

## NEW GENERATION DOPAMINERGIC AGENTS. 2. DISCOVERY OF 3-OH-PHENOXYETHYLAMINE AND 3-OH-*N'*-PHENYLPIPERAZINE DOPAMINERGIC TEMPLATES

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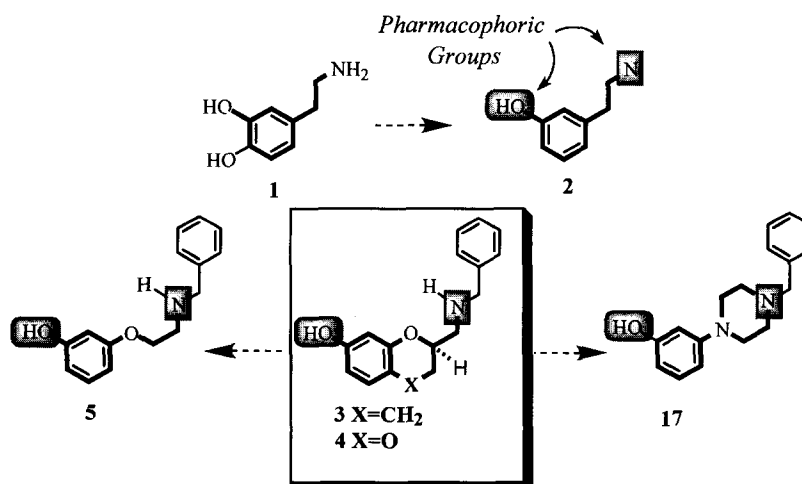
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**Abstract:** Described in this report is a systematic study which led to the identification of two new dopamine D<sub>2</sub> partial agonists (**5** and **17**). Phenols **5** and **17** represent prototypes of two new classes of D<sub>2</sub> partial agonists as well as templates for the future design of novel dopaminergic agents.

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The endogenous neurotransmitter dopamine (DA, **1**) has been extensively exploited in drug design strategies resulting in a large number of novel dopaminergic agents.<sup>1–3</sup> Traditionally dopamine agonists and partial agonists have been designed to access the D<sub>2</sub> 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<sub>2</sub> agonist pharmacophore using the chroman and benzodioxan ring systems as part of a scaffold to tether the pendant 7-OH and 2-aminomethyl groups.<sup>4</sup> Excellent selectivity was achieved by attaching the benzyl side chain, which led to the discovery of the potent D<sub>2</sub> partial agonists, **3** and **4**. Since our efforts were directed at



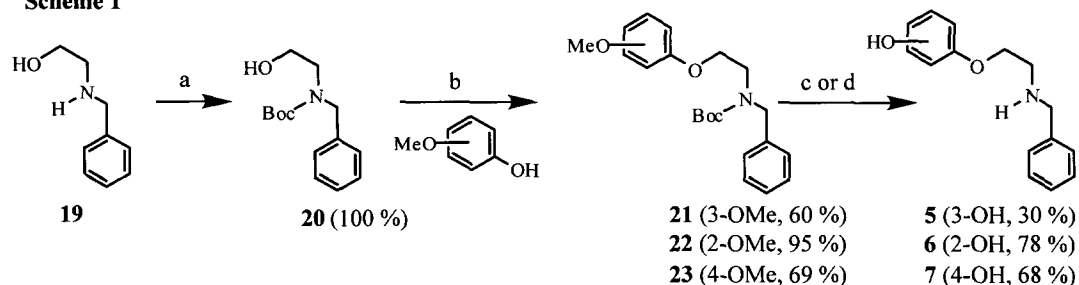
discovering new agents for the treatment of schizophrenia, we wanted to further expand upon our understanding of the roles of the chroman and benzodioxan rings by preparing phenol **5**.

Additionally, modeling studies suggested the D<sub>2</sub> agonist pharmacophore could also be accessed by the 3-OH-*N*<sup>l</sup>-phenylpiperazine framework (Figure 1). Surprisingly, the use of a *N*<sup>l</sup>-phenylpiperazine moiety as part of a scaffold for the D<sub>2</sub> pharmacophoric groups (i.e. **17**) appeared to be an unexploited dopaminergic D<sub>2</sub> drug design strategy. In this report, we describe our preliminary structure-activity relationship studies which led to the discovery of two novel prototypical D<sub>2</sub> templates (i.e. **5** and **17**).

## CHEMISTRY

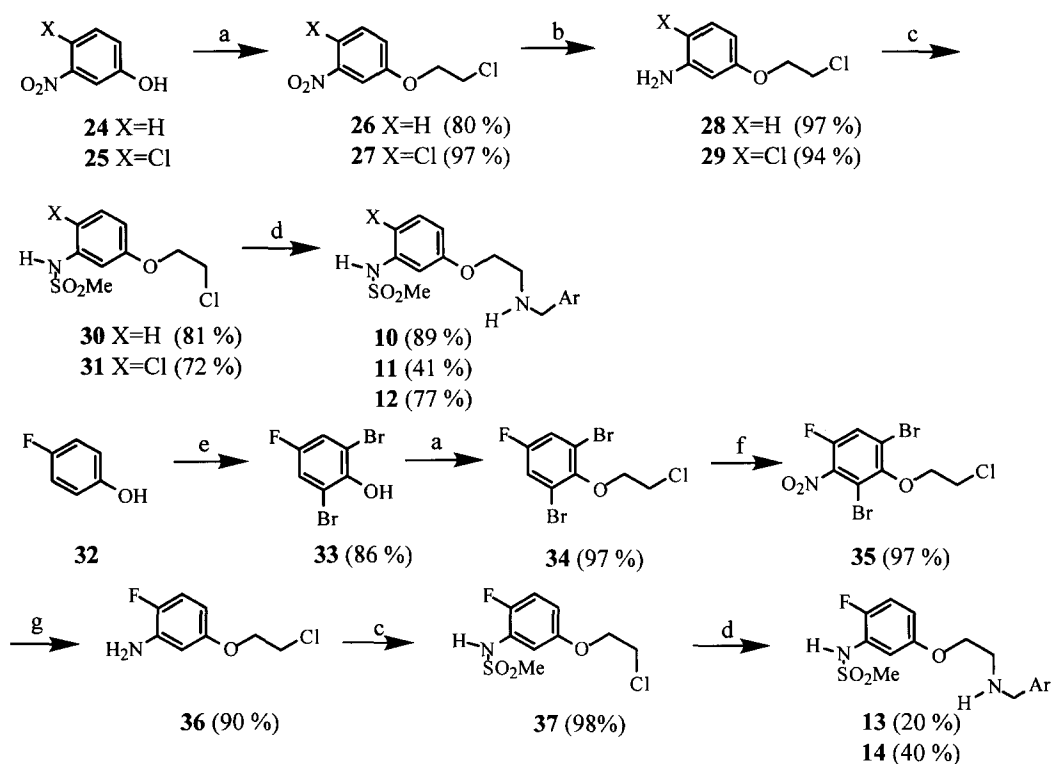
Phenols **5–7** were prepared as depicted in Scheme 1 by first protecting *N*-benzylaminoethanol (**19**) with the Boc group to afford **20** in quantitative yield. Coupling of the 2-, 3-, or 4-methoxyphenols with **20** under Mitsunobu conditions,<sup>5</sup> using diisopropyl azodicarboxylate (DIAD), 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

Scheme 1<sup>a</sup>

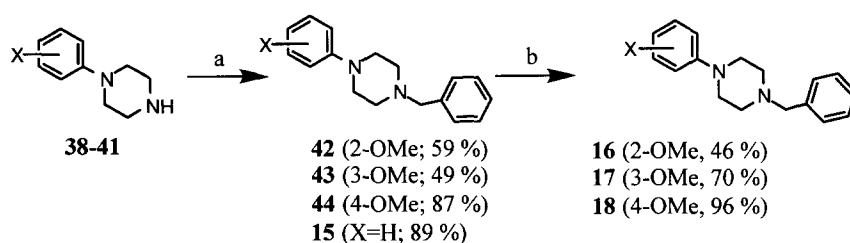


<sup>a</sup>Reagents and conditions: (a) Boc<sub>2</sub>O, THF; (b) DIAD, PPh<sub>3</sub>, THF; (c) 48 % aq. HBr (d) (i) TFA (ii) c

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*<sup>4</sup>-benzyl-*N*<sup>l</sup>-phenylpiperazines were prepared as shown in Scheme 3 starting with the commercially available *N*<sup>l</sup>-phenylpiperazines (**38–41**) to produce piperazines **15–18**.

**Scheme 2<sup>a</sup>**

<sup>a</sup>**Reagents and conditions:** (a) Br(CH<sub>2</sub>)<sub>2</sub>Cl, K<sub>2</sub>CO<sub>3</sub>, 2-butanone; (b) Raney Nickel, H<sub>4</sub>N<sub>2</sub>, EtOH  
 (c) MeSO<sub>2</sub>Cl (d) ArCH<sub>2</sub>NH<sub>2</sub>, DMSO (e) Br<sub>2</sub> (f) HNO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub> (g) Pd/C H<sub>2</sub>, EtOH

**Scheme 3<sup>a</sup>**

<sup>a</sup>**Reagents and conditions:** (a) BnBr, DMSO; (b) 48 % aq. HBr

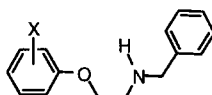
**RESULTS AND DISCUSSION**

Shown in Tables 1-3 are the affinities of the target compounds **5-18** for the D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> receptors. The affinities of compounds for the DA D<sub>2</sub> receptors in rat striatal membranes were determined for both the

agonist state (high affinity state,  $D_2^{\text{High}}$ ) and the antagonist state (low affinity state,  $D_2^{\text{Low}}$ ). The  $D_2^{\text{High}}$  state was labeled with [ $^3\text{H}$ ]quinpirole (in the absence of GTP and sodium) and the  $D_2^{\text{Low}}$  state was labeled with [ $^3\text{H}$ ]spiperone (using ketanserin to exclude 5-HT $_2$  receptor binding) in the presence of GTP. The ratio  $K_i(D_2^{\text{Low}})/K_i(D_2^{\text{High}})$  was used as a preliminary assessment of the compounds' intrinsic activity as described by Lahti<sup>6</sup> and Wasik.<sup>7</sup> The  $D_2$  partial agonist, (*S*)-3-PPP [ $(K_i(D_2^{\text{Low}})/K_i(D_2^{\text{High}})=33)$ ], 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 [ $^3\text{H}$ ]spiperone.

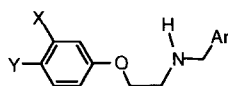
As shown in Table 1, the 3-hydroxy isomer (**5**) had higher affinity for the  $D_2^{\text{High}}$  receptor than the 2- or 4-isomeric phenols (i.e. **6** and **7**). A 19- and 7- fold increase in affinity, attributed to the hydrogen bond donating effect, was observed when **5** and **6** were compared to **8**, respectively. Comparison of the  $D_2^{\text{High}}$  affinities of the more conformationally promiscuous phenoxyethylamine **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.<sup>8</sup>

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

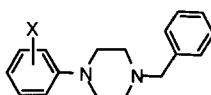


No.	X	$K_i$ (nM) <sup>9</sup>			hD $_{2s}$	hD $_3$	hD $_{4.4}$
		$D_2^{\text{High}}$	$D_2^{\text{Low}}$	$D_2^{\text{Low}}/D_2^{\text{High}}$			
<b>5</b>	3-OH	3.6	101	28	75.8	11.0	80.6
<b>6</b>	2-OH	9.6	191	20	456.0	281.5	297.00
<b>7</b>	4-OH	113	nd	-	> 10,000	> 5000	277.0
<b>8</b>	H	68.4	241	4	>300	>400	94.00
<b>3</b> <sup>4</sup>		0.16	3.3	21	10.4	2.4	116
<b>4</b> <sup>4</sup>		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  $D_2^{\text{High}}$  receptor, their intrinsic activities were predicted to be much lower [ $(K_i(D_2^{\text{Low}})/K_i(D_2^{\text{High}})<10)$ ].

**Table 2.** Affinity of Phenoxyethylamine Analogs of **5** for D<sub>2</sub>-D<sub>4</sub> Receptors

No.	X	Y	Ar	K <sub>i</sub> (nM) <sup>9</sup>			hD <sub>2s</sub>	hD <sub>3</sub>	hD <sub>4,4</sub>
				D <sub>2</sub> <sup>High</sup>	D <sub>2</sub> <sup>Low</sup>	D <sub>2</sub> <sup>Low</sup> /D <sub>2</sub> <sup>High</sup>			
<b>9</b>	NH <sub>2</sub>	Cl	Ph	237	nd	-	>1000	>1000	27.2
<b>10</b>	NHSO <sub>2</sub> Me	H	Ph	4.4	29.3	7	37.6	42.5	500.0
<b>11</b>	NHSO <sub>2</sub> Me	Cl	Ph	1.6	3.0	2	75.8	11.0	nd
<b>12</b>	NHSO <sub>2</sub> Me	Cl	2-Thienyl	2.6	6.0	2	9.00	27.8	137.0
<b>13</b>	NHSO <sub>2</sub> Me	F	Ph	7.9	24.1	3	>10,000	>5000	nd
<b>14</b>	NHSO <sub>2</sub> Me	F	2-Thienyl	19.7	11.7	1	>300	>400	>400

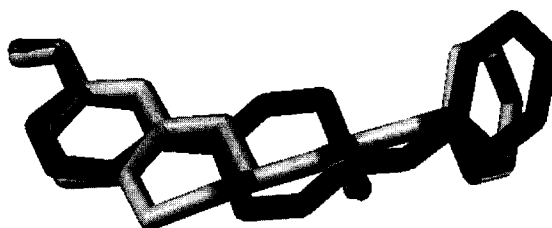
**Table 3.** Affinity of *N*<sup>4</sup>-Benzyl-*N*<sup>1</sup>-Phenylpiperazines (**15–18**) for D<sub>2</sub>-D<sub>4</sub> Receptors

No.	X	D <sub>2</sub> <sup>High</sup>	D <sub>2</sub> <sup>Low</sup>	K <sub>i</sub> (nM) <sup>9</sup>		hD <sub>2s</sub>	hD <sub>3</sub>	hD <sub>4,4</sub>
				D <sub>2</sub> <sup>Low</sup> /D <sub>2</sub> <sup>High</sup>				
<b>15</b>	H	16.2	124	8	>300	>400	267.0	
<b>16</b>	2-OH	64.7	1176	18	>300	>400	>400	
<b>17</b>	3-OH	5.5	95.1	17	246.0	28.90	>400	
<b>18</b>	4-OH	120	nd	-	>300	>400	91.8	

As shown in Table 3, 3-OH-*N*<sup>1</sup>-phenylpiperazine (**17**) resulted in higher affinity for the D<sub>2</sub><sup>High</sup> 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<sub>3</sub> receptor, suggests that **17** is accessing a similar D<sub>2</sub> agonist pharmacophore as that of **3** and **4**, though not as effectively. In contrast to the 2-OH-phenoxyethylamine (**6**), the 2-OH-*N*<sup>1</sup>-phenylpiperazine (**16**) was not as effective in binding to the D<sub>2</sub><sup>High</sup> receptor. Shown in Figure 1 is an overlay of the putative bioactive conformers<sup>10</sup> of **3** and **17** which adhere to the D<sub>2</sub> agonist pharmacophore criteria as represented by the McDermid model.<sup>11</sup> Phenols **5** and **17** were observed to have excellent selectivity over the α<sub>1</sub>-adrenergic (**5**; K<sub>i</sub>=5291 nM; **17**; K<sub>i</sub>>1 μM) and 5-HT<sub>1A</sub> receptors (**5**; K<sub>i</sub>=1782 nM; **17**; K<sub>i</sub>>1 μM). In vivo, **5** and **17** inhibited locomotor activity with ED<sub>50</sub> values of 0.08 and 1.4 mg/kg sc in mice, respectively.

In conclusion, we have discovered that the phenoxyethylamino and *N*<sup>1</sup>-phenylpiperazinyl moieties can be utilized as novel scaffolds to access the D<sub>2</sub> agonist pharmacophore. Phenols **5** and **17**, devoid of the traditional 3-OH-phenethylamine backbone, represent novel prototypical D<sub>2</sub> 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<sub>2</sub> Agonist Pharmacophoric Conformations.



## References and Notes

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9. K<sub>i</sub> 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 < ± 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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