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Design, Synthesis, and Discovery of 3-Piperazinyl-3,4-dihydro-2(1*H*)-quinolinone Derivatives: A Novel Series of Mixed Dopamine D_2/D_4 Receptor Antagonists

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Abstract—3-Piperazinyl-3,4-dihydro-2(1*H*)-quinolinone derivatives (δ-lactams) were designed, synthesized, and identified as a new series of mixed dopamine D_2/D_4 receptor antagonists. To further the structure–activity relationship (SAR) study, 3-piperazinyl-indolin-2-ones (γ-lactams) and 3-piperazinyl-3*H*,4*H*,5*H*-benzo[*f*]azepin-2-ones (ε-lactams) were also prepared and examined.

Introduction

Schizophrenia is a debilitating disease for which researchers believe that brain dopamine receptors are the primary targets for medical treatment.[1] Molecular biology studies have identified five dopamine receptor subtypes which can be classified into two classes, D_1-like (D_1 and D_5)[2,3] and D_2-like (D_2, D_4, and D_5),[4–6] based on their ability to stimulate or inhibit adenylate cyclase, respectively. In the last several years, intense research effort has been focused on the D_4 receptor. These efforts led to the clinical trials of a number of D_4 selective antagonists[7–18] including NGD94-1 (**1**),[19] L-745,870 (**2**),[20] U-101387 (**3**),[21] and CP-293019 (**4**)[22] in Figure 1. However, these compounds have not proved to be efficacious as potential antipsychotic agents. For example, compound **2** was found to be ineffective in humans.[23] Many laboratories have also identified a number of D_2 selective agonists[24,25] or antagonists,[26,27] but none of them are efficacious in treating all schizophrenic patients.

Clozapine (**5**)[28] is the first marketed antipsychotic agent which binds with substantially greater affinity to dopamine D_4 than to D_2 receptor subtype. Although D_4 may play an important role in the actions of clozapine, the association with D_2 may be also required for effective antipsychotic action. Therefore, we set out a research program to obtain a compound that possessed a D_2/D_4 binding ratio similar to that of clozapine. Furthermore, it was also desirable to minimize α_1 binding in order to avert undesirable cardiovascular effects. In the course of our studies, we identified two series of compounds having a combination of D_2 and D_4 receptor affinities comparable to clozapine **5**. They are *trans*-1-[2-(phenylcyclopropyl)methyl]-4-aryl-piperazines (e.g., **6**)[29] and benzylpiperazinyl ethanoindoline derivatives (e.g., **7**).[30] In this paper, we describe a new series of mixed dopamine D_2/D_4 receptor antagonists, the 3-piperazinyl-3,4-dihydro-2(1*H*)-quinolinones (e.g., **9**, Fig. 2), and demonstrate how they are genealogically related to the previously mentioned indoline derivatives.

Design and Synthesis

The indoline containing compound **7** was previously evaluated as a lead with potent D_4 binding activity and weak D_2 binding affinity.[30] Based on this lead compound, compound **8** was designed at first by removing one carbon from the indoline part of compound **7** and prepared starting from *N*-methylaniline.[31] Biological screening showed that this compound had not only lost some activity for D_4 binding, but it was totally inactive at D_2 receptors.

We reasoned that this decreasing affinity resulted from the loss of conformational restriction present in **7**. Molecular modeling studies indicated that the energetically most favorable presentation of the amide oxygen of **7** is directed away from the indoline phenyl, as shown in Figure 2. It seemed that an alternative conformational

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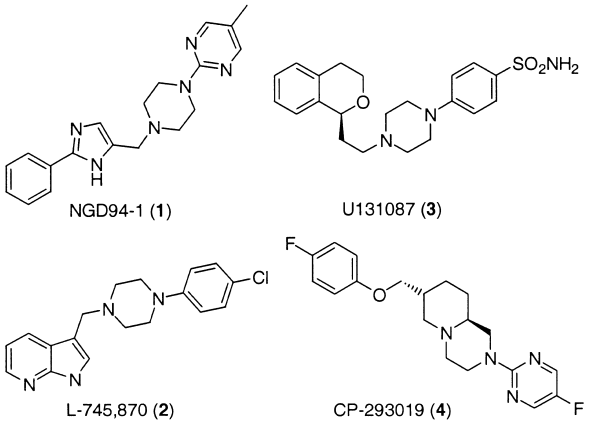


Figure 1.

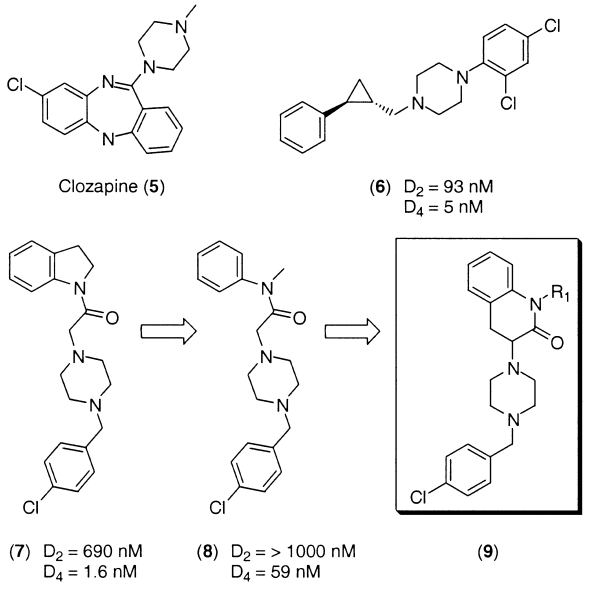
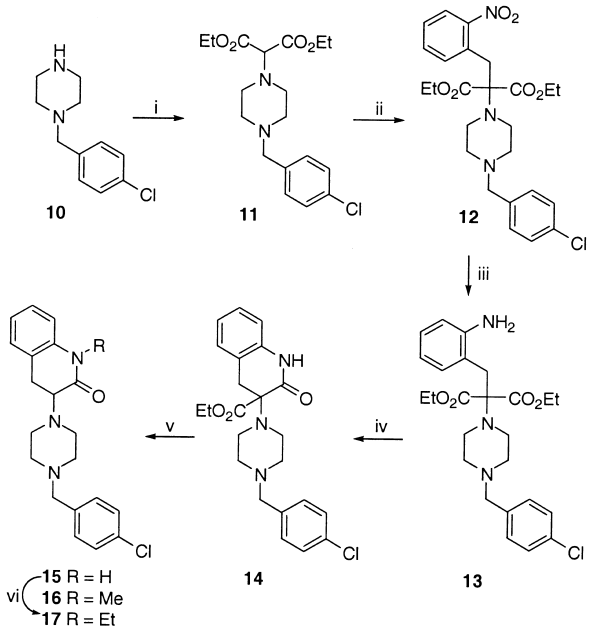


Figure 2.

restriction, which would hold the carbonyl in this orientation, might provide a more favorable receptor affinity profile. Consequently, compound **9** was designed by placing two carbons between the α position of the amide and the corresponding carbon of the phenyl ring to generate a new benzofused δ-lactam system.

Scheme 1 depicts the synthesis used to prepare these benzofused δ-lactams. Alkylation of 1-[(4-chlorophenyl)-methyl] piperazine **10** with diethyl bromomalonate and potassium carbonate in acetonitrile provided compound **11**, which was then treated with freshly prepared sodium ethoxide and alkylated with 2-nitrobenzyl chloride to give compound **12**. Hydrogenation of **12** with 10% Pd/C in ethyl acetate at atmospheric pressure generated the amine **13**, which could be cyclized to form the lactam **14**. Decarboxylation of **14** provided **15**, which was alkylated on the nitrogen with either iodomethane or iodoethane to provide compounds **16**[32] and **17**, respectively.

In order to better understand the structure–activity relationships of the lactam system, 3-indolin-2-one derivatives (γ-lactams) and 3-piperazinyl-3*H*,4*H*,5*H*-



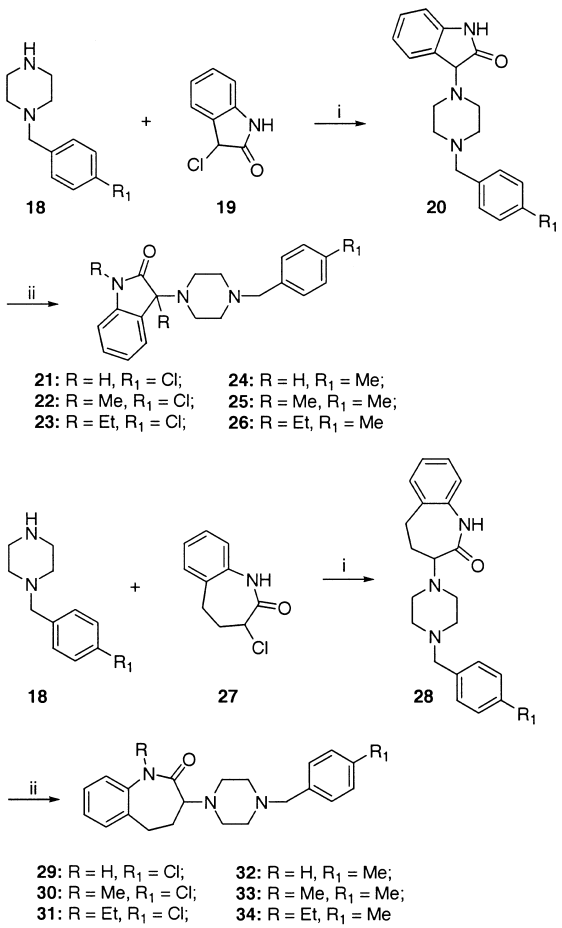
Scheme 1. Reagents and conditions: (i) diethyl bromomalonate, K_2CO_3, CH_3CN, rt, 18 h, 98%; (ii) 2-nitrobenzyl chloride, NaOEt, EtOH, reflux, 15 h, 54%; (iii) H_2, 10% Pd/C, 1 atm, EtOAc, rt, 24 h, 91%; (iv) EtOH, reflux, 4 h, 85%; (v) 20% NaOH, MeOH, reflux, 18 h; then 6 N HCl, 82%; (vi) MeI or EtI, NaH, THF, argon, rt, 5 h, 85% or 78%, respectively.

benzo[*f*]azepin-2-ones (ε-lactams) were also synthesized by direct condensation of the substituted phenylpiperazines with the corresponding α-halogen lactams as shown in Scheme 2. For example, when the substituted piperazine **18** was stirred with 3-chloroindolin-2-one **19**[33] and potassium carbonate at room temperature for 15 h, compound **20** (γ-lactam) was prepared. Although many alkylation conditions were tried for the *N*-monosubstitution of compound **20**, the disubstituted compounds (**21**, **22**[34]–**26**) were always the major products. No disubstituted compound was observed when compound **28** (ε-lactam), prepared from 3-iodo-1*H*,3*H*,4*H*,5*H*-benzo[*f*]azepin-2-one **27**,[35] was treated under the same reaction conditions. Only the monosubstituted compounds (**29**, **30**[36]–**34**) were produced. We were unable to prepare 3-bromo-1,3,4-trihydroquinolin-2-one due to rapid dehydrohalogenation. Thus, the direct condensation strategy was not applicable to the synthesis of δ-lactam series.

Results and Discussion

Table 1 shows the binding data for the target compounds at D_2, D_4, and α_1 receptors. Affinities at D_2 and D_4 receptors were determined via standard competitive displacement assays using human D_2 and D_4 clones with [^{3}H]YM 09151 as the competitive ligands. Affinity at the α_1 receptor was determined via standard competitive displacement assays using rat brain homogenate with [^{3}H]prazosin as the competitive ligand.

Surprisingly, all five- and seven-member ring lactams are inactive to both D_2 and D_4 binding. Only the six-



Scheme 2. Reagents and conditions: (i) K_2CO_3, CH_3CN, reflux, 15 h, 85–96%; (ii) MeI or EtI, NaH, THF, argon, rt, 5 h, 61–88%.

Table 1. Binding affinities

Compounds	K_i (nM)		
	D_2	D_4	α_1
Clozapine	113	17	4
6	93	5	322
7	690	1.6	88
8	>1000	59	>10,000
15	1373	100	2003
16	133	4	2003
17	21	4	1265
21	>1000	>1000	>10,000
22	>1000	>1000	>10,000
23	>1000	7018	>10,000
24	>1000	>1000	>10,000
25	>1000	>1000	>10,000
26	>1000	>1000	>10,000
29	>1000	>1000	9591
30	7367	2469	2878
31	>1000	1511	2678
32	>1000	>1000	3120
33	>1000	4377	2038
34	>1000	2960	815

member ring lactams displayed appreciable affinities for dopamine receptors. Compound **15** shows moderate binding to the D_4 receptor, but weak affinity for D_2. The methyl group of compound **16** improves both D_2 and D_4 binding by 10- and 25-fold, respectively, relative to the secondary lactam **15**. The affinity data of **16** for dopamine receptors are very close to those of clozapine. The *N*-ethyl compound **17** is 6-fold more potent than compound **16** for D_2 but equal for D_4. As above, the current δ-lactams **16** and **17** have more potent D_2 and D_4 affinity binding and better α_1 profile than clozapine **5** and another two series (**6** and **7**), which we identified earlier.

Compounds were also assessed as to their functional activity both at the D_2 and D_4 receptors. D_2 functional activity was assessed via compound reversal of quinpirole inhibited, forskolin stimulated cAMP production from whole cells, while D_4 functional activity was assessed via inhibition of quinpirole stimulated GTPγ^{35}S binding from cell membranes. Functional assessment of compounds **16** and **17** at both the D_2 and D_4 receptors indicates no agonist properties up to 10 μM, while demonstrating functional K_i values of 4 nm and 1.5 nm, respectively, at the D_2 receptor, and 1 nm and 1.5 nm at the D_4 receptor.

In conclusion, the δ-lactams **16** and **17** thus displayed a D_2 and D_4 affinity ratio similar to that of clozapine while being free of the liabilities caused by high α_1 affinity. Further structure–activity relationship investigations of this series of mixed dopamine D_2/D_4 receptor antagonists are in progress.

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35. Prepared from 1*H*,3*H*,4*H*,5*H*-benzo[*f*]azepin-2-one by treatment with TMEDA (3 equiv) and iodotrimethyl silane (3 equiv) in anhydrous dichloromethane at 0 °C under argon for 30 min, and subsequent treatment with solid iodine (1.5 equiv) at the same temperature for an additional 1 h. The reaction was quenched by addition of excess aqueous sodium sulfite and worked up as usual. The residue was purified by silica gel column chromatography to give the product as a white solid in 84% yield.
36. Mp 145 °C (2 HCl, dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.19 (m, 6H), 7.08–7.03 (m, 1H), 6.81 (d, J = 8.1 Hz, 1H), 3.42 (s, 2H), 3.18 (s, 3H), 2.67–2.63 (m, 4H), 2.41 (m, 4H), 1.49 (s, 3H); LC-MS (APCI, m/z) 370 (M + 1).