4-Heterocyclylpiperidines as Selective High-Affinity Ligands at the Human Dopamine D4 Receptor

Michael Rowley,* Ian Collins, Howard B. Broughton, William B. Davey, Raymond Baker, Frances Emms, Rosemarie Marwood, Shil Patel, Smita Patel, C. Ian Ragan, Stephen B. Freedman, Richard Ball,† and Paul D. Leeson

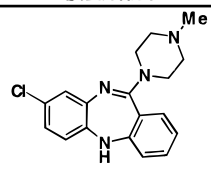
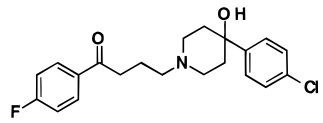
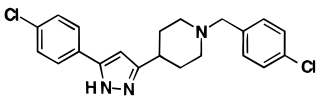
Merck Sharp and Dohme, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K., and Merck Research Laboratories, Rahway, New Jersey

Received February 24, 1997[⊗]

5-(4-Chlorophenyl)-3-(1-(4-chlorobenzyl)piperidin-4-yl)pyrazole (**3**) was identified from screening of the Merck sample collection as a human dopamine D4 (hD4) receptor ligand with moderate affinity (61 nM) and 4-fold selectivity over human D2 (hD2) receptors. Four separate parts of the molecule have been examined systematically to explore structure−activity relationships with respect to hD4 affinity and selectivity over other dopamine receptors. It was found that the 4-chlorophenyl group attached to the pyrazole is optimal, as is the 4-substituted piperidine. The lipophilic group on the basic nitrogen is more amenable to change, with the optimal group found to be a phenethyl. The aromatic heterocyle can be altered to a number of different groups, with isoxazoles and pyrimidines showing improved affinities. This heterocycle can also be advantageously alkylated, improving the selectivity of the compounds over D2 receptors. It is hypothesized that the conformation around the bond joining the aromatic heterocycle to the piperidine is important for D4 affinity, based on crystal structures of isoxazoles (**29** and **30**) and on a conformationally constrained compound (**28**). Putting all the favorable changes together led to the discovery that 5-(4-chlorophenyl)-4-methyl-3-(1-(2-phenylethyl)piperidin-4-yl)isoxazole (**36**) is a nanomolar antagonist at human dopamine D4 receptors with >500-fold selectivity over hD2 and >200-fold selectivity over hD3. Compound **36** is an antagonist of hD4 receptors with good oral bioavailability of 38%, a half life of 2 h, and brain levels 10-fold higher than plasma levels.

Schizophrenia is a mental illness for which there is still a great need for novel drug therapy. Classical neuroleptics, which are presumed to act by antagonism of dopamine D2-like receptors,[1] are useful for the treatment of the positive symptoms of schizophrenia but cause major movement disorders[2] which are thought to be due to blockade of D2 receptors in the striatum, along with increases in serum prolactin levels.[3] The atypical neuroleptic clozapine[4] (**1**; Table 1) can be used to treat both positive and negative symptoms and does not induce the extrapyramidal side effects. However, in 1−2% of patients the drug induces agranulocytosis, and its use is therefore limited and must be closely monitored.[5] In recent years the application of molecular biology techniques has seen the cloning of a number of different subtypes of dopamine receptors[6−10] which on the basis of their pharmacology can be divided into two classes: D1-like (D1, D5) and D2-like (D2, D3, D4). Clozapine, among its many actions, has higher affinity for the D4 subtype than for D2.[9] Recent reports[11] suggest that D4 receptor density is elevated in postmortem schizophrenic brain, although there is some disagreement about this.[12] Studies of mRNA distribution indicate that D4 receptors are preferentially located in the mesolimbic system,[13] with low density in the striatum. For these reasons it was decided to identify selective D4 receptor antagonists to investigate their potential as novel antipsychotics, possibly without the undesired side effects of classical neuroleptics. Until very lately there have been no reports in the literature on selective dopamine D4 antagonists, but we[14] and others[15] have recently communicated on a number of series of such ligands. In this paper we fully describe the synthesis and structure−affinity relationship studies leading to the discovery of high-affinity selective ligands for the human dopamine D4 (hD4) receptor.

Table 1. Reference Compounds and Lead Pyrazole

		K_i (nM) [a]		
Number	Structure	hD2	hD3	hD4
1		74	200	10
2		1.4	2.0	2.3
3		240	820	61

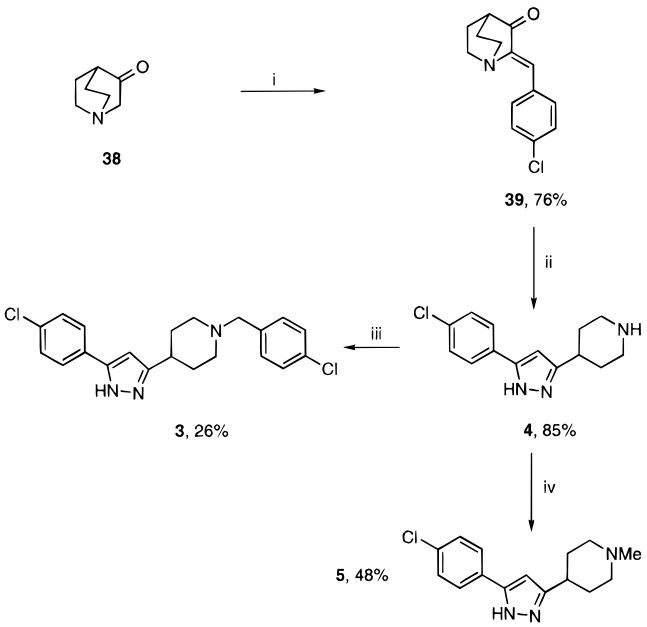
[a] Affinities at cloned human dopamine receptors stably expressed in cell lines.

Our strategy began with the screening of the Merck sample collection. A representative number of known, unselective dopamine antagonists were selected, and using the topological similarity probe method[16] as implemented in the in-house TOPOSIM[17] package, the collection was screened for chemicals that had affinity

* Corresponding author: e-mail, Michael_Rowley@Merck.com.
† Merck Research Laboratories, NJ.
⊗ Abstract published in *Advance ACS Abstracts,* June 15, 1997.

S0022-2623(97)00111-8 CCC: $14.00

Scheme 1[a]



[a] Reagents: (i) 4-chlorobenzaldehyde, NaOH, EtOH, reflux; (ii) $H_2NNH_2 \cdot H_2O$, KOH, ethylene glycol, 130−200 °C; (iii) 4-$ClPhCH_2Cl$, Et-*i*-Pr_2N, DMF; (iv) formaldehyde, $NaBH_4$, CF_3CO_2H, THF.

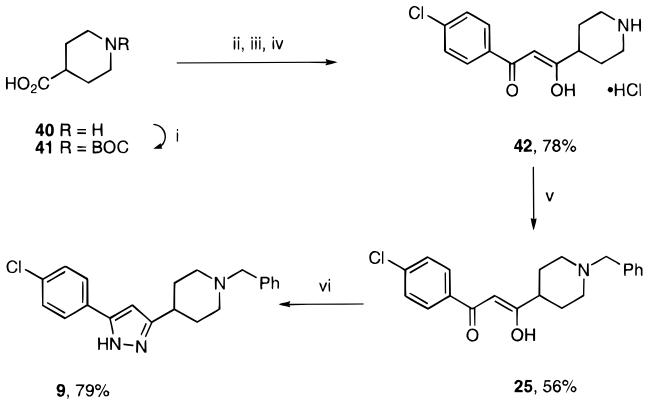
for dopamine receptors and possibly selectivity for D4 over other subtypes. One of these runs, based on the structure of the classical neuroleptic haloperidol (**2**), gave rise to a number of dopamine subtype selective ligands, from which 5-(4-chlorophenyl)-3-(1-(4-chlorobenzyl)piperidin-4-yl)pyrazole (**3**) was chosen as a suitable lead. This compound has moderate affinity for cloned human dopamine D4 receptors (K_i 61 nM) and 4-fold selectivity over D2. Efforts were initiated within medicinal chemistry to improve on the affinity and selectivity within this series of compounds.

Chemistry and Biology

The pyrazole **3** was synthesized (Scheme 1) starting from 3-quinuclidinone (**38**). Condensation with 4-chlorobenzaldehyde gave the unsaturated ketone **39**, which on treatment with hydrazine and base[18] ring opened to give pyrazole **4**. Alkylation with 4-chlorobenzyl chloride gave the lead compound **3**. Other compounds in Table 2 were made by alkylation of pyrazole **4** with alkyl halides, with the exception of the *N*-methylpiperidine **5**, which was made by a reductive amination of pyrazole **4** with formaldehyde and sodium borohydride.

A different route to the pyrazolylpiperidines, which also allowed access to alternative aromatic heterocycles, is shown in Scheme 2. Isonipecotic acid (**40**) was N-protected and then the acid function activated as its imidazolide. Displacement with 2 equiv of the enolate prepared from 4-chloroacetophenone and lithium diisopropylamide gave a mixture of the desired β-diketone and excess acetophenone, which could be most conveniently separated by treatment of the crude product with HCl in EtOAc and isolation of the amine hydrochloride salt **42**. It is necessary to use 2 equiv of the enolate, as the β-diketone product is more acidic than the acetophenone, thus quenching the enolate reagent. N-Alkylation at the diketone stage followed simply by treatment with hydrazine in methanol at room temperature gave the desired pyrazole. All the compounds in

Scheme 2[a]



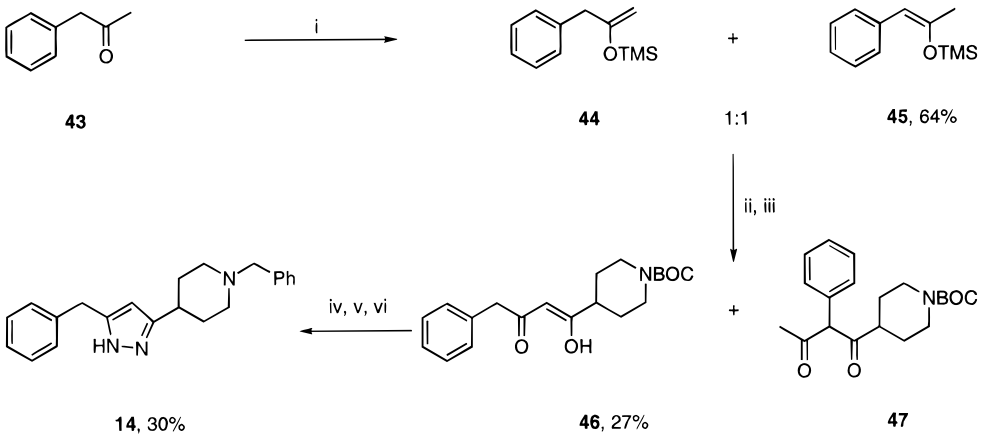
[a] Reagents: (i) BOC_2O, CH_2Cl_2; (ii) carbonyldiimidazole, THF; (iii) 2 equiv of 4-chloroacetophenone/LDA, −78 °C−room temperature; (iv) HCl, EtOAc; (v) $PhCH_2Br$, Et-*i*-Pr_2N, DMF; (vi) $H_2NNH_2 \cdot H_2O$, MeOH.

Table 3 were made in this way, except for the benzylpyrazole **14** where, when this route was tried, only the product (**47**; Scheme 3) of enolization toward the phenyl ring was isolated. It was reasoned that this was the product of the thermodynamic enolate and that if the reaction were repeated under nonequilibrating conditions, then the desired product might be obtained. Thus a 1:1 mixture of the silyl enol ethers derived from acetophenone **43** (Scheme 3) was treated with methyllithium to generate the enolates in the absence of a proton source. Addition of the imidazolide now gave a mixture of the wrong regioisomer (**47**) along with the desired product (**46**) which could be separated chromatographically and taken through to pyrazole **14**.

The 3-substituted piperidine **20** (Table 4) and the tetrahydropyridine **23** were made by the same route as the 4-piperidine and the 2-substituted piperidine **21** made in a similar way but using a benzoyl rather than BOC protection for the piperidine nitrogen. The synthesis (Scheme 4) of the pyrrolidine analogue **22** began with the pyrrolidinone ester **48**. Hydrolysis to the acid **49** and then activation and coupling with 4-chloroacetophenone enolate gave the diketone **50** which was condensed with hydrazine, and the lactam **51** was reduced with lithium aluminum hydride to give the desired product (**22**). Treatment[19] (Scheme 5) of *N*-phenethylpiperazine with *N*-methyl-*N*-phenylthiosemicarbazide gave the thiosemicarbazide **53**, which was condensed with phenacyl bromide to give the piperazine analogue **24**.

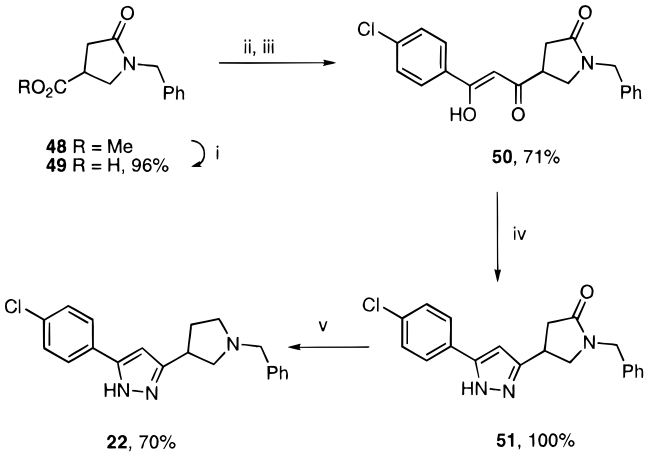
The 4-methylated piperidine **27** (Table 5) and its diketone intermediate **26** were made in the same way as **13** (Scheme 2) but starting with 4-methylpiperidine-4-carboxylic acid. The synthesis of the spirofused compound **28** began with iodobutyrophenone (**54**; Scheme 6). The ketone function was temporarily protected as its dimethyl acetal using trimethyl orthoformate and Montmorillonite K-10 clay. The iodide was then displaced with the anion derived from *N*-BOC ethyl isonipecotate, the ketone protection being removed in the workup of this reaction to yield the keto ester **56**. It was necessary to use potassium hexamethyldisilazide at low temperature to perform the Dieckman cyclization of this compound, because if sodium ethoxide in refluxing ethanol was used, only the product (**58**) of cyclization followed by retro-Claisen reaction was observed. With

Scheme 3[a]



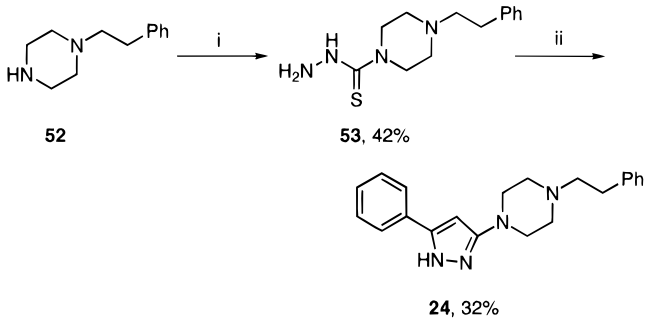
[a] Reagents: (i) LDA/TMSCl; (ii) MeLi, ether; (iii) **41**/carbonyldiimidazole, −78 °C−room temperature; (iv) $H_2NNH_2 \cdot H_2O$, MeOH; (v) HCl, EtOAc; (vi) $PhCH_2Br$, Et-*i*-Pr_2N, DMF.

Scheme 4[a]



[a] Reagents: (i) KOH, EtOH/H_2O; (ii) carbonyldiimidazole; (iii) 2 equiv of 4-chloroacetophenone/LDA, −78 °C−room temperature; (iv) $H_2NNH_2 \cdot H_2O$, MeOH; (v) $LiAlH_4$, 40 °C.

Scheme 5[a]



[a] Reagents: (i) $PhNMeCSNHNH_2$, acetonitrile, reflux; (ii) phenacyl bromide, EtOH, room temperature then HCl reflux.

potassium hexamethyldisilazide a 2:1 mixture of the desired diketone (**57**) and retro-Claisen product (**58**) was obtained. Condensation of diketone **57** with hydrazine, N-deprotection, and alkylation finished the preparation of the pyrazole **28**.

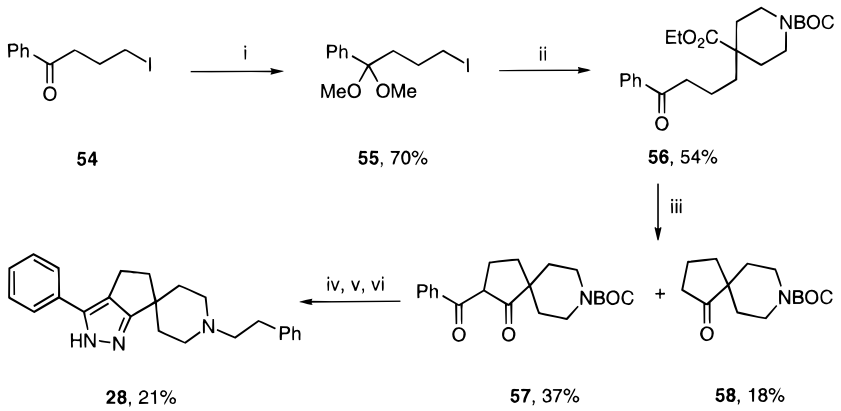
The 4-methylpyrazoles **32** and **34** (Table 6) were made in the same way as the 4-unsubstituted pyrazoles but starting with 4-chloropropiophenone rather than the acetophenone. It was also possible to alkylate the intermediate β-diketone **59** (Scheme 7) by evaporation of a mixture with tetrabutylammonium fluoride[20] followed by treatment with ethyl iodide in chloroform. This gave intermediate **60** which was elaborated to the ethylpyrazole **33**. The β-diketones also served as useful intermediates for the synthesis of alternative heterocycles (Scheme 8). Thus, condensation of **61** with hydroxylamine gave intermediate hydroxyisoxazolines, which were not purified but dehydrated with methanesulfonyl chloride to give a mixture of the isoxazoles **29** and **30** which were separated by chromatography. The regiochemistry of the isoxazoles was proved by X-ray crystallography on both compounds. Reaction of the diketone **25** with guanidine hydrochloride and sodium isopropoxide in refluxing 2-propanol gave the aminopyrimidine **31**. The aminopyrimidine **37** and the isoxazoles **35** and **36** were made using these procedures from the corresponding *N*-phenethyl diketone.

Compounds were tested for their ability to displace [^{3}H]spiperone from human cloned receptors, D2 stably expressed in CHO cells,[21] D3 and D4 in HEK-293 cells.[22] With the exception of compounds **4**, **5**, and **12** which have weak dopamine receptor affinities and were only tested once, binding data are the geometric mean of several independent determinations: errors of the mean were within 2-fold of the mean.

Discussion

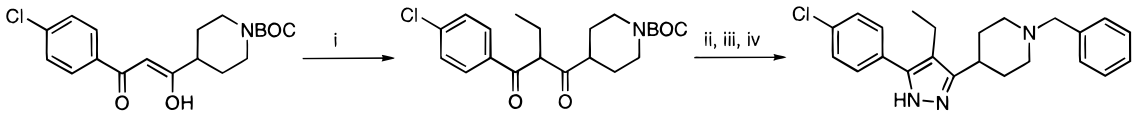
It is necessary to have a lipophilic group on the basic nitrogen of the piperidine, as neither the secondary amine **4** nor the *N*-methyl derivative **5** binds to dopamine receptors (Table 2). In the lead compound the lipophilic group is 4-chlorobenzyl, but it is not a requirement that it be aromatic, as the cyclohexylmethyl analogue **6** shows improved affinities. In the benzyl series, moving the chlorine atom from the *para* to the *meta* position (**7**) has little effect, whereas the *o*-chloro compound (**8**) has improved hD4 affinity and reduced hD2 affinity, leading to overall better selectivity. The biggest improvement in hD4 affinity however comes from removal of the chlorine atom altogether, leading to the unsubstituted benzyl analogue **9** with better than 10 nM affinity at hD4 and greater than 10-fold selectivity over hD2. Homologation of this to the phenethyl derivative **10** gives a further doubling of binding affinity at hD4 receptors and a marked reduction in binding to hD2, leading to a compound with almost 100-fold selectivity for hD4 over hD2. There is no measurable binding to the hD3 subtype in this compound. The two-carbon chain between the basic nitrogen and the lipo-

Scheme 6[a]



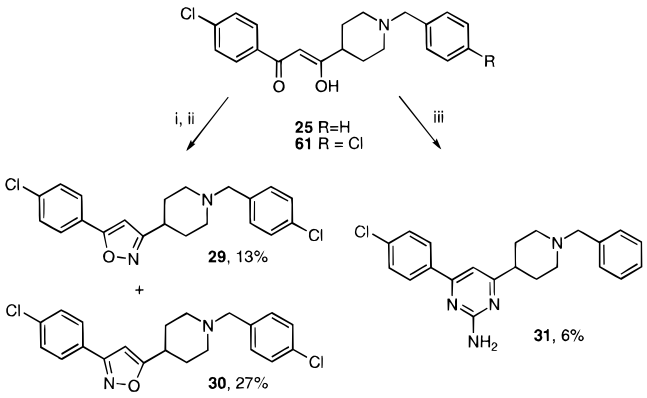
[a] Reagents: (i) trimethyl orthoformate, Montmorillonite K-10; (ii) *N*-BOC ethyl isonipocotate/KHMDS, THF, 0 °C; (iii) KHMDS, THF, 0 °C; (iv) $H_2NNH_2 \cdot H_2O$, MeOH; (v) HCl, EtOAc; (vi) $PhCH_2CH_2Br$, Et-*i*-Pr_2N, DMF, 60 °C.

Scheme 7[a]



[a] Reagents: (i) (a) TBAF, THF, (b) EtI, $CHCl_3$; (ii) HCl, ether; (iii) $PhCH_2Br$, Et-*i*-Pr_2N, DMF; (iv) $H_2NNH_2 \cdot H_2O$, MeOH.

Scheme 8[a]

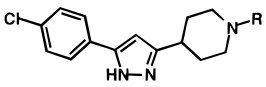


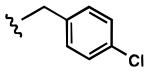
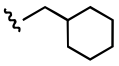
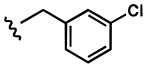
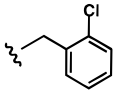
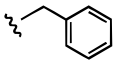
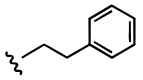
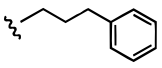
[a] Reagents: (i) $H_2NOH \cdot H_2Cl$, Et_3N, MeOH; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C; (iii) guanidine hydrochloride, NaO-*i*-Pr, *i*-PrOH, reflux.

philic benzene ring is optimal, with the phenylpropyl analogue **11** losing 20-fold in binding to hD4, with no change at hD2, giving a compound with a poorer profile than the lead.

The lipophilic group at the other end of the molecule is also important for binding (Table 3). When the 4-chlorophenyl ring attached to the pyrazole is replaced with a simple methyl group (**12**), binding to hD4 is reduced by a factor of 50 compared to the analogous compound (**9**). Again, the chlorine atom on this benzene ring is not required for binding, with removal giving a compound (**13**) with the same affinity for hD4 as that of compound **9**. However, there is a doubling of hD2 affinity on removal of this chlorine atom, so selectivity is correspondingly reduced. The attachment of the benzene ring directly to the pyrazole is important, with the homologous benzylpyrazole **14** losing 15-fold in hD4 binding, despite the fact that the distance (in number of atoms) between the two benzene rings is the same as for compound **10**. Since it had been established that the best substituent on the basic nitrogen is phenethyl,

Table 2. Substitution on the Basic Nitrogen

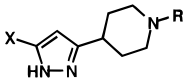


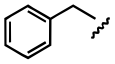
		K_i (nM) [a]		
Number	R	hD2	hD3	hD4
3		240	820	61
4	H	>1800	>4400	>3300
5	Me	>590	>1900	1200
6		120	720	13
7		570	4300	60
8		700	1300	20
9		125	160	9.1
10		520	>4000	5.5
11		560	870	110

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

further changes to the group attached to the pyrazole were performed with this arrangement. Reduction of the benzene ring to a cyclohexyl group (**15**) has little effect on hD4 binding but gives a marked increase in affinity at hD2, reducing selectivity. A similar effect is seen when the benzene ring is replaced with a thiophene

Table 3. Aromatic Substituent on the Pyrazole



Number	X	R	K_i (nM) [a] hD2	hD3	hD4
12	Me	$PhCH_2$	650	3400	470
13		$PhCH_2$	66	1400	11
14		$PhCH_2$	310	2100	160
15		$PhCH_2CH_2$	61	1200	10
16		$PhCH_2CH_2$	65	1100	19
17		$PhCH_2CH_2$	860	3600	22
18		$PhCH_2CH_2$	900	>4200	23
19		$PhCH_2CH_2$	1300	>4000	52

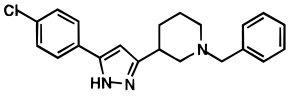
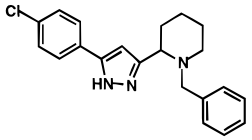
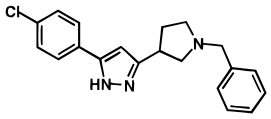
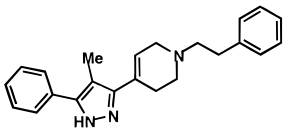
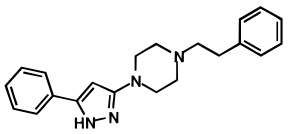
[a] Affinities at cloned human dopamine receptors stably expressed in cell lines.

(**16**). The three pyridyl isomers (**17**−**19**) have similar profiles, with a small reduction in binding to hD4 receptors when compared to the benzene ring, along with a smaller reduction in hD2 affinity. None of these changes show benefit over the (4-chlorophenyl)pyrazole present in the lead.

Similarly there is little gain to be had when the position and nature of the basic nitrogen in the piperidine ring are varied (Table 4). The 3- and 2-substituted piperidines **20** and **21** show marked reduction in hD4 affinity. The pyrrolidine **22**, in which the position of the basic nitrogen is intermediate between that of the 4-substituted (**9**) and 3-substituted (**20**) piperidines, has intermediate hD4 affinity as well. While the tetrahydropyridine **23** retains affinity, selectivity over hD2 is reduced, so there is no advantage with this change. The final alteration is the piperazine **24**. Again, affinity for the hD4 receptor is reduced over the corresponding piperidine **10**, as is binding at hD2. In this case, the reduction in affinity may be due to a reduction in the pK_a of the required basic nitrogen. For the piperidine **10** the pK_a is >7.5 (an exact measurement is not possible due to solubility problems), and for the piperazine **24** this is reduced to a pK_a of 7.2.

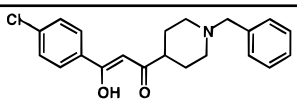
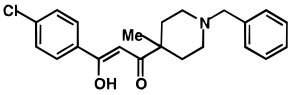
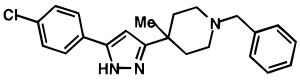
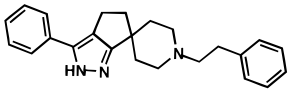
The importance of the pyrazole ring was investigated in two ways: by steric constraints to alter its conformation relative to the piperidine and by replacement with alternative aromatic heterocycles. The results of the first of these approaches is shown in Table 5. It was found that the β-diketone intermediate to the pyrazole also binds to dopamine receptors (**25**), but addition of a further methyl group in the 4-position of the piperidine severely reduces this binding. This is probably due to a conformational change of the diketone moiety relative to the piperidine. In the unmethylated compound **25**,

Table 4. Changes to the Piperidine

Number	Structure	K_i (nM) [a] hD2	hD3	hD4
20		960	240	410
21		3400	1800	4800
22		120	920	110
23		90	830	3.1
24		>1900	1200	23

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

Table 5. Conformational Restriction of the Piperidine

Number	Structure	K_i (nM) [a] hD2	hD3	hD4
25		120	510	12
26		410	510	350
27		240	1300	47
28		690	600	930

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

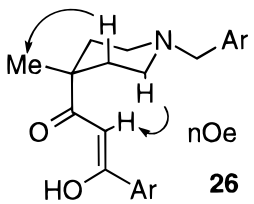
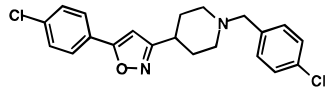
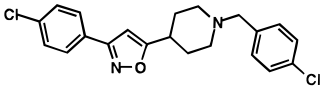
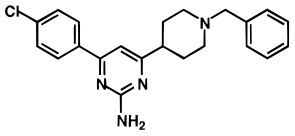
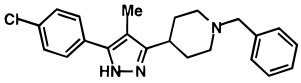
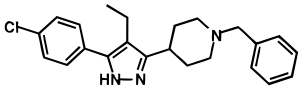
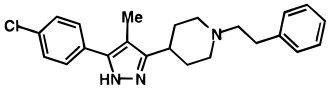
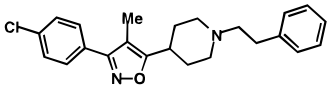
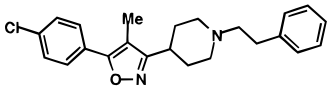
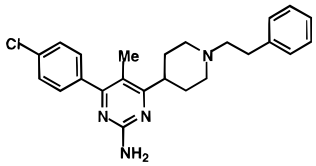


Figure 1. Solution conformation of the piperidine ring of **26** by NMR.

the diketone is equatorial to the ring, but NMR experiments (Figure 1) show that in the methylated analogue **26** it is the methyl group that becomes equatorial, with the diketone shifted to the axial conformation. For the methylated pyrazole **27** the effect on binding is less marked, but in this case molecular mechanics calculations suggest that there is little energy difference between the two ring flip conformations, and the pyrazole−equatorial conformation required for binding is energetically accessible. In the final compound (**28**) in

Table 6. Alternative Heterocycles

Number	Structure	K_i (nM) [a] hD2	hD3	hD4
29		160	430	44
30		130	80	3.6
31		8.6	140	1.0
32		200	430	1.6
33		35	46	1.5
34		290	1200	1.2
35		>1700	480	2.5
36		>1700	770	3.5
37		>1500	1100	4.7

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

Table 5, the pyrazole and the piperidine rings are locked essentially orthogonal to one another by the presence of an ethylene chain. This compound lacks activity despite the fact that alkylation at the 4-position of the piperidine **27** is allowed, as is methylation at the 4-position of the pyrazole **32** (Table 6). Again molecular mechanics calculations suggest little energetic difference between the conformers with the pyrazole axial or equatorial. However, for the equatorial conformer (Figure 2), the pyrazole nitrogens are locked on the same side of the piperidine as the basic nitrogen lone pair, an arrangement that might not be advantageous for binding (*vide infra*).

Changing the pyrazole to alternative heterocycles proved a more successful strategy. While one of the two regioisomeric isoxazoles (**29**) had a profile very similar to the lead, the other (**30**) gave almost 20-fold improvement in binding to the hD4 receptor, with a corresponding increase in selectivity. This may be due to the positioning of the heteroatoms within the ring, but isoxazoles **35** and **36**, which are regioisomers with similar binding affinities, suggest this is not the case. It is interesting to note that the proof of structure of these isomers by X-ray crystallography also showed differences in conformation around the bond joining the isoxazole to the piperidine (Figure 2). The solid state

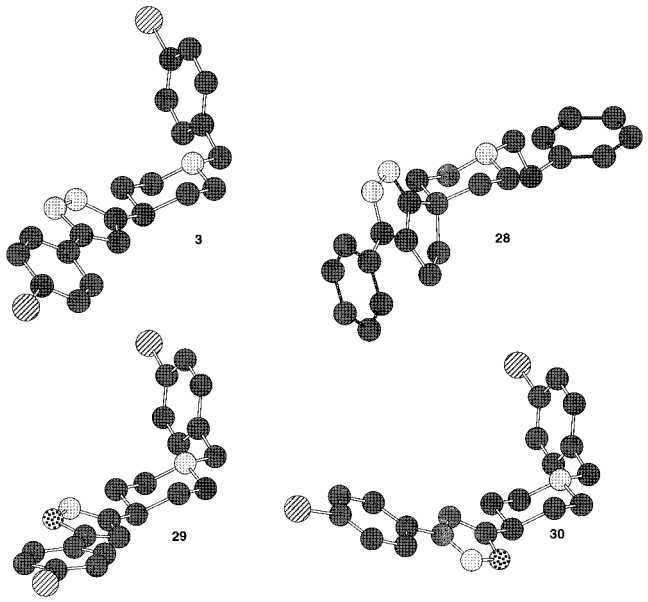


Figure 2. Conformations of compounds. **3**, **29**, and **30** are X-ray structures of oxalate salts. The oxalic acid and hydrogens are omitted for clarity. **28** is an energy-minimized structure (Chem3D v3.5.1) of the conformation with the pyrazole equatorial.

structure of isoxazole **29** is similar to that of pyrazole **3**, with the aromatic heterocycle coplanar with the C3−C4 bond of the piperidine and the heteroatoms of the isoxazole or pyrazole on the same face of the piperidine ring as the basic nitrogen lone pair. This is the same arrangement as for the equatorial conformer of the inactive spirofused compound **28** above. In contrast to this, the more active isomer (**30**) has the heterocycle turned approximately 180°, with the heteroatoms now toward the face opposite to the nitrogen lone pair. It may be that for optimal binding, the hD4 receptor prefers the nitrogen lone pair (or N−H bond of the protonated species) on the opposite face of the piperidine to the aromatic heteroatoms. The energetic price for achieving this in pyrazole **3** and isoxazole **29** is reflected in their relatively low affinities, and the inaccessibility of this conformer to the spirofused compound **28** precludes binding. Another successful replacement for the pyrazole is the aminopyrimidine **31** with nanomolar affinity at hD4, but selectivity over hD2 suffers in this case. Methylation (**32**) at the 4-position of the pyrazole also shows a beneficial effect on binding at hD4 receptors, but this time there is not the increase in hD2 binding, so the compound is highly selective. This again is probably a conformational effect rather that an increase in binding due to a lipophilic interaction, as the 4-ethylpyrazole **33**, in which the lipophilicity at the 4-position of the pyrazole is further increased, has similar hD4 affinity to the methyl analogue **32**.

Having established that the best basic nitrogen substituent for selectivity is a phenethyl group, that methylation at the 4-position of the heterocycle is beneficial to binding, and that isoxazole and aminopyrimidine offer improvements in affinity, combinations of these changes were made. The 4-methylpyrazole **34** has nanomolar affinity, with 200-fold selectivity over hD2, and the aminopyrimidine **37** has, if anything, better selectivity but somewhat reduced affinity. The best combination is seen in the isoxazoles **35** and **36**, both with low nanomolar affinity for the desired hD4 recep-

tor. Both have greater than 500-fold selectivity over the hD2 receptor, and one isomer (**36**) also has better than 200-fold selectivity over hD3.

This more selective isomer (**36**) has been further profiled pharmacologically and in pharmacokinetic studies. In D4 HEK cells isoxazole **36** (1 μM) alone had no effect but antagonized the dopamine (1 μM)-mediated inhibition of forskolin (10 μM)-induced elevation of cAMP levels.[22] Thus isoxazole **36** is an antagonist at the D4 receptor. It also has affinities weaker than micromolar at $5HT_{1A}$ and 5HT2 receptors. In rat it had 38% oral bioavailability after a 3 mg/kg dose, reaching a peak plasma concentration of 60 ng/mL with brain concentrations 10-fold higher than this at 630 ng/g. The half life in this species is 2 h.

Conclusions

A lead dopamine D4 ligand (**3**) has a number of important pharmacophoric features which have been explored to optimize dopamine D4 receptor affinity and selectivity. The lipophilic benzene rings at either end of the molecule are important for binding, and homologation of the benzyl group of the lead to a phenethyl group improves selectivity. The position of the basic nitrogen within a 6- or 5-membered ring has been explored and the 4-substituted piperidine found to be best for binding. The pyrazole can be replaced with a variety of other aromatic heterocycles or a β-diketone to retain or improve binding, but there are subtle conformational effects which can alter affinity at the hD4 receptor. By introduction of the best groups from the exploration of these structure−affinity relationship studies, the isoxazole **36** has been identified as an optimal ligand. Compound **36** not only is a high-affinity selective dopamine D4 antagonist but also has a good pharmacokinetic profile with high oral bioavailability and duration and very good brain penetration, making it an attractive tool to study the relevance and importance of the dopamine D4 receptor in the treatment of central nervous system disorders, particularly schizophrenia.

Experimental Section

Melting points were taken on a Reichert Thermovar apparatus and are uncorrected. Proton NMR spectra were measured on a Bruker AM 360 or AC 250 spectrometer, and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard; coupling constants are in hertz. Mass spectra were recorded on a VG 70/250 spectrometer. Merck Kieselgel (230−400) mesh was used for column chromatography. For reactions, dry solvents were used as bought from Aldrich. Organic solutions were dried with anhydrous magnesium sulfate. Elemental analyses were done by Butterworth Laboratories Ltd., Teddington, Middlesex, U.K.

2-(4-Chlorobenzylidene)quinuclidin-3-one (39). A solution of 3-quinuclidinone (**38**; 54.5 g, 0.34 mol), 4-chlorobenzaldehyde (84.0 g, 0.59 mol), and sodium hydroxide (3.50 g, 88 mmol) in EtOH (400 mL) was heated at reflux for 2.5 h. The mixture was cooled, and addition of H_2O (100 mL) caused the product to precipitate as an orange solid. The precipitate was collected and washed with 1:1 EtOH:H_2O (400 mL). The mother liquors stood for 2 days, after which time further precipitated material was collected. The orange solid was redissolved in CH_2Cl_2 (800 mL) and washed with H_2O (200 mL). The organic phase was dried and evaporated to give **39** as a bright yellow powder (86.2 g, 76%): mp 108−110 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.99−2.05 (4 H, m, NCH_2CH_2), 2.63 (1 H, quintet, J = 2.9, CHCO), 2.92−3.01 (2 H, m, NCH), 3.11−3.19 (2 H, m, NCH), 6.95 (1 H, s, C=CH), 7.33 (2 H, d, J = 8.6, ArH *o* to Cl), 7.98 (2 H, d, J = 8.6, ArH *m* to Cl); MS (CI^+; NH_3) m/z = 248 ($M^+ + H$).

3-(4-Piperidinyl)-5-(4-chlorophenyl)pyrazole (4). A mixture of **39** (35.0 g, 141 mmol), KOH (15.0 g, 267 mmol), and hydrazine hydrate (11.0 mL, 354 mmol) in ethylene glycol (100 mL) was heated at 110 °C for 15 min to produce a clear dark brown solution. Hydrazine hydrate and H_2O were distilled from the solution over 1 h at 110−195 °C. The brown solution was then heated at reflux for 3 h. The mixture was cooled to room temperature and diluted with H_2O (300 mL). The resulting white precipitate was collected and washed with H_2O (500 mL) and EtOAc (200 mL). The white powder was dried to give **4** (31.5 g, 85%): mp 174−176 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.52 (2 H, qd, J = 12, 4, $CHCH_AH_B$), 1.85 (2 H, d, J = 10, $CHCH_AH_B$), 2.56 (2 H, td, J = 12, 2, NCH_AH_B), 2.71 (1 H, tt, J = 8.1, 4.5, CH_2CH), 2.99 (2 H, d, J = 12, NCH_AH_B), 6.48 (1 H, s, N=CCH), 7.44 (2 H, d, J = 8.6, ArH *o* to Cl), 7.79 (2 H, d, J = 8.6, ArH *m* to Cl); MS (CI^+; NH_3) m/z = 262 ($M^+ + H$). Anal. ($C_{14}H_{16}ClN_3 \cdot 0.5H_2O$) C, H, N.

3-(1-(4-Chlorobenzyl)-4-piperidinyl)-5-(4-chlorophenyl)-pyrazole (3). A solution of **4** (1.50 g, 5.7 mmol), Et_3N (1.60 mL, 11.6 mmol), and 4-chlorobenzyl chloride (0.92 g, 5.7 mmol) in 3:1 CH_2Cl_2:DMF (20 mL) was stirred at room temperature for 4.5 h. CH_2Cl_2 was removed by evaporation, H_2O (25 mL) was added, and the mixture was extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with brine, dried, and evaporated to give an off-white solid. Recrystallization yielded the title compound as fine, white needles (0.575 g, 26%): mp 179−181 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.71 (2 H, qd, J = 12, 3, $CHCH_AH_B$), 1.84 (2 H, d, J = 11, $CHCH_AH_B$), 1.92 (2 H, t, J = 11, NCH_AH_B), 2.41−2.55 (1 H, m, CH_2CH), 2.84 (2 H, d, J = 11, NCH_AH_B), 3.44 (2 H, s, NCH_2Ar), 6.21 (1 H, s, N=CCH), 7.30−7.21 (6 H, m, ArH), 7.61 (2 H, d, J = 8.1, ArH), 11.6−12.0 (1 H, br s, NH); MS (CI^+; NH_3) m/z = 386 ($M^+ + H$). Anal. ($C_{21}H_{21}Cl_2N_3$) C, H, N.

The following compounds were made in the same way as **3** using the appropriate alkyl halide, with yields quoted for the final step.

3-(1-(Cyclohexylmethyl)-4-piperidinyl)-5-(4-chlorophenyl)pyrazole (6): white granules (5%), mp 186−187 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.88 (2 H, q, J = 11.6, CH_2), 1.10−1.29 (3 H, m, methylenes), 1.47−1.53 (1 H, m, NCH_2CH), 1.69−1.99 (11 H, m, methylenes), 2.14 (2 H, d, J = 7.0, NCH_2CH), 2.62 (1 H, tt, J = 11.5, 3.9, NCH_2CH_2CH), 2.93 (2 H, d, J = 11, NCH_AH_B), 6.33 (1 H, s, N=CCH), 7.33 (2 H, d, J = 8.4, ArH *o* to Cl), 7.65 (2 H, d, J = 8.4, ArH *m* to Cl); MS (CI^+; NH_3) m/z = 358 ($M^+ + H$). Anal. ($C_{21}H_{28}N_3Cl$) C, H, N.

3-(1-(3-Chlorobenzyl)-4-piperidinyl)-5-(4-chlorophenyl)-pyrazole (7): white granules (66%), mp 134−136 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.74 (2 H, qd, J = 12, 4, $CHCH_AH_B$), 1.87 (2 H, d, J = 12, $CHCH_AH_B$), 1.97 (2 H, t, J = 12, NCH_AH_B), 2.56 (1 H, tt, J = 12, 4, CH_2CH), 2.87 (2 H, d, J = 12, NCH_AH_B), 3.46 (2 H, s, NCH_2Ar), 6.31 (1 H, s, N=CCH), 7.17−7.33 (6 H, m, ArH), 7.62 (2 H, d, J = 8.4, ArH *m* to Cl), 10.07 (1 H, br s, NH); MS (CI^+; NH_3) m/z = 386 ($M^+ + H$). Anal. ($C_{21}H_{21}N_3Cl_2$) C, H, N.

3-(1-(2-Chlorobenzyl)-4-piperidinyl)-5-(4-chlorophenyl)-pyrazole (8): fine, pale yellow crystals (24%), mp 137−139 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.74 (2 H, dq, J = 3.5, 12, $CHCH_AH_B$), 1.92 (2 H, br d, J = 12, $CHCH_AH_B$), 2.19 (2 H, dt, J = 3.5, 11, NCH_AH_B), 2.67 (1 H, m, CH_2CH), 2.91 (2 H, br d, J = 12, NCH_AH_B), 3.58 (2 H, s, $ArCH_2$), 6.53 (1 H, s, N=CCH), 7.26−7.36 (2 H, m, ArH), 7.42−7.44 (3 H, m, ArH), 7.52 (1 H, dd, J = 2, 7, ArH), 7.76−7.80 (2 H, d, J = 8, ArH), 12.69 (1 H, br s, NH); MS (CI^+; NH_3) m/z = 386 ($M^+ + H$). Anal. ($C_{21}H_{21}N_3Cl_2$) C, H, N.

3-(1-Benzyl-4-piperidinyl)-5-(4-chlorophenyl)pyrazole (9): white needles (33%), mp 164−167 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.74 (2 H, qd, J = 12, 4, $CHCH_AH_B$), 1.86 (2 H, d, J = 10, $CHCH_AH_B$), 1.97 (2 H, t, J = 11, NCH_AH_B), 2.55 (1 H, tt, J = 11.6, 4, CH_2CH), 2.55 (2 H, d, J = 12, NCH_AH_B), 3.50 (2 H, br s, NCH_2Ph), 6.29 (1 H,

s, N=CCH), 7.18−7.38 (7 H, m, ArH), 7.61 (2 H, d, J = 8.3, ArH); MS (CI^+; NH_3) m/z = 352 (M^+ + H). Anal. ($C_{21}H_{22}N_3Cl$) C, H, N.

3-(1-(2-Phenylethyl)-4-piperidinyl)-5-(4-chlorophenyl)-pyrazole (10): beige granules (26%), mp 169−171 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.83 (2 H, qd, J = 12, 4, CHCH_AH$_B$), 2.00 (2 H, d, J = 11, CHCH$_A$$H_B$), 2.14 (2 H, t, J = 12, NCH_AH$_B$), 2.61−2.65 (2 H, m, NCH$_2$CH_2Ar), 2.70 (1 H, tt, J = 11.8, 3.9, CH$_2$CH), 2.81−2.86 (2 H, m, NCH_2CH$_2$-Ar), 3.08 (2 H, d, J = 12, NCH$_A$$H_B$), 6.34 (1 H, s, N=CCH), 7.35−7.16 (7 H, m, ArH), 7.69 (2 H, d, J = 8.4, ArH m to Cl); MS (CI^+; NH_3) m/z = 366 (M^+ + H). Anal. ($C_{22}H_{24}N_3Cl$) C, H, N.

3-(1-(3-Phenyl-1-propyl)-4-piperidinyl)-5-(4-chlorophenyl)pyrazole (11): fine, white crystals (57%), mp 165−167 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.61−1.78 (4 H, m, CHCH_AH$_B$, CH$_2$CH_2CH$_2$), 1.91 (2 H, br d, J = 12, CHCH$_A$$H_B$), 1.99 (2 H, t, J = 12, NCH_AH$_B$), 2.31 (2 H, t, J = 7, CH_2CH$_2$CH$_2$), 2.61 (2 H, t, J = 7, CH$_2$CH$_2$CH_2), 2.72 (1 H, tt, J = 12, 4, CH$_2$CH), 2.92 (2 H, br d, J = 12, NCH$_A$$H_B$), 6.51 (1 H, s, N=CCH), 7.14−7.22 (5 H, m, ArH), 7.44 (2 H, d, J = 7, ArH o to Cl), 7.79 (2 H, d, J = 7, ArH m to Cl), 12.67 (1 H, s, NH); MS (CI^+; NH_3) m/z = 380 (M^+ + H). Anal. ($C_{23}H_{26}N_3Cl$) C, H, N.

3-(1-Methyl-4-piperidinyl)-5-(4-chlorophenyl)pyrazole (5). Trifluoroacetic acid (20 mL, 260 mmol) was added dropwise over 1 h to a stirred suspension of **4** (1.00 g, 3.8 mmol), sodium borohydride (0.73 g, 19.1 mmol), and paraformaldehyde (1.15 g, 38.2 mmol) in dry THF (50 mL) under nitrogen. After stirring for 20 h the mixture was poured into ice-cold 10% aqueous NaOH (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried, and evaporated. Recrystallization yielded the title compound as white cubes (0.501 g, 48%): mp 209−211 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.77 (2 H, qd, J = 12, 4, CHCH_AH$_B$), 1.99 (2 H, d, J = 12, CHCH$_A$$H_B$), 2.07 (2 H, t, J = 12, NCH_AH$_B$), 2.30 (3 H, s, NCH$_3$), 2.65 (1 H, tt, J = 12, 4, CH$_2$CH), 2.91 (2 H, apparent d, J = 12, NCH$_A$$H_B$), 6.32 (1 H, s, N=CCH), 7.32 (2 H, d, J = 8.5, ArH), 7.72 (2 H, d, J = 8.5, ArH), 12.5 (1 H, br s, NH); MS (CI^+; NH_3) m/z = 276 (M^+ + H). Anal. ($C_{15}H_{18}N_3Cl$) C, H, N.

General Route for the Synthesis of Pyrazoles *via* β-Diketones. 1-Benzyl-4-(3-hydroxy-1-oxo-3-(4-chlorophenyl)prop-2-en-1-yl)piperidine (25). n-BuLi (28 mL, 1.6 M in hexanes, 44.8 mmol) was added to i-Pr$_2$NH (6.2 mL, 44.8 mmol) in THF (150 mL) at 0 °C. The solution was stirred at 0 °C for 15 min and then cooled to −78 °C, and a solution of 4-chloroacetophenone (6.8 g, 44 mmol) in THF (10 mL) was added over 5 min. In a separate vessel, carbonyldiimidazole (3.89 g, 24 mmol) was added to 1-(*tert*-butyloxycarbonyl)-4-piperidinecarboxylic acid (**41**; 5 g, 21.8 mmol) in THF (100 mL). After 45 min, the latter solution was cannulated into the former, stirred for 45 min at −78 °C, and then warmed to room temperature. EtOAc was added and the mixture washed with 1 M citric acid, saturated $NaHCO_3$ solution, and brine, dried, and evaporated to give a mixture of **59** and 4-chloroacetophenone: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.47 (9 H, s , t-Bu), 1.6−1.7 (2 H, m, CHCH_AH$_B$), 1.8−1.9 (2 H, m, CHCH$_A$$H_B$), 2.4−2.5 (1 H, m, C$HCH_2$), 2.7−2.8 (2 H, m, NC$H_AH_B$), 4.1−4.2 (2 H, m, N CH$_A$$H_B$), 6.14 (1 H, s, COCHCO), 7.42 (2 H, d, J = 7, ArH o to Cl), 7.81 (2 H, d, J = 7, ArH m to Cl), 16.0 (1 H, br s, OH); MS (CI^+; NH_3) m/z = 366 (M^+ + H).

A saturated solution of HCl in EtOAc (50 mL) was added to the crude oil, and the mixture stirred at room temperature for 30 min and then stood at 0 °C for 1 h. The resulting solid was collected, washed with EtOAc, and dried to give 4-(1-(3-hydroxy-1-oxo-3-(4-chlorophenyl)-2-propenyl))piperidine hydrochloride (**42**) as an off-white solid (5.1 g, 78%): ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.7−2.1 (4 H, m, CHCH_2), 2.7−2.8 (1 H, m, CHCH$_2$), 3.3−3.5 (4 H, m, NCH$_2$), 6.6 (1 H, s, COCHCO), 7.62 (2 H, d, J = 8, ArH o to Cl), 7.98 (2 H, d, J = 8, ArH m to Cl); MS (CI^+; NH_3) m/z = 266 (M^+ + H).

A 3 g (10 mmol) portion of this solid was suspended in DMF (30 mL) and CH_2Cl_2 (30 mL); then Et_3N (3.1 mL, 22 mmol) and benzyl bromide (1.86 g, 10.9 mmol) were added. After stirring for 24 h the mixture was evaporated, diluted with EtOAc, washed with H_2O and brine, dried, and evaporated to give **25** (1.97 g, 56%) as white needles: mp 84−86 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.8−2.0 (4 H, m, CH_2CH), 2.0−2.2 (2 H, m, NCH_AH$_B$), 2.3−2.4 (1 H, m, CHCH$_2$), 3.0 (2 H, d, J = 12, NCH$_A$$H_B$), 3.59 (2 H, s, ArCH$_2$), 6.15 (1 H, s, COCHCO), 7.2−7.4 (5 H, m, Ph), 7.42 (2 H, d, J = 8.6, ArH o to Cl), 7.81 (2 H, d, J = 8.6, ArH m to Cl), 15.9 (1 H, br s, OH); MS (CI^+; NH_3) m/z = 356 (M^+ + H). Anal. ($C_{21}H_{22}ClNO_2$) C, H, N.

3-(1-Benzyl-4-piperidinyl)-5-(4-chlorophenyl)pyrazole (9). A mixture of **25** (0.5 g, 1.4 mmol) and hydrazine hydrate (0.1 mL, 2 mmol) in EtOH (5 mL) was stirred at room temperature overnight. H_2O was added, the mixture was extracted with EtOAc (×2), and the combined organic layers were washed with H_2O and brine, dried, evaporated, and recrystallized from EtOH/H_2O to give **9** (0.39 g, 79%).

The following were made in the same way, using the appropriate ketone and alkylating reagent.

3-(1-Benzyl-4-piperidinyl)-5-methylpyrazole (12): oxalate salt (19% from **41**), mp 120−122 °C (from i-PrOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.8−1.9 (2 H, m, CH_AH$_B$CH), 2.02 (2 H, d, J = 11, CH$_A$$H_B$CH), 2.15 (3 H, s, Me), 2.75−2.85 (1 H, m, CHCH$_2$), 2.95 (2 H, t, J = 12, NCH_AH$_B$), 3.3 (2 H, d, J = 12, NCH$_A$$H_B$), 4.21 (2 H, s, NCH$_2$Ph), 5.81 (1 H, s, N=CCH), 7.4−7.5 (5 H, m, Ph); MS (CI^+; NH_3) m/z = 256 (M^+ + H). Anal. ($C_{16}H_{21}N_3$·1.5$C_2H_2O_4$) C, H, N.

3-(1-Benzyl-4-piperidinyl)-5-phenylpyrazole (13): white plates (39% from **41**), mp 130−131 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.7−1.8 (2 H, m, CH_AH$_B$CH), 1.9 (2 H, d, J = 12, CH$_A$$H_B$CH), 2.0−2.1 (2 H, m, NC$H_AH_B$), 2.6−2.7 (1 H, m, C$HCH_2$), 2.9 (2 H, d, J = 12, NCH$_A$$H_B$), 3.48 (2 H, s, NCH$_2$Ph), 6.49 (1 H, s, N=CCH), 7.2−7.4 (8 H, m, ArH), 7.75 (2 H, d, J = 7, ArH); MS (CI^+; NH_3) m/z = 318 (M^+ + H). Anal. ($C_{21}H_{23}N_3$·0.6H_2O) C, H, N.

3-(1-(2-Phenylethyl)-4-piperidinyl)-5-cyclohexylpyrazole (15): white needles (8% from **41**), mp 102−104 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.2−1.4 (5 H, m, CH$_2$), 1.5−1.6 (2 H, m, CH$_2$), 1.6−1.8 (2 H, m, CH$_2$), 2.02 (2 H, t, J = 11, NCH_AH$_B$), 2.4−2.5 (4 H, m, CH$_2$), 2.7−2.8 (1 H, m, CHCH$_2$), 2.96 (2 H, d, J = 11, NCH$_A$$H_B$), 5.79 (1 H, s, N=CCH), 7.2−7.4 (5 H, m, ArH), 12.03 (1 H, s, NH); MS (CI^+; NH_3) m/z = 323 (M^+ + H). Anal. ($C_{22}H_{31}N_3$·0.2H_2O) C, H, N.

3-(1-(2-Phenylethyl)-4-piperidinyl)-5-(2-thienyl)pyrazole (16): white crystals (4% from **41**), mp 183−185 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.6−1.7 (2 H, m, CHCH_AH$_B$), 1.9 (2 H, d, J = 12, CHCH$_A$$H_B$), 2.06 (2 H, t, J = 12, NCH_AH$_B$), 2.53 (2 H, t, J = 8, PhCH$_2$CH_2), 2.6−2.7 (1 H, m, CHCH$_2$), 2.75 (2 H, t, J = 8, PhCH$_2$), 3.00 (2 H, d, J = 12, NCH$_A$$H_B$), 6.36 (1 H, s, N=CCH), 7.05−7.38 (8 H, m, ArH), 12.6 (1 H, br s, NH); MS (CI^+; NH_3) m/z = 338 (M^+ + H). Anal. ($C_{20}H_{23}N_3S$) C, H, N.

3-(1-(2-Phenylethyl)-4-piperidinyl)-5-(2-pyridyl)pyrazole (17): orange cubes (3% from **41**), mp 155−157 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.6−1.7 (2 H, m, CHCH_AH$_B$), 1.92 (2 H, d, J = 11, CHCH$_A$$H_B$), 2.08 (2 H, t, J = 11, NCH_AH$_B$), 2.53 (2 H, t, J = 7.1, PhCH$_2$), 2.56−2.64 (1 H, m, CHCH$_2$), 2.75 (2 H, t, J = 7.1, PhCH$_2$CH_2), 3.00 (2 H, d, J = 11, NCH$_A$$H_B$), 6.59 (1 H, s, N=CCH), 7.1−7.3 (6 H, m, ArH), 7.76−7.82 (1 H, m, pyridine-H), 7.84−7.93 (1 H, m, pyridine-H), 8.52−8.60 (1 H, m, pyridine H-6), 12.75 (1 H, s, NH); MS (CI^+; NH_3) m/z = 333 (M^+ + H). Anal. ($C_{21}H_{24}N_4$) C, H, N.

3-(1-(2-Phenylethyl)-4-piperidinyl)-5-(3-pyridyl)pyrazole (18): off-white plates (13% from **41**), mp 151−152 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.6−1.7 (2 H, m, CHCH_AH$_B$), 1.92 (2 H, d, J = 11, CHCH$_A$$H_B$), 2.09 (2 H, t, J = 11, NCH_AH$_B$), 2.55 (2 H, t, J = 7.1, PhCH$_2$), 2.56−2.64 (1 H, m, CHCH$_2$), 2.76 (2 H, t, J = 7.1, PhCH$_2$CH_2), 3.02 (2 H, d, J = 11, NCH$_A$$H_B$), 6.61 (1 H, s, N=CCH), 7.1−7.3 (6 H, m, ArH), 7.38−7.42 (1 H, m, pyridine-H), 8.11 (1 H, d, J = 7.9, pyridine H-6), 8.47 (1 H, d, J = 2, pyridine H-2), 12.76 (1 H, s, NH); MS (CI^+; NH_3) m/z = 333 (M^+ + H). Anal. ($C_{21}H_{24}N_4$·H_2O) C, H, N.

3-(1-(2-Phenylethyl)-4-piperidinyl)-5-(4-pyridyl)pyrazole (19): brown plates (9% from **41**), mp 142−144 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.6−1.7 (2 H, m, CHCH_AH$_B$), 1.92 (2 H, d, J = 11, CHCH$_A$$H_B$), 2.09 (2 H, t, J =

11, NCH_AH_B), 2.54 (2 H, t, $J = 7$, $PhCH_2$), 2.6−2.7 (1 H, m, $CHCH_2$), 2.76 (2 H, t, $J = 7$, $PhCH_2CH_2$), 3.02 (2 H, d, $J = 11$, NCH_AH_B), 6.67 (1 H, s, N=CCH), 7.1−7.3 (5 H, m, ArH), 7.72 (1 H, d, $J = 5.4$, pyridine H-3), 8.58 (1 H, d, $J = 5.4$, pyridine H-2), 12.92 (1 H, s, NH); MS (CI^+; NH_3) $m/z = 333$ ($M^+ + H$). Anal. ($C_{21}H_{24}N_4$) C, H, N.

3-(1-Benzyl-3-piperidinyl)-5-(4-chlorophenyl)pyrazole (20): white cubes (7% from piperidine-3-carboxylic acid), mp 215−218 °C (from EtOH/EtOAc); ^1H NMR (360 MHz, $CDCl_3/CD_3OD$) δ 2.01−2.26 (4 H, m, piperidinyl CH), 3.28−3.37 (1 H, m, piperidinyl CH), 4.47 (1 H, br d, $J = 11$, piperidinyl CH), 3.57−3.64 (2 H, m, piperidinyl CH), 3.84−3.90 (1 H, m, piperidinyl CH), 4.43−4.49 (2 H, m, NCH_2Ph), 7.05 (1 H, s, N=CCH), 7.44−7.52 (5 H, m, ArH), 7.69−7.40 (4 H, m, ArH); MS (CI^+; NH_3) $m/z = 352$ ($M^+ + H$). Anal. ($C_{21}H_{22}N_3Cl \cdot 2HBr \cdot 0.25H_2O$) C, H, N.

3-(1-Benzyl-2-piperidinyl)-5-(4-chlorophenyl)pyrazole (21): white needles (6% from ethylpiperidine-2-carboxylate), mp 174−176 °C (from EtOH); ^1H NMR (360 MHz, $CDCl_3$) δ 1.30−1.44 (1 H, m, piperidinyl CH), 1.48−1.68 (2 H, m, piperidinyl CH), 1.70−1.85 (2 H, m, piperidinyl CH), 1.86−1.98 (1 H, m, piperidinyl CH), 2.05 (1 H, apparent t, $J = 10$, piperidinyl CH), 3.03 (2 H, apparent t, $J = 11$, NCH_2Ph), 3.45 (1 H, br d, $J = 9$, piperidinyl CH), 3.82 (1 H, d, $J = 13$, NCHAr), 6.54 (1 H, s, N=CCH), 7.16−7.32 (5 H, m, ArH), 7.33−7.37 (2 H, m, ArH), 7.69−7.40 (2 H, d, $J = 9$, ArH); MS (CI^+; NH_3) $m/z = 352$ ($M^+ + H$). Anal. ($C_{21}H_{22}N_3Cl$) C, H, N.

3-(1-(2-Phenylethyl)-1,2,3,6-tetrahydropyrid-4-yl)-4-methyl-5-phenylpyrazole (23): white crystals (6% from BOC-protected 1,2,3,4-tetrahydropyridine-4-carboxylic acid), mp 165−167 °C (from EtOH); ^1H NMR (360 MHz, DMSO-d_6) δ 2.18 (3 H, s, Me), 1.6−1.7 (2 H, m, $NCH_2CH_AH_B$), 2.48−2.52 (2 H, m, CH_2), 2.6−2.7 (4 H, m, CH_2), 2.80 (2 H, t, $J = 6.8$, CH_2), 3.17 (2 H, d, NCH_2CH), 5.98 (1 H, t, $J = 2.8$, NCH_2CH), 7.2−7.6 (10 H, m, ArH), 12.7 (1 H, s, NH); MS (CI^+; NH_3) $m/z = 344$ ($M^+ + H$). Anal. ($C_{23}H_{25}N_3$) C, H, N.

3-(1-Benzyl-4-piperidinyl)-4-methyl-5-(4-chlorophenyl)-pyrazole (32): colorless plates (20% from **41**), mp 188−190 °C (from EtOH); ^1H NMR (360 MHz, DMSO-d_6) δ 1.61 (2 H, d, $J = 12$, $CHCH_AH_B$), 1.90 (2 H, q, $J = 12$, $CHCH_AH_B$), 2.04−2.18 (5 H, m, NCH_AH_B, CH_3), 2.60−2.74 (1 H, m, CH_2CH), 2.99 (2 H, d, $J = 11$, NCH_AH_B), 3.53 (2 H, s, CH_2Ar), 7.12−7.34 (7 H, m, ArH), 7.54 (2 H, d, $J = 8$, ArH *m* to Cl), 11.98 (1 H, br s, NH); MS (CI^+; NH_3) $m/z = 366$ ($M^+ + H$). Anal. ($C_{22}H_{24}ClN_3$) C, H, N.

3-(4-(1-(2-Phenylethyl)piperidinyl))-4-methyl-5-(4-chlorophenyl)pyrazole (34): white needles (18% from **41**), mp 181−183 °C (from EtOH/H_2O); ^1H NMR (360 MHz, DMSO-d_6) δ 1.92−2.02 (4 H, m, $CHCH_2$), 2.14 (3 H, s, CH_3), 2.15−2.18 (2 H, m, NCH_AH_B), 2.65−2.77 (3 H, m, CH_2CH, CH_2Ph), 2.83−2.87 (2 H, m, NCH_2CH_2Ph), 3.16 (2 H, br d, $J = 12$, NCH_AH_B), 7.18−7.22 (3 H, m, ArH), 7.25−7.31 (2 H, m, ArH), 7.33−7.40 (2 H, m, ArH), 7.50 (2 H, d, $J = 8$, ArH); MS (CI^+; NH_3) $m/z = 380$ ($M^+ + H$). Anal. ($C_{23}H_{26}ClN_3 \cdot 0.4H_2O$) C, H, N.

3-(1-Benzyl-4-piperidinyl)-5-benzylpyrazole (14). Methyllithium (17.4 mL, 1.4 M in ether, 24.3 mmol) was added to a mixture of 3-phenyl-2-[(trimethylsilyl)oxy]propene and 1-phenyl-2-[(trimethylsilyl)oxy]propene[23] (5 g, 24.3 mmol, 1:1 mixture) in ether (150 mL) at room temperature and stirred for 1 h. Meanwhile a mixture of isonipecotic acid (2.8 g, 12.2 mmol) and carbonyldiimidazole (1.98 g, 12.2 mmol) was stirred in THF (80 mL) at room temperature for 15 min and cooled to −78 °C, and then the enolate solution was added *via* cannula. After 30 min at −78 °C, the mixture was warmed to room temperature for 30 min and then poured into 1 M citric acid (250 mL). The mixture was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with $NaHCO_3$, H_2O, and brine, dried, evaporated, and purified by flash chromatography eluting with hexanes:EtOAc (5:1, v/v) to give a mixture of **47** and phenylacetone as the less polar product and then **46** (1.153 g, 27%) as an oil: ^1H NMR (360 MHz, $CDCl_3$) δ 1.50 (9 H, s, *t*-Bu), 1.56 (2 H, d, $J = 12$, $CHCH_AH_B$), 1.6−1.8 (2 H, m, $CHCH_AH_B$), 1.87 (2 H, s, CH_2Ph), 2.2−2.3 (1 H, m, $CHCH_2$), 2.43 (2 H, t, $J = 12$, NCH_AH_B), 4.04 (2 H, d, $J = 12$, NCH_AH_B), 7.2−7.5 (5 H, m, Ph); MS (CI^+; NH_3) $m/z = 346$ ($M^+ + H$). (In this experiment, the yield of **47** was not determined. However, when **41**, carbonyldiimidazole, and phenylacetone were reacted under the conditions used in the general route for the synthesis of pyrazole *via* β-diketones, **47** was obtained in 36% yield.)

The oil **46** (1.15 g, 3.3 mmol) was stirred in MeOH (50 mL) with hydrazine hydrate (0.67 g, 13.3 mmol) at room temperature for 45 min and evaporated to give 3-(1-(*tert*-butyloxycarbonyl)-4-piperidinyl)-5-benzylpyrazole (1.1 g) as an oil: ^1H NMR (250 MHz, DMSO-d_6) δ 1.4 (9 H, s, *t*-Bu), 1.5−1.6 (2 H, m, $CHCH_AH_B$), 1.8 (2 H, d, $J = 12$, $CHCH_AH_B$), 2.7−2.9 (3 H, m, NCH_AH_B, $CHCH_2$), 3.8 (2 H, s, CH_2Ph), 3.9 (2 H, d, $J = 12$, NCH_AH_B), 5.8 (1 H, s, N=CCH), 7.1−7.4 (5 H, m, Ph).

A saturated solution of HCl in EtOAc (20 mL) was added, the mixture was warmed to reflux for 2 min and cooled, and the resulting solid was collected and washed with ether to give 3-(4-piperidinyl)-5-benzylpyrazole hydrochloride (680 mg) as a solid: ^1H NMR (250 MHz, DMSO-d_6) δ 1.7−1.8 (2 H, m, $CHCH_AH_B$), 2.0 (2 H, d, $J = 12$, $CHCH_AH_B$), 2.8−3.0 (3 H, m, NCH_AH_B, $CHCH_2$), 3.25 (2 H, d, $J = 12$, NCH_AH_B), 3.9 (2 H, s, CH_2Ph), 5.9 (1 H, s, N=CCH), 7.1−7.4 (5 H, m, Ph).

A 300 mg (1.1 mmol) portion of this solid was dissolved in DMF (10 mL), and Et-*i*-Pr_2N (280 mg, 2.2 mmol) and benyl bromide (204 mg, 1.2 mmol) were added. After 16 h H_2O was added, the mixture was extracted with EtOAc (×3), and the combined organic layers washed with H_2O and brine, dried, evaporated, and purified by flash chromatography eluting with CH_2Cl_2:MeOH:880 NH_3 (94:5:1, v/v) to give the title compound as an oil (150 mg, 30% over three steps): oxalate salt, mp 98−101 °C (from EtOH); ^1H NMR (360 MHz, DMSO-d_6) δ 1.8−1.9 (2 H, m, $CHCH_AH_B$), 2.0 (2 H, d, $J = 12$, $CHCH_AH_B$), 2.7−2.8 (1 H, m, $CHCH_2$), 2.9 (2 H, t, $J = 12$, NCH_AH_B), 3.2 (2 H, d, $J = 12$, NCH_AH_B), 3.87 (2 H, s, CH_2Ph), 4.16 (2 H, s, CH_2Ph), 5.81 (1 H, s, N=CCH), 7.1−7.5 (10 H, m, Ph); MS (CI^+; NH_3) $m/z = 332$ ($M^+ + H$). Anal. ($C_{22}H_{25}N_3 \cdot C_2H_2O_4 \cdot 0.2H_2O$) C, H, N.

3-(1-Benzyl-3-pyrrolidinyl)-5-(4-chlorophenyl)pyrazole (22). A solution of methyl 1-benzyl-5-oxo-3-pyrrolidinecarboxylate (**48**; 10.0 g, 43 mmol) and KOH (2.88 g, 52 mmol) in 1:1 EtOH:H_2O (100 mL) was stirred at room temperature for 18 h. EtOH was removed by evaporation, and the aqueous concentrate was washed with Et_2O (20 mL) prior to acidification with concentrated hydrochloric acid (pH 2) and extraction with EtOAc (2 × 50 mL). The combined extracts were dried and concentrated to give 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid (**49**) as a white powder (9.00 g, 96%): ^1H NMR (360 MHz, $CDCl_3$) δ 2.68 (1 H, dd, $J = 17$, 10, $COCH_AH_B$), 2.78 (1 H, dd, $J = 17$, 7, $COCH_AH_B$), 3.14−3.23 (1 H, m, $CHCO_2H$), 3.44−3.54 (2 H, m, NCH_2CH), 4.40 (1 H, d, $J = 15$, NCH_AH_BPh), 4.49 (1 H, d, $J = 15$, NCH_AH_BPh), 7.22−7.35 (5 H, m, Ph); MS (CI^+; NH_3) $m/z = 220$ ($M^+ + H$).

A mixture of **49** (3.00 g, 13.7 mmol) and *N*,*N*-carbonyldiimidazole (2.33 g, 14.4 mmol) in dry THF (20 mL) was stirred at room temperature under nitrogen for 50 min. Meanwhile, a solution of LDA in dry THF (30 mL) was prepared by the addition of *n*-butyllithium (1.6 M, 17.1 mL, 27.4 mmol) to diisopropylamine (3.85 mL, 27.4 mmol) at room temperature under nitrogen. The LDA solution was cooled to −78 °C, and 4-chloroacetophenone (3.55 mL, 27.4 mmol) was added dropwise. After the yellow enolate solution stirred for 15 min, the imidazolide suspension was introduced *via* cannula. The thick white suspension was stirred at −78 °C for 2 h, then warmed to room temperature, and quenched with saturated aqueous NH_4Cl (40 mL). The mixture was diluted with hydrochloric acid (2 M, 100 mL) and brine (100 mL) and then extracted with EtOAc (2 × 100 mL). EtOAc was removed by evaporation to yield a crude mixture (7.7 g) containing 1-benzyl-4-(3-(4-chlorophenyl)-1-hydroxy-3-oxo-propenyl)pyrrolidin-2-one (**50**), 4-chloroacetophenone, and unreacted carboxylic acid in a 3:5:1 ratio. The crude material was redissolved in MeOH (20 mL), then hydrazine hydrate (5 mL) was added, and the solution was stirred at room temperature for 17 h. MeOH was removed by evaporation, and the residue was dissolved in aqueous NaOH (0.3 M, 70 mL) before extraction with EtOAc (2 × 70 mL). The extracts were washed with brine, dried, and concentrated to give a yellow oil (6.77 g) containing a 1:2

mixture of 3-(1-benzyl-5-oxo-3-pyrrolidinyl)-5-(4-chlorophenyl)-pyrazole (**51**) and 4-chloroacetophenone hydrazone. Purification of a small sample (2.0 g) by flash column chromatography on silica gel, eluting with EtOAc and then 10% EtOH−EtOAc gave **51** (0.49 g) as a colorless glass: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.72 (1 H, br dd, J = 17, 6, $COCH_AH_B$), 2.95 (2 H, br dd, J = 17, 9, $COCH_AH_B$), 3.36−3.47 (1 H, m, NCH_2CHAr), 3.62−3.76 (2 H, m, NCH_2CHAr), 4.52 (2 H, br s, NCH_2Ph), 6.30 (1 H, s, N=CCH), 7.20−7.40 (7 H, m, ArH), 7.50−7.58 (2 H, m, ArH).

A solution of lithium aluminum hydride in THF (1 M, 7 mL) was added dropwise at room temperature to a stirred solution of **51** (1.40 g, 3.98 mmol) in THF:Et_2O (1:1, 20 mL) under nitrogen. An initial white precipitate was observed during addition which redissolved to give a yellow solution. The solution was stirred at 40 °C for 3.5 h. The reaction was quenched at room temperature by cautious addition of aqueous Rochelle salt (1 M, 20 mL). The emulsion was diluted with Et_2O (10 mL) and H_2O (10 mL) and was stirred vigorously until two distinct phases formed. The two phases were separated, and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined extracts were dried and concentrated. Flash column chromatography, eluting with EtOAc:EtOH:880 NH_3 (95:4.75:0.25, v/v), gave the title compound **22** as a white foam (0.94 g, 70%) which was characterized as the hydrochloride salt: white cubes, mp 155−159 °C (from EtOH/EtOAc); ^{1}H NMR (360 MHz, DMSO) δ 2.16−2.38 (1 H, br m, pyrrolidinyl CH), 2.45−2.64 (1 H, br m, pyrrolidinyl CH), 3.30−3.60 (3 H, br m, pyrrolidinyl CH), 3.64−3.90 (2 H, br m, pyrrolidinyl CH), 4.42 (2 H, s, NCH_2Ph), 6.76 (1 H, s, N=CCH), 7.36−7.41 (5 H, m, ArH), 7.50−7.53 (2 H, m, ArH), 7.63 (2 H, d, J = 9, ArH); MS (CI^+; NH_3) m/z = 338 (M^+ + H). Anal. ($C_{20}H_{22}N_3Cl_3$) C, H, N.

3-(1-(2-Phenylethyl)-4-piperazinyl)-5-phenylpyrazole (24). A solution of 1-(2-phenylethyl)piperazine (**52**) (1.8 g, 9.5 mmol) and 4-methyl-4-phenyl-3-thiosemicarbazide (1.72 g, 9.5 mmol) in acetonitrile (50 mL) was refluxed for 5 h. The solution was cooled at −40 °C for 2 h. The resulting white precipitate was collected and dried *in vacuo* to give 4-phenethylpiperazine-1-carbothioic acid hydrazide (**53**) (1.1 g, 35%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.56−2.62 (4 H, m, piperazinyl CH), 2.63−2.72 (2 H, m, NCH_2CH_2Ph), 2.76−2.88 (2 H, m, NCH_2CH_2Ph), 3.78−3.88 (4 H, m, piperazinyl CH), 6.98 (1 H, br s, NH), 7.16−7.34 (5 H, m, Ph); MS (CI^+; NH_3) m/z = 265 (M^+ + H).

A supension of **53** (0.50 g, 1.5 mmol) and 2-bromoacetophenone (0.30 g, 1.5 mmol) in EtOH (15 mL) was stirred at room temperature for 24 h, becoming bright yellow. Saturated ethanolic HCl (5 mL) was added, and the brown solution was refluxed for 2.5 h. The solution was cooled, poured into H_2O (100 mL), basified with aqueous NaOH (1 M), and extracted with EtOAc (3 × 50 mL). The combined extracts were dried and concentrated. Flash column chromatography eluting with dichloromethane:methanol (95:5, v/v) gave partly purified material which was recrystallized to yield the title compound **24** (0.159 g, 32%) as brown granules: mp 133−134 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, DMSO) δ 2.54−2.58 (6 H, m, NCH_2CH_2Ph, piperazinyl CH), 2.77 (2 H, br t, J = 7, NCH_2CH_2Ph), 3.14 (4 H, br t, J = 3, piperazinyl CH), 6.17 (1 H, br s, N=CCH), 7.18 (1 H, t, J = 7, ArH), 7.20−7.30 (5 H, m, ArH), 7.41 (2 H, t, J = 7, ArH), 7.68 (2 H, d, J = 7, ArH), 12.63 (1 H, br s, NH); MS (CI^+; NH_3) m/z = 333 (M^+ + H). Anal. ($C_{21}H_{24}N_4 \cdot 1.2H_2O$) C, H, N.

1-Benzyl-4-(3-hydroxy-1-oxo-3-(4-chlorophenyl)prop-2-en-1-yl)-4-methylpiperidine (26). This was made in the same way as **25** starting with 4-methyl-4-piperidinecarboxylic acid to give white granules: mp 70−71 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.22 (3 H, s, CH_3), 1.61 (2 H, ddd, J = 13, 9, 4, piperidinyl CH), 2.10−2.16 (2 H, m, piperidinyl CH), 2.33 (2 H, br dd, J = 9, 9, piperidinyl CH), 2.54−2.59 (2 H, m, piperidinyl CH), 3.48 (2 H, s, NCH_2Ph), 6.25 (1 H, s, C=CHC=O), 7.21−7.31 (5 H, m, ArH), 7.43 (2 H, d, J = 9, ArH), 7.81 (2 H, d, J = 9, ArH), 15.59 (1 H, br s, OH); MS (CI^+; NH_3) m/z = 370 (M^+ + H). Anal. ($C_{22}H_{24}NO_2Cl$) C, H, N.

3-(1-Benzyl-4-methyl-4-piperidinyl)-5-(4-chlorophenyl)-pyrazole (27): dihydrobromide salt, white granules, mp 222−225 °C (from EtOH/DMF); ^{1}H NMR (360 MHz, DMSO + CF_3CO_2H) (a 2.5:1 mixture of invertomers at the protonated nitrogen was observed) signals for major isomer δ 1.24 (3 H, s, CH_3), 1.86−2.04 (2 H, m, piperidinyl CH), 2.43 (2 H, d, J = 14, piperidinyl CH), 2.86−2.99 (2 H, m, piperidinyl CH), 3.24−3.36 (2 H, m, piperidinyl CH), 4.28 (2 H, d, J = 5, NCH_2Ph), 6.79 (1 H, s, N=CCH), 7.44−7.52 (7 H, m, ArH), 7.82 (2 H, d, J = 9, ArH), 9.5 (1 H, br s, NH); signals visible for minor isomer δ 2.14−2.23 (2 H, m, piperidinyl CH), 4.45 (2 H, d, J = 5, NCH_2Ph), 6.65 (1 H, s, N=CCH), 7.79 (2 H, d, J = 9, ArH); MS (CI^+; NH_3) m/z = 366 (M^+ + H). Anal. ($C_{22}H_{26}N_3ClBr_2$) C, H, N.

3-Phenyl-1′-(2-phenylethyl)-2,4,5,6-tetrahydrocyclopentapyrazole-6-spiro-4′-piperidine (28). Montmorillonite K-10 clay (40 g) was stirred with trimethyl orthoformate (60 mL) at room temperature for 20 min and then added to a solution of 4-iodo-1-phenylbutan-1-one (**54**) (8.0 g, 29 mmol) in toluene (70 mL). After the suspension stirred for 16 h at room temperature, the mixture was filtered, washing with toluene (100 mL). The filtrate was concentrated to give (4-iodo-1,1-dimethoxybutyl)benzene (**55**) (6.49 g, 70%) as a green oil: ^{1}H NMR (250 MHz, C_6D_6) δ 1.26−1.38 (2 H, m, CH_2CH_2I), 1.90−1.97 (2 H, m, $CH_2CH_2CH_2I$), 2.49 (2 H, t, J = 7, CH_2I), 2.96 (6 H, OCH_3), 7.00−7.20 (3 H, m, ArH), 7.48−7.53 (2 H, m, ArH).

A solution of potassium hexamethyldisilylamide in toluene (0.5 M, 40 mL) was added dropwise to a solution of *N*-(*tert*-butyloxycarbonyl)isonipecotic acid ethyl ester (5.1 g, 20 mmol) in dry THF (200 mL) at 0 °C under argon. After 0.5 h, a solution of the iodide **55** (6.49 g, 20 mmol) in dry THF (10 mL) was added. The cooling bath was removed, and the beige suspension was stirred for a futher 4 h. The mixture was diluted with aqueous citric acid (0.5 M, 200 mL) and stirred for 30 min before extraction with EtOAc (2 × 200 mL). The organic extracts were dried and concentrated to give a brown oil. Flash column chromatography on silica gel, eluting with EtOAc:hexane (9:1, v/v), gave ethyl 4-(4-oxo-4-phenylbutyl)-1-(*tert*-butyloxycarbonyl)piperidine-4-carboxylate (**56**; 4.34 g, 54%) as a yellow oil that crystallized on standing: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.26 (3 H, t, J = 7, OCH_2CH_3), 1.34−1.42 (2 H, m, CH_2), 1.46 (9 H, s, $C(CH_3)_3$), 1.56−1.71 (4 H, m, CH_2), 2.12 (2 H, br d, J = 14, piperidinyl CH), 2.89 (2 H, br d, J = 8, piperidinyl CH), 2.94 (2 H, t, J = 7, $COCH_2$), 3.86 (2 H, br d, J = 14, piperidinyl CH), 4.18 (2 H, t, J = 7, OCH_2), 7.45 (2 H, dd, J = 7, 7, ArH), 7.56 (1 H, tt, J = 7, 1, ArH), 7.92 (2 H, dd, J = 7, 1, ArH); MS (CI^+; NH_3) m/z = 404 (M^+ + H).

A solution of potassium hexamethyldisilylamide in toluene (0.5 M, 20 mL) was added dropwise to a solution of the ester **56** (2.0 g, 4.96 mmol) in dry THF (100 mL) at 0 °C under argon. After stirring for 1 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (100 mL). The extract was dried, concentrated, and purified by flash column chromatography, eluting with EtOAc:hexane (9:1, v/v) to give a yellow oil (0.88 g) containing *tert*-butyl 2-benzoyl-1-oxo-8-azaspiro[4.5]decane-8-carboxate (**57**) and *tert*-butyl 1-oxo-8-azaspiro[4.5]decane-8-carboxylate (**58**) as a 2:1 mixture by NMR. Analytical samples of the two products could be separated by preparative thin layer chromatography. **57:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.42−1.58 (11 H, m, $C(CH_3)_3$, CH_2), 1.78−1.96 (4 H, m, piperidinyl CH), 2.84 (2 H, t, J = 7, CH_2), 3.12 (2 H, ddd, J = 14, 11, 4, piperidinyl CH), 3.88−4.03 (2 H, m, piperidinyl CH), 7.40−7.54 (3 H, m, ArH), 7.76−7.82 (2 H, m, ArH); MS (CI^+; NH_3) m/z = 358 (M^+ + H). **58:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20−1.50 (11 H, m, $C(CH_3)_3$, CH_2), 1.66 (2 H, ddd, J = 14, 11, 6, piperidinyl CH), 1.87−1.96 (4 H, m, CH_2), 2.26−2.36 (2 H, m, CH_2), 3.06 (2 H, ddd, J = 14, 11, 4, piperidinyl CH), 4.87 (2 H, ddd, J = 14, 4, 4, piperidinyl CH).

The mixture of diketone **57** and ketone **58** (0.85 g) was dissolved in MeOH (20 mL), and hydrazine hydrate (5 mL, 0.1 mol) was added. After stirring for 45 min the deep orange solution had become very pale yellow. MeOH was removed by evaporation, and the residue was partitioned between H_2O (40 mL) and EtOAc (2 × 40 mL). The organic extracts were dried and concentrated. The crude pyrazole (0.91 g) was dissolved in EtOAc and treated with a saturated solution of

hydrogen chloride in EtOAc (50 mL). After gentle heating to initiate reaction, the mixture was chilled (4 °C) for 16 h. The resulting white precipitate was collected and dried *in vacuo* to give the crude deprotected piperidine as the hydrochloride salt (0.62 g). A portion of the crude piperidine salt (0.35 g), phenethyl bromide (0.25 mL, 1.8 mmol), and diisopropylethylamine (0.70 mL, 4.0 mmol) were dissolved in dimethylformamide (15 mL) and stirred at 60 °C for 24 h. The mixture was diluted with H_2O (40 mL) and extracted with 9:1 dichloromethane:methanol (2 × 20 mL). The organic extracts were concentrated, and the residue was redissolved in Et_2O (20 mL), washed with H_2O (20 mL), dried, and concentrated. Preparative thin layer chromatography, eluting with 90:8:2 dichloromethane:methanol:880 NH_3 (90:8:2, v/v), gave the title compound **28** (0.08 g, 8% from **56**) as a colorless oil: bis oxalate salt, white powder, mp 182−185 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO) δ 1.86−2.10 (4 H, m, piperidinyl CH), 2.32−2.48 (2 H, m, CH_2), 2.84 (2 H, t, J = 7, CH_2), 3.03−3.07 (2 H, m, $PhCH_2$), 3.33−3.37 (2 H, m, $PhCH_2CH_2N$), 3.40−3.62 (4 H, m, piperidinyl CH), 7.27−7.38 (6 H, m, ArH), 7.45 (2 H, dd, J = 8, 8, ArH), 7.65 (2 H, d, J = 7, ArH); MS (CI^+; NH_3) m/z = 358 ($M^+ + H$). Anal. ($C_{24}H_{27}N_3 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

3-(1-(4-Chlorobenzyl)-4-piperidinyl)-5-(4-chlorophenyl)-isoxazole (29) and 5-(1-(4-Chlorobenzyl)-4-piperidinyl)-3-(4-chlorophenyl)isoxazole (30). Alkylation of **42** (3 g, 10 mmol) with 4-chlorobenzyl chloride (1.77 g, 11 mmol) as above gave **61** (2.3 g, 59%) as cubes: mp 91−92 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.8−2.0 (4 H, m, NCH_2CH_2), 2.0−2.1 (2 H, m, NCH_AH_B), 2.3−2.4 (1 H, m, $CHCH_2$), 2.96 (2 H, d, J = 12, NCH_AH_B), 3.5 (2 H, s, $ArCH_2$), 6.14 (1 H, s, CHCO), 7.29 (4 H, s, ArH), 7.41 (2 H, d, J = 8.6, ArH *o* to Cl), 7.81 (2 H, d, J = 8.6, ArH *m* to Cl), 15.9 (1 H, br s, OH); MS (CI^+; NH_3) m/z = 390 ($M^+ + H$). Anal. ($C_{21}H_{21}ClNO_2$) C, H, N.

Hydroxylamine hydrochloride (139 mg, 2 mmol) was added to **61** (399 mg, 1.02 mmol) and Et-*i*-Pr_2N (0.35 mL, 2 mmol) in EtOH (5 mL) and DMF (2 mL). After stirring for 16 h hydroxylamine hydrochloride (139 mg, 2 mmol) and Et-*i*-Pr_2N (0.35 mL, 2 mmol) were added, and the mixture was stirred at 50 °C for 4 h. H_2O (50 mL) was added, the mixture was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with H_2O and brine, dried, evaporated, and purified by flash chromatography, eluting with CH_2Cl_2:EtOH:Et_3N (96:4:1, v/v) to give a mixture of 5-(1-(4-chlorobenzyl)-4-piperidinyl)-3-(4-chlorophenyl)-3-hydroxy-3,4-dihydroisoxazole and 3-(1-(4-chlorobenzyl)-4-piperidinyl)-5-(4-chlorophenyl)-3-hydroxy-3,4-dihydroisoxazole (287 mg, 71%); 209 mg (520 μmol) of this oil was dissolved in dichloromethane (5 mL) and cooled to 0 °C, and Et_3N (161 mg, 1.6 mmol) and methanesulfonyl chloride (81 mg, 710 μmol) were added. After 1 h EtOAc (25 mL) was added, and the mixture was washed with H_2O and brine, dried, evaporated, and purified by preparative thin layer chromatography, eluting with CH_2Cl_2:EtOH:Et_3N (97:3:1, v/v) to give **30** (107 mg, 27%): oxalate salt, white solid, mp 227−230 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.7−1.8 (2 H, m, $CHCH_AH_B$), 2.08 (2 H, d, J = 11, $CHCH_AH_B$), 2.3−2.4 (2 H, m, NCH_AH_B), 3.0−3.1 (3 H, m, NCH_AH_B, CH_2CH), 3.82 (2 H, s, $ArCH_2$), 6.92 (1 H, s, CHCO), 7.4−7.5 (4 H, m, ArH), 7.59 (2 H, d, J = 8, ArH *o* to Cl), 7.88 (2 H, d, J = 8, ArH *m* to Cl); MS (CI^+; NH_3) m/z = 387 ($M^+ + H$). Anal. ($C_{21}H_{20}Cl_2N_2O \cdot 0.8C_2H_2O_4$) C, H, N. **29** (251 mg, 13%): oxalate salt, white plates, mp 240−242 °C (from EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.8−1.9 (2 H, m, $CHCH_AH_B$), 2.05 (2 H, d, J = 11, $CHCH_AH_B$), 2.6−2.7 (2 H, m, NCH_AH_B), 2.9−3.0 (1 H, m, CH_2CH), 3.1−3.2 (2 H, m, NCH_AH_B), 3.97 (2 H, s, $ArCH_2$), 7.07 (1 H, s, CHCO), 7.4−7.5 (4 H, m ArH), 7.61 (2 H, d, J = 8, ArH *o* to Cl), 7.85 (2 H, d, J = 8, ArH *m* to Cl); MS (CI^+; NH_3) m/z = 387 ($M^+ + H$). Anal. ($C_{21}H_{20}Cl_2N_2O \cdot C_2H_2O_4$) C, H, N. The isoxazole regiochemistry was proved by X-ray.

3-(4-Chlorophenyl)-4-methyl-5-(4-(1-(2-phenylethyl)piperidinyl))isoxazole (35): white needles, mp 130−131 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.40−1.75 (2 H, m, $CHCH_AH_B$), 1.90−2.40 (4 H, m, $CHCH_AH_B$, NCH_AH_B), 2.09 (3 H, s, CH_3), 2.70−2.80 (2 H, m, CH_2Ph), 2.84−2.98 (3 H, m, NCH_2CH_2Ph, CH_2CH), 3.18 (2 H, br d, J = 12, NCH_AH_B), 7.20−7.33 (5 H, m, Ph), 7.43−7.46 (2 H, m, ArH *o* to Cl), 7.57−7.59 (2 H, m, ArH *m* to Cl); MS (CI^+; NH_3) m/z = 381 ($M^+ + H$). Anal. ($C_{23}H_{25}ClN_2O$) C, H, N.

3-(4-(1-(2-Phenylethyl)piperidinyl))-4-methyl-5-(4-chlorophenyl)isoxazole (36): white plates, mp 138−140 °C (from EtOH/H_2O); ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.00−2.10 (4 H, m, $CHCH_2$), 2.19 (3 H, s, CH_3), 2.12−2.32 (2 H, m, NCH_ACH_B), 2.65−2.75 (3 H, m, CH_2CH, CH_2Ph), 2.85−2.89 (2 H, m, NCH_2CH_2Ph), 3.15 (2 H, br d, J = 12, NCH_ACH_B), 7.18−7.32 (5 H, m, Ph), 7.44−7.47 (2 H, m, ArH *o* to Cl), 7.57−7.64 (2 H, m, ArH *m* to Cl); MS (CI^+; NH_3) m/z = 381 ($M^+ + H$). Anal. ($C_{23}H_{25}ClN_2O$) C, H, N. The isoxazole regiochemistry was proved by X-ray on this compound.

4-(1-Benzylpiperidin-4-yl)-6-(4-chlorophenyl)pyrimidin-2-ylamine (31). Sodium metal (0.15 g, 6.7 mmol) was dissolved in refluxing anhydrous *i*-PrOH (10 mL) under nitrogen. The solution was cooled to 50 °C, and guanidine hydrochloride (0.42 g, 4.4 mmol) was added. The suspension was refluxed for 15 min followed by addition of a slurry of ketone **25** (0.87 g, 2.2 mmol) in *i*-PrOH (10 mL). The suspension was refluxed for 17 h and then concentrated. The residues were diluted with H_2O (50 mL) and extracted with EtOAc (3 × 25 mL). The extracts were dried and concentrated. Flash column chromatography, eluting with EtOAc:hexane (2:1, v/v), followed by preparative thin layer chromatography, eluting with EtOAc:hexane (1:1, v/v), gave the title compound **31** (0.088 g, 10%) as an oil: bishydrochloride, white granules, mp 251−253 °C (from EtOH); in the ^{1}H NMR **31** appears as a 6:1 ratio of two protonated forms; the purity of the sample was checked by HPLC on three systems and was always >99.5%; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.10−2.20 (4 H, m, $CHCH_2$), 2.86−3.24 (3 H, m, NCH_AH_B, CH_2CH), 3.42−3.45 (2 H, m, NCH_AH_B), 4.32 and 4.49 (2 H, 2 × d, J = 5, NCH_2Ph), 7.24 (1 H, s, C=CH), 7.46−7.48 (3 H, m, 3 of Ph), 7.62−7.72 (4 H, m, Ph, ArH *o* to Cl), 8.15 and 8.23 (2 H, 2 × d, J = 8, ArH *o* to Cl), 11.03 and 11.16 (1 H, 2 × br s, NH); MS (CI^+; NH_3) m/z = 379 ($M^+ + H$). Anal. ($C_{21}H_{25}Cl_2N_4 \cdot 2HCl \cdot 0.4H_2O$) C, H, N.

2-Amino-4-(1-(2-phenylethyl)-4-piperidinyl)-6-(4-chlorophenyl)-5-methylpyrimidine (37): white granules, mp 179−180 °C (from DMF/H_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.65 (2 H, d, J = 12, $CHCH_AH_B$), 1.83 (2 H, q, J = 12, $CHCH_AH_B$), 2.02−2.08 (5 H, m, CH_3, NCH_AH_B), 2.54 (2 H, t, J = 8, CH_2Ph), 2.73−2.81 (3 H, m, NCH_2CH_2Ph, CH_2CH), 3.04 (2 H, d, J = 11, $ANCH_AH_B$), 6.28 (2 H, s, NH_2), 7.16−7.30 (5 H, m, Ph), 7.46−7.52 (4 H, m, ArH); MS (CI^+; NH_3) m/z = 407 ($M^+ + H$, 100). Anal. ($C_{24}H_{27}ClN_4$) C, H, N.

3-(1-Benzyl-4-piperidinyl)-4-ethyl-5-(4-chlorophenyl)-pyrazole (33). A solution of tetrabutylammonium fluoride in THF (1 M, 2 mL) was added to a solution of diketone **59** (0.705 g, 1.93 mmol) in THF (20 mL). The clear yellow solution was evaporated to give a yellow oil which was redissolved in chloroform (20 mL), and ethyl iodide (0.25 mL, 2.9 mmol) was added. The solution was refluxed under nitrogen for 4 h, then cooled, and poured into H_2O (50 mL). The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (40 mL). The organic extracts were dried, concentrated, and purified by flash column chromatography, eluting with hexane:EtOAc (9:1, v/v) to give 4-(2-(4-chlorobenzoyl)butyryl)-1-(*tert*-butylcarbonyloxy)piperidine (**60**; 0.49 g, 64%) as a yellow oil (contaminated with some unreacted starting material): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.93 (3 H, t, J = 7, CH_2CH_3), 1.43 (9 H, s, *t*-Bu), 1.52−1.70 (4 H, m, piperidinyl CH), 2.01 (2 H, dq, J = 7, 7, CH_2CH_3), 2.58−2.72 (3 H, m, piperidinyl CH), 4.00−4.16 (2 H, m, piperidinyl CH), 4.39 (1 H, t, J = 7, $CHCH_2CH_3$), 7.47 (2 H, d, J = 9, ArH), 7.90 (2 H, d, J = 9, ArH); MS (CI^+; NH_3) m/z = 294 ($M^+ + H$).

A solution of the diketone (0.47 g, 1.19 mmol) in Et_2O (20 mL) was cooled to 0 °C and saturated with hydrogen chloride gas. The solution was gently warmed until a white precipitate formed. The suspension was chilled overnight, and the crystalline material was collected to give 1-(4-chlorophenyl)-2-ethyl-3-piperidin-4-ylpropane-1,3-dione hydrochloride (0.384 g, 87%): ^{1}H NMR (360 MHz, DMSO) δ 0.85 (3 H, t, J = 7, CH_2CH_3), 1.52−2.98 (6 H, m, piperidinyl CH, CH_2CH_3), 2.75−2.98 (3 H, m, piperidinyl CH), 3.18−3.28 (2 H, m, piperidinyl CH), 5.02 (1 H, t, J = 6, $CHCH_2CH_3$), 7.65 (2 H, d, J = 8,

ArH), 8.04 (2 H, d, $J = 8$, ArH), 8.60 (1 H, br s, NH), 8.90 (1 H, br s, NH); MS (CI^+; NH_3) $m/z = 394$ ($M^+ + H$).

A solution of the piperidine hydrochloride salt (0.34 g, 1.03 mmol), diisopropylethylamine (0.36 mL, 2.06 mmol), and benzyl bromide (0.13 mL, 1.08 mmol) in dry DMF (10 mL) was stirred at 50 °C under nitrogen for 18 h and then at room temperature for 24 h. The mixture was poured into H_2O (50 mL) and extracted with EtOAc (2 × 20 mL). The combined extracts were dried, concentrated, and purified by flash column chromatography on silica gel, eluting with EtOAc:hexane (1:1, v/v) to give 1-(1-benzylpiperidin-4-yl)-3-(4-chlorophenyl)-2-ethylpropane-1,3-dione (0.146 g, 37%) as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (3 H, t, $J = 6$, CH_2CH_3), 1.52−2.18 (8 H, m, piperidinyl CH, CH_2CH_3), 2.40−2.55 (1 H, m, piperidinyl CH), 2.80−2.96 (2 H, m, piperidinyl CH), 3.48 (2 H, s, NCH_2Ph), 4.38 (1 H, t, $J = 6$, $CHCH_2CH_3$), 7.20−7.40 (5 H, m, Ph), 7.46 (2 H, d, $J = 8$, ArH), 7.90 (2 H, d, $J = 8$, ArH); MS (CI^+; NH_3) $m/z = 384$ ($M^+ + H$).

A solution of the diketone (0.14 g, 0.36 mmol) and hydrazine hydrate (1.0 mL) in methanol (5 mL) was stirred overnight at room temperature. The mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined extracts were dried, evaporated, and purified by preparative thin layer chromatography eluting with EtOAc to give a yellow oil that was triturated with aqueous ethanol and then recrystallized to yield the title compound **33** (0.036 g, 26%) as colorless cubes: mp 170−172 °C (from EtOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.09 (3 H, t, $J = 7.5$, CH_2CH_3), 1.67−1.89 (4 H, m, piperidinyl CH), 2.07−2.18 (2 H, m, piperidinyl CH), 2.56 (2 H, q, $J = 7.5$, CH_2CH_3), 2.69 (1 H, tt, $J = 8$, 8, piperidinyl CH), 3.03 (2 H, br d, $J = 12$, piperidinyl CH), 3.57 (2 H, s, NCH_2Ph), 7.26−7.39 (7 H, m, ArH), 7.50 (2 H, d, $J = 8$, ArH); MS (CI^+; NH_3) $m/z = 380$ ($M^+ + H$). Anal. ($C_{23}H_{26}N_3Cl$) C, H, N.

Acknowledgment. We would like to thank Steve Thomas for NMR experiments and Mike Graham for pharmacokinetics.

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JM970111H