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N-(1-Benzylpyrrolidin-3-yl)arylbenzamides as potent and selective human dopamine D_4 antagonists

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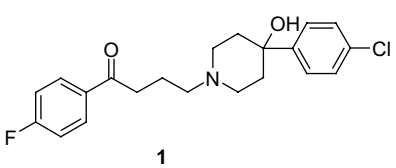
Abstract—A series of *N*-(1-benzylpyrrolidin-3-yl)arylbenzamides **8** has been prepared, and their structure–activity relationships studied. Potent ligands selective for human D_4 (hD_4) over hD_2 and α_1 have been identified. One example was determined to be an antagonist in a cAMP assay, with an IC_{50} of 1500 nM.

Dopamine D_4 selective antagonists have received renewed attention recently as potential therapeutics for the treatment of sexual dysfunction, attention-deficit hyperactivity disorder (ADHD), and other related disorders. To be complete however, a history of these agents must begin with a recount of their failed development as antipsychotics.

Schizophrenia is a devastating illness that affects up to 1% of the worldwide population.[1] It is a particularly tragic disease because the most severe symptoms typically manifest in early adulthood, what would otherwise be the prime of life.[2] The symptoms of the disease are categorized into positive (e.g., hallucinations), negative (e.g., anhedonia and poverty of speech), and cognitive deficits. For years the positive symptoms of schizophrenia have been adequately controlled by neuroleptic medications. These drugs, such as haloperidol **1**, are D_2 antagonists. Unfortunately, they are not as effective at controlling the negative or cognitive symptoms of the disease,[3] and long-term neuroleptic treatment can precipitate serious side effects such as tardive dyskinesia. These side effects often remain after neuroleptic treatment is terminated.[4]

Clozapine **2** was the first widely prescribed medication that exhibited efficacy in the alleviation of both positive and negative symptoms of schizophrenia.[5] Its use has been limited by the risk of development of potentially fatal agranulocytosis.[6] It also often fails to improve cognitive function.[7] Clozapine possesses a complicated pharmacological profile, with a D_4 affinity that is an order of magnitude greater than its D_2 affinity.[8] This, along with the observation that D_4 expression levels are elevated in the brains of schizophrenics, led to the initiation of several research programs aimed at developing D_4 selective antagonists, with the hope that such compounds would be efficacious against both positive and negative symptoms, and also lack the serious side effects of existing drugs.



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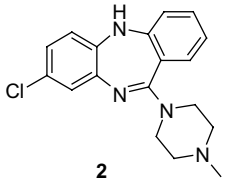

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Several such D_4 selective antagonists were developed and studied in clinical trials for the treatment of schizophrenia, including L-745,870 **3**,[9] and PNU-101387G **4**,[10] however none of them were found to be effective for this particular indication.[11] Recent evidence has been mounting for the application of D_4 selective antagonists for the treatment of sexual dysfunction, ADHD,

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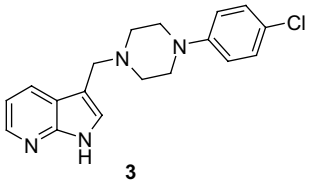
Parkinson's disease, or mood disorders.[12] It is this renewed interest that has encouraged us to report our identification of the highly selective hD_4 antagonists herein.[13]



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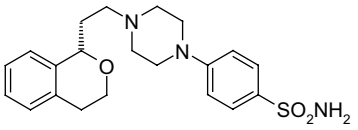

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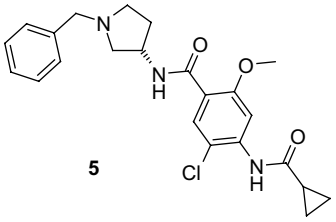
As a starting point we used YM-43611 **5**, a dopamine antagonist discovered by Yamanouchi Pharmaceuticals.[14] YM-43611 is a broad-spectrum dopamine ligand, with affinities for the D_2, D_3, and D_4 receptors of 220, 21, and 2.1 nM, respectively. The compounds for this study were prepared from commercially available 1-benzyl-3-aminopyrrolidine **6** in either its racemic, or enantiomerically pure forms. Compounds **8a** to **8j** were synthesized by a direct acylation reaction with the appropriate acid chloride. Compounds **8k** to **8s** were prepared in the two-step procedure outlined in Scheme 1. Pyrrolidine **6** was first acylated with either 3- or 4-iodobenzoyl chloride to provide the aryl iodide **7a** or **7b**, respectively,[15] which was subjected to typical Suzuki reaction conditions with the appropriate boronic acids in a parallel synthesis to yield final compounds **8k**–**s**.[16] These were determined to be of sufficient purity for pharmacological assessment by ^1H NMR following column chromatography. The chiral purity of the final compounds was not assessed, as it was believed to be unlikely that erosion of the enantiomeric purity would have occurred under the reaction conditions employed.



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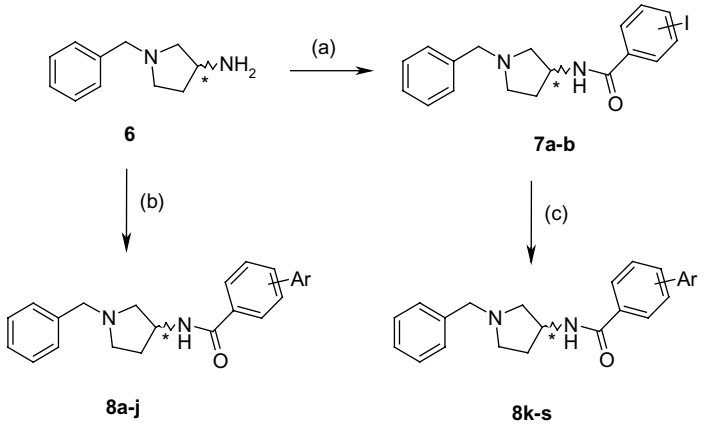
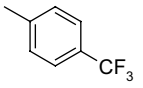
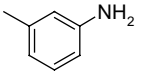
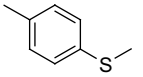
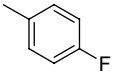
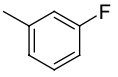
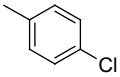
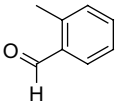
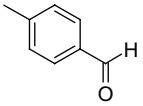
The hD_2 and hD_4 receptor binding profiles of compounds **8a**–**s** were evaluated by their ability to displace ^3H-spiperone, using clozapine as a reference. For the purposes of this assay, human embryonic kidney 298 cells were stably transfected with hD_4 ($D_{4.2}$ subtype) receptor, and GH_4C_1 (rat pituitary) cells were stably transfected with hD_2 (short isoform) receptor. Rat frontal cortex tissue was used for the α_1 assay, using 7-methoxy-[^3H]-prazosin as the radioligand and clozapine as the reference. K_i values for each compound were calculated by the Cheng and Prusoff transformation, and are reported here as the mean of at least two determinations, plus or minus the standard error of the mean.[13]

The binding data for compounds **8a**–**s** at the human D_2, D_4, and α_1 receptors is presented in Table 1. In general all of the compounds reported here exhibited good selectivity for D_4 versus D_2 or α_1. There was a general preference for the *S* enantiomer versus the *R*, not only were the *S* enantiomers more potent at the D_4 receptor (compare for example **8m** and **8n**), but in addition these enantiomers were also significantly less potent at the α_1 receptor, leading to a marked improvement in the selectivity ratio between these two receptors. The D_2 affinity did not show a clear preference for either enantiomer. Methylation of the amide nitrogen of **8p** substantially decreased the affinity for D_4 (40% inhibition @ 100 nM), as well as D_2 and α_1 (7.4% and 0.29%, respectively, @ 100 nM). Replacement of the amide with a sulfonamide also dramatically reduced affinity for all three receptors. For example, the sulfonamide analogue of **8n** exhibited 13% inhibition @ 100 nM for the D_4 receptor, and was inactive at D_2 and α_1 @ 100 nM.



Scheme 1. Reagents and conditions: (a) 3- or 4-iodobenzoyl chloride, Et_3N, CH_2Cl_2; (b) aroyl chloride, Et_3N, CH_2Cl_2; (c) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, Δ.

Table 1. Binding profile of series **8** at the hD_4, hD_2, and α_1 receptors

Compound	*	Biaryl isomer	Ar	D_4 K_i (nM)[a]	D_2 K_i (nM)[a]	α_1 K_i (nM)[a]
8a	*rac-*	*para-*		17 ± 5	8000 ± 6000	N.D.[b]
8b	*rac-*	*para-*		24 ± 2	5000 ± 2000	N.D.
8c	*rac-*	*para-*		17 ± 6	4000 ± 3000	N.D.
8d	*rac-*	*para-*		3 ± 1	600 ± 200	N.D.
8e	*rac-*	*meta-*		4 ± 1	150 ± 90	N.D.
8f	*rac-*	*para-*		8 ± 5	120 ± 20	N.D.
8g	*rac-*	*para-*		17 ± 7	4000 ± 1000	N.D.
8h	*rac-*	*para-*		5 ± 2	2600 ± 300	N.D.
8i	*rac-*	*para-*		36 ± 2	3100 ± 800	N.D.
8j	*rac-*	*para-*		70 ± 30	3700 ± 300	N.D.
8k	*rac-*	*para-*		3 ± 1	840 ± 30	N.D.
8l	*rac-*	*para-*		2.0 ± 0.7	1200 ± 400	N.D.
8m	*R-*	*para-*		24	1500	330
8n	*S-*	*para-*		3	980	1200
8o	*R-*	*para-*		18 ± 8	900 ± 300	170 ± 50
8p	*S-*	*para-*		2	1000	610
8q	*R-*	*meta-*		3.4 ± 0.6	94 ± 4	170 ± 30
8r	*S-*	*meta-*		2 ± 1	70 ± 20	140 ± 30
8s	*S-*	*meta-*		1.5 ± 0.3	60 ± 20	160 ± 50

[a] K_i values are reported as the mean of at least two independent determinations ± SEM. Where no SEM is reported, only a single determination was made.

[b] N.D. = not determined.

In order to determine whether these compounds possessed antagonist functional activity, the ability of **8d** to reverse the dopamine inhibition of forskolin-stimulated adenyl cyclase activity in Chinese hamster ovary cells stably expressing hD_4 receptor was measured. Compound **8d** was found to have an IC_{50} of 1500 nM in this assay, and thus is an antagonist of the hD_4 receptor. The reasons for the discrepancy between this result and the binding K_i of 3 nM are not clear from the present data. Owing to the structural similarity of the other compounds in this study, it reasonable to assume that they are likely also D_4 antagonists. Similarly, administration of **8d** plus forskolin to the same cell line failed to decrease the cAMP concentration in the cells below the level resulting from administration of forskolin alone. Thus, it can be expected that these compounds are unlikely to possess significant D_4 agonist activity.[13]

This body of work has successfully identified a novel class of highly potent D_4 antagonists that are selective over D_2 and α_1. Selective D_4 antagonists might be of value in the treatment of disorders including sexual dysfunction, ADHD, Parkinson's disease, and mood disorders.

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15. To a solution of **6** (100 mg, 0.567 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added Et_3N (0.79 mL, 574 mg, 5.67 mmol) and 4-iodobenzoyl chloride (151 mg, 0.567 mmol). After 1 h the reaction mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered, and concentrated to provide **7b** (196 mg, 85%).
16. As a representative procedure, to a solution of **7b** (10.0 g, 24.6 mmol) in DME (400 mL) was added thiophene-2-boronic acid (6.30 g, 49.24 mmol), $Pd(PPh_3)_4$ (1.42 g, 1.23 mmol), and 2 M Na_2CO_3 (100 mL). The mixture was refluxed for 8 h, cooled, poured into water, and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4) and charcoaled, filtered, and concentrated. Column chromatography (1% NH_4OH/5% MeOH/94% CH_2Cl_2) provided **8k** (5.90 g, 66%) as an off-white solid. Compound **8k**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.71–1.87 (m, 1H), 2.32–2.48 (m, 2H), 2.67 (dd, 1H), 2.79 (dd, 1H), 2.92–3.03 (m, 1H), 3.69 (s, 2H), 4.64–4.75 (m, 1H), 6.66 (br d, 1H), 7.12 (dd, 1H), 7.25–7.37 (m, 6H), 7.39 (dd, 1H), 7.67 (d, 2H), 7.78 (d, 2H).