# Identification of MK-944a: A Second Clinical Candidate from the Hydroxylaminepentanamide Isostere Series of HIV Protease Inhibitors

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Recent results from human clinical trials have established the critical role of HIV protease inhibitors in the treatment of acquired immune-deficiency syndrome (AIDS). However, the emergence of viral resistance, demanding treatment protocols, and adverse side effects have exposed the urgent need for a second generation of HIV protease inhibitors. The continued exploration of our hydroxylaminepentanamide (HAPA) transition-state isostere series of HIV protease inhibitors, which initially resulted in the identification of Crixivan (indinavir sulfate, MK-639, L-735,524), has now yielded MK-944a (L-756,423). This compound is potent, is selective, and competitively inhibits HIV-1 PR with a $K_i$ value of 0.049 nM. It stops the spread of the $HIV_{IIIb}$-infected MT4 lymphoid cells at 25.0−50.0 nM, even in the presence of $\alpha_1$ acid glycoprotein, human serum albumin, normal human serum, or fetal bovine serum. MK-944a has a longer half-life in several animal models (rats, dogs, and monkeys) than indinavir sulfate and is currently in advanced human clinical trials.

## Introduction

Human immunodeficiency virus (HIV), the etiologic agent of acquired immune-deficiency syndrome (AIDS), is a member of the *Lentiviridae* subfamily of retroviruses that contain three major genes (*gag*, *pol*, *env*).[1] Products of the *gag* gene include structural proteins of the virus nucleocapsid; the *pol* gene encodes three enzymes: a protease, a reverse transcriptase, and an endonuclease; and the *env* gene encodes the membrane proteins of the mature virus.[2] The *gag* and *pol* gene products are expressed as polyproteins that are processed by the HIV protease (PR), an essential step for virus maturation. In 1988, Sigal and others[3] determined that a functioning aspartyl protease was required for HIV replication. Throughout 1997−1998, Merck researchers and their colleagues have disclosed several landmark publications[4,5] which describe the clinical results of the treatment of HIV-infected patients using the potent protease inhibitor Crixivan (indinavir sulfate)[6] in combination with two nucleoside reverse transcriptase inhibitor analogues (zidovudine and lamivudine). These studies demonstrate that triple-combination therapy using indinavir, zidovudine, and lamivudine: (1) significantly slows the progress of HIV-1 disease in patients with 200 CD4 cells or less as compared with therapy using zidovudine and lamivudine alone[4] and (2) reduces the levels of HIV RNA to less than 500 copies/mL for as long as 100 weeks, in 78% of the contributing HIV-infected patients with prior antiretroviral exposure.[5] Both of these studies support the recent guidelines[7] for treatment of HIV disease which recommend early initiation of antiretroviral therapy; this includes the use of two nucleoside reverse transcriptase inhibitors and a protease inhibitor. Promising results have been presented for four other Food and Drug Administration approved HIV PR inhibitors: saquinavir mesylate,[8] ritonavir,[9] nelfinavir mesylate,[10] and amprenavir.[11] Conclusions drawn from all these studies suggest that we have entered into a new era for the treatment of AIDS.

Although these HIV PR inhibitors represent a major advance in the management of HIV disease, the difficulties in compliance with the treatment protocols, adverse side effects,[8c,9c,10c,11,12] and viral resistance[13] have encouraged medicinal chemistry researchers to develop second-generation inhibitors. To overcome these clinical concerns, the next generation HIV PR inhibitors should have improved in vitro and in vivo properties (i.e. improved potency against the enzyme, efficacy in a cell-based assay in the presence of biologically relevant protein, and improved pharmacokinetic parameters in animal models). Therefore, the criteria for a clinical backup to indinavir, the most widely prescribed HIV PR inhibitor in the world, would require a compound that addressed these aforementioned concerns. Herein, we disclose the development of a second clinical candidate from our hydroxylaminepentanamide (HAPA) isostere series of HIV PR inhibitors.

## Design Rationale

Previous work has described the design strategy which led to the introduction of the HAPA transition-state isostere and resulted in the identification of

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**Chart 1**

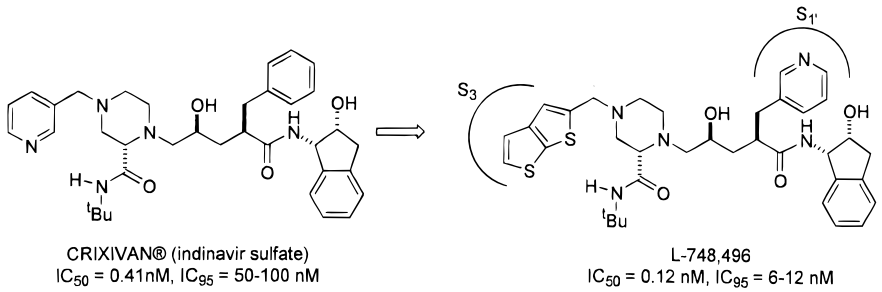
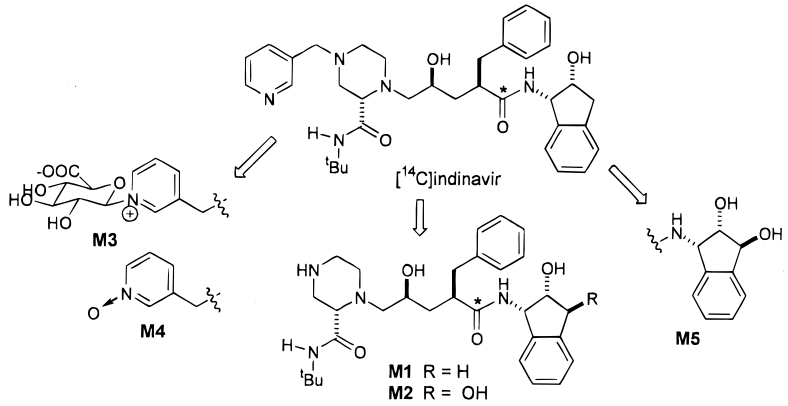



**Chart 2.** Disposition of Indinavir after Oral Dosing in Humans




indinavir.[14] The effects of placing large lipophilic heterocycles in the $S_3$ enzyme site in combination with a pyridyl P1′ ligand (Chart 1) has been described in a subsequent publication.[15] This research resulted in the identification of L-748,496, a potent, selective, and orally bioavailable protease inhibitor with pharmacokinetic profiles in rats, dogs, and monkeys comparable to those with indinavir. However, this compound did not demonstrate a pharmacokinetic half-life improvement over indinavir in several animal models. Human clinical studies have established that indinavir must be dosed every 8 h at a dose of 800 mg.[12] L-748,496 would not address the issue of an improved treatment protocol and consequently was dropped from further consideration.

The report of disposition of [$^{14}$C]indinavir after oral dosing in humans has recently been disclosed.[16] In summary, the metabolites found in both the urine and feces were the oxidative *N*-dealkylation of the 3-pyridylmethyl ligand **M1**, the quaternary pyridine *N*-glucuronide **M3**, the pyridine *N*-oxide **M4**, the hydroxylated aminohydroxyindan **M2**, **M5**, and derivatives thereof (Chart 2). These metabolism results combined with our reported structure−activity relationships suggested that one strategy to improve upon the pharmacokinetics of indinavir sulfate would be to block or avoid these metabolic pathways. Therefore, replacement of the metabolically labile 3-pyridylmethyl with either a large lipophilic heterocycle or a modified pyridine ring might provide a compound with a significantly longer half-life in animals. Toward this end, a series of 3-pyridylmethyl replacement analogues possessing a wide range of physical properties were designed and synthesized.

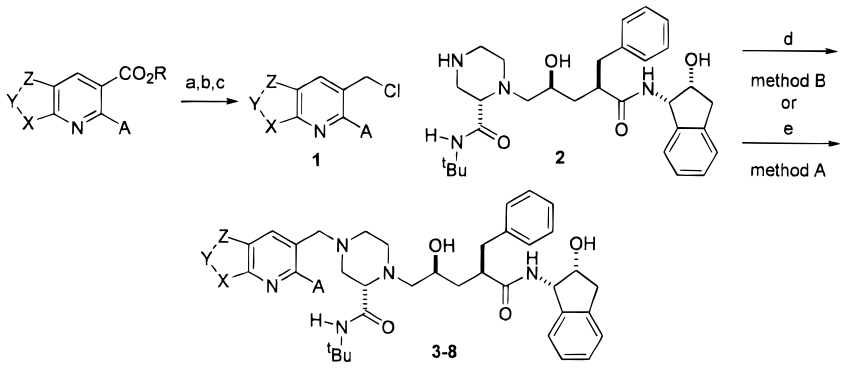
## Selection Criteria

Also, to improve upon the impressive clinical results of indinavir, we needed to establish stringent criteria for the selection of a backup candidate. In one drug candidate, several parameters would have to be optimally balanced. First, the requirements for potency (less than 1 nM $IC_{50}$) against HIV-1 protease,[6] and potency in our cell-based assay[6] in the presence of biologically relevant proteins ($IC_{95}$ value of less than 100 nM, as defined by the minimum inhibitor concentration of drug needed to inhibit 95% of replication of virus in MT4 human T-lymphoid cells infected with the IIIb isolate), had to be achieved. Protein binding can play a deleterious role in the efficacy of protease inhibitors as demonstrated in the viral spread assay.[17] The negative consequence of protein binding would have to be critically evaluated in the selection of a backup candidate. Compound solubilities in water were also measured and compared to that of indinavir (70 $\mu$g/mL at pH 7.4, phosphate buffer) because of the previously established relationship of solubility to oral bioavailability.[14] However, the most critical assay used for selection of a second clinical candidate was the determination of drug concentration in plasma after oral administration to dogs at a 10 mg/kg dose as a citric acid solution. Our criteria for success in this pharmacokinetic assay were plasma concentration maximum ($C_{max}$) levels of at least 10 $\mu$M and maintaince of drug concentrations after 8 h ($C_{8h}$) of 10-fold greater than the drug's $IC_{95}$ value (adjusted to include the negative effects of protein binding).

## Chemistry

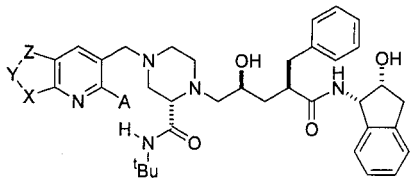
The synthesis of the versatile penultimate intermediate **2** has been previously described.[14,18] Scheme 1 illustrates two general methods developed to obtain the 3-pyridylmethyl analogues **3**−**8** (Table 1). First, a reductive amination protocol (method A) using quinoline-3-carboxaldehyde, amine **2**, and sodium triacetoxy-

**Scheme 1.** Synthesis of Analogues **3**−**8**[a]




[a] Reagents and conditions: (a) $TMSCHN_2$, $CHCl_3$, $CH_3OH$; (b) DIBAL-H, THF; (c) $SOCl_2$, $CH_2Cl_2$; (d) **1**, $Et_3N$, DMF; (e) **2**, quinoline-3-carboxaldehyde, $NaB(OAc)_3H$, AcOH.

**Table 1.** 3-Pyridylmethyl Analogues **3**−**8**



| Compd | X | Y | Z | A | $IC_{50}$ (nM)[a] | $IC_{95}$ (nM)[a] | Solubility[b] | LogP | $C_{max}$ (μM)[c] | $C_{8h}$ (μM)[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| indinavir | H | - | H | H | 0.59±0.2 n = 169 | 25-100[d] n =106 | 70.0 | 2.92 | 11.4± 2.3 n = 4 | 0.00 |
| **3** | CHCH | CH | CH | H | 0.14 | 25 | 35.1 | 3.67 | 0.102 ± 0.1 | 0.00 |
| **4** | EtO | - | H | H | 3.4 | 100 | 17.4 | 3.62 | 0.300 ± 0.269 | 0.00 |
| **5** | $CH_3$ | - | H | H | 0.62±0.05 n = 2 | 100 | 75.1 | 2.14 | na | na |
| **6** | Cl | - | H | H | 0.49 | 12-50 n = 2 | 2.41 | >3.84 | na | na |
| **7** | H | - | H | $OCH_3$ | 1.1 | 12 | 35.2 | >3.84 | 0.515 ± 0.13 | 0.00 |
| **8** | H | - | H | $SCH_3$ | 0.26 | 15.6 | 4.5 | 3.48 | 1.163 ± 0.042 | 0.00 |

[a] All entries are for $n = 1$ except where noted; data are the mean ± SEM. [b] Solubility determined at pH 7.4 in μg/mL. [c] $C_{max}$, maximum plasma concentration; $C_{8h}$, concentration after 8 h. Bioavailability in dogs, each compound was delivered orally in 0.05 M citric acid at 10 mg/kg. For all cases $n = 2$, except where noted. [d] Average determination was 50.5 nM.

borohydride in dichloroethane with a catalytic amount of acetic acid would provide target **3**. Alternatively, a procedure (method B) was developed which utilized the *N*-alkylation of piperazine **2** with an arylchloromethyl **1**, prepared from the commercially available arylcarboxylic acids via esterification, reduction, and activation as the chloromethyl electrophile. This would provide analogues **4**−**8** which represent the substituted 3-pyridylmethyl analogues prepared in Table 1. Also, this procedure was generalized to include the chloromethyl electrophiles described in Scheme 2 and used to prepare **11**, **13**, **15**, **16**, and **18**.

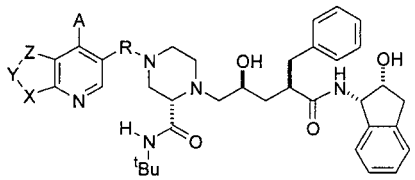
As illustrated in Scheme 2, intermediate **10**[19] was decarboxylated with copper(I) oxide in quinoline; then the ester functionality was reduced with DIBAL-H and converted into the chloromethyl electrophile **11** with thionyl chloride. The Boc-protected 3-aminofuran **12** was deprotected in hydrochloric acid and zinc chloride and condensed with ethoxycarbonylmalonaldehyde, following the method of Torii.[20] The resulting ethyl furo[2,3-*b*]pyridine-3-carboxylate was reduced and activated as previously described. Electrophiles **15** and **16** were prepared starting with the commercially available ester **14**. Reductive cleavage of the chlorine with zinc in acetic acid, followed by reduction of the ester functionality and activation, provided **16**. Compound **15** was prepared in an analogous manner. These electrophiles were reacted with piperazine **2** to provide analogues **19**, **22**, **24**, and **25**, as illustrated in Table 2.

The acid functionality of furo[2,3-*b*]pyridine-2,5-dicarboxylic acid 5-ethyl acid **17** could be activated with isobutyl chloroformate and selectively reduced with sodium borohydride. The alcohol was then treated with thionyl chloride to provide electrophile **18** which was reacted with piperazine **2** to provide analogue **30**, as illustrated in Table 3. The remaining derivatives in Table 3 were prepared from known arylaldehydes or manipulations of the targets as described in the Experimental Section.

## Results and Discussion

Table 1 illustrates our attempts to modify the 3-pyridyl P3 moiety of indinavir and to explore what the effects of these modifications had on pharmacokinetics in dogs. As noted, most of these analogues fulfilled our requirements of potency. The quinoline analogue **3**

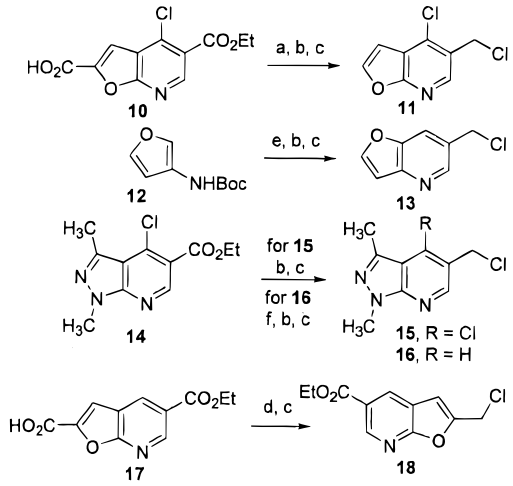
**Table 2.** Pyridyl Heterocycles **19**−**25**



| Compd | X | Y | Z | A | R | $IC_{50}$ (nM)[a] | $IC_{95}$ (nM)[a] | Solubility[b] | CLogP[c] | $C_{max}$ (μM)[d] | $C_{8h}$ (μM)[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **19** | O | CH | CH | Cl | $CH_2$ | 0.25 | 15.6 | <0.02 | 4.024 | 3.936 ± 0.15 | 2.055 ± 0.234 |
| **20** L-754,394 | O | CH | CH | H | $CH_2$ | 0.35±0.18 n = 8 | 6-25[e] n =5 | 9.1 | 3.246 | 14.99 ± 1.65 n = 4 | 9.428 ± 1.62 |
| **21** | O | $CH_2$ | $CH_2$ | H | $CH_2$ | 0.68 | 25 | na | 2.956 | 0.160[f] ± 0.9 | 0.00 |
| **22** | CH | CH | O | H | $CH_2$ | 0.17±0.01 n = 3 | 3-6 n = 2 | na | 3.456 | 9.72 ± 0.02 | 1.55 ± 0.95 |
| **23** | O | CH | CH | H | CO | 1.7 | 100 | na | 2.442 | 0.13 ± 0.01 | 0.00 |
| **24** | $NCH_3$ | N | $CCH_3$ | Cl | $CH_2$ | 0.14 | 12.5 | 6.3 | 4.179 | na | na |
| **25** | $NCH_3$ | N | $CCH_3$ | H | $CH_2$ | 0.35 | 6 | na | 3.409 | 0.19 ± 0.09 | 0.00 |

[a] All entries are for $n = 1$ except where noted; data are the mean ± SEM. [b] Solubility determined at pH 7.4 in μg/mL, for indinavir (70 μg/mL). [c] Clog *P* for indinavir was 2.44, and the measured log *P* was 2.92. [d] Bioavailability in dogs, each compound was delivered orally in 0.05 M citric acid at 10 mg/kg. For all cases $n = 2$, except where noted. [e] Average determination was 17.4 nM. [f] Delivered at 5 mg/kg.

**Scheme 2.** Synthesis of Heterobicyclic Chloromethyl Reagents[a]

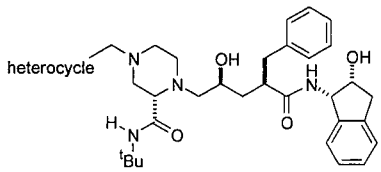


[a] Reagents and conditions: (a) quinoline, Cu, 210−230 °C; (b) DIBAL-H, THF; (c) $SOCl_2$, $CH_2Cl_2$; (d) NMM, $ClCO_2CH_2CH(CH_3)_2$, then $NaBH_4$, $H_2O$; (e) $EtO_2CCH(CHO)_2$, HCl, EtOH, $ZnCl_2$; (f) Zn, HOAc.

improved potency both intrinsically and in the cell-based assay. However, plasma levels of **3** in dogs after oral administration were 100-fold lower compared to those for indinavir. The thiomethylpyridine analogue **8** also showed an improvement in potency relative to indinavir. However, the plasma concentration of drug in dogs after oral administration reached a maximum of only 1.16 μM, and no drug could be detected after 8 h. Interestingly, this analogue also had low aqueous solubility (4.5 μg/mL) and a relatively high log *P* (3.48). It was an early example of a compound in the HAPA isostere series that had high lipophilicity and showed some oral bioavailability in dogs.

Having had limited success with simple substituted pyridine analogues, attention was turned to the incorporation of pyridine-based bicyclic heterocycles into the $S_3$ pocket. The hypothesis was that a modified pyridine bicyclic ring could balance lipophilicity and solubility of the molecule and at the same time redirect the route of metabolism away from either *N*-dealkylation of the arylmethyl moiety or *N*-glucuronidation of the pyridine nitrogen. Table 2 illustrates attempts in this regard. Upon the basis of the previous success of [2,3-*b*]- and [3,2-*b*]thienothiophenes,[15] the [2,3-*b*]- and [3,2-*b*]furopyridine moieties were incorporated into the $S_3$ pocket. Contrary to the thienothiophenes, the furopyridine ring contains a weakly basic nitrogen which should provide the target analogues with some aqueous solubility. The 4-chlorofuropyridine **19**, a synthetic intermediate to the parent series, provided the potency required in the cell-based assay. Importantly, significant amounts of compound **19** could be detected in the plasma of dogs at 8 h after an oral dosing, exceeding our requirement of a $C_{8h}/IC_{95}$ ratio of 10. Removal of the chlorine atom then provided the parent [2,3-*b*]furopyridine **20**, L-754,394. This compound also maintained potency and reached drug plasma levels of almost 10 μM at 8 h after oral dosing in dogs and could still be detected in plasma at approximately 1 μM after 24 h.[21] The isomeric [3,2-*b*]-furopyridine **22** demonstrated similar potency and excellent pharmacokinetics. Acylation of the piperazine ring with furo[2,3-*b*]pyridine-5-carboxylic acid resulted in a compound with a greatly reduced pharmacokinetic profile, analogue **23**. Interestingly, reduction of the olefin of furopyridine **20** provided analogue **21** which, although potent, did not provide the pharmacokinetic results seen with furopyridine **20**. Two azaindazoles, **24** and **25**, were also prepared but did not provide useful oral bioavailability.

**Table 3.** Bicyclic Heterocycles **26**−**38**




| Compd | Heterocycle | attachment position | $IC_{50}$ (nM)[a] | $IC_{95}$ (nM)[a] | Solubility[b] | LogP[c] (CLogP) | $C_{max}$ (μM)[d] | $C_{8h}$ (μM)[d] |
|---|---|---|---|---|---|---|---|---|
| **26** | furo[2,3-*b*]pyridine | 2 | 0.32 | 50 | na | (3.246) | 1.17 ± 0.3 | 0.00 |
| **27** | furo[2,3-*b*]pyridine-5-ethylcarboxylate | 2 | 0.27 | 25 | na | (4.168) | na | na |
| **28** | furo[2,3-*b*]pyridine-5-methanol | 2 | 0.18 | 62.5 | 13.0 | 2.99 (2.208) | 0.223 ± 0.027 | 0.00 |
| **29** | furo[2,3-*c*]pyridine | 2 | 0.39 n = 2 | 12.5 | na | (3.246) | 36.47 ± 3.35 | 0.00 |
| **30** | furo[3,2-*c*]pyridine | 2 | 0.22±0.03 n = 2 | 6-25 n = 3 | 8.6 | (3.246) | 34.65 ± 5.53 n = 4 | 0.05 |
| **31** | 6-methyl furo[3,2-*c*]pyridine | 2 | 0.19±0.02 n = 3 | 12 | 68.9 | >4.26 (3.975) | 11.54 ± 0.303 | 0.00 |
| **32** | thieno[2,3-*b*]pyridine | 3 | 0.20 | 6 | na | (3.602) | 0.23 ± 0.05 | 0.00 |
| **33** | thieno[2,3-*b*]pyridine | 2 | 0.11±0.02 n = 3 | 12.5 | 0.40 | (3.602) | 6.62 ± 2.71 | 0.00 |
| **34** **L-756,423** | benzo[*b*]furan | 2 | 0.18± 0.02 n = 4 | 25-50[e] n = 6 | 7.8 | >3.76 (4.513) | 28.3 ± 17.4 n = 5 | 0.80 ± 0.2 |
| **35** | benzo[*b*]furan | 5 | 1.70 | 100 | na | (4.513) | na | na |
| **36** | 3-methylbenzo[*b*]furan | 2 | 0.11 | 25 | na | (5.242) | 0.408 ± 0.1 | 0.00 |
| **37** | benzimidazole | 2 | 0.47 | 200 | 120 | (3.328) | na | na |
| **38** | indole | 3 | 1.7 | 50 | na | (3.923) | na | na |

[a] All entries are for $n = 1$ except where noted; data are the mean ± SEM. [b] Solubility determined at pH 7.4 in μg/mL, for L-735,524 (70 μg/mL). [c] Clog *P* for indinavir was 2.44, and the measured log *P* was 2.92. [d] Bioavailability in dogs, each compound was delivered orally in 0.05 M citric acid at 10 mg/kg. For all cases $n = 2$ except where noted. $C_{max}$, maximum plasma concentration; $C_{8h}$, plasma concentration after 8 h. [e] Average determination was 29 nM.

The unexpected improvement in the pharmacokinetic profile of furopyridine **20** (vs indinavir) and the lack of oral bioavailability observed for the saturated furopyridine **21** required an explanation. Analogue **21** can be viewed as the cyclic constrained version of **4** (Table 1). Both **4** and **21** displayed poor pharmacokinetics after oral dosing in dogs, and each has similar lipophilicities. Each compound lacks the olefin of the furan ring. The compounds which do possess good pharmacokinetics, **19**, **20**, and **22**, all belong to the furopyridine class, containing the furan olefin. The only pharmacokinetic exception to this group was analogue **23**, a compound which does possess the furopyridine moiety but which lacks oral bioavailability. It was hypothesized that the olefin of the furan moiety could be a factor in affecting the clearance of this class of compounds. To investigate this hypothesis, several pharmacological experiments were conducted. First, determination of the time- and dose-dependent pharmacokinetics of furopryidine **20** in rats, dogs, and monkeys revealed nonlinear kinetics in each species.[22] The apparent clearance of **20** in these species decreased with increasing doses, and the apparent half-life increased with increasing doses. Further investigation suggested that L-754,394 was acting as a mechanism-based inactivator of two cytochrome P-450 isozymes (CYP2C and CYP3A) in the liver. This result, when taken together with pharmacokinetic results illustrated in Table 2, suggests that the olefin of the furan moiety is converted into a reactive intermediate, possibly an epoxide, and is deactivating CYP3A and CYP2C. L-754,394 satisfied our criteria as a potential backup candidate to indinavir and was evaluated as a safety assessment candidate. After high oral dosing in rats and dogs, toxicity was observed. Further interest in the development of this compound was precluded because of this toxicity in combination with nonlinear pharmacokinetics.

Undaunted, we continued to examine pyridylmethyl replacements which would provide a potential drug that would satisfy the previously established criteria and, in addition, not inhibit the cytochrome P-450 isozmyes. The next set of analogues prepared in the furopyridine series reversed the position of attachment of the bicyclic heterocycle. The rationale was that a 5,6-heterocycle bridged to the piperazine moiety through a methylene linker connected to either the 2- or 3-carbon of the five-membered ring might shield the reactive olefin and prevent the CYP isozyme inhibition. The results are illustrated in Table 3. The isomeric furo[2,3-*b*]pyridine **26** was prepared, and comparison to L-754,394 revealed that potency was maintained but the pharmacokinetic profile changed dramatically. For **26**, the concentration

**Table 4.** Pharmacokinetic Profile of MK-944a in Animals[a]

| | | intravenous administration | | | oral administration | | |
|---|---|---|---|---|---|---|---|
| animal | dose (mg/kg) iv/po | $CL_p$ (mL/min/kg) | $V_{dss}$ (L/kg) | $t_{1/2}$ (min) | $C_{max}$ ($\mu$M) | $T_{max}$ (min) | *F*% |
| rat ($n = 4$) | 10/20 | 42.3 ± 9.5 | 1.9 ± 0.8 | 47.5 ± 4.5 | 0.34 ± 0.2 | 42.5 ± 12.6 | 11 |
| monkey ($n = 2$) | 2/10 | 13.9 | 1.45 ± 0.10 | 76.0 | nd | nd | nd |
| dog ($n = 5$) | 2/10 | 4.4 ± 1.05 | 2.61 ± 0.3 | 53.5 ± 16.9 | 28.3 ± 17.4 | 42.0 ± 16.4 | 68.9 ± 26.9 |

[a] MK-944a was delivered orally in 0.5 M citric acid. $CL_p$, plasma clearance rate; $V_{dss}$, volume of distribution; $t_{1/2}$, plasma half-life; $C_{max}$, maximum plasma concentration; $T_{max}$, time of maximum plasma concentration; *F*%, percent orally bioavailable. *F*% was determined by comparing the mean areas under the curves after iv and oral doses. Data are the mean ± SD; nd not detected.

maximum was 10-fold lower than for L-754,394, and no compound was detected after 8 h in dog plasma. This result suggested that the furopyridine moiety of **26** was not acting as a mechanism-based CYP inhibitor, reinforcing our working hypothesis. Two substituted furo-[2,3-*b*]pyridine derivatives, **27** and **28**, were prepared but offer no advantage in the pharmacokinetic studies. Interestingly, the [2,3-*c*]furopyridine **29** and [3,2-*c*]-furopyridine **30** provided maximum drug plasma concentrations in dogs of 36 and 34 $\mu$M, respectively. Although these peak plasma levels were high, the lack of appreciable levels after 8 h indicated a short half-life and precluded further interest in these analogues. The thieno[2,3-*b*]pyridine derivatives **32** and **33** demonstrated good potency, but again no advantages were seen in their pharmacokinetic profiles. Preparation of the benzofuran derivative **34** (MK-944a, L-756,423) revealed a compound with excellent in vitro potency, $IC_{50} = 0.18$ nM and $IC_{95} = 29$ nM, and also exceptional pharmacokinetics in dogs. MK-944a has low aqueous solubility and high lipophilicity. However, after oral dosing in dogs, it achieved a plasma concentration maximum of 28 $\mu$M, and after 8 h, drug concentrations of 800 nM were detected. The ratio of concentration of drug after 8 h in dog plasma to the $IC_{95}$ value is 27, which exceeds the criteria previously established. Unlike indinavir,[23] MK-944a did not demonstrate inhibition of substrates metabolized by CYP3A, CYP2C9, CYP2D6, and CYP1A2, indicating that it is not a potent liver microsome inhibitor.[24] Several other benzofuran, benzimidazole, and indole derivatives were prepared, represented by **35**−**38**, and they provided no advantages in either potency or pharmacokinetics. In light of the data generated, it is extremely difficult to draw trends between lipophilicity, solubility, and pharmacokinetics.

**Animal Pharmacokinetic Profile of MK-944a.** The pharmacokinetic profile of MK-944a in rats, dogs, and monkeys is summarized in Table 4. After iv administration (10 mg/kg) in rats, MK-944a was cleared rapidly with a large volume of distribution ($V_{dss}$). The half-life ($t_{1/2}$), although relatively short, was 60% longer than that of indinavir.[6] When MK-944a was given to rats orally (20 mg/kg) as a solution in 0.05 M citric acid, it was not well absorbed and the bioavailability (calculated by comparison between the iv and oral profiles) was only 11%. No drug (<30 nM) was detected in plasma of monkeys after a 10 mg/kg dose was given orally. However, after iv administration (2 mg/kg) in monkeys, MK-944a had a lower plasma clearance ($CL_p$) and a longer $t_{1/2}$ than indinavir by 2.6- and 2.5-fold, respectively. Although MK-944a and indinavir had similar bioavailabilities (69% and 72%, respectively) in dogs, the former had a lower clearance ($CL_p$ 4.4 mL/min/kg) than the latter ($CL_p$ 16 mL/min/kg). Therefore, the area under the curve (AUC) was 3.3-fold greater for MK-944a than for indinavir. The $V_{dss}$ in rats, monkeys, and dogs was large, suggesting that MK-944a is widely distributed in animal tissues. Compared to indinavir, MK-944a possesses a longer half-life and lower clearance in rats, monkeys, and dogs. As an animal species, dogs were the best predictor of the pharmacokinetic profile of indinavir in humans ($F = 72\%$ in dogs, $F = \sim 65\%$ in humans). If dogs are the best predictor of the pharmacokinetic profile of MK-944a as well, then MK-944a should demonstrate pharmacokinetic advantages over indinavir in clinical studies. Therefore, MK-944a was considered for further development.

**Table 5.** Comparative Antiviral Effects of Indinavir and MK-944a in Cell Culture[a]

| | $IC_{95}$ (nM) | |
|---|---|---|
| assay method[b] | indinavir | L-756,423 |
| +10% FBS | 50.0 | 25.0 |
| +50% NHS | 100.0 | 50.0 |
| +500 $\mu$M HSA | 100.0 | 25.0 |
| +2.0 $\mu$g/mL α-GP | 200.0 | 50.0 |

[a] MT-4 cells were infected with the LAI varient of HVI-1 as previously described.[6] [b] Assays were preformed using culture medium containing one of the following additives: 10% FBS, 10% fetal bovine serum; 50% NHS, 50% normal human serum; 500 $\mu$M HSA, 500 $\mu$M human serum abumin; 2.0 $\mu$g/mL α-GP, 2.0 $\mu$g/mL $\alpha_1$ acid glycoprotein.

**Protein Binding and Antiviral Activity.** The ability of plasma proteins to adversely affect the efficacy of HIV-1 protease inhibitors has been well documented.[17] The binding of MK-944a to human, dog, and rat plasma was determined by an ultrafiltration method.[6] The unbound fraction of the drug in plasma was approximately 2.1% for rats, 1% for dogs, and 2.7% for humans. In the cell-based antiviral assay,[6] as illustrated in Table 5, the addition of a variety of proteins had minimal effects on potency. The addition of 10% fetal bovine serum, standard conditions for the assay, resulted in an $IC_{95}$ determination of 25 nM for MK-944a and 50 nM for indinavir. The addition of either 50% normal human serum, 500 $\mu$M human serum albumin, or 2.0 $\mu$g/mL of $\alpha_1$ acid glycoprotein resulted in, at most, a 2-fold reduction in potency for MK-944a. This is in contrast to the results observed with most other HIV protease inhibitors which lose between 10- and 100-fold potency depending on cell type.[17] These results demonstrate that MK-944a is more effective than indinavir in suppressing the spread of acute HIV-1 infection in cells in the presence of biologically relavent proteins.

**Resistant Virus.** The emergence of drug-resistant mutants has been and will continue to be a critical issue in the treatment of HIV infection.[25] In vivo viral resistance has been demonstrated for all classes of HIV inhibitors: the nucleoside and nonnucleoside reverse transcriptase inhibitors as well as protease inhibitors.[26] For protease inhibitors, the appearance of virus with

**Table 6.** Resistant Mutant Sequences[a]

| wild-type | Leu10 | Lsy20 | Leu24 | Met36 | Ser37 | Met46 | Ile54 | Arg57 | Gln58 | Leu63 | Ile64 | Ala71 | Gly73 | Val77 | Val82 | Ile84 | Leu90 | Ile93 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A-44 | Val | Met | Ile | | Asp | Ile | Val | | | Pro | | Val | | Thr | **Thr** | | | |
| K-60 | Ile | | | | Asn | Ile | Val | | Glu | Pro | Val | | | Ile | **Phe** | | Met | Leu |
| V-18 | Ile | | | Ile | Asp | Ile | | Lys | | Pro | | Val | Ser | | | **Leu** | Met | Leu |

[a] The wild-type sequence, variant sequence, and patient codes have been defined by Olsen et al.[30] and Condra et al.[28a] The amino acid residues in bold indicate active site modifications.

**Table 7.** Comparison of Dissociation Constants ($K_i$) Obtained from Inhibition of Wild-Type HIV-1 Protease and Mutant Enzymes

| | $K_i$ (nM) | | | |
|---|---|---|---|---|
| inhibitor | wild-type | A-44 | K-60 | V-18 |
| MK-944a | 0.049 | 8 | 20 | 25 |
| indinavir | 0.24 | 15 | 50 | 40 |
| saquinavir | 0.062 | 15 | 3.7 | 117 |
| ritonavir | 0.062 | 60 | 40 | 23 |
| nelfinavir | 0.14 | 16 | 33 | 27 |

reduced susceptibility has occurred both in cell culture experiments[27] and in human clinical trials.[13,28] The use of suboptimal doses of indinavir (monothearpy) in initial clinical trials resulted in a lowering of viral load. However, over time mutant variants that exhibited resistance to indinavir began to emerge, and several of these have been characterized both phenotypically and genotypically.[28a] Not only was resistance to indinavir observed but also cross-resistance to a structurally diverse group of protease inhibitors. Also, researchers[28c,29] have reported that, in patients treated with other protease inhibitors, cross-resistant variants have developed.

Table 6 illustrates three high-level, cross-resistant mutant sequences originally identified by Condra et al.[13,28a] and the specific sites of mutation. Each variant has one specific active site mutation that is supported by 8−10 nonactive site mutations. Interestingly, the nonactive site amino acid substitutions have been estimated to account for 40−65% of the loss in inhibition binding energy.[30] Therefore, these nonactive site changes also contribute significantly to the issue of cross-resistance.

A comparison of dissociation constants between several Food and Drug Administration approved HIV-1 protease inhibitors and MK-944a versus selected high-level mutant proteases is illustrated in Table 7. All five compounds exhibit subnanomolar potency against the wild-type protease. However, each compound experiences a 60−1800-fold loss in potency against the mutant proteases (A-44, K-60, and V-18). MK-944a is slightly more active against the A-44 and K-60 strains than the other protease inhibitors and is equipotent to ritonavir and nelfinavir against the V-18 strain. However, for MK-944a each mutant viral protease increases the $K_i$ to 163 and 510 times the wild-type $K_i$ value of 0.049 nM, indicating significant resistance. In light of the previous investigations focused on the resistance issue, and the structural similarity to indinavir, it is not surprising that this HIV-1 protease inhibitor has a similar resistance profile. The inherent increase in potency for MK-944a against the wild-type enzyme and potential ease of dosing should translate into a decreased chance of development of resistance.

**Nephrolithiasis.** Clinical nephrolithiasis is a dose-limiting side effect associated with indinavir.[12] The stones are mainly comprised of indinavir which has precipitated in the kidneys. The assessment of radiolabled indinavir administered to humans and rats has recently been published.[16] In humans, a single oral dose of 400 mg [$^{14}$C]indinavir was administered, and 11% of unchanged indinavir was recovered in the urine. Bile-cannulated, fasted male Sprague−Dawley rats were dosed intravenously (10 mg/kg [$^{14}$C]indinavir), and urine was collected over a 4-h period. Analysis determined that 9.4% of unchanged drug was eliminated in the urine. In contrast, when MK-944a was administered to rats (10 mg/kg iv) no parent drug could be detected in the urine. These data would suggest that MK-944a might provide a lower incidence of nephrolithiasis in patients. Clinical studies will be required to answer this hypothesis.

## Conclusion

In summary, the modification of our HAPA transition-state isosteres has provided several compounds that exceeded our selection criteria for a backup candidate to indinavir. The first compound identified, L-754,394, was a potent CYP3A inhibitor, and this resulted in an extraordinary pharmacokinetic profile in animals. However, safety issues prevented the development of L-754,394 and the elimination of CYP3A inhibition became an additional criterion. By continuing to modify the physical properties of this series (i.e. solubility and lipophilicity) and maintaining potency, MK-944a was identified.

In vitro results demonstrate that MK-944a is potent and competitively inhibits HIV-1 PR with a $K_i$ value of 0.049 nM. Cell culture assays demonstrate that the compound is slightly more effective than indinavir in suppressing the spread of acute HIV-1 infection. More importantly, the addition of up to 50% human serum or $\alpha_1$ acid glycoprotein in the viral assay minimally affects the potency of MK-944a (25−50 nM). At 10 $\mu$M, the compound did not significantly inhibit a variety of other proteinases including human cathepsin D, porcine pepsin, and human gastric and bovine chymosin. MK-944a is not a competitive inhibitor for any of the major cytochrome P-450 isozymes tested. Also, low renal excretion of MK-944a suggests that nephrolithiasis may not be an issue in humans. Finally, no serious safety liabilities have been observed in several animal experiments.

Resistance to HIV-1 PR inhibitors currently plays a significant role in effective, long-term antiviral therapy. Viral replication under selective pressure drives the evolution of resistance, whereas potent inhibition of viral growth delays viral resistance. Therefore, to avoid resistance in a clinical setting, one should design a drug that has several characteristics. First, the compound should be potent in a cell-based assay and in the presence of biologically relevant proteins, and when

orally administered to humans it should maintain significantly higher plasma concentrations then its cell-based $IC_{95}$ value. If this can be achieved, this should completely restrict replication and, therefore, severely limit the chance of mutation selection. Second, a potential drug should have easy dosing requirements and have minimal side effects. The result would be an increase in patient compliance and, therefore, reduce the chances of the patient being exposed to suboptimal plasma concentrations of drug during antiviral therapy. The preclinical data suggest that MK-944a has the potential of having these characteristics, in humans, and is being pursued in humans clinical trials. Advanced human clinical trials with MK-944a, exploring once or twice a day dosing in combination with indinavir, have been ongoing, and those results will be presented when available.

## Experimental Section

**Biological Methods.** Protease inhibition assays,[30] acute infection assays, and animal pharmacokinetic studies have been previously described.[6]

**Chemical Methods.** Reactions were carried out in an argon atmosphere, using solvents and reagents from commercial suppliers which were used as received. All reactions were monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 $F_{254}$ plates (0.25-mm thickness). Flash column chromatography was performed with solvents indicated using E. Merck silica gel 60 (230−400 mesh). All melting points were obtained on a Thomas-Hoover apparatus and were uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Proton magnetic resonance spectra were obtained on either a Varian XL-300 (300 MHz) or a Varian VXR-400 (400 MHz) spectrometer using TMS as an internal standard. The abbreviations AcOH, DIBAL-H, DME, DMF, EDC, EtOAc, Hex, HCl, HOBt, MeOH, $NaB(OAc)_3H$, and THF refer to acetic acid, diisobutylaluminum hydride, 1,2-dimethoxyethane, *N*,*N*-dimethylformamide, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride, ethyl acetate, *n*-hexanes, hydrochloric acid, 1-hydroxybenzotriazole hydrate, sodium triacetoxyborohydride, and tetrahydrofuran, respectively.

**Preparation of *N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(3-quinolinylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (3). Method A:** To a solution of *N*-(2(*R*)-hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(2(*S*)-*N*-(*tert*-butylcarboxamido)piperazinyl))pentanamide (**2**) (0.40 g, 0.765 mmol) dissolved in 5 mL of dichloroethane were added 3-quinolinecarboxaldehyde (0.144 g, 0.916 mmol), AcOH (0.54 mL, 0.916 mmol) and then $Na(OAc)_3H$ (0.344 g, 1.53 mmol). After 48 h the solvent was removed in vacuo and the residue was dissolved in EtOAc (100 mL) and washed with saturated $NaHCO_3$ (1 × 30 mL), water (1 × 50 mL), brine (1 × 75 mL), dried over $MgSO_4$ and concentrated. The residue was purified via column chromatography [30- × 150-mm column, gradient elution $CH_2Cl_2$:$CHCl_3$ saturated with $NH_3$:MeOH 1% (1 L), 2% (1.5 L), 3% (0.5 L)]. This provided 0.335 g (66% yield) of a white foam which could be further purified by triturating with EtOAc and Hex: mp 168−170 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f = 0.5$; $[\alpha]^{22}_D$ +1.36 ($c$ = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.06 (d, $J$ = 3.7 Hz, 1H), 1.36 (s, 9H), 1.55−1.57 (m, 1H), 1.92−1.96 (m, 1H), 2.36−2.40 (m, 1H), 2.52 (dd, $J$ = 13.4, 2.8 Hz, 1H) 2.59−2.93 (m, 10H), 2.98−3.04 (m, 1H), 3.18−3.19 (m, 1H), 3.64 (d, $J$ = 13.0 Hz, 1H), 3.71 (d, $J$ = 13.0 Hz, 1H), 3.78−3.83 (m, 2H), 4.25−4.26 (m, 1H), 5.26 (dd, $J$ = 8.5, 4.9 Hz, 1H), 5.88 (d, $J$ = 8.8 Hz, 1H), 7.08−7.31 (m, 9H), 7.54−7.58 (m, 1H), 7.70−7.73 (m, 1H), 7.78−7.80 (m, 2H), 8.01 (s, 1H), 8.11 (d, $J$ = 8.4 Hz, 1H), 8.85 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 29.3 (3C), 38.3, 39.3, 39.9, 47.1, 47.8, 51.4, 53.0, 55.0, 57.7, 60.8, 61.6, 64.2, 66.0, 73.2, 124.1, 125.4, 126.7, 127.0, 127.3, 127.7, 127.9, 128.2, 128.7 (2C), 129.3 (2C), 129.5, 129.8 (2C), 136.2, 140.3, 140.5, 140.6, 148.0, 151.9, 169.3, 175.0. Anal. ($C_{40}H_{49}N_5O_4$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(3-(6-ethoxypyridyl)methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (4). Method B:** Preparation of 3-chloromethyl-6-ethoxypyridine followed a four-step sequence. **Step 1**: To a solution of ethyl 6-chloronicotinate (2.38 g, 12.85 mmol) in ethanol (120 mL) was added portionwise sodium hydride (1.56 g, 38.56 mmol) over 20 min. After 16 h of reflux, the mixture was cooled to room temperature and quenched with aqueous saturated $NH_4Cl$ (30 mL) and concentrated. The residue was partitioned between EtOAc and water and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with water (1 × 50 mL), brine (1 × 75 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified via column chromatography [50- × 150-mm column, gradient elution Hex:EtOAc, 9:1 (1 L) to 4:1 (1 L)] to provide 1.95 g (77% yield) of ethyl 6-ethoxynicotinate as a clear oil: TLC (Hex:EtOAc, 4:1) $R_f = 0.68$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.35−1.42 (m, 6H), 4.33−4.45 (m, 4H), 6.73 (d, $J$ = 8.8 Hz, 1H), 8.14 (d, $J$ = 8.8 Hz, 1H), 8.82 (s, 1H). **Step 2**: To a solution of ethyl 6-ethoxynicotinate (0.864 g, 4.43 mmol) in THF (12 mL) cooled to 0 °C was added DIBAL-H (1 M in Hex, 13.2 mL, 13.28 mmol) slowly. After 1 h Rochelle's salt (44 mL) was added and the mixture was stirred for 18 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc (100 mL) and washed with saturated $NaHCO_3$ (1 × 30 mL), water (1 × 50 mL), brine (1 × 75 mL), dried over $MgSO_4$ and concentrated. The residue was purified via column chromatography [30- × 150-mm column, gradient elution Hex:EtOAc, 4:1 (1 L) to 3:1 (1 L)]. This provided 0.622 g (91% yield) of 6-ethoxy-3-hydroxylmethylpyridine as a pale yellow oil: TLC (Hex:EtOAc, 4:1) $R_f$ = 0.2; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.38 (t, $J$ = 7.1 Hz, 3H), 2.76 (br s, 1H), 4.31 (q, $J$ = 7.1 Hz, 2H), 4.57 (s, 2H), 6.70 (d, $J$ = 8.4 Hz, 1H), 7.58 (dd, $J$ = 8.4, 2.2 Hz, 1H), 8.03 (d, $J$ = 2.2 Hz, 1H). **Step 3**: To a solution of 6-ethoxy-3-hydroxylmethylpyridine (0.924 g, 6.03 mmol) in $CH_2Cl_2$ was added thionyl chloride (2.5 mL, 34.2 mmol). After 3 h the solvent was removed in vacuo to provide 0.527 g of 3-chloromethyl-6-ethoxypyridine hydrochloride as a tan solid which was used directly in the next step: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.55 (t, $J$ = 6.9 Hz, 3H), 4.59 (s, 2H), 4.73 (q, $J$ = 6.9 Hz, 2H), 7.14 (d, $J$ = 9.0 Hz, 1H), 8.13 (dd, $J$ = 9.0, 2.2 Hz, 1H), 8.39 (d, $J$ = 2.0 Hz, 1H). **Step 4**: To a solution of amine **2** (0.40 g, 0.765 mmol) dissolved in 5 mL of DMF were added 3-chloromethyl-6-ethoxypyridine hydrochloride (0.191 g, 0.918 mmol) and triethylamine (0.30 mL, 2.14 mmol). After 48 h the solvent was removed in vacuo and the residue was dissolved in EtOAc (100 mL) and washed with water (6 × 30 mL), brine (1 × 30 mL), dried over $MgSO_4$ and concentrated. The residue was purified via column chromatography [30- × 150-mm column, gradient elution $CH_2Cl_2$:$CHCl_3$ saturated with $NH_3$:MeOH, 1% (1 L), 1.5% (1 L), 2% (1 L)]. This provided 0.387 g (77% yield) of a white foam which could be further purified by triturating with EtOAc and Hex: mp 88−93 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f = 0.5$; $[\alpha]^{22}_D$ +2.38 ($c$ = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.35 (s, 9H), 1.39 (t, $J$ = 7.0 Hz, 3 H), 1.54−1.58 (m, 1H), 1.91−1.97 (m, 1H), 2.26−2.32 (m, 1H), 2.48−2.53 (m, 2H), 2.64−3.05 (m, 9H), 3.17 (br s, 1H), 3.40 (s, 2H), 3.61−3.67 (m, 1H), 3.78−3.81 (m, 2H), 4.27 (d, $J$ = 4.4 Hz, 1H), 4.35 (q, $J$ = 7.1 Hz, 2H), 5.28 (dd, $J$ = 8.6, 4.9 Hz, 1H), 5.89 (d, $J$ = 8.4 Hz, 1H), 6.70 (d, $J$ = 8.4 Hz, 1H), 7.09−7.32 (m, 10 H), 7.47 (dd, $J$ = 8.5, 2.3 Hz, 1H), 7.88 (br s, 1H), 8.01 (d, $J$ = 2.3 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.6, 29.1 (3C), 38.1, 39.0, 39.6, 46.9, 51.1, 52.6, 54.3, 57.5, 59.6, 61.3, 61.8, 63.8, 65.6, 73.0, 110.9, 123.8, 124.6, 125.2, 126.5, 126.8, 128.0, 128.5 (2C), 129.1 (2C), 139.7, 140.0, 140.3, 140.4, 147.4, 155.6, 163.6, 169.1, 174.8. Anal. ($C_{38}H_{51}N_5O_4 \cdot 1.0H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(3-(6-methylpyridyl)methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (5).** Starting from methyl 6-methylnicotinate and following method B

steps 2−4 the title compound was prepared: mp 186−188 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f$ = 0.34; $[\alpha]^{22}_D$ +2.82 ($c$ = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.09 (d, $J$ = 3.8 Hz, 1H), 1.35 (s, 9H), 1.56−1.59 (m, 1H), 1.92−1.97 (m, 1H), 2.27−2.33 (m, 1H), 2.49−2.54 (m, 1H), 2.56 (s, 3H), 2.61−2.69 (m, 2H), 2.72−3.05 (m, 9H), 3.17 (t, $J$ = 3.4 Hz, 1H), 3.43 (d, $J$ = 13.0 Hz, 1H), 3.49 (d, $J$ = 13.0 Hz, 1H), 3.77−3.80 (m, 2H), 4.27 (m, 1H), 5.28 (dd, $J$ = 8.4, 4.8 Hz, 1H), 5.90 (d, $J$ = 8.6 Hz, 1H), 7.11−7.32 (m, 10H), 7.47 (dd, $J$ = 7.9, 2.2 Hz, 1H), 7.84 (br s, 1H), 8.40 (d, $J$ = 1.6 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 24.1, 29.0 (3C), 38.0, 39.1, 39.6, 46.7, 47.5, 51.1, 52.6, 54.6, 57.4, 59.9, 61.3, 63.9, 65.6, 72.9, 123.0, 123.9, 125.1, 126.4, 126.7, 127.9, 128.5 (2C), 129.0 (2C), 129.1, 137.2, 140.0, 140.4 (2C), 149.8, 157.9, 169.2, 174.9; HRMS (FAB-POSI; M + 1) calcd 628.3857, found 628.3839. Anal. ($C_{37}H_{49}N_5O_4$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(3-(6-chloropyridyl)methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (6).** Starting with methyl 6-chloronicotinate and following method B steps 2−4 the title compound was prepared: mp 168−170 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f$ = 0.48; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.35 (s, 9H), 1.55 (m, 1H), 1.97 (m, 1H), 2.31−2.39 (m, 1H), 2.55−2.72 (m, 7H), 2.74−3.05 (m, 5H), 3.15 (s, 1H), 3.42−3.53 (m, 2H), 3.81 (br s, 2H), 4.25 (d, $J$ = 3.9 Hz, 1H), 5.27 (dd, $J$ = 8.2, 4.8 Hz, 1H), 6.05 (d, $J$ = 8.4 Hz, 1H), 7.12−7.33 (m, 11 H), 7.51 (br s, 1H), 7.57−7.60 (m, 1H), 8.29 (s, 1H). Anal. ($C_{36}H_{46}N_5O_4Cl\cdot0.55H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(3-(2-methoxypyridyl)methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (7).** Methyl 2-methoxynicotinate was prepared from the commercially available acid and (trimethylsilyl)diazomethane in methanol and chloroform. 2-Methoxy-3-chloromethylpyridine was prepared from methyl 2-methoxynicotinate following method B, steps 2 and 3. The title compound **7** was prepared using amine **2** and following method B, step 4: mp 81−85 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f$ = 0.38; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.29 (s, 9H), 1.51−1.59 (m, 1H), 1.76 (br s, 2H), 1.92−1.98 (m, 1H), 2.32−2.39 (m, 1H), 2.47−3.04 (m, 12H), 3.14 (d, $J$ = 3.2 Hz, 1H), 3.44−3.47 (m, 2H), 3.78−3.82 (m, 1H), 3.91−3.95 (m, 1H), 3.94 (s, 3H), 4.26 (t, $J$ = 4.3 Hz, 1H), 5.24−5.29 (m, 1H), 6.03 (d, $J$ = 8.6 Hz, 1H), 6.86 (dd $J$ = 7.1, 5.0 Hz, 1H), 7.11−7.31 (m, 9H), 7.48 (dd, $J$ = 7.1, 1.8 Hz, 1H), 7.97 (br s, 1H), 8.11 (dd, $J$ = 5.0, 1.8 Hz, 1H); HRMS (FAB-POSI; M + 1) calcd 644.3811, found 644.3817. Anal. ($C_{37}H_{49}N_5O_4\cdot0.95H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(3-(2-thiomethylpyridyl)methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (8).** Methyl 2-(methylthio)nicotinate was prepared from the commercially available acid and (trimethylsilyl)diazomethane in methanol and chloroform. 2-Methylthio-3-chloromethylpyridine was prepared from methyl 2-(methylthio)nicotinate following method B, steps 2 and 3. Compound **8** was prepared using amine **2** and following method B, step 4: mp 85−93 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f$ = 0.39; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.30 (s, 9H), 1.54−1.64 (m, 1H), 1.68 (br s, 2H), 1.92−2.0 (m, 1H), 2.38−2.43 (m, 1H), 2.56 (s, 3H), 2.51−3.02 (m, 11 H), 3.17 (br s, 1H), 3.43 (d, $J$ = 13.7 Hz, 1H), 3.51 (d, $J$ = 13.7 Hz, 1H), 3.79−3.83 (m, 2H), 4.28 (br s, 1H), 5.27−5.29 (m, 1H), 5.99 (d, $J$ = 8.4 Hz, 1H), 6.99 (dd, $J$ = 7.3, 4.9 Hz, 1H), 7.13−7.33 (m, 9H), 7.42 (d, $J$ = 7.5 Hz, 1H), 7.50 (br s, 1H), 8.41 (dd, $J$ = 4.8, 1.6 Hz, 1H); MS (FAB-POSI) $m/z$ 660 (M + 1). Anal. ($C_{37}H_{49}N_5O_4S\cdot0.45H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(5-(4-chlorofuro[2,3-*b*]pyridyl)methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (19). 4-Chloro-5-(chloromethyl)furo[2,3-*b*]pyridine (11).** A solution of 4-chlorofuro[2,3-*b*]-2,5-dicarboxylic acid 5-ethyl ester **(10)**[19] (2.51 g, 9.3 mmol) in quinoline (4 mL) was treated with copper(I) oxide (0.251 g) and heated to 150 °C for 3 h. The thick slurry was cooled to 120 °C, diluted with toluene and filtered through Celite. The filtrate was concentrated and the residue was purified via column chromatography [40- × 150-mm column, gradient elution Hex:EtOAc, 4:1 (1 L) to 3:1 (1 L)] to provide 0.70 g (33% yield) of ethyl 4-chlorofuro[2,3-*b*]pyridine-5-carboxylate as a white solid: TLC (Hex:EtOAc, 2:1) $R_f$ = 0.41; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.44 (t, $J$ = 7.2 Hz, 3H), 4.46 (q, $J$ = 7.2 Hz, 2H), 6.98 (d, $J$ = 2.4 Hz, 1H), 7.78 (d, $J$ = 2.5 Hz, 1H), 8.88 (s, 1H). Following the procedure outlined in method B, steps 2−4 then provided the title compound **19**: mp 174−176 °C; $[\alpha]^{22}_D$ +1.82 ($c$ = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.30 (s, 9H), 1.54−1.58 (m, 1H), 1.84−2.06 (m, 3H), 2.44−3.04 (m, 13 H), 3.13 (t, $J$ = 3.5 Hz, 1H), 3.70 (s, 2H), 3.79−3.85 (m, 1H), 4.27 (dd, $J$ = 4.9, 3.9 Hz, 1H), 5.26 (dd, $J$ = 8.6, 4.9 Hz, 1H), 6.0.37−6.40 (m, 1H), 6.88 (d, $J$ = 2.5 Hz, 1H), 7.11−7.31 (m, 9 H), 7.56 (br s, 1H), 7.75 (d, $J$ = 2.5 Hz, 1H), 8.26 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 29.2, 38.3, 39.3, 39.9, 47.0, 47.7, 51.4, 53.0, 54.7, 56.9, 57.7, 61.5, 61.8, 64.3, 65.9, 73.2, 105.0, 119.6, 124.1, 125.4, 126.2, 126.7, 127.0, 128.2, 128.7, 129.3, 137.7, 140.2, 140.6, 146.0, 146.6, 161.7, 169.3, 175.1; MS (FAB-POSI) $m/z$ 688 (M + 1). Anal. ($C_{38}H_{46}N_5O_4Cl$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(5-furo[2,3-*b*]pyridylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (20).** From 5-(chloromethyl)furo[2,3-*b*]pyridine[19] and amine **2** and following the procedure outlined in method B, step 4, the title compound was prepared as a white solid in 84% yield: mp 184−185 °C; $[\alpha]^{22}_D$ +2.96 ($c$ = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.35 (s, 9H), 1.58−1.61 (m, 1H), 1.93−1.99 (m, 1H), 2.34−2.38 (m, 1H), 2.53−2.62 (m, 4H), 2.74−3.09 (m, 9H), 3.15 (d, $J$ = 3.3 Hz, 1H), 3.59 (s, 2H), 3.80 (s, 2H), 4.26 (d, $J$ = 4.2 Hz, 1H), 5.27 (dd, $J$ = 8.4, and 4.9 Hz, 1H), 5.96 (d, $J$ = 8.4 Hz, 1H), 6.76 (dd, $J$ = 2.6, 0.7 Hz, 1H), 7.10−7.32 (m, 10H), 7.73 (d, $J$ = 2.6 Hz, 1H), 7.85 (d, $J$ = 2.0 Hz, 1H), 8.25 (d, $J$ = 2.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 29.3 (3C), 38.3, 39.3, 39.9, 47.1, 47.8, 51.4, 52.9, 54.7, 57.7, 60.4, 61.6, 64.3, 65.9, 73.2, 105.9, 119.4, 124.1, 125.4, 126.7, 127.0, 128.2, 128.3, 128.7 (2C), 129.3 (2C), 131.1, 140.2, 140.5, 140.6, 145.4, 145.8, 162.0, 169.4, 175.0. Anal. ($C_{38}H_{47}N_5O_5\cdot0.25H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(5-(2,3-dihydrofuro[2,3-*b*]pyridyl)-methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))-pentanamide (21).** To a solution of **20** (0.5 g, 0.764 mmol) dissolved in THF (30 mL) and water (6 mL) were added ammonium formate (0.237 g, 3.82 mmol) and 5% Pd/C (0.7 g). After 1.5 h of reflux, the cooled mixture was filtered through a plug of Celite and washed with EtOAc (300 mL). Evaporation of volatiles provided a residue which was purified via column chromatography [25- × 150-mm column, gradient elution, $CH_2Cl_2$:$CHCl_3$ saturated with $NH_3$:MeOH 1% (1 L), 2% (1 L), 5% (1 L)]. The resulting solid was triturated with EtOAc and Hex to afford 0.23 g (46% yield) of the title compound as a white solid: mp 203−204 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f$ = 0.37; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.35 (s, 9H), 1.45 (br s, 1H), 1.52−1.60 (m, 1H), 1.90 (br s, 1H), 1.92−1.99 (m, 1H), 2.27−2.36 (m, 1H), 2.48−3.08 (m, 10H), 3.12 (br s, 1H), 3.23 (t, $J$ = 8.6 Hz, 2H), 3.38 (s, 2H), 3.77−3.83 (m, 1H), 3.95 (br s, 1H), 4.27 (br s, 1H), 4.63 (t, $J$ = 8.6 Hz, 2H), 5.27 (dd, $J$ = 8.6, 4.9 Hz, 1H), 6.11−6.19 (m, 1H), 7.09−7.10 (m, 2H), 7.16−7.17 (m, 2H), 7.23−7.32 (m, 6H), 7.40 (s, 1H), 7.78 (br s, 1H), 7.84 (s, 1H); MS (FAB-POSI) $m/z$ 656 (M + 1). Anal. ($C_{38}H_{49}N_5O_5$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(6-furo[3,2-*b*]pyridylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (22). 6-(Chloromethyl)furo[3,2-*b*]pyridine (13).** A solution of 3-*tert*-butyloxycarbonylaminofuran **(12)** (3.47 g, 18.94 mmol) in ethanol (25 mL) was treated with concentrated HCl (25 mL) and zinc chloride in ether (1.0 M, 20.8 mL). After 5 min, ethoxycarbonylmalonaldehyde[20] (3.0 g, 20.8 mmol) dissolved in ethanol (15 mL) was added to the green solution. After warming for 2 h at 80 °C, the mixture was cooled and the volatiles were removed in vacuo. The residue was dissolved

in $CH_2Cl_2$ and washed with NaOH (1 × 50 mL, 5 N) and water (1 × 50 mL), dried over $MgSO_4$, filtered, and concentrated to a brown oil. The residue was purified via column chromatography [40- × 150-mm column, gradient elution Hex:EtOAc, 3:2 (1 L) to 1:1 (1 L)] to provide 0.447 g (12% yield) of an orange solid: TLC (Hex:EtOAc, 1:2) $R_f = 0.44$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.43 (t, $J = 7.1$ Hz, 3H), 4.44 (q, $J = 7.1$ Hz, 2H), 7.05 (dd, $J = 2.2$, 1.1 Hz, 1H), 8.00 (d, $J = 2.2$ Hz, 1H), 8.37 (dd, $J = 2.2$, 1.1 Hz, 1H), 9.02 (d, $J = 1.7$ Hz, 1H). Following the procedure outlined in method B, steps 2−4 then provided the title compound **22** as a white solid: mp 160−161 °C; $[\alpha]^{22}_D$ +1.92 ($c = 1.00$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.35 (s, 9H), 1.52−1.58 (m, 1H), 1.93−2.01 (m, 1H), 1.96−2.16 (br s, 2H), 2.38−2.42 (m, 1H), 2.51−2.99 (m, 11 H), 3.10 (t, $J = 3.5$ Hz, 1H), 3.61 (s, 2H), 3.79−3.85 (m, 1H), 4.22−4.29 (m, 1H), 5.26 (dd, $J = 8.5$, 4.9 Hz, 1H), 6.33 (d, $J = 8.5$ Hz, 1H), 6.98 (dd, $J = 2.3$, 0.9 Hz, 1H), 7.10−7.30 (m, 10 H), 7.65 (br s, 1H), 7.71 (s, 1H), 7.86 (d, $J = 2.2$ Hz, 1H), 8.46 (d, $J = 1.5$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 29.0 (3C), 38.1, 39.0, 39.6, 46.8, 47.6, 51.2, 52.7, 54.5, 57.4, 60.4, 61.3, 64.0, 65.7, 73.0, 108.1, 118.9, 123.8, 125.1, 126.5, 126.8, 127.9, 128.2, 128.5 (2C), 129.0 (2C), 140.0, 140.3, 140.4, 147.1, 147.2, 147.6, 149.3, 169.1, 174.8; HRMS (FAB-POSI; M + 1) calcd 654.3655, found 654.3644. Anal. ($C_{38}H_{47}N_5O_5 \cdot 0.45H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(6-furo[2,3-*b*]pyridylcarbonyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (23). Furo[2,3-*b*]pyridine-5-carboxylic Acid.** A solution of LiOH monohydrate (0.208 g, 8.72 mmol) in water (10 mL) was added to a solution of ethyl furo[2,3-*b*]pyridine-5-carboxylate[19] (0.55 g, 2.91 mmol) and THF (10 mL). After 1 h the volatiles were removed in vacuo; the aqueous was acidified to pH 3 with 10% HCl, and the resulting solid was isolated by filtration. This solid was dried in vacuo at 50 °C to yield 0.433 g (91%) as a white solid: $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.15 (d, $J = 2.3$ Hz, 1H), 8.25 (d, $J = 2.3$ Hz, 1H), 8.68 (d, $J = 1.9$ Hz, 1H), 8.88 (d, $J = 1.9$ Hz, 1H). A solution of furo[2,3-*b*]pyridine-5-carboxylic acid (0.112 g, 0.689 mmol) in DMF (2.0 mL) was treated with amine **2** (0.30 g, 0.575 mmol), EDC hydrochloride (0.132 g, 0.689 mmol), HOBt (0.093 g, 0.689 mmol) and then triethylamine (0.192 mL, 1.38 mmol). After 24 h the mixture was diluted with EtOAc (100 mL) and washed with aqueous saturated $NaHCO_3$ (1 × 5 mL), water (4 × 5 mL) and brine (1 × 5 mL), and dried over $MgSO_4$, filtered, and concentrated to an oil. The residue was purified via column chromatography [20- × 150-mm column, gradient elution, $CH_2Cl_2$:$CHCl_3$ saturated with $NH_3$:MeOH, 1% (0.5 L), 2% (0.5 L), 3% (0.5 L)]. The resulting solid was triturated with EtOAc and Hex to afford 0.28 g (73% yield) of the title compound as a white solid: mp 114−124 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f = 0.44$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.34 (s, 9H), 1.58−1.61 (m, 1H), 1.95−2.08 (m, 1H), 2.41−3.11 (m, 10H), 3.45−3.98 (m, 7H), 4.23 (d, $J = 3.9$ Hz, 1H), 5.26 (d, $J = 4.4$ Hz, 1H), 6.27 (br s, 1H), 6.83 (d, $J = 2.4$ Hz, 1H), 7.10−7.32 (m, 10H), 7.77 (s, 1H), 8.02 (br s, 1H), 8.36 (d, $J = 1.9$ Hz, 1H); MS (FAB-POSI) *m*/*z* 668 (M + 1). Anal. ($C_{38}H_{45}N_5O_6 \cdot 0.4H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(6-(4-chloro-5,7-dimethylpyrazolo[3,4-*b*]-pyridyl)methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (24). 6-(Chloromethyl)-4-chloro-5,7-dimethylpyrazolo[3,4-*b*]pyridine (15).** Ethyl 4-chloro-5,7-dimethylpyrazolo[3,4-*b*]pyridine-3-carboxylate is commercially available from Maybridge Chemical Co. Following method B, steps 2−4, compound **24** was prepared in 55% yield as a white solid: mp 119−128 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f = 0.32$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.31 (s, 9H), 1.58−1.62 (m, 1H), 1.91−1.99 (m, 1H), 2.41−3.19 (m, 10H), 2.73 (s, 3H), 3.19−3.21 (m, 1H), 3.62−3.83 (m, 7H), 4.06 (s, 3H), 4.23−4.26 (m, 1H), 5.26 (dd, $J = 8.5$, 4.9 Hz, 1H), 5.88 (d, $J = 8.5$ Hz, 1H), 7.12−7.31 (m, 10H), 7.67 (br s, 1H), 8.38 (s,1H). Anal. ($C_{39}H_{50}N_7O_4Cl$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(6-(5,7-dimethylpyrazolo[3,4-*b*]pyridyl)-methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))-pentanamide (24). 6-(Chloromethyl)-5,7-dimethylpyrazolo-[3,4-*b*]pyridine (16)** To a solution of ethyl 4-chloro-5,7-dimethylpyrazolo[3,4-*b*]pyridine-3-carboxylate (0.502 g, 1.98 mmol) in AcOH (6 mL) was added zinc powder (0.259 g, 3.96 mmol). The mixture was warmed to 100 °C for 5 h, filtered (hot) through a plug of Celite and washed with AcOH (70 mL). The volatiles were removed in vacuo and the remaining oil was partitioned between $CH_2Cl_2$ (50 mL) and aqueous saturated $Na_2CO_3$ (50 mL). The aqueous was extracted with $CH_2Cl_2$ (2 × 50 mL) and the combined organic layer was washed with water (1 × 30 mL) and brine (1 × 30 mL), dried over $MgSO_4$, filtered and concentrated to a white solid (0.29 g, 67% yield): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.44 (t, $J = 7.1$ Hz, 3H), 2.61 (s, 3H), 4.12 (s, 3H), 4.45 (q, $J = 7.1$ Hz, 2H), 8.66 (d, $J = 2.0$ Hz, 1H), 9.15 (d, $J = 2.0$ Hz, 1H). Following method B, steps 2−4, compound **25** was prepared in 64% yield as a white solid: mp 163−168 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f = 0.37$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.36 (s, 9H), 1.55−1.62 (m, 3H), 1.92−1.98 (m, 1H), 2.31−2.36 (m, 1H), 2.51−3.01 (m, 10H), 2.56 (s, 3H), 3.19 (s, 1H), 3.59 (d, $J = 12.8$ Hz, 1H), 3.63 (d, $J = 12.8$ Hz, 1H), 3.78 (br s, 2H), 4.09 (s, 3H), 4.23−4.26 (m, 1H), 5.28 (dd, $J = 8.6$, 4.9 Hz, 1H), 5.89 (d, $J = 8.6$ Hz, 1H), 7.09−7.33 (m, 11H), 7.86 (s, 1H), 8.43 (s, 1H). Anal. ($C_{39}H_{51}N_7O_4 \cdot 0.1H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-furo[2,3-*b*]pyridylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (26).** Following method A and using 2-formylfuro[2,3-*b*]pyridine[31] and amine **2** compound **26** was prepared as a white solid in 72% yield: mp 92−96 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f = 0.37$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.36 (s, 9H), 1.54−1.62 (m, 1H), 1.90−1.96 (m, 1H), 2.18 (br s, 2H), 2.40−3.02 (m, 12 H), 3.13 (br s, 1H), 3.62 (d, $J = 14.2$ Hz, 1H), 3.71 (d, $J = 14.2$ Hz, 1H), 3.76−3.81 (m, 1H), 4.04 (br s, 1H), 4.27 (br s, 1H), 5.27 (dd, $J = 8.5$, and 4.8 Hz, 1H), 6.23 (br s, 1H), 6.61 (s, 1H), 7.06−7.29 (m, 10H), 7.86 (dd, $J = 7.6$, 1.6 Hz, 1H), 8.05 (br s, 1H), 8.28 (dd, $J = 4.9$, 1.6 Hz, 1H); HRMS (FAB-POSI; M + 1) calcd 654.3655, found 654.3649. Anal. ($C_{38}H_{47}N_5O_5 \cdot 0.5H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-(5-ethylcarboxylate furo[2,3-*b*]pyridyl)-methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))-pentanamide (27). Ethyl 2-Hydroxymethylfuro[2,3-*b*]pyridine-5-carboxylate.** To a solution of furo[2,3-*b*]pyridine-2,5-dicarboxylic acid 5-ethyl ester[19] (4.0 g, 17.01 mmol) in dry DME (34 mL) cooled to −15 °C was added *N*-methylmorpholine (1.87 mL, 17.01 mmol) and then isobutyl chloroformate (2.21 mL, 17.01 mmol). After 1 h, a solution of $NaBH_4$ (1.93 g, 51.03 mmol) in water (20 mL) was carefully added dropwise. The mixture was diluted with water (100 mL) and the aqueous was extracted with EtOAc (3 × 100 mL), the combined organic layer was washed with brine (1 × 30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The yellow oil was purified via column chromatography [40- × 150-mm column, gradient elution Hex:EtOAc, 3:2 (1 L) to 1:1 (1 L) to 2:3 (1 L)] to provide 1.21 g (32% yield) of the title compound as a yellow solid: TLC (Hex:EtOAc, 1:2) $R_f = 0.38$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.43 (t, $J = 7.1$ Hz, 3H), 2.42 (br s, 1H), 4.43 (q, $J = 7.1$ Hz, 2H), 4.84 (s, 2H), 6.76 (d, $J = 0.8$ Hz, 1H), 8.54 (d, $J = 2.0$ Hz, 1H), 8.98 (d, $J = 2.0$ Hz, 1H). Following the procedure outlined in method B, steps 3 and 4, then provided compound **27** as a white solid in 80% yield: mp 188−189 °C; $[\alpha]^{22}_D$ +0.65 ($c = 1.00$, $CHCl_3$); TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f = 0.48$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.38 (s, 9H), 1.43 (t, $J = 7.0$ Hz, 3H), 1.58−1.64 (m, 1H), 1.80 (br s, 2H), 1.94−1.99 (m, 1H), 2.44−2.58 (m, 2 H), 2.60−2.71 (m, 3H), 2.78−3.05 (m, 7H), 3.19 (br s, 1H), 3.66 (d, $J = 14.4$ Hz, 1H), 3.76 (d, $J = 14.4$ Hz, 1H), 3.76−3.82 (m, 1H), 4.27 (br s, 1H), 4.43 (q, $J = 7.0$ Hz, 2H), 5.27 (dd, $J = 8.5$, and 4.8 Hz, 1H), 6.03 (d, $J = 8.6$ Hz, 1H), 6.71 (s, 1H), 7.10−7.29 (m, 10H), 8.01 (br s,1H), 8.53 (d, $J = 2.0$ Hz, 1H), 8.99 (d, $J = 2.0$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 14.5, 29.2 (3C), 38.4, 39.3, 39.9, 47.1, 47.7, 51.5, 53.0, 54.4, 55.2, 57.7, 61.6 (2C), 63.9,

66.0, 73.2, 105.6, 112.0, 123.1, 124.1, 125.4, 126.7, 127.0, 128.2, 128.7 (2C), 129.3 (2C), 131.7, 140.3, 140.6 (2C), 146.7, 155.3, 164.3, 165.6, 169.0, 175.0; MS (FAB-POSI) *m*/*z* 726 (M + 1). Anal. ($C_{41}H_{51}N_5O_7 \cdot 0.7H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-(5-hydroxymethylfuro[2,3-*b*]pyridyl)-methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))-pentanamide (28).** A solution of ester **27** (0.635 g, 0.875 mmol) in dry THF (4 mL) at 0 °C was treated with $LiBH_4$ (0.65 mL, 2.0 M in THF, 1.312 mmol). After 18 h, the reaction was quenched with MeOH (20 mL) and the volatiles were removed in vacuo. The residue was dissolved in EtOAc (150 mL) and washed with saturated $NaHCO_3$ (1 × 15 mL), water (1 × 15 mL), brine (1 × 15 mL), dried, filtered and concentrated. The residue was purified via column chromatography [25- × 150-mm column, gradient elution, $CH_2Cl_2$:$CHCl_3$ saturated with $NH_3$:MeOH, 1% (0.5 L), 2% (0.5 L), 4% (0.5 L), 6% (0.5 L)]. The resulting solid was triturated with EtOAc and Hex to afford 0.392 g (65% yield) of the title compound as a white solid: mp 214−215 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f = 0.38$; $[\alpha]^{22}_D$ +1.20 ($c$ = 1.00, $CH_3OH$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.37 (s, 9H), 1.55 (br s, 1H), 1.54−1.60 (m, 1H), 1.94−1.99 (m, 1H), 2.44−2.52 (m, 2 H), 2.59−2.64 (m, 3H), 2.77−3.05 (m, 9H), 3.15 (d, $J$ = 3.2 Hz, 1H), 3.62 (d, $J$ = 14.1 Hz, 1H), 3.72 (d, $J$ = 14.1 Hz, 1H), 3.78−3.81 (m, 1H), 4.10 (br s, 1H), 4.26 (br s, 1H), 4.76 (s, 2H), 5.25 (dd, $J$ = 8.6, and 3.7 Hz, 1H), 6.60 (s, 1H), 7.11−7.31 (m, 10H), 7.89 (d, $J$ = 2.0 Hz, 1H), 8.09 (br s,1H), 8.23 (d, $J$ = 2.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 29.1 (3C), 38.2, 39.3, 39.8, 46.5, 48.2, 51.5, 52.9, 54.4, 55.2, 57.7, 61.5, 62.7, 63.9, 66.0, 73.1, 105.4, 112.4, 124.2, 125.3, 126.6, 126.9, 128.1, 128.7 (2C), 129.2 (2C), 129.3, 132.7, 140.1, 140.6 (2C), 143.5, 154.2, 161.9, 169.5, 175.5; MS (FAB-POSI) *m*/*z* 684 (M + 1). Anal. ($C_{39}H_{49}N_5O_6 \cdot 0.25H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-furo[2,3-*c*]pyridylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (29).** From 2-formylfuro[2,3-*c*]pyridine[32] and amine **2** and following the procedure outlined in method A, the title compound was prepared as a white solid in 67% yield: mp 100−106 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f = 0.37$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.37 (s, 9H), 1.52−1.60 (m, 1H), 1.92−2.01 (m, 2H), 2.42−2.54 (m, 2H), 2.59−2.68 (m, 3H), 2.76−3.07 (m, 9H), 3.15 (br s, 1H), 3.67 (d, $J$ = 14.5 Hz, 1H), 3.72 (d, $J$ = 14.5 Hz, 1H), 3.78−3.86 (m, 1H), 4.04 (br s, 1H), 4.28 (s, 1H), 5.27 (dd, $J$ = 8.5, and 4.8 Hz, 1H), 6.28 (d, $J$ = 8.6 Hz, 1H), 6.67 (s, 1H), 7.10−7.28 (m, 10H), 7.50 (d, $J$ = 5.2 Hz, 1H), 7.97 (br s, 1H), 8.39 (d, $J$ = 5.3 Hz, 1H), 8.78 (s, 1H); HRMS (FAB-POSI; M + 1) calcd 654.3655, found 654.3670. Anal. ($C_{38}H_{47}N_5O_5 \cdot 0.2$Hex) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-furo[3,2-*c*]pyridylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (30).** From 2-formylfuro[3,2-*c*]pyridine[33] and amine **2** and following the procedure outlined in method A, the title compound was prepared as a white solid in 66% yield: mp 175−177 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f = 0.41$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.37 (s, 9H), 1.52−1.61 (m, 1H), 1.94−1.99 (m, 1H), 2.44−2.53 (m, 3H), 2.61−2.66 (m, 3H), 2.76−3.03 (m, 8H), 3.17 (br s, 1H), 3.66 (d, $J$ = 14.3 Hz, 1H), 3.71 (d, $J$ = 14.3 Hz, 1H), 3.78−3.84 (m, 1H), 3.97 (br s, 1H), 4.25−4.27 (m, 1H), 5.27 (dd, $J$ = 8.6, and 4.9 Hz, 1H), 6.11 (dd, $J$ = 8.3, 0.4 Hz, 1H), 6.69 (s, 1H), 7.10−7.37 (m, 10H), 8.03 (br s,1H), 8.47 (d, $J$ = 5.7 Hz, 1H), 8.87 (s, 1H); HRMS (FAB-POSI; M + 1) calcd 654.3655, found 654.3640. Anal. ($C_{38}H_{47}N_5O_5 \cdot 0.35H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-(6-methylfuro[3,2-*c*]pyridyl)methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (31).** The preparation of 2-formyl-6-methylfuro[3,2-*c*]-pyridine followed in analogous fashion from the synthesis of 2-formylfuro[3,2-*c*]pyridine,[33] using $\beta$-(3-furyl)methacrylic acid in place of $\beta$-(3-furyl)acrylic acid. Starting from 2-formyl-6-methylfuro[3,2-*c*]pyridine and amine **2** and following the procedure outlined in method A, compound **31** was prepared as a white solid in 78% yield: mp 101−110 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f = 0.36$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.36 (s, 9H), 1.49−1.58 (m, 1H), 1.91−2.01 (m, 1H), 2.25 (br s, 1H), 2.43−2.50 (m, 2H), 2.52−2.62 (m, 4H), 2.64 (s, 3H), 2.70−3.03 (m, 7H), 3.09 (br s, 1H), 3.61 (d, $J$ = 14.1 Hz, 1H), 3.66 (d, $J$ = 14.1 Hz, 1H), 3.78−3.86 (m, 1H), 4.14 (br s, 1H), 4.28 (dd, $J$ = 4.9, 3.9 Hz, 1H), 5.26 (dd, $J$ = 8.4, and 4.9 Hz, 1H), 6.43 (d, $J$ = 8.6 Hz, 1H), 6.62 (s, 1H), 7.05−7.29 (m, 10H), 7.92 (br s,1H), 8.70 (s, 1H); HRMS (FAB-POSI; M + 1) calcd 668.3811, found 688.3803. Anal. ($C_{39}H_{49}N_5O_5$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(3-thieno[2,3-*b*]pyridylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (32).** Following method A and using 3-formylthieno[2,3-*b*]pyridine[34] and amine **2,** the title compound was prepared as a white solid in 56% yield: mp 101−110 °C; $[\alpha]^{22}_D$ +1.72 ($c$ = 1.00, $CHCl_3$); TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f$ = 0.48; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.26 (s, 9H), 1.48−1.58 (m, 1H), 1.71 (br s, 1H), 1.95−2.03 (m, 1H), 2.37−2.45 (m, 1H), 2.48−3.07 (m, 12H), 3.67 (s, 2H), 3.76−3.90 (m, 2H), 4.24 (br s, 1H), 5.26 (dd, $J$ = 8.5, and 4.8 Hz, 1H), 6.30 (d, $J$ = 8.6 Hz, 1H), 7.07−7.31 (m, 12H), 7.35 (s, 1H), 8.16 (dd, $J$ = 8.1, 1.5 Hz, 1H), 8.55 (dd, $J$ = 4.6, 1.6 Hz, 1H); $^{13}$C NMR (75.6 MHz, $CDCl_3$) $\delta$ 28.9 (3C), 38.0, 39.1, 39.6, 46.8, 48.6, 51.0, 52.5, 54.7, 56.3, 57.4, 61.4, 64.6, 65.9, 73.0, 119.2, 123.8, 125.1, 125.2, 126.5, 126.8, 128.0, 128.5 (2C), 129.0 (2C), 129.9, 130.0, 132.0, 139.9, 140.3 (2C), 146.8, 162.4, 169.6, 174.8; HRMS (FAB-POSI; M + 1) calcd 670.3427, found 670.3414. Anal. ($C_{38}H_{47}N_5O_4S \cdot 0.2$EtOAc) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-thieno[2,3-*b*]pyridylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (33).** Following method A and using 2-formylthieno[2,3-*b*]pyridine[34] and amine **2,** the title compound was prepared as a white solid in 76% yield: mp 193−194 °C; $[\alpha]^{22}_D$ +1.68 ($c$ = 1.00, $CHCl_3$); TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f$ = 0.42; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.42 (s, 9H), 1.54−1.62 (m, 1H), 1.79 (br s, 1H), 1.92−1.99 (m, 1H), 2.28−2.37 (m, 1H), 2.53−2.70 (m, 4H), 2.78−3.04(m, 9H), 3.47 (s, 1H), 3.73−3.84 (m, 3H), 3.95 (br s, 1H), 4.27 (d, $J$ = 4.6 Hz, 1H), 5.27 (dd, $J$ = 8.5, and 4.9 Hz, 1H), 6.05 (d, $J$ = 8.5 Hz, 1H), 7.10−7.32 (m, 10H), 7.75 (br s, 1H), 7.96 (dd, $J$ = 8.1, 1.7 Hz, 1H), 8.52 (dd, $J$ = 4.6, 1.7 Hz, 1H); $^{13}$C NMR (75.6 MHz, $CDCl_3$) $\delta$ 29.2 (3C), 38.1, 39.0, 39.6, 46.8, 47.2, 51.3, 52.7, 54.7, 57.4, 58.5, 61.2, 63.8, 65.7, 72.9, 119.6, 120.5, 123.9, 125.1, 126.5, 126.7, 127.9, 128.5 (2C), 129.1 (2C), 130.6, 132.8, 140.0, 140.3, 140.4, 142.0, 146.4, 162.0, 168.9, 174.8; HRMS (FAB-POSI; M + 1) calcd 670.3427, found 670.3422. Anal. ($C_{38}H_{47}N_5O_4S \cdot 0.25CHCl_3$) C, H, N.

**MK-944a: *N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-benzo[*b*]furanylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (34).** To a solution of amine **2** (37 g, 63.71 mmol) and commercially available benzofuran-2-carboxaldehyde (10 g, 70.08 mmol) dissolved in 700 mL of 1,2-dichloroethane was added $NaB(OAc)_3H$ (24.9 g, 0.114 mol) portionwise followed by AcOH (4 mL, 67.65 mmol). After 16 h the solvent was removed in vacuo and the residue was dissolved in EtOAc (1.5 L). The organic layer was washed with saturated $NaHCO_3$ (1 × 400 mL), $H_2O$ (3 × 350 mL), brine (1 × 200 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford a yellow foam. The residue was purified via column chromatography [100- × 150-mm column, gradient elution $CH_2Cl_2$:$CHCl_3$ saturated with $NH_3$:$^i$PrOH, 3% (4 L), 4% (4 L)]. A white solid was recovered which was recrystallized from EtOAc/Hex to provide 19.61 g (47% yield) as a white crystalline solid (a second batch provided 7.6 g of material): mp 152−153.5 °C; $[\alpha]^{22}_D$ +1.25 ($c$ = 1.00, $CHCl_3$); TLC $R_f$ (0.45, 5% MeOH in $CH_2Cl_2$ 1/2 saturated with $NH_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.15 (d, $J$ = 3.6 Hz, 1H), 1.38 (s, 9H), 1.55−1.62 (m, 1H), 1.90−1.96 (m, 1H), 2.41 (dd, $J$ = 10.8, 3.3 Hz, 1H), 2.49−2.59 (m, 2H), 2.64−2.94 (m, 9H), 2.96−3.05 (m, 1H), 3.21 (t, $J$ = 3.1

Hz, 1H), 3.62 (d, $J$ = 13.9 Hz, 1H), 3.91 (d, $J$ = 13.9 Hz, 1H), 3.77−3.82 (m, 1H), 3.99 (br s, 1H), 4.11−4.29 (m, 1H), 5.28 (dd, $J$ = 4.8, 8.5 Hz, 1H), 5.95 (d, $J$ = 8.6 Hz, 1H), 6.61 (s, 1H), 7.09−7.32 (m, 11H), 7.40−7.42 (m, 1H), 7.53−7.55 (m, 1H), 8.26 (br s, 1H); $^{13}$C NMR (75.6 MHz, $CDCl_3$) $\delta$ 29.0 (3C), 38.1, 39.1, 39.6, 46.6, 47.2, 51.1, 52.7, 54.2, 54.9, 57.5, 61.3, 63.5, 65.6, 72.9, 106.1, 111.0, 120.9, 122.8, 123.9, 124.3, 125.1, 126.4, 126.7, 127.9, 128.0, 128.4 (2C), 129.1 (2C), 140.0, 140.4 (2C), 153.3, 155.1, 168.9, 174.9; HRMS (FAB-POSI; M + 1) calcd 653.3702, found 653.3721. Anal. ($C_{39}H_{48}N_4O_5$) C, H, N.

**MK-944a: *N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-benzo[*b*]furanylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide Hydrochloride Dihydrate.** To MK-944a (1.11 g, 1.70 mmol) dissolved in 16 mL of absolute ethanol cooled to 0 °C was added 1.70 mL of 1 N HCl (1.70 mmol) dropwise. After 30 min the solvent was removed in vacuo to provide a white foam. This foam was suspended in $H_2O$ and the pH was adjusted to 2 with 1 N HCl. After 48 h the solid was filtered and washed with cold $H_2O$ to provide 1.06 g of a white crystalline solid (86% yield): mp 128−133 °C. Anal. ($C_{39}H_{48}N_4O_5$·1.0HCl·1.90$H_2O$) C, H, N.

**MK-944a: *N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-benzo[*b*]furanylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide Mesylate.** To MK-944a (1.0 g, 1.53 mmol) dissolved in 15 mL of absolute ethanol cooled to 0 °C was added methane sulfonate (0.10 mL, 1.53 mmol) dropwise. After 30 min the solvent was removed in vacuo to provide a white foam. This foam was suspended in 50 mL of EtOAc, aged 3 h and filtered to provide a white solid. This was dried at 50 °C for 18 h to afford 1.064 g (93% yield) of a white crystalline solid: mp 153−155.5 °C. Anal. ($C_{39}H_{48}N_4O_5$·1.0$CH_3SO_3H$·0.40$H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(5-benzo[*b*]furanylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (35).** Ethyl benzofuran-5-carboxylate was converted into 5-(chloromethyl)-benzo[*b*]furan following the procedures outlined in method B, steps 2 and 3. Benzofuran **35** was prepared following the procedures outlined in method B, step 4, utilizing amine **2** and 5-(chloromethyl)benzo[*b*]furan. This provided the title compound as a white solid in 56% yield: mp 105−110 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f$ = 0.41; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.36 (s, 9H), 1.56−1.61 (m, 1H), 1.68 (br s, 2H), 1.94−1.99 (m, 1H), 2.24−2.36 (m, 1 H), 2.46−2.52 (m, 2H), 2.62−3.05 (m, 10H), 3.17 (t, $J$ = 3.0 Hz, 1H), 3.53 (d, $J$ = 12.5 Hz, 1H), 3.56 (d, $J$ = 12.5 Hz, 1H), 3.72−3.82 (m, 1H), 4.26−4.29 (m, 1H), 5.25−5.29 (m, 1H), 5.99 (d, $J$ = 8.4 Hz, 1H), 6.73 (dd, $J$ = 1.3, 0.8 Hz, 1H), 7.09−7.32 (m, 10H), 7.46 (s, 1H), 7.48 (s, 1H), 7.64 (d, $J$ = 2.0 Hz, 1H), 8.12 (br s, 1H); HRMS (FAB-POSI; M + 1) calcd 653.3702, found 653.3702. Anal. ($C_{39}H_{48}N_4O_5$·0.65$H_2O$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-(3-methylbenzo[*b*]furanyl)methyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (36).** 3-Methylbenzo[*b*]furan-2-carboxylic acid was converted into 2-(chloromethyl)benzo[*b*]furan by esterification with (trimethylsilyl)diazomethane in methanol and chloroform. The resulting ester was converted into the **36** following the procedures outlined in method B, steps 2−4. This provided the title compound as a white solid in 76% yield: mp 111−118 °C; $[\alpha]^{22}_D$ +1.03 ($c$ = 1.00, $CHCl_3$); TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f$ = 0.54; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.35 (s, 9H), 1.52−1.60 (m, 1H), 1.72 (br s, 2H), 1.87−1.97 (m, 1H), 2.23 (s, 3H), 2.34−2.42 (m, 1 H), 2.45−3.04 (m, 11H), 3.15 (br s, 1H), 3.57 (d, $J$ = 13.5 Hz, 1H), 3.61 (d, $J$ = 13.5 Hz, 1H), 3.73−3.82 (m, 1H), 4.06 (br s, 1H), 4.25−4.30 (m, 1H), 5.25−5.29 (m, 1H), 6.23 (d, $J$ = 8.6 Hz, 1H), 7.11−7.30 (m, 11H), 7.38 (d, $J$ = 7.2 Hz, 1H), 7.49 (d, $J$ = 7.3 Hz, 1H), 8.29 (br s, 1H); $^{13}$C NMR (75.6 MHz, $CDCl_3$) $\delta$ 7.9, 28.8 (3C), 38.0, 39.0, 39.5, 46.6, 47.0, 51.0, 52.3, 52.5, 54.0, 57.4, 61.2, 63.3, 65.5, 72.8, 110.7, 114.1, 119.3, 122.3, 123.8, 124.3, 125.0, 126.3, 126.6, 127.8, 128.3 (2C), 129.0 (2C), 129.4, 139.9, 140.3 (2C), 148.1, 154.0, 168.8, 174.8; MS (FAB-POSI) $m/z$ 667 (M + 1). Anal. ($C_{40}H_{50}N_4O_5$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-benzimidazolylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (37).** Following method B, step 4, and using 2-(chloromethyl)benzimidazole and amine **2,** the title compound was prepared as a white solid in 58% yield: mp 127−133 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 10:30:60) $R_f$ = 0.37; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.42 (s, 9H), 1.58−1.68 (m, 3H), 1.97−2.09 (m, 1H), 2.53−3.19 (m, 15H), 3.15 (br s, 1H), 3.82 (d, $J$ = 14.5 Hz, 1H), 3.89 (d, $J$ = 14.5 Hz, 1H), 4.21−4.28 (m, 1H), 5.25−5.29 (m, 1H), 6.09 (d, $J$ = 8.5 Hz, 1H), 7.09−7.34 (m, 14H), 7.60 (d, $J$ = 3.1 Hz, 1H), 7.62 (d, $J$ = 3.2 Hz, 1H); MS (FAB-POSI) $m/z$ 653 (M + 1). Anal. ($C_{40}H_{50}N_4O_5$·0.55$CHCl_3$) C, H, N.

***N*-(2(*R*)-Hydroxy-1(*S*)-indanyl)-2(*R*)-phenylmethyl-4(*S*)-hydroxy-5-(1-(4-(2-benzimidazolylmethyl)-2(*S*)-*N*′-(*tert*-butylcarboxamido)piperazinyl))pentanamide (38).** Following method A and using indole-3-carboxaldehyde and amine **2**, the title compound was prepared as a white solid in 41% yield: mp 125−131 °C; TLC (MeOH:$CHCl_3$ saturated with $NH_3$:$CH_2Cl_2$, 5:30:65) $R_f$ = 0.43; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.25 (s, 9H), 1.54−1.60 (m, 3H), 1.62 (br s, 1H), 1.89−1.94 (m, 1H), 2.33 (br s, 1H), 2.48−2.54 (m, 2H), 2.61−3.05 (m, 10H), 3.17 (br s, 1H), 3.68 (2, 2H), 3.78 (br s, 1H), 4.27 (t, $J$ = 4.4 Hz, 1H), 5.27 (dd, $J$ = 8.1, 5.0 Hz, 1H), 5.97 (d, $J$ = 8.4 Hz, 1H), 7.10−7.31 (m, 12H), 7.38 (d, $J$ = 8.1 Hz, 1H), 7.63 (d, $J$ = 7.7 Hz, 1H), 7.98 (br s, 1H), 8.20 (s, 1H); HRMS (FAB-POSI; M + 1) calcd 652.3862, found 652.3866. Anal. ($C_{40}H_{50}N_4O_5$·1.0EtOAc) C, H, N.

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**Supporting Information Available:** Elemental analyses of compounds **3**−**8** and **19**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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