A New Arylpiperazine Antipsychotic with High $D_2/D_3/5\text{-}HT_{1A}/\alpha_{1A}$-Adrenergic Affinity and a Low Potential for Extrapyramidal Effects

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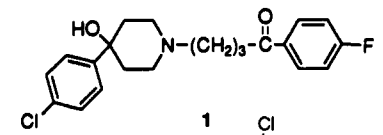
Received December 17, 1993

Schizophrenia is a debilitating disease that afflicts ca. 1% of humanity. Current drug therapy with antipsychotics such as haloperidol (1) is limited by partial efficacy and a significant incidence of unwanted extrapyramidal symptoms (EPS) and tardive dyskinesia.[1] Although antipsychotics typically antagonize D_2 receptors, therapeutic advantages may be offered by compounds with affinities for multiple receptors. One such compound is clozapine (2), which binds to D_4 and serotonin 5-HT_2 receptors and is devoid of EPS side effects, but which unfortunately causes a low incidence of agranulocytosis and requires periodic blood monitoring for continued therapy.[2,3] Another example is risperidone (3), which antagonizes both D_2 and 5-HT_2 receptors.[4] Risperidone appears to offer therapeutic advantages over classical antipsychotics and is also associated with fewer EPS side effects.[4] In this paper we describe the synthesis and activity of 4 (RWJ-37796), an arylpiperazine derivative which binds with high affinity (K_i < 4 nM) to D_2, D_3, 5-HT_{1A}, and α_{1A}-adrenergic receptors and displays potent and selective activity in animal models predictive of antipsychotic activity in humans.



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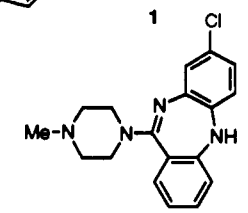

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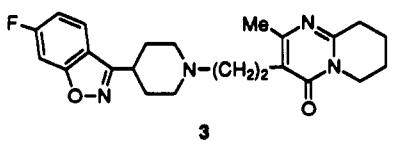

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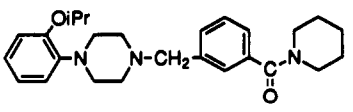
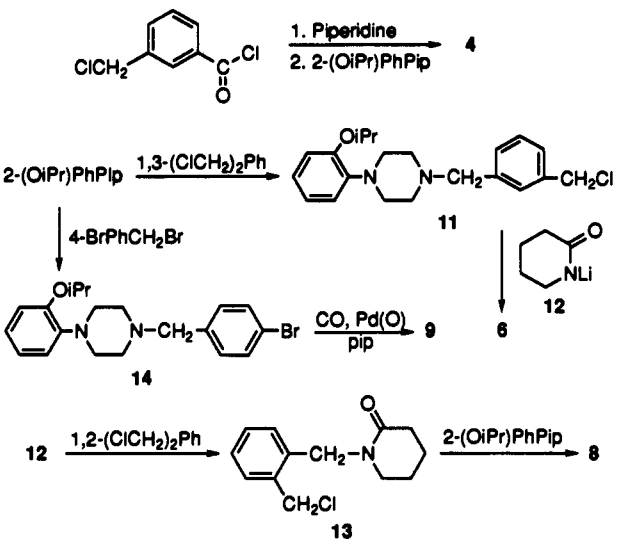
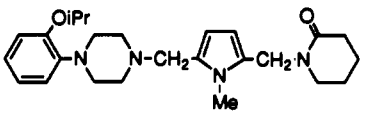


4: RWJ-37796

Scheme 1



Compound 4 was synthesized by reaction of 3-(chloromethyl)benzoyl chloride with piperidine followed by 2-(isopropoxy)phenylpiperazine [2-(OiPr)PhPip] as shown in Scheme 1, as part of an effort to improve upon the profile of earlier lead 5 (RWJ-25730).[5] We had found that certain D_2, 5-HT_{1A} ligands such as 5 displayed a favorable pharmacological profile, which we hoped to amplify.[5,6] The direct phenyl replacement analog (6) was



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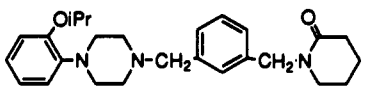

6

prepared by reaction of 2-(OiPr)PhPip with α,α'-dichloro-*m*-xylene to give 11, followed by treatment of 11 with the lithium anion of δ-valerolactam (12, see Scheme 1). We also evaluated other positional isomers with respect to substitution about the middle aromatic ring (viz. 6–8, see Table 1). 1,4-Disubstituted analog 7 was synthesized by the same sequence as 6 starting with α,α'-dichloro-*p*-xylene, but 1,2-analog 8 was obtained by conversion of lactam 12 to give 13, which was carried on to 8. Corresponding benzamides 4, 9, and 10 were synthesized and evaluated to examine the effect of moving the carbonyl to the position adjacent to the middle aryl ring. 1,2-Analog 10 was prepared in the same manner as 4, starting with 2-(bromomethyl)benzoyl bromide. The 1,4-congener (9) was synthesized by a Pd(0)-mediated coupling of 14 with piperidine in the presence of carbon monoxide as shown.[7]

Compound 4 has an octanol–water partition coefficient (log *P*) of 4.00 (experimentally determined), predicting fair blood–brain barrier penetration.[8] The pK_a for 4 was determined to be 7.01, indicating that slightly more than half of the drug would be expected to be unprotonated in the blood (pH ca. 7.3). An X-ray structure determination on the succinate salt of 4 reveals a bent, extended conformation, which is supported by MM2 energy minimization (gas phase). The considerable flexibility due to

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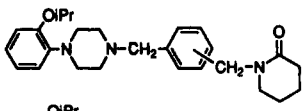
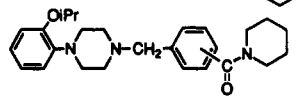
0022-2623/94/1837-1060$04.50/0

Table 1. Receptor Affinity and Primary Screen Activity for Isomeric Lactams and Benzamides

compound	substitution pattern	compd no.	receptor affinity (K_i, nM)[a] D_2	D_3	5-HT_{1A}	α-1	α-2	CAR test[b] (ip)
	1,3	6	120	ND	10	4.0	ND	-89%
	1,4	7	23	ND	5.9	0.7	1000	-29%
	1,2	8	46	ND	1.6	32	ND	-6%
	1,3	4	2.2	1.8	1.7	1.3	17	0.66 mg/kg
	1,4	9	100	ND	560	3.0	ND	-35%
	1,2	10	37	ND	6.8	220	16	-95%
		5	0.8	ND	3.3	8.2	ND	2.2 mg/kg
haloperidol		1	0.37	3	>1000	1.0	>1000	0.17 mg/kg
clozapine		2	82.0	500	111	1.4	58	4.0 mg/kg

[a] ND = not determined. D_2, 5-HT_{1A}, α_1-adrenergic, and α_2-adrenergic data were obtained using rat brain synaptosomal preparations as described in the supplementary material. D_3 data were obtained from rat membrane receptors derived from baculovirus expression of cloned receptor in the case of 4, or are taken from the literature (ref 12). [b] Conditioned avoidance response data (CAR, rat) are either inhibition at 5 mg/kg, $N = 4$, or ED_{50}'s with 95% confidence limits as listed in ref 17.

bond rotation between the rings may allow the compound to adjust as required for binding at the different receptors (e.g., D_2, D_3, 5-HT_{1A}, α_{1A}-adrenergic) to which it has high affinity.

Receptor binding data at the D_2, 5-HT_{1A}, and α_1-adrenergic receptors for compounds 4 and **6–10** is displayed in Table 1, along with that for haloperidol, clozapine, and **5**. Our primary in vivo screen for activity was the rat conditioned avoidance response (CAR) test,[9] and this data is shown in Table 1 as well. Direct comparison of the isomeric target compounds established 4 as especially potent and worthy of further investigation. The brevity of synthesis to give 4 has allowed for the rapid preparation of ca. 250 related structures; 4 compares favorably with any of the other outstanding compounds in the series and has been investigated to the greatest degree.[10]

Compound 4 has high affinities ($K_i < 4$ nM) for D_2, D_3, 5-HT_{1A}, and α_1-adrenergic receptors and weaker affinities for 5-HT_2 (165 nM), 5-HT_{1b} (2880 nM), and α_2-adrenergic (17 nM) sites as shown in Table 1. α_1-Adrenergic binding has been broken into α_{1A} (0.20 nM) and α_{1B} (47 nM) components by competition experiments with the α_{1A} ligand WB 4101.[11] As D_3 receptors are localized in limbic areas associated with emotional function, it has been proposed that affinity there may be useful in the treatment of the negative symptoms (e.g., apathy) of schizophrenia.[12] In addition, 4 shows no appreciable affinity for binding ($K_i > 5000$ nM) at D_1 (human clone), D_5 (rat clone), σ, and muscarinic sites. In the CAR assay[9] in rats, 4 displays ED_{50} values of 0.23 mg/kg (iv), 0.66 mg/kg (ip), and 13.8 mg/kg (po). In addition, 4 exhibits an ED_{50} of 0.6 mg/kg (po) for the inhibition of apomorphine induced climbing behavior in mice, generally the result of direct dopaminergic antagonism.[13] In dogs, 4 inhibits apomorphine-induced emesis with an ED_{50} = 0.03 mg/kg (iv) and 0.038 mg/kg (po).[14] Compound 4 inhibited 8-OH-DPAT induced reciprocal forepaw treading in reserpinized rats (ED_{50} = 5.24 mg/kg, ip),[15] indicating some degree of 5-HT_{1A} antagonism.[16–18]

There is a good correlation between catalepsy in rats and the liability for producing EPS.[19] Compound 4 does not cause >30% catalepsy at any dose (10–1000 mg/kg, po) in rats, and the maximal catalepsy we observed (ca. 30% at 100 mg/kg po) diminished at higher doses. Thus, 4 may prove to be relatively free of EPS in humans.[20]

Compound 4 was administered (iv) to healthy human volunteers 2.5 h prior to giving [^{11}C]raclopride, and the subjects were evaluated by PET scanning. A dose-dependent decrease in putamen/cerebellum binding was observed, indicating inhibition of [^{11}C]raclopride binding.[21] Fifty percent occupancy, an important clinical marker, was estimated to occur at a dose of 0.035 mg/kg (iv). The compound has been reported to be well-tolerated up to doses of 20 mg/kg po in healthy human volunteers and is being further evaluated in schizophrenics.[22]

In summary, 4 exhibits high affinity for D_2, D_3, 5-HT_{1A}, and α_{1A}-adrenergic receptor subtypes and potency in preclinical animal models predictive of antipsychotic activity. Based on a lack of catalepsy production in animals, it may be relatively free of EPS in humans, and has been chosen for development as an antipsychotic drug.

Acknowledgment. We thank A. Abdel-Magid, E. W. Baxter, R. E. Boyd, F. A. Chrzanowski, B. Dubinsky, J. Gheuens, A. D. Jordan, Jr., M. J. Kukla, J. E. Leysen, B. E. Maryanoff, M. E. McDonnell, C. R. Rasmussen, and many others within Johnson & Johnson for their contributions related to RWJ-37796.

Supplementary Material Available: Detailed synthetic procedures and analytical data for compounds 4 and **6–10** and pharmacological methods for the in vivo tests and in vitro receptor assays (7 pages). Ordering information is given on any current masthead page.

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