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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 15 (2005) 4560–4563

8-Substituted 3,4-dihydroquinolinones as a novel scaffold for atypical antipsychotic activity

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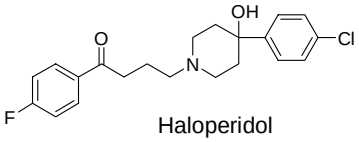
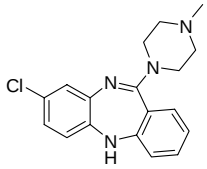
Received 31 May 2005; revised 22 June 2005; accepted 29 June 2005
Available online 8 August 2005

Abstract—Several new, potent dopamine subtype 2 (DA D_2) active compounds with serotonin subtype 2A (5-HT_{2A}) pharmacology are presented. 8-Substituted 3,4-dihydroquinolinones, tetrahydroquinolines, and *N*-acyl tetrahydroquinolines were evaluated in primary assays. Subtle changes on this novel scaffold translated to large changes in potency and selectivity in vitro. These compounds show promise as novel atypical antipsychotics for the treatment of schizophrenia.

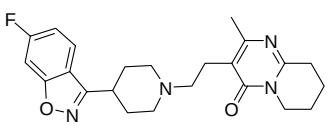
Nearly 24 million people worldwide are afflicted with schizophrenia, a chronic debilitating mental disorder.[1] It is thought that excess dopamine in the brain underlies the positive symptoms of schizophrenia and that blockade of dopamine receptors is a prerequisite for antipsychotic activity. There is a clearly established relationship between the dose that is adequate to treat positive symptoms and the drug's affinity for the DA D_2 receptor.[2] Older standards of treatment such as haloperidol, a non-subtype selective dopamine antagonist without significant serotonergic pharmacology, have little effect on negative symptoms and are implicated in the development of extra-pyramidal side effects (EPS).[3]



Haloperidol



Clozapine



Risperidone

The newer generation of treatments, referred to as atypical antipsychotics, incorporate potent activity at serotonin (5-HT) receptors. It is thought that 5-HT_{2A} antagonism together with relatively weaker dopamine antagonism are principal features that differentiate the side-effect profile of atypical antipsychotics, such as clozapine, from the first generation of treatments.[4] Although the newer atypical antipsychotics olanzapine, risperidone, and quetiapine have brought about improvements in toleration and negative symptomology, chronic treatment may lead to unwanted weight gain, blood dycrasias, and motor dysfunctions, such as EPS and tardive dyskinesia (TD).[5] These side effects may be linked to drug-dependent affinity for other receptors.[6] The search continues for new atypical antipsychotics that are more efficacious and have fewer side effects than currently available treatments. In this paper, we describe our recent efforts to discover novel templates in the area of selective dual 5-HT_{2A}/D_2 antagonists for potential use as treatments for schizophrenia.

The compounds prepared in this program include a unique 8-linked 3,4-dihydroquinolinone scaffold (Scheme 1). The chemistry affording aniline **1** was readily scaleable and amenable to rapid diversification.[7] Nitration of commercially available phenylacetic acids proceeded smoothly to provide a coupling substrate for benzisothiazole and benzisoxazole piperazines.[8] The piperazine was efficiently coupled to the acid using BOP-Cl. Borane-methyl sulfide complex was utilized to reduce the amide and treatment with Raney Ni afforded **1**. From

Keywords: Atypical Antipsychotics; Dopamine; Serotonin.
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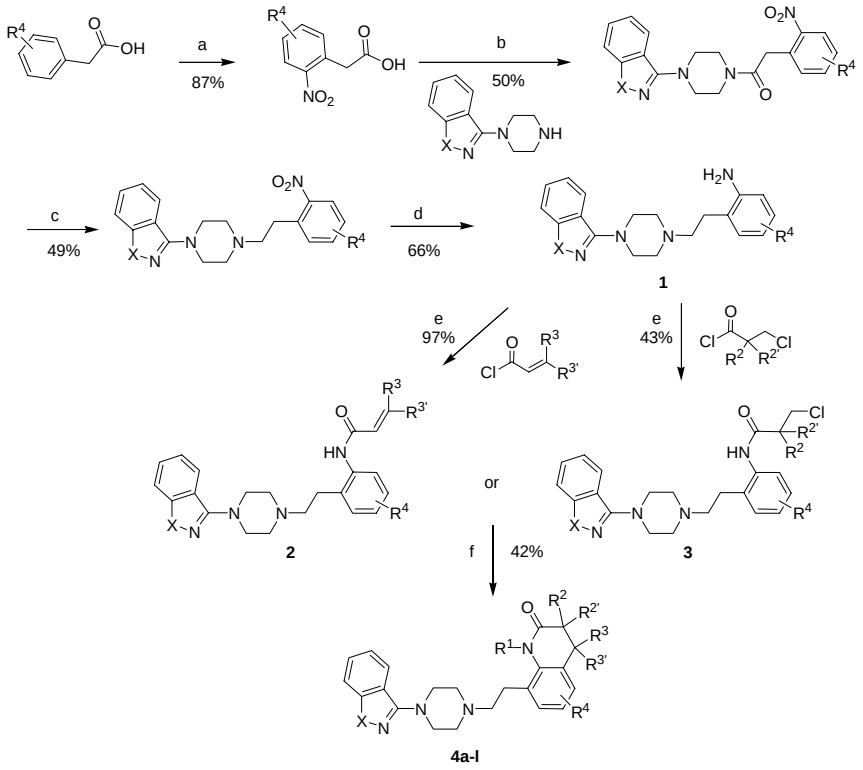
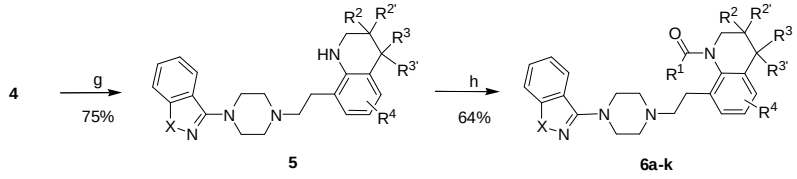
doi:10.1016/j.bmcl.2005.06.097



Scheme 1. Reagents: (a) TFAA, NH_4NO_3, $CHCl_3$; (b) BOP-Cl, Et_3N, CH_2Cl_2; (c) BMS complex, toluene, reflux; (d) Raney Ni, H_2, cat. Et_3N; (e) Et_3N, THF; (f) $AlCl_3$, chlorobenzene, reflux.



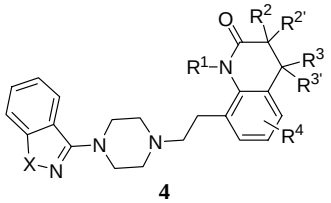
Scheme 2. Reagents: (g) BH_3 THF; (h) R^1COCl, Et_3N, THF.

this common intermediate, appropriate acid chlorides were employed to yield **2**. Alternatively, chloropropionyl chlorides may be used to afford cyclization substrates (amide **3**). Friedel–Crafts cyclization to the lactam yielded the first targets **4a**–**l**, which were then further derivatized via a reduction–acylation procedure (Scheme 2). In selected cases, borane was again used to reduce the amide of the 3,4-dihydroquinolinone (**5a** and **5b**). *N*-Acyl tetrahydroquinolines were prepared via acylation of **5** with the appropriate acid chlorides to furnish compounds **6a**–**k**.

The affinities of target compounds for DA D_2 and 5-HT_{2A} receptors were evaluated in in vitro binding assays using the radioligands [^{3}H]spiperone or [^{3}H]ketanserin, respectively.[9]

The in vitro results for **4a**–**l** are given in Table 1. Substitutions at R^3,$R^{3'}$ are required for potency in DA D_2. While fluoro is tolerated at the 6-position, chloro substitution is not (entries **4c** and **4k**). Methyl groups at the 5-position seem to enhance affinity in DA D_2 (see **4j** vs. **4g**). When the lactam nitrogen is substituted with a methyl group, (**4e**) a fourfold reduction in DA D_2

Table 1. 3,4-Dihydroquinolinones



4

Entry	X	R^1	R^2, $R^{2'}$	R^3, $R^{3'}$	R^4	D_2 K_i (nM)[a]	5HT_{2A} K_i (nM)[a]
4a	S	H	H	H	H	>100	0.28
4b	S	H	H	CH_3	H	21	0.22
4c	S	H	H	CH_3	6-F	15	0.17
4d	S	H	CH_3	H	H	73	1.06
4e	S	CH_3	H	CH_3	H	81	0.17
4f	S	H	H	H, Ph	H	15	0.18
4g	O	H	H	CH_3	H	>100	190
4h	S	H	H	CH_3	5-CH_3	11	0.13
4i	SO	H	H	CH_3	6-F	92	2.23
4j	O	H	H	CH_3	5-CH_3	35	0.28
4k	S	H	H	CH_3	6-Cl	>100	0.05
4l	O	H	H	CH_3	6-F	>100	0.28

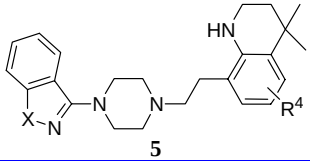
[a] Values are means of at least three experiments, see Ref. 8.

potency takes place. Replacement of benzisothiazole with benzisoxazole results in compounds with conserved 5-HT_{2A} affinity, except in the case of **4g**, which shows a significant reduction of affinity for both receptors. Oxidation of the benzisothiazole is detrimental both to DA D_2 and 5-HT_{2A} potency. In general, these compounds retain the desired 10-fold ratio of DA D_2 to 5-HT_{2A} affinity.

To determine whether the lactam carbonyl was essential for binding, selected compounds were reduced. The resultant tetrahydroquinolines given in Table 2 retain 5-HT_{2A} potency, but with a threefold decrease in affinity for the DA D_2 receptor when compared to analogs from Table 1. Owing to this characteristic drop in D_2 affinity, these intermediates were not routinely screened.

Table 3 (compounds **6a**–**k**) shows that the potency is recovered by introduction of acyl groups on the tetrahydroquinoline. Again, 6-chloro substitutions adversely affect DA D_2 affinity for these compounds, as seen in **6h**. Although tolerated in DA D_2, large acyl groups (**6c**, **6d**) result in reduced affinity for 5-HT_{2A}. Interestingly, the cyclohexyl group (**6e**) does not cause this change. When comparing **6j** to **4f** from Table 1, it seems that the large phenyl group at R^3 has a deleterious effect on 5-HT_{2A} potency in the *N*-acyl series.

Table 2. Tetrahydroquinolines



5

Entry	X	R^4	D_2 K_i (nM)[a]	5HT_{2A} K_i (nM)[a]
5a	S	H	59	0.18
5b	S	6-F	55	0.28

[a] Values are means of at least three experiments see Ref. 8.

In general, the lactam scaffold is useful for modulating DA D_2 affinity and the *N*-acyl scaffold reveals robust 5-HT_{2A} potency. This trend can be seen more clearly in the plot (Fig. 1).

In summary, a series of novel 8-substituted 3,4-dihydroquinolinones, tetrahydroquinolines, and *N*-acyltetrahydroquinolines were synthesized and evaluated in vitro for affinity to DA D_2 and 5-HT_{2A} receptors. This flexible scaffold proves useful for promoting atypical antipsychotic activity.[10] Additionally, this series of compounds provides options for the development of SAR in either DA D_2 or 5-HT_{2A}. The optimal separation of at least 10-fold ratio of DA D_2/5-HT_{2A} binding translates to a lack of EPS in a rat model.[11] Although the SAR for both receptors does not track together, small changes on this scaffold can have a large impact in tuning DA D_2 or 5-HT_{2A} affinities or both.

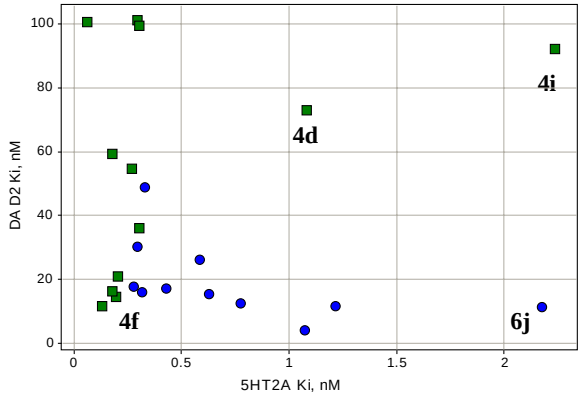
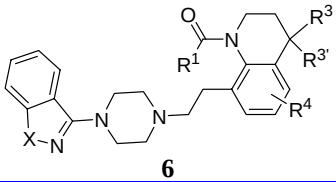


Figure 1. Plot DA D_2 vs. 5-HT_{2A} for *N*-acyl and lactam analogs. Blue dots represent tetrahydroquinoline analogs from Tables 2 and 3, while green squares represent 3,4-dihydroquinolinone analogs from Table 1. Four compounds are shown with their Table reference.

Table 3. *N*-Acyl tetrahydroquinolines



6

Entry	X	R^1	R^3, $R^{3'}$	R^4	D_2 K_i (nM)[a]	5HT_{2A} K_i (nM)[a]
6a	S	Phenyl	CH_3	H	16	0.61
6b	S	CH_3	CH_3	H	17	0.30
6c	S	2,5-Dimethyoxy benzyl	CH_3	H	11	1.24
6d	S	3-Methoxy benzyl	CH_3	H	4	1.07
6e	S	Cyclohexyl	CH_3	H	25	0.59
6f	S	CH_3	CH_3	6-F	18	0.44
6g	O	CH_3	CH_3	5-CH_3	17	0.32
6h	S	CH_3	CH_3	6-Cl	>50	0.31
6i	O	CH_3	CH_3	6-F	29	0.29
6j	S	CH_3	H, phenyl	H	12	2.15
6k	S	CH_3	CH_3	5-CH_3	12	0.75

[a] Values are means of at least three experiments see Ref. 8.

Acknowledgments

The authors acknowledge Susan Borosky, John Cordon, and Kevin Serpa for generation of in vitro and in vivo data.

References and notes

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9. Standard filtration receptor binding techniques were used to evaluate the affinity of compounds for recombinant receptors. The DA D_2 receptor binding assay utilized cell membranes prepared from CHO cells expressing human DA D_2 receptors. The 5-HT_{2A} receptor binding assay utilized cell membranes prepared from Swiss 3T3 cells expressing human 5-HT_{2A} receptors. Membrane and radioligand were incubated in the presence, or absence, of varying concentrations of the compound of interest for 120 min. Nonspecific binding was determined by addition of high concentrations of haloperidol or unlabeled ketanserin for the DA D_2 or 5-HT_{2A} assays respectively. Unbound radiolabel was separated from bound radiolabel by vacuum filtration. The amount of bound radiolabel was determined by liquid scintillation spectrophotometry. The relationship between concentration and percent inhibition of specific binding was fit using nonlinear regression to determine IC_{50} concentration. IC_{50} concentrations were converted to K_i affinity constants using the Cheng–Prusoff equation.
10. Compounds **4b** and **4c** were determined to be active in the d-amphetamine-stimulated locomotor activity (LMA) in vivo model.
11. None of the compounds tested from this series produced a minimally effective dose (MED) below 30 mg/kg in an in vivo catalepsy test.