



Profiling of LINS01 compounds at human dopamine D₂ and D₃ receptors

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Abstract. Histamine and dopamine neuronal pathways display interesting overlapping in the CNS, especially in the limbic areas, making them very attractive to designing drugs with synergistic and/or additive effects. The roles of these systems to treat schizophrenia, drug addiction, Parkinson's and Alzheimer's diseases, among others are widely known. The LINS01 compounds were previously reported as histamine H₃ receptor (H₃R) antagonists and some of them are under evaluation in rodent memory models. Considering their pharmacological potential and similarities to literature dopamine D₂ receptor (D₂R) and dopamine D₃ receptor (D₃R) ligands, this work aimed to evaluate these compounds as ligands these receptors by using [³H]piperone displacement assays. A set of 11 compounds containing the dihydrobenzofuranyl-piperazine core with substituents at 5-position of dihydrobenzofuran ring and at the piperazine nitrogen was examined. The compounds showed low to moderate affinities at both, D₂R and D₃R. *N*-Phenyl compounds LINS01005 (**1d**), LINS01011 (**1h**), LINS01012 (**1i**) and LINS01016 (**1k**) showed the highest affinities in the set to D₃R (K_i 0.3–1.5 μ M), indicating that *N*-phenylpiperazine moiety increases the affinity to this receptor subtype with some selectivity, since they showed lower affinities to D₂R (K_i 1.3–5.5 μ M). With the LINS01 compounds showing moderate binding affinity, new lead structures for optimization with regards to combined H₃R and D₂R/D₃R-ligands are provided.

Keywords. Antihistamine; dopamine receptor ligand; D₂ receptor; D₃ receptor.

1. Introduction

Classically, the drug discovery process focuses on the “one drug, one target” paradigm, which means that a drug must interact specifically with a defined biological target in the organism, to assure the maximum efficacy (potency) and fewer side effects (selectivity). However, this philosophy has changed in the last years to a more comprehensive view of the diseases, coining a “one drug, multiple targets” paradigm, also known as polypharmacology.^{1,2} Several diseases have been treated using a polypharmacological approach with multitarget drugs that were not designed by purpose.

For example, schizophrenia is an affective disorder that has been treated with typical and atypical antipsychotics, targeting the dopamine receptors but far from being defined as “selective drugs”. The efficacy of the classical antipsychotics such as haloperidol is attributed to the dopamine receptor antagonism, leading to the desired therapeutic outcome, but also causing extrapyramidal side effects (EPS) and worsening the cognitive and negative symptoms.³ On the other hand, atypical antipsychotics display a better therapeutic profile (especially against the negative and cognitive symptoms of schizophrenia) possibly due to their additional actions on

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serotonin and histamine systems in the brain.⁴ Considering that most of these effects are attributed to the GPCR targeting, and taking advantage of the anatomy and physiology of the neural network of the synapses, CNS diseases have been explored for designing multi target GPCR ligands.¹

The histamine receptors are class-A GPCRs that are divided into 4 subtypes, H₁R to H₄R.⁵ The H₁R and H₂R are widely expressed in the brain and are related to the control of sleep, food intake, body temperature and cognition. The H₄R is expressed in glial cells and may play a role in the inflammatory processes in the CNS.⁶ The H₃R is mainly distributed in the CNS as an auto and/or heteroreceptor that regulates the production and releasing of histamine and other neurotransmitters, such as dopamine, and so it is a potential target for several CNS disorders.^{7,8}

The dopamine receptors are also class-A GPCRs which are expressed in 5 subtypes, D₁R-D₅R. Considering their signalling profile, they are grouped into D₁-like (coupled to G_s) and D₂-like (coupled to G_{i/o}) families.³ Classically, D₂-like receptors (D₂R, D₃R and possibly D₄R) have been widely explored to the treatment of schizophrenia. However, the distribution profile of the subtypes in CNS may lead to different applications. For instance, the high density of D₂R in the movement-related and cortical areas and the high density of both D₂R and D₃R in brain areas such as the limbic system may explain why non-selective D₂R antagonists lead to the motor-related EPS and cognitive decline as caused by the classical antipsychotics, but also the efficacy in the psychotic effects.^{9,10} D₃R blockade also increases the acetylcholine release in the cortex, related to the improvement in the cognitive processes.¹¹ In spite of this, selective D₃R antagonists would be effective drugs against conditions such as schizophrenia, drug addiction, AD, PD and depression.⁹

The histamine and dopamine systems in the brain are noteworthy due to very interesting common characteristics. Both systems are originated in the tuberomammillary nucleus (TMN), with projections to the cortex, (hypo)thalamus, hippocampus, striatum and amygdala. In particular, H₃R and D₃R present a considerable density distribution overlapping in the limbic areas, such as hippocampus, striatum and amygdala.¹² It is interesting to note that 95% of the neurons expressing dopamine D₁-like receptors and 89% of those expressing D₂-like receptors in the striatum also express H₃R leading to complex interactions between both neurotransmitter systems.¹³ Several results from pharmacological studies suggest that antagonists of both H₃R and D₃R can present additive and/or

synergistic effects, making them attractive multi-targeting tools for the treatment of schizophrenia, drug addiction, PD, AD, dementias and certain types of epilepsy.^{8,14,15}

The LINSO1 compounds (e.g., **1c** and **1g**, Figure 1) were previously described as selective H₃R antagonists.^{16,17} However, these compounds present some similarity to dopamine D₂R/D₃R ligands, since the overlap between the H₃R and D₂R/D₃R pharmacophores can be noted.^{8,18} The *N*-phenylpiperazine motif present in some LINSO1 compounds is found in several D₂R/D₃R ligands such as compounds **2**, **3** and **4** in Figure 1.^{19,20} Moreover, the similarity of LINSO1 compounds to compound **4** and its analogue **5** is clearly evident, which are potent ligands of D₂R and D₃R.¹¹ Considering the potential of these compounds and the similarities, the present report intended to assess the affinity of the LINSO1 compounds to the D₂R/D₃R.

2. Experimental

2.1 Preparation of the compounds LINSO1

All chemicals were purchased with adequate purity from Sigma-Aldrich Co. (Brazil) and LabSynth (Brazil) and used as supplied. The compounds were prepared and characterized as described in previous reports from our group (Figure 2).^{16,17,21,22} The analytical characterization of the newly synthesized compounds **1j** and **1k** is stated below. All

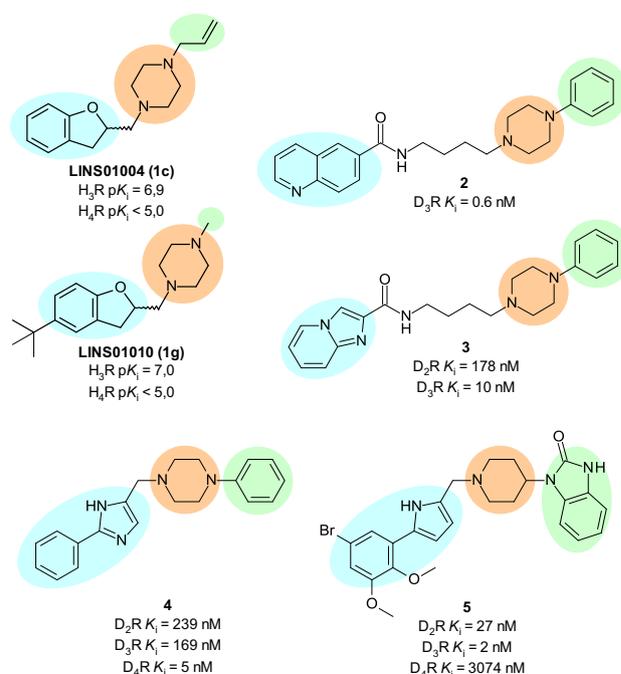


Figure 1. LINSO1 compounds and literature ligands of D₂R/D₃R.

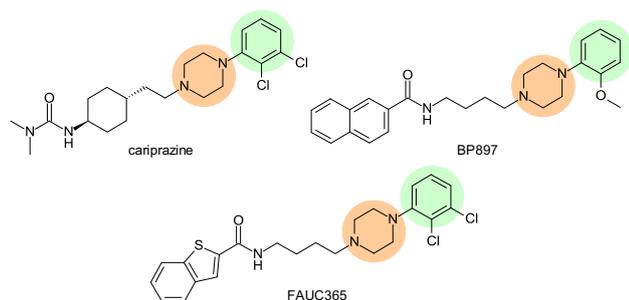


Figure 2. Ligands of D₂R and D₃R reported in the literature.

compounds were checked for purity through chromatography and considered adequate when purity was >95%.

1-Methyl-4-[(5-phenyl-2,3-dihydro-1-benzofuran-2-yl)methyl]piperazine (1j). The reaction between 1-methylpiperazine and prepared 2-(iodomethyl)-5-phenyl-2,3-dihydrobenzofuran yielded 45% of **1j**. ¹H NMR (300 MHz, CDCl₃): δ 2.31 (s, 3H), 2.41–2.74 (m, 9H), 2.82 (dd, 1H, *J* = 13.3, 7.7 Hz), 3.0 (dd, 1H, *J* = 15.7, 8.0 Hz), 3.32 (dd, 1H, *J* = 15.6, 9.1 Hz), 5.01 (dq, 1H, *J* = 8.2, 4.1 Hz), 6.85 (d, 1H, *J* = 8.3 Hz), 7.27–7.46 (m, 5H), 7.52 (d, 2H, *J* = 7.2 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 34.2, 46.1, 53.8, 55.0, 63.2, 81.3, 109.8, 123.8, 126.5, 126.8, 127.1, 127.2, 128.9, 133.9, 141.3, 159.2.

1-Phenyl-4-[(5-phenyl-2,3-dihydro-1-benzofuran-2-yl)methyl]piperazine (1k). The reaction between 1-phenylpiperazine and prepared 2-(iodomethyl)-5-phenyl-2,3-dihydrobenzofuran yielded 78% of **1k**. ¹H NMR (300 MHz, CDCl₃): δ 2.67 (dd, 1H, *J* = 13.3, 4.1 Hz), 2.72–2.81 (m, 4H), 2.88 (dd, 1H, *J* = 13.4, 7.8 Hz), 2.98–3.10 (m, 2H), 3.26 (t, 4H, *J* = 4.9 Hz), 3.36 (dd, 1H, *J* = 15.8, 9.2 Hz), 5.00–5.13 (m, 1H), 6.83–6.91 (m, 2H), 6.95 (d, 2H, *J* = 8.2 Hz), 7.28–7.45 (m, 6H), 7.52 (d, 2H, *J* = 7.2 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 34.2, 49.1, 53.9, 63.2, 77.3, 81.3, 109.8, 116.1, 119.7, 123.8, 126.5, 126.8, 127.2, 128.7, 129.1, 134.1, 141.3, 151.3, 159.2.

2.2 Binding assays on D₂R and D₃R

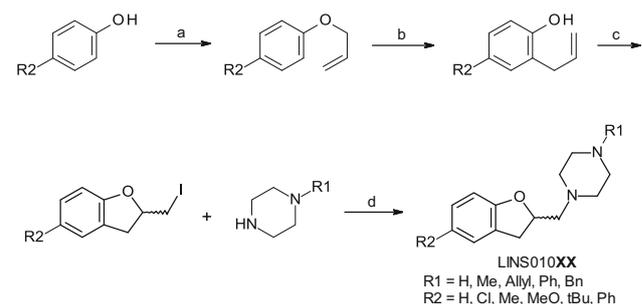
Membranes from CHO cells stably expressing either the short transcript of D₂ receptors or D₃ receptors were prepared as described previously.²³ For inhibition screening, freshly thawed membrane preparations (containing 25 and 20 μg/well of D₂R and D₃R, respectively) were incubated on microtiter plates with the indicated concentration of compounds and 0.2 nM [³H]spiperone in binding buffer [50 mM TRIS (pH = 7.4), 120 mM NaCl, 5 mM KCl, 1 mM CaCl₂ and 1 mM MgCl₂]. After an incubation period of 120 min, the mixture was harvested on glass-fiber mats, presoaked with 3% polyethylene-imine solution, followed by three wash-steps using cold demineralized water (approx. 1 mL/sample). The workup for scintillation-counting followed the standard procedure described before.²⁴ Non-specific binding was determined by an excess of unlabeled

haloperidol (10 μM). Inhibition was calculated as residual of specific binding of [³H]spiperone in presence of compound relative to specific binding in the absence of inhibitor. For affinity measurements, the same procedure as above was used but including a titration pattern of the investigated ligands (0.01–100,000 nM, final concentration). The finally determined specific binding was analyzed by non-linear least-square fitting to a four-parameter logistic equation. Conversion of the determined IC₅₀ to K_i values was performed as described elsewhere.²⁵

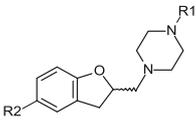
3. Results and Discussion

The LINS01 compounds (**1a–1k**, Scheme 1) were prepared as reported previously by our group.^{16,17} The derivatives **1a–1d** were prepared from 2-allylphenol through iodine-promoted cyclization, using water as a solvent.²¹ Finally, the iodinated heterocycle was used to alkylate the *N*-substituted piperazine in aprotic solvent (THF), with potassium carbonate as base, with moderate yield (~50%). The 5-phenyl derivatives **1j** and **1k** were prepared from the corresponding 4-phenyl-phenol following the same procedure, with moderate to good yields (45–78%). A novel microwave-assisted methodology¹⁷ was employed to avoid the considerable excess of 1-phenylpiperazine to obtain compounds **1h**, **1i** and **1k**, leading to good yields (>60%). Although this method gave comparable yields to the conventional methodology, it also saved reaction time and required less 1-phenylpiperazine (1.1 eq.) indeed, therefore comprising the green chemistry principles.²² The spectroscopic data for the final compounds and intermediates are in accordance with the literature reports.^{16,17,21, 26}

In an initial screening as shown in Table 1, the LINS01 compounds showed variable inhibition profiles at D₂R and D₃R, depending on the presence of certain groups. In general, a slight preference for



Scheme 1. Reagents and conditions. (a) Allyl bromide (2 eq.), K₂CO₃ (2 eq.), acetone, 60 °C, 2–4 h; (b) DMF, MW 200 °C (300 psi, 300 W), 1.5 h; (c) I₂ (1.1 eq.), water or EtOH/water, *r.t.*, 4–6 h; (d) K₂CO₃ (1.2 eq.), THF, reflux, 12–24 h or MW 120 °C (300 psi, 300 W), 1.5 h.

Table 1. Screening of the compounds LINS01 towards inhibition and affinity at the human dopamine D₂R and D₃R.


Compounds	R 1	R 2	% inhibition (10 μM) ± SD (n)		K _i (μM) [95% CI]	
			D ₂ R	D ₃ R	D ₂ R	D ₃ R
1a (LINS01001)	H	H	0.0 ± 0.0 (12)	9.0 ± 6.4 (12)	n.d. (>10 μM)	n.d. (>10 μM)
1b (LINS01003)	Me	H	1.5 ± 13.9 (15)	23.5 ± 11.7 (15)	n.d. (>10 μM)	n.d. (>10 μM)
1c (LINS01004)	Allyl	H	33.6 ± 9.7 (15)	62.3 ± 14.4 (15)	5.5 [5.0–6.0]	1.5 [0.8–3.0]
1d (LINS01005)	Ph	H	34.1 ± 10.5 (15)	55.1 ± 10.3 (15)	2.4 [2.0–2.9]	0.89 [0.45–1.75]
1e (LINS01007)	Me	Cl	10.3 ± 10.9 (15)	31.6 ± 10.1 (15)	n.d. (>10 μM)	n.d. (>10 μM)
1f (LINS01008)	Me	Me	11.1 ± 11.7 (15)	29.9 ± 9.6 (15)	n.d. (>10 μM)	n.d. (>10 μM)
1g (LINS01010)	Me	<i>t</i> Bu	12.9 ± 12.7 (15)	31.7 ± 8.5 (15)	n.d. (>10 μM)	n.d. (>10 μM)
1h (LINS01011)	Ph	Cl	44.0 ± 3.6 (6)	64.0 ± 7.1 (6)	2.6 [1.2–6.1]	0.50 [0.10–2.66]
1i (LINS01012)	Ph	Me	45.1 ± 4.2 (6)	60.9 ± 10.7 (6)	2.4 [1.1–5.3]	1.5 [0.4–4.8]
1j (LINS01016)	Me	Ph	3.3 ± 12.3 (15)	27.2 ± 7.1 (15)	n.d. (>10 μM)	n.d. (>10 μM)
1k (LINS01017)	Ph	Ph	39.5 ± 9.6 (6)	62.0 ± 5.7 (6)	1.3 [0.6–3.0]	0.39 [0.04–3.40]
Haloperidol			100.0 ± 2.5 (15)	99.3 ± 2.6 (15)	n.d.	n.d.

inhibiting [³H]spiperone binding to D₃R was observed. Compounds **1a** to **1d** bear the 1-(2,3-dihydrobenzofuran)methylpiperazine core with different substituents attached to the nitrogen. Whereas **1a** did not show important inhibition at both D₂R and D₃R, compounds presenting bigger and/or aromatic substituents attached to the piperazine displayed increased inhibition at the dopamine receptors. The *N*-methylpiperazine analogues (**1e–1g**, **1j**) displayed inhibition below 50% at both receptors leading to affinities above the 10 μM concentration range. There instead, substitution of *N*-allylpiperazine by *N*-phenylpiperazine (compounds **1c** and **1d**, respectively) showed comparable inhibition profiles at both receptors but a slight increase in affinity at D₂R. Furthermore, the results suggest that the presence of these groups drive the preference toward D₃R.

These results motivated us to further explore the affinities of the *N*-phenylpiperazine derivatives. The *N*-aryl piperazine group can be considered a privileged

group to design ligands of D₂-like receptors as embodied in the LINS01 series.^{10,11} The compounds **1d**, **1h**, **1i** and **1k** presented the highest inhibition at the investigated targets with affinities in the low micromolar concentration range at D₂R. Though only **1d** showing significant D₃R preference among them, even submicromolar K_i values were determined at the D₃R.

The influence of the groups attached in 5-position of dihydrobenzofuran (R₂) on the affinity of the compounds seems minor. When comparing compounds with different substitution profiles in this part of the molecule, it can be noted that the inhibition did not significantly change among the *N*-methylpiperazine derivatives **1e**, **1f** and **1g**, as well as comparable affinities were observed among the *N*-phenylpiperazine compounds **1d**, **1h**, **1i** and **1k**.

The role of the 2,3-dihydrobenzofuran group in the affinity of the compounds remains unclear as this element originates from the initial H₃R design

strategy. A search in literature reveals that several compounds containing the aromatic benzofuran were already reported as dopamine receptor ligands, however, only few compounds containing the dihydro analogue were tested so far. The aromatic analogues of LINS01 compounds have been demonstrating activity as sigma- and serotonin receptor ligands,^{27,28} but usually with poor affinity to dopamine receptors,^{26,29} Despite a closely related aromatic *N*-benzylpiperazine analogue being reported in literature,²⁹ no compounds containing the unsubstituted *N*-allyl-, *N*-methyl- or *N*-phenylpiperazine moieties were found. On the other hand, homologues containing a longer linker between the benzofuran and the piperazine showed increased affinity to dopamine receptors,³⁰ suggesting that longer homologues of LINS01 compounds would shed light on the role of the dihydrobenzofuran in the D₂R and D₃R affinities, and should be considered in future evaluations. Secondly, derivatization of *N*-phenylpiperazine may be used for enhancing affinity at D₂R and D₃R. For instance, the substitution with a 2-methoxy or 2,3-dichloro groups in the phenyl ring usually leads to increased D₃R selectivity, as can be seen in cariprazine (a subnanomolar affinity D₃R ligand and nanomolar affinity at D₂R) and other compounds such as BP897 (bearing a 2-methoxyphenyl piperazine) and FAUC365 (bearing a 2,3-dichlorophenyl piperazine), indicating potential substitutions in this direction for designing improved ligands¹⁰ (Figure 2).

4. Conclusions

This is the first report exploring the histamine H₃R-targeting LINS01 compounds being ligands at dopamine receptors as well. Although these molecules showed low affinity to D₂R and D₃R, some of them show slight D₃R preference. The *N*-phenylpiperazine and *N*-benzylpiperazine fragments increased the binding of these compounds to D₂R and D₃R, although the latter reduces the selectivity. Additionally, the substitution in the dihydrobenzofuran seems not to influence the affinity of these compounds to D₂R or D₃R. The presented characterization of the LINS01 series lays the foundation for further profiling of the detected hits, profiling them towards attractive lead-compounds with combined dopaminergic and histaminergic activity.

Supplementary Information (SI)

Supplementary information is available at www.ias.ac.in/chemsci.

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