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Indoline and Piperazine Containing Derivatives as a Novel Class of Mixed D_2/D_4 Receptor Antagonists. Part 1: Identification and Structure–Activity Relationships

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Abstract—Optimization of the lead compound 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2,3-dihydro-indol-1-yl)-ethanone **1** by systematic structure–activity relation (SAR) studies lead to two potent compounds 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2-methy-2,3-dihydro-indol-1-yl)-ethanone **2n** and 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2-methy-2,3-dihydro-indol-1-yl)-ethanone **7b**. Their related synthesis was also reported.

The oldest and most enduring hypothesis for the etiology of schizophrenia is that it results from a hyperfunctioning of central dopaminergic systems.[1] In 1963, Carlsson and Lindquist reported that dopamine turnover as measured by homovanillic acid levels was increased in laboratory animals following the administration of neuroleptic drugs.[2] Major support for this hypothesis has also come from the observation that antipsychotic medications exert their therapeutic effects via dopamine receptor blockade.[3]

Although most clinically available drugs for schizophrenia are dopamine D_2 receptor antagonists, they are not efficacious in treating all schizophrenic patients and generally cause motor disorders such as extrapyramidal side effects (EPS). Clozapine and olanzepine are regarded as an atypical antipsychotics in that they provide relief from many of the positive florid symptoms of the disease without any significant EPS. The observation that clozapine has a high affinity for the D_4 receptor subtype raised the possibility that clozapine's efficacy might, at least in part, be attributed to D_4 antagonism.[4] Therefore, the development of selective D_4 receptor antagonists has become an active field of research, and this lead to the identification of a number of D_4 specific antagonists[5–15] some of which advanced to clinical trials.[16–21]

L-745,870 is the first selective dopamine D_4 receptor antagonist to have been tested in both behavioral experimental animal studies and in clinical trials. L-745,870 was ineffective in reversing apomorphine-induced disruption of pre-pulse inhibition,[22] although this result is controversial.[23] In two other classic tests of neuroleptic activity and EPS liability, L-745,870 was ineffective in reversing amphetamine-induced hyperactivity and apomorphine-induced stereotypy.[22] In a small phase II trial in acutely psychotic, neuroleptic responsive patients L-745,870 was ineffective.[24] As these studies have cast a shadow on the importance of the D_4 receptor, we considered the possibility that a combination of D_4 and D_2 receptor affinities could be a more reasonable target for antipsychotic drugs like clozapine,[25,26] based on the fact that this agent shows a unique high D_4/moderate D_2 binding affinity feature. In addition, although clozapine binds to a wide array of receptors which may influence its atypical profile, there are no effective antipsychotic agents which lack significant D_2 affinity. Therefore, we set out a research program to obtain a compound with a receptor profile having high D_4 (<10 nM) and moderate D_2 (<200 nM) receptor affinities and also with lower binding affinities to α_1 (>1000 nM) to avert undesirable cardiovascular

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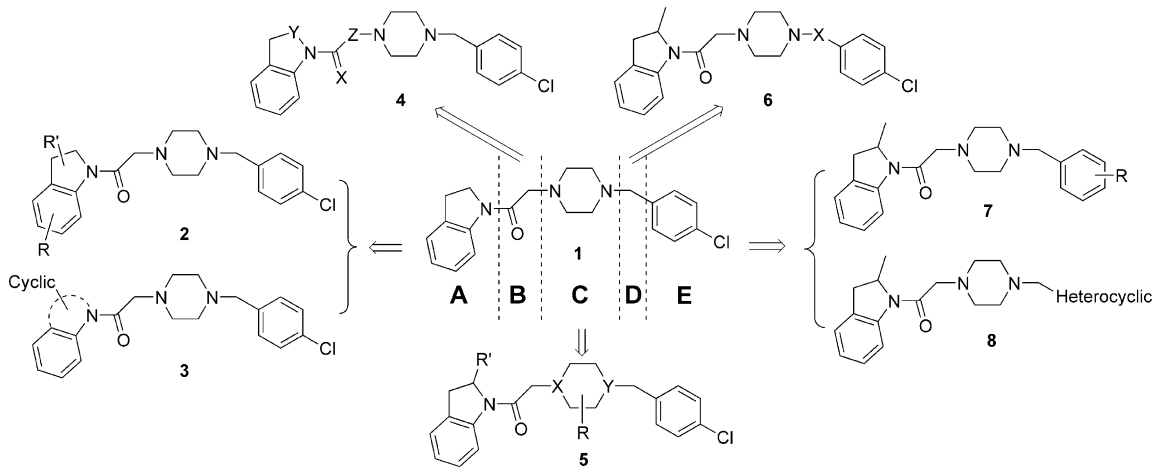


Figure 1.

effects.[27,28] Ideally the target would possess a similar D_2/D_4 binding ratio to that of clozapine ($2\sim10/1$, $D_2 = 138$ nM, $D_4 = 9$ nM).[4]

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 ligand. Affinity at the α_1 receptor was determined via standard competitive displacement assays using rat brain homogenate with [^{3}H]prazosine as the competitive ligand. Screening of a chemical library uncovered 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2,3-dihydro-indol-1-yl)-ethanone **1** showing high affinity binding for D_4 (1.6 nM), relatively modest binding for D_2 (690 nM) and significant affinity for α_1 (88 nM). For the purposes of our SAR studies, compound **1** was divided into five subunits (Parts A–E) from left to right as shown in Figure 1.

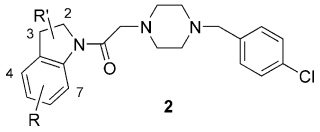
Exploration of the SAR began by varying the aromatic substitutions on the indoline ring (Fig. 1, Part A). It was found that both electron-withdrawing and electron-releasing groups decrease dopamine receptor and α_1 binding activities relative to the parent compound **1** (Table 1, compounds **2a**–**2m**). We then turned our attention to exploration of indoline positions 2 and 3. Alkyl substitutions provided three promising compounds (**2n, 2s** and **2w**) fitting our criteria.

In order to better understand the importance of indoline as a pharmacophoric subunit, a number of heterocyclic ring systems were examined (Table 2). It is notable that the directly homologous examples of the tetrahydroquinolines **3a** and **3b** are less active than the corresponding indolines **1** and **2n**.

We next studied the glycine spacer, Part B in Figure 1 (Table 3). Compound **4a**, with a reverse glycine, is essentially inactive. Substitution at α position (**4i**) or chain length changes (**4j** and **4k**) resulted in loss of affinity at all three binding sites. These results appear to demonstrate the importance of spacer length and oxygen position[26] for activity. Shifting the carbonyl out of the chain gave oxindole **4b** and its sulfonamide analogue **4c** which were found to be fully D_4 selective compounds. This finding encouraged us to explore other heterocyclic groups to replace oxindole (**4b**–**4h**). Each of these isosteric replacements resulted in D_4 selective antagonists.

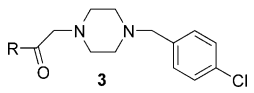
As a result of our studies on Parts A and B, we had promoted **2n** as the target reference compound to be used for Part C studies. Examination of the isomeric piperidines **5a** and **5b** indicated that a nitrogen at position 4 (Y = N) was required for receptor binding (Table

Table 1. Effect of substitution within the indoline ring system



Compd	R	R′	K_i (nM)		
			D_2	D_4	α_1
1	H	H	690	1.6	88
2a	4-Cl	H	2145	992	988
2b	6-Cl	H	607	701	3545
2c	4-F	H	> 1000	145	261
2d	6-F	H	2552	51	3122
2e	4-Me	H	3431	462	—
2f	5-Me	H	1692	37	—
2g	6-Me	H	6357	771	2805
2h	7-Me	H	4623	48	2624
2i	4-OMe	H	487	6392	972
2j	5-NO_2	H	> 1000	3394	> 1000
2k	6-NO_2	H	450	> 1000	—
2l	5-SMe	H	3780	235	> 1000
2m	5-SO_2NMe_2	H	3780	235	> 1000
2n	H	2-Me	209	5.4	2655
2o	H	3-Me	4375	96	1800
2p	H	2-Et	509	6	2202
2q	H	2-isoPr	2524	549	—
2r	H	2-isoBu	341	622	> 1000
2s	H	2,2-diMe	117	4.3	5006
2t	H	2,2-diEt	129	31	2834
2u	H	2,2-$(CH_2)_4$–	187	36	909
2v	H	2,2-$(CH_2)_5$–	3325	1563	983
2w	H	*cis*-2,3-diMe	120	7	2544
2x	H	*trans*-2,3-diMe	183	206	3386
2y	H	2,3,3-triMe	883	108	2845
2z	H	*cis*-2,3-$(CH_2)_4$–	377	726	8994

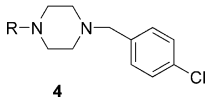
Table 2. Effect of non-indoline ring



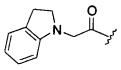
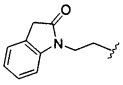
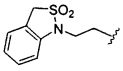
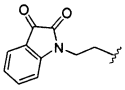
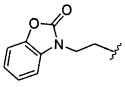
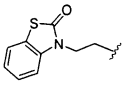
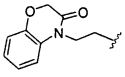
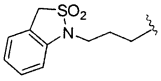
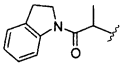
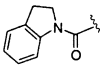
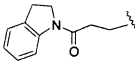
3

Compd	R	K_i (nM)		
		D_2	D_4	α_1
3a		2629	47	> 10000
3b		4126	95	—
3c		2220	37	> 1000
3d		35	50	> 1000
3e		1926	81	> 1000
3f		5847	726	> 1000
3g		2610	429	—
3h		> 10,000	14.2	2298
3i		> 5000	59	—

Table 3. Effect of changes to the glycine spacer



4

Compd	R	K_i (nM)		
		D_2	D_4	α_1
4a		> 10,000	3854	—
4b		1642	8	598
4c		> 10,000	7	161
4d		1225	259	8445
4e		8053	73	1694
4f		1207	3	1052
4g		> 1000	522	5136
4h		979	13	36
4i		> 7000	281	4819
4j		> 1000	> 1000	> 1000
4k		5847	726	1000

4). Furthermore, the C-1 carbon led to potent α_1 binding affinity which might increase cardiovascular effect risks. Various mono and dimethylated piperazines displayed generally unfavorable D_2 affinities.

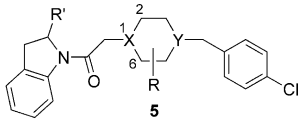
The next area to explore was the benzylic methylene spacer of **2n**. The results of this study (Table 5) indicate that either shortening or lengthening of the carbon chain as well as substitution onto the methylene of **2n** resulted in significant loss of affinity at dopamine D_2 and D_4 receptors.

Finally, we attempted to optimize the activities of **2n** and **5a** by varying the substituent pattern of the *N*-benzyl group (Table 6). The 4-methylbenzyl compound **7b** was identified having similar binding potency as **2n**. This indicated that the steric rather than electronic effects influence biological properties for this substitution. In addition, all three pyridylmethyl (2, 3 and 4) analogues **8** (Fig. 1) show no activity.

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 **2n** and **7b** at both the D_2 and D_4 receptors indicates no agonist properties up to 10 μM, while demonstrating functional K_i values of 960 nM and 140 nM, respectively, at D_2 receptor, and 9 nM and 7 nM, at D_4 receptor.

Scheme 1 represents the general procedure used to prepare most indoline piperazine compounds **12**. Indoline and 2-methylindoline are commercially available. Other substituted indolines (**9a**–**9m**, **9o**, and **9w**–**9z** relative to Table 2) were prepared by reduction of the corresponding indoles with trimethylamine-borane complex following Berger's method.[29] The synthesis of 2-ethylindoline,[30] 2-isopropyl and 2-isobutylindolines[31] have been previously reported. 2,2-Disubstituted indolines (**9s**–**9v** relative to **2s**–**2v**) were prepared by treatment of 2,2-disubstituted-1,2-dihydro-3*H*-indol-3-ones[32] with LAH–$AlCl_3$ complex (rt, 1 h). The fragments selected in Table 2 are commercially available and have been

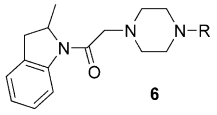
Table 4. Effect of piperidine and substituted piperazine



5

Compd	R	R′	X	Y	K_i (nM)		
					D_2	D_4	α_1
2n	H	Me	N	N	209	5.4	2655
5a	H	Me	CH	N	92	4	162
5b	H	Me	N	CH	—	7264	>10,000
5c	*cis*-1,6-diMe	H	N	N	4742	1361	508
5d	*cis*-3,5-diMe	H	N	N	8620	>10,000	—
5g	*trans*-2,5-diMe	H	N	N	6740	335	1300
5h	(2R)-Me	H	N	N	5839	14	594
5i	(5R)-Me	H	N	N	>1000	—	—

Table 5. Effect of methylene spacer change



6

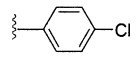
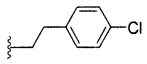
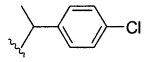
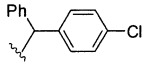
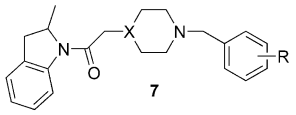
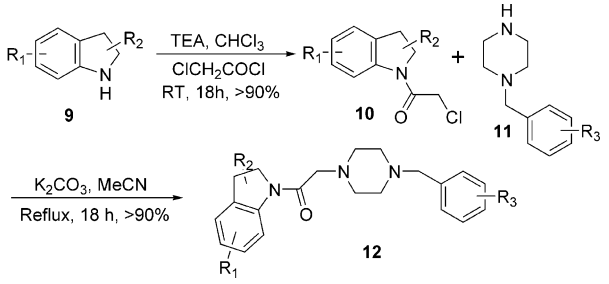
Compd	R	K_i (nM)		
		D_2	D_4	α_1
6a		—	5745	—
6b		5247	134	115
6c		1252	67	937
6d		>1000	>1000	2076

Table 6. Effect of substitution on benzylic ring



7

Compd	R	X	K_i (nM)		
			D_2	D_4	α_1
2n	4-Cl	N	209	5.4	2655
7a	4-F	N	887	7	671
7b	4-Me	N	188	3	1257
7c	4-Et	N	753	6	1184
7d	4-isoPr	N	1784	12	504
7e	4-tertBu	N	1918	12	320
7f	4-CF_3	N	5287	11	7125
7g	4-OMe	N	2094	15	872
7h	4-OCF_3	N	3823	5	4165
7i	3-OCF_3	N	620	6	>1000
7j	2-Me	N	1530	7	1324
7k	2-OMe	N	225	25	>1000
7l	3,5-diF	N	3011	12	2056
7m	3,5-diCl	N	214	15	>1000
7n	2,5-diMe	N	119	8	—
7o	2-F	CH	1414	40	—
7p	3-F	CH	52	7	118
7q	4-F	CH	71	6	236
7r	2-Cl	CH	834	29	—
7s	3-Cl	CH	62	4	127
7t	3-Me	CH	166	5	95
7u	4-Me	CH	39	2	327
7v	4-OMe	CH	158	10	142
7w	4-NO_2	CH	>10,000	2	—
7x	3,4-diMe	CH	306	4	118
7y	3-F, 4-Me	CH	23	3	103
7z	2-Cl, 4-F	CH	518	21	—



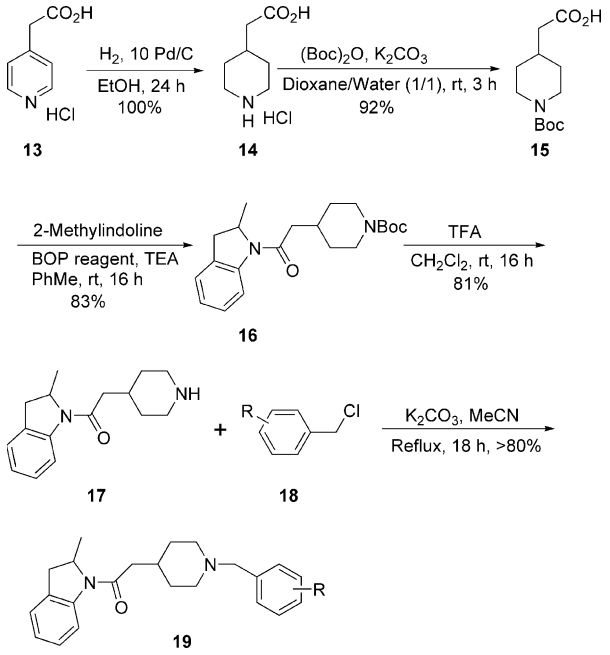
Scheme 1.

used for preparation of **3** in the same manner as indicated in Scheme 1.

1-Bromo-2-chloroethane and 1-bromo-3-chloropropane were employed to react with various amides in the presence of sodium hydride in DMF for 24 h, yielding **4b**–**4g** and **4h** (Table 3). Using the appropriate chloro acid chlorides gave **4i** and **4k**, while changing the reaction order of Scheme 1 generated compound **4a**. Urea **4j** was prepared by treatment of indoline with sodium hydride and ethyl 4-(4-chlorobenzyl)piperazine-1-carboxylate[33] in THF (reflux, 24 h, 83% yield).

Piperidine containing compounds (**5a** in Table 4 and **7o**–**7z** in Table 6) were prepared as illustrated in Scheme 2. Compound **5b** was prepared by the same procedure as Scheme 1. Compounds **5c**–**5i** in Table 4 were synthesized by controlling the coupling sequences using steric effects. Substituted benzyl piperazines were usually formed by the reported procedures[34] and further applied to the preparation of compounds **6** (Table 5) and **7a**–**7n** (Table 6).

Using the lead compound **1** as reference, a systematic SAR study has been carried out with the goal of identifying compounds with a D_2/D_4 affinity ratio similar to that found in the atypical antipsychotic clozapine. The compounds 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2-methy-2,3-dihydro-indol-1-yl)-ethanone **2n** and 2-[-4-(4-chloro-benzyl)-piperazin-1-yl]-1-(2-methy-2,3-dihydro-indol-1-yl)-ethanone **7b**, were found to meet this criteria. The asymmetric synthesis, further SAR and biological evaluation are decribed in the proceeding paper.[35]



Scheme 2.

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