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NEW GENERATION DOPAMINERGIC AGENTS. 2. DISCOVERY OF 3-OH-PHENOXYETHYLAMINE AND 3-OH-N^1-PHENYLPIPERAZINE DOPAMINERGIC TEMPLATES

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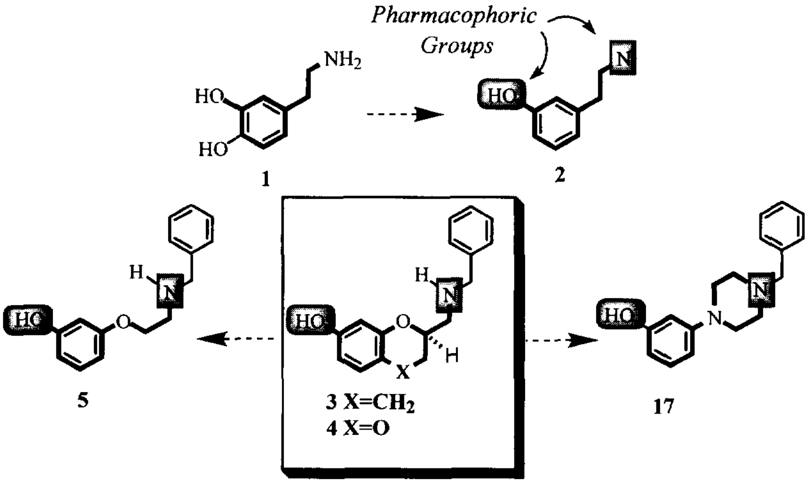
Abstract: Described in this report is a systematic study which led to the identification of two new dopamine D_2 partial agonists (**5** and **17**). Phenols **5** and **17** represent prototypes of two new classes of D_2 partial agonists as well as templates for the future design of novel dopaminergic agents.

The endogenous neurotransmitter dopamine (DA, **1**) has been extensively exploited in drug design strategies resulting in a large number of novel dopaminergic agents.[1-3] Traditionally dopamine agonists and partial agonists have been designed to access the D_2 agonist pharmacophore by tethering the vital 3-OH group and basic nitrogen, in an almost coplanar arrangement, by means of the phenethyl scaffold (i.e. **2**). Previous reports from our laboratories have revealed a novel approach to access the D_2 agonist pharmacophore using the chroman and benzodioxan ring systems as part of a scaffold to tether the pendant 7-OH and 2-aminomethyl groups.[4] Excellent selectivity was achieved by attaching the benzyl side chain, which led to the discovery of the potent D_2 partial agonists, **3** and **4**. Since our efforts were directed at



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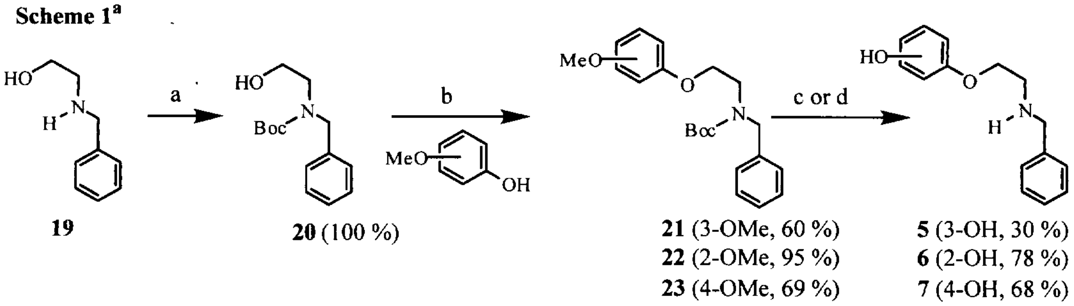
discovering new agents for the treatment of schizophrenia, we wanted to further expand upon our understanding of the roles of the chroman and benzodioxan rings by preparing phenol **5**.

Additionally, modeling studies suggested the D_2 agonist pharmacophore could also be accessed by the 3-OH-*N¹*-phenylpiperazine framework (Figure 1). Surprisingly, the use of a N^1-phenylpiperazine moiety as part of a scaffold for the D_2 pharmacophoric groups (i.e. **17**) appeared to be an unexploited dopaminergic D_2 drug design strategy. In this report, we describe our preliminary structure-activity relationship studies which led to the discovery of two novel prototypical D_2 templates (i.e. **5** and **17**).

CHEMISTRY

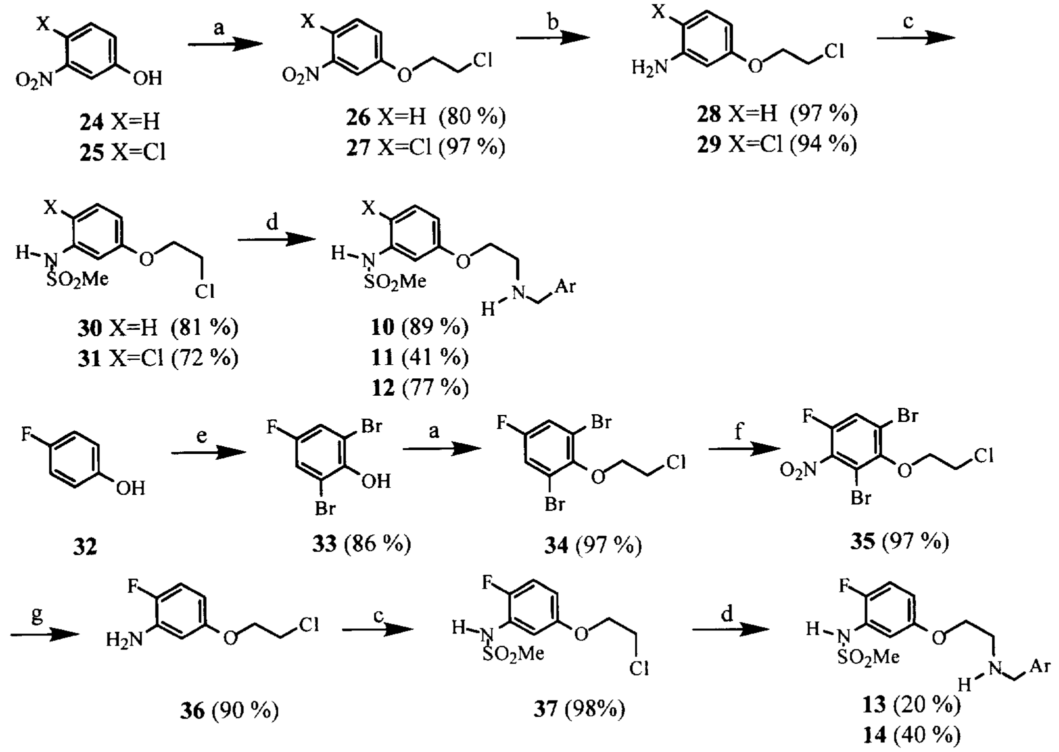
Phenols **5-7** were prepared as depicted in Scheme 1 by first protecting *N*-benzylaminoethanol (**19**) with the Boc group to afford **20** in quantitative yield. Coupling of the 2-, 3-, or 4-methoxyphenols with **20** under Mitsunobu conditions,[5] using diisopropyl azodicarboxylate (DIAD), gave the desired products **21-23**. Deprotection and demethylation could be achieved in one-pot using 48 % HBr to afford **5**, or as in the cases of **6** and **7**, in a two-step sequence using trifluoroacetic acid followed by 48 % HBr. Compounds **9-14** were prepared according to the general synthetic route depicted in Scheme 2. Nitrophenols **24** and **25** were alkylated with 1,2-bromochloroethane followed by reduction with Raney nickel to give the anilines **28** and **29**. Aniline **9** (Table 2) was prepared by treatment of **29** with benzylamine. Reaction with methanesulfonyl chloride, followed by treatment with either benzylamine or 2-thienylmethylamine, afforded target sulfonamides **10-12**. 4-Fluorosulfonamides **13** and **14** were prepared in 6 steps beginning with 4-fluorophenol (**32**). Bromination of **32** gave phenol **33** which was alkylated with 1,2-bromochloroethane and sequentially mononitrated and hydrogenated to afford aniline **36**. Mesylation, followed by treatment with benzylamine or 2-thienylmethylamine, gave the desired target sulfonamides **13** and **14**. The N^4-benzyl-N^1-phenylpiperazines were prepared as shown in Scheme 3 starting with the commercially available N^1-phenylpiperazines (**38-41**) to produce piperazines **15-18**.

Scheme 1[a]



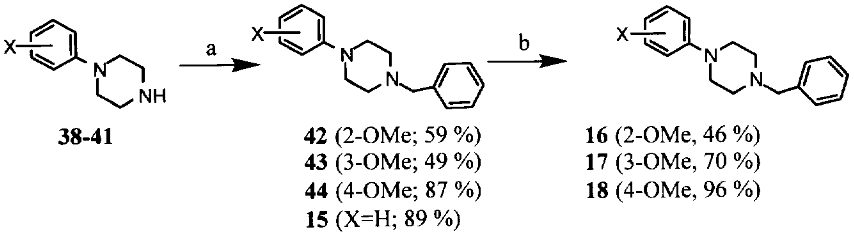
[a]**Reagents and conditions**: (a) Boc_2O, THF; (b) DIAD, PPh_3, THF; (c) 48 % aq. HBr (d) (i) TFA (ii) c

Scheme 2[a]



[a]**Reagents and conditions**: (a) $Br(CH_2)_2Cl$, K_2CO_3, 2-butanone; (b) Raney Nickel, H_4N_2, EtOH (c) $MeSO_2Cl$ (d) $ArCH_2NH_2$, DMSO (e) Br_2 (f) HNO_3/H_2SO_4 (g) Pd/C H_2, EtOH

Scheme 3[a]



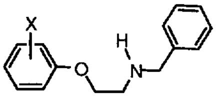
[a]**Reagents and conditions**: (a) BnBr, DMSO; (b) 48 % aq. HBr

RESULTS AND DISCUSSION

Shown in Tables 1-3 are the affinities of the target compounds **5-18** for the D_2, D_3, and D_4 receptors. The affinities of compounds for the DA D_2 receptors in rat striatal membranes were determined for both the agonist state (high affinity state, D_2^{High}) and the antagonist state (low affinity state, D_2^{Low}). The D_2^{High} state was labeled with [^{3}H]quinpirole (in the absence of GTP and sodium) and the D_2^{Low} state was labeled with [^{3}H]spiperone (using ketanserin to exclude 5-HT_2 receptor binding) in the presence of GTP. The ratio $K_i(D_2^{Low})/K_i(D_2^{High})$ was used as a preliminary assessment of the compounds' intrinsic activity as described by Lahti[6] and Wasik.[7] The D_2 partial agonist, (*S*)-3-PPP [$(K_i(D_2^{Low})/K_i(D_2^{High})=33$], was used as a benchmark from which a compound's estimated intrinsic activity was compared. Affinity for the human cloned receptors was determined using membranes from CHO cells labeled with [^{3}H]spiperone.

As shown in Table 1, the 3-hydroxy isomer (**5**) had higher affinity for the D_2^{High} receptor than the 2- or 4-isomeric phenols (i.e. **6** and **7**). A 19- and 7- fold increase in affinity, attributed to the hydrogen bond donating effect, was observed when **5** and **6** were compared to **8**, respectively. Comparison of the D_2^{High} affinities of the more conformationally promiscuous phenoxyethyamine **5** (K_i=3.6 nM) with its constrained analogs **3** (K_i=0.16 nM) and **4** (K_i=0.35 nM), revealed that the dihydropyran and dioxan rings were playing a beneficial role towards accessing the D_2 agonist pharmacophore. Phenol **5** was observed to have good affinity for cloned human dopamine receptors (hD_{2s}, hD_3, $hD_{4.4}$), especially for the D_3 receptor, believed to exist predominantly in its high affinity state.[8]

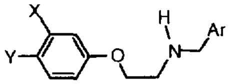
Table 1. Affinity of Phenoxyethylamines **5-8** for D_2-D_4 Receptors



		K_i (nM)[9]					
No.	X	D_2^{High}	D_2^{Low}	D_2^{Low}/D_2^{High}	hD_{2s}	hD_3	$hD_{4.4}$
5	3-OH	3.6	101	28	75.8	11.0	80.6
6	2-OH	9.6	191	20	456.0	281.5	297.00
7	4-OH	113	nd	-	> 10,000	> 5000	277.0
8	H	68.4	241	4	>300	>400	94.00
3[4]		0.16	3.3	21	10.4	2.4	116
4[4]		0.35	4.8	14	7.2	1.1	16.6

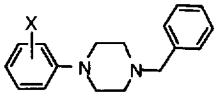
Though the sulfonamido analogs (**10-14**) of **5** were observed to have good affinity for the D_2^{High} receptor, their intrinsic activities were predicted to be much lower [$(K_i(D_2^{Low})/K_i(D_2^{High})<10$].

Table 2. Affinity of Phenoxyethylamine Analogs of **5** for D_2-D_4 Receptors



				K_i (nM)^9					
No.	X	Y	Ar	D_2^{High}	D_2^{Low}	D_2^{Low}/D_2^{High}	hD_{2s}	hD_3	$hD_{4.4}$
9	NH_2	Cl	Ph	237	nd	-	>1000	>1000	27.2
10	NHSO2Me	H	Ph	4.4	29.3	7	37.6	42.5	500.0
11	NHSO2Me	Cl	Ph	1.6	3.0	2	75.8	11.0	nd
12	NHSO2Me	Cl	2-Thienyl	2.6	6.0	2	9.00	27.8	137.0
13	NHSO2Me	F	Ph	7.9	24.1	3	>10,000	>5000	nd
14	NHSO2Me	F	2-Thienyl	19.7	11.7	1	>300	>400	>400

Table 3. Affinity of *N*^{4}-Benzyl-*N*^{1}-Phenylpiperazines (**15-18**) for D_2-D_4 Receptors

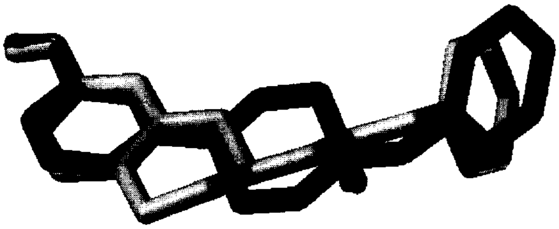


				K_i(nM)^9			
No.	X	D_2^{High}	D_2^{Low}	D_2^{Low}/D_2^{High}	hD_{2s}	hD_3	$hD_{4.4}$
15	H	16.2	124	8	>300	>400	267.0
16	2-OH	64.7	1176	18	>300	>400	>400
17	3-OH	5.5	95.1	17	246.0	28.90	>400
18	4-OH	120	nd	-	>300	>400	91.8

As shown in Table 3, 3-OH-*N*^{1}-phenylpiperazine (**17**) resulted in higher affinity for the D_2^{High} receptor than its 2- and 4-OH analogs. Though **17** had only a 3-fold increase in affinity with respect to the deshydroxy analog (**15**), comparison of its predicted intrinsic activity level to that of **15**, and its affinity for the D_3 receptor, suggests that **17** is accessing a similar D_2 agonist pharmacophore as that of **3** and **4**, though not as effectively. In contrast to the 2-OH-phenoxyethylamine (**6**), the 2-OH-*N*^{1}-phenylpiperazine (**16**) was not as effective in binding to the D_2^{High} receptor. Shown in Figure 1 is an overlay of the putative bioactive conformers[10] of **3** and **17** which adhere to the D_2 agonist pharmacophore criteria as represented by the McDermed model.[11] Phenols **5** and **17** were observed to have excellent selectivity over the α_1-adrenergic (**5**; K_i=5291 nM: **17**; K_i>1 μM) and 5-HT_{1A} receptors (**5**; K_i=1782 nM; **17**; K_i>1μM). In vivo, **5** and **17** inhibited locomotor activity with ED_{50} values of 0.08 and 1.4 mg/kg sc in mice, respectively.

In conclusion, we have discovered that the phenoxyethylamino and N^1-phenylpiperazinyl moieties can be utilized as novel scaffolds to access the D_2 agonist pharmacophore. Phenols **5** and **17**, devoid of the traditional 3-OH-phenethylamine backbone, represent novel prototypical D_2 agonist templates for the future design of a new generation of dopaminergic agents currently being investigated in our laboratories.

Figure 1. Overlay of **3** and **17** in Putative D_2 Agonist Pharmacophoric Conformations.



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9. K_i values are the means of n = 2-3 experiments run at six different concentrations. Each experiment was carried out in triplicate. 95% confidence limits were generally $< \pm$ 15 % of the mean value.
10. All computations were performed using Sybyl software package version 6.3. The basic phenylpiperazine framework of **17** was identified from the Cambridge database and used as a starting point; further computations were performed using Sybyl v6.3.
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