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AZEPINOINDOLE DERIVATIVES WITH HIGH AFFINITY FOR BRAIN DOPAMINE AND SEROTONIN RECEPTORS

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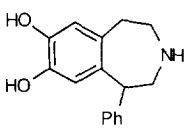
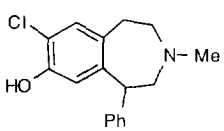
Abstract: We synthesized **20** and **21** as conformationally constrained analogues of the dopamine receptor antagonist SKF-83742, as well as analogues **6–9**, **16**, and **18–22**. Although **20** and **21** were inactive, **7**, **9**, and **19** showed strong binding to D-1, D-2, S-2, and α-1 receptors, as well as antipsychotic activity in vivo.

Antipsychotic drugs that are used in the treatment of schizophrenia typically target dopamine receptors in the central nervous system (CNS), decreasing their functional activity.[1] In this context, antagonism of the D-2 receptor subtype has been recognized as important. However, in the quest to avoid the untoward side effects of extrapyramidal symptoms (EPS) and tardive dyskinesia, researchers have directed attention to compounds with affinities for multiple CNS receptors.[2,3] For example, the atypical antipychotic drug clozapine, which is devoid of EPS, binds to both dopamine D-4 and serotonin S-2 receptors,[3,4] and risperidone, which offers therapeutic advantages over classical antipsychotics as well as diminished EPS liability, binds with high affinity to D-2 and S-2 receptors.[2d,3,5] Thus, new types of compounds that can act simultaneously at specific dopamine and serotonin receptors in the CNS would be valuable in expanding this antipsychotic drug class.[2,3]



SKF-38393



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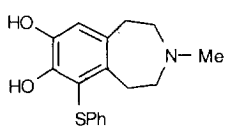
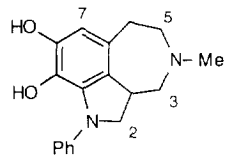


SKF-83742



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The 2,3,4,5-tetrahydro-3-benzazepines have attracted considerable interest because they constituted the first chemical series to exhibit selectivity for dopamine receptor subtypes, as both agonists and antagonists.[6] This is exemplified by the D-1 agonist SKF-38393 and the D-1 antagonist Sch-23390. Structural elaboration led Kaiser and coworkers[6a,7] to SKF-83742, which is a rare example of a dopamine receptor antagonist that contains a complete catecholamine substructure. Consequently, we developed an interest in SKF-83742 as a basis for devising new antipsychotic drug candidates, with a eye for introducing conformational restriction by connecting the sulfur atom to the C1 position. However, since this alteration would generate an undesirable, polar sulfonium functionality, we decided to change the sulfur to a nitrogen, resulting in a target structure such as azepinoindole **1**. We describe herein the synthesis and biological evaluation of a series of related azepinoindoles, including **6**, **7**, **9**, **16**, and **18–22**. Surprisingly, close SKF-83742 analogues **20** and **21** were found to be

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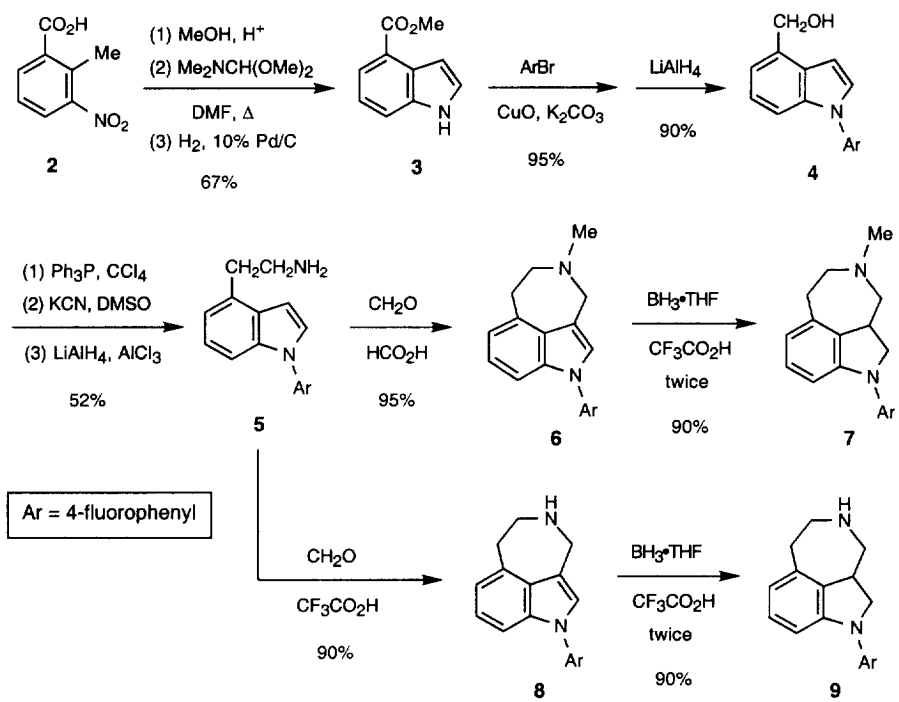
devoid of both D-1 and D-2 receptor affinity. However, we were fortunate to discover related compounds, such as **7** and **19**, that bind with high affinity to central D-1, D-2, and S-2 receptors, and possess antipsychotic activity in rats as determined by the conditioned-avoidance response (CAR) assay.[8]

Synthetic Chemistry. N-Arylation of **3**, prepared by the Batcho–Leimgruber indole synthesis,[9] with 4-fluorobromobenzene under normal Ullmann coupling conditions[10] (Cu or CuO in DMF or pyridine) resulted in impure N-arylated indole 4-ester (Scheme 1). However, arylation in neat, refluxing 4-fluorobromobenzene gave a clean reaction and an excellent yield of the arylated ester, which was readily converted without purification to alcohol **4**. The indole 4-acetonitrile was prepared from **4** and reduced with AlH_2Cl[11] to amine **5** in high yield. Mannich reaction of **5** with 37% aqueous formaldehyde under Eschweiler–Clarke conditions nicely afforded N-methyl azepinoindole **6**, while the use of trifluoroacetic acid (TFA) produced N-H azepinoindole **8** (HCl salt, from MeOH: mp 295-298 °C). In the reduction of indole **6** or **8** to the corresponding indoline with BH_3•THF in TFA,[12] the conversion was incomplete; thus, the procedure was repeated to furnish excellent yields of **7** or **9**.

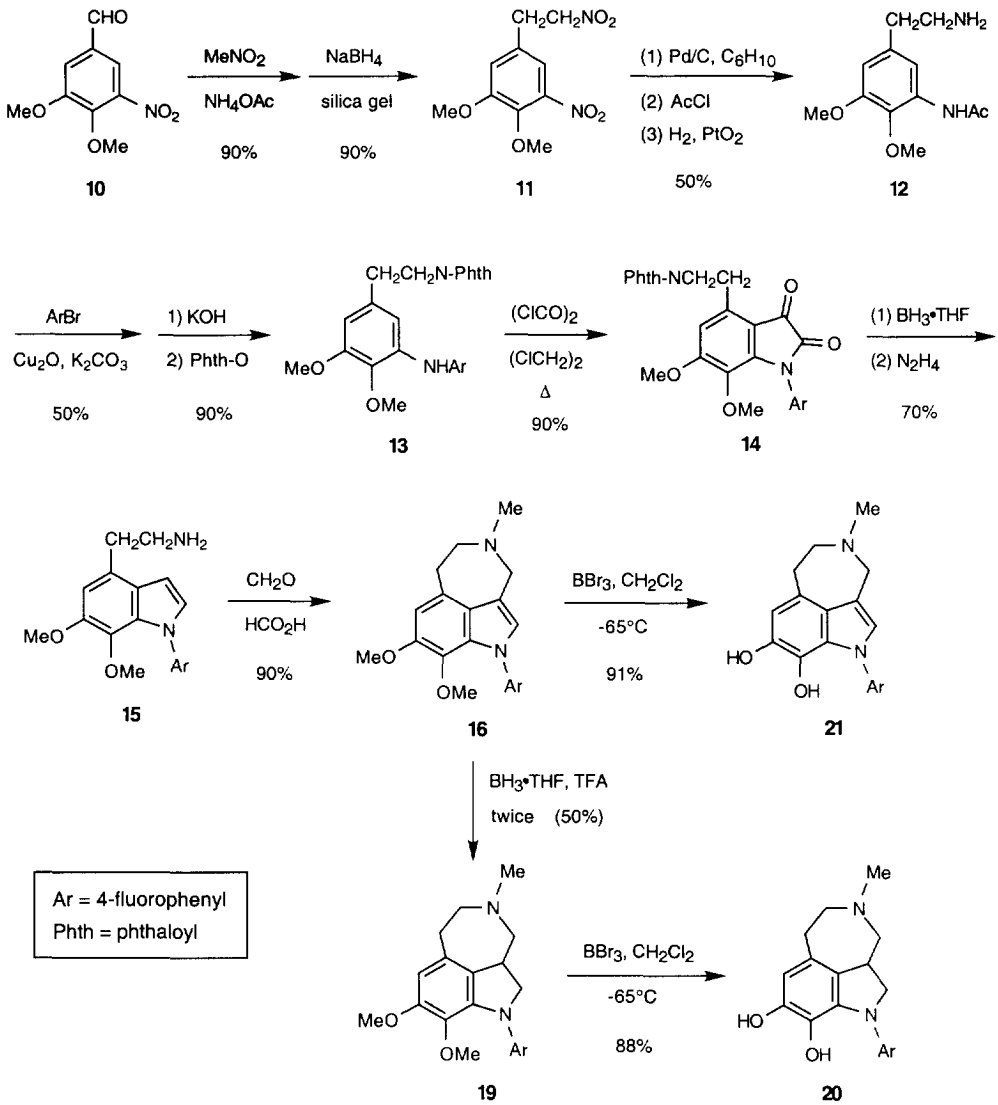
Benzaldehyde **10** was homologated to **11**,[13] and the aromatic nitro group was selectively hydrogenated with cyclohexene and 10% Pd/C in refluxing EtOH (Scheme 2).[14] The aniline intermediate was acetylated and the aliphatic nitro group was hydrogenated to afford **12**. Since arylation of **12**, or its nitro precursor, under standard or modified Ullmann conditions (above) gave variable results, we explored other copper catalysts[15] and obtained superior results with Cu_2O. Hydrolysis of this arylated acetanilide, then phthalimide protection, smoothly supplied **13**. The oxalyl chloride step was tricky in that the initial N-acylation had to be performed at

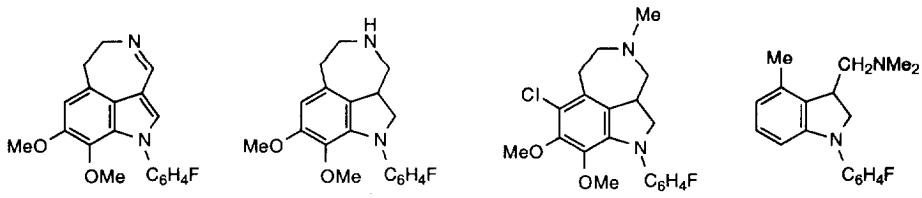
Scheme 1



0 °C without base present, followed by cyclization to isatin **14**, which was then cleanly reduced[16] to the indole and deprotected with hydrazine to give **15**. Mannich reaction of **15** under Eschweiler–Clarke conditions gave **16**, along with a small amount of imine **17**, which was isolated and reduced sequentially with $NaBH_4$ (in MeOH) and BH_3•THF/TFA to indoline **18**. Demethylation of the HBr salts of **16** or **19** with 1 M BBr_3,[17] followed by MeOH workup, furnished solid HBr salts of **21** and **20**, respectively. The 5-chloro derivative of isatin **14** (from **14** and Cl_2) was converted to the 5-chloro analogue of **16**, reduction of which to indoline **22** failed under standard conditions (BH_3•THF or $NaBH_4$ with TFA or HCl). However, by employing triflic acid

Scheme 2





with BH_3•THF, we were able to obtain **22** in 30% yield. More favorably, we prepared **22** in 60% yield by chlorination of **19** with *N*-chlorosuccinimide in DMF.[18]

Ester **3** was converted to amine **23** in four high-yielding steps (Scheme 3). However, the cyclization of **23** gave a moderate purified yield of **24**, which was then reduced in high yield to **25**. The ester precursor of **4** was reacted with 37% formaldehyde and dimethylamine to give the Mannich base (58% yield), which was reduced sequentially with $LiAlH_4$ and $NaBH_4$ pellets in TFA[19] to afford seco analogue **26** (48% yield).

Biological Results. The test compounds, fully characterized as indicated in Table 1, were examined for their binding to the D-1, D-2, S-1, and S-2 receptors, as well as the α-1 adrenergic receptor (Table 2).[8] Potential antipsychotic activity was assessed in the rat CAR assay (Table 2).[8b] Compounds **20** and **21**, the specific conformationally constrained analogues of SKF-83742, were virtually devoid of affinity for the D-1 and D-2 receptors, as well as for the S-1, S-2, and α-1 receptors. Also, as expected from the binding data, **20** and **21** showed no better than weak activity in the CAR test. However, several azepinoindoles exhibited high affinities for D-1, D-2, S-1, S-2, and/or α-1 receptors, as well as good potency in the CAR test, suggesting

Scheme 3

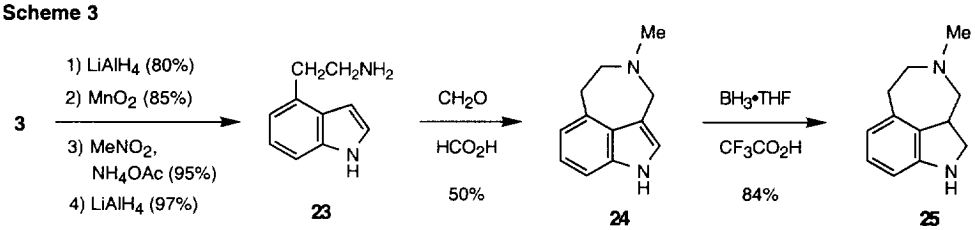


Table 1. Chemical Properties[a]

No.	formula	mp, °C (solv)[b]	No.	formula	mp, °C (solv)[b]
6	$C_{18}H_{17}FN_2$•HBr•0.6H_2O	224–227 (E)	**20**	$C_{18}H_{19}FN_2O_2$•2HBr•H_2O	209–212 (I)
7	$C_{18}H_{17}FN_2$•HBr•0.5H_2O	202–205 (E)	**21**	$C_{18}H_{17}FN_2O_2$•HBr•0.3H_2O[c]	180 dec (M/EE)
9	$C_{17}H_{17}FN_2$•HBr	231–235 (M)	**22**	$C_{20}H_{22}ClFN_2O_2$•HBr[d]	194–195 (I)
16	$C_{20}H_{21}FN_2O_2$•HBr	232–235 (M/I)	**24**	$C_{12}H_{14}N_2$	142–150 (EA)
18	$C_{19}H_{21}FN_2O_2$•HBr[e]	225–227 (I)	**25**	$C_{12}H_{16}N_2$•1.8HCl•0.7H_2O	233–240 (M/I)
19	$C_{20}H_{23}FN_2O_2$•HBr	209–211 (I)	**26**	$C_{18}H_{21}FN_2$•HBr	230–232 (I)

(a) Test compounds were purified by recrystallization and characterized by mass spectrometry and high-field proton NMR. Microanalytical data (C, H, N) were within the accepted range (±0.4%); % water was determined by Karl-Fisher analysis (b) Mp values are corrected. The recrystallization solvent is given in parentheses: E = EtOH, EA = ethyl acetate, EE = ethyl ether, I = 2-propanol, M = MeOH. (c) 0.5 mol of ether present. (d) 0.1 mol of 2-propanol present. (e) 0.2 mol of 2-propanol present.

Table 2. Biological Data[a]

	K_i, nM[b]					CAR, i.p.
No.	D-1	D-2	S-1	S-2	α-1	ED_{50}, mg/kg[c]
6	72 (67-77)	83 (57-120)	190 (120-330)	13 (6.4-29)	29 (23-38)	15% @ 15
7	2.8 (1.9-4.0)	9.2 (7.4-12)	210 (205-215)	0.62 (0.49-0.77)	4.7 (3.2-6.7)	2.5 (1.5-3.4)
9	9.2 (7.1-12)	34 (20-67)	120 (64-300)	1.3 (0.58-2.5)	14 (7.6-27)	3.7 (2.6-4.9)
16	>1000	370 (250-520)	135 (120-150)	3.6 (2.6-5.0)	>100	10% @ 7.5
18	88 (77-100)	67 (38-140)	19 (8.0-32)	1.0 (0.4-3.1)	57 (41-83)	90% @ 15[d]
19	40 (27-60)	31 (24-41)	34 (28-42)	0.41 (0.13-0.90)	21 (18-25)	5.8 (-)
20	>1000	>1000	>1000	1700	660	32% @ 15
21	>1000	>1000	>1000	>1000	>500	40% @ 15
22	11 (7.9-16)	6.8 (3.7-13)	16 (11-24)	0.09 (0.06-0.13)	22 (15-34)	IA
24	>1000	>1000	>1000	>1000	<1000	IA
25	>1000	>1000	~1000	>1000	<1000	IA
26	24 (17-35)	3.0 (2.5-3.6)	230 (205-265)	7.2 (6.0-8.8)	35 (24-58)	6.8 (5.8-8.4)
haloperidol	20 (18-22)	0.20 (0.09-0.38)	400 (190-1000)	11 (8.0-15)	23 (12-32)	0.17 (0.13-0.27)
risperidone	22 (15-34)	2.1 (1.9-2.4)	55 (33-99)	0.20 (0.11-0.33)	3.0 (2.0-4.5)	1.2 (0.8-1.9)

(a) 95% Confidence interval is given in parentheses. (b) Receptor binding assays were performed as reported in ref 8. (c) Blockade of conditioned avoidance in rats (IA = inactive at 15 mg/kg); the test was performed as reported in ref 8b. (d) High escape loss.

dopamine antagonism. Compound **7** showed very high affinities (K_i < 10 nM) for the D-1, D-2, S-2, and α-1 receptors, and an ED_{50} in the CAR test of 2.5 mg/kg, whereas its corresponding indole, **6**, was considerably less potent in these parameters. Nor-indoline **9** had ca. three-fold weaker affinity than **7** for the D-1, D-2, S-2, and α-1 receptors, but about the same potency in the CAR test (ED_{50} = 3.7 mg/kg). Dimethoxy indoline **19** showed respectable binding to all five receptors, particularly *subnanomolar potency at the S-2 receptor*, and an ED_{50} of 5.8 mg/kg in the CAR test, whereas corresponding indole **16** was much less potent. Nor-indoline **18** had nearly the same potency as **19**. Chloro analogue **22** exhibited good binding to all five receptors, but with an *impressive K_i of 0.09 nM at the S-2 receptor*, making it rather selective for this target (S-2/D-2 = 75; S-2/D-1 = 120; S-2/S-1 = 180; S-2/α-1 = 240). Paradoxically, **22** was inactive in the CAR test, although it displayed *potent serotonin antagonism* by inhibiting L-5-hydroxytryptophan-induced head twitches in mice, as did **7**.[20] The seco analogue of **7**, **26**, had notable binding to D-2 and S-2 receptors, as well as an ED_{50} of 6.8 mg/kg in the CAR test.[21] Removal of the aryl substituent from **6** and **7**, as in **24**[22] and **25**, virtually abolished biological activity. Hence, although conformational constraint of SKF-83742 as in **20** and **21** is unfavorable for dopamine and serotonin receptor affinity, related indolines **7**, **9**, **18**, **19**, and **22**, which lack the catechol motif, are generally quite potent ligands.[23] The CAR activity of **7**, **9**, and **19** (**18** excluded due to high escape loss) suggests their potential as antipsychotic agents, although they are less potent in vivo than haloperidol or risperidone. The binding profile for these azepinoindoles is analogous to that for an atypical antipsychotic drug, like risperidone[3,5] or sertindole.[21] Given the potent serotonin antagonism for **7** and **22**,[20] **7**, **9**, **18**, **19**, and **22** define a novel 1-aryl-azepino[3,4,5-*cd*]indole class of S-2 receptor antagonists.[2a,2d,21,24]

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