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Design, Synthesis, and Discovery of 5-Piperazinyl-1,2,6,7-tetrahydro-5*H*-azepino[3,2,1-*hi*]indol-4-one Derivatives: A Novel Series of Mixed Dopamine D_2/D_4 Receptor Antagonist

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Abstract—5-Piperazinyl-1,2,6,7-tetrahydro-5*H*-azepino[3,2,1-*hi*]indol-4-one derivatives were designed, synthesized, and identified as a new series of mixed dopamine D_2/D_4 receptor antagonists. This series featured a rigid tricyclic ring system as an important pharmacophore core structure for high binding affinity. Molecular modeling studies are also described.

Dopamine has been implicated in the pathophysiology of schizophrenia for decades. The traditional antipsychotic agents provide very good correlation between their clinical efficacies and binding affinities for dopamine D_2 receptor. These 'typical' antipsychotic agents are used for treatment of positive symptoms of schizophrenia, but their use is limited by disabling side effects such as extrapyramidal syndrome (EPS), tardive dyskinesia, and hormonal side effects.[1] On the other hand, the 'atypical' antipsychotic agent clozapine has several clinical advantages over classical antipsychotic agents. This drug displays not only high effects in positive and negative symptoms without producing side effects, but also prevents psychosis in some patients who were either refractory or intolerant to the effects of classic neuroleptics.[2,3] The higher affinity of clozapine for D_4 over D_2 receptors (about 10-fold) sparked research efforts in the D_4 receptor as a potential target for antipsychotic therapy.[4] Several laboratories have examined their highly selective dopamine D_4 antagonists in clinical trials, but, to date there is no positive efficacy result for these agents.[5] Therefore, we hypothesized that the unique profile of clozapine may be a result of a particular ratio of D_4 and D_2 receptor affinities. Thus, we set out to identify mixed D_2/D_4 receptor antagonists having high D_4 (<10 nM) and moderate D_2 (<200 nM) affinities which maintained a similar binding ratio to that of clozapine, and the postulate has been supported by our recent studies.[6,7] A secondary criteria of our search required lower binding affinity to α_1 (>1000 nM) in order to avert undesirable cardiovascular effects.

Design and Molecular Modeling

In a previous paper,[8] we identified a novel series of benzofused δ-lactam piperazine mixed D_2/D_4 receptor antagonists which were discovered through the systematic transformation of lead compound 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2,3-dihydro-indol-1-yl)-ethanone (**1**). A good example from this δ-lactam series is 3-[4-(4-chloro-benzyl)-piperazin-1-yl]-1-ethyl-3,4-dihydro-1*H*-quinolin-2-one (**2**) which showed high affinity for both D_2 (21 nM) and D_4 (4 nM) receptors in a ratio as that of clozapine. However, further studies of structure–activity relationships indicated that seven-member ring lactam containing compound 3-[4-(4-chloro-benzyl)-piperazin-1-yl]-1-ethyl-1,3,4,5-tetrahydro-benzo[*b*]azepine-2-one (**3**) had a less favorable profile. These results suggested that a suitable conformationally constrained structure is required for both D_2 and D_4 receptors binding. Therefore, we decided to expand the conformational SAR studies on the previous series, and designed new compounds (e.g., **4**) having a tricyclic ring

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system by either adding two carbons between the α position of the amide and the corresponding carbon of the phenyl ring of compound **1**, or simply connecting the ethyl and phenyl group of compound **3** as shown in Figure 1.

To seek further support on this drug design strategy and predict the biological profiles for the new tricyclic lactam compounds, we subsequently performed molecular modeling studies. The low energy conformers of **1** and **2** have many common features. The amide bond is coplanar with the aromatic ring (φ_1, Table 1), the carbonyl and C–N (piperazine) bonds are nearly eclipsed (φ_2), both the substituents on the piperazinyl ring are diequatorial and the chlorophenyl ring is oriented in the same way. The removal of the indoline fusion in **1** allows the ethyl substituent on the nitrogen to swing out of plane (φ_3) but does not result in any other distortion of the molecule. The additional methylene unit in the lactam **2** is incorporated in the twist conformation without disrupting the conjugation between the aromatic ring and the amide bond. All the potential pharmacophore points are nearly superimposable in the low-energy conformations of **1** and **2**.

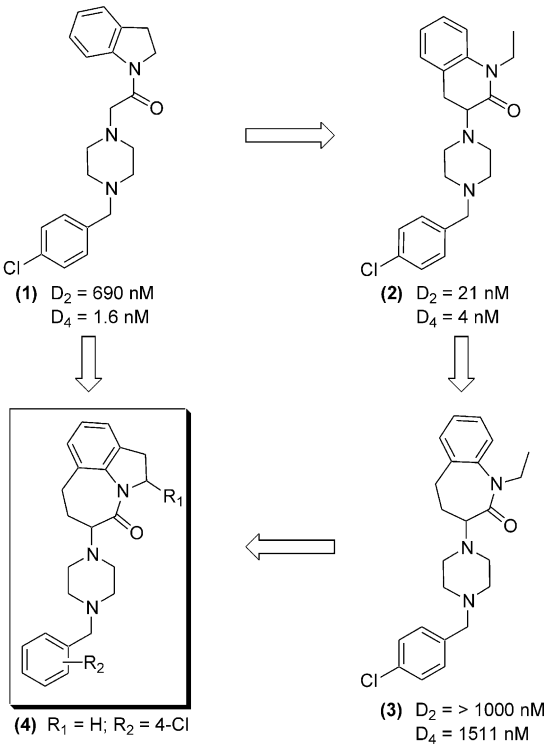
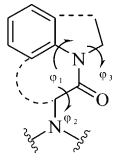


Figure 1.

When **2** is expanded by one methylene group to form **3**, the additional flexibility in the seven-membered ring leads to substantial geometric changes. In the more stable conformers, the ring is calculated to prefer a boat conformation in which the arene ring and the amide bond are not fully in conjugation. The corresponding dihedral angle (φ_1) is 34°, substantially higher than in **1** and **2** (Table 1). This twist is noted in all the low energy conformers within 20 kJ/mol of the global minimum. The relative positions of the arene ring, the amide bond and the piperazinyl ring are therefore quite different from those in **1** and **2**. Interestingly, fusing the amide nitrogen to the arene unit through a five-membered ring (**4**) acts as a strong restraint and, as a result, the amide bond is nearly coplanar with the arene ring (Table 1). The key geometric features of **4** are therefore nearly the same as in **1** and **2** as shown in Figure 2.

In order to estimate the energetic cost involved in retaining perfect conjugation between the aromatic ring and the amide bond, additional calculations were carried out on **1** and **3** in which the dihedral angle φ_1 was constrained to be 0° but all other geometric parameters were fully optimized. For **1**, the constrained structure was computed to be only 0.2 kJ/mol higher in energy than the fully optimized form. In contrast, forcing the dihedral angle φ_1 to be 0° was computed to result in an energy penalty of 19.8 kJ/mol for **3**. The calculations confirm that the relative spatial disposition of the different functional groups of **1**, **2** and **4** is similar but that of **3** is quite different. The overall shapes of these compounds may therefore account for the trends in the observed D_4 binding. If the coplanarity of the aryl ring

Table 1. Calculated dihedral angles in the lowest energy conformers of 1–4[a]



Compd	φ_1	φ_2	φ_3
1	7.3	18.8	14.6
2	1.6	13.2	91.7
3	34.0	26.6	105.0
4	7.3	3.2	12.7

[a]Details of calculations: A Monte Carlo conformational search was performed on compounds **1**–**4** using Macromodel's Batchmin program (v7.2). The 'mixed MCMM/low mode' method was used with the MMFF94s force field and water as solvent. For each compound, 1000 structures were generated and optimized using the conjugate-gradient energy minimization method. These searches were run on a SGI Octane workstation with an R12000 CPU.

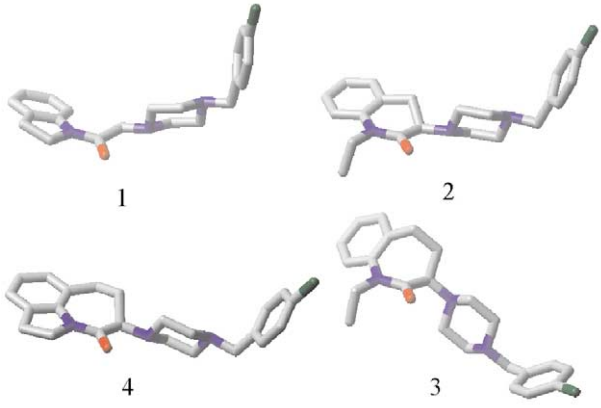


Figure 2. Low energy confirmations of structures **1**–**4**.

and the amide bond is the principal determinant of activity, distal modifications on the benzyl ring of **4** may not have too much of an impact on D_4 binding affinities. Structure **4** would then represent an attractive core for fine-tuning D_2/D_4 selectivity.

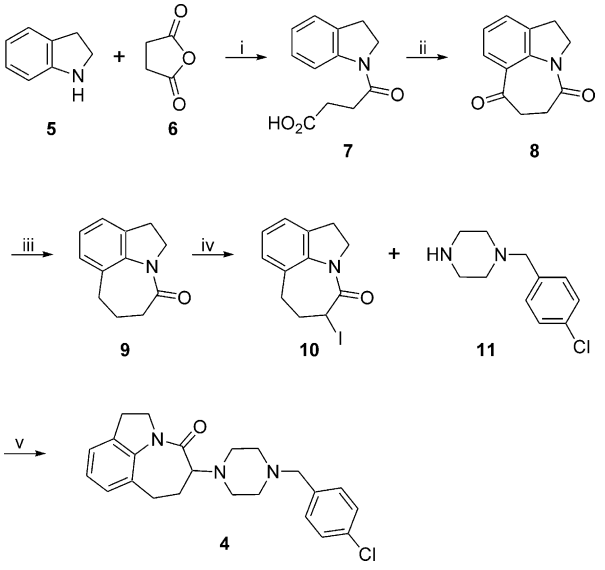
Synthesis, Biological Results and Discussion

Scheme 1 depicts the synthesis of 5-[4-(4-chloro-benzyl)-piperazin-1-yl]-1,2,6,7-tetrahydro-5*H*-azepino[3,2,1-*hi*]indol-4-one **4**. Acylation of indoline **5** with succinic anhydride **6** in the presence of triethyl amine in dichloromethane gave amide acid **7**, which was then converted to keto-lactam **8** by intramolecular Friedel–Crafts cyclization in low yield (15%). Several reaction conditions were examined for the cyclization, but no improvement could be achieved, possibly due to features of the seven-membered ring. Hydrogenation of compound **8** yielded ε-lactam **9**, followed by silylation with iodotrimethylsilane and iodination to give 5-iodo-1,2,6,7-tetrahydro-5*H*-azepino[3,2,1-*hi*]indol-4-one **10**. Finally, compound **4** was obtained in high yield by refluxing of compound **10** and 1-(4-chloro-benzyl)-piperazine **11** with potassium carbonate in acetonitrile. In addition, a number of methyl indoline and substituted benzylpiperazine containing compounds have been prepared using the same synthetic pathway.

The binding affinity data for D_2, D_4 and α_1 are summarized in Table 2. 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. The conformationally restricted ε-lactam subunit tremendously changes the compound biological properties. In particular, compared with compound **1,** all nine ε-lactam compounds (**4**, **12**–**19**) showed lower binding affinities for α_1. Among them, compounds **4** and **12** display binding affinities and affinity ratio in the desired range. Compound **4** displays 6-fold greater potency for D_2 and 3-fold lower for D_4 than compound **1**. The 4-methyl-benzyl compound **12** showed a profile similar to 4-chlorobenzyl compound **4**.

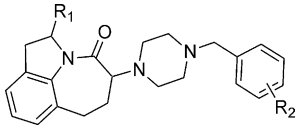
Compounds were also assessed as to their functional activity both at the D_2 and D_4 receptors. D_2 functional activity was assessed via compound reversal of quinpirole inhibited, forskolin stimulated cAMP production from whole cells, while D_4 functional activity was assessed via inhibition of quinpirole stimulated GTPγ^{35}S binding from cell membranes. Functional assessment of compound **4** at both the D_2 and D_4 receptors indicates no agonist properties up to 10 μM, while demonstrating functional K_i values of 62 nM at the D_2 receptor and 3 nM at the D_4 receptor.

In conclusion, with the assistance of molecular modeling studies, a new series of mixed dopamine D_2/D_4 receptor antagonist 5-piperazinyl-1,2,6,7-tetrahydro-5*H*-azepino[3,2,1-*hi*]indol-4-one derivatives were designed and synthesized. As a result of SAR studies, the highly conformationally restricted tricyclic compounds **4** and **12** 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. These two representative compounds from the new tricyclic series are currently under further pharmacological evaluation.



Scheme 1. Reagents and conditions: (i) TEA, DCM, rt, 16 h, 78%; (ii) oxalyl chloride, DMF (cat), DCE, rt, 3 h; then 2 equiv anhydrous $AlCl_3$, DCE, 0 °C to rt, 4 h, additional 2 equiv anhydrous $AlCl_3$, DCE, 60 °C, 16 h, 15%; (iii) H_2, 10% Pd/C, 50 psi, HOAc, rt, 24 h, 98%; (iv) TMSI, TMEDA, DCM, 0 °C, 30 min; then iodine, 0 °C, 40 min, 74%; (v) K_2CO_3, CH_3CN, reflux, 18 h, 90%.

Table 2. Binding affinities



Compd	R_1	R_2	K_i (nM)		
			D_2	D_4	α_1
Clozapine	—	—	113	17	4
1	—	—	690	1.6	88
2	—	—	21	4	1265
3	—	—	>1000	1511	2678
4	H	4-Cl	116	5	2284
12	H	4-Me	209	4	1361
13	Me	4-Cl	139	9	1000
14	Me	4-Me	26	10	1000
15	di-Me	4-Cl	201	19	1735
16	di-Me	4-Me	165	12	490
17	di-Me	2-OMe-4-Me	952	34	653
18	di-Me	2-OMe-5-Me	313	65	983
19	di-Me	5-Cl-2-OMe	220	29	1056

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