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Original article

Synthesis and pharmacological evaluation of new *N*-phenylpiperazine derivatives designed as homologues of the antipsychotic lead compound LASSBio-579

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ABSTRACT

In an attempt to increase the affinity of our antipsychotic lead compound LASSBio-579 (1-((1-(4-chlorophenyl)-1H-pyrazol-4-yl)methyl)-4-phenylpiperazine; (**2**)) for the 5-HT$_{2A}$ receptor, we synthesized five new *N*-phenylpiperazine derivatives using a linear synthetic route and the homologation strategy. The binding profile of these compounds was evaluated for a series of dopaminergic, serotonergic and alpha-adrenergic receptors relevant for schizophrenia, using classical competition assays. Increasing the length of the spacer between the functional groups of (**2**) proved to be appropriated since the affinity of these compounds increased 3–10-fold for the 5-HT$_{2A}$ receptor, with no relevant change in the affinity for the D$_2$-like and 5-HT$_{1A}$ receptors. A GTP-shift assay also indicated that the most promising derivative (1-(4-(1-(4-chlorophenyl)-1*H*-pyrazol-4-yl) butyl)-4-phenylpiperazine) (LASSBio-1635) (**6**) has the expected efficacy at the 5-HT$_{2A}$ receptors, acting as an antagonist. Intraperitoneal administration of (**6**) prevented apomorphine-induced climbing behavior and ketamine-induced hyperlocomotion in mice, in a dose dependent manner. Together, these results show that (**6**) could be considered as a new antipsychotic lead compound.

1. Introduction

Schizophrenia is a severe neuropsychiatric disorder that affects about 24 million people worldwide [1] and is characterized by positive or psychotic symptoms (e.g. hallucinations, delusions and disorganized thoughts), negative symptoms (e.g. social withdrawal, anhedonia, avolition, alogia) and cognitive dysfunction (e.g. memory deficits, attention impairment) [2,3]. Since the discovery of chlorpromazine, in 1952, schizophrenia has been treated with drugs now classified as typical or first-generation antipsychotics (e.g. haloperidol, chlorpromazine) acting as postsynaptic dopamine D$_2$ receptor antagonists and effective against positive symptoms [4]. However, these drugs have little effects on negative and cognitive symptoms and elicit severe extrapyramidal side effects due an excessive D$_2$ receptor blockade in the striatum. A second generation of antipsychotics (e.g. risperidone, olanzapine and quetiapine) emerged after the introduction of clozapine (**1**) [4]. These drugs were named atypical based on their low propensity to

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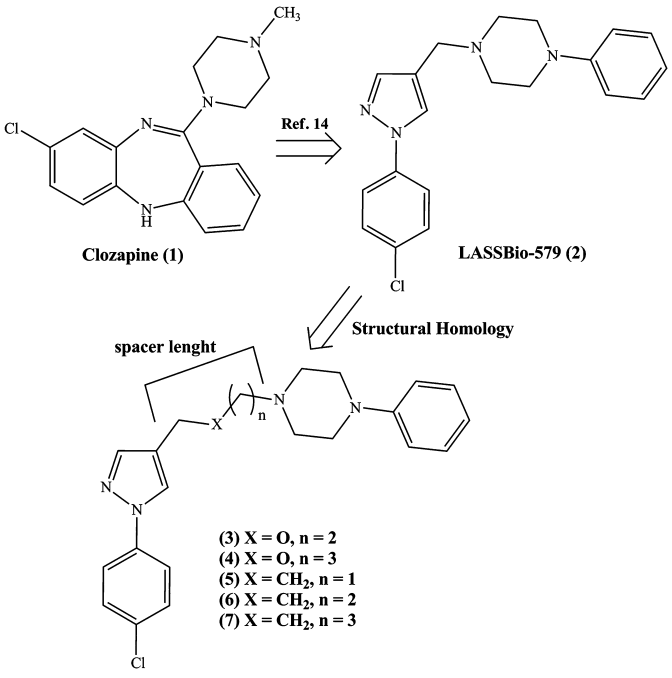
elicit extrapyramidal effects, claimed relative efficacy against negative and cognitive symptoms and multi-target profile [5,6]. Initially, a key role has been attributed to the 5-HT_{2A} receptors since the potent blockade of these receptors coupled to weaker antagonism of D_2 receptors has been found to be the feature shared by these atypical antipsychotics [7]. More recently, the 5-HT_{1A} receptors have attracted the attention since their activation should also be a crucial element in the mechanism of action of these atypical antipsychotics [7–9]. As a result, the present prevailing idea is that improvement of positive symptoms is due to D_2 antagonism whereas the lower liability to induce extrapyramidal symptoms and the improvement of negative symptoms are a result of an increase dopamine release in striatum and frontal cortex, respectively, which can be achieved either by 5-HT_{2A} blockade or 5-HT_{1A} activation [6–11]. However, there is a high level of treatment discontinuation due to both low tolerability and insufficient effectiveness, supporting the need for developing more effective and safer antipsychotics [4,12,13]. In previous studies our group described a series of *N*-phenylpiperazine derivatives in the search for new atypical antipsychotic prototypes [14,15]. Based on these results, (**2**) (Scheme 1), was selected for a more detailed characterization of its pharmacological profile both in vitro and in vivo [16,17]. Oral administration of (**2**) inhibited the apomorphine-induced climbing, ketamine-induced hyperlocomotion and deficit of prepulse inhibition of acoustic startle reflex induced by apomorphine, (±)-DOI and ketamine, indicating that it acts more like clozapine than haloperidol. The participation of a serotonergic effect was compatible with preliminary results [18] and with its detailed binding profile defining it as a dual D_2-like/5-HT_{1A} ligand [17]. However, (**2**) has a relatively low affinity for the 5-HT_{2A} receptor, classically considered as an important target for the atypical antipsychotics (see above), and its pharmacodynamic profile could be further optimized. For this purpose, homologation [19] could be a suitable strategy since the presence of two planar aromatic or heterocyclic ring systems separated by an aliphatic or alicyclic chain containing basic protonable nitrogen has been reported to favor binding to the 5-HT_{2A} receptor [20,21]. In the present study, we report the synthesis of five new derivatives obtained through the extension of the methylene spacer between the 4-chloro-*N*-phenylpyrazolyl and *N*-phenylpiperazine subunits of (**2**). The binding profiles of these compounds to monoaminergic receptors relevant to the treatment of schizophrenia as well as their effectiveness in pharmacological models of schizophrenia symptoms in mice were assessed. Present results indicate that a significant increase in affinity for the 5-HT_{2A} receptor has been achieved and one of these compounds (**6**) is a better hit than (**2**) and is active in two mice models of schizophrenia positive symptoms at doses without effect on spontaneous locomotion.

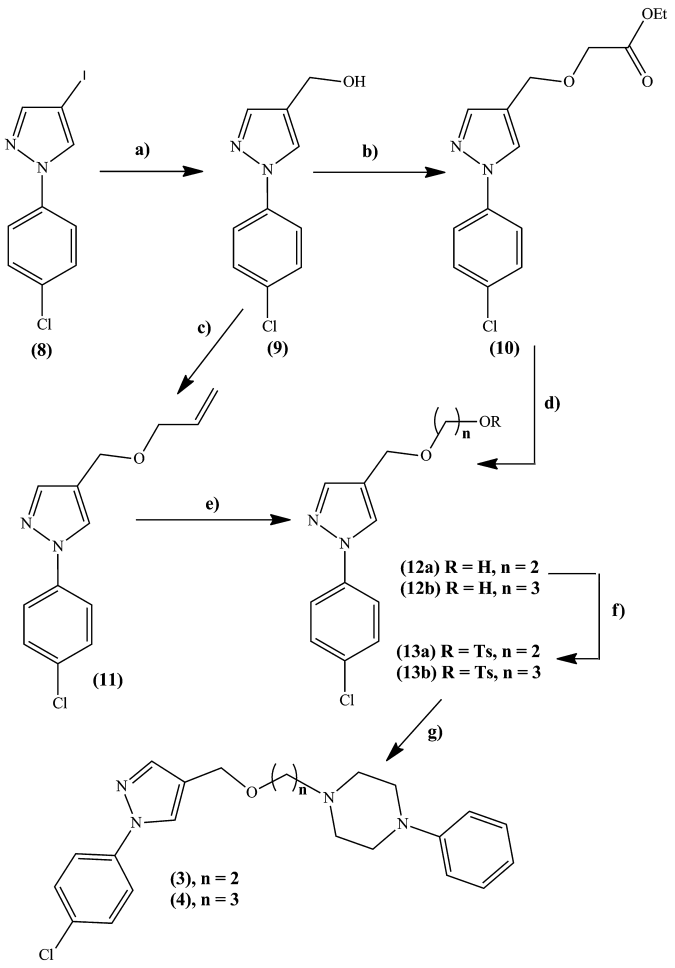


Scheme 1. Design Concept of novel oxa- and carba-homologue pyrazole *N*-phenylpiperazine derivatives (**3**–**7**).

2. Results and discussion

2.1. Chemistry

The novel series of pyrazole *N*-phenylpiperazine derivatives (**3**–**7**) was prepared by classical synthetic methodologies, using 4-formyl-*N*-(4′-chlorophenyl)pyrazole (**8**) and *N*-(4′-chlorophenyl) pyrazole (**14**) as starting material (Schemes 2 and 3). The initial step used for the construction of pyrazole *N*-phenylpiperazine oxanalogue derivatives **3** (n = 2) and **4** (n = 3) consisted of the



Scheme 2. Synthesis of oxa-homologue pyrazole *N*-phenylpiperazine derivatives (**3**) and (**4**). Reagents and Conditions: a) $NaBH_4$, MeOH, 0 °C, 15 min, 80%; b) 1) NaH, THF, 0 °C, 1 h, 2) $BrCH_2CO_2Et$, 0 °C, 4 h; 70%; c) 1) NaH, THF, 0 °C, 1 h, 2) $BrCH_2CH{=}CH_2$, 0 °C, 4h; 70%; d) $LiAlH_4$, THF, 70 °C, 4h, 70%; e) 1) BH_3, THF, 0 °C, 2h, 2) 30% aq. H_2O_2, 10% aq. NaOH, reflux, 12h, 50%; f) TsCl, KOH, K_2CO_3, rt, 20 min [60% for (**13a**) and (**13b**)]; g) *N*-phenylpiperazine, Li_2CO_3, CH_3CN, 80 °C, 20h [60% for (**3**) and (**4**)].