_1R-like ligands with regards to the effect of ring C *ortho* halogen substituents. As is evident from examination of the data, the compounds in this study maintain selectivity for D_1-like receptors over D_2R, with modest selectivity for either D_1R or D_5R. As compared to known 1-phenylbenzapeine D_1R-like tools such as **1** and **2**, it is apparent that the *ortho* halogen group does not significantly improve D_1R or D_5R affinity. However, one of the findings from this work is that compounds with di-*ortho*-halo substituents (i.e. *C2′/C6′* substitution) favor binding to D_5R, whereas compounds with a mono-*ortho*-halo (*C2′*) substituent favor D_1R binding over D_5R. In addition, the SAR data suggests that the most favorable outcome for good D_1R affinity is to have either mono-*ortho*-halogenation in tandem with *N*-alkyl substitution or di-*ortho*-halogenation without *N*-alkyl substitution.

Evaluation of the functional activity of **10a** reaffirms the idea that an 8-hydroxy-7-methoxy moiety favors antagonist rather than agonist activity. This result is in line with the generally accepted view that a catechol motif is required for agonist activity in the 1-phenylbenzazepine scaffold.

Our molecular docking studies revealed interactions that were relevant for affinity of the molecules at D_1R and D_5R, but were unable to resolve interactions necessary for the observed modest D_1R sub-type selectivity of **7**, **10a** and **10c**. Examination of larger sets of compounds with *ortho* halogenated patterns in future, including enantiopure analogs, may provide a larger body of data to aid in the challenging optimization of these ligands towards D_1R or D_5R potency and sub-type selectivity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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PDSP). The NIMH PDSP is directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscol at NIMH, Bethesda MD, USA. For experimental details please refer to the PDSP website http://pdsp.med.unc.edu/ and click on "Binding Assay" or "Functional Assay" on the menu bar.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127305.

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