# Preparation and Optimization of a Series of 3-Carboxamido-5-phenacylaminopyrazole Bradykinin B1 Receptor Antagonists

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*Received December 29, 2005*

The B1 receptor is an attractive target for the treatment of pain and inflammation. A series of 3-carboxamido-5-phenacylamino pyrazole B1 receptor antagonists are described that exhibit good potency against B1 and high selectivity over B2. Initially, *N*-unsubstituted pyrazoles were studied, but these compounds suffered from extensive glucuronidation in primates. This difficulty could be surmounted by the use of *N*-substituted pyrazoles. Optimization efforts culminated in compound **41**, which has high receptor potency and metabolic stability.

## Introduction

The kinins, bradykinin (BK, Arg-Pro−Pro-Gly-Phe-Ser-Pro-Phe-Arg) and kallidin (KD, Lys-BK), along with their metabolites, des-Arg$^9$-bradykinin (DABK) and des-Arg$^{10}$-kallidin (DAKD), are endogenous peptides whose action is mediated by two G-protein coupled receptors (GPCRs), B1 and B2. These peptides have been implicated in a variety of physiological and pathological responses, including pain and inflammation. Both DABK and DAKD have high affinity for the B1 receptor, which is induced after tissue damage or inflammation.[1,2] It has been shown that B1 receptor agonists produce hyperalgesia, an effect that is blocked by B1 receptor antagonists. A recent study has shown that treatment with a B1 selective antagonist, des-Arg$^9$-[Leu$^8$]-BK, reduced mechanical allodynia in a mouse model after partial ligation of the sciatic nerve.[3] Also, B1 receptor deficient mice are outwardly normal but show a tempered response to chemical and thermal nociception as well as reduced inflammatory responses.[4] These factors, as well as the need for safe and effective analgesics, make the B1 receptor an attractive target for the treatment of pain and inflammation.

A number of selective B1 inhibitors have been described. These compounds display a wide range of structural diversity and include benzodiazepines such as compound **I**,[5] dipeptides such as compound **II**,[6] sulfamoylbenzamides like compound **III**,[7] and quinoxalines such as compound **IV**[8] (Figure 1).

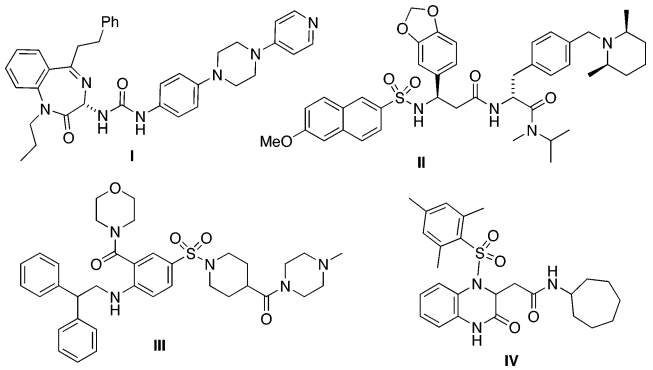


**Figure 1.** Small molecule bradykinin B1 receptor antagonists.

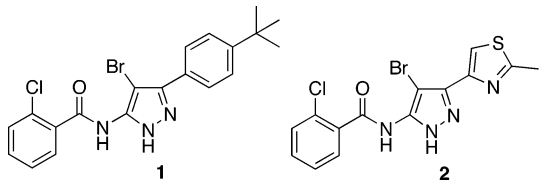


**Figure 2.** Initial lead structures.

Our efforts to find effective small molecule B1 receptor antagonists have revealed a novel class of pyrazolecarboxamides that are potent and highly selective. A broad screen of our in-house sample library was conducted, which identified pyrazole **1** as a B1 antagonist with an $IC_{50} = 3.2 \pm 0.4$ $\mu$M (FLIPR) and greater than 10-fold selectivity over B2 (Figure 2). The pyrazole core easily lent itself to analog development and a small set of compounds was then prepared using **1** as a scaffold. This led to the preparation of pyrazole **2**. The 2-methylthiazolyl substituent provided an increase in potency ($IC_{50} = 1.1 \pm 0.1$ $\mu$M) over the 4-*tert*-butylphenyl substituent while exhibiting greater than 100-fold selectivity over B2.

Considering that an amide might act as an isosteric replacement for the thiazole moiety, a synthesis was devised and several 3-carboxamide-5-acylamino pyrazoles were prepared. An exploratory set of three compounds was initially selected, each of which showed encouraging $IC_{50}$ and $K_i$ values (Table 1). Optimization of this structural class has revealed compounds that exhibit subnanomolar activity.

**Chemistry.** The compounds were prepared as follows. Fischer esterification of commercially available 5-nitro-3-pyrazolecarboxylic acid (**6**) followed by catalytic hydrogenolysis gave methyl 5-amino-3-pyrazole carboxylate (**8**). Addition of 2-chlorobenzoic acid using a variety of coupling reagents was low yielding, however, addition of 2-chlorobenzoyl chloride (**9**) using DMAP[a] and pyridine in $CH_2Cl_2$ afforded the pyrazole ester **10**. Hydrolysis to acid **11** and coupling with the appropriate amine using conventional carbodiimide coupling methods or bromination with NBS followed by coupling gave either pyrazole **13** or **14** (Scheme 1). Pyrazole acid **11** could also be treated with NCS to afford 4-chloropyrazoles.

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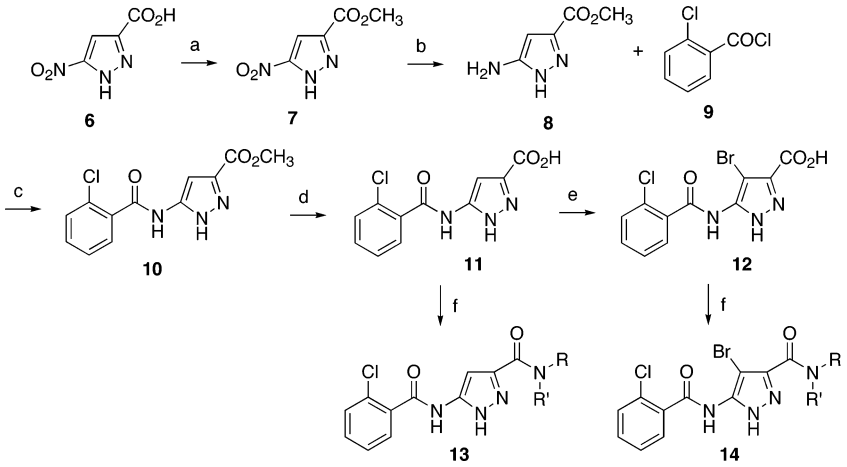
[a] Abbreviations: DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; TFA, trifluoroacetic acid; NMM, 4-methylmorpholine; HOBT, 1-hydroxybenzotriazole hydrate; EDC·HCl, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

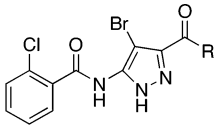
10.1021/jm051292n CCC: $37.00 
Published on Web 09/19/2007

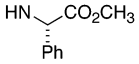
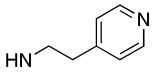
**Scheme 1.** Synthesis of Pyrazole B1 Receptor Antagonists[a]



[a] Reagents and conditions: (a) HCl, MeOH; (b) $H_2$, Pd/C, MeOH; (c) DMAP, pyridine, $CH_2Cl_2$; (d) LiOH·$H_2O$, MeOH, $H_2O$; (e) NBS, DMF; (f) EDC, HOBT, NMM, DMF, HNRR′.

**Table 1.** B1 Antagonist Receptor Potency and Binding Affinity of Pyrazole Carboxylate Analogues



| compound | R | FLIPR $IC_{50}$ (nM) | Binding $K_i$ (nM) |
|---|---|---|---|
| **3** |  | 290 ± 40 | 73 ± 17 |
| **4** | HNPh | 530 ± 80 | 200 ± 40 |
| **5** |  | 490 ± 80 | 120 ± 10 |

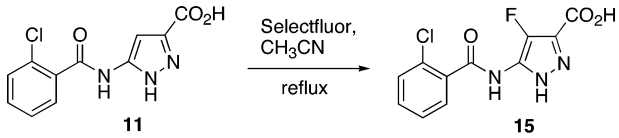
In addition, treatment of carboxylic acid **11** with Selectfluor in refluxing acetonitrile, as previously described,[9] afforded 4-fluoropyrazoles (Scheme 2).

**Biology.** Human B1 receptor antagonist potency was evaluated using a fluorescent imaging plate reader (FLIPR) assay employing IL-1$\beta$ stimulated IMR-90 human lung fibroblast cells. Inhibition of Ca-dependent fluorescence was measured after addition of DAKD as agonist. B1 receptor affinity was determined in binding studies using [$^3$H]DAKD as radioligand and membranes prepared from IL-1$\beta$ stimulated IMR-90 cells. Test compounds were dissolved in DMSO, diluted in buffer, and assayed at seven concentrations in triplicate. FLIPR $IC_{50}$ values and binding $K_i$ values are expressed as the means ± SEM of at least three independent experiments.

## Results and Discussion

Following our initial success, we synthesized and screened several hundred pyrazoles, a small subset of which is presented here. Initially we elected to optimize the *C*-terminus while keeping the remainder of the molecule unchanged. In so doing, we could rapidly prepare a large basis set from which to gauge the SAR of this portion of the molecule. Conscious of the basic nature of DABK and DAKD as well as the importance of aspartic acid residues for ligand binding in GPCRs,[10] we weighted our analogs in favor of those with an amine-containing

**Scheme 2.** Synthesis of 4-Fluoropyrazoles



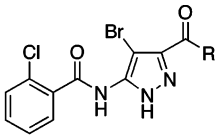
*C*-terminus (Table 2). We found that a variety of alkyl and aryl amines as well as amino esters and amides were acceptable substituents. The cyclic amidine **16** was found to be one of the most potent analogs with subnanomolar in vitro activity. While the most active compounds such as **16** and **17** tended to contain strongly basic side chains; this was not necessarily required to achieve good potency. The alanine amide **19** has a low nanomolar $IC_{50}$ (16 nM) and the weakly basic aminopyridine **20** is equipotent (13 nM). Other pyrazoles with nonbasic *C*-termini include two other amino amides, **23** and **27**, and the phenethylamine **25**. This region of the binding pocket appears to be fairly accommodating, accepting bridged bicyclic ring systems such as the quinuclidine **21** as well as large rings such as azepinone **24** and in particular benzodiazepine **18**.

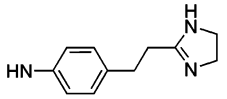
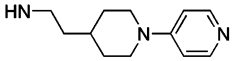
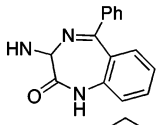
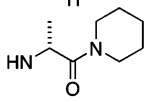
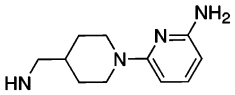
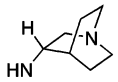
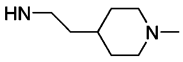
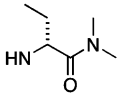
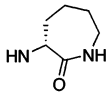
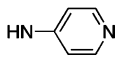
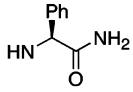
A number of pyrazole 4-position replacements were examined (Table 3). Although we found cases where chlorine was a suitable replacement for bromine (*cf*. **17** and **29**), no substituent was found that afforded analogs with greatly improved potency. A further increase in electron withdrawing character by incorporation of fluorine, compound **30**, caused a drop in potency. Pyrazoles with unsubstituted 4-positions such as **28** and **32** invariably gave analogs with the poorest $IC_{50}$ values. 4-Methylpyrazole analogs, **31** and **34**, showed only a slight decrease in potency as compared to 4-bromopyrazoles. Based on these observations, we reasoned that bromine substitution provides optimal electron withdrawing and lipophilic characteristics.

Once we had obtained compounds exhibiting low nanomolar potency, we looked at modifications to the *N*-terminus (Figure 3). Replacing the 2-chlorobenzoylamide of benzodiazepine **18** with a 2-fluorobenzoylamide (**35**) resulted in a slight drop in potency. A greater drop was observed for benzolyamide **36**. Replacement of the arylamide with an alkylamide such as 2-methylpropanoylamide, **37**, or acetamide, **38**, resulted in a substantial loss of inhibition.

Unfortunately, as our work progressed, in vivo experiments established that compound **17** was rapidly cleared in cynomologous monkeys. Conjugation is known to be a metabolic route

**Table 2.** Receptor Potency for *C*-Terminal Variant Analogs

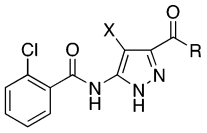


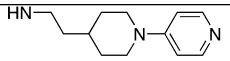
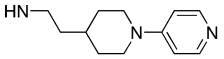
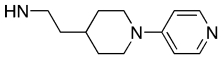
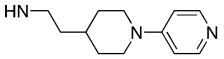
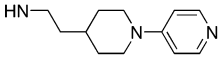
| compound | R | FLIPR $IC_{50}$ (nM) |
|---|---|---|
| **16** |  | 0.075 ± 0.005 |
| **17** |  | 3.0 ± 0.2 |
| **18**[a] |  | 5.2 ± 0.6 |
| **19** |  | 16 ± 1 |
| **20** |  | 13 ± 2 |
| **21** |  | 60 ± 3 |
| **22** |  | 86 ± 9 |
| **23** |  | 82 ± 9 |
| **24** |  | 290 ± 60 |
| **25** |  | 210 ± 20 |
| **26** |  | 560 ± 60 |
| **27** |  | 1700 ± 300 |

[a] Racemic compound.

for *N*-unsubstituted pyrazoles,[11] and in vitro assays of compound **17** as well as other *N*-unsubstituted pyrazoles determined that *N*-glucuronidation was a major clearance pathway in both monkey and human. We sought to remedy this problem by preparing a suitable *N*-substituted pyrazole. This, however, was complicated by not knowing which pyrazole tautomeric form

**Table 3.** 4-Substituted Pyrazole Analogs



| compound | X | R | $IC_{50}$ (nM) |
|---|---|---|---|
| **17** | Br |  | 3.0 ± 0.2 |
| **28** | H |  | 200 ± 30 |
| **29** | Cl |  | 3.9 ± 0.3 |
| **30** | F |  | 23 ± 2 |
| **31** | Me |  | 9.3 ± 0.4 |
| **4** | Br | HNPh | 530 ± 80 |
| **32** | H | HNPh | >10,000 |
| **33** | Cl | HNPh | 700 ± 110 |
| **34** | Me | HNPh | 2000 ± 300 |

was preferred. Two isomeric pyrazoles, **39** and **40** (Figure 4), were synthesized and tested. These were prepared by *N*-alkylation of pyrazole **7** to give a mixture of *N*-methyl pyrazoles. Hydrogenolysis followed by chromatographic separation and elaboration as shown in Scheme 1 afforded pyrazoles **39** and **40**. Structural assignment was determined by comparison of the $^1$H NMR spectra of the separated methyl aminopyrazole carboxylates with reported spectra[12] as well as X-ray crystallographic analysis of a crystal of the TFA salt of pyrazole **40** grown in MeOH.

While compound **39** exhibited better potency than **40**, it was 10-fold less active than the equivalent unsubstituted pyrazole, **17**. However, testing revealed that *N*-alkylation effectively blocked glucuronidation. A variety of other substituents were subsequently examined while keeping the 2-chlorobenzamide and the 1-(4-pyridinyl)-4-piperidinylethylamide termini constant (Table 4). We found that the *N*-phenyl substituted pyrazole **41** was almost equipotent to the unsubstituted pyrazole **17**. Other substituents that were examined displayed reduced inhibition.

*N*-Substituted pyrazoles were prepared as shown in Scheme 3. Addition of phenylhydrazine to sodium enolate **46** gave exclusively the 5-amino-3-ethoxycarbonyl-1-phenyl pyrazole

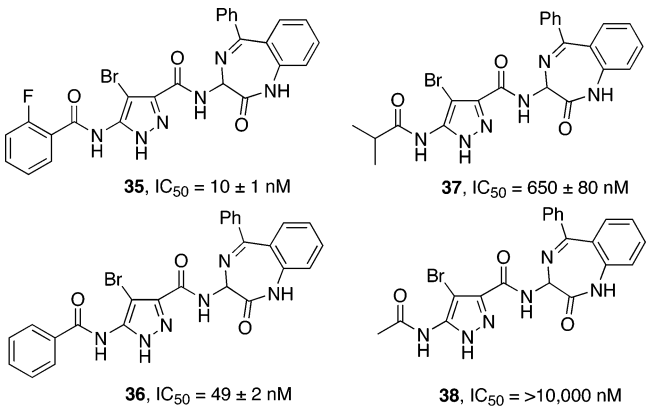
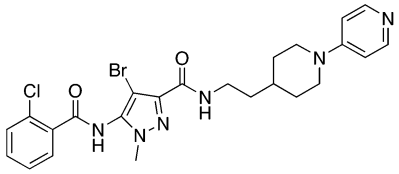
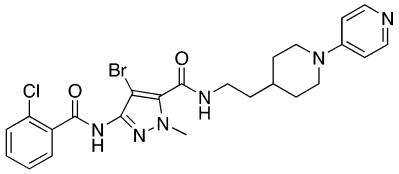



**Figure 3.** *N*-Terminal modifications.



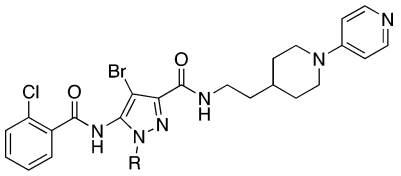
**39**, $IC_{50}$ = 44 ± 4 nM



**40**, $IC_{50}$ = 640 ± 70 nM

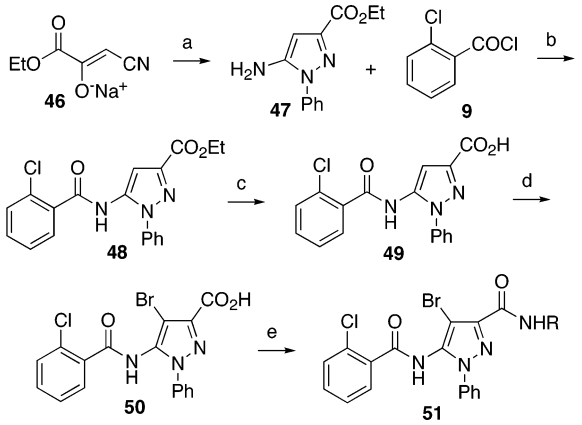
**Figure 4.** Regioisomeric *N*-substituted pyrazoles.

**Table 4.** FLIPR Values for *N*-Substituted Pyrazoles



| compound | R | FLIPR $IC_{50}$ (nM) |
|---|---|---|
| **17** | H | 3.0 ± 0.2 |
| **41** | Ph | 3.5 ± 0.4 |
| **42** | 2-pyridyl | 12 ± 1 |
| **43** | benzyl | 71 ± 13 |
| **44** | 4-methoxyphenyl | 1200 ± 100 |
| **45** | 2-dimethylaminoeth-1-yl | 1600 ± 300 |

**Scheme 3.** Synthesis of *N*-Phenyl Pyrazoles[a]



[a] Reagents and conditions: (a) $PhNHNH_2$, EtOH; (b) DMAP, pyridine, $CH_2Cl_2$; (c) LiOH·$H_2O$, MeOH, $H_2O$; (d) NBS, DMF; (e) $H_2NR$, BOP, NMM, DMF.

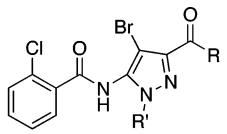
(**47**). Acylation followed by hydrolysis and bromination as outlined in Scheme 1 afforded carboxylic acid **50** which could then be coupled with an appropriate amine.

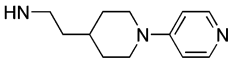
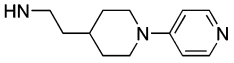
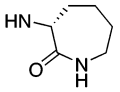
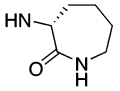
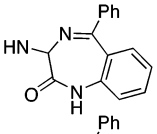
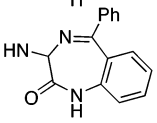
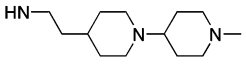
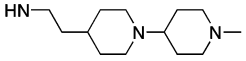
Next we prepared a number of *N*-phenylpyrazoles with various *C*-termini. Unfortunately, very few *C*-terminal modifications afforded compounds with acceptable potency and none improved on the activity of **41**. We also observed that the SAR that had been accumulated for the unsubstituted series was no longer predictive. Table 5 lists a representative set of *N*-phenylpyrazoles along with their corresponding unsubstituted analogs. As can be seen from this data, the potency between substituted and unsubstituted pyrazole analogs varied greatly depending on the *C*-terminal amide. Compound **53** exhibited one of the largest discrepancies with a loss in potency of greater than three orders of magnitude.

## Conclusion

We have identified and developed a class of potent pyrazolecarboxamide bradykinin B1 antagonists. These pyrazoles exhibit high selectivity for the B1 receptor. Optimization of 1*H*-pyrazolecarboxamides led to highly potent antagonists that, unfortunately, suffered from rapid first-pass metabolism. The synthesis of 1-phenylpyrazolecarboxamides inhibited the conjugative metabolic pathway culminating in the preparation of compound **41**.

**Table 5.** Comparison of 1*H* and 1-Phenyl Pyrazole Inhibitory Potencies



| compound | R | R' | FLIPR $IC_{50}$ (nM) |
|---|---|---|---|
| **17** |  | H | 3.0 ± 0.2 |
| **41** |  | Ph | 3.5 ± 0.4 |
| **24** |  | H | 290 ± 60 |
| **52** |  | Ph | >10,000 |
| **18** |  | H | 5.2 ± 0.6 |
| **53** |  | Ph | >10,000 |
| **54** |  | H | 1.8 ± 0.1 |
| **55** |  | Ph | 320 ± 40 |

## Experimental Section

**General.** Reagents and solvents obtained from commercial suppliers were used without further purification unless otherwise stated. Thin layer chromatography was performed on precoated 0.25 mm silica gel plates (E. Merck, silica gel 60, $F_{254}$). Visualization was achieved using UV illumination or staining with phosphomolybdic acid, ninhydrin, or other common staining reagents. Flash chromatography was performed using either a Biotage Flash 40 system and prepacked silica gel columns or hand-packed columns (E. Merck silica gel 60, 230−400 mesh). Preparatory HPLC was performed on a Varian Prepstar high performance liquid chromatograph. $^1$H NMR spectra were recorded on either a Varian Gemini

300 MHz spectrometer or a Bruker Avance 300 MHz spectrometer. Chemical shifts are reported in ppm ($\delta$) and were calibrated using the undeuterated solvent resonance as internal standard. Mass spectra were recorded on an Agilent series 1100 mass spectrometer connected to an Agilent series 1100 HPLC.

**(*S*)-α-[[[4-Bromo-5-[(2-chlorobenzoyl)amino]-1*H*-pyrazol-3-yl]carbonyl]amino]benzeneacetic Acid Methyl Ester (3).** Compound **3** was prepared as described for compound **17** using carboxylic acid **12** and (*S*)-methyl phenylglycinate. MS *m*/*z* 491.0 $(M + H)^+$. $^1$H NMR ($CDCl_3$) $\delta$ 9.21 (br, 1H), 8.12 (br, 1H), 7.97, (br, 1H), 7.45 (m, 5H), 7.30 (m, 4H), 5.78 (m, 1H), 3.71 (s, 3H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-*N*-phenyl-1*H*-pyrazole-3-carboxamide (4).** Compound **4** was prepared as described for compound **17** using carboxylic acid **12** and aniline. MS *m*/*z* 419.0 $(M + H)^+$. $^1$H NMR (DMSO-$d_6$) $\delta$ 10.83 (br, 1H), 10.20 (br, 1H), 7.77 (m, 2H), 7.54 (m, 4H), 7.34 (m, 2H), 7.10 (m, 1H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-*N*-[2-(4-pyridinyl)ethyl]-1*H*-pyrazole-3-carboxamide (5).** Compound **5** was prepared as described for compound **17** using carboxylic acid **12** and 4-(2-aminoethyl)pyridine. MS *m*/*z* 450.0 $(M + H)^+$. $^1$H NMR ($CD_3OD$) $\delta$ 8.45 (d, $J = 4.5$ Hz, 2H), 7.65 (d, $J = 7.2$ Hz, 1H), 7.47 (m, 5H), 3.69 (t, $J = 6.9$ Hz, 2H), 3.01 (t, 6.9 Hz, 2H).

**3-Methoxycarbonyl-5-nitropyrazole (7).** A solution of 10.0 g (0.06 mol) of 5-nitro-1*H*-pyrazole-3-carboxylic acid in 100 mL of MeOH was vigorously stirred as HCl gas was bubbled through the solution. The resulting homogeneous solution was heated at reflux for 2 h followed by stirring at rt for an additional 15 h. The solvent was evaporated under reduced pressure to dryness. The residue was diluted with 250 mL of EtOAc and neutralized with sat. aq. $NaHCO_3$. The layers were separated, and the organic layer was successively washed with sat. aq. $NaHCO_3$, water, and brine and dried over $Na_2SO_4$. The solids were removed by filtration and the solvent was evaporated under reduced pressure to afford 9.95 g (91%) of compound **7** as a white solid. MS *m*/*z* 172.1 $(M + H)^+$. $^1$H NMR ($CDCl_3$) $\delta$ 7.42 (s, 1H), 4.02 (s, 3H).

**5-[(2-Chlorobenzoyl)amino]-1*H*-pyrazole-3-carboxylic Acid Methyl Ester (10).** To a solution of 9.35 g (0.05 mol) of 3-methoxycarbonyl-5-nitropyrazole (**7**) in 100 mL of MeOH was added 1.0 g of 5% Pd/C. The resulting mixture was vigorously stirred under 40 psi of $H_2$ until absorption ceased (~2 h). The catalyst was removed by filtration through Celite, rinsing with additional MeOH. The filtrate was evaporated to dryness to afford compound **8** which was clean enough for further elaboration. Compound **8** was then dissolved in a mixture of $CH_2Cl_2$−THF (3:2 v/v, 130 mL) and cooled in an ice bath. The mixture was stirred, and 7.9 g of pyridine (0.10 mol) was added followed by 0.2 g (1.6 mmol) of DMAP. After 10 min, a solution of 10.9 g (0.063 mol) of 2-chlorobenzoyl chloride in 20 mL of $CH_2Cl_2$ was added dropwise over 10 min. The resulting solution was stirred at 0 °C for 2 h, then allowed to warm to rt, and stirred for another 15 h. Sat. aq. $NaHCO_3$ (100 mL) was added, and the mixture was stirred at rt for 1 h. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were successively washed with water, 3 N HCl (3 × 100 mL), and water (100 mL) and finally dried over $Na_2SO_4$. The solvent was removed under reduced pressure, and the residue was dissolved in hot EtOAc (100 mL), diluted with hexane (100 mL), and left to stand for 2 h at rt followed by an additional 2 h in the refrigerator. The precipitated solids were collected by filtration, washed with cold hexane, and air-dried to give 13.5 g (88%) of methyl ester **10**. MS *m*/*z* 280.0 $(M + H)^+$. $^1$H NMR ($CDCl_3$) $\delta$ 10.39 (s, 1H), 7.70 (d, 1H), 7.46 (m, 4H), 3.63 (s, 3H).

**5-[(2-Chlorobenzoyl)amino]-1*H*-pyrazole-3-carboxylic Acid (11).** A mixture of 27.8 g (0.10 mol) of methyl ester **10** in 400 mL of THF was stirred as a solution of 20.7 g (0.49 mol) of $LiOH\cdot H_2O$ in 100 mL of MeOH, and 100 mL of water was added. The resulting yellow-green solution was stirred at rt for 20 h and then concentrated to about 200 mL. The solution was acidified with 2 N HCl to pH 2. The precipitated solids were collected by filtration, washed with water (3 × 100 mL), and dried under vacuum for 24 h to afford 25.7 g (97%) of acid **11** as a pale yellow solid. MS *m*/*z* 266.0 $(M + H)^+$. $^1$H NMR (DMSO-$d_6$) $\delta$ 11.14 (s, 1H), 7.53 (m, 4H), 7.01 (s, 1H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-1*H*-pyrazole-3-carboxylic Acid (12).** A solution of 12.3 g (0.05 mol) of acid **11** in 80 mL of anhydrous DMF was stirred at rt as a solution of 10.2 g (0.06 mol) of NBS in 20 mL of anhydrous DMF was added dropwise over 25 min. The reaction mixture was stirred at rt for 1 h, then diluted with 200 mL of water, and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with dilute aq HCl and dried over $MgSO_4$. The solvent was evaporated and the residue was triturated with $CH_2Cl_2$ (100 mL). The resulting solid was collected by filtration and air-dried for 2 h to afford 9.95 g (62%) of acid **12** as a cream-colored solid. MS *m*/*z* 343.9 $(M + H)^+$, 345.9 $(M + H)^+$. $^1$H NMR (DMSO-$d_6$) $\delta$ 10.41 (bs, 1H), 7.55 (m, 4H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-*N*-[4-[2-(4,5-dihydro-1*H*-imidazol-2-yl)ethyl]phenyl]-1*H*-pyrazole-3-carboxamide (16).** Compound **16** was prepared as described for compound **17** using carboxylic acid **12** and 4-[2-(4,5-dihydro-1*H*-imidazol-2-yl)ethyl]-benzenamine. MS *m*/*z* 513.1 $(M + H)^+$. $^1$H NMR ($CD_3OD$) $\delta$ 7.70−7.47 (m, 6H), 7.25 (m, 2H), 3.89 (m, 4H), 3.00 (m, 2H), 2.85 (m, 2H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-*N*-[2-[1-(4-pyridinyl)-4-piperidinyl]ethyl]-1*H*-pyrazole-3-carboxamide (17).** A mixture of 2.89 g (9.5 mmol) of [2-(3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-4-yl)ethyl]carbamic acid *tert*-butyl ester in 10 mL of neat TFA was stirred for 20 min at rt. Vigorous bubbling was observed as the carbamic ester dissolved. The TFA was then removed by rotary evaporation, and the residue was heated at 70 °C in vacuo (2 mm Hg) for 1 h to afford 2-(3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-4-yl)ethylamine as a viscous amber oil.

A solution of the ethylamine obtained above, 3.27 g (9.5 mmol) of carboxylic acid **12**, 7.3 mL (66.4 mmol) of NMM, and 1.54 g (11.4 mmol) of HOBT in 23.5 mL of DMF was stirred at rt as 2.19 g (11.4 mmol) of EDC·HCl was added. The reaction mixture was stirred for 18 h, and the white solid precipitate was collected by filtration. The solid was washed with warm (80 °C) water followed by washing with MeOH. The solid was dissolved in 1 M HCl and extracted with $CHCl_3$. The aqueous layer was then neutralized with solid $NaHCO_3$ at which point a white solid precipitated. The solid was collected by filtration and washed with EtOH to afford 2.67 g (53%) of compound **17**. MS *m*/*z* 531.0 $(M + H)^+$. $^1$H NMR (DMSO-$d_6$) $\delta$ 8.07 (m, 3H), 7.48−7.37 (m, 4H), 7.08 (d, $J = 6.2$ Hz, 2H), 4.12 (d, $J = 13.6$ Hz, 2H), 3.19 (s, 2H), 3.02 (dd (app. t), $J = 12.6$ Hz, 2H), 1.77 (d, $J = 12.4$ Hz, 2H), 1.63 (s, 1H), 1.37 (d, $J = 6.1$ Hz, 2H), 1.03 (m, 2H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-*N*-(2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-1*H*-pyrazole-3-carboxamide (18).** Compound **18** was prepared as described for compound **17** using carboxylic acid **12** and 3-amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one. MS *m*/*z* 579.0 $(M + H)^+$. $^1$H NMR (MeOD) $\delta$ 7.64 (m, 2H), 7.21−7.66 (m, 11H), 5.54 (s, 1H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-*N*-[(1*R*)-1-methyl-2-oxo-2-(1-piperidinyl)ethyl]-1*H*-pyrazole-3-carboxamide (19).** Compound **19** was prepared as described for compound **17** using carboxylic acid **12** and 1-[(2*R*)-2-amino-1-oxopropyl]piperidine. MS *m*/*z* 484.0 $(M + H)^+$. $^1$H NMR ($CDCl_3$) $\delta$ 9.20 (s, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 7.95 (d, $J = 7.1$ Hz, 1H), 7.41 (m, 3H), 5.05 (m, 1H), 3.50 (m, 4H), 1.53 (m, 5H), 1.38 (d, $J = 6.6$ Hz, 3H).

***N*-[[1-(6-Amino-2-pyridinyl)-4-piperidinyl]methyl]-4-bromo-5-[(2-chlorobenzoyl)amino]-1*H*-pyrazole-3-carboxamide (20).** A solution of 0.20 g (1.0 mmol) of 4-(*tert*-butoxycarbonylaminomethyl)piperidine and 0.50 g (2.9 mmol) of 2-amino-6-bromopyridine in 4.0 mL of toluene was stirred at 100 °C in a sealed tube. After 18 h, the reaction temperature was raised to 150 °C and stirring was continued for an additional 64 h. The reaction mixture was cooled to rt, quenched with sat. aq. $NaHCO_3$, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The product was isolated by flash chromatography on silica gel using 3:97 MeOH−$CH_2Cl_2$ as

eluant to afford 0.09 g (30%) of *tert*-butyl (1-(3-aminophenyl)-piperidin-4-yl)methylcarbamate as an amber oil.

A solution of 0.09 g (0.3 mmol) of *tert*-butyl (1-(3-aminophenyl)-piperidin-4-yl)methylcarbamate in 3.0 mL of neat TFA was stirred at rt for 30 min. The TFA was then removed by rotary evaporation, and the residue was concentrated in vacuo to afford 0.18 g of a mixture of 3-(4-(aminomethyl)piperidin-1-yl)aniline and entrained TFA. The aniline was coupled to carboxylic acid **12** as described for compound **17**. MS *m*/*z* 532.0 $(M + H)^+$. $^1$H NMR ($CD_3OD$) $\delta$ 8.28 (br, 1H), 7.63 (m, 2H), 7.56−7.42 (m, 3H), 6.22 (d, $J = 8.4$ Hz, 1H), 6.10 (d, $J = 8.4$ Hz, 1H), 3.97 (d, $J = 13.2$ Hz, 2H), 3.33 (m, 2H), 3.11 (t, $J = 12.1$ Hz, 2H), 1.94 (m, 3H), 1.40 (m, 2H).

***N*-(3*S*)-1-Azabicyclo[2.2.2]oct-3-yl-4-bromo-5-[(2-chlorobenzoyl)amino]-1*H*-pyrazole-3-carboxamide (21).** Compound **21** was prepared as described for compound **17** using carboxylic acid **12** and (*S*)-3-aminoquinuclidine dihydrochloride. MS *m*/*z* 451.9 $(M + H)^+$. $^1$H NMR ($CDCl_3$) $\delta$ 8.35 (br, 1H), 7.89 (d, $J = 7.0$ Hz, 1H), 7.51−7.38 (m, 3H), 7.22 (d, $J = 7.3$ Hz, 2H), 4.12 (m, 1H), 3.37 (dd, $J = 14.1$, 9.7 Hz, 1H), 2.84 (m, 4H), 2.67 (dd, $J = 14.0$, 4.5 Hz, 1H), 2.03 (m, 1H), 1.79−1.66 (m, 3H), 1.50−1.45 (m, 1H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-*N*-[2-(1-methyl-4-piperidinyl)ethyl]-1*H*-pyrazole-3-carboxamide (22).** Prepared as described for compound **17** using carboxylic acid **12** and 1-methyl-4-piperidineethanamine. MS *m*/*z* 468.0 $(M + H)^+$. $^1$H NMR ($CDCl_3$) $\delta$ 7.98 (d, $J = 7.7$ Hz, 1H), 7.54 (m, 2H), 7.50−7.43 (m, 1H), 7.22 (m, 1H), 3.49 (m, 3H), 2.81 (d, $J = 11.6$ Hz, 2H), 2.24 (s, 3H), 1.89 (m, 2H), 1.69 (m, 2H), 1.57 (m, 2H), 1.29 (m, 4H).

**(*R*)-4-Bromo-5-(2-chlorobenzamido)-*N*-(2-oxoazepan-3-yl)-1*H*-pyrazole-3-carboxamide (24).** Compound **24** was prepared as described for compound **17** using carboxylic acid **12** and (*R*)-3-amino-azepan-2-one. MS *m*/*z* 454.0 $(M + H)^+$. $^1$H NMR ($CD_3OD$) $\delta$ 7.65 (m, 1H), 7.40−7.52 (m, 3H), 5.48 (s, 3H), 4.72 (d, $J = 9.9$ Hz, 1H), 3.31 (m, 2H), 2.25−1.95 (m, 2H), 1.82−1.95 (m, 2H), 1.60 (m, 1H), 1.45 (m, 1H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-*N*-[(1*R*)-1-phenylethyl]-1*H*-pyrazole-3-carboxamide (25).** Compound **25** was prepared as described for compound **17** using carboxylic acid **12** and (*R*)-α-methylbenzylamine. MS *m*/*z* 448.9 $(M + H)^+$. $^1$H NMR ($CD_3OD$) $\delta$ 7.61 (d, $J = 7.1$ Hz, 1H), 7.37 (m, 8H), 5.19 (q, $J = 7.1$ Hz, 1H), 1.55 (d, $J = 7.1$ Hz, 1H).

**4-Bromo-5-[(2-chlorobenzoyl)amino]-*N*-4-pyridinyl-1*H*-pyrazole-3-carboxamide (26).** Compound **26** was prepared as described for compound **17** using carboxylic acid **12** and 4-aminopyrdine. MS *m*/*z* 421.9 $(M + H)^+$. $^1$H NMR (DMSO-$d_6$) $\delta$ 8.63 (d, $J = 7.1$ Hz, 2H), 8.17 (m, 2H), 7.55 (m, 4H).

***N*-[(1*S*)-2-Amino-2-oxo-1-phenylethyl]-4-bromo-5-[(2-chlorobenzoyl)amino]-1*H*-pyrazole-3-carboxamide (27).** Compound **27** was prepared as described for compound **17** using carboxylic acid **12** and (*S*)-α-aminobenzeneacetamide. MS *m*/*z* 475.9 $(M + H)^+$. $^1$H NMR (DMSO-$d_6$) $\delta$ 7.88 (s, 1H), 7.60−7.47 (m, 9H), 7.40−7.28 (m, 3H), 5.53 (bs, 2H).

**5-[(2-Chlorobenzoyl)amino]-*N*-[2-[1-(4-pyridinyl)-4-piperidinyl]ethyl]-1*H*-pyrazole-3-carboxamide (28).** Compound **28** was prepared as described for compound **17** using carboxylic acid **11**. MS *m*/*z* 453.1 $(M + H)^+$. $^1$H NMR (DMSO-$d_6$) $\delta$ 13.14 (s, 1H), 11.06 (s, 1H), 8.54 (s, 1H), 8.11 (d, $J = 6.0$ Hz, 2H), 7.40−7.56 (m, 4H), 6.80 (d, $J = 6.0$ Hz, 2H), 3.92 (m, 2H), 3.33 (m, 2H), 2.76 (m, 2H), 1.80 (m, 2H), 1.59 (m, 1H), 1.51 (m, 2H), 1.14 (m, 2H).

**5-Amino-1-phenyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (47).** A suspension of 1.01 g (6.2 mmol) of 3-cyano-2-oxo-propionic acid ethyl ester sodium salt and 1.08 g (7.5 mmol) of phenylhydrazine hydrochloride in 25 mL of ethanol was stirred and refluxed for 64 h. The reaction mixture was cooled to rt and filtered through Celite, and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel using 1:1 EtOAc−hexanes as eluant to afford 0.93 g (65%) of compound **47** as a rust-colored solid.

**5-[[[2-Chlorophenyl]carbonyl]amino]-1-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (48).** A solution of 0.31 g (1.3 mmol) of ethyl ester **47**, 0.17 mL (2.1 mmol) of pyridine, 0.18 g (1.4 mmol) of 2-chlorobenzoyl chloride, and 0.02 g (0.2 mmol) of DMAP in 4.0 mL of methylene chloride was stirred at rt for 18 h. The reaction mixture was adsorbed onto silica gel and chromatographed using 1:1 EtOAc−hexanes to afford 0.45 g (91%) of compound **48** as a clear, colorless, glassy solid. MS *m*/*z* 370.1 $(M + H)^+$. $^1$H NMR ($CDCl_3$) $\delta$ 8.67 (s, 1H), 7.75 (d, $J = 6.8$ Hz, 1H), 7.48 (s, 5H), 7.34 (m, 3H), 4.37 (q, $J = 7.2$ Hz, 2H), 1.38 (t, $J = 7.2$ Hz, 3H).

**5-[[[2-Chlorophenyl]carbonyl]amino]-1-methyl-1*H*-pyrazole-3-carboxylic Acid (49).** A solution of 0.43 g (1.2 mmol) of ethyl ester **48** and 0.25 g (6.0 mmol) of $LiOH\cdot H_2O$ in 4.0 mL of MeOH and 1.0 mL of water was stirred at rt for 64 h. The reaction mixture was concentrated by rotary evaporation and diluted with water. The pH was lowered to 3 with 1 M HCl. A gray precipitate formed that was triturated with ether and collected by filtration to afford 0.23 g (58%) of carboxylic acid **49**. MS *m*/*z* 342.0 $(M + H)^+$. $^1$H NMR ($CD_3OD$) $\delta$ 7.60−7.38 (m, 9H), 7.06 (s, 1H).

**Supporting Information Available:** Mass and $^1$H NMR characterization of compounds **23**, **29**−**45**, and **52**−**55** and purity determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM051292N