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NEW GENERATION DOPAMINERGIC AGENTS. 7. HETEROCYCLIC BIOISOSTERES THAT EXPLOIT THE 3-OH-PHENOXYETHYLAMINE D_2 TEMPLATE

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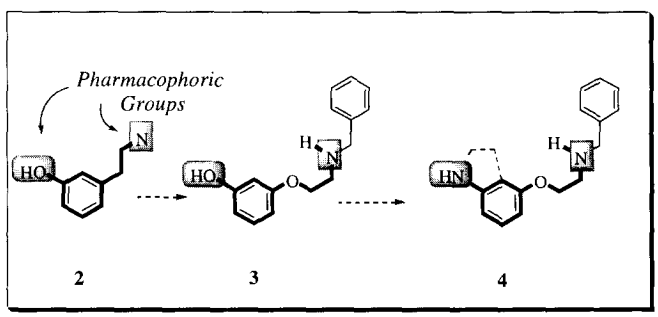
Abstract: The synthesis of several bioisosteric analogs based on the 3-OH-phenoxyethylamine dopamine D_2 agonist template (i.e., **3**) is described. The benzimidazol-2-ones and benzthioimidazol-2-ones (**7–10**) and 2-trifluoromethyl-benzimidazole (**13**) were observed to have excellent affinity for the D_2 receptor.

Clinically effective antipsychotics agents effective for the treatment of schizophrenia inhibit dopamine (DA, **1**) neurotransmission by blockade of postsynaptic DA receptors.[1] Unfortunately, typical D_2 antagonists exert extrapyramidal side effects (EPS), associated with dopaminergic blockade in the nigrostriatal regions of the brain. One approach towards normalizing dopaminergic activity while alleviating EPS involves stimulation of the D_2 autoreceptors, which regulate neurotransmitter synthesis, release, and neuronal firing by a negative feedback mechanism.[2] Recently, our laboratories have been searching for new D_2 partial agonists with the proper level of intrinsic activity to capitalize upon this therapeutic strategy.[3] Our findings have resulted in the



emergence of a new generation of dopaminergic agents that no longer rely upon the ubiquitous '3-OH-phenethylamine' framework (i.e., **2**), commonly exploited in dopamine D_2 drug design strategies.[4] We have identified several new scaffolds that can also access the D_2 agonist pharmacophore. In part 6, we reported our preliminary studies to prepare bioisosteric analogs based on the 3-OH-phenoxyethylamine D_2 template (i.e., **3**).[5,6] Our investigations have led to an expanded version of template **3** (i.e., **4**), which is embraced by the

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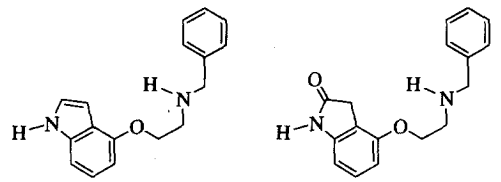
D_2 partial agonists **5** and **6**.[6] In this report we will describe the synthesis and structure-activity relationships of several novel series of D_2 partial agonists (**7–15**), also based upon templates **3** and **4**.



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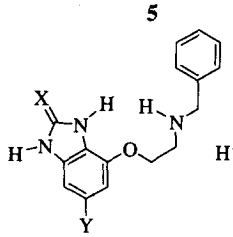
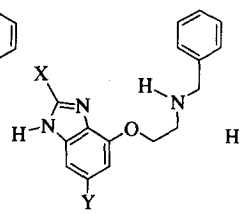
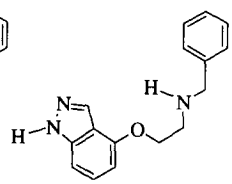
6







7 X = O; Y = H
8 X = O; Y = Cl
9 X = S; Y = H
10 X = S; Y = Cl

11 X = H; Y = H
12 X = CH_3; Y = H
13 X = CF_3; Y = H
14 X = CF_3; Y = Cl

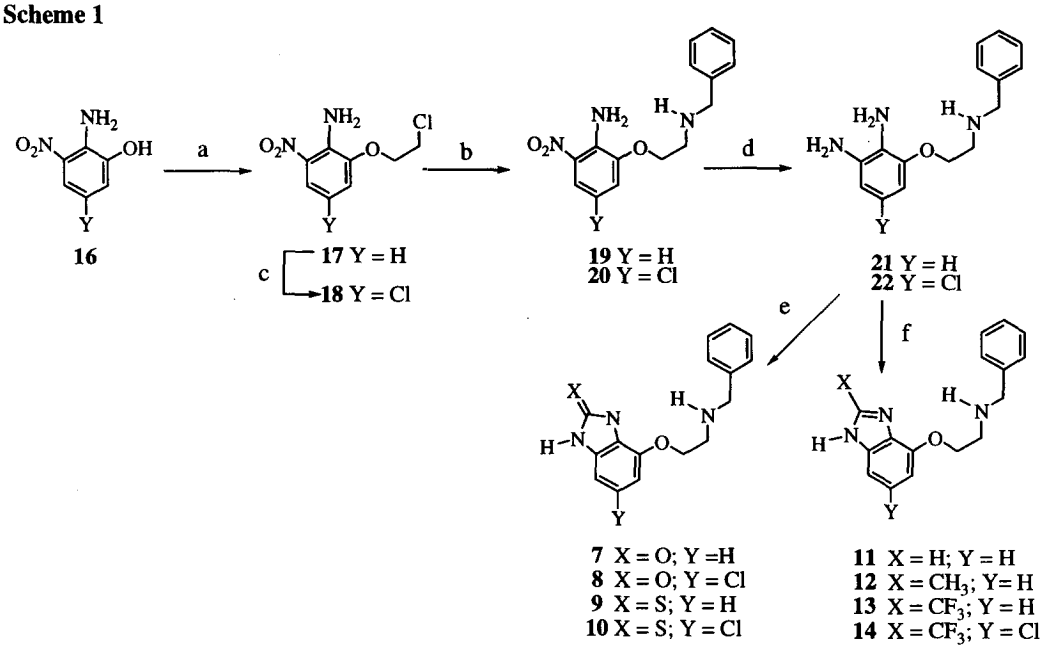
15

Chemistry

Shown in Schemes 1 and 2 are the syntheses of target molecules (i.e., **7–15**). Alkylation of commercially available **16** with 1,2-dichloroethane (10 equiv) in 2-butanone at 80 °C (24 h) afforded **17** in 85 % yield without chromatography. Chlorination of **17** using NCS in acetonitrile at 80 °C gave exclusively **18** in quantitative yield. Treatment of **17** and **18** with 3 equivalents of benzylamine in DMSO at 75 °C afforded **19** and **20** in approximately 90% yield. Reduction of the nitro groups using 10% palladium on carbon and hydrazine in ethanol led to the key intermediates **21** and **22**. Target molecules **7–10** were prepared in yields ranging from 85-99% by reacting either 1,1-diimidazole carbonyl or 1,1-diimidazole thiocarbonyl with **21** and **22**. Treatment of **21** and **22** with formic, acetic, or trifluoroacetic acids produced the corresponding benzimidazoles (**11–14**).

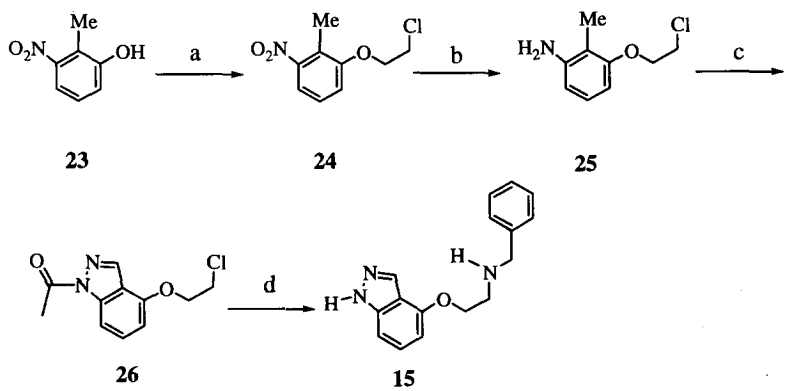
Indazole **15** was prepared in four steps as shown in Scheme 2. Attachment of the chloroethyl side chain onto **23** using Mitsunobu conditions,[7] followed by reduction of the nitro group led to **25** in 98% overall yield. Formation of the indazole ring system occurred in 80% yield by reaction of **25** with acetic anhydride (3.3 equiv), potassium acetate (1.1 equiv), followed by the addition of isoamyl nitrite (1.5 equiv) for 18 h at 80 °C. Treatment of **26** with benzylamine (4 equiv) resulted in displacement of the chloride along with concomitant deprotection affording indazole **15** in 53% yield.

Scheme 1



[a]**Reagents and conditions** (a) 1,2-dichloroethane, K_2CO_3, 2-butanone (b) $BnNH_2$, DMSO (c) NCS, MeCN (d) 10% Pd/C, EtOH, hydrazine (e) DCI/THF or diimidazolethiocarbonyl/THF (f) RCHOOH, reflux

Scheme 2



[a]**Reagents and conditions** (a) 1-chloroethanol, PPh_3, DEAD, THF (b) 5 % Pd/C, EtOH, H_2 (c) Ac_2O, KOAc, isoamyl nitrite (d) $BnNH_2$, DMSO

Results and Discussion

Shown in Tables 1 and 2 are the affinities of the target compounds (i.e. **7–15**) for the $D_{2\text{-like}}$ receptors. The affinities of compounds for the 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 and sodium. The ratio $K_i(D_2^{Low})/K_i(D_2^{High})$ was used as a preliminary and reliable estimate of the compound's intrinsic activity as determined by other assays described by Lahti[8] and Wasik.[9] The D_2 partial agonist, (*S*)-3-PPP [$(K_i(D_2^{Low})/K_i(D_2^{High}) = 33$[9,10]], 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.

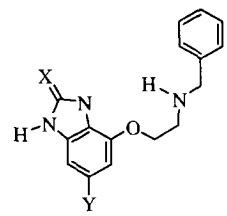
As shown in Table 1, compounds **7–10** had 14- to 20-fold higher affinity at the D_2^{High} receptors than the prototypic phenolic template **3**. Attachment of a chlorine atom to the aromatic ring as in **8** and **10** had little effect on affinities or the predicted intrinsic activity ratios, when compared to their respective deschloro analogs. As shown in Table 2, though benzimidazole **11** had modest affinity for the D_2^{High} receptor, a remarkable 54-fold increase in affinity for the D_2^{High} receptor was observed when the trifluoromethyl group was attached to the 2 position (**13** vs **11**). Apparently acidification of the benzimidazole NH optimizes hydrogen bonding with the D_2^{High} receptor. In contrast to the benzimidazol-2-ones and 2-thiones, attachment of a chlorine in the benzimidazole class led to a fourfold loss in D_2^{High} affinity (**13** vs **14**). One explanation for this detrimental effect may be that the chlorine of **14** is shifting the tautomeric equilibrium of the benzimidazole proton, thereby not allowing **14** to access the D_2^{High} pharmacophore as efficiently as **13**. The corresponding indazole analog (**15**) was found to have threefold higher affinity for the D_2^{High} affinity state than phenol **3**. Interestingly, the indazole has ninefold higher affinity than the corresponding indole analog (**15** vs **5**), suggesting that the indazole is a better hydrogen bond donating group than both the phenol and indole moieties. The predicted intrinsic activity ratio of **15** was the largest observed in this study [$(K_i(D_2^{Low})/K_i(D_2^{High}) = 33$] and also found to be the most selective compound for the hD_3 receptor.

Dopamine agonists are known to reduce locomotor activity by stimulation of presynaptic receptors while dopamine antagonists reduce locomotor activity by antagonism of dopamine at postsynaptic receptors. Dopamine partial agonists with low intrinsic activity levels will predominantly block postsynaptic receptors to produce a reduction in locomotor activity and antagonize apomorphine-induced stereotypy and climbing behaviors in mice.

Consistent with the predicted low intrinsic activity, in vivo studies showed both **13** and **14** to reduce spontaneous locomotor activity in mice (ED_{50} = 0.007 and 0.35 mg/kg sc, respectively). Compound **13** also blocked apomorphine-induced climbing (ED_{50} = 0.09 mg/kg sc) and stereotypy (ED_{50} = 0.33 mg/kg sc) in mice

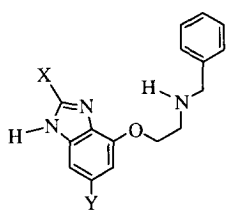
while compound **14** was less effective (no significant effect up to 3 mg/kg sc). These results are consistent with the rank order of intrinsic activity estimates and potency estimates.

Table 1. Affinity of Benzimidazolone (**7–10**) for D_2-D_4 Receptors



			K_i (nM)[11]					
No.	X	Y	D_2^{High}	D_2^{Low}	D_2^{Low}/D_2^{High}	hD_{2s}	hD_3	$hD_{4.4}$
3[5]			3.6	101	28	75.8	11.0	80.6
5[6]			9.7	39.3	4	81.8	19.5	230.2
6[6]			0.21	11.4	54	4.25	2.80	10.0
7	O	H	0.18	4.7	18	3.9	4.1	6.3
8	O	Cl	0.25	2.7	11	2.6	7.4	15.8
9	S	H	0.18	2.6	14	3.0	2.0	3.8
10	S	Cl	0.21	4.5	21	6.5	12.2	11.2

Table 2. Affinities of Benzimidazoles (**11–14**) and Indazole **15** for D_2-D_4 Receptors



			K_i (nM)[11]					
No.	X	Y	D_2^{High}	D_2^{Low}	D_2^{Low}/D_2^{High}	hD_{2s}	hD_3	$hD_{4.4}$
11	H	H	9.8	128	13	85.6	67.2	51.6
12	CH_3	H	4.4	26.6	6	15.2	94.6	61.1
13	CF_3	H	0.18	1.9	10	1.75	1.15	3.10
14	CF_3	Cl	0.71	11.6	16	32.4	41.8	7.0
15			1.1	35.9	33	79.8	8.80	315.5

In conclusion we have identified several novel D_2 partial agonists which are heterocyclic bioisosteric analogs of the recently discovered DA D_2 template (**3**). These compounds have allowed us to understand and further refine **3** into its modified heterocyclic template counterpart (**4**). We are continuing to investigate and probe the boundaries of the D_2 agonist pharmacophoric criteria by identifying potential antipsychotic agents that belong to this new generation of dopaminergic agents.

References and Notes

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11. 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 ±15% of the mean value