# Identification and Characterization of 4-Methylbenzyl 4-[(Pyrimidin-2-ylamino)methyl]piperidine-1-carboxylate, an Orally Bioavailable, Brain Penetrant NR2B Selective *N*-Methyl-D-Aspartate Receptor Antagonist

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The discovery of a novel series of NR2B subtype selective *N*-methyl-D-aspartate (NMDA) antagonists is reported. Initial optimization of a high-throughput screening lead afforded an aminopyridine derivative **13** with significant NR2B antagonist potency but limited selectivity over hERG-channel and other off-target activities. Further structure−activity studies on the aminoheterocycle moiety and optimization of the carbamate led to the highly potent 2-aminopyrimidine derivative **20j** with a significantly improved off-target activity profile and oral bioavailability in multiple species coupled with good brain penetration. Compound **20j** demonstrated efficacy in in vivo rodent models of antinociception, allodynia, and Parkinson's disease.

## Introduction

Glutamate receptors can be broadly divided into four separate classes: *N*-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate, and metabotropic glutamate (mGlu) receptors.[1] NMDA receptors have demonstrated a rich pharmacology that has provided a number of different modulatory sites as targets for medicinal chemists. The earliest work was done on noncompetitive compounds such as MK-801 (**1**) (Figure 1) and ketamine (**2**) that bind in the pore of the open channel at the magnesium binding site. Later, significant effort was devoted to the development of competitive antagonists, such as CPP (**3**), which interact at the glutamate binding site as well as compounds which act at the co-agonist glycine binding site, e.g., quinolinedione (**4**).[2] Representative compounds from these classes have demonstrated significant activity in preclinical models of chronic pain, stroke, and Parkinson's disease.[3] While clinical studies with ketamine[4,5] have offered tantalizing glimpses of therapeutic potential in treatment of neuropathic pain,[6] widespread use has been severely limited by the narrow therapeutic window and the serious side effects observed clinically, including psychotomimetic effects and cognitive disruption.[7]

The structure of the NMDA receptor has been elucidated in greater detail as a heteromultimeric complex made up of a combination of NR1 and NR2 subunits,[8] with eight splice variants of the NR1 subunit (a−h) characterized as well as four variants of the NR2 subunit (A−D).[9] Distribution of NR2B subunit mRNA is largely limited to the forebrain which suggested a potentially reduced propensity toward the side effects observed with nonselective compounds.[6,10] Additional evidence suggestive of a significant role for NR2B receptors in pain derives from mice overexpressing the NR2B subunit, which show enhanced sensitivity toward persistent pain.[11] The discovery that ifenprodil (**5**) binds selectively to NR2B sites[12] and the fact that the compound shows a much better separation of efficacy in animal models versus side effects[10] have resulted in significant efforts being devoted to identification of novel and selective NR2B antagonists.

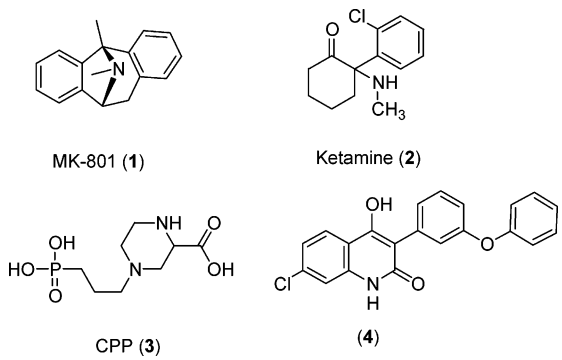


**Figure 1.** NMDA antagonists.

A number of phenol (or phenol surrogate) containing compounds derived from ifenprodil such as Ro25-6981 (**6**),[13] CP101,606 (**7**),[14] and CI-1041 (**8**)[15] (Figure 2), which demonstrate the desired selectivity profile over other NR2 receptor subtypes, have been identified. More recently, non-phenol classes of NR2B antagonists have been described,[16] for example amidines (e.g., **10**),[17] from these laboratories.

In this paper we report optimization of a series of structurally novel, non-phenol containing NR2B antagonists, which demonstrate good selectivity over other NR2 subtypes as well as good oral pharmacokinetics and robust effects in preclinical models of pain and Parkinson's disease.

High-throughput screening of the Merck sample collection led to identification of the 4-aminopyridine derivative **11**[18] (Figure 3) as a compound that showed significant NR2B activity in both a binding assay ($K_i$ = 93 nM) (Table 1) and cell based NR2B calcium flux assay[19,20] ($IC_{50}$ = 102 nM), with counterscreening showing no activity in a corresponding NR2A calcium flux assay $IC_{50}$ > 20 $\mu$M). While selectivity over other NR2 subtypes has generally not been an issue in designing NR2B

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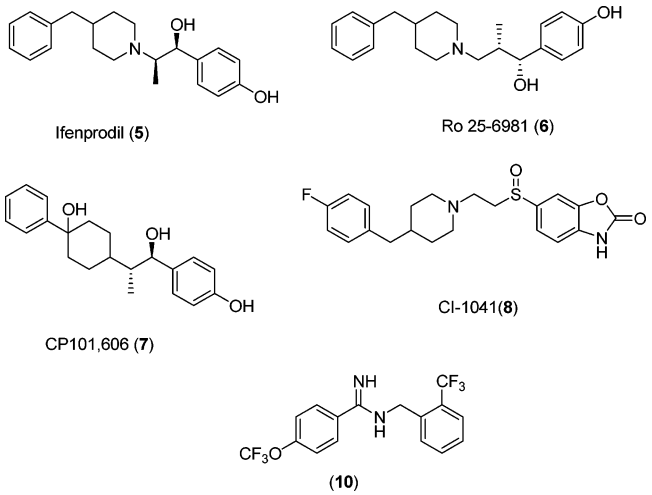



**Figure 2.** NR2B selective NMDA antagonists.

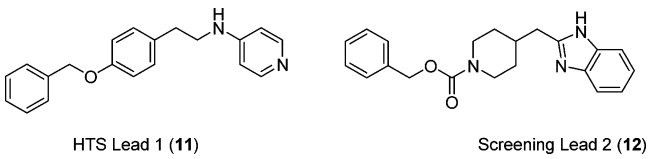
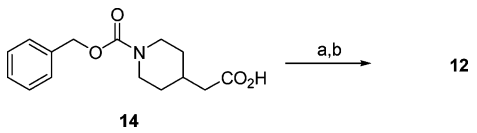



**Figure 3.** Screening leads.

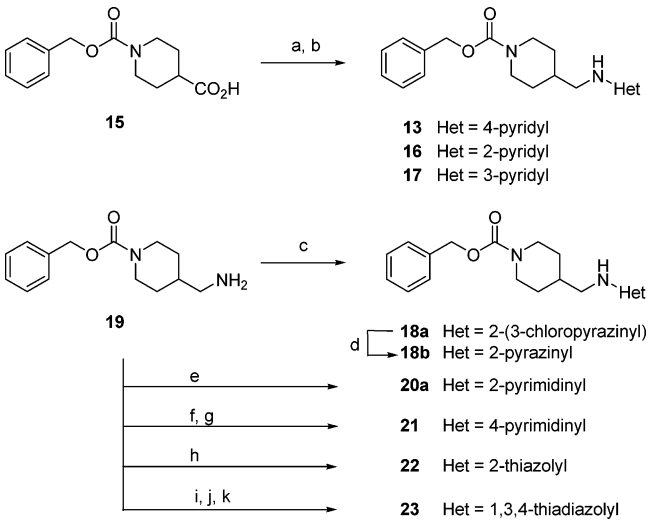
selective antagonists, in common with many other drug discovery programs, activity at the human ether-a-go-go (hERG) encoded channel[21] has been a more significant problem.[22,23] This channel is responsible for the $I_{Kr}$ current, a critical component in ventricular repolarization, with blockade leading to increased $QT_c$ interval and potentially to ventricular arrhythmias.[24] Binding to the hERG channel was identified as a serious issue for **11**, with no selectivity over hERG activity ($IC_{50}$ = 130 nM) as determined in an MK-499 binding assay.[25,26] While the $I_{Kr}$ activity clearly represented a major concern, the novelty of the parent structure convinced us that this could prove a valuable entry point for medicinal chemistry. We were intrigued by the potential relationship of **11** to another lead compound, benzimidazole **12**, which appeared to show some separation of NR2B activity ($K_i$ = 220 nM) and $IK_r$ activity (MK-499 $IC_{50}$ = 9600 nM). In particular we considered the possibility that, in the protonated state, the aminopyridine moiety could offer a hydrogen bond in a similar manner to the benzimidazole and that the remote aryl groups were separated by similar linker lengths of 8 and 7 atoms, respectively. A hybrid structure **13** was prepared and found to show enhanced NR2B activity ($K_i$ = 10.6 nM) and significantly reduced MK-499 binding liability ($IC_{50}$ = 960 nM). On the basis of this promising initial result, an in depth evaluation of the structure−activity relationship (SAR) around **13** was initiated.

**Scheme 1**[a]




[a] Reagents and conditions: (a) EDC, HOBt, 1,2-phenylenediamine, DMF, rt, 3 h; (b) acetic acid, reflux, 18 h.

**Scheme 2**[a]




[a] Reagents and conditions: (a) EDC, HOAt, $HetNH_2$, DMF, rt, 18 h; (b) $BH_3$·THF, THF, 0−25 °C, 18 h; (c) 2,3-dichloropyrazine, DIPEA, iPrOH, reflux 72 h; (d) i. $H_2$, Pd/C, $K_2CO_3$, EtOH, ii. benzylsuccinimidyl carbonate, DIPEA, DMF, rt, 4 h; (e) 2-chloropyrimidine, $Cs_2CO_3$, DMF, 70 °C, 18 h; (f) 4-chloro-2-methylthiopyrimidine, DIPEA, DMF, rt, 4 h; (g) Raney Ni, EtOH, $H_2$; (h) 2-bromothiazole, DIPEA, neat, 180 °C, 2 h; (i) *N*,*N*′-thiocarbonyldiimidazole, THF, 0 °C, 30 min; (j) hydrazine, rt, 30 min; (k) $(EtO)_3CH$, cat. HCl (concd), EtOH, reflux, 1.5 h.

## Chemistry

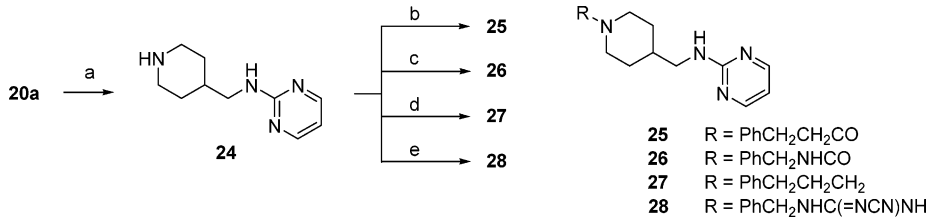
The benzimidazole **12** was readily prepared from CBZ protected piperidine acid **14**[27] via coupling with *o*-phenylenediamine and cyclization of the intermediate acid in acetic acid (Scheme 1).[28] Preparation of the hybrid aminopyridine compound **13** was straightforward via coupling of 4-aminopyridine with CBZ protected acid **15**,[29] followed by borane reduction (Scheme 2). The 2-aminopyridine and 3-aminopyridine analogues **16** and **17**, respectively, were prepared in a similar fashion.

**Table 1.** Aminoheterocycle Derivatives[a]

| compd | NR2B binding $K_i$ (nM)[b] | MK-499 IP (nM)[c] | [plasma] (nM)[d] | [brain] (nM)[d] | CYP2D6 $IC_{50}$ ($\mu$M)[e] | CYP2C9 $IC_{50}$ ($\mu$M)[f] | CYP3A4 $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|---|---|
| **11** | 93 ± 9 | 110 ± 26 | | | | | |
| **12** | 220 | 9600 | | | | | |
| **13** | 10.6 ± 4.1 | 960 | 8100 | 11000 | 15 | 6.5 | >25 |
| **16** | 37 ± 5 | 2900 ± 600 | 180 | 170 | >25 | >25 | >25 |
| **17** | 180 ± 40 | 2300 ± 2500 | | | 1.7 | 12 | 9.1 |
| **18b** | 14 ± 2 | 4200 | | | 1.7 | 12 | 22 |
| **20a** | 23 ± 8 | >10000 | 7200 | 3100 | >25 | >25 | >25 |
| **21** | 75 ± 5 | >10000 | 1100 | 700 | 1.3 | 0.5 | 5.1 |
| **22** | 122 ± 24 | 1070 ± 200 | | | >10[g] | >10[g] | >10[g] |
| **23** | 190 ± 32 | >10000 | | | >25 | >25 | >25 |

[a] All values are the mean ± standard deviation of at least $n$ = 3 measurements, except for **12**, where $n$ = 1. [b] Inhibition of $^3$H-[(E)-*N*$^1$-(2-methoxybenzyl)-cinnamamidine] binding to hNR1a/NR2B receptors expressed in Ltk- cells.[19,41] [c] Inhibition of MK-499 binding to hERG in HEK293 cells.[26] [d] Dosed at 30 mg/kg po; plasma and brain concentrations determined at 60 min after dosing. [e] Assay standard quinidine: $IC_{50}$ = 0.41 $\mu$M. [f] Assay standard sulfaphenazole: $IC_{50}$ = 0.35 $\mu$M. [g] Solubility limited.

**Scheme 3.** Synthesis of Piperidine Derivatives [a]




[a] Reagents and conditions: (a) $H_2$, 10% Pd/C, EtOH, rt, 18 h; (b) EDC, HOBt, 3-phenylpropionic acid, DMF, rt, 18 h; (c) benzyl isocyanate, THF, rt, 3 h; (d) phenylpropionaldehyde, AcOH, $NaBH(OAc)_3$, 4 Å sieves, DCE, rt, 30 min; (e) i. $(PhO)_2N{=}CN$, benzylamine, THF, −80 C to rt; ii. **24**, reflux, 15 h.

The 2-pyrazinyl analogue was prepared via displacement of the relatively reactive 2,3-dichloropyrazine to give **18a**, which after reductive dechlorination and reformation of the benzyl carbamate gave **18b**. 2-Aminopyrimidine **20a** was synthesized by direct nucleophilic displacement of the corresponding 2-chloropyrimidine with **19**, while formation of the 4-aminopyrimidine utilized a similar initial displacement with 2-chloro-4-methylthiopyrimidine, followed by Raney nickel mediated removal of the methylthio substituent to give **21**. More forcing conditions were required to effect the corresponding displacement in 2-bromothiazole—reaction with amine **19** in the presence of diisopropylethylamine in a sealed tube at 180 °C afforded a modest 24% yield of **22**. The 2-amino-1,3,4-thiadiazolyl derivative **23** was synthesized by sequential treatment of amine **19** with 1,1′-thiocarbonyldiimidazole and hydrazine hydrate, followed by treatment with triethyl orthoformate and catalytic HCl at reflux to effect cyclization.

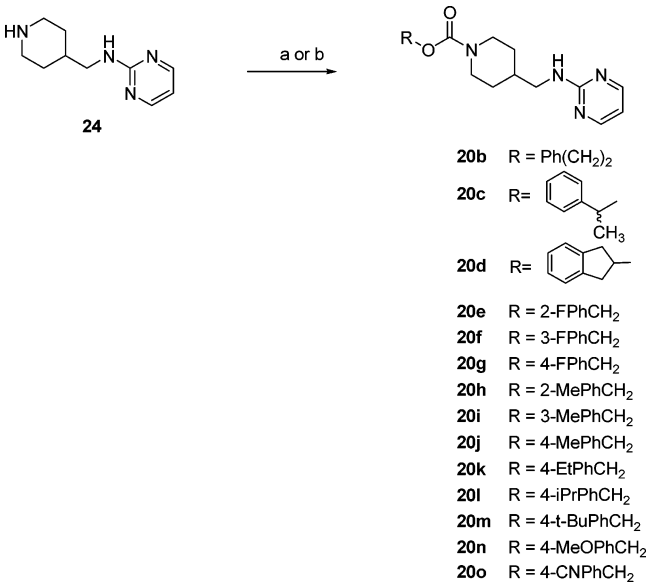
Derivatives in which alternative linker functionalities were employed on the piperidine nitrogen were readily accessible from **24** (Scheme 3) obtained by hydrogenation of benzyl carbamate **20a**: phenylpropionamide **25** via an EDC coupling; benzyl urea **26** by reaction with benzyl isocyanate in the presence of triethylamine; and phenylpropylamine **27** through a sodium triacetoxyborohydride mediated reductive amination. Cyanoguanidine analogue **28** was synthesized by stepwise reaction of diphenyl cyanocarbonimidate, first with benzylamine and then with amine **24**.

Alternative carbamate derivatives of **20a**, (**20b**−**n**), were prepared by one of two routes shown in Scheme 4. DMAP catalyzed reaction of the appropriate alcohol with disuccinimidyl carbonate[30] gave the corresponding alkoxy succinimidyl carbonate which reacted readily at room temperature with piperidine **24** in either DMF or DCM. Alternatively, in a single flask preparation, the alcohol was reacted with *N*,*N*′-carbonyldiimidazole in DMF, followed by addition of amine **24** and heating to complete carbamate formation.

The aminopiperidine analogue (**32**) of **20a** was prepared from mono-BOC protected aminopiperidine **29** (Scheme 5) via formation of the 4-methylbenzyl carbamate **30** with 4-methylbenzyl succinimidyl carbonate, TFA removal of the BOC group to afford **31**, and reaction with 2-chloropyrimidine. A reversed sequence of reactions was employed to synthesize aminoethyl analogue **36** based on availability of the monoprotected aminoethypiperidine **33**. Reaction of **33** with 2-chloropyrimidine and subsequent BOC removal from the product **34** gave after benzyl carbamate formation the desired derivative **36**. Ether linked analogue, **41**, was readily available in two steps from 4-hydroxymethylpiperidine **40**, by carbamate formation with 4-methylbenzylsuccinimidyl carbonate and subsequent reaction of the sodium alkoxide with 2-chloropyrimidine.

To satisfy requirements for larger quantities of methylbenzylcarbamate **20j** for in vivo studies, a more direct synthesis was developed (Scheme 6) which involved only a single

**Scheme 4**[a]



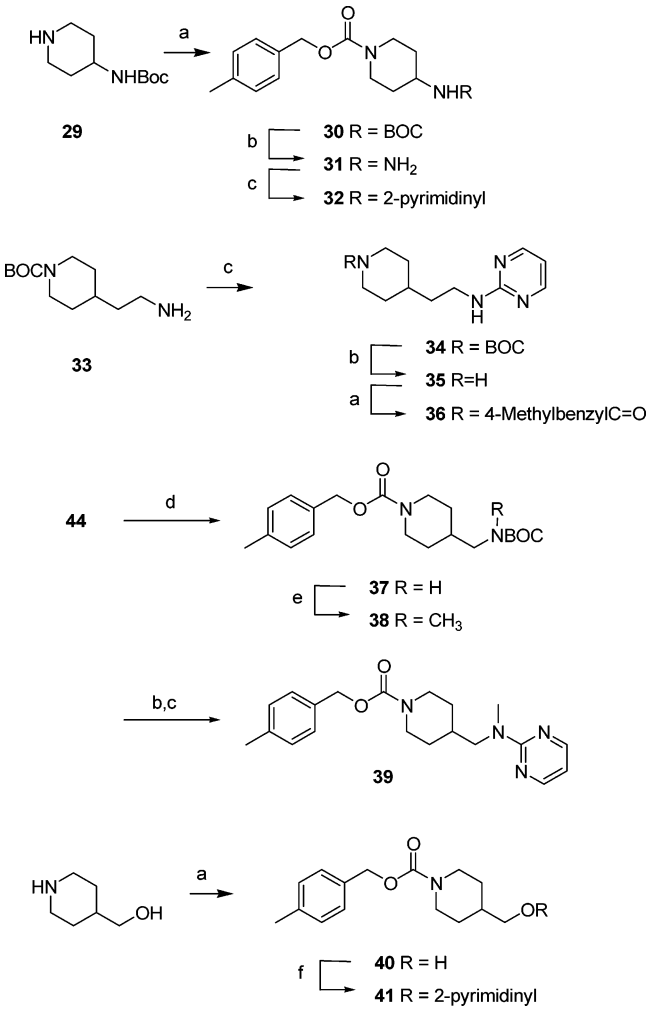

[a] Reagents and conditions: (a) i. disuccinimidyl carbonate, ROH, MeCN, DCM, rt, 2 h; ii **24**, DMF, rt, 18 h; (b) i. *N*,*N*′-carbonyldiimidazole, ROH, DMF, rt, 1 h; ii. **24**, HCl salt, $Et_3N$, 55 °C, 18 h.

chromatographic purification of final product. The Schiff's base of 4-aminomethylpiperidine (**42**) was prepared by treatment with benzaldehyde under Dean−Stark conditions in toluene, followed by a solvent switch to DCM, and reaction with 4-methylbenzyl succinimidyl carbonate **43**. A second solvent switch to THF and treatment with 2 M HCl resulted in hydrolysis of the imine, and acid base extraction yielded the aminopiperidine **44**. Reaction of **44** and 2-chloropyrimidine in a 1:1 *n*-butanol/diisopropylethylamine mixture at reflux followed by chromatographic purification and crystallization from 2-propanol/hexane gave **20j** in 75% overall yield on a >100 g scale.

## Results and Discussion

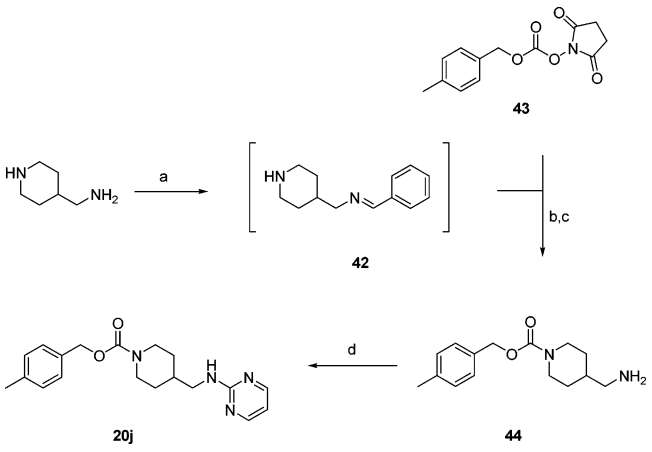
On the basis of the enhanced 90-fold selectivity for NR2B binding over MK-499 binding exhibited by aminopyridine **13**, a more detailed evaluation of the compound was undertaken. In a functional NR2B calcium flux assay, **13** showed potent inhibition of calcium entry into NR1a/2B receptor transfected Ltk cells with an $EC_{50}$ of 1.6 nM. In contrast, **13**, showed no activity in a corresponding assay utilizing NR1a/2A receptor transfected Ltk cells ($EC_{50}$ >10 000 nM). Pharmacokinetic experiments in rat and dog (Table 2) showed that the compound was orally bioavailable in both species, albeit with relatively high clearance. The >100% bioavailability in rat suggested inhibition or saturation of a clearance mechanism, and indeed **13** was found to be a moderate reversible inhibitor of the CYP2D6 isoform of p450 ($IC_{50}$ = 6.5 $\mu$M), thereby presenting another potential issue for this structural series. When **13** was

**Scheme 5**[a]




[a] Reagents and conditions: (a) 4-methylbenzyl succinimidyl carbonate, $Et_3N$, $CH_2Cl_2$, rt, 1 h; (b) TFA, $CH_2Cl_2$, rt, 20 min; (c) 2-chloropyrimidine, *n*-BuOH, DIPEA, 140 °C, 4 h; (d) $(BOC)_2O$, DCM, rt, 30 min; (e) NaH, DMF:THF 1:1, t, 2 h; (f) NaHMDS, DMF, 2-chloropyrimidine, 0 °C, 30 min.

**Scheme 6**[a]




[a] Reagents and conditions: (a) PhCHO, toluene, reflux, 2 h; (b) $CH_2Cl_2$, 5 °C to rt, 1 h; (c) 2 M HCl, THF, rt, 1 h; (d) 2-chloropyrimidine, *n*-BuOH, DIPEA, reflux 3 h.

dosed to rats at 30 mg/kg orally, brain levels were shown to be greater than plasma levels (Table 1), and consistent with this observation and the in vitro data, **13** demonstrated activity in the carageenan induced hyperalgesia assay with an $ED_{50}$ of 3 mg/kg after iv dosing and 10 mpk after po administration. While **13** exhibited an attractive profile in some important respects, a broad based Panlabs receptor/ion channel screen identified 12 activities at $<5\ \mu$M, and these, coupled with the p450 inhibition and unacceptable remaining level of hERG activity, represented significant unsolved issues. We considered that a number of these off-target activities, particularly the remaining hERG activity, could be related to the strongly basic nature of the 4-aminopyridine moiety. It has previously been proposed that basic amine containing hERG blockers are involved in a $\pi$-cation interaction with Y652,[31,32] and this suggested a focus on alternative less basic heterocycles to the pyridine. The first compound prepared, 2-aminopyridine **16**, showed a moderate approximately 3-fold loss in both NR2B and MK499 activity. Of more concern were the radically different plasma and brain levels relative to **13** after oral dosing, with an approximately 40-fold reduction in each observed, albeit with a 1:1 brain: plasma partitioning maintained. 3-Amino analogue **17** proved to have a less encouraging in vitro profile, with a larger 17-fold drop in NR2B activity, accompanied by significantly increased CYP2D6 inhibition as well as some modest CYP2C9 activity. 2-Aminopyrazine analogue **18b** showed no significant loss in NR2B activity relative to pyridine lead **13**, but improvement in MK-499 binding was a relatively modest 4-fold, and once again with a nitrogen meta to the point of attachment, significant CYP2D6, 2C9 and 3A4 activity was apparent. The 4-aminopyrimidine **20a** and 2-aminopyrimidine **21** both fully addressed the MK-499 binding issue with $IC_{50} > 10\ \mu$M. In terms of NR2B binding activity, a smaller 2-fold loss in activity was observed with **20a** vs 7-fold for **21**. However the largest differentiating in vitro factor proved to be radically different p450 inhibition profiles. The 4-aminopyrimidine analogue **21**, exhibited more potent activity vs CYP2D6 and 2C9 isoforms than the lead 4-aminopyridine **13**, while in contrast, the 2-aminopyrimidine analogue **20a** lacked significant activity vs the same isoforms as well as CYP3A4. The thiazolyl and thiadiazolyl analogues **22** and **23** both demonstrated 10- to 20-fold losses in NR2B activity with only modest improvements in MK-499 binding, giving lower selectivity ratios and making them less attractive for follow up.

One hour after oral dosing at 30 mg/kg, 2-aminopyrimidine **20a** maintained high plasma levels coupled with good partitioning into brain while 4-aminopyrimidine analogue **21** afforded somewhat intermediate levels in both plasma and brain. On the basis of the clear advantages in the profile of **20a**, which addressed all of the key issues with lead **13**, 2-aminopyrimidine **20a** was selected as a heterocyclic terminus for SAR studies around the carbamate moiety. Alternative linking functionalities in place of the carbamate were evaluated first, with the amide **25** demonstrating a relatively modest 13-fold loss in NR2B binding, while the urea **26** and cyanoguanidine **28** showed larger shifts (50- and 130-fold, respectively). None of these non-basic piperidine derivatives was associated with significant MK-499 binding; however, in the phenylpropylamino analogue **27** which did retain reasonable NR2B binding, significant MK-499 activity reemerged, most likely due to the reintroduction of a strongly basic amine center. With these linkers proving inferior from an NR2B binding standpoint and with no clear advantages over the initially discovered carbamate, a more detailed study of carbamate substituents was undertaken to optimize the parent compound **20a**.

Homologation of the benzyl carbamate to the phenethyl derivative **20b** resulted in approximately 100-fold loss in NR2B activity (Table 3), and introduction of an α-methyl substituent

**Table 2.** Pharmacokinetic Parameters of Key Compounds[a]

| compd | species | iv dose (mg/kg) | Clp (mL/min/kg) | $T_{1/2}$ (h) | AUC (mM h) | po dose (mg/kg) | $C_{max}$(nM) | $F$ (%) |
|---|---|---|---|---|---|---|---|---|
| **13** | rat | 2 | 70 | 1.4 | 1.9 | 10 | 5200 | >100 |
| **13** | dog | 0.5 | 14 | 6.5 | 1.7 | 1 | 50 | 11 |
| **20j** | rat | 2 | 26 | 2.7 | 7.1 | 10 | 3900 | 45 |
| **20j** | dog | 1 | 6.7 | 6.9 | 7.5 | 1 | 840 | 24 |
| **20j** | rhesus | 1 | 9.5 | 2.2 | 5.2 | 1 | 600 | 26 |

[a] Plasma levels from PK experiments carried out as described in Experimental Section.

**Table 3.** 2-Aminopyrimidines[a]

| compd | NR2B binding $K_i$ (nM)[b] | MK-499 IP (nM)[c] |
|---|---|---|
| **20b** | 227 ± 48 | >10000 |
| **20c** | 540 ± 75 | >10000 |
| **20d** | 23 ± 5 | 6100 ± 700 |
| **20e** | 18 ± 3 | >10000 |
| **20f** | 150 ± 17 | >10000 |
| **20g** | 18 ± 6 | >10000 |
| **20h** | 227 ± 46 | >10000 |
| **20i** | 206 ± 15 | 9200 ± 1500 |
| **20j** | 3.4 ± 2.2 | >10000 |
| **20k** | 3.7 ± 1.6 | 5200 ± 2300 |
| **20l** | 7.8 ± 4.1 | 5800 ± 200 |
| **20m** | 720 ± 310 | 4200 ± 500 |
| **20n** | 460 ± 530 | >10000 |
| **20o** | 1250 ± 310 | 5000 ± 100 |
| **25** | 310 ± 47 | >10000 |
| **26** | 1170 ± 280 | >10000 |
| **27** | 266 ± 11 | 470 ± 40 |
| **28** | 3100 ± 170 | >10000 |
| **32** | >15000 | >10000 |
| **36** | 3180 ± 430 | 3100 ± 700 |
| **39** | 2100 ± 110 | >10000 |
| **41** | 7400 ± 300 | >10000 |

[a] All values are the mean ± standard deviation of at least $n = 3$ measurements. [b] Inhibition of $^3$H-[(E)-*N*$^1$-(2-methoxybenzyl)-cinnamamidine] binding to hNR1a/NR2B receptors expressed in Ltk-cells.[19,41] [c] Inhibition of MK-499 binding to hERG in HEK293 cells.[26]

into the carbamate also yielded a significantly less active compound **20c**. As demonstrated by **20d**, by incorporating an α-substituent into a cyclopentyl ring to give the indanyl analogue, potency comparable to **20a** was retained. The data from a relatively small initial study of fluoro and methyl substituents on the benzyl carbamate indicated the presence of a lipophilic binding pocket at the 4-position of the phenyl ring, with the 4-methyl substituent present in **20j** imparting a 7-fold improvement in NR2B binding activity over the parent compound while maintaining the MK-499 binding above 10 μM. Corresponding 2- and 3-methyl analogues **20h** and **20i**, in contrast, led to significant decreases in NR2B binding potency. Additional follow-up with larger 4-alkyl substituents demonstrated that NR2B activity did not increase further with an ethyl group (**20k**) and began to decrease slightly with isopropyl derivative **20l** and more dramatically with *t*-butyl compound **20m**. At the same time, MK-499 binding began to reemerge as an issue with the larger substituents, particularly in **20m**. More polar substituents were not well tolerated at the 4-position, with the methoxy analogue **20n** showing a 250-fold loss in activity relative to the isosteric ethyl derivative **20k** and a similar loss observed for the 4-cyano compound **20o**.

Several structural variants of **20j** were prepared to probe the optimal piperidine-pyrimidine spacer as well as the potential hydrogen-bonding role of the aminopyrimidine NH. The importance of the spacer length at each end of derivative **20j** was demonstrated by the aminopiperidine derivative **32** and aminoethylpiperidine analogue **36** which both showed >200-fold decreases in NR2B binding. The critical role of the aminopyrimidine NH was demonstrated by synthesis of the *N*-methyl analogue **39** and the ether linked compound **41**, which also showed dramatic losses in activity.

On the basis of the SAR data obtained in this series, 2-aminopyrimidine **20j** was selected for more detailed evaluation of the in vitro and in vivo profile. In an NR2B calcium flux assay, **20j** showed potent activity ($EC_{50}$ = 5.6 nM, maximum block ≥95%). The selectivity of **20j** vs the other three NR2 subtypes containing receptors was determined by a patch clamp assay on Ltk cells expressing NR1a and NR2A, C, D, with no significant activity observed at concentrations up to 30 μM (<25% block). Off-target activity was assessed in a broad based Panlabs in vitro screening assay of **20j** and, in contrast to **13**, showed no significant liabilities, with <50% activity in all assays at 10 μM. In addition, **20j** showed no significant CYP2D6, 2C9, or 3A4 inhibition.

Oral bioavailability of **20j** across rat, dog, and rhesus was >20%, coupled with moderate clearance and an iv $T_{1/2}$ > 2 h in all three species. On the basis of this favorable combination of in vitro activity, selectivity, and pharmacokinetics, the behavior of **20j** in a number of in vivo rodent models of pain and Parkinson's disease was investigated.

Efficacy of **20j** in a carageenan induced hyperalgesia assay was determined 60 min after oral dosing (Figure 4a), with approximately 50% reversal of hyperalgesia observed at 10 mg/kg. At this dose and time-point, plasma levels were 1800 ± 150 nM, with brain levels of 850 ± 40 nM. In an iv dosing protocol, with activity and compound levels measured 15 min post dosing, an $ED_{50}$ of 1 mg/kg was determined, and relatively consistent with the oral dosing data, plasma levels at the 1 mg/kg dose were 960 ± 60 nM with brain levels of 510 ± 50 nM. Comparison of levels of **20j** in brain and plasma from iv and po hyperalgesia assay animals across doses showed that **20j** was highly brain penetrant with a brain/plasma ratio ∼1.4 that was consistent across a broad range of concentrations from 300 nM to 60 000 nM (Figure 4b). Relatively rapid equilibration between brain and plasma was apparent with intravenous dosing and measurement at 15 min giving the same distribution as oral dosing and 1 h measurements. In common with other NR2B selective antagonists, a dramatic separation of antinociceptive effect from motor coordination deficit as determined in the rotarod assay was seen, with no motor impairment observed at doses up to 100 mg/kg po.

While the carageenan induced hyperalgesia model is often used as a first line antinociceptive assay with relevance to inflammatory pain, other assays are considered more predictive of clinical efficacy in treatment of neuropathic pain. Many rodent models of neuropathic pain have been developed, one of the foremost among these is the rat L5/L6 spinal nerve ligation model (SNL).[33] In this assay, compounds such as indomethacin, which shows a robust effect in the hyperalgesia assay, show no reduction in allodynia, paralleling a lack of efficacy observed in patients with neuropathic pain. In contrast, the widely clinically used gabapentin demonstrated good efficacy and tricyclic antidepressant amitriptyline showed a

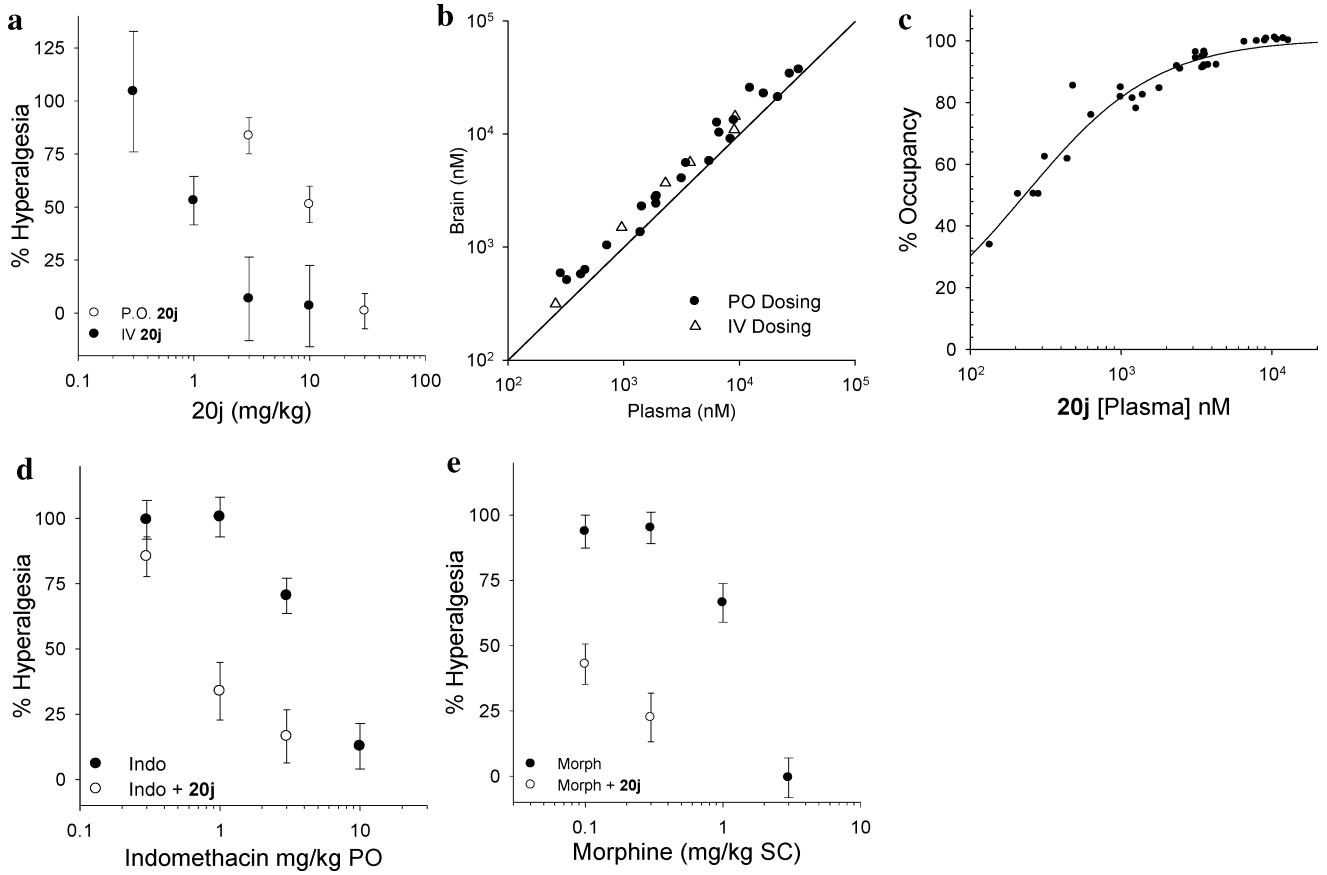



**Figure 4.** Rat in vivo antinociceptive assay data for **20j**: (a) iv and po hyperalgesia ± SEM $n = 6$ for iv, $n = 24$ for po; (b) brain and plasma levels from hyperalgesia experiments; (c) relationship of plasma level and ex vivo receptor occupancy; (d) hyperalgesia synergy with indomethacin and 3 mg/kg **20j** ± SEM $n = 32$, activity of 3 mg/kg **20j** alone 101.9 ± 8.1%; (e) hyperalgesia synergy with morphine and 3 mg/kg **20j** ± SEM $n = 32$, activity of 3 mg/kg **20j** alone 92.4 ± 5%.

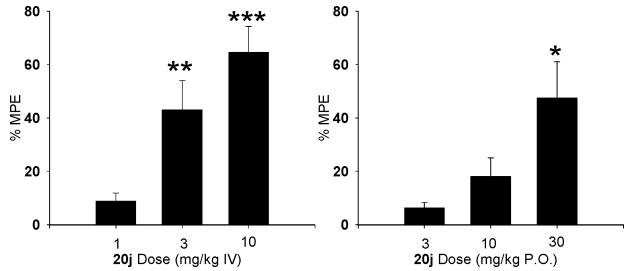



**Figure 5.** Effect of **20j** on allodynia in rat SNL model ($n = 10$ ± SEM, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$).

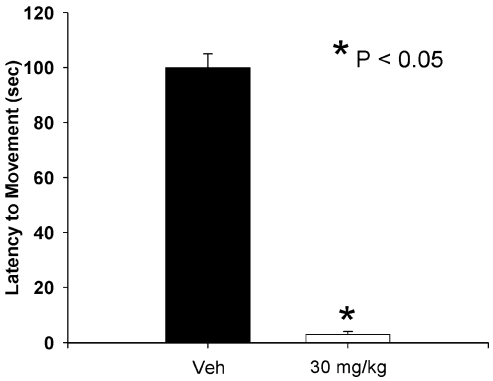



**Figure 6.** Haloperidol induced catalepsy data for **20j** after po dosing ($n = 6$).

positive trend.[34] In this model, treatment with **20j** via iv administration elicited a significant reversal of allodynia at doses of 3 and 10 mg/kg ($P < 0.01$ and $P < 0.001$, respectively) (Figure 5). After po dosing, a significant effect was observed at 30 mg/kg ($P < 0.05$).

Having thus demonstrated activity of **20j** in two preclinical pain models, we sought to evaluate the effect in a preclinical model of Parkinson's disease, a potential alternative therapeutic use of NMDA antagonists. In this model, a cataleptic state is induced by treatment of rats with the dopamine antagonist in haloperidol as previously described,[35] and therapeutic agents are evaluated for their ability to reverse this state. Compound **20j** in 1% methylcellulose was dosed orally to rats 1 h after haloperidol administration; after an additional 30 min, catalepsy was measured by placing rats on a vertical grid and measuring latency to forepaw movement. In the vehicle control group, the level of haloperidol induced catalepsy is reflected by a latency to forepaw movement of approximately 100 s. Compound **20j** when administered at a dose of 30 mg/kg (corresponding to measured plasma levels of experiment 10 200 ± 2 200 nM; $n = 6$) (Figure 6).

In order to make some assessment of receptor occupancy associated with activity in these assays, brain receptor occupancy of **20j** in rat was determined in an ex vivo binding assay using $^3$H-(E)-$N^1$-(2-methoxybenzyl)-cinnamamidine[36] (Figure 4c). This provided a plasma level of 230 nM corresponding to 50% occupancy of receptors ($Occ_{50}$) in brain.

A theoretical $Occ_{50}$ plasma level was derived as follows with key assumptions: (1) rapid equilibration exists between drug in brain and plasma; (2) drug is freely brain penetrant by passive diffusion with no Pgp substrate activity; and (3) free drug concentration in brain under these conditions is equal to free

drug concentration in plasma. Evidence to support the first of these assumptions is provided by the brain/plasma level data shown in Figure 4b, where sampling at 15 and 60 min post dosing affords the same brain plasma ratio. The lack of Pgp substrate activity was confirmed in in vitro experiments with human (L-MDR1) and mouse (L-mdr1a) transfected cells (transcellular transport ratio B-A/A-B 0.7, 0.7) and passive permeability was found to be high ($32 \times 10^{-6}$ cm$^{-1}$),[37] again suggesting that brain/plasma partitioning should be rapid and that there should not be a free drug concentration gradient maintained across the blood−brain barrier. The NR2B $K_i$ was measured at 37 °C (9.7 ± 2.6 nM, $n = 6$) vs the standard experimental procedure run at room temperature. Rat plasma protein binding of **20j** measured with $^{14}$C material was found to be 84.7%, providing a calculated free plasma and brain drug level at 50% receptor occupancy of 35 nM (free fraction of 0.153 × 230 nM), in reasonable agreement with the experimentally derived value. Similar calculations can provide a prediction of receptor occupancy in other species where measurement is precluded.

Using the observed plasma levels from hyperalgesia experiments and the experimental occupancy data suggest occupancy of 80−90% is necessary for 50% efficacy. Additional hyperalgesia experiments were carried out with a relatively low occupancy dose (3 mg/kg po, predicted occupancy 50−60%) in combination with two other agents acting via different mechanisms, indomethacin (Figure 4d) and morphine (Figure 4e). In both cases, addition of **20j** caused a significant leftward shift in the dose−response curve, while the 3 mg/kg dose of **20j** alone resulted in no significant efficacy (101.9 ± 8.1% and 92.4 ± 5.7%, respectively), suggesting synergy between different mechanisms of action in this assay.

## Conclusions

Optimization of a hybrid structure of two lead compounds led to the identification of 4-methylbenzyl 4-[(pyrimidin-2-ylamino)methyl]piperidine-1-carboxylate, **20j**, an orally bioavailable and brain penetrant compound that shows good receptor occupancy in rat, together with efficacy in antinociceptive assays including the rodent L5/L6 nerve ligation model of neuropathic pain. In addition, **20j** demonstrates a significant reversal of haloperidol induced catalepsy in a preclinical model of Parkinson's disease. This activity in models of two key proposed therapeutic uses of NR2B antagonists, coupled with the lack of off-target activity suggests that **20j** could be useful in more advanced models of these disease states as well as establishing the role of NR2B antagonists in models of other diseases in which NR2B has been implicated[38] such as Huntingdon's disease.[39] Additional data on the effects of **20j** in some of these models will be reported elsewhere.

## Experimental Section

**General Information.** All reagents and solvents were of commercial quality and used without further purification unless indicated otherwise. All reactions were carried out under an inert atmosphere of nitrogen. $^1$H NMR spectra were obtained on a Varian VXR-300S spectrometer, a Varian Unity Inova 400 spectrometer, or a Varian Unity Inova 500 spectrometer. Chemical shifts are reported in parts per million relative to TMS as internal standard. Samples provided for accurate mass measurement were taken up in acetonitrile:water:glacial acetic acid (50:50:0.1%v/v). The solutions were analyzed by use of electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on either a Bruker Daltonics 3T or 7T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. External calibration was accomplished with polypropylene glycol (425 or 750). Melting points were determined in open glass capillaries using a Thomas-Hoover UniMelt melting point apparatus and are uncorrected. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Silica gel chromatography was carried out with an ISCO CombiFlash Sg 100c purification system using ISCO silica gel RediSep cartridges. Preparative reverse-phase HPLC was performed using a Gilson 215 liquid handler and a Phenomenex Luna C18 column (150 × 20 mm I.D.) with a linear gradient over 15 min (95:5 to 5:95 $H_2O$:acetonitrile, containing 0.1% trifluoroacetic acid).

**Pharmacokinetics.** Pharmacokinetic characterization of test agents was conducted in conscious male Sprague−Dawley rats (300−500 grams; $n = 3-4$/ study), male and female beagle dogs (13−15 kg; $n = 2$/study), or male rhesus (4−6 kg, $n = 2$/study). In all species, single doses of test agents were administered either intravenously in a vehicle of 100% DMSO or orally by gavage in a vehicle of 1% methylcellulose aqueous suspension. Typical test doses were 2 mg/kg iv and 10 mg/kg po to rats; 0.5−1 mg/kg iv and 1−3 mg/kg po to dogs, and 1 mg/kg iv and po to rhesus. Blood samples for the determination of test agent plasma concentration were obtained at multiple time points up to 24 h after single dose test agent administration.

Inhibition of NMDA receptor-activated currents at recombinant human NMDA receptor subtypes was determined as described previously.[28]

Carrageenan induced mechanical hyperalgesia in rat was determined as described previously.[28]

Rat spinal nerve ligation model was carried out according to the procedure previously described.[40] The %MPE was calculated as follows:

$$\%\text{MPE} = (\text{posttreatment value} - \text{pretreatment value})/(\text{preoperation cutoff value} - \text{pretreatment value})$$

**Ex Vivo Rat Receptor Occupancy Assay.** At 15 min following iv dosing and 60 min following po dosing of **20j**, rats were anesthetized with isoflurane. A 1 mL blood sample was obtained by cardiac puncture and centrifuged to obtain plasma which was frozen and later assayed for test agent concentration by LC/MS/MS. A sample of frontal cortex was removed, rinsed, weighed, and frozen. A homogenate of the frontal cortex was added to wells contain 10 nM [$^3$H]-[(*E*)-*N*$^1$-(2-methoxybenzyl)-cinnamamidine] in the presence or absence of 10 μM of **20j** (all at 4 °C). Following incubation at 4 °C, the amount of specific binding of [$^3$H]-[(*E*)-*N*$^1$-(2-methoxybenzyl)-cinnamamidine] was determined and compared to an untreated animal. The specific binding observed in the untreated animal defines 0% occupancy and the absence of any specific binding defines 100% occupancy. The observed occupancies (i.e., % inhibition of the ex vivo binding of [$^3$H]-[(*E*)-*N*$^1$-(2-methoxybenzyl)-cinnamamidine]) were plotted vs total drug levels determined by LC/MS/MS. This data was fit using SigmaPlot to a single binding site isotherm to obtain the reported $Occ_{50}$ values.

Reversal of haloperidol induced catalepsy was determined as described elsewhere,[37] with **20j** being dosed 1 h after haloperidol and latency to paw movement times on a vertical grid measured 30 min later.

**CYP Inhibition Assays.** Incubations (100 μL) containing 100 mM potassium phosphate buffer (pH 7.4), NADP (1 mM), glucose-6-phosphate (2 mM), glucose-6-phosphate dehydrogenase (0.3 U/mL), $MgCl_2$ (5 mM), test compound at various concentrations, 0.25 mg/mL (3A4 and 2C9) or 0.5 mg/mL (2D6) pooled human liver microsomes, and substrate (3A4, 50 μM testosterone; 2D6, 10 μM dextromethorphan; 2C9, 10 μM diclofenac) were incubated for 15 min (3A4, 2C9) or 45 min (2D6) at 37 °C. The incubations were stopped by the addition of 20 μL of a solution that containing an internal standard (3A4, 5 μM cortisone; 2D6, 7 μM propanolol; 2C9, 5 M labetalol), 3.4% formic acid, and 5% $CH_3CN$. The degree of product formation, 3A4, 6β-hydroxytestosterone; 2D6, dextrorphan; 2C9, 4-hydroxydiclofenac), was quantified using reverse phase liquid chromatography and a Sciex API3000 triple quadrupole mass spectrometer for detection. The mass spectrometer was

equipped with an APCI source using positive ionization in selected reaction monitoring (SRM) mode.

**Benzyl 4-(1*H*-Benzimidazol-2-ylmethyl)piperidine-1-carboxylate (12).** To a solution of {1-[(benzyloxy)carbonyl]piperidin-4-yl}acetic acid **14** (185 mg, 0.67 mmol) in DMF (3 mL) were added 1-hydroxybenzotriazole (HOBt) (100 mg, 0.74 mmol), *o*-phenylenediamine (80 mg, 0.74 mmol), and EDC (141 mg, 0.74 mmol). The reaction mixture was stirred at room temperature for 3 h and partitioned between EtOAc and aqueous $NaHCO_3$ (×3). The combined organic phases were washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated to afford a solid which was taken up in acetic acid (5 mL) and heated to 100 °C for 18 h. The reaction mixture was cooled and concentrated, and the oily residue partitioned between EtOAc and saturated aqueous $NaHCO_3$ (×3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated, and the residue was purified by chromatography on silica gel (2% MeOH/EtOAc) to give **12** as a solid: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.55 (br s, 1 H), 7.52 (br s, 2 H), 7.35 (m, 5 H), 7.21 (m, 4 H), 5.12 (s, 2 H), 4.17 (br s, 2 H), 2.9 (m, 4 H), 2.11 (m, 1 H), 1.72 (br d, 2 H), 1.25 (m, 2 H) ppm; HRMS (ESI) *m*/*z* 350.1869 [$(M + H)^+$; calcd for $C_{21}H_{24}N_3O_2$: 350.1863].

**Benzyl 4-[(Pyridin-4-ylamino)methyl]piperidine-1-carboxylate (13).** To a solution of benzyl 4-(aminomethyl)piperidine-1-carboxylate **15** (5.45 g, 20.7 mmol) in DMF (50 mL) were added 1-hydroxy-7-azabenzotriazole (HOAt) (3.10 g, 20.8 mmol), 4-aminopyridine (3.12 g, 33.1 mmol), and EDC (4.37 g, 22.8 mmol). The reaction mixture was stirred at room temperature for 18 h and partitioned between EtOAc and aqueous $NaHCO_3$ (×3). The combined organic phases were washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by silica gel chromatography (99:1:0.1 to 75:25:2.5 DCM:MeOH:$NH_4OH$) afforded a foam (4.34 g) that was dissolved in THF (50 mL), treated with borane (1M THF complex, 100 mL, 100 mmol), and stirred at room temperature for 18 h. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of 2 M HCl, stirred for 30 min at room temperature, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic phase was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by silica gel chromatography (99:1:0.1 to 90:10:1 DCM:MeOH:$NH_4OH$) afforded **13** (2.7 g, 40%). The oxalate salt of **13** was prepared by treatment with oxalic acid (0.748 g, 8.31 mmol) in ethanol: mp (oxalate salt) 145−147 °C; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.9−8.15 (m, 2 H), 7.35 (m, 5 H), 6.88 (br s, 2 H), 5.10 (s, 2 H), 4.18 (br d, $J$ = 11.6 Hz, 2 H), 3.24 (d, $J$ = 6.8 Hz, 2 H), 2.85 (m, 2 H), 1.75−1.95 (m 3 H), 1.22 (m, 2 H) ppm; HRMS (ESI) *m*/*z* 326.1872 [$(M + H)^+$; calcd for $C_{19}H_{24}N_3O_2$: 326.1863]. Anal. ($C_{19}H_{23}N_3O_2 \cdot C_2O_4$) C, H, N.

**Benzyl 4-[(Pyridin-2-ylamino)methyl]piperidine-1-carboxylate (16).** Utilizing the procedure for **13** with 2-aminopyridine afforded **16**, characterized as the oxalate salt: mp 132−134 °C; $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 7.80−7.85 (m, 2 H), 7.30−7.40 (m, 5 H), 6.98 (d, $J$ = 9.0 Hz, 1 H), 6.82 (t, $J$ = 6.2 Hz, 1 H), 5.11 (s, 2 H), 4.19 (br d, $J$ = 13.4 Hz, 2 H), 3.24 (d, $J$ = 7.1 Hz, 2 H), 2.86 (br s, 2 H), 1.80−1.95 (m, 3 H), 1.22 (dq, $J$ = 4.1, 12.3 Hz, 2 H) ppm; HRMS (ESI) *m*/*z* 326.1872 [$(M + H)^+$; calcd for $C_{19}H_{24}N_3O_2$: 326.1863]. Anal. ($C_{19}H_{23}N_3O_2 \cdot C_2H_2O_4$) C, H, N.

**Benzyl 4-[(Pyridin-3-ylamino)methyl]piperidine-1-carboxylate (17).** Using the procedure for **13** with 3-aminopyridine afforded **17**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (br s, 2 H), 7.30−7.37 (m, 5 H), 7.10 (br s, 1 H), 6.85 (d, $J$ = 8.0 Hz, 1 H), 5.13 (s, 2 H), 4.23 (br s, 2 H), 3.78 (br s, 1 H), 3.04 (t, $J$ = 6.0 Hz, 2 H), 2.78 (m, 2 H), 1.70−1.90 (m, 2 H), 1.15−1.30 (m, 2 H) ppm; HRMS (ESI) *m*/*z* 326.1839 [$(M + H)^+$; calcd for $C_{19}H_{24}N_3O_2$: 326.1863]. Anal. ($C_{19}H_{23}N_3O_2 \cdot 0.25H_2O$) C, H, N.

**Benzyl 4-{[(3-Chloropyrazin-2-yl)amino]methyl}piperidine-1-carboxylate (18a)**. A mixture of amine **19** (749 mg, 3.02 mmol), 2,3-dichloropyrazine (900 mg, 6.04 mmol), and diisopropylethylamine (2.10 mL, 12.08 mmol) in iPrOH (50 mL) was heated to reflux for 72 h, the volatiles evaporated, and the residue partitioned between EtOAc and aqueous $NaHCO_3$ solution. The organic extract was washed with brine and dried over anhydrous $MgSO_4$, solvent evaporated, and the crude product purified by chromatography on silica (30% EtOAc/hexane) to afford a colorless oil (1.02 g, 94%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.93 (d, $J$ = 2.8 Hz, 1 H), 7.58 (d, $J$ = 2.8 Hz, 1 H), 7.30−7.39 (m, 5 H), 5.28 (br s, 1 H), 5.14 (s, 2 H), 4.23 (br s, 2 H), 3.39 (t, $J$ = 6.4 Hz, 2 H), 2.80 (m, 2 H), 1.70−1.90 (m, 3 H), 1.10−1.30 (m, 2 H) ppm; HRMS (ESI) *m*/*z* 361.1440 [$(M + H)^+$; calcd for $C_{18}H_{22}ClN_4O_2$: 361.1426]. Anal. ($C_{18}H_{21}ClN_4O_2 \cdot 0.1H_2O$) C, H, N.

**Benzyl 4-[(Pyrazin-2-ylamino)methyl]piperidine-1-carboxylate (18b)**. A solution of chloropyrazine **18a** (727 mg, 2.01 mmol) in EtOH (50 mL) was treated with 10% Pd/C (150 mg) and $K_2CO_3$ (556 mg, 4.03 mmol) and hydrogenated under a balloon of $H_2$ for 1 h. The mixture was filtered through Celite and the filtrate evaporated, taken up in EtOAc/$CH_2Cl_2$ (20 mL, 1:1), filtered, and the filtrate evaporated to a solid (260 mg) which was dissolved in DMF (5 mL) and diisopropylethylamine (704 $\mu$L, 4.05 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (403 mg, 1.62 mmol) added. The reaction mixture was stirred at room temperature for 4 h and partitioned between EtOAc and saturated $NaHCO_3$ solution, the organic layer was washed with brine and dried over anhydrous $MgSO_4$, and solvent was evaporated in vacuo. Chromatography on silica gel (97:3:0.3 DCM:MeOH:$NH_4OH$) afforded **18b** (333 mg, 51%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.97 (br s, 1H), 7.88 (s, 1 H), 7.80 (d, $J$ = 2.8 Hz, 1 H), 7.28−7.40 (m, 5 H), 5.13 (s, 2 H), 4.64 (br s, 1 H), 4.23 (br s, 2 H), 3.28 (m, 2 H), 2.79 (m, 2 H), 1.70−1.90 (m, 3 H), 1.15−1.30 (m, 2 H) ppm; HRMS (ESI) *m*/*z* 327.1826 [$(M + H)^+$; calcd for $C_{18}H_{23}N_4O_2$: 327.1816]. Anal. ($C_{18}H_{22}N_4O_2 \cdot 0.5H_2O$) C, H, N.

**Benzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20a).** A mixture of amine **19** (13.29 g, 53 mmol) and 2-chloropyrimidine (6.43 g, 56.2 mmol) and $Cs_2CO_3$ (34.9 g, 107 mmol) in DMF (50 mL) was heated to 70 °C for 18 h, cooled to room temperature, and partitioned between water and EtOAc. The organic layer was washed with water and brine and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated in vacuo. The residue was purified by chromatography on silica (DCM:iPrOH: hexane 10:1:89 to 10:20:70) to afford **20a** (12.02 g, 69%). A portion (200 mg) of this was converted to the oxalate salt as described in the preparation of **13** to give **20a** oxalate salt: mp 99−100 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J$ = 4.8 Hz, 2 H), 7.25 (d, $J$ = 7.8 Hz, 2 H), 7.16 (d, $J$ = 7.8 Hz, 2 H), 6.51 (t, $J$ = 4.8 Hz, 1 H), 5.32 (br t, $J$ = 5.6 Hz, 1 H), 5.07 (s, 2 H), 4.19 (br s, 2 H), 3.32 (t, $J$ = 6.4 Hz, 2 H), 2.76 (br t, $J$ = 12.1 Hz, 2 H), 2.35 (s, 3 H), 1.77 (m, 3 H), 1.19 (m, 2 H) ppm; HRMS (ESI) *m*/*z* 327.1824 [$(M + H)^+$; calcd for $C_{18}H_{23}N_4O_2$: 327.1816]. Anal. ($C_{18}H_{22}N_4O_2 \cdot C_2H_2O_4$) C, H, N.

**Phenethyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20b).** A mixture of phenethyl alcohol (253 mg, 2.1 mmol) and disuccinimidyl carbonate (530 mg, 2.1 mmol) in acetonitrile (10 mL) and $CH_2Cl_2$ (10 mL) was treated with 4-dimethylaminopyridine (84 mg, 0.68 mmol), and the reaction mixture stirred for 2 h at room temperature. Amine **24** (400 mg, 2.1 mmol) was added, followed by DMF (2 mL), and the mixture stirred at room temperature for 18 h. The reaction mixture was concentrated and partitioned between pH 5.2 citrate buffer and EtOAc, and the organic layer was washed with $NaHCO_3$ solution and brine and dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was purified by chromatography on silica (50 to 100% EtOAc/hexane) to give **20b** (263 mg, 37%): mp 85−86 °C (triturated from ether/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 4.8 Hz, 2 H), 7.20−7.34 (m, 5 H), 6.53 (t, $J$ = 4.75 Hz, 1 H), 5.16 (br t, 1 H), 4.29(t, $J$ = 6.9 Hz, 2 H), 4.10 (br m, 2 H), 3.32 (t, $J$ = 6.5 Hz, 2 H), 2.94 (t, $J$ = 6.9 Hz, 2 H), 2.73 (br t, $J$ = 12.1 Hz, 2 H), 1.78 (m, 3 H), 1.20 (m, 2 H) ppm; HRMS (ESI) *m*/*z* 341.1985 [$(M + H)^+$; calcd for $C_{19}H_{25}N_4O_2$: 341.1972]. Anal. ($C_{19}H_{24}N_4O_2$) C, H, N.

**(±)-1-Phenethyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20c).** Using the above procedure for **20b**, with (±)-1-phenethanol provided **20c** (23%): mp 95−96 °C (triturated from ether/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 4.8 Hz,

2 H), 7.30 (m, 5 H), 6.52 (t, $J = 4.8$ Hz, 1 H), 5.81 (q, $J = 6.3$ Hz, 1 H), 5.17 (br s, 1 H), 4.20 (br d, $J = 13.3$ Hz, 2 H), 3.33 (br s, 2 H), 2.77 (m, 2 H), 1.81 (m, 3 H), 1.53 (d, 3 H, $J = 6.6$ Hz), 1.20 (m, 2 H) ppm; HRMS (ESI) *m/z* 341.1990 [(M + H)$^+$; calcd for $C_{19}H_{25}N_4O_2$: 341.1972]. Anal. ($C_{19}H_{24}N_4O_2$) C, H, N.

**2,3-Dihydro-1*H*-inden-2-yl 4-[(Pyrimidin-2-ylamino)methyl]-piperidine-1-carboxylate (20d).** Using the above procedure for **20b**, with 2-indanol provided **20d** (46%): mp 104−105 °C (triturated from ether/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J = 4.8$ Hz, 2 H), 7.16−7.36 (m, 4 H), 6.52 (t, $J = 4.8$ Hz, 1 H), 5.47 (m, 1 H), 5.14 (br m, 1 H), 4.21 (br s, 1 H), 4.01 (br s, 1 H), 3.31 (m, 4 H), 3.02 (dd, $J = 3.2$, 16.9 Hz, 2 H), 2.72 (dt, $J = 13.2$, 2.7 Hz, 2 H), 1.60−1.90 (m, 3 H), 1.00−1.20 (m, 2 H) ppm; HRMS (ESI) *m/z* 352.1975 [(M + H)$^+$; calcd for $C_{20}H_{25}N_4O_2$: 353.1972]. Anal. ($C_{20}H_{24}N_4O_2 \cdot C_2H_2O_4$) C, H, N.

**2-Fluorobenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20e).** 2-Fluorobenzyl alcohol (83 mg, 0.66 mmol) was added to a solution of *N*,*N*′-carbonyldiimidazole in DMF (4 mL), the mixture was stirred at room temperature for 1 h, and amine **24** dihydrochloride (175 mg, 0.66 mmol) was added, followed by triethylamine (202 $\mu$L, 1.452 mmol), and the reaction mixture was heated to 55 °C for 18 h. The cooled mixture was partitioned between aqueous $NH_4Cl$ solution and EtOAc, the organic layer was washed with water and brine and dried over anhydrous $Na_2SO_4$, and solvent was evaporated in vacuo. The crude product was purified by chromatography on silica (30−100% EtOAc/hexane) to afford **20e** (147 mg): mp 46−47 °C (triturated from ether/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J = 4.8$ Hz, 2 H), 7.00−7.40 (m, 4 H), 6.52 (t, $J = 4.8$ Hz, 1 H), 5.19 (s, 2 H), 5.15 (m, 1 H), 4.10−4.30 (m, 2 H), 3.33 (t, $J = 6.4$ Hz, 2 H), 2.70−2.90 (m, 2 H), 1.70−1.90 (m, 3 H), 1.10−1.30 (m, 2 H) ppm; HRMS (ESI) *m/z* 345.1723 [(M + H)$^+$; calcd for $C_{18}H_{22}FN_4O_2$: 345.1722]. Anal. ($C_{18}H_{21}FN_4O_2$) C, H, N.

**3-Fluorobenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20f).** Using the above procedure for **20e**, with 3-fluorobenzyl alcohol provided **20f** (67%): mp 70−71 °C (triturated from ether/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J = 4.8$ Hz, 2 H), 7.31 (q, $J = 7.9$ Hz, 1 H), 7.11 (d, $J = 7.6$ Hz, 1 H), 7.05 (d, $J = 9.6$ Hz, 1 H), 6.99 (dt, $J = 2.4$, 8.5 Hz, 1 H), 6.53 (t, $J = 4.8$ Hz, 1 H), 5.17 (m, 1 H), 5.11 (s, 2 H), 4.10−4.30 (m, 2 H), 3.33 (t, $J = 6.5$ Hz, 2 H), 2.70−2.90 (m, 2 H), 1.70−1.90 (m, 3 H), 1.10−1.30 (m, 2 H) ppm; HRMS (ESI) *m/z* 345.1722 [(M + H)$^+$; calcd for $C_{18}H_{22}FN_4O_2$: 345.1722]. Anal. ($C_{18}H_{21}FN_4O_2$) C, H, N.

**4-Fluorobenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20g).** Using the above procedure for **20b**, with 4-fluorobenzyl alcohol provided **20g**, characterized as the HCl salt (43%): mp 125−127 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J = 4.8$ Hz, 2 H), 7.33 (m, 2 H), 7.03 (m, 2 H), 6.51 (t, $J = 4.8$ Hz, 1 H), 5.72 (br t, $J = 5.9$ Hz, 1 H), 5.08 (s, 2 H), 4.10−4.30 (m, 2 H), 3.32 (t, $J = 6.2$ Hz, 2 H), 2.70−2.90 (m, 2 H), 1.70−1.90 (m, 3 H), 1.10−1.30 (m, 2 H) ppm; HRMS (ESI) *m/z* 345.1726 [(M + H)$^+$; calcd for $C_{18}H_{22}FN_4O_2$: 345.1722]. Anal. ($C_{18}H_{21}FN_4O_2 \cdot HCl$) C, H, N.

**2-Methylbenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20h).** Using the above procedure for **20e**, with 2-methylbenzyl alcohol provided **20h** (60%) as an oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J = 4.8$ Hz, 2 H), 7.32 (d, $J = 7.1$ Hz, 1 H), 7.15−7.30 (m, 3 H), 6.51 (t, $J = 4.8$ Hz, 1 H), 5.42 (m, 1 H), 5.13 (s, 2 H), 4.10−4.30 (m, 2 H), 3.33 (t, $J = 6.4$ Hz, 2 H), 2.70−2.90 (m, 2 H), 2.34 (s, 3 H), 1.70−1.90 (m, 3 H), 1.10−1.30 (m, 2 H) ppm; HRMS (ESI) *m/z* 341.1980 [(M + H)$^+$; calcd for $C_{19}H_{25}N_4O_2$: 341.1972].

**3-Methylbenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20i).** Using the above procedure for **20e**, with 3-methylbenzyl alcohol provided **20i** (53%) as an oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J = 4.8$ Hz, 2 H), 7.10−7.30 (m, 4 H), 6.51 (t, $J = 4.8$ Hz, 1 H), 5.27 (m, 1 H), 5.08 (s, 2 H), 4.10−4.30 (m, 2 H), 3.33 (t, $J = 6.4$ Hz, 2 H), 2.70−2.90 (m, 2 H), 2.35 (s, 3 H), 1.70−1.90 (m, 3 H), 1.10−1.30 (m, 2 H) ppm; HRMS (ESI) *m/z* 341.1981 [(M + H)$^+$; calcd for $C_{19}H_{25}N_4O_2$: 341.1972].

**4-Methylbenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20j).** 4-Aminomethylpiperidine (56 g, 495 mmol) and benzaldehyde (52 g, 495 mmol) in toluene (1,100 mL) were heated to reflux under Dean−Stark conditions for 2 h, until the accumulation of water ceased. The reaction mixture was cooled, and the toluene was removed under reduced pressure. To the resulting oil was added $CH_2Cl_2$ (1,100 mL), and the solution was cooled to 5 °C and treated with 4-methyl-*N*-(benzyloxycarbonyloxy)succinimide[30] (130 g, 495 mmol). After 10 min, the cooling bath was removed and the resulting reaction mixture stirred for 1 h. The solvents were evaporated, and the residue was stirred with THF (550 mL) and 2 M HCl (550 mL) for 1 h. The mixture was concentrated to remove organics and extracted with ether (3 × 300 mL). The cooled (0 °C) aqueous phase was adjusted to pH 14 with 50% NaOH and extracted with EtOAc. The organic layer was washed with water and brine and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated to give **42** as an oil. Compound **42** (138 g crude weight) was dissolved in *n*-butanol/ diisopropylethylamine (1:1 mixture, 380 mL) and treated with 2-chloropyrimidine (66.0 g, 576 mmol). The reaction mixture was heated to reflux for 3 h, cooled to room temperature, and concentrated to an oil which was chromatographed on silica (EtOAc to 1% MeOH/EtOAc). This material was dissolved in 2-propanol (556 mL) with gentle warming and allowed to cool and crystallize. Upon stirring 3 h at room temperature, hexane (556 mL) was added dropwise, and the mixture was stirred for 18 h. The solids were filtered, washed with 2-propanol/hexane (1:1, 50 mL), and dried to give **20j** (127 g, 75% overall yield): mp 99−100 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J = 4.8$ Hz, 2 H), 7.25 (d, $J = 7.8$ Hz, 2 H), 7.16 (d, $J = 7.8$ Hz, 2 H), 6.51 (t, $J = 4.8$ Hz, 1 H), 5.32 (br t, $J = 5.6$ Hz, 1 H), 5.07 (s, 2 H), 4.19 (br s, 2 H), 3.32 (t, $J = 6.4$ Hz, 2 H), 2.76 (br t, $J = 12.1$ Hz, 2 H), 2.35 (s, 3 H), 1.77 (m, 3 H), 1.19 (m, 2 H) ppm; HRMS (ESI) *m/z* 341.1968 [(M + H)$^+$; calcd for $C_{19}H_{25}N_4O_2$: 341.1972]. Anal. ($C_{19}H_{24}N_4O_2$) C, H, N.

**4-Ethylbenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20k).** Using the above procedure for **20b**, with 4-ethylbenzyl alcohol provided **20k** (42%): mp 132−134 °C (triturated from iPrOH/hexane); $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 8.60 (br s, 2 H), 7.28 (d, $J = 8.1$ Hz, 2 H), 7.22 (d, $J = 7.8$ Hz, 2 H), 7.00 (t, $J = 5.4$ Hz, 1 H), 5.09 (s, 2 H), 4.19 (br d, $J = 13.4$ Hz, 2 H), 3.43 (d, $J = 6.8$ Hz, 2 H), 2.86 (br s, 2 H), 2.66 (q, $J = 7.6$ Hz, 2 H), 1.93 (m, 1 H), 1.81 (br d, $J = 12.2$ Hz, 2 H), 1.15−1.30 (m, 5 H) ppm; HRMS (ESI) *m/z* 355.2131 [(M + H)$^+$; calcd for $C_{20}H_{27}N_4O_2$: 355.2129]. Anal. ($C_{20}H_{26}N_4O_2 \cdot HCl$) C, H, N.

**4-Isopropylbenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20l).** Using the above procedure for **20b**, with 4-isopropylbenzyl alcohol provided **20l** (48%): mp 74−75 °C (triturated from ether/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J = 4.8$ Hz, 2 H), 7.28 (d, $J = 8.1$ Hz, 2 H), 7.21 (d, $J = 8.1$ Hz, 2 H), 6.52 (t, $J = 4.8$ Hz, 1 H), 5.20 (m, 1 H), 5.09 (s, 2 H), 4.20 (br s, 2 H), 3.33 (t, $J = 6.4$ Hz, 2 H), 2.91 (sept, $J = 6.9$ Hz, 1 H), 2.77 (m, 2 H), 1.78 (m, 3 H), 1.24 (d, $J = 6.9$ Hz, 6 H), 1.20 (m, 2 H) ppm; HRMS (ESI) *m/z* 369.2311 [(M + H)$^+$; calcd for $C_{21}H_{29}N_4O_2$: 369.2285]. Anal. ($C_{21}H_{28}N_4O_2$) C, H, N.

**4-*tert*-Butylbenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20m).** Using the above procedure for **20e**, with 4-*tert*-butylbenzyl alcohol provided **20m** (61%): mp 107−109 °C (triturated from ether/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J = 4.8$ Hz, 2 H), 7.38 (d, $J = 8.2$ Hz, 2 H), 7.29 (d, $J = 8.2$ Hz, 2 H), 6.52 (t, $J = 4.8$ Hz, 1 H), 5.16 (m, 1 H), 5.09 (s, 2 H), 4.10−4.30 (m, 2 H), 3.33 (t, $J = 6.4$ Hz, 2 H), 2.70−2.90 (m, 2 H), 1.70−1.90 (m, 3 H), 1.10−1.30 (m, 2 H) ppm; HRMS (ESI) *m/z* 383.2439 [(M + H)$^+$; calcd for $C_{22}H_{31}N_4O_2$: 383.2442]. Anal. ($C_{22}H_{30}N_4O_2$) C, H, N.

**4-Methoxybenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20n).** Using the above procedure for **20e**, with 4-methoxybenzyl alcohol provided **20n** (55%): mp 95−96 °C (triturated from ether/hexane); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J = 4.9$ Hz, 2 H), 7.29 (d, $J = 8.6$ Hz, 2 H), 6.88 (d, $J = 8.6$ Hz, 2 H), 6.52 (t, $J = 4.9$ Hz, 1 H), 5.19 (m, 1 H), 5.05 (s, 2 H), 4.10−4.30 (m, 2 H), 3.81 (s, 2 H), 3.32 (t, $J = 6.4$ Hz, 2 H), 2.70−

2.90 (m, 2 H), 1.70−1.90 (m, 3 H), 1.10−1.30 (m, 2 H) ppm; HRMS (ESI) *m/z* 379.1740 [(M+Na)$^+$; calcd for $C_{19}H_{24}N_4O_3Na$: 379.1740]. Anal. ($C_{19}H_{24}N_4O_3$) C, H, N.

**4-Cyanobenzyl 4-[(2-Pyrimidinylamino)methyl]-1-piperidinecarboxylate (20o).** Using the above procedure for **20b**, with 4-cyanobenzyl alcohol provided **20o** (68%): mp = 123−124 °C (triturated from ether/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 4.9 Hz, 2 H), 7.65 (d, $J$ = 6.6 Hz, 2 H), 7.44 (d, $J$ = 6.6 Hz, 2 H), 6.53 (t, $J$ = 4.8 Hz, 1 H), 5.20 (br m, 3 H), 4.19 (br s, 2 H), 3.35 (t, $J$ = 6.4 Hz, 2 H), 2.81 (br s, 2 H), 1.84 (m, 3 H), 1.23 (m, 2 H) ppm; HRMS (ESI) *m/z* 352.1790 [(M + H)$^+$; calcd for $C_{19}H_{22}N_5O_2$: 352.1768]. Anal. ($C_{19}H_{21}N_5O_2$) C, H, N.

**Benzyl 4-[(Pyrimidin-4-ylamino)methyl]piperidine-1-carboxylate (21).** A mixture of amine **19** (2.00 g, 8.05 mmol), 4-chloro-2-methylthiopyrimidine (1.36 g, 8.45 mmol), and diisopropylethylamine (1.68 mL, 12.1 mmol) in DMF (10 mL) was stirred at room temperature for 18 h, poured into aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with water and brine and dried over anhydrous $Na_2SO_4$, and solvent was evaporated in vacuo to afford, after chromatography on silica gel (99:1:0.1 to 90:10:1 $CH_2Cl_2$:MeOH:$NH_4OH$), a white solid (2.34 g). Raney nickel (1.1 g) was washed with ethanol (×2) and resuspended in ethanol (20 mL) to which a solution of the solid from the first step in ethanol (10 mL) was added. The reaction mixture was stirred under a hydrogen atmosphere for 18 h. Additional Raney nickel (11 g) as an ethanol suspension was added, and the mixture was shaken under hydrogen at 55 psi for 18 h. The reaction mixture was filtered through Celite, the filtrate was evaporated, and the residue was purified by chromatography on silica gel (99:1:0.1 to 90:10:1 $CH_2Cl_2$:MeOH:$NH_4OH$, to afford **21** as an oil (720 mg, 27% overall yield). Conversion to the oxalate salt was accomplished by treatment of this oil (710 mg, 2.18 mmol) in ethanol (10 mL) with oxalic acid (196 mg, 2.18 mmol), filtration, and drying in vacuo: mp 179−181 °C; $^1$H NMR (400 MHz, $CD_3$-OD) $\delta$ 8.61 (br s, 1 H), 8.02 (br d, 1 H), 7.2−7.4 (m, 5 H), 6.70 (br d, 1 H), 5.10 (s, 2 H), 4.17 (br d, $J$ = 13.3 Hz, 2 H), 3.47 (br d, 2 H), 2.7−2.95 (br s, 2 H), 1.7−1.95 (m, 3 H), 1.15−1.25 (m, 2 H) ppm; HRMS (ESI) *m/z* 327.1824 [(M + H)$^+$; calcd for $C_{18}H_{23}N_4O_2$: 327.1816]. Anal. ($C_{18}H_{22}N_4O_2 \cdot C_2H_2O_4$) C, H, N.

**Benzyl 4-[(1,3-Thiazol-2-ylamino)methyl]piperidine-1-carboxylate (22).** A mixture of amine **19**, (300 mg, 1.21 mmol), 2-bromothiazole (198 mg, 1.21 mmol), and diisopropylethylamine (420 $\mu$L, 2.42 mmol) was heated to 180 °C in a sealed tube for 2 h, cooled to room temperature, and partitioned between pH 5.2 citrate buffer and EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution and brine and dried over anhydrous sodium sulfate, solvent was evaporated in vacuo, and the residue was purified by chromatography on silica gel (50 to 100% EtOAc/hexane) to provide **22** (24%) as a white solid: mp 111−113 °C (triturated from ether/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.28−7.38 (m, 5 H), 7.10 (d, $J$ = 3.7 Hz, 1 H), 6.48 (d, $J$ = 3.7 Hz, 1 H), 5.28 (br s, 1 H), 5.13 (s, 2 H), 4.22 (br s, 2 H), 3.20 (m, 2 H), 2.79 (m, 2 H), 1.86 (m, 3 H), 1.21 (m, 2 H) ppm; HRMS (ESI) *m/z* 332.1443 [(M + H)$^+$; calcd for $C_{17}H_{22}N_3O_2S$: 332.1427]. Anal. ($C_{17}H_{21}N_3O_2S$) C, H, N.

**Benzyl 4-[(1,3,4-Thiadiazol-2-ylamino)methyl]piperidine-1-carboxylate (23).** A solution of amine **19** (1.00 g, 4.03 mmol) in DMF (2 mL) was added to a cooled (0 °C) solution of *N*,*N*′-thiocarbonyldiimidazole (718 mg, 4.03 mmol) in DMF (10 mL). The reaction mixture was stirred at 0 °C for 30 min, the cooling bath was removed, and the mixture was stirred for 1 h before addition of hydrazine (250 $\mu$L, 8.05 mmol) and stirring for an additional 30 min. The mixture was then partitioned between dilute $NaHCO_3$ solution and EtOAc, the organic layer was washed with water and brine and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated in vacuo to a solid. The crude solid was triturated with MeOH (5 mL) for 1 h, filtered, and dried in vacuo to afford 940 mg of a solid.

A portion of this solid (366 mg, 1.14 mmol) was suspended in EtOH (5 mL), and triethyl orthoformate (378 $\mu$L, 2.27 mmol) was added, followed by concentrated HCl (40 $\mu$L, catalytic). The reaction mixture was heated to reflux for 1.5 h, cooled to room temperature, and partitioned between dilute $NaHCO_3$ solution and EtOAc, the organic layer was washed with water and brine and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated in vacuo. The crude product was purified by chromatography on silica (50% EtOAc/hexane to 20% MeOH/EtOAc to give **23** (300 mg, 45% overall): mp 94−95 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.37 (s, 1 H), 7.15−7.33 (m, 5 H), 6.23 (br s, 1 H), 5.12 (s, 2 H), 4.22 (br s, 2 H), 3.26 (br d, $J$ = 6.6 Hz, 2 H), 2.80 (m, 2 H), 1.95 (m, 1 H), 1.79 (br d, $J$ = 12.6 Hz, 2 H), 1.21 (m, 2 H) ppm; HRMS (ESI) *m/z* 333.1394 [(M + H)$^+$; calcd for $C_{16}H_{21}N_4O_2S$: 333.1380]. Anal. ($C_{16}H_{20}N_4O_2S$) C, H, N.

***N*-(Piperidin-4-ylmethyl)pyrimidin-2-amine (24).** A mixture of **20a** (9.81 g, 30.1 mmol) and 10% Pd/C (3.2 g) in EtOH (200 mL) was hydrogenated under a balloon for 18 h and filtered, and the filtrate was evaporated to a white solid: mp 73−75 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 4.8 Hz, 2 H), 6.51 (t, $J$ = 4.8 Hz, 1 H), 5.23 (br s, 1 H), 3.31 (t, $J$ = 6.3 Hz, 2 H), 3.10 (br d, 2 H), 2.60 (dt, $J$ = 2.4, 12.2 Hz, 2 H), 1.70−1.85 (m, 2 H), 1.19 (dq, $J$ = 3.7, 11.5 Hz, 2 H) ppm; HRMS (ESI) *m/z* 193.1487 [(M + H)$^+$; calcd for $C_{10}H_{17}N_4$: 193.1448].

***N*-{[1-(3-Phenylpropanoyl)piperidin-4-yl]methyl}pyrimidin-2-amine (25).** Amine **24** dihydrochloride (250 mg, 0.943 mmol), was suspended in DMF (5 mL), and triethylamine (289 $\mu$L, 2.07 mmol), HOBt (159 mg, 1.04 mmol), 3-phenylpropionic acid (156 mg, 1.04 mmol), and EDC (199 mg, 1.04 mmol) were added. The reaction mixture was stirred at room temperature for 18 h and partitioned between water and EtOAc, the organic layer was washed with water and brine and dried over anhydrous $Na_2SO_4$, and solvent was evaporated in vacuo. The crude product was purified on silica gel (30 to 100% EtOAc/hexane) to afford a solid, which was recrystallized from EtOAc/hexane to give **25** (230 mg, 75%): mp 86−88 °C (triturated from EtOAc/hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 4.8 Hz, 2 H), 7.15−7.33 (m, 5 H), 6.53 (t, $J$ = 4.8 Hz, 1 H), 5.18 (br t, 2 H), 4.66 (br d, $J$ = 13.3 Hz, 1 H), 3.81 (br d, $J$ = 13.6 Hz, 1 H), 3.30 (t, $J$ = 6.2 Hz, 2 H), 2.95 (m, 3 H), 2.62 (dt, $J$ = 2.5, 7.9 Hz, 2 H), 2.54 (dt, $J$ = 2.2, 12.8 Hz, 1 H), 1.6−1.9 (m, 4 H), 1.14 (dq, $J$ = 4.3, 12.4 Hz, 1 H), 1.01 (dq, $J$ = 4.0, 12.2 Hz, 1 H) ppm; HRMS (ESI) *m/z* 325.2023 [(M + H)$^+$; calcd for $C_{19}H_{25}N_4O$: 325.2023]. Anal. ($C_{19}H_{24}N_4O$) C, H, N.

***N*-Benzyl-4-[(pyrimidin-2-ylamino)methyl]piperidine-1-carboxamide (26).** To a solution of amine **24** (200 mg, 1.04 mmol) in THF (10 mL) at room temperature were added benzyl isocyanate (128 $\mu$L, 1.04 mmol) and diisopropylethylamine (182 $\mu$L, 1.04 mmol), and the reaction mixture was stirred for 1 h, concentrated to a solid, and purified by silica gel chromatography (EtOAc to 10% MeOH/EtOAc), followed by trituration from ether to afford **26** (275 mg, 81%): mp 136−137 °C, $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 4.9 Hz, 2 H), 7.24−7.36 (m, 5 H), 6.52 (t, $J$ = 4.9 Hz, 1 H), 5.18 (br t, 1 H), 4.69 (br t, 1 H), 4.42 (d, $J$ = 5.4 Hz, 2 H), 3.99 (br d, 2 H), 3.34 (t, $J$ = 6.2 Hz, 2 H), 2.79 (dt, $J$ = 2.1, 12.7 Hz, 2 H), 1.80 (m, 3 H), 1.20 (m, 2 H) ppm; HRMS (ESI) *m/z* 326.1985 [(M + H)$^+$; calcd for $C_{18}H_{24}N_5O$: 326.1976]. Anal. ($C_{18}H_{23}N_5O$) C, H, N.

***N*-{[1-(3-Phenylpropyl)piperidin-4-yl]methyl}pyrimidin-2-amine (27).** To a stirred solution of amine **24** (250 mg, 1.3 mmol) in 1,2-dichloroethane (10 mL) were added 4 Å molecular sieves (1 g), 3-phenylpropionaldehyde (208 $\mu$L, 1.6 mmol), acetic acid (75 $\mu$L, 1.3 mmol), and sodium triacetoxyborohydride (692 mg, 3.2 mmol). After 2 h, the reaction mixture was partitioned between EtOAc and aqueous $NaHCO_3$ solution, the organic layer was washed with water and brine and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated to give crude product, purified by silica gel chromatography ($CH_2Cl_2$ to 90:10:1 $CH_2Cl_2$:MeOH:$NH_4$-OH, followed by trituration from 1:1 ether:hexane to afford **27** (230 mg, 57%): mp 69−70 °C, $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J$ = 4.6 Hz, 2 H), 7.14−7.30 (m, 5 H), 6.50 (t, $J$ = 4.7 Hz, 1 H), 5.22 (br s, 1 H), 3.31 (t, $J$ = 6.3 Hz, 2 H), 2.93 (br d, $J$ = 11.2 Hz, 2 H), 2.62 (t, $J$ = 7.7 Hz, 2 H), 2.35 (br t, 2 H), 1.83 (br t $J$ = 7.7 Hz, 2 H), 1.73−1.86 (m, 4 H), 1.55−1.65 (m, 1 H), 1.30−1.40

(m, 2 H) ppm; HRMS (ESI) *m/z* 311.2242 [(M + H)$^+$; calcd for $C_{19}H_{27}N_4$: 311.2230]. Anal. ($C_{19}H_{26}N_4 \cdot 0.1H_2O$) C, H, N.

***N*-Benzyl-*N*′-cyano-4-[(pyrimidin-2-ylamino)methyl]piperidine-1-carboximidamide (28).** To a stirred solution of diphenyl cyanocarbonimidiate (310 mg, 1.3 mmol) in THF (10 mL) at −80 °C was added benzylamine (142 μL, 1.3 mmol), the reaction mixture was allowed to warm to room temperature over 1 h, and amine **24** (250 mg, 1.3 mmol) was added, followed by diisopropylethylamine (454 μL, 2.6 mmol). The reaction mixture was stirred at room temperature for 2 h and then heated to reflux for 5 h, cooled to room temperature, and partitioned between EtOAc and water, the organic layer was washed with brine and dried over anhydrous $Na_2SO_4$, and the solvent was evaporated to give crude product, purified by silica gel chromatography (50% EtOAc/hexane to 20% EtOH/EtOAc) followed by trituration from ethyl acetate to afford **28** (210 mg, 46%): mp 168−170 °C; $^1$H NMR (500 MHz, $CDCl_3$ δ 8.25 (d, *J* = 4.6 Hz, 2 H), 7.73 (t, *J* = 5.9 Hz, 1 H), 7.20−7.35 (m, 5 H), 6.53 (t, *J* = 4.6 Hz, 1 H), 4.46 (d, *J* = 5.9 Hz, 2 H), 3.99 (d, *J* = 13.2 Hz, 2 H), 3.17 (t, *J* = 6.5 Hz, 2 H), 2.91 (br t, *J* = 12.5 Hz, 2 H), 1.69−1.86 (m, 3 H), 1.09−1.20 (m, 2 H) ppm; HRMS (ESI) *m/z* 350.2093 [(M + H)$^+$; calcd for $C_{19}H_{24}N_7$: 350.2088]. Anal. ($C_{19}H_{23}N_7 \cdot 0.1H_2O$) C, H, N.

**4-Methylbenzyl 4-[(*tert*-Butoxycarbonyl)amino]piperidine-1-carboxylate (30).** To a solution of *tert*-butyl piperidin-4-ylcarbamate **29** (300 mg, 1.50 mmol) in $CH_2Cl_2$ (5 mL) were added 1-({[(4-methylbenzyl)oxy]carbonyl}oxy)pyrrolidine-2,5-dione (394 mg, 1.5 mmol) and triethylamine (0.42 mL, 3.00 mmol). The reaction mixture was stirred at room temperature for 1 h and poured onto EtOAc and water. The layers were separated, and the organic layer was washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by silica gel chromatography (20% EtOAc/hexane to EtOAc) provided **30** (450 mg, 86% yield) as a clear oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.0 Hz, 2 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 5.04 (s, 2 H), 4.39 (br s, 1 H), 4.05 (br s, 2 H), 3.56 (br s, 1 H), 2.87 (t, *J* = 12.1 Hz, 2 H), 2.32 (s, 3 H), 1.88 (d, *J* = 11.0 Hz, 2 H), 1.41 (s, 9 H), 1.25 (m, 2 H) ppm; HRMS (ESI) *m/z* 349.2117 [(M + H)$^+$; calcd for $C_{19}H_{29}N_2O_4$: 349.2122].

**4-Methylbenzyl 4-(Pyrimidin-2-ylamino)piperidine-1-carboxylate (32).** To a solution of BOC-protected amine **30** (300 mg, 0.86 mmol) in $CH_2Cl_2$ (1 mL) at room temperature was added trifluoroacetic acid (1 mL). The reaction mixture was stirred for 20 min and concentrated. The resultant amine (**31**) trifluoroacetate salt (210 mg, 0.85 mmol) was dissolved in a 1:1 mixture of *n*-butanol and diisopropylethylamine (1 mL), 2-chloropyrimidine (97 mg, 0.85 mmol) was added, and the reaction mixture was heated to 140 C in a sealed tube for 4 h, cooled, and poured into EtOAc and water. The layers were separated, and the organic layer was washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by silica gel chromatography (25% EtOAc/hexane to EtOAc) provided **32** as a clear oil which crystallized from ether (120 mg, 43%, 2 steps) as a white solid: mp 96−97 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 4.8 Hz, 2 H), 7.22 (d, *J* = 7.9 Hz, 2 H), 7.13 (d, *J* = 7.9 Hz, 2 H), 6.49 (t, *J* = 4.8 Hz, 1 H), 5.16 (d, *J* = 7.6 Hz, 1 H), 5.05 (s, 2 H), 4.09 (br s, 2 H), 3.96 (m, 1 H), 2.98 (t, *J* = 12.0 Hz, 2 H), 2.31 (s, 3 H), 2.01 (d, *J* = 11.0 Hz, 2 H), 1.36 (m, 2 H) ppm; HRMS (ESI) *m/z* 327.1818 [(M + H)$^+$; calcd for $C_{18}H_{23}N_4O_2$: 327.1816]. Anal. ($C_{18}H_{22}N_4O_2$) C, H, N.

**4-Methylbenzyl 4-[2-(Pyrimidin-2-ylamino)ethyl]piperidine-1-carboxylate (36).** HCl was bubbled through a cooled (0 °C) solution of **34** (140 mg, 0.46 mmol) in EtOAc for 45 min, the volatiles evaporated to give **35** as the HCl salt which was dissolved in DMF (4 mL). Diisopropylethylamine (238 μL, 1.37 mmol) and 1-({[(4-methylbenzyl)oxy]carbonyl}oxy)pyrrolidine-2,5-dione (144 mg, 0.55 mmol) were added, and the reaction mixture was stirred at room temperature for 18 h and partitioned between EtOAc and aqueous $NaHCO_3$ solution. The organic layer was washed with brine and dried over $MgSO_4$, the solvent was evaporated in vacuo, and the product was purified by chromatography on silica (60% EtOAc hexane to 5% MeOH/EtOAc) to give **36** (75 mg, 42%), characterized as the HCl salt: mp 130−132 °C; $^1$H NMR (400 MHz, $CD_3$-OD) δ 8.56 (br s, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 6.97 (t, *J* = 5.3 Hz, 1 H), 5.05 (s, 2 H), 4.12 (br d, *J* = 14.0 Hz, 2 H), 3.54 (t, *J* = 7.0 Hz, 2 H), 2.82 (br s, 2 H), 2.33 (s, 3 H), 1.76 (br d, *J* = 12 Hz, 2 H), 1.63 (m, 3 H), 1.15 (m, 2 H) ppm; HRMS (ESI) *m/z* 355.2116 [(M + H)$^+$; calcd for $C_{20}H_{27}N_4O_2$: 355.2129]. Anal. ($C_{20}H_{26}N_4O_2 \cdot HCl$) C, H, N.

**4-Methylbenzyl 4-{[(*tert*-Butoxycarbonyl)amino]methyl}-piperidine-1-carboxylate (37).** To a solution of amine **44** (400 mg, 1.53 mmol) in $CH_2Cl_2$ (5 mL) was added di-*tert*-butyl dicarbonate (330 mg, 1.53 mmol). The reaction mixture was stirred at room temperature for 30 min and poured into EtOAc and water. The layers were separated, and the organic layer was washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by silica gel chromatography (10 to 80% EtOAc/hexane) provided **37** (530 mg, 96%) as a clear oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.9 Hz, 2 H), 7.12 (d, *J* = 7.9 Hz, 2 H), 5.03 (s, 2 H), 4.61 (br s, 1 H), 4.14 (br s, 2 H), 2.97 (br s, 2 H), 2.71 (t, *J* = 12.2 Hz, 2 H), 2.31 (s, 3 H), 1.61 (m, 3 H), 1.40 (s, 9 H), 1.09 (m, 2 H) ppm; HRMS (ESI) *m/z* 363.2285 [(M + H)$^+$; calcd for $C_{20}H_{31}N_2O_4$: 363.2279].

**4-Methylbenzyl 4-{[(*tert*-Butoxycarbonyl)(methyl)amino]-methyl}piperidine-1-carboxylate (38).** To a solution of amine **37** (400 mg, 1.10 mmol) in 1:1 THF:DMF (8 mL) were added sodium hydride (53 mg, 2.21 mmol) and methyl iodide (0.22 mL, 2.21 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched carefully with water, and poured onto EtOAc and water. The layers were separated, and the organic layer was washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by silica gel chromatography (10 to 80% EtOAc/hexane) provided **38** (390 mg, 94%) as a clear oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.8 Hz, 2 H), 7.12 (d, *J* = 7.8 Hz, 2 H), 5.04 (s, 2 H), 4.12 (br s, 2 H), 3.05 (s, 2 H), 2.81 (s, 3 H), 2.72 (t, *J* = 12.2 Hz, 2 H), 2.31 (s, 3 H), 1.71−1.56 (m, 3 H), 1.41 (s, 9 H), 1.11 (m, 2 H) ppm; HRMS (ESI) *m/z* 377.2452 [(M + H)$^+$; calcd for $C_{21}H_{33}N_2O_4$: 377.2475].

**4-Methylbenzyl 4-{[Methyl(pyrimidin-2-yl)amino]methyl}-piperidine-1-carboxylate (39).** To a solution of BOC-protected amine **38** (370 mg, 0.98 mmol) in $CH_2Cl_2$ (1 mL) at room temperature was added trifluoroacetic acid (1 mL). The reaction mixture was stirred for 10 min and quenched with aqueous $NaHCO_3$. The mixture was poured into EtOAc and aqueous $NaHCO_3$, the layers were separated, and the organic layer was washed with aqueous $NaHCO_3$, water and brine, dried over $Na_2SO_4$, filtered, and concentrated. The resultant amine (270 mg, 0.98 mmol) was dissolved in a 1:1 mixture of *n*-butanol and diisopropylethylamine (4 mL). 2-Chloropyrimidine (112 mg, 0.98 mmol) was added, and the reaction mixture was heated to 140 °C in a sealed tube for 2 h, cooled, and poured into EtOAc and water. The layers were separated, and the organic layer was washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by silica gel chromatography (25 to 100% EtOAc/hexane) provided **39** (260 mg, 75%, 2 steps) as a clear oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 4.7 Hz, 2 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 7.12 (d, *J* = 7.9 Hz, 2 H), 6.41 (t, *J* = 4.7 Hz, 1 H), 5.04 (s, 2 H), 4.13 (br s, 2 H), 3.49 (d, *J* = 7.1 Hz, 2 H), 3.11 (s, 3 H), 2.72 (t, *J* = 11.8 Hz, 2 H), 2.31 (s, 3 H), 1.93 (m, 1 H), 1.60 (m, 2 H), 1.19 (m, 2 H) ppm; HRMS (ESI) *m/z* 355.2140 [(M + H)$^+$; calcd for $C_{20}H_{27}N_4O_2$: 355.2129]. Anal. ($C_{20}H_{26}N_4O_2$) C, H, N.

**4-Methylbenzyl 4-(Hydroxymethyl)piperidine-1-carboxylate (40).** A solution of 4-(hydroxymethyl)piperidine (1.00 g, 8.68 mmol), 4-methyl-*N*-(benzyloxycarbonyloxy)succinimide (2.29 g, 8.68 mmol) and triethylamine (1.21 mL, 8.68 mmol) in DMF (10 mL) was stirred at 22 °C for 2 h. The reaction mixture was diluted with EtOAc (200 mL), washed with aqueous saturated $NaHCO_3$, water, and brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was chromatographed on silica, eluting with 10 to 100% EtOAc/hexane to give **40** (1.05 g, 46%): $^1$H NMR (400 MHz, $CD_3OD$) δ 7.23 (d, *J* = 7.9 Hz, 2 H), 7.16 (d, *J* = 7.9 Hz, 2 H), 5.00 (s, 2 H), 4.14 (d, *J* = 13.3 Hz, 2 H), 3.39 (d, *J* = 6.2 Hz, 2 H), 2.81 (br s, 2 H), 2.32 (s, 3 H), 1.72 (d, *J* = 13.3 Hz,

2 H), 1.64 (m, 1 H), 1.10 (dq, $J$ = 3.8, 12.1, 2 H) ppm; HRMS (ESI) *m/z*: 263.1521 [$(M + H)^+$; calcd for $C_{15}H_{21}NO_3$: 263.1521].

**4-Methylbenzyl 4-[(Pyrimidin-2-yloxy)methyl]piperidine-1-carboxylate (41)** To a stirred solution of 4-methylbenzyl 4-(hydroxymethyl)piperidine-1-carboxylate (**40**) (1.00 g, 3.80 mmol) and 2-chloropyrimidine (0.44 g, 3.80 mmol) in DMF (20 mL), at 0 °C, under nitrogen, was added NaHMDS (1M in THF, 5.70 mL, 5.70 mmol). This reaction mixture was then stirred at 22 °C for 30 min, diluted with EtOAc (200 mL), washed with aqueous saturated $NaHCO_3$, water, and brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was chromatographed on silica, eluting with 10 to 100% EtOAc/hexane. Crystallization from ether gave **41** (0.97 g, 75%): mp 101−103 °C; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.54 (d, $J$ = 4.9 Hz, 2 H), 7.24 (d, $J$ = 7.9 Hz, 2 H), 7.16 (d, $J$ = 7.9 Hz, 2 H), 7.08 (t, $J$ = 4.8 Hz, 1 H), 5.06 (s, 2 H), 4.24 (d, $J$ = 6.4 Hz, 2 H), 4.18 (d, $J$ = 13.4 Hz, 2 H), 2.87 (br s, 2 H), 2.33 (s, 3 H), 2.05 (m, 1 H), 1.83 (d, $J$ = 12.7 Hz, 2 H), 1.29 (dq, $J$ = 4.2, 12.3 Hz, 2 H) ppm; HRMS (ESI) *m/z*: 342.1812 [$(M + H)^+$; calcd for $C_{19}H_{24}N_3O_3$: 342.1815]; Anal. ($C_{19}H_{23}N_3O_3$) C, H, N.

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**Supporting Information Available:** Elemental analysis data for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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