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NEW GENERATION DOPAMINERGIC AGENTS. 5. HETEROCYCLIC BIOISOSTERES THAT EXPLOIT THE 3-OH-N^1-PHENYLPIPERAZINE DOPAMINERGIC TEMPLATE

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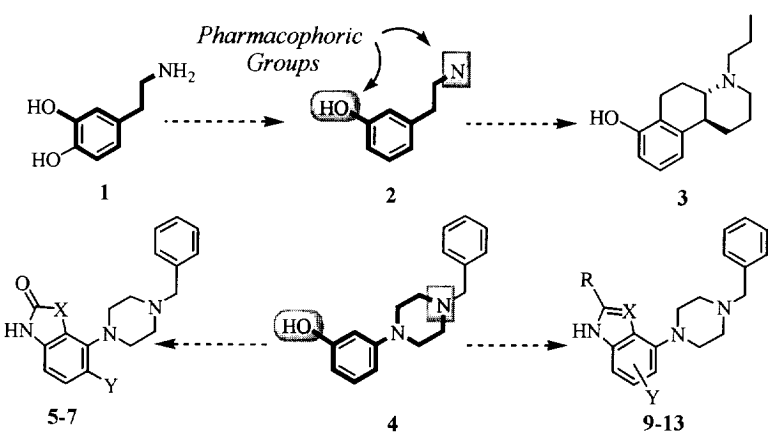
Abstract: The synthesis of several bioisosteric analogs based on the 3-OH-N^1-phenylpiperazine dopamine D_2 agonist template (i.e., **4**) is described. The indolone (**5**) and 2-CF_3-benzimidazole (**13**) were observed to have excellent affinity for the D_2 receptor. Several D_4 selective compounds were also identified. Molecular modeling studies and a putative bioactive conformation are discussed.

Drug design strategies toward novel dopamine D_2 agonists have been based predominately around the endogenous neurotransmitter dopamine (DA, **1**).[1–3] Traditional dopamine agonists have a close resemblance to DA (**1**), most having the '3-OH-phenethylamine' DA pharmacophore (**2**) or a bioisosteric surrogate embedded within their molecular structure (e.g., **3**[4]). Studies from our laboratories have resulted in the emergence of a new generation of dopaminergic agents that no longer rely upon the '3-OH-phenethylamine' framework.[5] Our initial efforts resulted in the identification of several phenolic D_2 agonist prototypes (e.g., **4**)[6] that can be used as templates for the design of bioisosteric analogs. As part of a program to discover compounds that could be



potentially useful as antipsychotic drugs, we have embarked on exploiting these phenolic prototypes by preparing several heterocyclic bioisosteric analogs. In this report is disclosed the synthesis and structure-activity relationships of various indole, indolone, benzimidazolone, and benzimidazole derivatives (i.e., **5–7** and **9–13**) based on the 3-OH-N^1-phenylpiperazine DA D_2 template (**4**).

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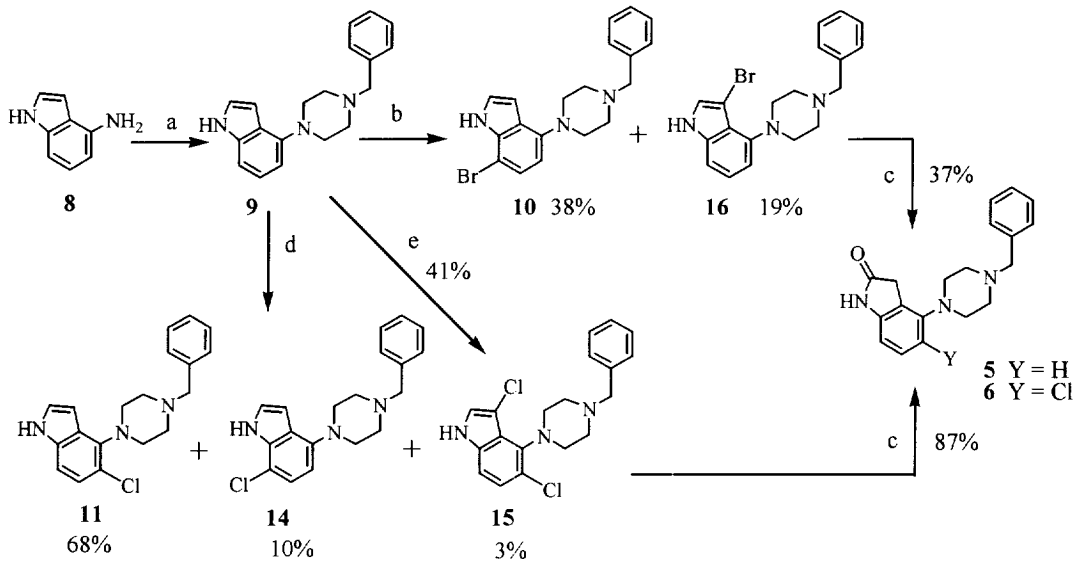
Chemistry

Shown in Schemes 1–3 are the syntheses of target molecules (i.e., **5**–**7** and **9**–**13**). Indole **9** was prepared from commercially available **8** in 40–80% yield. Bromination of the indole piperazine (**9**) led to a 2:1 mixture of monobrominated indoles **10** and **16**. The 3-bromoindole (**16**) was hydrolyzed using H_3PO_4 to afford indolone **5**. Interestingly, chlorination of **9** using 1 equiv of NCS led to the isolation of three chlorinated compounds (**11**, **14**, and **15**), the major product being the 5-chloroindole (**11**). By using 2 equiv of NCS, **15** could be isolated as the major product. Hydrolysis of **15** afforded indolone **6**.

Scheme 1[a]

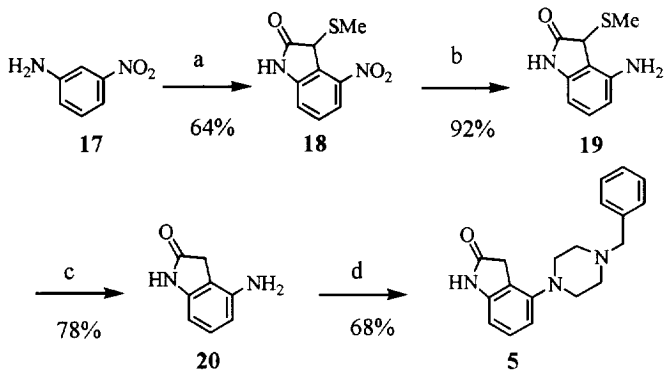


[a]**Reagents and conditions**: (a) $BnN(CH_2CH_2Cl)_2$, *n*-butanol (b) 1 equiv NBS (c) H_3PO_4, 2-$MeOCH_2CH_2OH$ (d) 1 equiv NCS, THF (e) 2 equiv NCS, MeCN

Shown in Scheme 2 is a more efficient 4-step route to indolone **5**. Commercially available **17** was converted into the 3-thiomethyl-indolone (**18**)[7] using a known procedure.[8] Reduction of the 4-nitro-3-thiomethyl-indolone (**18**) afforded the corresponding 4-amino-3-thiomethyl-indolone (**19**). Raney nickel reduction produced the 4-amino-indolone (**20**) which was converted into the target indolone (**5**).

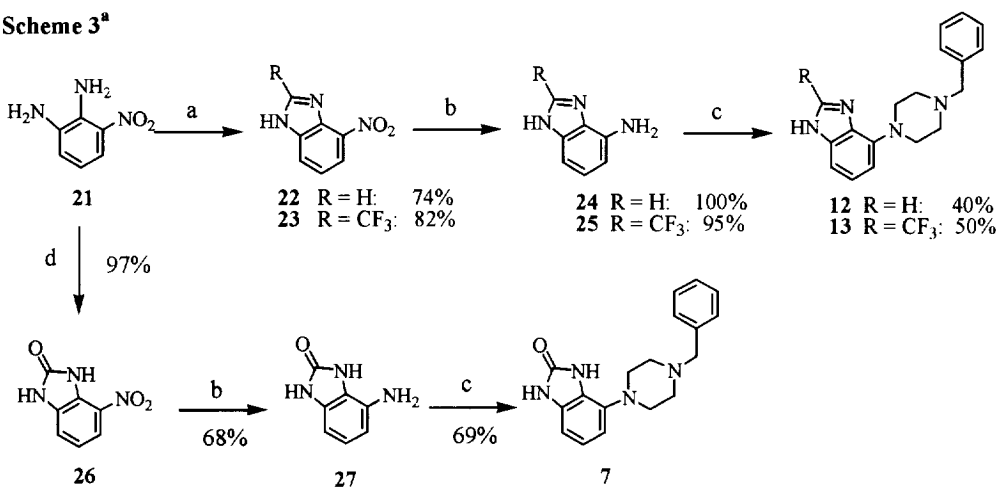
The synthesis of benzimidazolone **7** and benzimidazoles **12** and **13** are depicted in Scheme 3. Commercially available **21** was treated with formic acid or trifluoroacetic acid to afford **22** and **23**, respectively. Reduction of the nitro group led to the 4-amino-benzimidazoles (**24** and **25**), which were converted into the target piperazinyl derivatives (**12** and **13**). Heating **21** in the presence of urea led to the 4-nitro-benzimidazolone (**26**). Reduction of **26** and construction of the piperazine moiety afforded the target benzimidazolone (**7**).

Scheme 2[a]



[a]**Reagents and conditions**: (a) (i) $MeSCH_2CO_2Et$, SO_2Cl_2 (ii) NEt_3 (b) $SnCl_2$ (c) Ra Ni, EtOH (d) $BnN(CH_2CH_2Cl)_2$, *n*-butanol

Scheme 3[a]



[a]**Reagents and conditions:** (a) RCO_2H; (b) H_2 Pd/C, EtOH; (c) $BnN(CH_2CH_2Cl)_2$, *n*-butanol (d) urea, DMSO

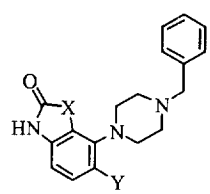
Results and Discussion

Shown in Tables 1 and 2 are the affinities of the target compounds (i.e. **5–7** and **9–13**) 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. The ratio $K_i(D_2^{Low})/K_i(D_2^{High})$ was used as a preliminary and reliable estimate of the compounds' intrinsic activity as determined by other assays described by Lahti[9] and Wasik.[10] The D_2 partial agonist, (*S*)-3-PPP

[$(K_i(D_2^{Low})/K_i(D_2^{High})=33$[10,11]], 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, replacement of the phenol moiety of **4** with the indolone bioisostere (i.e., **5**) resulted in a 10-fold increase in affinity for the D_2^{High} receptor and a similar predicted intrinsic activity ratio [$(K_i(D_2^{Low})/K_i(D_2^{High})=14$]. Indolone **5** was observed to have high affinity for all of the $D_{2\text{-like}}$ receptors and was one of the most potent compounds identified in this study. Though the 5-chloro derivative (**6**) had unimpressive affinity for the D_2^{High} receptor, it was observed to exhibit selectivity for the $hD_{4.4}$ receptor. Benzimidazolone 7 had similar affinity to its phenol analog (**4**) with a slight preference for the $hD_{4.4}$ receptor. Indole **9** (Table 2) was

Table 1. Affinity of Indolones (**5** and **6**) and Benzimidazolone 7 for D_2-D_4 Receptors



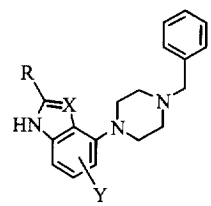
			K_i (nM)[12]					
No.	X	Y	D_2^{High}	D_2^{Low}	D_2^{Low}/D_2^{High}	hD_{2s}	hD_3	$hD_{4.4}$
4[6]			5.5	95.1	17	246.0	28.9	>400
5	CH_2	H	0.56	8.1	14	8.0	5.4	3.0
6	CH_2	Cl	54.8	403	7	540.0	591.3	8.8
7	NH	H	4.2	45.8	11	87.3	56.5	14.4

found to have similar D_2^{High} affinity as its phenol prototype (i.e. **4**), however, a lower predicted intrinsic activity than **4** was observed [**9**; $(K_i(D_2^{Low})/K_i(D_2^{High})=5$]. Introduction of either a bromine or chlorine into **9** (i.e., **10** and **11**) resulted in compounds having selectivity for the $hD_{4.4}$ receptor. Though benzimidazole **12** had good affinity for the D_2^{High} receptor, introduction of the trifluoromethyl group led to a 19-fold increase in D_2^{High} affinity. In fact, the benzimidazole (**13**) had similar affinity as its indolone analog (**5**) for the D_2^{High} receptor, revealing that the indolone and 2-CF_3-benzimidazole groups can both serve as surrogate phenol bioisosteres.

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. Excessive blockade of postsynaptic dopamine receptors can also produce catalepsy, a maintenance of an awkward body posture.

Consistent with the predicted low intrinsic activity, in vivo studies showed both **5** and **13** to reduce spontaneous locomotor activity (ED_{50} = 0.12 mg/kg sc for **13**; **5** decreased activity at 0.01, 0.03, 1 and 3 mg/kg sc) and to inhibit apomorphine-induced stereotypy (S) and climbing (C) in mice (ED_{50}s for **13**: S = 0.8 mg/kg sc, C = 0.4 mg/kg sc; for **5**: S = 1.5 mg/kg sc, C = 2.3 mg/kg sc). Unlike **5**, benzimidazole **13** induced catalepsy at 10 mg/kg sc in mice, which correlates with their predicted intrinsic activity ratios (6 vs 14).

Table 2. Affinities of Indoles (**9–11**) and Benzimidazoles (**12** and **13**) and for D_2-D_4 Receptors

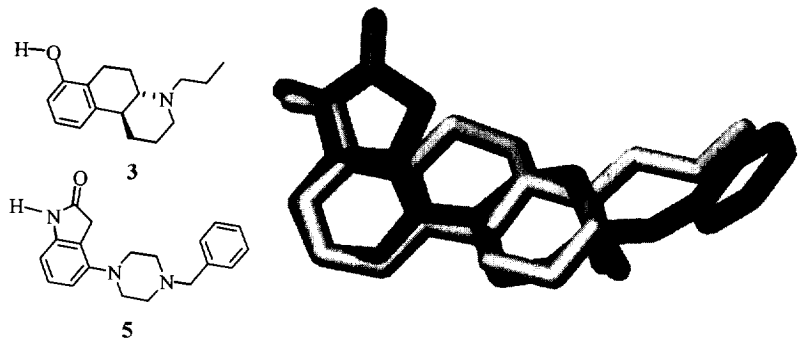


				K_i (nM)[12]					
No.	X	Y	R	D_2^{High}	D_2^{Low}	D_2^{Low}/D_2^{High}	hD_{2s}	hD_3	$hD_{4.4}$
9	CH	H	H	3.2	17.4	5	53.0	35.4	14.7
10	CH	7-Br	H	26.8	12.2	0.5	47.0	56.0	2.6
11	CH	5-Cl	H	9.1	42.3	5	81.3	95.3	1.7
12	N	H	H	9.7	107	11	257.5	870.5	47.0
13	N	H	CF_3	0.51	3.3	6	4.1	14.7	2.9

A conformational analysis[13] was performed on compounds **4**, **5**, and **6** in order to rationalize affinity, intrinsic activity, and selectivity. In contrast to **4**, whose global minimum conformation meets the D_2 agonist pharmacophoric criteria,[14] the putative bioactive conformation of indolone **5** (Figure 1) lies at an energy level approximately 1 kcal/mol above its global minimum which may explain its low predicted intrinsic activity. The low energy conformations of **5** apparently are not selective enough to discriminate between the agonist and antagonist states of the D_2 receptor. Conformational analysis of **6** revealed an even higher energy requirement was needed to satisfy the D_2 agonist pharmacophoric criteria and may explain the observed 60-fold loss in affinity when comparing **6** to **5**. In terms of affinity for the $hD_{2\text{-like}}$ receptors, **6** was observed to be selective for the $hD_{4.4}$ receptor suggesting the 5-chloro substituent may be responsible for 'freezing out' a conformation preferred only by the $hD_{4.4}$ receptor.

In conclusion we have identified several potent heterocyclic piperazinyl derivatives, based on our recently discovered DA D_2 template (**4**), which were found to have low intrinsic activity. Studies are continuing in our laboratories to expand our knowledge of the D_2 agonist pharmacophoric criteria by identifying novel D_2 ligands which belong to this new generation of dopaminergic agents.

Figure 1. Superposition of **3** and Indolone **5** in Putative D_2 Agonist Pharmacophoric Conformations.



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12. 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.
13. All computations were performed using MM3 as implemented in Macromodel 6.0.
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