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REGULAR ARTICLE

Profiling of LINS01 compounds at human dopamine D_2 and D_3 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 H_3 receptor (H_3R) antagonists and some of them are under evaluation in rodent memory models. Considering their pharmacological potential and similarities to literature dopamine D_2 receptor (D_2R) and dopamine D_3 receptor (D_3R) ligands, this work aimed to evaluate these compounds as ligands these receptors by using [^{3}H]spiperone 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, D_2R and D_3R. *N*-Phenyl compounds LINS01005 (**1d**), LINS01011 (**1h**), LINS01012 (**1i**) and LINS01016 (**1k**) showed the highest affinities in the set to D_3R (K_i 0.3–1.5 μM), indicating that *N*-phenylpiperazine moiety increases the affinity to this receptor subtype with some selectivity, since they showed lower affinities to D_2R (K_i 1.3–5.5 μM). With the LINS01 compounds showing moderate binding affinity, new lead structures for optimization with regards to combined H_3R and D_2R/D_3R-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, H_1R to H_4R.[5] The H_1R and H_2R are widely expressed in the brain and are related to the control of sleep, food intake, body temperature and cognition. The H_4R is expressed in glial cells and may play a role in the inflammatory processes in the CNS.[6] The H_3R 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, D_1R-D_5R. Considering their signalling profile, they are grouped into D_1-like (coupled to G_s) and D_2-like (coupled to $G_{i/o}$) families.[3] Classically, D_2-like receptors (D_2R, D_3R and possibly D_4R) 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 D_2R in the movement-related and cortical areas and the high density of both D_2R and D_3R in brain areas such as the limbic system may explain why non-selective D_2R 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] D_3R blockade also increases the acetylcholine release in the cortex, related to the improvement in the cognitive processes.[11] In spite of this, selective D_3R 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, H_3R and D_3R present a considerable density distribution overlapping in the limbic areas, such as hippocampus, stratum and amygdala.[12] It is interesting to note that 95% of the neurons expressing dopamine D_1-like receptors and 89% of those expressing D_2-like receptors in the striatum also express H_3R leading to complex interactions between both neurotransmitter systems.[13] Several results from pharmacological studies suggest that antagonists of both H_3R and D_3R 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 LINS01 compounds (e.g., **1c** and **1g**, Figure 1) were previously described as selective H_3R antagonists.[16,17] However, these compounds present some similarity to dopamine D_2R/D_3R ligands, since the overlap between the H_3R and D_2R/D_3R pharmacophores can be noted.[8,18] The *N*-phenylpiperazine motif present in some LINS01 compounds is found in several D_2R/D_3R ligands such as compounds **2**, **3** and **4** in Figure 1.[19,20] Moreover, the similarity of LINS01 compounds to compound **4** and its analogue **5** is clearly evident, which are potent ligands of D_2R and D_3R.[11] Considering the potential of these compounds and the similarities, the present report intended to assess the affinity of the LINS01 compounds to the D_2R/D_3R.

2. Experimental

2.1 *Preparation of the compounds LINS01*

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

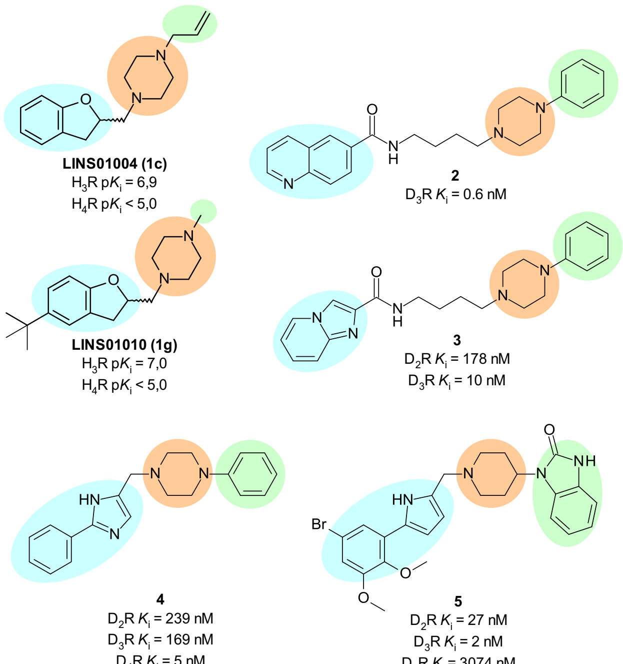

Figure 1. LINS01 compounds and literature ligands of D_2R/D_3R.

Figure 2. Ligands of D_2R and D_3R 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**. ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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**. ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 D_2R and D_3R*

Membranes from CHO cells stably expressing either the short transcript of D_2 receptors or D_3 receptors were prepared as described previously.[23] For inhibition screening, freshly thawed membrane preparations (containing 25 and 20 µg/well of D_2R and D_3R, respectively) were incubated on microtiter plates with the indicated concentration of compounds and 0.2 nM [^{3}H]spiperone in binding buffer [50 mM TRIS (pH = 7.4) 120 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$ and 1 mM $MgCl_2$]. 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 [^{3}H]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 IC_{50} 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 methodology[17] 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 D_2R and D_3R, depending on the presence of certain groups. In general, a slight preference for

Scheme 1. Reagents and conditions. (a) Allyl bromide (2 eq.), K_2CO_3 (2 eq.), acetone, 60 °C, 2–4 h; (b) DMF, MW 200 °C (300 psi, 300 W), 1,5 h; (c) I_2 (1.1 eq.), water or EtOH/water, *r.t.*, 4–6 h; (d) K_2CO_3 (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 D_2R and D_3R.

Compounds	R 1	R 2	% inhibition (10 μM) ± SD (n)		K_i (μM) [95% CI]	
			D_2R	D_3R	D_2R	D_3R
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	*t*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 [^{3}H]spiperone binding to D_3R was observed. Compounds **1a** to **1d** bear the 1-(2,3-dihydrobenzofuranyl)methylpiperazine core with different substituents attached to the nitrogen. Whereas **1a** did not show important inhibition at both D_2R and D_3R, 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 D_2R. Furthermore, the results suggest that the presence of these groups drive the preference toward D_3R.

These results motivated us to further explore the affinities of the *N*-phenylpiperazine derivatives. The *N*-arylpiperazine group can be considered a privileged group to design ligands of D_2-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 D_2R. Though only **1d** showing significant D_3R preference among them, even submicromolar K_i values were determined at the D_3R.

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 H_3R 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 D_2R and D_3R affinities, and should be considered in future evaluations. Secondly, derivatization of *N*-phenylpiperazine may be used for enhancing affinity at D_2R and D_3R. For instance, the substitution with a 2-methoxy or 2,3-dichloro groups in the phenyl ring usually leads to increased D_3R selectivity, as can be seen in cariprazine (a subnanomolar affinity D_3R ligand and nanomolar affinity at D_2R) 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 ligands[10] (Figure 2).

4. Conclusions

This is the first report exploring the histamine H_3R-targeting LINS01 compounds being ligands at dopamine receptors as well. Although these molecules showed low affinity to D_2R and D_3R, some of them show slight D_3R preference. The *N*-phenylpiperazine and *N*-benzylpiperazine fragments increased the binding of these compounds to D_2R and D_3R, although the latter reduces the selectivity. Additionally, the substitution in the dihydrobenzofuran seems not to influence the affinity of these compounds to D_2R or D_3R. 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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