1-(3-Cyanobenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one: A Selective High-Affinity Antagonist for the Human Dopamine D_4 Receptor with Excellent Selectivity over Ion Channels

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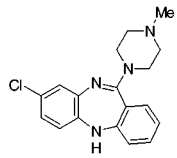
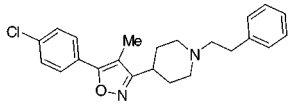
After the requirement of pseudocycle formation in the ureas **3** and **7** for hD_4 binding and selectivity was confirmed, structural hybridization with the known hD_4 ligand **2** led to the design and identification of the lead 4-(2-oxo-1,3-dihydroimidazol-2-yl)piperidine **8**. Optimization studies were carried out on **8** with the aim of achieving 1000-fold selectivity for hD_4 over all other receptors while retaining the good pharmacokinetic properties of the lead. After initial preparation of **8** as a minor component in a low-yielding reaction, a novel and regioselective "four-step/one-pot" procedure was developed which proved to be applicable to rapid investigation of the SAR of the 1,3-dihydroimidazol-2-one ring. Various changes to substituents attached to the 3-, 4-, or 5-position of the 1,3-dihydroimidazol-2-one core of **8** did not significantly improve selectivity for hD_4 over hD_2 and hD_3. Greater selectivity (>1000-fold) was ultimately achieved by *meta* substitution of the benzyl group of **8** with various substituents. Compounds **28**, **31**, and **32** all possess the required selectivity for hD_4 over the other dopamine subtypes, but only **32** has >1000-fold selectivity over all the key counterscreens we tested against. Compound **32** is an antagonist at hD_4 and has a good pharmacokinetic profile in the rat, with excellent estimated in vivo receptor occupancy, thus making it a potentially useful pharmacological tool to investigate the role of the D_4 receptor.

Introduction

For the debilitating mental illness schizophrenia, it is widely accepted that brain dopamine receptors are the primary targets for medical treatment.[1] There are five cloned subtypes of the human dopamine receptor which have been divided into two pharmacological classes: D_1-like (D_1 and D_5)[2,3] and D_2-like (D_2, D_3, and D_4).[4−6] Classical neuroleptic drugs such as haloperidol are believed to work through nonselective antagonism of D_2-like dopamine receptors;[7] however, severe movement disorders[8] are also manifested (probably due to blockade of D_2 receptors in the striatum) along with hyperprolactinemia.[9] Since the revelation[6] that the atypical neuroleptic clozapine (**1**; Table 1), which treats both the positive and negative symptoms of schizophrenia without producing extrapyramidal side effects, has higher affinity for the human dopamine D_4 receptor than the D_2 receptor, there has been a huge surge of interest in the D_4 area as a possible new approach toward the treatment of schizophrenia.[10−30]

Further evidence of the possible importance of D_4 receptors in schizophrenia has been provided by Matsumoto et al.[31] who claimed that human D_4 receptors were localized in areas of the brain that are associated with antipsychotic activity. In addition, several independent groups have claimed that D_4 receptor density is elevated in postmortem schizophrenic brain;[32−34] however, this finding has been disputed.[35,36] Although a significant amount of evidence has been accumulated to support the D_4/antipsychotic hypothesis, recently hD_4 antagonists have been demonstrated to be ineffective in clinical trials of schizophrenia, and thus the hD_4 receptor is probably not the prime target through which clozapine exerts its atypical antipsychotic activity.[37]

Table 1. Reference Compounds

Number	Structure	Ki (nM)[a] hD2	hD3	hD4
1		74	200	10
2		>1700	770	3.5

[a] Affinities at cloned human dopamine receptors stably expressed in cell lines.

We have previously reported the discovery of the isoxazolopiperidine[10,11] **2** (Table 1) as a highly selective D_4 antagonist, but more recently we have also disclosed[13] that **2** possesses significant activity at voltage-sensitive sodium and calcium ion channels. These findings were a potential bar to the use of this compound in the clinic as an investigational tool since such activities may be indicative of adverse cardiovascular effects. In this manuscript we describe the discovery of a novel series of 4-(2-oxo-1,3-dihydroimidazol-2-yl)-piperidines, discovered by hybridizing the structures of the ureas **3** and **7** with the known hD_4 antagonist **2**, as

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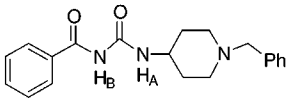
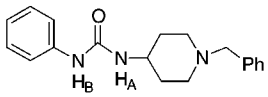
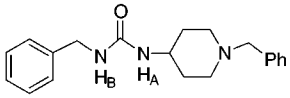
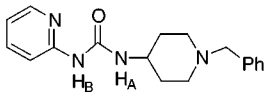
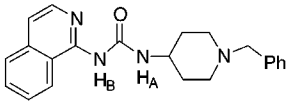
Table 2. 4-Ureido-*N*-benzylpiperidines

Number	Structure	δH_A[a]	δH_B[a]	Ki (nM)[b] hD2	hD3	hD4	Na[c]	Ca[d]
3		8.7	10.7	>1700	>4400	34	21%	n.d.[e]
4		6.1	8.3	86	700	390	n.d.	n.d.
5		5.8	6.2	>1600	>4200	2700	n.d.	n.d.
6		8.2	9.1	190	950	150	n.d.	n.d.
7		10.2	9.6	150	2000	5.5	68%	12.4

[a] Proton magnetic resonance chemical shift in DMSO-d_6. [b] Affinities at cloned human dopamine receptors stably expressed in cell lines. [c] Inhibition of specific binding of [^{3}H]batrachotoxin to rat cortex at 10 μM concentration of test compound. [d] Inhibition of specific binding of [^{3}H]diltiazem to rabbit skeletal muscle at 10 μM concentration of test compound or K_i (μM). [e] n.d., not determined.

selective human D_4 antagonists with generally reduced ion channel activities.

Results and Discussion

Biology. Compounds were tested for their ability to displace [^{3}H]spiperone from human cloned receptors, D_4 and D_3 stably expressed in HEK-393 cells,[38] and D_2 in CHO cells.[39] The binding data for all compounds are the geometric mean of at least three independent determinations, and the errors of the mean are within 2-fold of the mean (see Experimental Section for more details). Counterscreen activities at voltage-dependent ion channels (calcium, sodium, and potassium), which may be indicative of adverse cardiovascular effects in vivo,[40−42] are also the geometric means of at least two independent determinations, and the relevant radioligand binding assays are described in detail in the Experimental Section.

Synthesis and SAR of *N*-Benzyl-4-piperidinylureas. Compound **3** (Table 2), prepared by the method of Ward,[43] was identified from in-house screening as a moderately active and selective hD_4 ligand with relatively low activity at sodium ion channels.[40] The chemical shift of the NH proton H_A in compound **3** was further downfield (δ = 8.7, DMSO-d_6) than would normally be anticipated for such a proton unless intramolecular hydrogen bonding was invoked to form a six-membered pseudocycle[44] (Figure 1). To evaluate this hypothesis and elucidate structure−activity relationships within the series, compounds **4**,[45] **5**, **6**, and **7** were synthesized and evaluated.

The benzylurea **5** was prepared by reaction of commercially available **33** with benzyl isocyanate (Scheme 1). The pyridyl- and isoquinolylureas **6** and **7** were synthesized by in situ formation of a piperidinyl isocyanate (derived from **33** by reaction with phosgene in the presence of triethylamine) followed by reaction with the appropriate amino heterocycle. In the case of the benzylurea **5**, where the possibility of intramolecular hydrogen bonding to form a pseudocycle did not exist (δH_A = 5.8, DMSO-d_6), the compound was inactive in the binding assay (Table 2). The phenylurea **4** was also significantly lower in affinity than **3**, and so the pyridylurea **6** was made. Despite the fact that compound **6** apparently existed in a pseudocyclic conformation in solution (Figure 2; δH_A = 8.2, DMSO-d_6), it had only weak activity at the hD_4 receptor presumably due to the absence of an appropriately positioned phenyl ring. Thus, the isoquinolylurea **7** was made (Figure 3), and

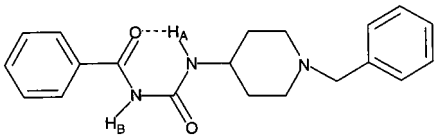
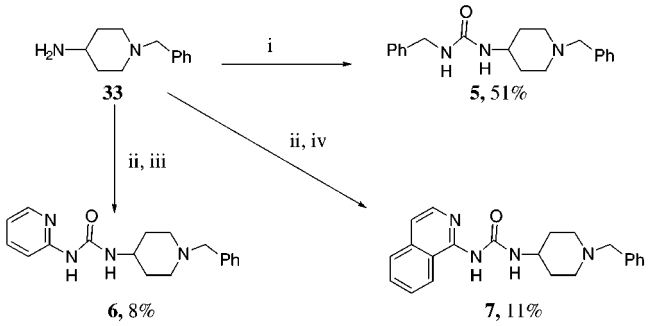


Figure 1. 2-Dimensional representation of pseudocyclic conformation of compound **3**.

Scheme 1[a]



[a] Reagents: (i) $PhCH_2NCO$, CH_2Cl_2; (ii) $(COCl)_2$, toluene, THF, 0 °C, Et_3N; (iii) 2-aminopyridine, 0 °C; (iv) 1-aminoisoquinoline, 0 °C.

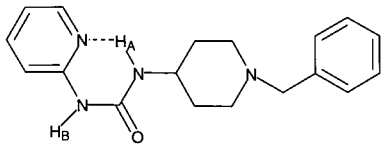


Figure 2. 2-Dimensional representation of pseudocyclic conformation of compound **6**.

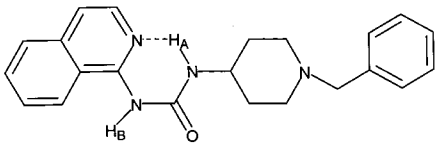
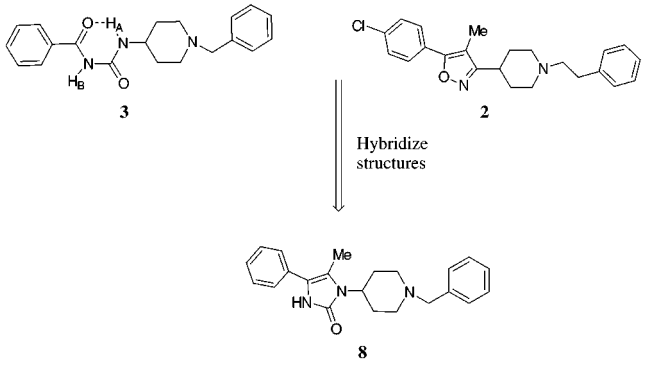
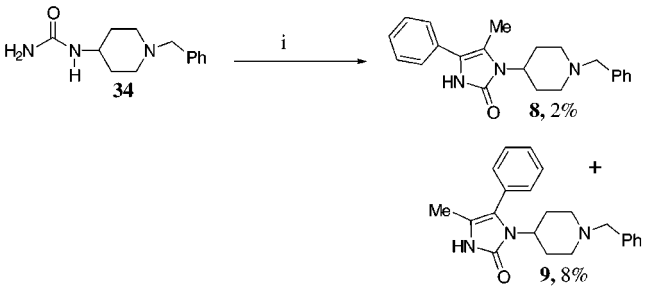


Figure 3. 2-Dimensional representation of pseudocyclic conformation of compound **7**.

Scheme 2



Scheme 3[a]



[a] Reagents: (i) $PhCOCH(OH)CH_3$, TFA, toluene, reflux.

the high affinity and selectivity of this compound indicated that the purported requirements for selective binding to the hD_4 receptor of both a pseudocycle (δ = 10.2, DMSO-d_6) and an optimally positioned phenyl ring were confirmed. By analogy with **3**, compound **7** was also relatively inactive at sodium and calcium ion channels, but it was only poorly bioavailable in the rat and was therefore not considered a useful pharmacological tool.

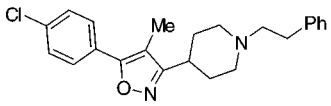
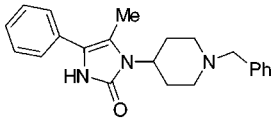
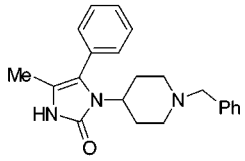
Design and Synthesis of 4-(2-Oxo-1,3-dihydroimidazolyl)piperidines. Hybridization of the pseudocyclic conformation of the lead urea **3** with the known isoxazole **2**[10,11] led to the design of the 1,3-dihydroimidazol-2-one **8** (Scheme 2). The target molecule **8** was initially synthesized in low yield by condensation of the primary urea **34**[46] with 2-hydroxypropiophenone[47] under acidic conditions in refluxing toluene (Scheme 3).[48] Also produced in the same reaction was the 4-methyl-5-phenyl-1,3-dihydroimidazol-2-one regioisomer **9** as the more abundant product. Evaluation of **8** in the D_2-like dopamine binding assays showed that the designed target has a very good in vitro profile with subnanomolar activity at hD_4 receptors and 2 orders of magnitude selectivity over hD_2 and hD_3 receptors (Table 3). Although the dopamine subtype selectivity of **8** is inferior to that of **2**, the 5-methyl-4-phenyl-1,3-dihydroimidazol-2-one has a significantly superior ion channel counterscreen profile having lower than 10 μM binding affinity in the calcium[40] and sodium[41] binding assays and only 2.3 μM activity at potassium channels.[42] Furthermore, **8** has good pharmacokinetic properties in the rat (>50% oral bioavailability after a 20 mg/kg dose reaching a peak plasma concentration > 1100 ng/mL, half-life 1 h), and the overall profile of this prototypical molecule made optimization studies in this series compelling.

The synthetic route to **8** was improved by the development of a regioselective "four-step/one-pot" procedure (Scheme 4). Reaction of 4-amino-1-benzylpiperidine (**33**) with 2-bromopropiophenone[49] at room temperature for 24 h generated the unstable amino ketone **35** in solution, and this was treated in situ with benzoyl isocyanate to produce the crude tertiary urea intermediate **36**. The solvent was removed by rotary evaporation to leave a residue (**36**) which was dissolved in methanol and treated with sodium methoxide to effect cyclization (**37**) and deprotection (**38**). Finally, addition of trifluoroacetic acid to the reaction mixture brought about dehydration to produce the required product **8** in high overall yield (76%). The improved route was amenable to introducing diversity to the 3- (R_2), 4- (Ar), and 5- (R_1) positions of the 1,3-dihydroimidazol-2-one nucleus (Scheme 5) by simple variation of the bromo ketones (step i) and isocyanates (step ii). The *N*-phenethyl analogue **25** was prepared in an identical way to **8** but starting with 4-amino-1-phenethylpiperidine (**39**) which was prepared by the lengthy route outlined in Scheme 6.

A more efficient approach toward exploration of substituents attached to the basic nitrogen of the piperidine was developed as outlined in Scheme 7. The *N*-benzyl group of **8** was efficiently removed to form **40** in 68% yield, by use of a two-step process involving reaction with 2-chloroethyl chloroformate followed by treatment with methanol under reflux. Liberation of the hydrochloride salt **40** to give the free base **41** was achieved by treatment with sodium hydroxide solution and extraction into CH_2Cl_2. The secondary amine **41** proved to be a valuable intermediate for optimization of the 1-piperidinyl position, with substituents being easily introduced by reaction with an appropriate alkyl bromide in dimethylformamide in the presence of Hunigs base to give, for example, the *m*-cyanobenzyl derivative **32** in 60% yield. Reductive alkylations could also be carried out efficiently on **41** to give, for example, the *N*-methyl analogue **23** by reaction with formaldehyde in the presence of sodium cyanoborohydride.

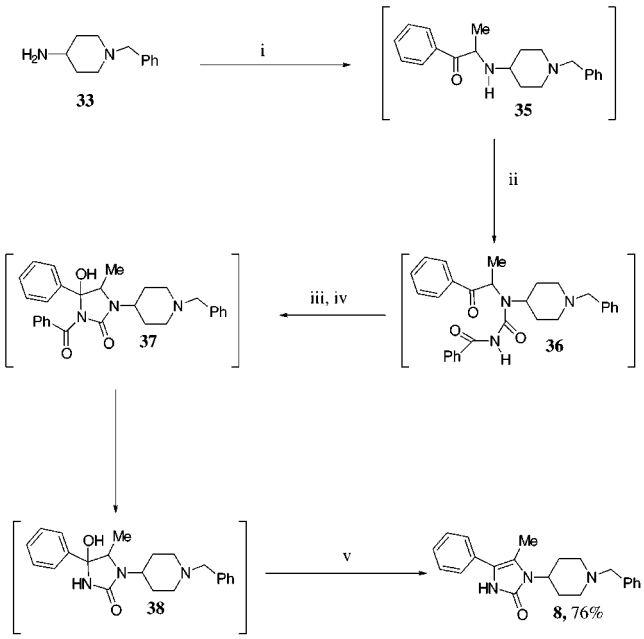
Optimization of 4-(2-Oxo-1,3-dihydroimidazolyl)-piperidines. The aim of the optimization study described in this section was to retain subnanomolar hD_4 affinity and increase selectivity to greater than 1000-fold over all other receptors (including hD_2 and hD_3) while retaining the good pharmacokinetic properties of **8**. Removal of the methyl group from the 5-position of the 1,3-dihydroimidazol-2-one nucleus of **8** to give **10** results in 30-fold loss of hD_4 binding affinity and significantly reduces subtype selectivity (Table 4). Reintroduction of an ethyl group to the 5-position (**11**)

Table 3. Comparison of Lead Imidazolone **8** with the Lead Isoxazole **2**

Number	Structure	Ki (nM)[a] hD2	hD3	hD4	Ki (μM)[b,c] Na[b]	Ca[c]
2		>1700	770	3.5	1.9	0.82
8		56	240	0.60	14%	41%
9		280	3600	71	n.d.[d]	n.d.

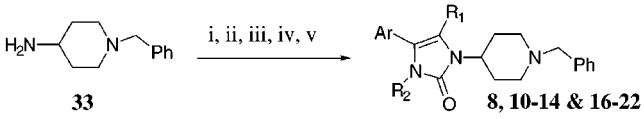
[a] Affinities at cloned human dopamine receptors stably expressed in cell lines. [b] Inhibition of specific binding of [^{3}H]diltiazem to rabbit skeletal muscle at 10 μM concentration of test compound or K_i (μM). [c] Inhibition of specific binding of [^{3}H]batrachotoxin to rat cortex at 10 μM concentration of test compound or K_i (μM). [d] n.d., not determined.

Scheme 4[a]



[a] Reagents: (i) $PhCOCH(CH_3)Br$, Et_3N, CH_2Cl_2, 24 h; (ii) PhCONCO, 1 h; (iii) evaporation; (iv) MeOH, NaOMe; (v) TFA.

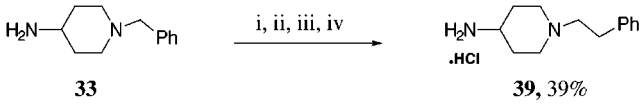
Scheme 5[a]



[a] Reagents: (i) $ArCOCH(R_1)Br$, Et_3N, CH_2Cl_2, 24 h; (ii) R_2NCO*, 1 h; (iii) evaporation; (iv) MeOH, NaOMe; (v) TFA. *When R_2 = PhCO, then the final product has R_2 = H (compounds **8**, **10**, **11**, and **15**−**22**).

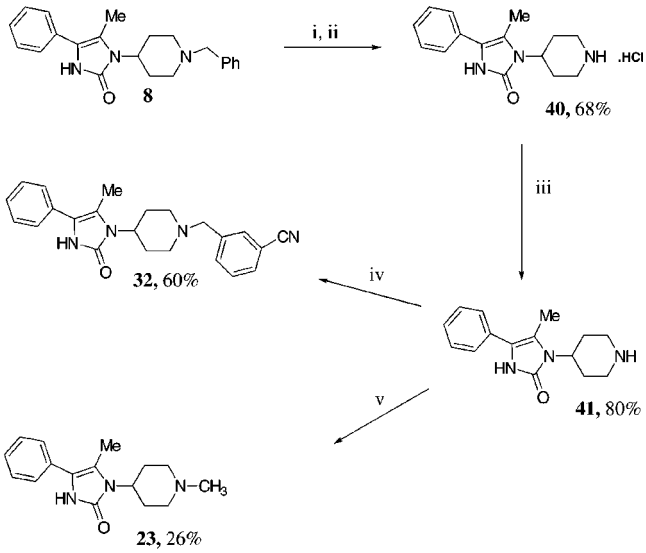
restores but does not increase affinity at hD_4. This result suggests that the improved activity of compound **8** over **10** is due to a conformational effect of the 5-methyl substituent on the 4-phenyl ring and not because of a direct hydrophobic effect. The 3-methyl-5-desmethyl

Scheme 6[a]



[a] Reagents: (i) Boc_2O, CH_2Cl_2; (ii) H_2, 10% Pd−C, MeOH; (iii) $Ph(CH_2)_2Br$, DMF, Hunig's base; (iv) HCl, MeOH.

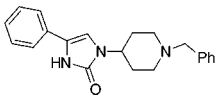
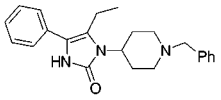
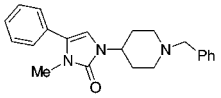
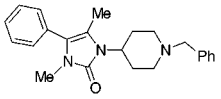
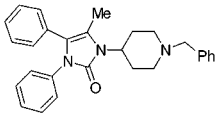
Scheme 7[a]



[a] Reagents: (i) $CH_3CH(Cl)OCOCl$, CH_2Cl_2; (ii) MeOH, reflux; (iii) NaOH, H_2O, extraction into CH_2Cl_2; (iv) RBr, DMF, Hunig's base; (v) CH_2O, $NaCNBH_3$, MeOH, AcOH.

analogue **12** also has improved affinity over **10** at hD_4 receptors, and this must also be due to a conformational effect on the 4-phenyl ring because the 3,5-dimethyl derivative **13** does not show a further improvement in binding affinity. The modest increase of hD_2 affinity seen with the 3-substituted derivatives **12**−**14** suggests that there is a beneficial direct hydrophobic effect adjacent to the 3-position of the 1,3-dihydroimidazol-2-one ring for binding to the hD_2 receptor. In conclusion, none of the substituent changes to the 1,3-dihydroimi-

Table 4. Substitution on the Imidazolone Heterocyclic Core

Number	Structure	Ki (nM)[a] hD2	hD3	hD4
10		82	630	18
11		26	130	0.86
12		11	150	0.84
13		15	140	0.75
14		8.8	15	4.5

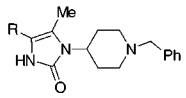
[a] Affinities at cloned human dopamine receptors stably expressed in cell lines.

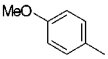
dazol-2-one nucleus of the lead compound **8** (Table 4) improved affinity or selectivity for the hD_4 subtype.

Substitution and replacement of the phenyl group attached to the 4-position of the 1,3-dihydroimidazol-2-one of **8** was investigated next (Table 5). Introduction of chlorine to the para position of the phenyl ring to give **15** results in retention of hD_4 affinity and marginally improved selectivity over hD_2. *m*-Chloro substitution (**16**) produces an order of magnitude reduction in hD_4 affinity, while introduction of an *o*-chlorine atom (**17**) has little effect on affinity at any of the human dopamine subtypes. Incorporation of alternative substituents to the para position was investigated (**18**−**20**), but no improvement in either affinity or selectivity resulted. Replacement of the 4-phenyl group of **8** with 2-thienyl (**21**) compromised selectivity, and substitution with 2-pyridyl (**22**) reduced hD_4 affinity. In summary, none of the changes to the phenyl group attached to the 4-position of the 1,3-dihydroimidazol-2-one nucleus of the lead compound **8** (described in Table 5) were beneficial.

As the final part of the optimization strategy, changes to the substituent attached to the basic nitrogen atom of **8** were explored (Table 6). It is essential to have a hydrophobic group attached to the 1-position of the piperidine ring since the 1-methyl derivative **23** is inactive while the cyclohexylmethyl analogue **24** retains low-nanomolar affinity. Homologation of the benzyl group to phenethyl (**25**) results in retention of activity at hD_4 and improved selectivity over both hD_2 and hD_3; however, further homologation to the phenylpropyl analogue **26** is detrimental to hD_4 affinity. Because of the improved dopamine selectivity profile of **25**, the compound was tested in the ion channel screens described previously, and although **25** has only weak affinity for the calcium ion channel, the compound has

Table 5. Aromatic Substitution/Replacement on the Imidazolone Heterocyclic Core



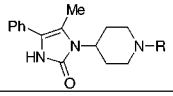
Number	R	Ki (nM)[a] hD2	hD3	hD4
15		170	380	0.71
16		73	250	5.2
17		38	220	1.1
18		110	360	12
19		290	930	1.7
20		52	220	1.1
21		7.8	38	1.0
22		270	1200	4.5

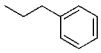
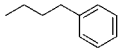
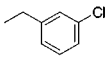
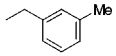
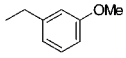
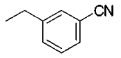
[a] Affinities at cloned human dopamine receptors stably expressed in cell lines.

higher affinity for sodium (K_i = 1 μM) and potassium (K_i = 0.7 μM) ion channels. Substitution of the benzyl aromatic ring with chlorine at the para position (**29**) had little effect on dopamine affinity at all three subtypes, but both *o*-chloro (**27**) and *m*-chloro (**28**) substitution resulted in significantly lower hD_2 and hD_3 activity, while binding to hD_4 was largely retained. Compound **28** is noteworthy since it meets the target of subnanomolar affinity at hD_4 receptors and >1000-fold selectivity over other hD_2-like receptors. Secondary screening studies on **28** revealed that the compound has a clean ion channel profile (K_i's >10 μM versus calcium, sodium, and potassium channels) and good pharmacokinetics in the rat (oral bioavailability = 70%, half-life ~1 h). Further profiling of **28** for activity at other receptors showed no effect on $5HT_2$ receptors, but the compound had significant $5HT_{1A}$ binding affinity (IC_{50} = 70 nM) and so was not considered further as a potential clinical tool.

On the basis of the improved dopamine binding profile of **28**, meta substitution of the benzyl ring was explored further. The methyl compound **30** retained high affinity at hD_4 receptors, but selectivity over hD_2 receptors was only marginally better than that of the lead compound **8**. The 3-methoxy derivative **31** had the required affinity and selectivity for hD_4 over other dopamine receptors and calcium and sodium ion channels (K_i's >10 μM), but it was compromised by having significant potassium channel (K_i = 0.9 μM) and $5HT_{1A}$ (IC_{50} = 70 nM) activity. Compound **31** also has relatively poor pharmacokinetics in the rat (oral bioavailability = 16%, half-life = 0.8 h) and so was considered unsuitable for clinical evaluation. The *m*-cyano analogue **32** is the optimal

Table 6. Substitution on the Basic Nitrogen



Number	R	Ki (nM)[a] hD2	hD3	hD4	Ca[b]
23	Me	>1600	>4400	>2500	41%
24		83	1100	2.0	28%
25		220	>3200	0.56	47%
26		330	1900	5.5	n.d.[c]
27		>1500	>4000	2.1	n.d.
28		1300	>4700	0.46	16%
29		60	180	1.3	n.d.
30		95	320	0.33	42%
31		900	>3900	0.64	22%
32		>1900	>4800	0.96	9%

[a] Affinities at cloned human dopamine receptors stably expressed in cell lines. [b] Inhibition of specific binding of [^{3}H]diltiazem to rabbit skeletal muscle at 10 μM concentration of test compound or K_i (μM). [c] n.d., not determined.

derivative identified from the studies described in this manuscript since it has subnanomolar affinity at hD_4 receptors and greater than 1000-fold selectivity over other dopamine receptors and all other previously mentioned counterscreens (calcium channel, K_i > 10 μM; sodium channel, K_i > 10 μM; potassium channel, (IK_R) EC_{25} > 10 μM; $5HT_{1A}$, IC_{50} = 0.97 μM; $5HT_2$, IC_{50} > 10 μM). Compound **32** has a good pharmacokinetic profile in the rat (69% oral bioavailability after a 3 mg/kg dose reaching a peak plasma concentration of 815 ng/mL, half-life 1.1 h, brain/plasma ratio = 0.33) and has excellent receptor occupancy in the rat (estimated ED_{50} = 1.6 μg/kg po) as estimated by an in vivo σ receptor (IC_{50} = 5.9 μM vs [^{3}H]SKF10047 (σ radioligand)) binding assay.[50] Furthermore **32** has been proven to be an antagonist at the D_4 receptor since it blocks the dopamine (1 μM)-mediated inhibition of forskolin (10 μM)-induced elevation of cAMP levels.[38] All of the above attributes potentially make 1-(3-cyanobenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (**32**) an attractive tool to study the relevance of selectively antagonizing hD_4 receptors in vivo (p.o).

Conclusions

1-Benzyl-4-[(phenylcarbonylamino)carbonylamino]-piperidine (**3**), identified from screening of the Merck sample collection, exhibited moderate affinity (34 nM) for hD_4 receptors with some selectivity (>10-fold) over hD_2 receptors. The compound was hypothesized to be active through adopting a pseudocyclic conformation brought about by intramolecular hydrogen bonding (δH_A = 8.7 in DMSO-d_6), and this was proven to be the case with the design and evaluation of the isoquinolylurea analogue **7** (5.5 nM, δH_A = 10.2, DMSO-d_6). Although high in affinity at hD_4 receptors with approximately 50-fold selectivity over hD_2 receptors and 1000-fold selectivity over voltage-sensitive calcium and sodium ion channels, **7** has a poor pharmacokinetic profile. This issue was addressed by hybridizing the structure of **3** with the known, highly bioavailable hD_4 antagonist 5-(4-chlorophenyl)-4-methyl-3-(1-(2-phenylethyl)piperidin-4-yl)isoxazole (**2**) to design 1-(1-benzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (**8**). Compound **8** and analogues with variations at the 3-, 4-, and 5-positions of the 1,3-dihydroimidazol-2-one ring were efficiently constructed through a novel regioselective "four-step/one-pot" procedure. Changes to the group attached to the basic nitrogen of the piperidine ring of **8** were optimally carried out by alkylation of the advanced intermediate 5-methyl-4-phenyl-1(1*H*)-piperidin-4-yl-1,3-dihydroimidazol-2-one (**41**). No significant improvements to hD_4 affinity and/or selectivity were obtained by modification/substitution of the 1,3-dihydroimidazol-2-one nucleus or by substitution/replacement of the 4-phenyl group attached to the 1,3-dihydroimidazol-2-one core. Greater success was obtained with exploration of aromatic substitution on the benzyl group attached to the basic piperidine nitrogen with meta substitution in particular giving rise to several subnanomolar affinity hD_4 ligands with increased selectivity over other hD_2-like receptors. The optimal derivative identified from the studies described in this manuscript is the *m*-cyano analogue **32** since it has subnanomolar affinity for hD_4 (0.96 nM) and greater than 1000-fold selectivity over other dopamine D_2-like receptors as well as voltage-sensitive ion channels and G-protein-linked receptors. Compound **32** is an antagonist of hD_4 receptors and has a good pharmacokinetic profile in the rat (69% oral bioavailability, half-life 1.1 h, brain/plasma ratio = 0.33) and excellent receptor occupancy in the rat (estimated ED_{50} = 1.6 μg/kg po), thus making it a potentially useful pharmacological and clinical tool to investigate the role of the D_4 receptor in vivo.

Experimental Section

Biochemical Methods. 1. [^{3}H]Spiperone Binding Studies.[38,39] Clonal cell lines expressing the human dopamine D_2, D_3, and D_4 receptor subtypes were harvested in PBS (phosphate-buffered saline) and then lysed in 10 mM Tris-HCl (pH 7.4) buffer containing 5 mM $MgSO_4$. Membranes were centrifuged at 50000*g* for 15 min at 4 °C and the resulting pellets resuspended in assay buffer (50 mM Tris-HCl (pH 7.4) containing 5 mM EDTA, 1.5 mM $CaCl_2$, 5 mM $MgCl_2$, 5 mM KCl, 120 mM NaCl, and 0.1% ascorbic acid) at 20 mg of wet weight/mL (human D_4 HEK cells, 10 mg of wet weight/mL human D_2 CHO cells and D_3 HEK cells). Incubations were carried out for 120 min at ambient temperature (22 °C) in the presence of 0.2 nM [^{3}H]spiperone for displacement studies and were initiated by the addition of 20−100 mg of protein in a final assay volume of 0.5 mL. The incubation was terminated by rapid filtration over GF/B filters presoaked in 0.3% PEI (poly(ethylenimine)) and washed with ice-cold 50 mM Tris-

HCl, pH 7.4. Specific binding was determined by 10 μM apomorphine and radioactivity determined by counting in a LKB beta counter. Binding parameters were determined by nonlinear least-squares regression analysis, from which the inhibition constant K_i could be calculated for each test compound.

2. Ion Channel Activities.[40−42] Activity at the voltage-sensitive calcium channel (diltiazem allosteric site) was evaluated by displacement of [^{3}H]diltiazem (60−87 Ci mmol^{-1}; NEN) binding to rabbit sketetal muscle.[40] Binding to the voltage-sensitive sodium channel was evaluated by displacement of [^{3}H]batrachotoxin (30−60 Ci mmol^{-1}; NEN) binding to rat cerebral cortex.[41] Binding to the voltage sensitive potassium channels (particularly IK_R channels) was estimated by measurement of the prolongation of effective refractory (ERP) in ferret papilliary muscle.[42]

General directions have appeared previously.[11]

1-Benzyl-4-[(phenylcarbonylamino)carbonylamino]-piperidine (3). To an ice-bath-cooled solution of benzoyl isocyanate (7.7 mL, 0.053 mol) in CH_2Cl_2 (400 mL) was added 4-amino-1-benzylpiperidine (**33**; 10.72 mL, 0.053 mol), dropwise. When the addition was complete the solution was allowed to stir at room temperature for 1 h; then the solvent was removed by rotary evaporation. The residue was triturated with Et_2O and collected by filtration to give **3** as a white solid: 15.4 g (87%); mp 179−180 °C; ^{1}H NMR (DMSO) δ 1.51 (2 H, m), 1.86 (2 H, m), 2.14 (2 H, m), 2.69 (2 H, m), 3.47 (2 H, s), 3.65 (1 H, m), 7.24−7.33 (5H, m), 7.50 (2 H, t, J = 7.9 Hz), 7.61 (1 H, t, J = 7.9 Hz), 7.96 (2 H, d, J = 7.9 Hz), 8.69 (1 H, d, J = 7.8 Hz), 10.67 (1 H, br s); MS (CI) *m/e* 338 [MH]$^+$. Anal. ($C_{20}H_{23}N_3O_2$) C, H, N.

Compounds **4** and **5** were made in the same way as described for the synthesis of **3** using the appropriate isocyanate.

1-Benzyl-4-[(phenylaminocarbonyl)amino]piperidine (4): free base; mp 170 °C (methanol−ethyl acetate); ^{1}H NMR (DMSO) δ 1.36 (2 H, m), 1.80 (2 H, m), 2.07 (2 H, m), 2.69 (2 H, m), 3.45 (2 H, s), 3.47 (1 H, m), 6.10 (1 H, d, J = 7.6 Hz), 6.85 (1 H, t, J = 7.4 Hz), 7.17−7.45 (9 H, m), 8.30 (1 H, s); MS (CI) *m/e* 310 [MH]$^+$. Anal. ($C_{19}H_{23}N_3O\cdot0.1H_2O$) C, H, N.

1-Benzyl-4-[(benzylaminocarbonyl)amino]piperidine (5): free base; mp 124−125 °C (methanol−ethyl acetate); ^{1}H NMR (DMSO) δ 1.33 (2 H, m), 1.73 (2 H, m), 2.02 (2 H, m), 2.68 (2 H, m), 3.39 (1 H, m), 3.41 (2 H, s), 4.18 (2 H, J = 5.9 Hz), 5.86 (1 H, d, J = 7.8 Hz), 6.19 (1 H, t, J = 5.9 Hz), 7.21−7.33 (10 H, m); MS (CI) *m/e* 324 [MH]$^+$. Anal. ($C_{20}H_{25}N_3O$) C, H, N.

1-Benzyl-4-[((2-pyridyl)aminocarbonyl)amino]piperidine (6). To an ice-bath-cooled solution of 4-amino-1-benzylpiperidine (**33**; 1.07 mL, 0.0052 mol) in THF (40 mL) was added phosgene (12.9 mL of a CH_2Cl_2 1.93 M solution in toluene, 0.021 mol), in one portion. After 5 min triethylamine (6.9 mL, 0.042 mol) was added in one portion, and the reaction mixture was stirred at 0 °C for 15 min. The suspension was filtered, and the filtrate was concentrated by use of rotary evaporation. The residue was redissolved in THF (40 mL) and cooled again to ice-bath temperature, 2-aminopyridine (0.75 g, 0.0083 mol) was added, and the reaction mixture was allowed to slowly warm to room temperature and left to stir for 18 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 (200 mL) and 1 N sodium hydroxide solution (2 × 60 mL) and then water (2 × 60 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to leave a residue which was purified by silica gel chromatography using 0.5% ammonia solution/3% methanol/96.5% CH_2Cl_2 to give a product which was recrystallized from methanol−ethyl acetate to give **6** as a white solid: 0.13 g (8%); mp 178−179 °C; ^{1}H NMR (DMSO) δ 1.43 (2 H, m), 1.83 (2 H, m), 2.13 (2 H, m), 2.50 (2 H, m), 3.47 (2 H, s), 3.58 (1 H, m), 6.90 (1 H, m) 7.23−7.35 (6 H, m), 7.65 (1 H, dt, J = 7.9 and 2.0 Hz), 8.15 (1 H, dd, J = 5.2 and 2.0 Hz), 8.22 (1 H, d, J = 7.6 Hz), 9.09 (1 H, s); MS (CI) *m/e* 311 [MH]$^+$. Anal. ($C_{18}H_{22}N_4O$) C, H, N.

1-Benzyl-4-[((1-isoquinolyl)aminocarbonyl)amino]-piperidine (7). This compound was prepared in the same way as described for compound **6** except using 1-aminoisoquinoline instead of 2-aminopyridine: mp 190−191 °C; ^{1}H NMR (DMSO) δ 1.55 (2 H, m), 1.91 (2 H, m), 2.20 (2 H, m), 2.69 (2 H, m), 3.49 (2 H, s), 3.74 (1 H, m), 7.25 (1 H, m) 7.30−7.39 (5 H, m), 7.60 (1 H, t, J = 7.3 Hz), 7.76 (1 H, t, J = 7.3 Hz), 7.88 (1 H, d, J = 7.8 Hz), 8.05 (1 H, d, J = 5.8 Hz), 8.62 (1 H, d, J = 7.8 Hz), 9.56 (1 H, s), 10.19 (1 H, d, J = 7.4 Hz); MS (CI) *m/e* 361 [MH]$^+$. Anal. ($C_{22}H_{24}N_4O$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (8) and 1-(1-Benzylpiperidin-4-yl)-4-methyl-5-phenyl-1,3-dihydroimidazol-2-one (9). 1-Benzyl-4-[(phenylcarbonylamino)carbonylamino]piperidine (**3**; 15 g, 0.0445 mol) was dissolved in 50% aqueous methanol (400 mL) with NaOH (30 g) and stirred at room temperature for 48 h. The solvents were removed in vacuo, and the residue obtained was suspended in water and heated at reflux for 1 h. After allowing to cool, the required product **34** was collected by filtration and washed with Et_2O (10.4 g, 99%): mp 148 °C; ^{1}H NMR (DMSO) δ 1.30 (2 H, m), 1.71 (2 H, m), 1.99 (2 H, m), 2.68 (2 H, m), 3.32 (1 H, m), 3.42 (2 H, s), 5.32 (2 H, br s), 5.86 (1 H, d, J = 7.8 Hz), 7.21−7.34 (5 H, m); MS (CI) *m/e* 234 [MH]$^+$.

Method A (Scheme 3). 4-[(Aminocarbonyl)amino]-1-benzyl-piperidine[46] (**34**; 1.86 g, 0.008 mol) and 2-hydroxypropiophenone (1.2 g, 0.008 mol) were suspended in toluene (15 mL) with TFA (3 mL) and heated under reflux, using a Dean−Stark trap, for 2 h. The solvents were removed under vacuum, and the residue was partitioned between CH_2Cl_2 (2 × 40 mL) and 1 N sodium hydroxide solution (1 × 30 mL). The combined organic layers were washed with brine (1 × 30 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography using 0−5% methanol in CH_2Cl_2 as eluent to give **8** as the less polar isomer and **9** as the more polar isomer. Compound **8** was recrystallized from ethyl acetate to give the required compound as a white solid (0.045 g, 2%): mp 230 °C dec; ^{1}H NMR (DMSO) δ 1.60 (2 H, m), 2.02 (2 H, m), 2.20 (3 H, s), 2.43 (2 H, m), 2.89 (2 H, m), 3.49 (2 H, s), 3.75 (1 H, m), 7.21−7.40 (10 H, m), 10.25 (1 H, br s); the regiochemistry of this compound was assigned by observation of an NOE between the methyl protons at δ 2.20 and the piperidine methine proton at δ 3.75; MS (CI) *m/e* 348 [MH]$^+$. Anal. ($C_{22}H_{25}N_3O\cdot0.1H_2O$) C, H, N.

The more polar compound was recrystallized from methanol−ethyl acetate to give **9** as a white solid (0.24 g, 9%): mp 249 °C; ^{1}H NMR (DMSO) δ 1.49 (2 H, m), 1.74 (2 H, m), 1.89 (3 H, s), 2.45 (2 H, m), 2.79 (2 H, m), 3.49 (1 H, m), 3.38 (2 H, s), 7.20−7.47 (10 H, m), 10.05 (1 H, br s); MS (CI) *m/e* 348 [MH]$^+$. Anal. ($C_{22}H_{25}N_3O$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (8). Method B (Scheme 4). To a solution of 4-amino-1-benzylpiperidine (**33**; 35 g, 0.17 mol) in CH_2Cl_2 (500 mL) were added 2-bromopropiophenone (44 g, 0.2 mol) and Et_3N (60 mL, 0.43 mol), and the reaction mixture was stirred for 14 h. Benzoyl isocyanate (25.3 g, 0.17 mol) was added, and the solution was stirred for a further 1 h. Methanol (200 mL) was added, and the solvents were removed in vacuo. The residue was redissolved in methanol (500 mL), and sodium methoxide (27 g, 0.5 mol) was added. After stirring for 1 h, trifluoroacetic acid (200 mL) was added, and after a further 0.5 h, the reaction mixture was concentrated under vacuum. The residue was partitioned between CH_2Cl_2 (1 L) and saturated potassium carbonate solution (800 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo. On reducing the volume to approximately 200 mL, **8** (37 g) crystallized out and was collected by filtration. A further amount was isolated using silica gel chromatography using 0−5% methanol/CH_2Cl_2 as eluent, and the combined solids were recrystallized from methanol−ethyl acetate to give **8** (45 g, 76%) which was identical with the product obtained using method A.

Compounds **10**−**12** were all prepared by the procedure described for the formation of compound **8** described above

(method B), using the appropriate 2-bromo ketone instead of 2-bromopropiophenone.

1-(1-Benzylpiperidin-4-yl)-4-phenyl-1,3-dihydroimidazol-2-one (10): mp 306−308 °C; ^{1}H NMR (DMSO) δ 1.65 (4 H, m), 2.03 (2 H, m), 2.88 (2 H, m), 3.48 (2 H, s), 3.82 (1 H, m), 6.73 (1 H, s), 6.94−7.62 (10 H, m), 10.21 (1 H, s); MS (CI) *m/e* 334 $[MH]^+$. Anal. ($C_{21}H_{23}N_3O$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-5-ethyl-4-phenyl-1,3-dihydroimidazol-2-one (11): mp 235 °C; ^{1}H NMR (DMSO) δ 1.42 (3 H, t, J = 7.3 Hz), 1.56 (2 H, m), 2.03 (2 H, m), 2.53 (4 H, m), 2.88 (2 H, m), 3.49 (2 H, s), 3.55 (1 H, m), 7.21−7.40 (10 H, m), 10.25 (1 H, s); MS (CI) *m/e* 362 $[MH]^+$. Anal. ($C_{23}H_{27}N_3O$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-3-methyl-4-phenyl-1,3-dihydroimidazol-2-one hydrochloride (12): Purified as a hydrochloride salt; mp 227 °C dec; ^{1}H NMR (DMSO) δ 2.00 (2 H, m), 2.29 (2 H, m), 3.15 (2 H, m), 3.33 (3 H, s), 3.38 (2 H, m), 4.20 (1 H, m), 4.30 (2 H, s), 6.61 (1 H, s), 7.35−7.70 (10 H, m), 10.96 (1 H, br s); MS (CI) *m/e* 348 $[MH]^+$. Anal. ($C_{22}H_{25}N_3O\cdot HCl\cdot 0.4H_2O$) C, H, N.

Compounds **13** and **14** were both prepared by the procedure described for the formation of compound **8** described above (method B), using the appropriate isocyanate instead of benzoyl isocyanate.

1-(1-Benzylpiperidin-4-yl)-3,5-dimethyl-4-phenyl-1,3-dihydroimidazol-2-one hydrochloride (13): purified as a hydrochloride salt; mp 295 °C dec; ^{1}H NMR (DMSO) δ 1.62 (2 H, m), 2.04 (2 H, m), 2.06 (3 H, s), 2.40 (2 H, m), 2.90 (2 H, m), 3.33 (3 H, s), 3.49 (2 H, s), 3.79 (1 H, m), 7.24−7.49 (10 H, m), 10.96 (1 H, br s); MS (CI) *m/e* 362 $[MH]^+$. Anal. ($C_{23}H_{27}N_3O\cdot HCl$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-3,4-diphenyl-5-methyl-1,3-dihydroimidazol-2-one hydrochloride(14): purified as a hydrochloride salt; mp 253 °C dec; ^{1}H NMR (DMSO) δ 1.98 (2 H, m), 2.18 (3 H, s), 2.79 (2 H, m), 3.12 (2 H, m), 3.44 (2 H, m), 4.23 (1 H, m), 4.30 (2 H, s), 7.03−7.05 (4 H, m), 7.18−7.30 (6 H, m), 7.47 (3 H, m), 7.60 (2 H, m), 10.63 (1 H, br s); MS (CI) *m/e* 424 $[MH]^+$. Anal. ($C_{28}H_{29}N_3O\cdot HCl\cdot H_2O$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-5-methyl-4-(4-chlorophenyl)-1,3-dihydroimidazol-2-one (15): This compound was prepared and isolated as the less polar regioisomer using the procedure described above for the formation of **8** (method A) using 4′-chloro-2-hydroxypropiophenone instead of 2-hydroxypropiophenone: mp 240 °C dec ^{1}H NMR (DMSO) δ 1.60 (2 H, m), 2.02 (2 H, m), 2.19 (3 H, s), 2.42 (2 H, m), 2.89 (2 H, m), 3.49 (2 H, s), 3.75 (1 H, m), 7.25−7.44 (9 H, m), 10.31 (1 H, br s); MS (CI) *m/e* 384 & 382 $[MH]^+$. Anal. ($C_{22}H_{24}ClN_3O$) C, H, N.

Compounds **16**−**22** were all prepared by the procedure described for the formation of compound **8** described above (method B), using the appropriate 2-bromo ketone instead of 2-bromopropiophenone.

1-(1-Benzylpiperidin-4-yl)-4-(3-chlorophenyl)-5-methyl-1,3-dihydroimidazol-2-one (16): mp 248 °C; ^{1}H NMR (DMSO) δ 1.60 (2 H, m), 2.02 (2 H, m), 2.21 (3 H, s), 2.44 (2 H, m), 2.89 (2 H, m), 3.49 (2 H, s), 3.76 (1 H, m), 7.24−7.42 (9 H, m), 10.34 (1 H, br s); MS *m/z* (CI) 382 (M^+ + H). Anal. ($C_{22}H_{34}ClN_3O$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-4-(2-chlorophenyl)-5-methyl-1,3-dihydroimidazol-2-one (17): mp 218 °C; ^{1}H NMR (DMSO) δ 1.61 (2 H, m), 1.95 (3 H, s), 2.01 (2 H, m), 2.40 (2 H, m), 2.90 (2 H, m), 3.49 (2 H, s), 3.74 (1 H, m), 7.26 (1 H, m), 7.31−7.33 (4 H, m), 7.35−7.38 (3 H, m), 7.51 (1 H, m), 10.08 (1 H, br s); MS *m/z* (CI) 382 (M^++ H). Anal. ($C_{22}H_{34}ClN_3O\cdot 0.2H_2O$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-4-(4-methoxyphenyl)-5-methyl-1,3-dihydroimidazol-2-one (18): mp 242 °C; ^{1}H NMR (DMSO) δ 1.59 (2 H, m), 2.01 (2 H, m), 2.15 (3 H, s), 2.42 (2 H, m), 2.89 (2 H, m), 3.23 (1 H, m), 3.49 (2 H, s), 3.76 (3 H, s), 6.95 (2 H, d, J = 8.8 Hz), 7.26 (2 H, d, J = 8.8 Hz), 7.33 (5 H, m), 10.16 (1 H, br s); MS *m/z* (CI) 378 (M^+ + H). Anal. ($C_{23}H_{27}N_3O_2$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-4-(4-fluorophenyl)-5-methyl-1,3-dihydroimidazol-2-one (19): mp 235 °C; ^{1}H NMR (DMSO) δ 1.91 (2 H, m), 2.18 (3 H, s), 2.75 (2 H, m), 3.12 (2 H, m), 3.47 (2 H, m), 4.07 (1 H, m), 4.33 (2 H, s), 7.23 (2 H, m), 7.38 (2 H, m), 7.50 (5 H, m), 10.41 (1 H, br s); MS *m/z* (CI) 366 (M^+ + H). Anal. ($C_{22}H_{24}FN_3O$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-4-(4-methyl-phenyl)-5-methyl-1,3-dihydroimidazol-2-one (20): mp 255 °C; ^{1}H NMR (DMSO) δ 1.59 (2 H, m), 2.01 (2 H, m), 2.17 (3 H, s), 2.29 (3 H, s), 2.42 (2 H, m), 2.89 (2 H, m), 3.48 (2 H, s), 3.74 (1 H, m), 7.17−7.27 (5 H, m), 7.30−7.36 (4 H, m), 10.19 (1 H, br s); MS *m/z* (CI) 362 (M^+ + H). Anal. ($C_{23}H_{27}N_3O$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-5-methyl-4-thiophene-2-yl-1,3-dihydroimidazol-2-one (21): mp 225 °C; ^{1}H NMR (DMSO) δ 1.59 (2 H, m), 2.01 (2 H, m), 2.24 (3 H, s), 2.41 (2 H, m), 2.89 (2 H, m), 3.49 (2 H, s), 3.73 (1 H, m), 7.05 (1 H, t, J = 4 Hz), 7.12 (1 H, d, J = 4) 7.26 (1 H, m), 7.33 (4 H, m), 7.42 (1 H, d, J = 5 Hz), 10.41 (1 H, br s); MS *m/z* (CI) 354 (M^+ + H). Anal. ($C_{20}H_{23}N_3OS$) C, H, N.

1-(1-Benzylpiperidin-4-yl)-5-methyl-4-pyridin-2-yl-1,3-dihydroimidazol-2-one (22): mp 194 °C; ^{1}H NMR (DMSO) δ 1.60 (2 H, m), 1.99 (2 H, m), 2.45 (2 H, m), 2.53 (3 H, s), 2.89 (2 H, m), 3.49 (2 H, s), 3.77 (1 H, m), 7.12 (1 H, m), 7.26 (1 H, m) 7.32 (4 H, m), 7.42 (1 H, d, J = 11 Hz), 7.75 (1 H, m, J = 11 and 3 Hz), 8.49 (1 H, m), 10.46 (1 H, br s); MS *m/z* (CI) 349 (M^+ + H). Anal. ($C_{21}H_{24}N_4O\cdot 0.3H_2O$) C, H, N.

1-(1-Methylpiperidin-4-yl)-5-methyl-4-pyridin-2-yl-1,3-dihydroimidazol-2-one (23). To a solution of **41** (0.5 g, 0.0019 mol) in methanol (75 mL) under nitrogen was added sodium cyanoborohydride (0.153 g, 1.25 mol equiv) followed by acetic acid (0.29 mL). The reaction mixture was cooled in an ice bath, and formaldehyde (0.192 g, 1.25 mol equiv) was added in methanol (2 mL). After 30 min the reaction mixture was allowed to warm to room temperature and stirred for 14 h. The reaction mixture was basified with saturated potassium carbonate solution (20 mL), and the methanol was removed on the rotary evaporator. The aqueous residue was extracted into ethyl acetate (3 × 50 mL), dried ($MgSO_4$), filtered, and evaporated under vacuum to leave a solid which was purified by chromatography on silica gel using 2−10% methanol in CH_2Cl_2 as eluent. Recrystallization from ethyl acetate/hexane gave pure product: mp 251−253 °C; ^{1}H NMR (DMSO) δ 1.58 (2 H, d, J = 11 Hz), 1.94 (2 H, m), 2.18 (3 H, s), 2.20 (3 H, s), 2.41 (2 H, m), 2.84 (2 H, d J = 11 Hz), 3.73 (1 H, m), 7.21 (1 H, m), 7.33−7.40 (4 H, m), 10.25 (1 H, s); MS (CI) *m/e* 272 $[MH]^+$. Anal. ($C_{16}H_{21}N_3O$) C, H, N.

5-Methyl-1-(1-phenethylpiperidin-4-yl)-4-phenyl-1,3-dihydroimidazol-2-one (25). To a solution of 1-benzyl-4-aminopiperidine (**33**; 40 g, 0.21 mol) in CH_2Cl_2 (500 mL) was added di-*tert*-butyl dicarbonate (50.4 g, 0.23 mol), and the reaction mixture was stirred under nitrogen for 18 h at room temperature. The solvent was removed by rotary evaporation, and the residue was triturated with Et_2O and then collected by filtration to give 1-benzyl-4-(*tert*-butyloxycarbonylamino)-piperidine as a white solid (60.29 g, 99%): mp 135−138 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (9 H, m), 1.53 (2 H, m), 1.92 (2 H, s), 2.12 (2 H, m), 2.83 (2 H, m), 3.51 (2 H, s), 4.42 (1 H, s), 7.22−7.32 (5 H, m).

To a suspension of 1-benzyl-4-(*tert*-butyloxycarbonylamino)-piperidine (60.29 g, 0.20 mol) in methanol (700 mL) was added (under nitrogen) 10% palladium on carbon catalyst (3.0 g), and the mixture was shaken under 50 psi of hydrogen for 18 h. The solution was filtered and the solvent was removed by rotary evaporation to give 4-(*tert*-butyloxycarbonylamino)-piperidine as a white solid (40 g, 97%): mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (9 H, s), 1.97(4 H, s), 2.65 (2 H, m), 3.60 (2 H, m), 4.47 (1 H, s).

To a suspension of 4-(*tert*-butyloxycarbonylamino)piperidine (3.5 g, 0.0175 mol) in dimethylformamide (10 mL) were added ethyldiisopropylamine (6.1 mL, 0.035 mol) and 2-bromoethylbenzene (2.64 mL, 0.0193 mol), and the solution was stirred at room temperature for 42 h under nitrogen. The reaction mixture was poured into water (500 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were washed with brine (1 × 30 mL), then dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was triturated

with Et_2O/hexane (1:1) and collected by filtration to give a white solid, which was dissolved in a saturated solution of hydrogen chloride in methanol (100 mL) and stirred at room temperature for 18 h. The solvent was removed by rotary evaporation; then the residue was triturated with Et_2O and collected by filtration to give **39** as a white solid (1.55 g, 39%): mp 200−201 °C; ^{1}H NMR δ 1.89 (2 H, m), 2.80 (2 H, m), 3.04 (2 H, m), 3.30 (2 H, m), 3.64 (1 H, m), 3.72 (2 H, s), 3.86 (2 H, s), 7.26−7.44 (5 H, m).

5-Methyl-1-(1-phenethyl-piperidin-4-yl)-4-phenyl-1,3-dihydroimidazol-2-one (**25**) was prepared using the procedure described for the formation of compound **8** (method B) using **39** (and an extra molar equivalent of triethylamine) instead of 4-amino-1-benzylpiperidine: mp 232−236 °C; ^{1}H NMR (DMSO) δ 1.60 (2 H, m), 2.04 (2 H, m), 2.21 (3 H, s), 2.40 (4 H, m), 2.74 (2 H, m), 3.05 (2 H, m), 3.75 (1 H, m), 7.16−7.40 (10 H, m), 10.23 (1 H, br s); MS (CI) *m/e* 362 $[MH]^+$. Anal. ($C_{23}H_{27}N_3O$) C, H, N.

1-(3-Cyanobenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (32). Compound **8** (40 g, 0.115mol) was dissolved in CH_2Cl_2 (600 mL) at 0 °C, and 1-chloroethyl chloroformate (18.66 mL, 1.5 mol equiv) was added dropwise over 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 14 h. The solvents were removed under vacuum, and the residue was redissolved in methanol (500 mL) and heated under reflux for 2 h. After cooling, the solid produced was collected by filtration and recrystallized from methanol to give a hydrochloride salt (**40**) as a white solid (23.14 g, 68%): ^{1}H NMR (DMSO) δ 1.83 (2 H, m), 2.22 (3 H, s), 2.66 (2 H, m), 3.00 (2 H, m), 3.34 (2 H, m), 4.10 (1 H, m), 7.22−7.44 (5 H, m), 8.66 (1 H, br s), 9.31 (1 H, br s), 10.36 (1 H, s); MS (CI) *m/e* 258 $[MH]^+$.

Compound **40** (23.1 g) was added to aqueous sodium hydroxide (800 mL of 1 M solution), the aqueous solution was extracted with CH_2Cl_2 (4 × 200 mL), and the combined organic layers were washed with brine (1 × 200 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to yield a free base **41** (16 g, 80%, mp 235−238 °C) which was used directly in the formation of compounds **24** and **26**−**32**.

To a solution of **41** (1.0 g, 3.9 mmol) in anhydrous dimethylformamide (50 mL) were added bromo-*m*-tolunitrile (0.84 g, 4.4 mmol) and ethyldiisopropylamine (1.35 mL, 7.8 mmol), and the reaction mixture was stirred at room temperature for 18 h under nitrogen. This mixture was poured into sodium hydroxide solution (200 mL, 1 M) and extracted into CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL) and dried ($MgSO_4$), and the solvent was removed by rotary evaporation to yield the crude product which was recrystallized from ethyl acetate/hexane to yield **32** (0.86 g, 60%): mp 254−256 °C dec; ^{1}H NMR (DMSO) δ 1.61 (2 H, d, J = 11 Hz), 2.06 (2 H, m), 2.19 (3 H, s), 2.44 (2 H, m), 2.88 (2 H, d, J = 11 Hz), 3.56 (2 H, s), 3.75 (1 H, m), 7.21−7.75 (9 H, m), 10.26 (1 H, s); MS (CI) *m/e* 373 $[MH]^+$. Anal. ($C_{23}H_{24}N_4O$) C, H, N.

The following compounds were made in the same way as described for **32** using the appropriate alkyl halide.

1-(Cyclohexylmethylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (24): mp 255−256 °C; ^{1}H NMR (DMSO) δ 0.83 (2 H, m), 1.17−1.24 (4 H, m), 1.46 (1 H, m), 1.58−1.76 (6 H, m), 1.91 (2 H, m), 2.08 (2 H, d, J = 7.2 Hz), 2.19 (3 H, s), 2.40 (2 H, m), 2.89 (2 H, d, J = 11 Hz), 3.72 (1 H, m), 7.25 (1 H, m), 7.33−7.40 (4 H, m), 10.25 (1 H, s); MS (CI) *m/e* 354 $[MH]^+$. Anal. ($C_{22}H_{31}N_3O$) C, H, N.

1-(Phenylpropylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (26): mp 181−182 °C; ^{1}H NMR (DMSO) δ 1.60 (2 H, d, J = 11 Hz), 1.74 (2 H, m), 2.04 (2 H, m), 2.18 (3 H, s), 2.29 (2 H, m), 2.44 (2 H, m), 2.61 (2 H, m), 2.88 (2 H, d, J = 11 Hz), 3.73 (1 H, m), 7.34−7.58 (10 H, m), 10.26 (1 H, s); MS (CI) *m/e* 376 $[MH]^+$. Anal. ($C_{24}H_{29}N_3O$) C, H, N.

1-(2-Chlorobenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (27): mp 236−237 °C; ^{1}H NMR (DMSO) δ 1.62 (2 H, d, J = 11 Hz), 2.14 (2 H, m), 2.20 (3 H, s), 2.45 (2 H, m), 2.93 (2 H, d, J = 11 Hz), 3.59 (2 H, s), 3.77 (1 H, m), 7.20−7.54 (9 H, m), 10.27 (1 H, s); MS (CI) *m/e* 382 $[MH]^+$. Anal. ($C_{23}H_{24}N_3OCl\cdot0.2H_2O$) C, H, N.

1-(3-Chlorobenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (28): mp 248−249 °C; ^{1}H NMR (DMSO) δ 1.61 (2 H, d, J = 11 Hz), 2.04 (2 H, m), 2.19 (3 H, s), 2.44 (2 H, m), 2.88 (2 H, d, J = 11 Hz), 3.51 (2 H, s), 3.74 (1 H, m), 7.23−7.40 (9 H, m), 10.26 (1 H, s); MS (CI) *m/e* 382 $[MH]^+$. Anal. ($C_{23}H_{24}N_3OCl\cdot0.1H_2O$) C, H, N.

1-(4-Chlorobenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (29): mp 266 °C; ^{1}H NMR (DMSO) δ 1.59 (2 H, d, J = 11 Hz), 2.03 (2 H, m), 2.19 (3 H, s), 2.45 (2 H, m), 2.87 (2 H, d, J = 11 Hz), 3.48 (2 H, s), 3.75 (1 H, m), 7.21−7.40 (9 H, m), 10.26 (1 H, s); MS (CI) *m/e* 382 $[MH]^+$. Anal. ($C_{23}H_{24}N_3OCl$) C, H, N.

1-(3-Methylbenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (30): mp 234−236 °C; ^{1}H NMR (DMSO) δ 1.60 (2 H, d, J = 11 Hz), 2.00 (2 H, m), 2.19 (3 H, s), 2.31 (3 H, s), 2.43 (2 H, m), 2.89 (2 H, d, J = 11 Hz), 3.44 (2 H, s), 3.74 (1 H, m), 7.05−7.40 (9 H, m), 10.26 (1 H, s); MS (CI) *m/e* 362 $[MH]^+$. Anal. ($C_{23}H_{27}N_3O$) C, H, N.

1-(3-Methoxybenzylpiperidin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimidazol-2-one (31): mp 227−228 °C; ^{1}H NMR (DMSO) δ 1.6 (2 H, d, J = 10 Hz), 2.01 (2 H, m), 2.19 (3 H, s), 2.4 (2 H, m), 2.9 (2 H, d, J = 11 Hz), 3.46 (2 H, s), 3.75 (4 H, m), 6.8−6.9 (3 H, m), 7.21−7.4 (6 H, m), 10.26 (1 H, s); MS (CI) *m/e* 378 $[MH]^+$. Anal. ($C_{23}H_{27}N_3O_2$) C, H, N.

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