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Communications to the Editor

(*S*)-(−)-4-[4-[2-(Isochroman-1-yl)ethyl]-piperazin-1-yl]benzenesulfonamide, a Selective Dopamine D_4 Antagonist

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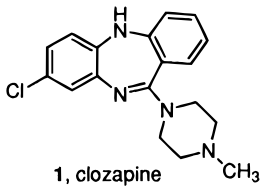
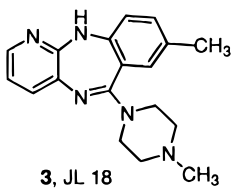
Schizophrenia affects about 1% of the population worldwide.[1] The onset of symptoms is generally in the late teens to early twenties. There is no cure for the disease, and current therapies have numerous, debilitating side effects. The combination of early onset of chronic disease and problematic therapies results in high costs for the patient, his or her family, and society at large.[2] While the etiology of schizophrenia remains unknown, several lines of research point to the dopaminergic system,[3] and, in particular, the dopamine D_4 receptor, as important in schizophrenia and psychotic-type diseases in general.[4]

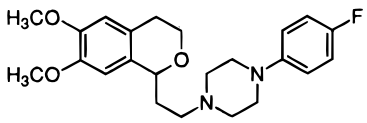
Classical antipsychotics such as haloperidol, though effective in treating certain schizophrenic states, cause extrapyramidal side effects and tardive dyskinesias. These side effects have been linked to the blockade of dopamine receptors in the striatum.[5] Clozapine (**1**), an "atypical" antipsychotic, is relatively free of extrapyramidal side effects, but causes tachycardia (25%), sialorrhea (30%), dizziness (20%), drowsiness and sedation (40%), and agranulocytosis (1−3%). Many of these side effects can be attributed to clozapine's high affinity for a number of central nervous system (CNS) receptors.[6] At the same time, clozapine's affinity for the D_4 receptor may play a part in its atypical nature.



1, clozapine



3, JL 18



2, U-54537

Some years ago, we prepared a series of dimethoxyisochromans, typified by **2**, as antihypertensives working through the α-adrenergic receptors.[7] More recently, the *in vitro* examination of these compounds against a panel of CNS receptors revealed them to have high affinity for the D_4 ($hD_{4.2}$) receptor (*vide infra*) and, importantly, some preference for the D_4 vs the D_2 receptor.[8] We then set out to prepare analogs with high affinity and selectivity for the D_4 receptor with the expectation that side effects would be reduced with minimal binding at other receptors.

Scheme 1

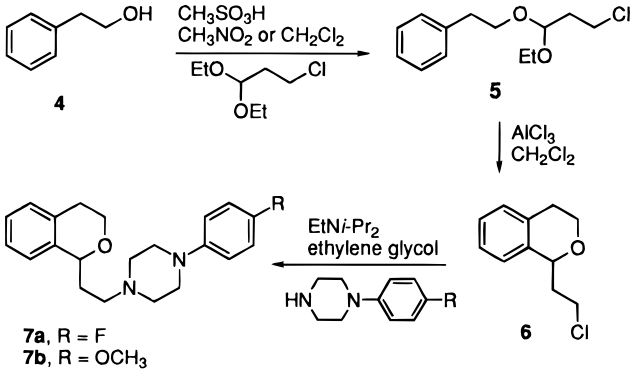


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Table 1. Binding Affinities (Ki, nM) of Isochromans at Various CNS Receptors[a]

compd	D_1	D_2	D_3	D_4	5-HT_{1A}	5-HT_2	α_1	α_2
2	26 (24−29)	400 (280−560)	nt	24	93 (72−120)	2.1 (1.9−2.3)	(100%)	(75%)
7a	410 (310−540)	160 (140−180)	240 (220−270)	3.0 (2.8−3.3)	120 (100−130)	5.8 (5.7−5.9)	38 (36−40)	140 (120−170)
7b	>2400	1100 (800−1500)	1200 (950−1500)	1.4 (1.3−1.6)	1100 (860−1340)	76 (69−84)	1280 (900−1800)	1800 (1200−2700)
S-(−)-**7b**	>2400	790 (590−1100)	1300 (930−1700)	2.2 (2.0−2.5)	490 (400−600)	28 (27−29)	(20%)	(9%)
R-(+)-**7b**	>2400	>1800	220 (170−290)	25 (23−28)	>1600	30 (28−32)	(36%)	(0%)
S-(−)-**15**	(20%)	>4300	5800 (3900−8600)	7.2 (6.6−7.8)	>3700	>1800	>4900	>2600
R-(+)-**15**	(17%)	5600 (3600−8800)	2900 (1900−4300)	100 (90−110)	2400 (1600−3800)	(4%)	(41%)	(15%)
1	170 (140−200)	55 (46−65)[b] 138[c] 82[d]	280 (230−350)[b]	32 (30−35)[b] 9[c] 29[d]	150 (140−160)	3.8 (3.4−4.2)		
3	398	530		21		94		

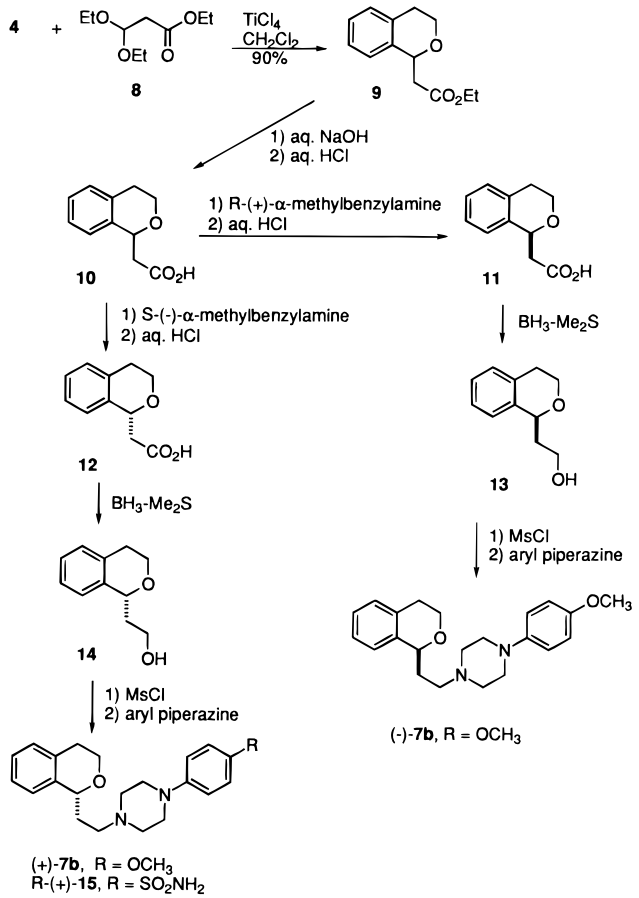
[a] The numbers in parentheses represent 95% confidence intervals associated with the Ki values. Membranes prepared from cloned mammalian receptors expressed in cultured cells or from rat whole brain (adrenergic receptors) were used as the source of binding sites. The radioligands used were [^{3}H]SCH23390 (D_1), [^{3}H]U-86170 (D_2),[12] [^{3}H]spiperone (D_3 and D_4),[13] [^{3}H]-8-OH-DPAT (5-HT_{1A}), [^{3}H]ketanserin (5-HT_2), [^{3}H]prazosin (α_1-adrenergic), and [^{3}H]clonidine (α_2-adrenergic). Binding data are given either as binding constant (K_i) in nM ± SEM or as % inhibition when tested at 1 μM concentration ($n = 3$). [b] Reference 14. [c] Reference 4a. The ligand is [^{3}H]spiperone for both D_2 and D_4. [d] Reference 8. The ligand is [^{3}H]YM-09151−2 for both D_2 and D_4.

Results and Discussion. Removal of the dimethoxy groups of **2** led to **7a**, which exhibited an increased preference for the D_4 over the D_2 receptor. However, **7a** retained significant binding at other CNS receptors (Table 1). Additional racemic, desmethoxyisochromans were synthesized by the method shown in Scheme 1. Mixed acetal **5**, prepared from **4**, was isolated and carried on to the chloromethyl intermediate **6**, using $AlCl_3$ as the Lewis acid. Displacement of the chloro group with aryl piperazines gave final products **7a** and **7b**. Compound **7b** was found to have a 400-fold preference for the D_4 vs D_2 receptors.

Further analog work required an improved synthesis of the isochroman system, as well as a handle for resolution at the chiral center. The route shown in Scheme 2, using $TiCl_4$ as the Lewis acid and ethyl 3,3-diethoxypropionate (**8**) as the acetal, gave ester **9** in excellent yield. Originally, the enantiomers of **7b** were obtained through fractional crystallization of racemic acid **10** with (*R*)-(+)-α-methylbenzylamine and (*S*)-(−)-α-methylbenzylamine, followed by borane reduction of **11** and **12** to give alcohols **13** and **14**, respectively. HPLC using a Daicel OJ column indicated >99% ee for **13** by this method. Another method of resolution involved the Amano PS-30 lipase-mediated hydrolysis of ester **9** to give **11** (Scheme 3). Acid **11** was then reduced to the alcohol **13** with borane−methyl sulfide. HPLC analysis (Daicel OJ or OD column) of the alcohol indicated >99% ee. Mesylation of the alcohol, followed by displacement of the mesylate with 4-(piperazin-1-yl)-benzenesulfonamide, gave (*S*)-(−)-**15** (U-101387), whose absolute configuration was determined by X-ray crystallography.[9] Chiral chromatography using a Chiralpak AD column immersed in an ice bath (40% 2-propanol + 0.1% trifluoroacetic acid in hexane as eluant) gave nearly baseline separation ($\alpha = 1.33$) of (*S*)-(−)-**15** and (*R*)-(+)-**15**, but tailing precluded an accurate estimation of % ee; the chiral purity of alcohol **13** was taken as indicative of the % ee of the final product, (*S*)-(−)-**15**.

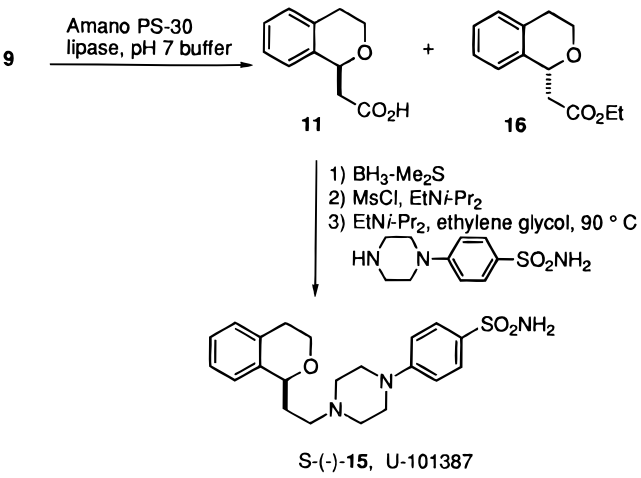
Table 1 details the binding affinities of selected isochromans and also, for comparison, clozapine and JL 18 (**3**), a clozapine analog reported to have increased

Scheme 2



dopamine D_4 selectivity over that of clozapine.[10] The first analog in the isochroman series to show a reasonable degree of selectivity was **7b**. When the individual enantiomers were prepared, (*S*)-(−)-**7b** was shown to have a higher affinity for the dopamine D_4 receptor when compared to (*R*)-(+)-**7b**, while binding at the D_2 receptor remained the same. Unfortunately, metabolism and bioavailability studies indicated (*S*)-(−)-**7b** was rapidly metabolized, principally through an O-demethy-

Scheme 3



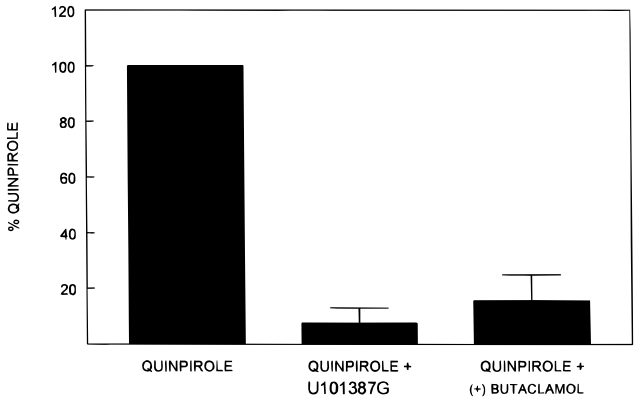


Figure 1. Antagonism of quinpirole-induced mitogenesis in CHO cells expressing the human D4 receptor.[15] Quinpirole (300 nM) was added to cells, along with the test compound (1μ M) or sterile water, 16−18 h prior to the addition of [^{3}H]-thymidine (1 μCi/well). After 2 h of incubation, the cells were harvested onto filter mats and counted.

lation (as indicated by monkey and human microsome studies). Further analog work led to benzenesulfonamide (*S*)-(−)-**15**; this compound exhibits remarkable selectivity for the D_4 receptor (Table 1) vs both the receptors shown in Table 1 and a panel of some 50 receptors as assayed by Novascreen (Oceanix Biosciences, Inc.). As with **7b**, the (*S*)-(−)-**15** has higher affinity at the D_4 receptor when compared to the (*R*)-(+)-enantiomer.

A comparison of (*S*)-(−)-**7b** and (*S*)-(−)-**15** (as the maleate salt) indicated a 15% oral bioavailability in the rat for S-(−)-**7b**, vs a 66% oral bioavailability for the sulfonamide analog (*S*)-(−)-**15**. Indeed, (*S*)-(−)-**15** was found to be a potent D_4 antagonist (Figure 1) with a monkey oral bioavailability of 76% and a half-life of 13.6 h. Penetration into the brain (mouse parenchyma) is rapid, and brain vs plasma concentration is high.[11] In summary, the high affinity and specificity of (*S*)-(−)-**15** for the dopamine D_4 receptor make this compound a unique tool for the study of the role of the D_4 receptor in normal and pathological states. (*S*)-(−)-**15** has been entered into phase II clinical trials for the treatment of schizophrenia.

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Supporting Information Available: Experimental data for compounds in this paper (8 pages). Ordering information is given on any current masthead page.

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