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# Piperazinyl Glutamate Pyridines as Potent Orally Bioavailable $P2Y_{12}$ Antagonists for Inhibition of Platelet Aggregation

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Polymer-assisted solution-phase (PASP) parallel library synthesis was used to discover a piperazinyl glutamate pyridine as a $P2Y_{12}$ antagonist. Exploitation of this lead provided compounds with excellent inhibition of platelet aggregation as measured in a human platelet rich plasma (PRP) assay. Pharmacokinetic and physiochemical properties were optimized through modifications at the 4-position of the pyridine ring and the terminal nitrogen of the piperazine ring, leading to compound (4*S*)-4-[({4-[4-(methoxymethyl)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic acid **47s** with good human PRP potency, selectivity, in vivo efficacy, and oral bioavailability. Compound **47s** was selected for further preclinical evaluations.

## Introduction

Cardiovascular and cerebrovascular diseases are still the most common causes of mortality in the Western world. Thrombotic complications of atherosclerosis such as acute coronary syndrome (ACS[a]), and ischemic stroke are one of the leading causes of this morbidity and mortality. Current therapy includes antiplatelet agents such as aspirin, dipyridamole, glycoprotein IIb/IIIa antagonists, and thienopyridines.[1] Clopidogrel, a thienopyridine, is an oral prescription antiplatelet drug approved for the reduction of atherosclerotic events (stroke, myocardial infarction, and death) in patients with ACS that acts by blocking adenosine diphosphate (ADP)-stimulated platelet aggregation. ADP is an important platelet agonist that induces a primary aggregation response and contributes to secondary aggregation following release from platelet dense granules upon activation by other agonists. ADP-induced platelet aggregation is mediated by a dual receptor system involving activation of $P2Y_1$ and $P2Y_{12}$ receptors, both members of the G-protein-coupled receptor (GPCR) family.[2] Experimental studies have demonstrated that selective blockade of either receptor is sufficient to inhibit platelet activation. However, $P2Y_1$ has ubiquitous expression whereas $P2Y_{12}$ is primarily a platelet specific receptor and thus represents a more attractive therapeutic target for selective modulation of ADP-induced platelet activation.

$P2Y_{12}$ has been identified as the molecular target of clopidogrel.[3] Clopidogrel is a prodrug, the active metabolite of which irreversibly and selectively inhibits the $P2Y_{12}$ receptor; thus, antiplatelet efficacy requires a loading dose and several days to achieve its full effect.[4] Once it is activated, the drug becomes irreversibly bound to platelets. As a result, clopidogrel has a slow onset and slow offset of pharmacological action. This makes it less effective in acute settings and difficult to manage if a patient bleeds, experiences a trauma, or requires emergency surgery. In addition, there are subsets of individuals either who do not metabolize the prodrug adequately or who are resistant to the effects of clopidogrel.[5] It is anticipated that a direct acting, orally bioavailable $P2Y_{12}$ inhibitor will not be associated with such difficulties and will therefore exhibit a significant improvement in efficacy while maintaining a better safety profile. Accordingly, a need still exists for new drug therapies for the treatment of subjects suffering from or susceptible to a platelet aggregation mediated condition. In particular, a need still exists for new $P2Y_{12}$ antagonists having one or more improved properties, such as safety profile, efficacy, or physical properties, relative to currently available $P2Y_{12}$ antagonists. Several groups have described their research efforts aimed toward discovering ADP receptor antagonists, including some recent patents issued by Actelion.[6,7] Moreover, several new $P2Y_{12}$ antagonists, including cangrelor (AR-C69931MX) and ticagrelor (AZD-6140, **84**),[8] are currently in late stage clinical trials.[6] Herein, we report our efforts to discover and develop potent, selective $P2Y_{12}$ antagonists to address the unmet medical need for safe and effective oral antiplatelet agents.[9]

## Results and Discussion

Quinoline derivatives **1** have been reported as antagonists of the platelet $P2Y_{12}$ receptor.[10] The general structure is shown in Figure 1, in which the lead compound from this class is a prodrug where the $R_4$ side chain possesses an ethyl ester. Metabolism by systemic esterases of the ester prodrug to its corresponding acid provides the active metabolite, which

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[a] Abbreviations: PASP, polymer-assisted solution-phase; PRP, platelet rich plasma; ACS, acute coronary syndrome; ADP, adenosine diphosphate; GPCR, G-protein-coupled receptor; b.i.d., twice daily.

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contains two carboxylic acid groups ($R_2$ and $R_4$ side chains). It would be desirable to eliminate the need for a prodrug and improve upon the physical chemical properties (diacid) as well as potency. Interestingly, only quinolines and naphthalenes were reported as the right-hand aryl moieties. We approached analogue synthesis by considering the molecule as being composed of three parts: the piperazine, the amino acid, and the quinoline. Parallel syntheses allowing for variations of all three parts of the molecule were then developed.

Initial efforts were focused at replacing the quinoline ring with other heteroaryl and aryl ring systems. It was envisioned that a PASP synthesis approach for the arylcarboxamides could be accomplished through a simple amide bond-forming reaction (Scheme 1). Thus, reacting arylcarboxylic acids with the amine would afford analogues with alternative aryl ring systems. Three amine templates **2**−**4** were selected for initial library synthesis in which an ethyl carbamate and a *m*-tolyl ring system were substituted on the terminal piperazine nitrogen ($R_1$) with either a glycine or *S*-glutamic acid as the amino acid ($R_2$). The aryl acid inputs **5** were initially biased toward fused ring systems mimicking the quinoline and naphthalene. The amines **2**−**4** were coupled to the aryl acids **5** using polymer-bound carbodiimide **6** as the coupling agent with hydroxybenzotriazole to afford the crude amide products. Upon completion of the reaction, a mixed resin bed containing polymer-bound amine **8** and polymer-bound isocyanate **7** was added to the reaction mixture to sequester hydroxybenzotriazole and any unreacted acid **5** or amine starting materials **2**−**4** followed by filtration and evaporation to afford purified products. Deprotection of the *tert*-butyl ester using TFA in DCM provided the desired products **9**−**11**.

Several hundred compounds were prepared by this synthesis and screened in a human $P2Y_{12}$ receptor binding assay at 5−10 $\mu$M, and $K_i$'s were determined for those compounds with ≥50% inhibition.[11] These compounds were also tested as antiplatelet agents by measuring their inhibitory action on the in vitro aggregation of human platelet rich plasma (PRP) stimulated by 20 $\mu$M ADP using a turbidity method.[11] The compounds were initially assayed at 100 or 50 $\mu$M, and $IC_{50}$ values were determined for compounds with ≥50% inhibition of platelet aggregation. Historical analysis of human PRP potency data for $P2Y_{12}$ antagonists revealed significant donor-to-donor variability. To reduce this effect, the potency data for a reference standard **84** (AZD-6140)[8] were determined on each 96-well plate and the data for the test compounds were normalized to that standard from that same plate. Emphasis, in regard to the SAR, was placed on the PRP potency as this was an indication of the functional activity taking into account the effect of protein binding.

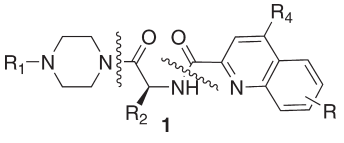


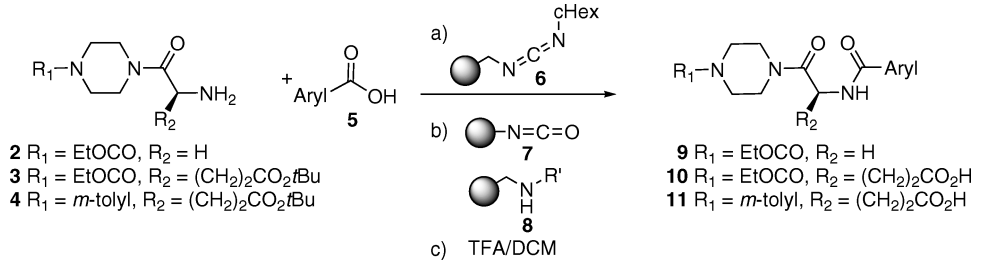

**Figure 1.** Quinoline core structures.

Many different heterocyclic ring systems were evaluated, and an apparent trend was observed. Compounds with a heteroatom, preferably a nitrogen, ortho to the amide position and a phenyl ring ortho to the heteroatom exhibited $P2Y_{12}$ binding activity. A second iteration with the heteroaryl acids possessing this type of substitution pattern led to the discovery of compound **10a** possessing a 4,6-diphenylpyridine ring system with a $P2Y_{12}$ binding $K_i$ of 15 nM and a PRP $IC_{50}$ of 76 $\mu$M (Table 1). In an effort to follow-up on the lead compound **10a**, a focused library was prepared that explored elementary structural changes around the pyridine ring system. A representative set of compounds from this library is shown in Table 1. The unsusbstituted pyridine ring, compound **10b**, was devoid of any type of activity. Replacing the 6-phenyl ring with a hydrogen, compound **10c**, also resulted in a loss of activity. However, when replacing the 4-phenyl ring with a hydrogen, compound **10d**, PRP activity was maintained. Removing the nitrogen from the pyridine ring system, regardless of the phenyl substitution, resulted in loss of binding activity with no PRP activity (**10e**,**f**). An additional nitrogen at the 3-position with a 6-phenyl substitution, compound **10i**, maintained PRP activity, whereas the additional nitrogen at the 5-position, compound **10h**, resulted in no PRP activity.

The SAR trends across the different amine templates were consistent. The glycine analogues (**9a**,**b**, $R_2$ = H) had reduced binding activity and no PRP activity, indicating the *S*-glutamic acid piece ($R_2$ = $(CH_2)_2CO_2H$) was required for PRP activity. Replacing the ethyl carbamate group on the piperazine nitrogen of the lead (**10a**) with the *m*-tolyl (**11a**) resulted in decreased binding activity and no PRP potency. While the *m*-tolyl substitution provided compounds with good binding activity (data not shown), no PRP activity was observed with any of these analogues presumably because of high protein binding.[12] For example, when compound **11a** was run in the binding assay with 0.4% human serum albumin, no binding activity was observed ($K_i$ > 4.74 $\mu$M).

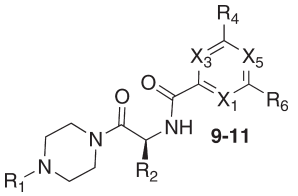
Upon discovery of the pyridine ring system, modifications to other parts of the molecule were explored. Efforts were focused on derivatization of the piperazine nitrogen ($R_1$). With no difference in PRP activity of the 4,6-diphenyl (**10a**) vs 6-phenylpyridine (**10d**) ring system, the 6-phenylpyridine ring was used as the starting template for piperazine derivatization. Scheme 2 shows the synthesis of substituted piperazine analogues. The commercially available 6-phenylpicolinic acid **13** was coupled with 1-allyl 5-*tert*-butyl L-glutamate **12** using

**Scheme 1.** Polymer-Assisted Solution-Phase (PASP) Library Synthesis[a]




[a] Reagents and conditions: (a) 1.5 equiv of **6**, NMM, HOBt, DCM/DMF; (b) excess **7** and **8**, additional DCM; (c) 10% TFA/DCM.

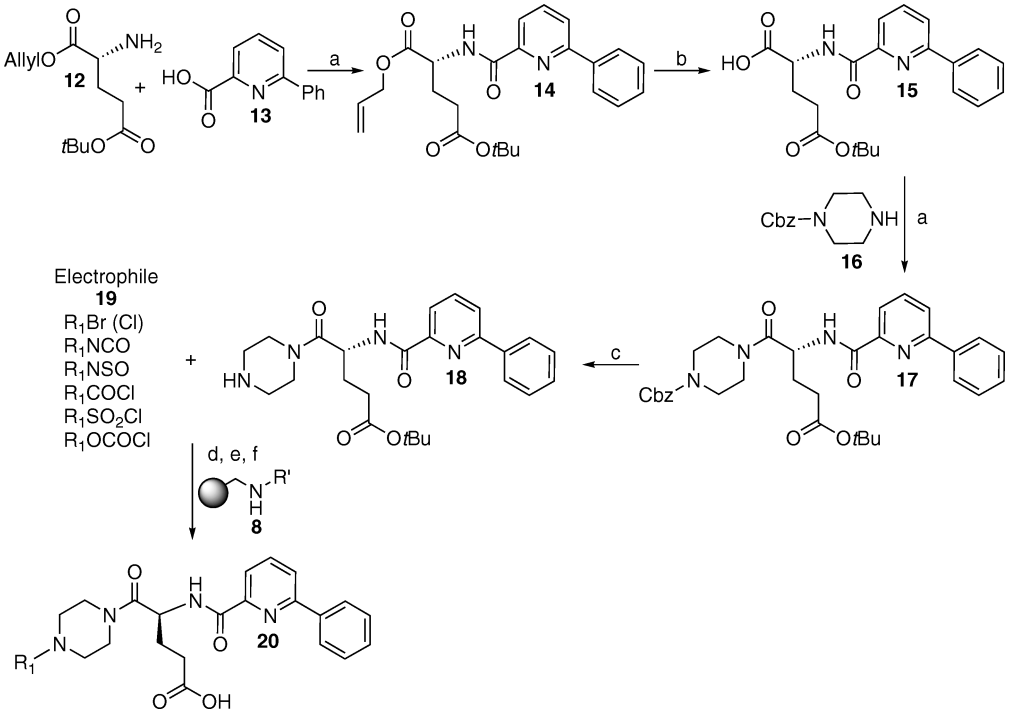
**Table 1.** Binding and PRP Activity Data for Selected Library Compounds **9**−**11**




| Cpd | $R_4$ | $R_6$ | $X_1$ | $X_3$ | $X_5$ | $R_1$ | $R_2$ | $K_i$ [a] (nM) | $IC_{50}$ [b] ($\mu$M) |
|---|---|---|---|---|---|---|---|---|---|
| **10a** | Ph | Ph | N | CH | CH | EtOCO | $(CH_2)_2CO_2H$ | 15 | 76 |
| **10b** | H | H | N | CH | CH | EtOCO | $(CH_2)_2CO_2H$ | > 5400 | > 100 |
| **10c** | Ph | H | N | CH | CH | EtOCO | $(CH_2)_2CO_2H$ | > 5700 | > 100 |
| **10d** | H | Ph | N | CH | CH | EtOCO | $(CH_2)_2CO_2H$ | 209 | 71 |
| **10e** | Ph | Ph | CH | CH | CH | EtOCO | $(CH_2)_2CO_2H$ | 373 | > 100 |
| **10f** | H | Ph | CH | CH | CH | EtOCO | $(CH_2)_2CO_2H$ | 3640 | > 100 |
| **10g** | Ph | Ph | CH | CH | N | EtOCO | $(CH_2)_2CO_2H$ | 484 | > 50 |
| **10h** | H | Ph | N | CH | N | EtOCO | $(CH_2)_2CO_2H$ | 356 | > 100 |
| **10i** | H | Ph | N | N | CH | EtOCO | $(CH_2)_2CO_2H$ | 1190 | 74 |
| **9a** | Ph | Ph | N | CH | CH | EtOCO | H | 733 | > 50 |
| **9b** | H | Ph | N | CH | CH | EtOCO | H | 1610 | > 100 |
| **11a** | Ph | Ph | N | CH | CH | *m*-tolyl | $(CH_2)_2CO_2H$ | 150 | > 100 |
| **11b** | Ph | H | N | CH | CH | *m*-tolyl | $(CH_2)_2CO_2H$ | > 5700 | > 100 |
| **11c** | H | Ph | N | CH | CH | *m*-tolyl | $(CH_2)_2CO_2H$ | > 5700 | > 100 |
| **11d** | Ph | Ph | CH | CH | CH | *m*-tolyl | $(CH_2)_2CO_2H$ | 1430 | > 100 |
| **11e** | H | Ph | CH | CH | CH | *m*-tolyl | $(CH_2)_2CO_2H$ | 1310 | > 100 |

[a] Membranes from CHO cells expressing recombinant human $P2Y_{12}$ receptors incubated with $^{33}P$ ADP and compound. $K_i$ values are corrected from $IC_{50}$ using the Cheng and Prusoff equation and are the geometric mean of $n = 2$ or greater. [b] $IC_{50}$ values are from human PRP incubated with 20 $\mu$M ADP.

**Scheme 2.** Synthesis of Substituted Piperazine Analogues **20**[a]




[a] Reagents and conditions: (a) 1.5−2.2 equiv of **6**, NMM, HOBt, DCM/DMF; (b) $Pd(PPh_3)_4$, morpholine, MeCN; (c) $H_2$, Pd/C, MeOH; (d) 4 equiv of **19**, TEA, DCM; (e) excess **8**, additional DCM; (f) 20% TFA/DCM.

polymer-bound carbodiimide **6** with HOBt and NMM as base to afford the allyl ester intermediate **14**. Deprotection of the allyl ester using tetrakis(triphenylphosphine)palladium as the catalyst and morpholine provided the carboxylic acid intermediate **15**. A second coupling with the acid **15** and the Cbz protected piperazine **16** followed by deprotection of the Cbz using hydrogen with palladium on carbon afforded the piperazine intermediate **18**. The piperazine **18** was reacted with an excess of electrophile **19** in the presence of triethylamine. The electrophiles used (alkyl halides, chloroformates, acid halides,

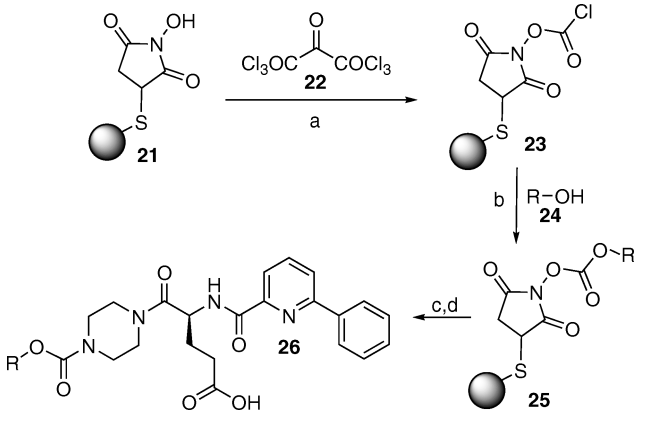
isocyanates, thioisocyanates, and sulfonyl halides) were selected to represent a diverse set, affording products **20** containing alkyl, carbamate, amide, urea, thiourea, or sulfonamide functionality. Upon completion of the reaction, polymer-bound amine **8** was added to the reaction mixture to sequester any unreacted electrophile **19** followed by filtration and evaporation to afford purified products. Deprotection of the *tert*-butyl ester using TFA in DCM provided the desired substituted piperazine products **20**.

Many substituted piperazine compounds were prepared, and in general the unsubstituted compound (**18**), aliphatics, amides, and sulfonamides were inactive while several of the aliphatic ureas exhibited modest binding activity with little to no PRP activity (Supporting Information). The thioureas exhibited good binding activity and moderate PRP activity, while the aliphatic carbamates were optimal with respect to both binding and PRP activity. To further explore the carbamate SAR in a parallel format, a PASP library synthesis of piperazine carbamate analogues was employed as shown in Scheme 3.[13] The synthesis allowed for the carbamate to be prepared from the corresponding alcohol, as many of the corresponding chloroformates were not commercially available. Polymer-supported *N*-hydroxysuccinimide **21** was treated with bistrichloromethyl carbonate **22** to afford polymer-supported chloroformate **23**. Treatment of **23** with the alcohol **24** provided, after removal of excess reagents by filtration, the polymer-bound activated *N*-hydroxysuccinimide carbonate **25**. The piperazine **18** was added to a slight excess of polymer-bound carbonate **25** followed by filtration and evaporation to afford the purified products. Deprotection of the *tert*-butyl ester using TFA in DCM provided the desired carbamate products **26**.

A representative set of carbamate analogues **26** is shown in Table 2. The SAR is very clear with the carbamates as aliphatic straight chains of four to six carbon length preferred (**26c**−**e**). When unsaturation, branching, or a heteroatom is introduced into the carbamate side chain, PRP activity is lost.

Additional chemistry efforts explored replacing the 4-phenyl substituent on the pyridine ring of lead **10a** with other groups such as substituted amines and ethers. Synthesis of the pyridine intermediates is depicted in Scheme 4. The commercially available 4-hydroxy-6-phenylpicolinic acid **27** was converted to the methyl ester **28** followed by treatment with phosphorus oxychloride to afford methyl 4-chloro-6-phenylpicolinate **29**. Hydrolysis of the methyl ester **29** with potassium hydroxide provided the key 4-chloro-6-phenylpicolinic acid intermediate **30**. Synthesis of the 4-aminopyridines and the intermediate for the 4-oxygen substituted pyridine analogues is depicted in Scheme 5. The BOC protected piperazine **32** was reacted with the chloroformate **33** followed by BOC deprotection with hydrochloric acid or TFA to afford the piperazine carbamate **35**. Coupling of the piperazine **35** with *N*-benzyloxycarbonyl-L-glutamic acid γ-*tert*-butyl ester **36** using carbodiimide and *N*-methylmorpholine as base afforded the intermediate **37**. Removal of the Cbz group via hydrogenation using palladium on carbon provided the amine intermediate **38**. A second coupling using the amine **38** with the 4-chloro-6-phenylpicolinic acid **30** afforded the 4-chloropyridine intermediate **43**. The 4-chloropyridine intermediate **43** allows for substitution at the 4-position with nitrogen nucleophiles. The 4-chloro was

**Scheme 3.** PASP Synthesis of Piperazine Carbamate Analogues **26**[a]



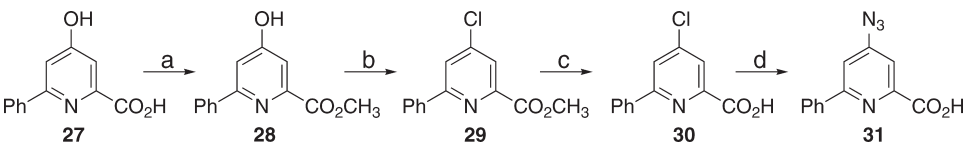

[a] Reagents and conditions: (a) 2.2 equiv of **22**, pyridine, DCM; (b) excess **24**, pyridine, DCM; (c) 0.75 equiv of **18**, DCM; (d) 20% TFA/DCM.

**Table 2.** Binding and PRP Activity Data for a Representative Set of Piperazine Carbamate Analogues **26**

| Cpd | R | $K_i$[a] (nM) | $IC_{50}$[b] (μM) |
|---|---|---|---|
| **26a** | Me | 2440 | > 100 |
| **10d** | Et | 209 | 71 |
| **26b** | Pr | 27 | 62 |
| **26c** | Bu | 29 | 28 |
| **26d** | Pent | 11 | 15 |
| **26e** | Hex | 43 | 19 |
| **26f** | Hept | 7 | 56 |
| **26g** | Oct | 14 | > 100 |
| **26h** | $CH_2CF_3$ | 94 | > 100 |
| **26i** | *i*-Pr | 280 | > 100 |
| **26j** | $(CH_2)_3CF_3$ | 18 | 70 |
| **26k** | $(CH_2)_2CCH$ | 79 | > 100 |
| **26l** | *c*Pent | 47 | > 100 |
| **26m** | *c*Hex | 44 | > 100 |
| **26n** | $CH_2$*c*Bu | 28 | > 100 |
| **26o** | $CH_2$*c*Pent | 46 | 82 |
| **26p** | $(CH_2)_2$*c*Pr | 15 | > 100 |
| **26q** | $(CH_2)_2CH(CH_3)_2$ | 33 | 88 |
| **26r** | $(CH_2)_2C(CH_3)_3$ | 42 | > 100 |
| **26s** | $(CH_2)_2OMe$ | 492 | > 100 |
| **26t** | $CH_2Ph$ | 196 | > 100 |

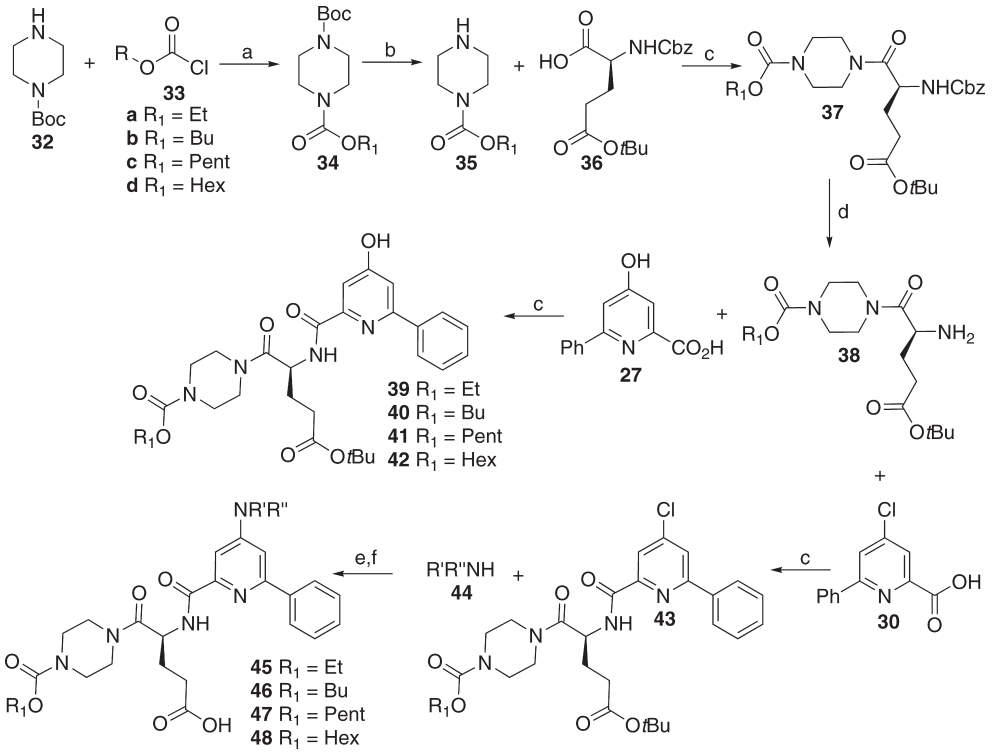
[a] Membranes from CHO cells expressing recombinant human $P2Y_{12}$ receptors incubated with $^{33}P$ ADP and compound. $K_i$ values are corrected from $IC_{50}$ using the Cheng and Prusoff equation and are the geometric mean of $n = 2$ or greater. [b] $IC_{50}$ values are from human PRP incubated with 20 μM ADP.

**Scheme 4.** Preparation of 6-Phenylpyridine Intermediates[a]



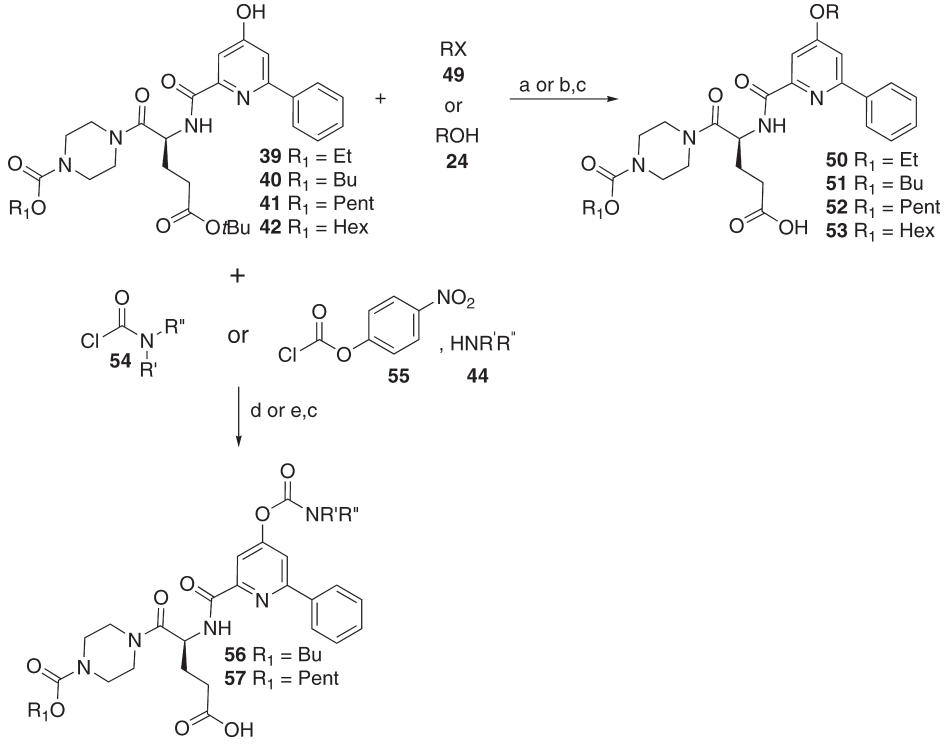

[a] Reagents and conditions: (a) $H_2SO_4$, MeOH, reflux; (b) $POCl_3$, reflux; (c) KOH, $H_2O$/dioxane; (d) $NaN_3$, Aliquat 336, EtOH/$H_2O$, 100 °C.

**Scheme 5.** Synthesis of 4-Hydroxypyridines **39-42** and 4-Aminopyridine Analogues **45**−**48**[a]




[a] Reagents and conditions: (a) 1.1 equiv of **33**, DIEA, DCM; (b) 4 M HCl/dioxane or TFA, DCM; (c) EDC, HOBt, NMM, DCM; (d) $H_2$, Pd/C, MeOH; (e) excess **44**, TEA, DMSO, 50−100 °C; (f) 10% TFA/DCM.

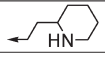
**Scheme 6.** Synthesis of 4-Ether Pyridines **50**−**53** and 4-Carbamate Pyridine Analogues **56** and **57**[a]




[a] Reagents and conditions: (a) 2 equiv of **49**, $Cs_2CO_3$, KI, DMF, room temp to 100 °C; (b) 2 equiv of **24**, DEAD, $PPh_3$, THF; (c) 10% TFA/DCM; (d) 2.7 equiv of **54**, TEA, DCM; (e) 1.1 equiv of **55**, TEA, DCM, 1 h, 3.0 equiv of **44**, TEA, DCM.

displaced by heating intermediate **43** with an excess of amine **44** and triethylamine in DMSO, followed by deprotection of the *tert*-butyl ester group to afford the desired 4-aminopyridine analogues **45**−**48**. Displacement of the chlorine at the 4-position afforded clean products with either the free carboxylic acid or the *tert*-butyl ester group present. Initial concerns for racemization under these conditions were eliminated by several studies, one of which included heating enantiomerically pure (*S*)-**45i** at

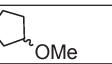
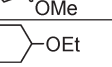
**Table 3.** Binding and PRP Activity Data for a Representative Set of 4-Ether Pyridine Analogues **50**−**53**

| Cpd | $R_1$ | R | $K_i$[a] (nM) | $IC_{50}$[b] (μM) | Relative Potency to **84**[c] |
|---|---|---|---|---|---|
| **50a** | Et | H | 62 | 24 | 41 |
| **51a** | Bu | | 31 | 8.8 | 9.7 |
| **52a** | Pent | | 11 | 10 | 7.2 |
| **53a** | Hex | | 20 | 21 | 21 |
| **50b** | Et | Me | 96 | 39 | 55 |
| **50c** | Et | Et | 94 | 31 | 44 |
| **52c** | Pent | | 7.9 | 17 | 23 |
| **50d** | Et | Pr | 120 | 36 | 46 |
| **52d** | Pent | | 18 | 22 | 28 |
| **50e** | Et | Bu | 60 | 34 | 32 |
| **51e** | Bu | | 35 | 27 | 18 |
| **52e** | Pent | | 49 | 28 | 28 |
| **53e** | Hex | | 89 | 97 | 65 |
| **50f** | Et | $-(CH_2)_2OH$ | 157 | 7.6 | 12 |
| **51f** | Bu | | 20 | 7.9 | 5.1 |
| **52f** | Pent | | 31 | 12 | 10 |
| **53f** | Hex | | 18 | 21 | 13 |
| **50g** | Et | $-(CH_2)_3OH$ | 68 | 9.0 | 12 |
| **51g** | Bu | | 6.9 | 2.9 | 5.1 |
| **50h** | Et | $-(CH_2)_4OH$ | 132 | 13 | 13 |
| **51h** | Bu | | 4.9 | 4.5 | 6.7 |
| **50i** | Et | $-(CH_2)_2OMe$ | 140 | 6 | 8.0 |
| **51i** | Bu | | 18 | 4.5 | 2.9 |
| **52i** | Pent | | 9.9 | 4.3 | 3.2 |
| **53i** | Hex | | 14 | 8.3 | 7.1 |
| **50j** | Et | $-(CH_2)_3OMe$ | 69 | 8.2 | 11 |
| **51j** | Bu | | 5.9 | 2.2 | 3.9 |
| **51k** | Bu |  | 10 | 4.1 | 6.3 |
| **51l** | Bu |  | 11 | 2.3 | 3.6 |
| **50m** | Et | $-(CH_2)_2NH_2$ | 328 | 7.5 | 11 |
| **52m** | Pent | | 8.8 | 2.4 | 3.0 |
| **53m** | Hex | | 8.4 | 4.5 | 7.9 |
| **50n** | Et |  | 68 | 1.9 | 2.5 |
| **51n** | Bu | | 12 | 1.1 | 0.99 |
| **52n** | Pent | | 3.5 | 0.50 | 0.64 |
| **53n** | Hex | | 9.4 | 2.4 | 1.8 |
| **51o** | Bu |  | 6.9 | 3.9 | 1.8 |
| **51p** | Bu |  | 3.7 | 2.6 | 1.3 |
| **50q** | Et |  | 76 | 4.0 | 2.7 |
| **51q** | Bu | | 4.2 | 0.21 | 0.37 |
| **52q** | Pent | | 4.5 | 0.82 | 0.82 |
| **53q** | Hex | | 4.5 | 0.64 | 1.3 |
| **51r** | Bu |  | 3.7 | 1.2 | 0.57 |
| **51s** | Bu |  | 11 | 1.8 | 2.0 |
| **51t** | Bu |  | 3.0 | 0.46 | 0.45 |
| **51u** | Bu |  | 2.5 | 1.0 | 0.67 |
| **51v** | Bu |  | 3.7 | 0.81 | 0.88 |
| **50w** | Et | $-CH_2Ph$ | 28 | 31 | 42 |

[a] Membranes from CHO cells expressing recombinant human $P2Y_{12}$ receptors incubated with $^{33}P$ ADP and compound. $K_i$ values are corrected from $IC_{50}$ using the Cheng and Prusoff equation and are the geometric mean of $n = 2$ or greater. [b] $IC_{50}$ values are from human PRP incubated with 20 μM ADP. [c] ($IC_{50}$ value of compound)/($IC_{50}$ value of **84** control from same plate) = normalized $IC_{50}$ ratio.

100 °C for 64 h with less than 6% of the *R* enantiomer detected by chiral LC and circular dichroism.[14]

**Table 4.** Binding and PRP Activity Data for a Representative Set of 4-Carbamate Pyridine Analogues **56** and **57**

| Cpd | $R_1$ | R' | R'' | $K_i$[a] (nM) | $IC_{50}$[b] (μM) | Relative Potency to **84**[c] |
|---|---|---|---|---|---|---|
| **56a** | Bu | Me | Me | 2.0 | 1.1 | 1.1 |
| **57a** | Pent | Me | Me | 5.5 | 2.9 | 1.7 |
| **56b** | Bu | Me |  | 1.5 | 0.59 | 0.87 |
| **57b** | Pent | Me | | 4.5 | 0.47 | 0.82 |
| **56c** | Bu | Me |  | 1.8 | 0.52 | 0.63 |
| **57c** | Pent | Me | | 2.3 | 0.47 | 0.59 |
| **57d** | Pent |  | | 7.7 | 1.8 | 1.0 |
| **57e** | Pent |  | | 11 | 2.1 | 1.3 |
| **56f** | Bu |  | | 1.7 | 0.76 | 0.75 |
| **57f** | Pent | | | 4.8 | 1.7 | 0.99 |
| **56g** | Bu |  | | 1.5 | 0.77 | 0.97 |
| **57g** | Pent | | | 4.9 | 0.69 | 1.0 |
| **56h** | Bu |  | | 2.1 | 1.0 | 1.2 |
| **57h** | Pent | | | 6.0 | 0.59 | 1.2 |

[a] Membranes from CHO cells expressing recombinant human $P2Y_{12}$ receptors incubated with $^{33}P$ ADP and compound. $K_i$ values are corrected from $IC_{50}$ using the Cheng and Prusoff equation and are the geometric mean of $n = 2$ or greater. [b] $IC_{50}$ values are from human PRP incubated with 20 μM ADP. [c] ($IC_{50}$ value of compound)/($IC_{50}$ value of **84** control from same plate) = normalized $IC_{50}$ ratio.

Attempts to displace the 4-chloro with oxygen nucleophiles provided limited success. As a result, the 4-hydroxypyridines were prepared in a similar fashion by coupling the 4-hydroxy-6-phenylpicolinic acid **27** with the amine **38** using carbodiimide and *N*-methylmorpholine as base to afford the 4-hydroxypyridine intermediates **39**−**42** (Scheme 5). Direct alkylation or employing Mitsunobu conditions with the 4-hydroxypyridine intermediates **39**−**42** provided 4-ether pyridine analogues **50**−**53** as shown in Scheme 6. Direct alkylation of the 4-hydroxypyridines **39**−**42** using 2 equiv of the electrophile **49** with cesium carbonate as the base and a catalytic amount of potassium iodide in DMF, followed by deprotection of the *tert*-butyl ester group, afforded the desired 4-ether pyridine analogues **50**−**53**. Alternatively, employing Mitsunobu conditions with 2 equiv of the alcohol **24** using DEAD and triphenylphosphine in THF, followed by deprotection of the *tert*-butyl ester group, afforded the desired 4-ether pyridine analogues **50**−**53**. Using both procedures allowed for a greater diversity of monomer inputs **24** and **49**, ultimately providing a wide array of 4-ether pyridine analogues.

The 4-hydroxypyridine intermediates **40** and **41** were also used to prepare 4-carbamate pyridine analogues **56**−**57** as shown in Scheme 6. The 4-hydroxypyridines **40** and **41** were reacted directly with a carbamoyl chloride **54** using triethylamine as base in DCM to provide the carbamate. Deprotection of the *tert*-butyl ester using TFA in DCM afforded the desired 4-carbamate pyridine products **56** and **57**. Because of the limited commercial availability of carbamoyl chlorides **54**, a second procedure was employed using the 4-hydroxypyridines **40** and **41** and *p*-nitrophenylchloroformate **55** to provide the activated carbonate followed by addition of the amine **44** and triethylamine as base in DCM to afford the carbamate. Deprotection of the *tert*-butyl ester using TFA in DCM afforded the desired 4-carbamate pyridine products **56** and **57**.

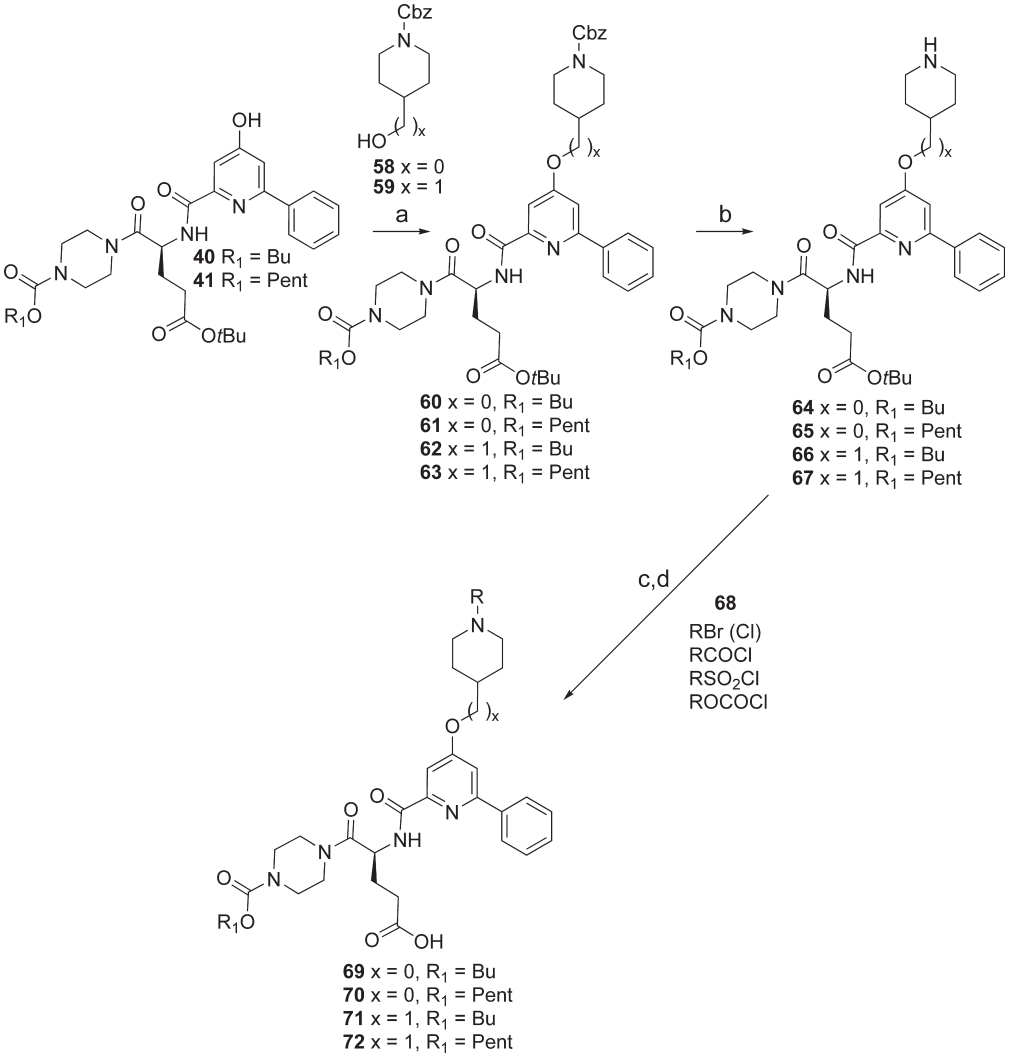
Table 3 shows the data for a representative set of 4-oxygen analogues. The unsubstituted (hydroxy) analogues (**50a**−**53a**) had modest binding and PRP potency, while substitution of

the oxygen with alkyl chains of varying length (**50b**−**53e**) tended to slightly decrease the potency. Comparable PRP activity was observed with the benzyl ether analogue **50w**, and relatively flat SAR was observed across various substituted benzyl ether analogues with PRP activity in the range of 9−39 $\mu$M (data not shown). Extending a hydroxy or alkyl ether two to four carbon atoms away from the 4-oxygen atom increased the PRP activity (**50f**−**51l**). A similar trend was observed by extending a primary or secondary amine two to five carbon atoms away from the 4-oxygen atom (**50m**−**53v**). In particular, the 4-oxypiperidine (**50n**−**53n**), 4-oxymethylpiperidine (**50q**−**53q**), and 4-oxyethylpiperidine (**51t**) analogues were the most potent compounds of the series. Replacing the 4-oxypiperidine (**51n**) with 3-oxypyrrolidine (**51p**) or with the regioisomer 3-oxypiperidine (**51o**) resulted in a slight decrease in PRP activity. Similarly, replacing the 4-oxymethylpiperidine (**51q**) with the 2- and 3-regioisomers (**51r**,**s**) resulted in a slight loss in PRP activity. The same trend was observed with the 4-oxyethylpiperidine regioisomers (**51u**,**v**). The nitrogen of the 4-piperidine and 4-oxymethylpiperidine was essential because when replaced with an oxygen a significant decrease in PRP activity was observed (**51k**, **51l**). Overall, the butyl and pentyl carbamates of the piperazine tail ($R_1$) were superior relative to the ethyl and hexyl carbamates with respect to both binding and PRP potency.

Table 4 shows the data for a representative set of 4-carbamate pyridine analogues **56** and **57**. These compounds when compared to the unsubstituted oxygen (**51a**, **52a**, Table 4) were considerably more potent in both the binding and PRP assays. The carbamates had relatively flat SAR with respect to the binding activity with most of them at the single digit nanomolar level, but having an oxygen within the amine side chain of the carbamate tended to increased the PRP potency, with compounds **56b**−**57c** having exceptional PRP potency. Again, the butyl and pentyl carbamates of the piperazine tail ($R_1$) were optimal for both binding and PRP activity with no significant difference between the two in terms of potency.

The 4-ether pyridine analogues, **51q** and **52n**, were two of the most potent compounds of the series. Further efforts focused on the synthesis of additional analogues with various substitutions on the 4-nitrogen of the 4-oxypiperidine and 4-oxymethylpiperidine pyridine analogues. The synthesis is depicted in Scheme 7. The 4-oxypiperidine and 4-oxymethyl piperidine intermediates **60**−**63** were prepared under Mitsunobu conditions, reacting the 4-hydroxy intermediates **40** and

**Scheme 7.** Synthesis of Substituted 4-Oxypiperidine **69** and **70** and 4-Oxymethylpiperidine Pyridine Analogues **71** and **72**[a]




[a] Reagents and conditions: (a) 2 equiv of **58** or **59**, DEAD, $PPh_3$, THF; (b) $H_2$, Pd/C, EtOH; (c) 2.0 equiv of **68**, TEA or NMM, DCM or DMF; (d) 10% TFA/DCM.

**41** with *N*-Cbz-4-hydroxy-1-piperidine **58** and 1-*N*-Cbz-4-hydroxymethylpiperidine **59** to afford the Cbz protected piperidines **60**−**63**. Deprotection of the Cbz group by hydrogenation using palladium on carbon afforded the unsubstituted nitrogen intermediates **64**−**67**. The amines **64**−**67** were reacted with an excess of electrophile **68** in the presence of a base to afford the 4-nitrogen substituted analogues. The electrophiles **68** used (alkyl halides, acid halides, sulfonyl halides, and chloroformates) were selected to represent a diverse set, affording products containing alkyl, amide, sulfonamide, or carbamate functionality. Deprotection of the *tert*-butyl ester using TFA in DCM provided the desired substituted piperazine products **69**−**72**.

A representative set of 4-substituted oxypiperidine analogues **69**, **70** is depicted in Table 5. The 4-substituted oxypiperidines had exceptional PRP potency with relatively flat SAR across various functionalities at the 4-piperidine position with the carbamates **69g**, **70g** and sulfonamides **69h**, **70h** slightly less active in the PRP assay compared to the other analogues. There was no significant difference in PRP activity between the butyl carbamates and the corresponding pentyl carbamates ($R_1$) for the 4-substitued piperidines.

The same holds true for the 4-substituted oxymethylpiperidine compounds **71**, **72**, with the amides and alkylated analogues exhibiting exceptional binding and PRP activity, while the carbamates **71g**, **72g** and sulfonamides **71h**, **72h** were slightly less potent in the PRP assay (Table 6). The 4-substituted oxymethylpiperidine analogues **71**, **72** were more potent than the corresponding 4-substituted oxypiperidines **69**−**70**, and there was no significant difference in PRP activity between the butyl carbamates and the corresponding pentyl carbamates.

Several libraries of the 4-aminopyridine analogues **45**−**48** were synthesized (Scheme 5), and the data for a representative set are shown in Table 7. As has been the trend, the butyl and pentyl carbamates were superior to the ethyl and hexyl carbamates in terms of both binding and PRP potency. The 4-aminopyridine analogues substituted with two alkyl groups (**45b**, **45d**) were inactive in the PRP assay, while the secondary amines with a single alkyl group (**45a**,**c**, **47c**) had modest potency. The 4-amine analogues substituted with alkyl groups were less active than compounds with a heteroatom present in the side chain. Compounds **45e**,**47e** and **45g**−**48g** provide examples of secondary amine analogues with an oxygen heteroatom, as a hydroxy or ether, as part of the amine group with good binding and PRP activity. The corresponding tertiary amine analogues **45f**, **46h**, and **47h** were considerably less active in the PRP assay. Interestingly, the piperidine analogues (alkyl tertiary amines **45i** and **47i**) exhibited modest PRP potency. Replacing the piperidine ring with morpholino (**45j** and **46j**) provided a slight increase in the PRP potency. Substitution at the 4-position of the piperidine ring with hydroxy (**45k** and **47k**) or alkoxy (**47l**) increased both the binding and PRP activity, while extending the hydroxy or methoxy from the 4-position of the piperidine with a methylene (**47r**,**s**) maintained binding and PRP activity. The hydroxy analogues could be capped with a methyl and maintain PRP activity, but capping with any alkyl group larger than a methyl tended to decrease the PRP activity (**47t**). Direct substitution from the 4-position of the piperidine with an amine increased PRP activity with no significant difference in PRP activity from the primary (**45m**−**48m**), secondary (**46n** and **47n**), or tertiary amines (**46o**, **47o**, **45o**−**48p**). Extending the amine from the 4-position of the piperidine with a methylene (**45u**−**47x**) provided some of the most potent compounds of the series in terms of both binding and PRP activity.

**Table 5.** Binding and PRP Activity Data for a Representative Set of 4-Substituted Oxypiperidine Pyridine Analogues **69** and **70**

| Cpd | $R_1$ | R | $K_i$ [a] (nM) | $IC_{50}$ [b] ($\mu$M) | relative potency to **84** [c] |
|---|---|---|---|---|---|
| **51n** | Bu | H | 12 | 1.1 | 0.99 |
| **52n** | Pent | H | 4 | 0.50 | 0.64 |
| **69a** | Bu | Me | 2.5 | 2.0 | 1.9 |
| **70a** | Pent | Me | 5.0 | 1.8 | 1.8 |
| **69b** | Bu | *i*-Pr | 10 | 0.88 | 0.75 |
| **70b** | Pent | *i*-Pr | 7.0 | 0.48 | 0.68 |
| **69c** | Bu | $(CH_2)_2OMe$ | 9.4 | 1.2 | 1.1 |
| **70c** | Pent | $(CH_2)_2OMe$ | 9.9 | 1.7 | 1.7 |
| **69d** | Bu | COMe | 2.8 | 1.2 | 1.1 |
| **70d** | Pent | COMe | 3.6 | 1.8 | 1.8 |
| **69e** | Bu | $COCF_3$ | 12 | 2.1 | 3.4 |
| **70e** | Pent | $COCF_3$ | 19 | 4.7 | 4.4 |
| **69f** | Bu | $COCH_2OMe$ | 2.4 | 0.52 | 0.78 |
| **70f** | Pent | $COCH_2OMe$ | 11 | 1.5 | 1.5 |
| **69g** | Bu | $CO_2Et$ | 20 | 3.7 | 5.9 |
| **70g** | Pent | $CO_2Et$ | 6.5 | 8.2 | 8.1 |
| **69h** | Bu | $SO_2Et$ | 7.6 | 3.3 | 3.1 |
| **70h** | Pent | $SO_2Et$ | 5.1 | 5.3 | 5.0 |

[a] Membranes from CHO cells expressing recombinant human $P2Y_{12}$ receptors incubated with $^{33}P$ ADP and compound. $K_i$ values are corrected from $IC_{50}$ using the Cheng and Prusoff equation and are the geometric mean of $n = 2$ or greater. [b] $IC_{50}$ values are from human PRP incubated with 20 $\mu$M ADP. [c] ($IC_{50}$ value of compound)/($IC_{50}$ value of **84** control from same plate) = normalized $IC_{50}$ ratio.

**Table 6.** Binding and PRP Activity Data for a Representative Set of 4-Substituted Oxymethylpiperidine Pyridine Analogues **71** and **72**

| Cpd | $R_1$ | R | $K_i$ [a] (nM) | $IC_{50}$ [b] ($\mu$M) | relative potency to **84** [c] |
|---|---|---|---|---|---|
| **51q** | Bu | H | 4.2 | 0.21 | 0.37 |
| **52q** | Pent | H | 4.5 | 0.82 | 0.82 |
| **71a** | Bu | Me | 2.5 | 0.24 | 0.38 |
| **72a** | Pent | Me | 5.3 | 0.33 | 0.62 |
| **71b** | Bu | *i*-Pr | 4.5 | 0.41 | 0.33 |
| **72b** | Pent | *i*-Pr | 5.5 | 0.38 | 0.50 |
| **71c** | Bu | $(CH_2)_2OMe$ | 5.3 | 0.62 | 0.53 |
| **72c** | Pent | $(CH_2)_2OMe$ | 5.3 | 0.55 | 0.73 |
| **71d** | Bu | COMe | 3.9 | 2.1 | 1.4 |
| **72d** | Pent | COMe | 1.3 | 1.3 | 1.8 |
| **71e** | Bu | $COCF_3$ | 10 | 3.0 | 2.8 |
| **72e** | Pent | $COCF_3$ | 4.5 | 3.5 | 4.8 |
| **71f** | Bu | $COCH_2OMe$ | 2.6 | 1.5 | 1.4 |
| **72f** | Pent | $COCH_2OMe$ | 12 | 1.3 | 1.3 |
| **71g** | Bu | $CO_2Et$ | 7.6 | 4.0 | 2.2 |
| **72g** | Pent | $CO_2Et$ | 1.3 | 7.4 | 5.1 |
| **71h** | Bu | $SO_2Et$ | 5.3 | 3.0 | 2.8 |
| **72h** | Pent | $SO_2Et$ | 7.4 | 2.8 | 1.9 |

[a] Membranes from CHO cells expressing recombinant human $P2Y_{12}$ receptors incubated with $^{33}P$ ADP and compound. $K_i$ values are corrected from $IC_{50}$ using the Cheng and Prusoff equation and are the geometric mean of $n = 2$ or greater. [b] $IC_{50}$ values are from human PRP incubated with 20 $\mu$M ADP. [c] ($IC_{50}$ value of compound)/($IC_{50}$ value of **84** control from same plate) = normalized $IC_{50}$ ratio.

Other 4-substituted amines were also prepared as shown in Scheme 8. Attempts to prepare the unsubstituted 4-aminopyridine intermediate by simple displacement of the 4-chloropyridine intermediate **43** with ammonia or ammonia equivalents could not be efficiently accomplished. As a result, the 4-azido-6-phenylpicolinic acid **31** was prepared from reacting sodium azide with 4-chloro-6-phenylpicolinic acid **30** (Scheme 4). Coupling of the 4-azido intermediate **31** with pentyl (*S*)-4-(2-amino-4-*tert*-butoxycarbonylbutyryl)piperazine-1-carboxylate

**Table 7.** Binding and PRP Activity Data for a Representative Set of 4-Aminopyridine Analogues **45**−**48**

| Cpd | $R_1$ | R' | R'' | $K_i$[a] (nM) | $IC_{50}$[b] (μM) | Relative Potency to **84**[c] |
|---|---|---|---|---|---|---|
| **45a** | Et | H | Me | 35 | 45 | 36 |
| **45b** | Et | Me | Me | 45 | >100 | - |
| **45c** | Et | H | Pr | 64 | 28 | 28 |
| **47c** | Pent | H | Pr | 12 | 13 | 14 |
| **45d** | Et | Pr | Pr | 45 | >100 | - |
| **45e** | Et | H | $(CH_2)_2OH$ | 117 | 12 | 14 |
| **47e** | Pent | H | $(CH_2)_2OH$ | 5.7 | 3.8 | 3.2 |
| **45f** | Et | Me | $(CH_2)_2OH$ | 87 | 57 | 26 |
| **45g** | Et | H | $(CH_2)_2OMe$ | 99 | 14 | 13 |
| **46g** | Bu | H | $(CH_2)_2OMe$ | 2.4 | 3.2 | 2.4 |
| **47g** | Pent | H | $(CH_2)_2OMe$ | 9.8 | 3.2 | 4.9 |
| **48g** | Hex | H | $(CH_2)_2OMe$ | 11 | 7.3 | 9.6 |
| **46h** | Bu | Me | $(CH_2)_2OMe$ | 4.0 | >100 | - |
| **47h** | Pent | Me | $(CH_2)_2OMe$ | 2.1 | >100 | - |
| **45i** | Et |  | | 112 | 29 | 34 |
| **47i** | Pent | | | 5.5 | 16 | 18 |
| **45j** | Et |  | | 39 | 25 | 22 |
| **46j** | Bu | | | 3.3 | 7.2 | 11 |
| **45k** | Et |  | | 42 | 9.9 | 10 |
| **47k** | Pent | | | 11 | 2.5 | 3.2 |
| **47l** | Pent |  | | 15 | 3.9 | 3.0 |
| **45m** | Et |  | | 10 | 2.8 | 8.1 |
| **46m** | Bu | | | 3.5 | 0.91 | 1.2 |
| **47m** | Pent | | | 17 | 1.1 | 1.2 |
| **48m** | Hex | | | 3.3 | 2.4 | 3.4 |
| **46n** | Bu |  | | 2.7 | 1.2 | 0.86 |
| **47n** | Pent | | | 6.5 | 1.0 | 1.1 |
| **46o** | Bu |  | | 5.0 | 1.9 | 1.4 |
| **47o** | Pent | | | 22 | 1.8 | 2.1 |
| **45p** | Et |  | | 34 | 2.0 | 6.0 |
| **46p** | Bu | | | 6.4 | 0.56 | 1.7 |
| **47p** | Pent | | | 9 | 1.2 | 0.57 |
| **48p** | Hex | | | 2.6 | 1.2 | 2.3 |
| **47q** | Pent |  | | 10 | 2.0 | 0.95 |
| **45r** | Et |  | | 54 | 19 | 22 |
| **47r** | Pent | | | 2.4 | 1.8 | 6.3 |
| **45s** | Et |  | | 18 | 10 | 9.7 |
| **47s** | Pent | | | 15 | 3.9 | 3.3 |
| **48s** | Hex | | | 33 | 7.6 | 8.9 |
| **47t** | Pent |  | | 22 | 8.9 | 12 |
| **45u** | Et |  | | 14 | 3.3 | 3.4 |
| **47u** | Pent | | | 15 | 0.78 | 0.62 |
| **48u** | Hex | | | 18 | 1.6 | 1.7 |
| **46v** | Bu |  | | 4.0 | 0.91 | 1.0 |
| **47v** | Pent | | | 1.5 | 0.71 | 0.99 |
| **46w** | Bu |  | | 3.2 | 0.89 | 1.3 |
| **47w** | Pent | | | 1.9 | 1.0 | 1.3 |
| **46x** | Bu |  | | 1.5 | 0.80 | 1.0 |
| **47x** | Pent | | | 1.1 | 0.74 | 0.93 |

[a] Membranes from CHO cells expressing recombinant human $P2Y_{12}$ receptors incubated with $^{33}P$ ADP and compound. $K_i$ values are corrected from $IC_{50}$ using the Cheng and Prusoff equation and are the geometric mean of $n = 2$ or greater. [b] $IC_{50}$ values are from human PRP incubated with 20 μM ADP. [c] ($IC_{50}$ value of compound)/($IC_{50}$ value of **84** control from same plate) = normalized $IC_{50}$ ratio.

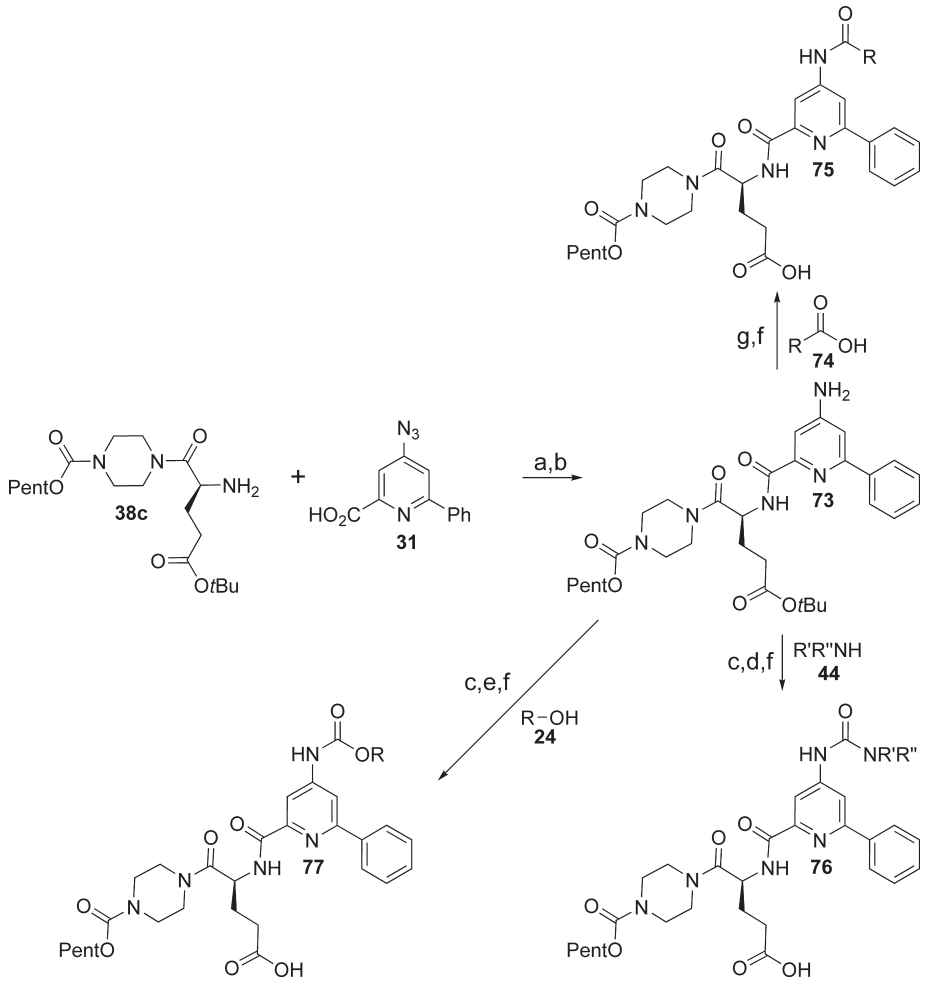
**38c** using EDC, HOBt, and *N*-methylmorpholine as base afforded the azide intermediate. Reduction of the azide using palladium on carbon afforded the 4-aminopyridine intermediate **73**. The 4-aminopyridine **73** was reacted with acid chlorides to afford the amides albeit in low yields. Because of the poor nucleophilic nature of the 4-aminopyridine, many of the acid chlorides would not react and required using propylphosphonic anhydride as a coupling reagent with the carboxylic acid **74** to afford the desired amides. Deprotection of the *tert*-butyl ester using TFA in DCM provided the desired 4-amide pyridine products **75**. The 4-carbamate and 4-urea analogues were prepared from the 4-chloroformate intermediate. The 4-aminopyridine **73** was treated with bistrichloromethyl carbonate **22** to afford the chloroformate. Treatment of chloroformate with the alcohol **24** provided the carbamates, followed by deprotection of the *tert*-butyl ester to afford the desired 4-carbamate pyridine products **77**. Similarly, treatment of chloroformate with the amine **44** provided the ureas, followed by deprotection of the *tert*-butyl ester to afford the desired 4-urea pyridine products **76**.

The 4-amide pyridine analogues **75** provided compounds with good binding activity. However, little to no PRP activity was observed with these compounds. Similarly, the 4-carbamate pyridine analogues **77** exhibited good binding activity but poor PRP activity, and the 4-urea pyridine analogues **76** showed good binding activity with poor to moderate PRP activity. In general, these compounds (**75**−**77**) were less active than the 4-aminopyridines (**45**−**48**) (Supporting Information).

Thus far, substitutions at the 4-position of the pyridine ring included nitrogen and oxygen. Other substitutions were explored such as carbon−carbon to include carboxamides and aliphatics. Scheme 9 shows the synthesis of 4-carboxamide and 4-aliphatic pyridine analogues. The 4-hydroxypyridine intermediate **41** was reacted with triflic anhydride to afford the triflate intermediate **78**. A palladium catalyzed carbonylation reaction with the triflate **78** afforded the 4-carboxylic acid intermediate **79**.[15] The acid **79** was reacted with various amines **44** using polymer-bound carbodiimide **6** with HOBt and NMM as base to afford the amide. Deprotection of the *tert*-butyl ester using TFA gave the desired 4-carboxamide pyridine products **80**. The triflate intermediate was also used for 4-aliphatic pyridine analogues. The triflate **78** was reacted with various substituted alkynes **82** using Sonogashira conditions followed by reduction of the triple bond using hydrogen with palladium on carbon to provide the 4-aliphatic pyridines. Deprotection of the *tert*-butyl ester using TFA provided the desired 4-aliphatic pyridine products **83**. Alternatively, the triflate **78** could be reacted with various substituted alkenes **81** using Heck reaction conditions followed by reduction of the double bond using hydrogen with palladium on carbon to provide the 4-aliphatic pyridines. Deprotection of the *tert*-butyl ester using TFA provided the desired 4-aliphatic pyridine products **83**. Employing both reaction procedures allowed for a greater diversity of monomer inputs **81** and **82**, providing a wide array of 4-aliphatic pyridine products **83**.

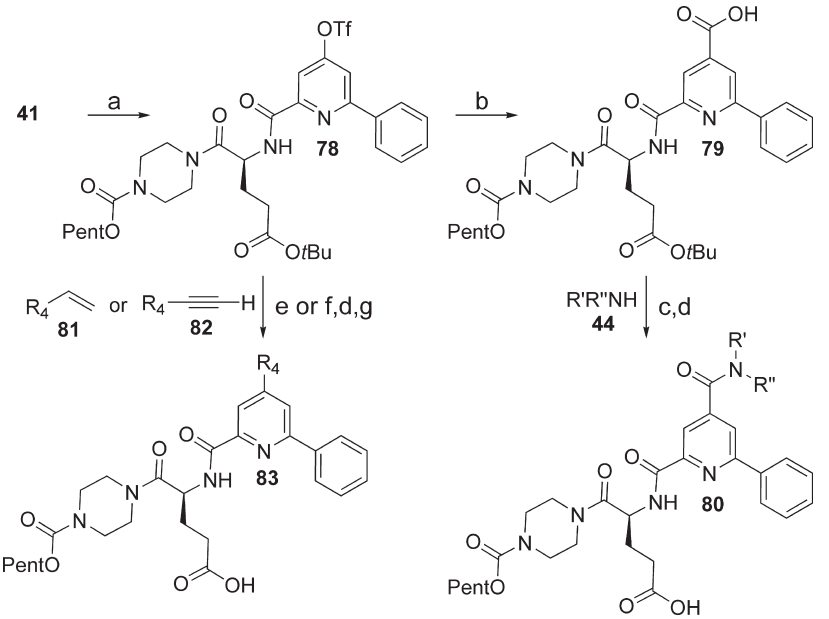
Table 8 shows a representative set of 4-carboxamide pyridine products **80**. In general, the secondary amides were less potent in the PRP assay than the tertiary amides. The amides with dimethyl substitution (**80e**) or methyl, ethyl substitution (**80f**) were optimal for alkyl tertiary amides. When the alkyl group was extended beyond a methyl or ethyl group, a decrease in the PRP potency was observed (**80g**). The tertiary amides, having a methyl as one substituent and extending a methoxy or amine two to four carbon atoms away from the amide nitrogen, provided compounds with excellent PRP activity (**80k**−**m**). Cyclic tertiary amides also exhibited excellent potency in terms of both binding and PRP activity. The unsubstituted piperidine amide **80n** exhibited good PRP

**Scheme 8.** Synthesis of 4-Amide, 4-Urea, and 4-Carbamate Pyridine Analogues **75**−**77**[a]




[a] Reagents and conditions: (a) EDC, HOBt, NMM, DCM; (b) $H_2$, Pd/C, MeOH; (c) 1.0 equiv of **22**, pyridine, DCM, 0 °C; (d) 0.75 equiv of **44**, DCM; (e) 0.75 equiv of **24**, DCM; (f) 10% TFA/DCM; (g) 1.4 equiv of **74**, 1-methylimidazole, PPA, EtOAc.

**Scheme 9.** Synthesis of 4-Aliphatic **83** and 4-Carboxamide **80** Pyridine Analogues[a]




[a] Reagents and conditions: (a) 3.0 equiv of $Tf_2O$, pyridine, 0−20 °C; (b) CO, $Pd(Ph_3P)_4$, TEA, DMSO, 60 °C; (c) 1.5 equiv of **44**, excess **6**, NMM, HOBt, DCM; (d) 10% TFA/DCM; (e) 2.8−4.0 equiv of **81**, $Cl_2Pd(Ph_3P)_2$, TEA, LiBr, DMF, 100 °C; (f) 2.8 equiv of **82**, $Pd(Ph_3P)_4$, diethylamine, CuI, THF; (g) $H_2$, Pd/C, MeOH.

**Table 8.** Binding and PRP Activity Data for a Representative Set of 4-Carboxamide Pyridine Analogues **80**

| Cpd | R' | R" | $K_i$[a] (nM) | $IC_{50}$[b] (μM) | Relative Potency to 84[c] |
|---|---|---|---|---|---|
| **80a** | H | H | 7.5 | 8.9 | 9.0 |
| **80b** | H | Me | 10 | 6.8 | 9.7 |
| **80c** | H | Et | 13 | 9.7 | 13 |
| **80d** | H | Pr | 11 | 12 | 20 |
| **80e** | Me | Me | 2.4 | 1.1 | 1.0 |
| **80f** | Me | Et | 2.6 | 0.58 | 1.3 |
| **80g** | Me | Bu | 5.8 | 1.8 | 3.3 |
| **80h** | H | $(CH_2)_2OMe$ | 7.9 | 8.0 | 18 |
| **80i** | H | $(CH_2)_3OMe$ | 6.1 | 4.6 | 12 |
| **80j** | H |  | 4.6 | 5.6 | 10 |
| **80k** | Me | $(CH_2)_3OMe$ | 2.6 | 0.63 | 1.4 |
| **80l** | Me | $-(CH_2)_3NMe_2$ | 8.6 | 0.42 | 0.96 |
| **80m** | Me |  | 11 | 0.35 | 0.83 |
| **80n** | $-(CH_2)_5-$ | | 2.8 | 0.91 | 2.2 |
| **80o** | $-(CH_2)_2O(CH_2)_2-$ | | 4.4 | 0.71 | 1.0 |
| **80p** | $-(CH_2)_2CHOMe(CH_2)_2-$ | | 3.2 | 0.46 | 0.99 |
| **80q** | $-(CH_2)_2CHNMe_2(CH_2)_2-$ | | 5.4 | 0.58 | 1.0 |
| **80r** | $-(CH_2)_2NMe(CH_2)_2-$ | | 5.8 | 0.53 | 0.72 |
| **80s** | $-(CH_2)_2NCOMe(CH_2)_2-$ | | 1.7 | 0.32 | 0.48 |

[a] Membranes from CHO cells expressing recombinant human $P2Y_{12}$ receptors incubated with $^{33}P$ ADP and compound. $K_i$ values are corrected from $IC_{50}$ using the Cheng and Prusoff equation and are the geometric mean of $n = 2$ or greater. [b] $IC_{50}$ values are from human PRP incubated with 20 μM ADP. [c] ($IC_{50}$ value of compound)/($IC_{50}$ value of **84** control from same plate) = normalized $IC_{50}$ ratio.

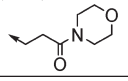
potency, while substitution at the 4-position of the piperidine with methoxy (**80p**) or an amine (**80q**) provided very potent compounds. Similarly, the 4-substituted piperazine amides **80r** and **80s** exhibited exceptional binding and PRP potency.

Table 9 contains analogues with aliphatic chains substituted at the 4-position of the pyridine. Alkyl chains of varying length and/or branching exhibited binding activity but no PRP activity (**83a**).[12] The aliphatic chains extending a hydroxy, methoxy, or amine three to four carbon atoms away from the pyridine ring (**83b**−**j**) and the propanamides **83k**−**l** provided compounds with good to moderate PRP activity.

Many libraries containing several hundred compounds were prepared with varying substituents at the 4-position of the pyridine ring and varying carbamate chain lengths on the piperazine terminal nitrogen. The SAR clearly showed that butyl and pentyl carbamates of the piperazine terminal nitrogen were optimal and modulation of potency and other properties could be obtained by variations at the 4-position of the pyridine, providing compounds with submicromolar PRP levels of activity.

Having identified many inhibitors with exceptional potency, we sought to evaluate the chemical and in vivo pharmacokinetic properties of selected analogues. In general, this class of compounds had good solubility and was chemically stable. These inhibitors also showed excellent metabolic stability in both the rat and human microsomal assays. Many compounds were evaluated for their in vivo pharmacokinetic characteristics in the rat, and a representative set of pharmacokinetic profiles is shown in Table 10. Compounds **10d**, **26d**, and **26e** each possessing a hydrogen at the 4-position of the pyridine, with an ethyl, pentyl, and hexyl carbamate on the piperazine terminal nitrogen, respectively, were selected to profile the general template and to test if the carboxylic acid would be detrimental to oral absorption. Gratifyingly, all of the compounds were bioavailable with high bioavailabilities for the pentyl and hexyl carbamate analogues. However, all

**Table 9.** Binding and PRP Activity Data for a Representative Set of 4-Aliphatic Pyridine Analogues **83**

| Cpd | $R_4$ | $K_i$[a] (nM) | $IC_{50}$[b] (μM) | Relative Potency to 84[c] |
|---|---|---|---|---|
| **83a** | $-CH_2CH-(CH_2)_5-$ | 8.6 | >10 | - |
| **83b** | $-(CH_2)_3OH$ | 3.8 | 1.9 | 2.6 |
| **83c** | $-(CH_2)_4OH$ | 3.6 | 3.2 | 4.2 |
| **83d** | $-(CH_2)_5OH$ | 2.8 | >10 | - |
| **83e** | $-(CH_2)_3OMe$ | 8.4 | 5.0 | 6.6 |
| **83f** | $-(CH_2)_4OMe$ | 8.3 | 4.2 | 4.5 |
| **83g** | $-(CH_2)_3NHCH_2CHMe_2$ | 12 | 1.0 | 1.5 |
| **83h** | $-(CH_2)_3NMe_2$ | 1 | 1.3 | 1.3 |
| **83i** | $-(CH_2)_3NEt_2$ | 22 | 1.1 | 1.6 |
| **83j** | $-(CH_2)_4NMe_2$ | 3.3 | 1.0 | 1.0 |
| **83k** | $-(CH_2)_2CONMe_2$ | 2.1 | 2.9 | 2.7 |
| **83l** |  | 3.7 | 3.1 | 2.4 |

[a] Membranes from CHO cells expressing recombinant human $P2Y_{12}$ receptors incubated with $^{33}P$ ADP and compound. $K_i$ values are corrected from $IC_{50}$ using the Cheng and Prusoff equation and are the geometric mean of $n = 2$ or greater. [b] $IC_{50}$ values are from human PRP incubated with 20 μM ADP. [c] ($IC_{50}$ value of compound)/($IC_{50}$ value of **84** control from same plate) = normalized $IC_{50}$ ratio.

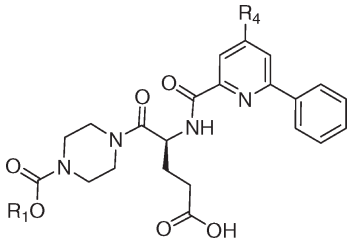
three of the compounds had high clearance values. Another concern with oral absorption was the molecular weight. The core templates **26d** and **26e** have molecular weights over 500. Substituting at the pyridine 4-position only adds to the molecular weight, potentially resulting in the loss of good bioavailability. Despite high molecular weight and, in numerous cases, poor Caco-2 permeability values, many compounds had good bioavailability as exemplified by **51i** (molecular weight of 570, $P_{app} = 1.1 \times 10^{-6}$).

Many compounds were profiled from the 4-oxygen pyridine series which included the 4-ether and 4-carbamate pyridine analogues. Included in this series was the general template, the hydroxy intermediate **52a**, which had high clearance but good bioavailability. This was the general trend for the ether series in which all of the compounds evaluated had high clearance, oftentimes above the liver blood flow, yet several had moderate to good bioavailability (**51i**, **52i**). Some of the most active compounds of the series, including the 4-oxypiperidine (**52n**, **53n**) and 4-oxymethyl piperidine ether analogues (**52q**), had high clearance. Capping the 4-nitrogen of the 4-oxypiperidine (**70c**,**d**) and 4-oxymethyl piperidine (**72a**−**c**) with various functionalities still resulted in compounds with high clearance. All of the 4-carbamate pyridine analogues (**57b**,**d**,**f**) profiled also exhibited high clearance values.

Several compounds from the carbon−carbon series at the 4-position were evaluated that included both the carboxamides and aliphatics. The carboxamides (**80o**−**q**) had improved, but still unacceptable, clearance values, while the aliphatics (**83g**−**i**) had relatively high clearance.

Many compounds were profiled from the 4-aminopyridine series. However, most of the initial compounds profiled had high clearance values. The secondary alkyl (**45c**) and aliphatic (**47e**) amines typically had high clearance, while the tertiary amines, piperidine (**45i**) and morpholine (**45j**), were still high but shifted in the right direction. The 4-piperidine analogues typically provided the more potent compounds and provided a handle to modulate the pharmacokinetic properties by varying the substituent at the 4-position of the piperidine ring. It was found that compounds with a basic amine directly linked (**47m**,**o**,**p**) or extended by a methylene (**47u**,**w**) to the

**Table 10.** Rat Pharmacokinetic Profiles of Selected $P2Y_{12}$ Antagonists[a,b]



| Cpd | $R_4$ | CL (mL/min/kg) | Vdss (L/kg) | $T_{1/2,\ eff}$ (h) | $F_{oral}$ (%) |
|---|---|---|---|---|---|
| **10d** | | 98 | 15.5 | 1.8 | 34 |
| **26d** | ←H | 89 | 10.3 | 1.3 | 70 |
| **26e** | | 29 | 1.7 | 0.7 | >95[c] |
| **50e** | | 109 | 3.9 | 0.4 | 72 |
| **50i** | | 94 | 13.6 | 0.2 | 33 |
| **51i** | | 49 | 1.5 | 0.4 | 77 |
| **52a** | | 675 | 29 | 0.5 | 66 |
| **52i** | | 46 | 2.3 | 0.6 | 100[d] |
| **52n** | ←O–R | 133 | 3.1 | 0.3 | 1 |
| **52q** | | 62 | 1.3 | 0.2 | - |
| **53n** | | 150 | 6.9 | 0.5 | 1 |
| **70c** | | 94 | 5.2 | 0.64 | - |
| **70d** | | 36 | 0.58 | 0.2 | - |
| **72a** | | 130 | 6.9 | 0.6 | - |
| **72b** | | 63 | 3.4 | 0.6 | - |
| **72c** | | 141 | 10.9 | 0.89 | - |
| **57b** | | 109 | 8.6 | 1.3 | - |
| **57d** | ←O(C=O)NR'R" | 46 | 2.3 | 0.6 | - |
| **57f** | | 220 | 31 | 1.6 | - |
| **80o** | | 51 | 1.1 | 0.24 | - |
| **80p** | ←C(=O)NR'R" | 54 | 1.2 | 0.25 | - |
| **80q** | | 37 | 0.77 | 0.2 | - |
| **83g** | | 112 | 5.6 | 0.6 | - |
| **83h** | ←R | 38 | 3.2 | 1.0 | - |
| **83i** | | 96 | 9.2 | 1.1 | - |
| **45c** | | 85 | 3.8 | 0.5 | 80 |
| **45i** | | 34 | 1.3 | 0.4 | - |
| **45j** | | 58 | 3.4 | 0.7 | - |
| **47e** | | 103 | 3.9 | 0.4 | 8 |
| **47m** | ←N(R')R" | 32 | 0.38 | 0.1 | - |
| **47o** | | 81 | 2.3 | 0.3 | - |
| **47p** | | 52 | 7.3 | 1.6 | - |
| **47s** | | 3 | 0.3 | 0.7 | 89 |
| **47u** | | 70 | 2.6 | 0.4 | - |
| **47w** | | 92 | 2.1 | 0.3 | - |

[a] Male Sprague–Dawley rats ($n$ = 2–4 rats). [b] Dose: iv infusion at 2 mg/kg; po at 5 mg/kg. Vehicle: 50% PEG400/40% PBS/10% ethanol. [c] $F_{oral}$ ($n$ = 3): 92%, 95%, and 181%. [d] $F_{oral}$ ($n$ = 1): 183%.

4-position of the piperidine usually had high clearance values. One strategy to reduce the basicity was to replace the basic amine on the piperidine with an alkoxy group. Replacing the amine group with a methoxy resulted in compounds with acceptable clearance values, although a slight loss in potency was observed. This exercise led to the discovery of compound **47s**, with a low clearance of 3 (mL/min)/kg in rat (1 (mL/min)/kg, dog) with good bioavailability ( > 90%, dog). Clearance of **47s** in rats appears to be mediated through extensive biliary excretion, with roughly 70% of an iv dose (2 mg/kg) recovered in the bile within 4 h. Oral bioavailability in a definitive rat study (2 mpk) averaged 25% (22%, 25%, and 27%), leading to a predicted human bioavailability of 30% with the projected human dose of 250 mg b.i.d. Oral bioavailability in a definitive dog study (0.2 mpk) averaged 67% (33%, 80%, and 87%), leading to a predicted human bioavailability of 70% with the projected human dose of 85 mg b.i.d.

Further evaluation of compound **47s** showed good solubility and chemical stability with the crystalline form of the compound. Compound **47s** was found to have acceptable margins vs hERG activity and a satisfactory CYP inhibition profile. Further evaluation on the potency of compound **47s** was determined by measuring the $IC_{50}$ in 13 human donors using 20 $\mu$M ADP-stimulated PRP aggregation with the 4-well Chronolog PRP aggregometry assay and found the average $IC_{50}$ to be 1.8 $\mu$M. Compound **47s** was orally efficacious in the rat ferric chloride model in which it dose-dependently prevented thrombus formation in this model of injury induced thrombosis.

In vitro receptor binding, signaling, and functional studies have shown that **47s** is a high affinity, selective, and competitive antagonist at $P2Y_{12}$ receptors. Compound **47s** is more than 340-fold selective for $P2Y_{12}$ over the other purinergic receptors tested, including the closest homologue, $P2Y_{13}$ (48% homology to $P2Y_{12}$), and a second platelet purinergic GPCR, $P2Y_1$ (19% homology to $P2Y_{12}$). The $K_b$ (8.5 nM) for functional antagonism in the $P2Y_{12}$ signaling assay is in good agreement with the $K_i$ (15 nM) for the receptor. The $K_b$ in human PRP platelet aggregation assays (300 nM) is higher because of the presence of plasma proteins. Schild analysis indicates that the interaction of **47s** with the receptor in the aggregation assays is competitive with ADP.

In summary, we have utilized PASP parallel library synthesis to identify a $P2Y_{12}$ lead. This lead was quickly followed-up with the generation of structure–activity relationships leading to highly potent $P2Y_{12}$ antagonists. With sufficient levels of potency attained, pharmacokinetic and physiochemical properties were modulated through various substituents at the 4-pyridine position. Fine-tuning the PK properties led to **47s**, an orally bioavailable, direct acting, reversible $P2Y_{12}$ antagonist. This compound is a selective antagonist of the human $P2Y_{12}$ receptor and demonstrates oral antiplatelet and antithrombotic efficacy in preclinical species. No safety issues were observed with **47s**, as it was inactive in both the Ames and micronucleus assays and has been evaluated in both rat and dog safety studies (single dose and 7-day repeat dose) without significant toxicological findings. The potency, selectivity, safety, and overall pharmacokinetic profile for **47s** support advancement for clinical evaluation. Reports from our backup program where efforts are focused on refining the SAR for more potent analogues with improved pharmacokinetic properties will be forthcoming.

## Experimental Section

**General Conditions.** Solvents and chemicals were reagent grade or better and were obtained from commercial sources. All polymeric reagents and sequestering resins were obtained from commercial sources. $^1H$ and $^{13}C$ NMR spectra were recorded using a 300, 400, or 500 MHz NMR spectrometer. Chemical shifts are reported in ppm, using the solvent as internal standard. High-resolution mass spectral (HRMS) data were recorded on a Mariner TOF from a Perseptive Biosystems instrument with electrospray ionization of a loop inject with 10 mM ammonium acetate in methanol at 50 mL/min and a lockmass of $m/z$ 387 from AlaLeuAlaLeu. All tested compounds were at least 95% pure as determined by HPLC analysis equipped with a mass spectrometry detector using a C18 3.5 $\mu$m, 30 mm × 2.1 mm column, eluting with a gradient system of 5/95 to 95/5 acetonitrile/$H_2O$ with a buffer consisting of 0.1% TFA over 4.5 min at 1 mL/min and detected by UV at 254 and 210 nm using a diode array detector. Preparative column chromatography was performed on a preparative liquid chromatography

instrument using silica gel columns and/or on a HPLC system using an 8 $\mu$m 60 A, C18 column (41 mm i.d. × 100 mm length). Reported yields are not optimized, with emphasis on purity of products rather than quantity.

**General Procedure A. Coupling of Carboxylic Acid 5 with Amine Templates 2−4 To Afford Products 9−11.** To a mixture of carboxylic acid **5** (0.26 mmol), 1-hydroxybenzotriazole (0.02 mmol), and *N*-methylmorpholine (44.0 uL, 0.40 mmol) in dichloromethane/dimethylformamide (4 mL, 7:1) in a 30 mL vial were added amine templates **2**−**4** (0.38 M in dimethylformamide) (526 uL, 0.20 mmol) and polymer-bound carbodiimide reagent **6** (1.17 mmol/g) (0.26 g, 0.30 mmol). The suspension was agitated 16 h. Upon completion of the reaction, dichloromethane (6 mL) was added followed by polyamine resin **8** (0.90 g, 2.5 mmol) (2.87 mmol/g) and isocyanate resin **7** (200 mg, 0.30 mmol) (1.47 mmol/g) and the suspension was agitated for 1−20 h. The reaction mixtures were filtered and rinsed with dichloromethane (1 × 4 mL). The combined filtrate and washings were dried in vacuo to afford the *tert*-butyl ester products.

**General Procedure B. Deprotection of the *tert*-Butyl Ester Group.** A solution of 10% trifluoroacetic acid/dichloromethane solution (2.0 mL) was added to the *tert*-butyl ester (~0.20 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The products were purified by HPLC to afford the pure products **9**−**11**.

**Ethyl 4-{*N*-[(4,6-Diphenylpyridin-2-yl)carbonyl]glycyl}piperazine-1-carboxylate (9a).** General procedure A afforded 61.0 mg (65%) of product **9a**. HRMS calcd for $C_{27}H_{28}N_4O_4$ ($M^+ + H$) 473.2183, found 473.2151.

**Ethyl 4-{*N*-[(6-Phenylpyridin-2-yl)carbonyl]glycyl}piperazine-1-carboxylate (9b).** General procedure A afforded 240 mg (92%) of product **9b**. $^1$H NMR ($CD_3OD$) $\delta$ 1.24 (t, 3H, $J$ = 8.0 Hz), 3.48−3.62 (m, 8H), 4.12 (q, 2H, $J$ = 12.0 Hz), 4.35 (s, 2H), 7.42−7.50 (m, 3H), 7.99−8.05 (m, 3H), 8.16 (d, 2H, $J$ = 8.0 Hz); MS (ESI+) $m/z$ 397 (M + H). Anal. Calcd for $C_{21}H_{24}N_4O_4 \cdot 0.2H_2O$: C, 63.05; H, 6.15; N, 14.00. Found: C, 62.88; H, 5.94; N, 13.91.

**(4*S*)-4-{[(4,6-Diphenylpyridin-2-yl)carbonyl]amino}-5-[4-(ethoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (10a).** General procedures A and B afforded 107.0 mg (66%) of product **10a**. HRMS calcd for $C_{30}H_{32}N_4O_6$ ($M^+ + H$) 545.2395, found 545.2375.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-[(pyridin-2-ylcarbonyl)amino]pentanoic Acid (10b).** General procedures A and B afforded 19 mg (22%) of product **10b**. HRMS calcd for $C_{18}H_{24}N_4O_6$ ($M^+ + H$) 393.1769, found 393.1765.

**(42*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-{[(4-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (10c).** General procedures A and B afforded 82.0 mg (63%) of product **10c**. $^1$H NMR (DMSO-$d_6$) $\delta$ 8.85 (d, 1H, $J$ = 8.1 Hz), 8.71 (dd, 1H, $J$ = 5.2 Hz, $J'$ = 0.5 Hz), 8.28 (d, 1H, $J$ = 1.2 Hz), 7.95 (dd, 1H, $J$ = 5.2 Hz, $J'$ = 1.9 Hz), 7.85 (dd, 2H, $J$ = 8.2 Hz, $J'$ = 1.5 Hz), 7.51 (m, 3H), 5.03 (m, 1H), 4.05 (q, 2H, $J$ = 7.0 Hz), 3.64 (br, 2H), 3.42 (m, 6H), 2.30 (m, 2H), 2.05 (m, 1H), 1.85 (m, 1H), 1.17 (t, 3H, $J$ = 7.0 Hz); HRMS calcd for $C_{24}H_{28}N_4O_6$ ($M^+ + H$) 469.2082, found 469.2051.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (10d).** General procedures A and B afforded 37.9 mg (43%) of product **10d**. HRMS calcd for $C_{24}H_{28}N_4O_6$ ($M^+ + H$) 469.2082, found 469.2082.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-[(1,1′:3′,1″-terphenyl-5′-ylcarbonyl)amino]pentanoic Acid (10e).** General procedures A and B afforded 36.0 mg (29%) of product **10e**. HRMS calcd for $C_{31}H_{33}N_3O_6$ ($M^+ + H$) 544.2442, found 544.2420.

**(4*S*)-4-[(1,1′-Biphenyl-3-ylcarbonyl)amino]-5-[4-(ethoxycarbonyl)-piperazin-1-yl]-5-oxopentanoic Acid (10f).** General procedures A and B afforded 45.0 mg (41%) of product **10f**. HRMS calcd for $C_{25}H_{29}N_3O_6$ ($M^+ + H$) 468.2129, found 468.2141.

**(4*S*)-4-[(2,6-Diphenylisonicotinoyl)amino]-5-[4-(ethoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (10g).** General procedures A and B afforded 54.0 mg (50%) of product **10g**. HRMS calcd for $C_{30}H_{32}N_4O_6$ ($M^+ + H$) 545.2395, found 545.2432.

**(*S*)-Ethyl 4-{4-Carboxy-2-[(2-phenylpyrimidine-4-carbonyl)-amino]butyryl}piperazine-1-carboxylate (10h).** General procedures A and B afforded 15.8 mg (69%) of product **10h**. Mp 60−68 °C; $[\alpha]_D^{25}$ +23.9° ($c$ 0.18); $^1$H NMR (DMSO-$d_6$) $\delta$ 12.1 (br s, 1H), 9.20 (d, 1H, $J$ = 7.6 Hz), 9.15 (d, 1H, $J$ = 5.0 Hz), 8.57 (m, 2H), 7.93 (d, 1H, $J$ = 4.9 Hz), 7.60 (m, 3H), 5.05 (m, 1H), 4.06 (q, 2H, $J$ = 7.1 Hz), 3.60 (m, 3H), 3.44 (m, 4H), 2.35 (m, 2H), 2.08 (m, 1H), 1.93 (m, 1H), 1.19 (t, 3H, $J$ = 7.1 Hz); MS (ESI+) $m/z$ 470 (M + H). Anal. Calcd for $C_{23}H_{27}N_5O_6S \cdot 0.35H_2O$: C, 58.06; H, 5.87; N, 14.72. Found: C, 58.17; H, 5.82; N, 14.56.

**(*S*)-Ethyl 4-{4-Carboxy-2-[(4-phenylpyrimidine-2-carbonyl)-amino]butyryl}piperazine-1-carboxylate (10i).** General procedures A and B afforded 55 mg (56%) of product **10i**. $^1$H NMR ($CDCl_3$) $\delta$ 9.12 (s, 1H), 8.93 (d, 1H, $J$ = 5.0 Hz), 8.19 (dd, 2H, $J$ = 5.0, 1.5 Hz), 7.84 (d, 1H, $J$ = 5.0 Hz), 7.84−7.53 (m, 3H), 5.33−5.30 (m, 1H), 4.16 (q, 1H, $J$ = 7.0 Hz), 3.72−3.44 (m, 8H), 2.62−2.50 (m, 2H), 2.27−2.23 (m, 1H), 1.97−1.94 (m, 1H), 1.30 (t, 3H, $J$ = 7.0 Hz); MS (ESI+) $m/z$ 470 (M + H).

**(4*S*)-4-{[(4,6-Diphenylpyridin-2-yl)carbonyl]amino}-5-[4-(3-methylphenyl)piperazin-1-yl]-5-oxopentanoic Acid (11a).** General procedures A and B afforded 126.0 mg (62%) of product **11a**. HRMS calcd for $C_{34}H_{34}N_4O_4$ ($M^+ + H$) 563.2653, found 563.2655.

**(4*S*)-5-[4-(3-Methylphenyl)piperazin-1-yl]-5-oxo-4-{[(4-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (11b).** General procedures A and B afforded 131.0 mg (91%) of product **11b**. HRMS calcd for $C_{28}H_{30}N_4O_4$ ($M^+ + H$) 487.2340, found 487.2377.

**(4*S*)-5-[4-(3-Methylphenyl)piperazin-1-yl]-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (11c).** General procedures A and B afforded 28.0 mg (19%) of product **11c**. HRMS calcd for $C_{28}H_3N_4O_4$ ($M^+ + H$) 487.2340, found 487.2379.

**(4*S*)-5-[4-(3-Methylphenyl)piperazin-1-yl]-5-oxo-4-[(1,1′:3′,1″-terphenyl-5′-ylcarbonyl)amino]pentanoic Acid (11d).** General procedures A and B afforded 52.0 mg (38%) of product **11d**. HRMS calcd for $C_{35}H_{35}N_3O_4$ ($M^+ + H$) 562.2700, found 562.2715.

**(4*S*)-4-[(1,1′-Biphenyl-3-ylcarbonyl)amino]-5-[4-(3-methylphenyl)-piperazin-1-yl]-5-oxopentanoic Acid (11e).** General procedure A afforded 21.0 mg (33%) of product **11e**. HRMS calcd for $C_{29}H_{31}N_3O_4$ ($M^+ + H$) 486.2387, found 486.2418.

**1-Allyl 5-*tert*-Butyl-*N*-[(4-phenylpyridin-2-yl)carbonyl]-L-glutamate (14).** To a mixture of 6-phenylpyridine-2-carboxylic acid **13** (11.3 g, 56.7 mmol), hydroxybenzotriazole (763 mg, 5.7 mmol), and *N*-methylmorpholine (24.9 mL, 226 mmol) in dichloromethane/dimethylformamide (140 mL, 5:2) were added 1-allyl 5-*tert*-butyl L-glutamate hydrochloride **12** (10.7 g, 38.2 mmol) and polymer-bound carbodiimide reagent **6** (1.27 mmol/g) (66.9 g, 85.0 mmol). The suspension was agitated 16 h, and the resin was filtered and rinsed with dichloromethane (4 × 10 mL). The filtrate and washings were dried in vacuo to afford 16.3 g (68%) of product **14**. $^1$H NMR ($CDCl_3$) $\delta$ 1.33 (s, 9H), 2.08−2.46 (m, 4H), 4.63 (d, 2H), 4.80 (m, 1H), 5.19−5.32 (m, 2H), 5.83−5.96 (m, 1H), 7.40−7.50 (m, 3H), 7.85−7.87 (m, 2H), 7.94 (s, 1H), 8.01−8.04 (m, 2H), 8.77 (d, NH).

**5-*tert*-Butyl *N*-[(4-phenylpyridin-2-yl)carbonyl]-L-glutamic Acid (15).** Tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.25 mmol) was added to a solution of 1-allyl 5-*tert*-butyl-*N*-[(4-phenylpyridin-2-yl)carbonyl]-L-glutamate **14** (16.3 g, 38.4 mmol) and morpholine (3.36 mL, 38.4 mmol) in acetonitrile (200 mL) under nitrogen. The mixture was stirred at room temperature for 1 h. Upon completion, the product mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by reverse-phase HPLC (10−60% acetonitrile/water with 0.1% TFA modifier) to afford 11.5 g (78%) of product **15**. $^1$H NMR ($CDCl_3$) $\delta$ 1.36 (s, 9H),

2.11−2.51 (m, 4H), 4.85 (m, 1H), 7.39−7.47 (m, 3H), 7.85 (m, 2H), 8.02−8.01 (m, 3H), 8.91 (d, NH).

**Benzyl 4-((2*S*)-5-*tert*-Butoxy-5-oxo-2-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoyl)piperazine-1-carboxylate (17).** To a mixture of 5-*tert*-butyl *N*-[(4-phenylpyridin-2-yl)carbonyl]-L-glutamic acid **15** (11.5 mL, 29.9 mmol), hydroxybenzotriazole (1.2 g, 3.0 mmol), and *N*-methylmorpholine (13.1 mL, 119.6 mmol) in dichloromethane/dimethylformamide (140 mL, 13:1) were added benzyl 1-piperazinecarboxylate **16** (5.8 mL, 29.9 mmol) and polymer-bound carbodiimide reagent **6** (1.27 mmol/g) (35.3 g, 44.8 mmol). The suspension was agitated for 16 h, and the resin was filtered and rinsed with dichloromethane (4 × 10 mL). The filtrate and washings were dried in vacuo to afford 15.8 g (90%) of product **17**. $^1$H NMR ($CDCl_3$) $\delta$ 1.42 (s, 9H), 1.90−2.18 (m, 2H), 2.29−2.41 (m, 2H), 3.62 (m, 8H), 5.14 (s, 2H), 5.22 (m, 1H), 7.34 (m, 4H), 7.47 (m, 3H), 7.88 (m, 3H), 8.07 (m, 3H), 8.96 (d, NH).

***tert*-Butyl (4*S*)-5-Oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}-5-piperazin-1-ylpentanoate (18).** Benzyl 4-((2*S*)-5-*tert*-butoxy-5-oxo-2-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoyl)piperazine-1-carboxylate **17** (15.8 g, 26.9 mmol) was dissolved in methanol (200 mL), and the reaction vessel was flushed with $N_{2(g)}$. Then 10% Pd/C (1.6 g, 10% by weight) was added to the solution, and the reaction vessel was flushed with $N_{2(g)}$ then $H_{2(g)}$. The mixture was stirred for 16 h under a balloon of $H_{2(g)}$. The mixture was filtered through a pad of Celite. The filtrate and cake rinses were dried in vacuo to afford 11.0 g (81%) of product **18**. $^1$H NMR ($CDCl_3$) $\delta$ 1.40 (s, 9H), 1.83−2.42 (m, 12H), 5.19 (m, 1H), 7.41−7.50 (m, 3H), 7.82−8.09 (m, 3H), 8.94 (d, NH).

**General Procedure C. Reaction of Amine 18 with Electrophiles 19 To Afford Products 20.** A solution of *tert*-butyl (4*S*)-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}-5-piperazin-1-ylpentanoate **18** (0.15 M in dichloromethane) (1 mL, 0.15 mmol) was added to each reaction well containing the electrophile **19** (0.6 mmol) (which included chloroformates, acid chlorides, isocyanates, thioisocyanates, sulfonyl isocyanates, and sulfonyl chlorides), triethylamine (125 $\mu$L, 0.9 mmol) (wells with chloroformates and acid chlorides only) and dichloromethane (6 mL). The vials were agitated for 1 to several hours. Upon completion of the reaction, the product mixture was dried under a stream of nitrogen gas and, if necessary, diluted with dichloromethane (8 mL) and scavenged with PS-diethylenetriamine **8** (0.6 mmol). The resin was filtered and rinsed with dichloromethane (2 × 6 mL). The filtrate and washings were dried in vacuo to afford the *tert*-butyl ester products.

**Deprotection of the *tert*-Butyl Ester Group.** A solution of 20% trifluoroacetic acid/dichloromethane solution (8.0 mL) was added to the *tert*-butyl ester (~0.15 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The products were purified by HPLC to afford the pure products **20**.

**General Procedure D. Preparation of Piperazine Carbamate Analogues 26. Preparation of Polymer-Supported NHS-Chloroformate (23).** Polymer supported *N*-hydroxysuccinimide resin **21** (1.09 mmol/g) (300 mg, 0.33 mmol) was placed in a Quest 210 (Argonaut) disposable, fritted reaction vessel and swelled with dichloromethane (2 mL). Triphosgene **22** (0.72 M in dichloromethane) (1 mL, 0.72 mmol) and pyridine (32 uL, 0.40 mmol) were delivered to the reaction vessels followed by agitation for 1 h. Upon completion of the reaction, the vessels were drained and rinsed with dichloromethane (4 × 3 mL) to remove excess reagents to afford polymer-supported NHS-chloroformate **23**.

**Preparation of Polymer-Supported NHS-Carbonates (25).** The alcohol **24** (0.6 M in dichloromethane) (4 mL, 2.4 mmol) and pyridine (32 $\mu$L, 0.40 mmol) were added to the polymer-supported NHS-chloroformate **23**. The reaction mixtures were agitated for 2 h before the vessels were drained and rinsed with dichloromethane (4 × 3 mL) to afford polymer-supported NHS-carbonate **25**.

**Carbamate Formation with *tert*-Butyl (4*S*)-5-Oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}-5-piperazin-1-ylpentanoate 18 and Polymer-Supported NHS-Carbonate 25.** *tert*-Butyl (4*S*)-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}-5-piperazin-1-ylpentanoate **18** (0.25 M in dichloromethane) (1 mL, 0.25 mmol) was added to the preswelled polymer-supported NHS-carbonate **25** in dichloromethane (2 mL). The reaction mixtures were agitated for 16 h before the vessels were drained and rinsed with dichloromethane (4 × 3 mL), and the combined filtrate and washings were dried in vacuo to afford the *tert*-butyl ester products.

**Deprotection of the *tert*-Butyl Ester Group.** A solution of 20% trifluoroacetic acid/dichloromethane solution (8.0 mL) was added to the residue (~0.25 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the products **26**. The products were purified by HPLC to afford the pure products **26**.

**(4*S*)-5-[4-(Methoxycarbonyl)piperazin-1-yl]-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26a).** General procedure D afforded 28.1 mg (41%) of product **26a**. HRMS calcd for $C_{23}H_{26}N_4O_6$ ($M^+ + H$) 455.1925, found 455.1912.

**(4*S*)-5-Oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}-5-[4-(propoxycarbonyl)piperazin-1-yl]pentanoic Acid (26b).** General procedure D afforded 38.9 mg (44%) of product **26b**. HRMS calcd for $C_{25}H_{30}N_4O_6$ ($M^+ + H$) 483.2238, found 483.2254.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26c).** General procedure D afforded 17.3 mg (23%) of product **26c**. HRMS calcd for $C_{26}H_{32}N_4O_6$ ($M^+ + H$) 497.2395, found 497.2403.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26d).** General procedure D afforded 17.4 mg (23%) of product **26d**. HRMS calcd for $C_{27}H_{34}N_4O_6$ ($M^+ + H$) 511.2551, found 511.2543.

**(4*S*)-5-{4-[(Hexyloxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26e).** General procedure D afforded 61.6 mg (64%) of product **26e**. HRMS calcd for $C_{28}H_{36}N_4O_6$ ($M^+ + H$) 525.2708, found 525.2705.

**(4*S*)-5-{4-[(Heptyloxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26f).** General procedure D afforded 45.2 mg (46%) of product **26f**. HRMS calcd for $C_{29}H_{38}N_4O_6$ ($M^+ + H$) 539.2864, found 539.2901.

**(4*S*)-5-{4-[(Octyloxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26g).** General procedure D afforded 66 mg (66%) of product **26g**. HRMS calcd for $C_{30}H_{40}N_4O_6$ ($M^+ + H$) 553.3021, found 553.3045.

**(4*S*)-5-Oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}-5-{4-[(2,2,2-trifluoroethoxy)carbonyl]piperazin-1-yl}pentanoic Acid (26h).** General procedure D afforded 110.0 mg (83%) of product **26h**. HRMS calcd for $C_{24}H_{25}F_3N_4O_6$ ($M^+ + H$) 523.1799, found 523.1791.

**(4*S*)-5-[4-(Isopropoxycarbonyl)piperazin-1-yl]-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26i).** General procedure D afforded 11.5 mg (16%) of product **26i**. HRMS calcd for $C_{25}H_{30}N_4O_6$ ($M^+ + H$) 483.2238, found 483.2213.

**(4*S*)-5-Oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}-5-{4-[(4,4,4-trifluorobutoxy)carbonyl]piperazin-1-yl}pentanoic Acid (26j).** General procedure D afforded 89.4 mg (64%) of product **26j**. HRMS calcd for $C_{26}H_{29}F_3N_4O_6$ ($M^+ + H$) 551.2112, found 551.2075.

**(4*S*)-5-{4-[(But-3-yn-1-yloxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26k).** General procedure D afforded 47.3 mg (52%) of product **26k**. HRMS calcd for $C_{26}H_{28}N_4O_6$ ($M^+ + H$) 493.2082, found 493.2094.

**(4*S*)-5-{4-[(Cyclopentyloxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26l).** General procedure D afforded 38.0 mg (30%) of product **26l**. HRMS calcd for $C_{27}H_{32}N_4O_6$ ($M^+ + H$) 509.2395, found 509.2405.

**(4*S*)-5-{4-[(Cyclohexyloxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26m).** General

procedure D afforded 54.3 mg (41%) of product **26m**. HRMS calcd for $C_{28}H_{34}N_4O_6$ ($M^+ + H$) 523.2551, found 523.2530.

**(4*S*)-5-{4-[(Cyclobutylmethoxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26n).** General procedure D afforded 38.5 mg (30%) of product **26n**. HRMS calcd for $C_{27}H_{32}N_4O_6$ ($M^+ + H$) 509.2395, found 509.2432.

**(4*S*)-5-{4-[(Cyclopentylmethoxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26o).** General procedure D afforded 55.2 mg (42%) of product **26o**. HRMS calcd for $C_{28}H_{34}N_4O_6$ ($M^+ + H$) 523.2551, found 523.2541.

**(4*S*)-5-{4-[(2-Cyclopropylethoxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26p).** General procedure D afforded 20.9 mg (16%) of product **26p**. HRMS calcd for $C_{27}H_{32}N_4O_6$ ($M^+ + H$) 509.2395, found 509.2400.

**(4*S*)-5-{4-[(3-Methylbutoxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26q).** General procedure D afforded 90.2 mg (16%) of product **26q**. HRMS calcd for $C_{27}H_{34}N_4O_6$ ($M^+ + H$) 511.2551, found 511.2559.

**(4*S*)-5-{4-[(3,3-Dimethylbutoxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26r).** General procedure D afforded 80.7 mg (61%) of product **26r**. HRMS calcd for $C_{28}H_{36}N_4O_6$ ($M^+ + H$) 525.2708, found 525.2696.

**(4*S*)-5-{4-[(2-Methoxyethoxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26s).** General procedure D afforded 23.6 mg (32%) of product **26s**. HRMS calcd for $C_{25}H_{30}N_4O_7$ ($M^+ + H$) 499.2187, found 499.2182.

**(4*S*)-5-{4-[(Benzyloxy)carbonyl]piperazin-1-yl}-5-oxo-4-{[(6-phenylpyridin-2-yl)carbonyl]amino}pentanoic Acid (26t).** General procedure D afforded 20 mg (45%) of product **26t**. $^1$H NMR ($CD_3OD$) 1.94−1.99 (m, 1H), 2.17−2.20 (m, 1H), 2.41−2.45 (m, 2H), 3.40−3.74 (m, 6H), 3.76 (br s 2H), 5.11 (s, 2H), 5.21 (m, 1H), 7.25−7.33 (m, 5H), 7.44−7.50 (m, 3H), 7.99−8.03 (m, 3H), 8.12 (d, 2 H, $J$ = 8.0 Hz); HRMS calcd for $C_{29}H_{30}N_4O_6$ ($M^+ + H$) 531.2244, found 531.2258.

**Methyl 4-Hydroxy-6-phenylpyridine-2-carboxylate (28).** A solution of 4-hydroxy-6-phenylpyridine-2-carboxylic acid **27** (15.1 g, 70.2 mmol), concentrated sulfuric acid (14 mL), and methanol (400 mL) was heated to reflux for 24 h with the condensate passing through a 100 mL addition funnel filled with 3 Å molecular sieves. Upon completion of the reaction, the solution was cooled to ambient temperature and neutralized with solid sodium bicarbonate (80 g) and then filtered. The filtrate was dried in vacuo and purified on silica gel to afford 15.3 g (95%) of product **28**. Mp 49−52 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 11.19 (s, 1H), 8.05 (m, 2H), 7.42−7.54 (m, 5H), 3.90 (s, 3H); MS (ESI+) $m/z$ 230 (M + H).

**Methyl 4-Chloro-6-phenylpyridine-2-carboxylate Hydrochloride (29).** A mixture of methyl 4-hydroxy-6-phenylpyridine-2-carboxylate **28** (7.56 g, 33.0 mmol) and phosphorus oxychloride (70 mL) was heated to reflux under nitrogen for 20 h. The reaction mixture was cooled to ambient temperature and dried in vacuo. In an ice−water bath, methanol (70 mL) was slowly added to the reaction residue. Once this addition was complete, the resulting solution was concentrated to ~30 mL and diluted with water (100 mL). The resulting precipitate was collected by vacuum filtration, washed with water (50 mL), and dried in vacuo to give 7.68 g (82%) of product **29**. Mp 86−88 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.03 (m, 3H), 7.88 (d, 1H, $J$ = 1.8 Hz), 7.48 (m, 3H), 4.03 (s, 3H); MS (ESI+) $m/z$ 248 (M + H).

**4-Chloro-6-phenylpyridine-2-carboxylate (30).** To a solution of methyl 4-chloro-6-phenylpyridine-2-carboxylate hydrochloride **29** (10.0 g, 35.2 mmol) in dioxane (50 mL) was slowly added potassium hydroxide (0.26 M in water) (40 mL, 105.6 mmol). Additional water (50 mL) was added to facilitate stirring. After the mixture was stirred for 30 min, the slurry was cooled in an ice−water bath and then acidified with 3 N HCl to pH 5. The crude product was isolated by vacuum filtration and washed with water (1 × 100 mL) and diethyl ether (3 × 50 mL). Residual solvents were removed in vacuo to afford 7.83 g (95%) of product **30**. $^1$H NMR (DMSO-$d_6$) $\delta$ 8.31 (d, 1H, $J$ = 1.7 Hz), 8.20 (m, 2H), 7.97 (d, 1H, $J$ = 1.7 Hz), 7.52 (m, 3H); MS (ESI+) $m/z$ 234 (M + H).

**4-Azido-6-phenylpyridine-2-carboxylate (31).** To a solution of 4-chloro-6-phenylpyridine-2-carboxylate **30** (200 mg, 0.83 mmol) and Aliquat 336 (33.5 mg, 0.083 mmol) in ethanol/water (2 mL/1 mL) was slowly added sodium azide (65.0 mg, 1.0 mmol), and the mixture was heated to 100 °C for 1 h. After cooling, the mixture was poured onto ice/water to provide a solid. The precipitate was filtered, washed with water, and dried in a vacuum oven overnight to provide 163 mg (79%) of product **31**. $^1$H NMR (methanol-$d_4$) $\delta$ 4.53 (br s, 1H), 7.35−7.43 (m, 4H), 7.61 (m, 1H), 8.04 (d, 2H, $J$ = 4.0 Hz).

**General Procedure E. Coupling of *tert*-Butyl Piperazine-1-carboxylate 32 with Chloroformates 33. Piperazine-1,4-dicarboxylic Acid *tert*-Butyl Ester Butyl Ester (34b).** To a mixture of *tert*-butyl piperazine-1-carboxylate **32** (5.0 g, 26.8 mmol) and *N*,*N*-diisopropylethylamine (5.14 mL, 29.5 mmol) in anhydrous methylene chloride (50 mL) at 0 °C was added *n*-butyl chloroformate **33b** (4.45 g, 29.5 mmol) dropwise over 15 min. The mixture warmed to room temperature and stirred for 3 h. The mixture was poured into 10% aqueous citric acid (200 mL), and the organic layer was isolated, dried over sodium sulfate, filtered, and concentrated to give 8.05 g (99%) of product **35b**. $^1$H NMR ($CDCl_3$) $\delta$ 4.08 (t, 2H, $J$ = 6.7 Hz), 3.42 (m, 8H), 1.63 (m, 2H), 1.47 (s, 9H), 1.33 (m, 2H), 0.91 (t, 2H, $J$ = 6.5 Hz).

**Piperazine-1,4-dicarboxylic Acid *tert*-Butyl Ester Pentyl Ester (34c).** General procedure E afforded 3.40 g (100%) of product **33**. $^1$H NMR ($CDCl_3$) $\delta$ 4.09 (m, 2H), 3.43 (m, 8H), 1.63 (m, 2H), 1.47 (s, 9H), 1.26−1.36 (m, 4H), 0.91 (m, 3H).

**Piperazine-1,4-dicarboxylic Acid *tert*-Butyl Ester Hexyl Ester (34d).** General procedure E afforded crude product **34d**. $^1$H NMR ($CDCl_3$) $\delta$ 4.06 (m, 2H), 3.40 (m, 8H), 1.62 (m, 2H), 1.44 (s, 9H), 1.26−1.36 (m, 6H), 0.87 (m, 3H).

**General Procedure F. Boc Deprotection. Butyl Piperazine-1-carboxylate (35b). Method A.** To a solution of piperazine-1,4-dicarboxylic acid *tert*-butyl ester butyl ester **34b** (7.67 g, 26.8 mmol) in methylene chloride (50 mL) was added trifluoroacetic acid (25.0 mL, 336 mmol). The mixture was stirred for 3 h at room temperature. The mixture was concentrated to an oily residue in vacuo and dissolved in methylene chloride (20 mL), and sodium carbonate (25% by weight in water) was added with vigorous stirring until the aqueous phase reached pH 10. The organic phase was separated, dried over sodium sulfate, filtered, and dried in vacuo to afford 4.94 g (99%) of product **34b**. $^1$H NMR ($CDCl_3$) $\delta$ 4.08 (t, 2H, $J$ = 6.7 Hz), 3.43 (t, 4H, $J$ = 5.0 Hz), 2.82 (t, 4H, $J$ = 5.0 Hz), 1.63 (m, 2H), 1.37 (m, 2H), 0.93 (t, 3H, $J$ = 6.4 Hz); MS (ESI+) $m/z$ 187 (M + H).

**Method B: Pentyl Piperazine-1-carboxylate Hydrochloride (35c).** To a solution of piperazine-1,4-dicarboxylic acid *tert*-butyl ester pentyl ester **34c** (1.77 g, 5.90 mmol) in methylene chloride (15 mL) was added hydrochloric acid (4 M in 1,4-dioxane) (15.0 mL, 60.0 mmol). The mixture was stirred at room temperature for 2 h and was dried in vacuo to afford 1.20 g (87%) of product **35c**. $^1$H NMR ($CDCl_3$) $\delta$ 10.00 (br s, 1H), 4.12 (m, 2H), 3.84 (s, 4H), 3.21 (s, 4H), 1.64 (m, 2H), 1.33 (m, 4H), 0.91 (m, 3H); MS (ESI+) $m/z$ 201 (M + H).

**Hexyl Piperazine-1-carboxylate Hydrochloride (35d).** General procedure F, method B, afforded 41.7 g (99%) of product **35d**. $^1$H NMR ($CDCl_3$) $\delta$ 4.09 (m, 2H), 3.83 (s, 4H), 3.19 (s, 4H), 1.71 (m, 2H), 1.61 (m, 2H), 1.29 (m, 4H), 0.88 (m, 3H).

**General Procedure G. Coupling of Piperazines 35 with *N*-Benzyloxycarbonyl-L-glutamic Acid $\gamma$-*tert*-Butyl Ester 36. Ethyl 4-((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-5-*tert*-butoxy-5-oxopentanoyl)piperazine-1-carboxylate (37a).** To a solution

of *N*-benzyloxycarbonyl-L-glutamic acid γ-*tert*-butyl ester **36** (53.0 g, 0.16 mol) in dichloromethane (250 mL) chilled to 5 °C with an ice/water bath were added hydroxybenzotriazole (24.4 g, 0.18 mol) and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (36.0 g, 0.19 mol). *N*-Methylmorpholine (21.0 mL, 0.19 mol) was introduced into the flask in three portions, and stirring continued for 20 min. Ethyl 1-piperazinecarboxylate **35a** (27.6 mL, 0.19 mol) was added dropwise to the reaction mixture, keeping the temperature between 5 and 11 °C. The mixture came to room temperature, was stirred for 16 h, and was dried in vacuo. The residue was diluted with ethyl acetate (500 mL) and then washed with water (2 × 250 mL), citric acid (10% by weight in water) (2 × 150 mL), sodium bicarbonate (saturated in water) (2 × 500 mL), and brine (2 × 150 mL). The organic phase was dried over sodium sulfate and dried in vacuo. The crude residue was purified on silica gel (50−100% ethyl acetate/heptane) to afford 62.3 g (83% yield) of product **37a**. $^1$H NMR (DMSO-$d_6$) δ 7.54 (d, 1H, $J$ = 8.2 Hz), 7.33 (m, 5H), 5.02 (s, 2H), 4.47 (m, 1H), 4.03 (q, 2H, $J$ = 7.1 Hz), 3.26−3.51 (m, 8H), 2.25 (t, 2H, $J$ = 7.0 Hz), 1.80 (m, 1H), 1.67 (m, 1H), 1.39 (s, 9H), 1.19 (t, 3H, $J$ = 7.1 Hz); MS (APCI+) $m/z$ 478 (M + H).

**Butyl (*S*)-4-(2-Benzyloxycarbonylamino-4-*tert*-butoxycarbonylbutyryl)piperazine-1-carboxylate (37b).** General procedure G afforded 4.27 g (86%) of product **37b**. $^1$H NMR ($CDCl_3$) δ 7.32 (m, 5H), 5.79 (d, 1H, $J$ = 8.3 Hz), 5.10 (m, 2H), 4.73 (m, 1H), 4.10 (t, 2H, $J$ = 6.7 Hz), 3.40−3.72 (m, 8H), 2.30 (m, 2H), 1.97 (m, 1H), 1.70 (m, 1H), 1.64 (m, 2H), 1.45 (s, 9H), 1.38 (m, 2H), 0.95 (t, 3H, $J$ = 6.4 Hz); MS (ESI+) $m/z$ 506 (M + H).

**Pentyl (*S*)-4-(2-Benzyloxycarbonylamino-4-*tert*-butoxycarbonylbutyryl)piperazine-1-carboxylate (37c).** General procedure G afforded 4.24 g (92%) of product **37c**. $^1$H NMR ($CDCl_3$) δ 7.32 (m, 5H), 5.69 (d, 1H, $J$ = 8.3 Hz), 5.10 (m, 2H), 4.73 (m, 1H), 4.10 (t, 2H, $J$ = 6.7 Hz), 3.40−3.70 (m, 8H), 2.30 (m, 2H), 1.97 (m, 1H), 1.70 (m, 1H), 1.64 (m, 2H), 1.45 (s, 9H), 1.34 (m, 4H), 0.92 (t, 3H, $J$ = 6.4 Hz); MS (ESI+) $m/z$ 520 (M + H).

**Hexyl 4-[(2*S*)-2-{[(Benzyloxy)carbonyl]amino}-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate (37d).** General procedure G afforded 95.5 g (99%) of product **37d**. $^1$H NMR (DMSO-$d_6$) δ ppm 0.84 (t, 3H, $J$ = 6.7 Hz), 1.25 (m, 6 H), 1.36 (s, 9 H), 1.54 (m, 2 H), 1.65 (m, 1 H), 1.80 (m, 1 H), 2.23 (m, 2H), 3.48 (m, 8H), 4.00 (t, 2H, $J$ = 6.6 Hz), 4.44 (m, 1H), 4.99 (s, 2H), 7.31 (m, 5H), 7.50 (d, 1H, $J$ = 8.2 Hz).

**General Procedure H. Cbz Deprotection. Ethyl 4-[(2*S*)-2-Amino-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate (38a).** To a 2.5 L Parr shaker bottle were added ethyl 4-((2*S*)-2-{[(benzyloxy)carbonyl]amino}-5-*tert*-butoxy-5-oxopentanoyl-piperazine-1-carboxylate **37a** (62.3 g, 130 mmol), ethanol (700 mL), and 10% Pd/C (3.6 g, 5% by weight). The mixture was stirred for 16 h under 40 psi of $H_{2(g)}$. The reaction mixture was filtered through Celite and the filtrate dried in vacuo, dissolved in dichloromethane (500 mL), and treated with hydrochloric acid (1 N in diethyl ether) (144 mL, 144 mmol) under $N_{2(g)}$ at 0 °C. The reaction mixture was concentrated in vacuo and the residue triturated with heptane. A solid was collected by vacuum filtration, washed with heptane, and dried in vacuo to afford 43.1 g (92% yield) of product **38a**. $^1$H NMR (DMSO-$d_6$) δ 4.05 (q, 2H, $J$ = 7.1 Hz), 3.61 (m, 1H), 3.32−3.51 (m, 8H), 2.30 (m, 2H), 1.68 (m, 1H), 1.44 (m, 1H), 1.41 (s, 9H), 1.19 (t, 3H, $J$ = 7.1 Hz); MS (APCI+) $m/z$ 344 (M + H); mp = 137.5−141.2 °C (dec).

**Butyl (*S*)-4-(2-Amino-4-*tert*-butoxycarbonylbutyryl)piperazine-1-carboxylate (38b).** General procedure H afforded 3.11 g (99%) of a light-yellow oil of product **38b**. $^1$H NMR ($CDCl_3$) δ 4.11 (t, 2H, $J$ = 6.7 Hz), 3.76 (d, 1H, $J$ = 6.0 Hz), 3.40−3.72 (m, 8H), 2.54 (m, 1H), 2.35 (m, 1H), 1.99 (br s, 3H), 1.90 (m, 1H), 1.64 (m, 2H), 1.44 (s, 9H), 1.40 (m, 2H), 0.95 (t, 3H, $J$ = 6.4 Hz); MS (ESI+) $m/z$ 372 (M + H).

**Pentyl (*S*)-4-(2-Amino-4-*tert*-butoxycarbonylbutyryl)piperazine-1-carboxylate (38c).** General procedure H afforded 3.24 g (94%) of a yellow oil of product **38c**. $^1$H NMR ($CDCl_3$) δ 4.10 (t, 2H, $J$ = 6.7 Hz), 3.76 (d, 1H, $J$ = 6.0 Hz), 3.40−3.72 (m, 8H), 2.54 (m, 1H), 2.35 (m, 1H), 1.90 (br s, 3H), 1.64 (m, 2H), 1.55 (m, 1H), 1.44 (s, 9H), 1.34 (m, 4H), 0.91 (t, 3H, $J$ = 6.4 Hz); MS (ESI+) $m/z$ 386 (M + H).

**Hexyl 4-[(2*S*)-2-Amino-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate (38d).** General procedure H afforded 85.0 g (85%) of a clear oil of product **38d**. $^1$H NMR (DMSO-$d_6$) δ ppm 0.83 (t, 3H, $J$ = 6.7 Hz), 1.24 (m, 6H), 1.36 (s, 9H), 1.53 (m, 3H), 1.68 (m, 1H), 2.30 (m, 2H), 3.47 (m, 10H), 3.71 (m, 1H), 3.97 (t, 2 H, $J$ = 6.6 Hz).

**General Procedure I. Coupling of Amines 38 with Pyridine Acids. Ethyl 4-((2*S*)-5-*tert*-Butoxy-2-{[(4-hydroxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoyl)piperazine-1-carboxylate (39).** To a mixture of 4-hydroxy-6-phenylpyridine-2-carboxylic acid hydrochloride salt **27** (3.0 g, 7.95 mmol), 1-hydroxybenzotriazole (0.215 g, 1.59 mmol), and *N*-methylmorpholine (2.6 mL, 23.8 mmol) in anhydrous dichloromethane/dimethylformamide (100 mL, 20:1) were added ethyl 4-[(2*S*)-2-amino-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate **38a** (3.0 g, 7.95 mmol) and polymer-bound carbodiimide reagent **6** (1.3 mmol/g, 9.9 g, 12.7 mmol). The suspension was agitated for 16 h. Upon completion of the reaction, the reaction mixture was filtered and rinsed with dichloromethane (4 × 10 mL) and concentrated in vacuo. Compound was purified on silica gel (30−50% ethyl acetate/hexanes with 5.0% methanol) to afford 3.72 g (87%) of product **39**. $^1$H NMR (DMSO-$d_6$) δ ppm 1.19 (t, 3H, $J$ = 7.12 Hz), 1.34 (s, 9H), 1.77−1.96 (m, 1H, $J$ = 7.79 Hz), 1.93−2.12 (m, 1H), 2.19−2.39 (m, 2H), 3.20−3.54 (m, 5H), 3.52−3.77 (m, 3H), 4.06 (q, 2H, $J$ = 6.98 Hz), 4.80−5.15 (m, 1H), 7.34−7.63 (m, 5H), 8.01−8.23 (m, 2H), 8.95 (d, 1H, $J$ = 8.06 Hz), 11.13 (s, 1H); HRMS calcd for $C_{28}H_{35}N_4O_7$ ($M^+$ + H) 541.2657, found 541.2628.

**Butyl 4-((2*S*)-5-*tert*-Butoxy-2-{[(4-hydroxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoyl)piperazine-1-carboxylate (40).** General procedure I afforded 11.5 g (74%) of product **40**. $^1$H NMR (DMSO-$d_6$) δ ppm 0.72−1.07 (m, 3H), 1.19−1.45 (m, 11H), 1.47−1.66 (m, 2H), 1.69−1.94 (m, 1H), 1.97−2.16 (m, 1H), 2.15−2.43 (m, 2H), 3.19−3.79 (m, 8H), 4.01 (t, 2H, $J$ = 6.44 Hz), 4.90−5.14 (m, 1H), 7.34−7.64 (m, 5H), 8.06−8.24 (m, 2H), 8.95 (d, 1H, $J$ = 8.32 Hz), 11.11 (s, 1H); HRMS calcd for $C_{30}H_{41}N_4O_7$ ($M^+$ + H) 569.2970, found 569.2957.

**Pentyl 4-((2*S*)-5-*tert*-Butoxy-2-{[(4-hydroxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoyl)piperazine-1-carboxylate (41).** General procedure I afforded 0.45 g (59%) of product **41**. $^1$H NMR (DMSO-$d_6$) δ ppm 0.84 (t, 3H), 1.15−1.41 (m, 13H), 1.44−1.65 (m, 2H), 1.72 1.89 (m, 1H), 1.90−2.11 (m, 1H), 2.16−2.36 (m, 2H), 3.05−3.70 (m, 8H), 3.97 (t, 2H, $J$ = 6.58 Hz), 4.84−5.16 (m, 1H), 7.23−7.62 (m, 5H), 7.99−8.21 (m, 2H), 8.91 (d, 1H, $J$ = 8.06 Hz), 11.10 (s, 1H); HRMS calcd for $C_{31}H_{43}N_4O_7$ ($M^+$ + H) 583.3126, found 583.3094.

**Hexyl 4-((2*S*)-5-*tert*-Butoxy-2-{[(4-hydroxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoyl)piperazine-1-carboxylate (42).** General procedure I afforded 1.35 g (71%) of product **42**. $^1$H NMR (DMSO-$d_6$) δ ppm 0.86 (t, 3H), 1.03−1.43 (m, 15H), 1.46−1.66 (m, 2H), 1.84 (d, 1H, $J$ = 6.98 Hz), 1.91−2.14 (m, 1H), 2.20−2.40 (m, 2H), 3.20−3.73 (m, 8H), 4.00 (t, 2H, $J$ = 6.71 Hz), 4.85−5.14 (m, 1H), 7.38−7.60 (m, 5H), 8.05−8.18 (m, 2H), 8.95 (d, 1H, $J$ = 8.32 Hz), 11.13 (s, 1H); HRMS calcd for $C_{32}H_{45}N_4O_7$ ($M^+$ + H) 597.3283, found 597.3276.

**Ethyl 4-[(2*S*)-5-*tert*-Butoxy-2-{[(4-chloro-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoyl]piperazine-1-carboxylate (43a).** General procedure I using 4-chloro-6-phenylpyridine-2-carboxylic acid **30** (0.68 g, 2.90 mmol), 1-hydroxybenzotriazole (3.68 g, 4.70 mmol), polymer-bound carbodiimide reagent **6** (1.3 mmol/g, 3.68 g, 4.70 mmol), ethyl 4-[(2*S*)-2-amino-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate **38a** (84 mg, 0.62 mmol), and *N*-methylmorpholine (1.0 mL, 9.1 mmol) to afford 0.98 g (61%) of product **43a**. $^1$H NMR ($CDCl_3$) δ ppm 1.26 (t, 3H, $J$ = 7.12 Hz), 1.43 (s, 9H), 1.89 (m, 1H), 2.14 (m, 1H), 2.34 (m, 2H), 3.58 (m, 8H), 4.15 (q, 2H, $J$ = 7.25 Hz), 5.20

(m, 1H), 7.49 (m, 3H), 7.85 (d, 1H, $J$ = 1.61 Hz), 8.03 (m, 2H), 8.09 (d, 1H, $J$ = 1.61 Hz), 8.86 (d, 1H, $J$ = 8.59 Hz).

**Butyl 4-[(2*S*)-5-*tert*-Butoxy-2-{[(4-chloro-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoyl]piperazine-1-carboxylate (43b).** General procedure I afforded 5.47 g (92%) of product **43b**. $^1$H NMR ($CDCl_3$) $\delta$ ppm 0.96 (t, 3H, $J$ = 7.25 Hz), 1.35−1.44 (m, 2H), 1.46 (s, 9H), 1.58−1.71 (m, 2H), 1.86−1.98 (m, 1H), 2.11−2.24 (m, 1H), 2.28−2.50 (m, 2H), 3.41−3.79 (m, 8H), 4.12 (t, 2H, $J$ = 6.58 Hz), 5.18−5.28 (m, 1H), 7.45−7.57 (m, 3H), 7.88 (d, 1H, $J$ = 1.88 Hz), 8.03−8.09 (m, 2H), 8.11 (d, 1H, $J$ = 1.88 Hz), 8.88 (d, 1H, $J$ = 8.59 Hz).

**Pentyl 4-((2*S*)-5-*tert*-Butoxy-2-{[(4-chloro-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoyl)piperazine-1-carboxylate (43c).** General procedure I afforded 12.2 g (96%) of product **43c**. $^1$H NMR ($CDCl_3$) $\delta$ ppm 0.89 (t, 3H, $J$ = 6.8 Hz), 1.21−1.40 (m, 4H), 1.42 (s, 9H), 1.59−1.66 (m, 2H), 1.85−1.91 (m, 1H), 2.11−2.43 (m, 3H), 3.42−3.69 (m, 8H), 4.08 (t, 2H, $J$ = 6.58 Hz), 5.17−5.22 (m, 1H), 7.43−7.52 (m, 3H), 7.84−8.08 (m, 4H), 8.90 (d, 1H, $J$ = 8.40 Hz); HRMS calcd for $C_{31}H_{41}ClN_4O_6$ ($M^+$ + H) 601.2787, found 601.2750.

**Hexyl 4-[(2*S*)-5-*tert*-Butoxy-2-{[(4-chloro-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoyl]piperazine-1-carboxylate (43d).** General procedure I afforded 8.02 g (65%) of product **43d**. $^1$H NMR ($CDCl_3$) $\delta$ ppm 0.84 0.96 (m, 3H), 1.26−1.43 (m, 6H), 1.46 (s, 9H), 1.56−1.72 (m, 2H), 1.84−2.00 (m, 1H), 2.11−2.25 (m, 1H), 2.27−2.51 (m, 2H), 3.39−3.81 (m, 8H), 4.11 (t, 2H, $J$ = 6.71 Hz), 5.15−5.29 (m, 1H), 7.46−7.57 (m, 3H), 7.88 (d, 1H, $J$ = 1.88 Hz), 8.04−8.08 (m, 2H), 8.12 (d, 1H, $J$ = 1.61 Hz), 8.88 (d, 1H, $J$ = 8.59 Hz).

**General Procedure J. Displacement of 4-Chloropyridines 43a−d with Amine 44.** A solution of the 4-chloropyridine intermediate **43** (0.09 M in DMSO) (2 mL, 0.18 mmol) was added to each secondary amine (0.80 mmol) or primary amine (2.0 mmol) in a vial, followed by the addition of triethylamine (with secondary amine, 0.1 mL, 0.72 mmol) (with primary amine, 0.3 mL, 2.2 mmol). The mixtures were agitated at 50−100 °C for 16−168 h until judged complete or no longer progressing by LC/MS analysis. The reaction solutions were concentrated in vacuo. If necessary, the residue was purified by HPLC.

**Deprotection of the *tert*-Butyl Ester Group.** A solution of 10% trifluoroacetic acid/dichloromethane solution (1.5 mL) was added to the *tert*-butyl ester agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The products were purified by HPLC to afford the pure products **45**−**48**.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-({[4-(methylamino)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (45a).** General procedure J afforded 33.0 mg (85%) of product **45a**. HRMS calcd for $C_{25}H_{31}N_5O_6$ ($M^+$ + H) 498.2347, found 498.2316.

**(4*S*)-4-({[4-(Dimethylamino)-6-phenylpyridin-2-yl]carbonyl}amino)-5-[4-(ethoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (45b).** General procedure J afforded 36.1 mg (82%) of product **45b**. HRMS calcd for $C_{26}H_{33}N_5O_6$ ($M^+$ + H) 512.2504, found 512.2512.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(propylamino)pyridin-2-yl]carbonyl}amino)pentanoic Acid (45c).** General procedure J afforded 101.7 mg (97%) of product **45c**. HRMS calcd for $C_{27}H_{35}N_5O_6$ ($M^+$ + H) 526.2660, found 526.2631.

**(4*S*)-4-({[4-(Dipropylamino)-6-phenylpyridin-2-yl]carbonyl}amino)-5-[4-(ethoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (45d).** General procedure J afforded 21.4 mg (19%) of product **45d**. HRMS calcd for $C_{30}H_{41}N_5O_6$ ($M^+$ + H) 568.3130, found 568.3120.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-[({4-[(2-hydroxyethyl)amino]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (45e).** General procedure J afforded 62.7 mg (75%) of product **45e**. HRMS calcd for $C_{26}H_{33}N_5O_7$ ($M^+$ + H) 528.2453, found 528.2477.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-[({4-[(2-hydroxyethyl)(methyl)amino]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (45f).** General procedure J afforded 41.7 mg (39%) of product **45f**. HRMS calcd for $C_{27}H_{35}N_5O_7$ ($M^+$ + H) 542.2609, found 542.2582.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-[({4-[(2-methoxyethyl)amino]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (45g).** General procedure J afforded 81.9 mg (76%) of product **45g**. HRMS calcd for $C_{27}H_{35}N_5O_7$ ($M^+$ + H) 542.2609, found 542.2574.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-{[(6-phenyl-4-piperidin-1-ylpyridin-2-yl)carbonyl]amino}pentanoic Acid (45i).** General procedure J afforded 103 mg (94%) of product **45i**. HRMS calcd for $C_{29}H_{37}N_5O_6$ ($M^+$ + H) 552.2817, found 552.2800.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-{[(4-morpholin-4-yl-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (45j).** General procedure J afforded 35.2 mg (75%) of product **45j**. HRMS calcd for $C_{28}H_{35}N_5O_7$ ($M^+$ + H) 554.2609, found 554.2628.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-({[4-(4-hydroxypiperidin-1-yl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (45k).** General procedure J afforded 83.2 mg (74%) of product **45k**. HRMS calcd for $C_{29}H_{37}N_5O_7$ ($M^+$ + H) 568.2766, found 568.2758.

**(4*S*)-4-({[4-(4-Aminopiperidin-1-yl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-[4-(ethoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (45m).** General procedure J afforded 20.6 mg (56%) of product **45m**. HRMS calcd for $C_{29}H_{38}N_6O_6$ ($M^+$ + H) 567.2931, found 567.2927.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(4-pyrrolidin-1-ylpiperidin-1-yl)pyridin-2-yl]carbonyl}amino)pentanoic Acid (45p).** General procedure J afforded 33.2 mg (82%) of product **45p**. HRMS calcd for $C_{33}H_{44}N_6O_6$ ($M^+$ + H) 621.3400, found 621.3428.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-[({4-[4-(hydroxymethyl)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (45r).** General procedure J afforded 60.2 mg (52%) of product **45r**. HRMS calcd for $C_{30}H_{39}N_5O_7$ ($M^+$ + H) 582.2922, found 582.2940.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-[({4-[4-(methoxymethyl)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (45s).** General procedure J afforded 91.7 mg (78%) of product **45s**. HRMS calcd for $C_{31}H_{41}N_5O_7$ ($M^+$ + H) 596.3079, found 596.3062.

**(4*S*)-4-[({4-[4-(Aminomethyl)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-[4-(ethoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (45u).** General procedure J afforded 93.8 mg (82%) of product **45u**. HRMS calcd for $C_{30}H_{40}N_6O_6$ ($M^+$ + H) 581.3082, found 581.3080.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-[({4-[(2-methoxyethyl)amino]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (46g).** General procedure J afforded 46.1 mg (67%) of product **46g**. HRMS calcd for $C_{29}H_{39}N_5O_7$ ($M^+$ + H) 570.2928, found 570.2953.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-[({4-[(2-methoxyethyl)(methyl)amino]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (46h).** General procedure J afforded 62.5 mg (90%) of product **46h**. HRMS calcd for $C_{30}H_{41}N_5O_7$ ($M^+$ + H) 584.3084, found 584.3068.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-morpholin-4-yl-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (46j).** General procedure J afforded 54.6 mg (78%) of product **46j**. HRMS calcd for $C_{30}H_{39}N_5O_7$ ($M^+$ + H) 582.2928, found 582.2923.

**(4*S*)-4-({[4-(4-Aminopiperidin-1-yl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-[4-(butoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (46m).** General procedure J afforded 18 mg (%) of product **46m**. HRMS calcd for $C_{31}H_{42}N_6O_6$ ($M^+$ + H) 595.3244, found 595.3206.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-[({4-[4-(methylamino)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (46n).** General procedure J afforded 107.6 mg (100%) of product **46n**. HRMS calcd for $C_{32}H_{44}N_6O_6$ ($M^+ + H$) 609.3400, found 609.3439.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-[({4-[4-(dimethylamino)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (46o).** General procedure J afforded 33.8 mg (46%) of product **46o**. HRMS calcd for $C_{33}H_{46}N_6O_6$ ($M^+ + H$) 623.3557, found 623.3586.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(4-pyrrolidin-1-ylpiperidin-1-yl)pyridin-2-yl]carbonyl}amino)-pentanoic Acid (46p).** General procedure A afforded 31.6 mg (63%) of product **46p**. HRMS calcd for $C_{35}H_{48}N_6O_6$ ($M^+ + H$) 649.3713, found 649.3708.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{4-[(methylamino)methyl]piperidin-1-yl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (46v).** General procedure J afforded 92.7 mg (100%) of product **46v**. HRMS calcd for $C_{33}H_{46}N_6O_6$ ($M^+ + H$) 623.3552, found 623.3560.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{4-[(dimethylamino)methyl]piperidin-1-yl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (46w).** General procedure J afforded 46.5 mg (77%) of product **46w**. HRMS calcd for $C_{34}H_{48}N_6O_6$ ($M^+ + H$) 637.3708, found 637.3684.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-[({6-phenyl-4-[4-(pyrrolidin-1-ylmethyl)piperidin-1-yl]pyridin-2-yl}carbonyl)amino]pentanoic Acid (46x).** General procedure J afforded 86.1 mg (100%) of product **46x**. HRMS calcd for $C_{36}H_{50}N_6O_6$ ($M^+ + H$) 663.3870, found 663.3882.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-({[6-phenyl-4-(propylamino)pyridin-2-yl]carbonyl}amino)pentanoic Acid (47c).** General procedure J afforded 59.1 mg (26%) of product **47c**. HRMS calcd for $C_{30}H_{41}N_5O_6$ ($M^+ + H$) 568.3130, found 568.3130.

**(4*S*)-4-[({4-[(2-Hydroxyethyl)amino]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-pentanoic Acid (47e).** General procedure J afforded 420 mg (74%) of product **47e**. HRMS calcd for $C_{29}H_{39}N_5O_7$ ($M^+ + H$) 570.2922, found 570.2940.

**(4*S*)-4-[({4-[(2-Methoxyethyl)amino]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-pentanoic Acid (47g).** General procedure J afforded 144.0 mg (56%) of product **47g**. HRMS calcd for $C_{30}H_{41}N_5O_7$ ($M^+ + H$) 584.3079, found 584.3070.

**(4*S*)-4-[({4-[(2-Methoxyethyl)(methyl)amino]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (47h).** General procedure J afforded 55 mg (77%) of product **47h**. HRMS calcd for $C_{31}H_{43}N_5O_7$ ($M^+ + H$) 598.3240, found 598.3252.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-{[(6-phenyl-4-piperidin-1-ylpyridin-2-yl)carbonyl]amino}pentanoic Acid (47i).** General procedure J afforded 54.2 mg (23%) of product **47i**. HRMS calcd for $C_{32}H_{43}N_5O_6$ ($M^+ + H$) 594.3286, found 594.3280.

**(4*S*)-4-({[4-(4-Hydroxypiperidin-1-yl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-pentanoic Acid (47k).** General procedure J afforded 93.6 mg (65%) of product **47k**. HRMS calcd for $C_{32}H_{43}N_5O_7$ ($M^+ + H$) 610.3213, found 610.3235.

**(4*S*)-4-({[4-(4-Methoxypiperidin-1-yl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-pentanoic Acid (47l).** General procedure J afforded 68.6 mg (47%) of product **47l**. HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+ + H$) 624.3392, found 624.3388.

**(4*S*)-4-({[4-(4-Aminopiperidin-1-yl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-pentanoic Acid (47m).** General procedure J afforded 97.7 mg (68%) of product **47m**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.84 (t, 3H), 1.26 (m, 4H), 1.46−1.57 (m, 4H), 1.80 (m, 1H), 1.94−2.04 (m, 3H), 2.28 (m, 2H), 3.05 (t, 2H), 3.33−3.99 (m, 10H), 3.97 (t, 2H), 4.18 (d, 2H), 4.99 (m, 1H), 7.43−7.51 (m, 5H), 7.91 (d, 2H), 8.12 (d, 2H), 8.98 (d, 2H); HRMS calcd for $C_{32}H_{44}N_6O_6$ ($M^+ + H$) 609.3395, found 609.3361.

**(4*S*)-4-[({4-[4-(Methylamino)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (47n).** General procedure J afforded 64.2 mg (58%) of product **47n**. HRMS calcd for $C_{33}H_{46}N_6O_6$ ($M^+ + H$) 623.3552, found 623.3531.

**(4*S*)-4-[({4-[4-(Dimethylamino)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (47o).** General procedure J afforded 40.2 mg (27%) of product **47o**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.86 (t, 3H), 1.28 (m, 4H), 1.56 (m, 2H), 2.05 (m, 4H), 2.29 (m, 2H), 2.68 (m, 1H), 2.74 (s, 3H), 2.76 (s, 3H), 2.98 (t, 2H), 3.38−3.64 (m, 10H), 3.99 (t, 2H), 4.30 (m, 2H), 5.00 (m, 1H), 7.47−7.53 (m, 5H), 8.16 (d, 2H), 8.97 (d, 1H); HRMS calcd for $C_{34}H_{48}N_6O_6$ ($M^+ + H$) 637.3708, found 637.3721.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-({[6-phenyl-4-(4-pyrrolidin-1-ylpiperidin-1-yl)pyridin-2-yl]carbonyl}-amino)pentanoic Acid (47p).** General procedure J afforded 66.4 mg (57%) of product **47p**. HRMS calcd for $C_{36}H_{50}N_6O_6$ ($M^+ + H$) 663.3865, found 663.3860.

**(4*S*)-4-({[4-(4-Morpholin-4-ylpiperidin-1-yl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (47q).** General procedure J afforded 31.2 mg (26.2%) of product **47q**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.84 (t, 3H), 1.26 (m, 4H), 1.54 (m, 4H), 1.48−1.65 (m, 4H), 1.81 (m, 1H), 1.97−2.31 (m, 6H), 2.92−3.15 (m, 6H), 3.29−3.68 (m, 12H), 3.97 (t, 2H), 4.30 (m, 2H), 4.99 (m, 1H), 7.44−7.51 (m, 5H), 8.14 (d, 2H), 8.96 (d, 1H); HRMS calcd for $C_{36}H_{50}N_6O_7$ ($M^+ + H$) 679.3814, found 679.3828.

**(4*S*)-4-[({4-[4-(Hydroxymethyl)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (47r).** General procedure J afforded 17 mg (45%) of product **47r**. HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+ + H$) 624.3397, found 624.3342.

**(4*S*)-4-[({4-[4-(Methoxymethyl)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (47s).** General procedure J afforded 60 mg (40%) of product **47s**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.84 (t, 3H), 1.14−1.28 (m, 6H), 1.54 (m, 2H), 1.71−1.85 (m, 4H), 2.01 (m, 1H), 2.93 (t, 2H), 3.17 (d, 2H), 3.20 (s, 3H), 3.37−3.63 (m, 8H), 3.97 (t, 2H), 4.10 (m, 2H), 5.00 (m, 1H), 7.37−7.49 (m, 5H), 8.14 (d, 2H), 8.83 (d, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 14.27, 22.21, 27.99, 28.30, 28.58, 29.20, 31.83, 35.96, 41.79, 44.96, 46.34, 48.99, 58.57, 65.40, 77.03, 105.23, 106.64, 127.26, 128.94, 129.42, 139.14, 150.44, 155.05, 156.29, 156.61, 164.37, 170.42, 175.65; HRMS calcd for $C_{34}H_{47}N_5O_7$ ($M^+ + H$) 638.3548, found 638.3529; mp = 173 °C. Optical rotation: $[\alpha]_D^{25}$ +32.1° (*c* 0.01 M, MeOH).

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-[({6-phenyl-4-[4-(propoxymethyl)piperidin-1-yl]pyridin-2-yl}carbonyl)-amino]pentanoic Acid (47t).** General procedure J afforded 30 mg (39%) of product **47t**. HRMS calcd for $C_{36}H_{52}N_5O_7$ ($M^+ + H$) 666.3861, found 666.3843.

**(4*S*)-4-[({4-[4-(Aminomethyl)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (47u).** General procedure J afforded 109.2 mg (74%) of product **47u**. HRMS calcd for $C_{33}H_{46}N_6O_6$ ($M^+ + H$) 632.3552, found 623.3549.

**(4*S*)-4-{[(4-{4-[(Methylamino)methyl]piperidin-1-yl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]-piperazin-1-yl}pentanoic Acid (47v).** General procedure J afforded 40.2 mg (67%) of product **47v**. HRMS calcd for $C_{34}H_{48}N_6O_6$ ($M^+ + H$) 637.3708, found 637.3695.

**(4*S*)-4-{[(4-{4-[(Dimethylamino)methyl]piperidin-1-yl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]-zpiperazin-1-yl}pentanoic Acid (47w).** General procedure J afforded 27.6 mg (45%) of product **47w**. HRMS calcd for $C_{35}H_{50}N_6O_6$ ($M^+ + H$) 651.3865, found 651.3875.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-[({6-phenyl-4-[4-(pyrrolidin-1-ylmethyl)piperidin-1-yl]pyridin-2-yl}carbonyl)amino]pentanoic Acid (47x).** General procedure J afforded 84.7 mg (100%) of product **47x**. HRMS calcd for $C_{37}H_{52}N_6O_6$ ($M^+ + H$) 677.4026, found 677.4036.

**(4*S*)-5-{4-[(Hexyloxy)carbonyl]piperazin-1-yl}-4-[({4-[(2-methoxyethyl)amino]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (48g).** General procedure J afforded 219.7 mg (83%) of product **48g**. HRMS calcd for $C_{31}H_{43}N_5O_7$ ($M^+ + H$) 598.3235, found 598.3260.

**(4*S*)-4-({[4-(4-Aminopiperidin-1-yl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-{4-[(hexyloxy)carbonyl]piperazin-1-yl}-5-oxopentanoic Acid (48m).** General procedure J afforded 18.9 mg (47%) of product **48m**. HRMS calcd for $C_{33}H_{46}N_6O_6$ ($M^+ + H$) 623.3557, found 623.3551.

**(4*S*)-5-{4-[(Hexyloxy)carbonyl]piperazin-1-yl}-5-oxo-4-({[6-phenyl-4-(4-pyrrolidin-1-ylpiperidin-1-yl)pyridin-2-yl]carbonyl}amino)-pentanoic Acid (48p).** General procedure J afforded 31.4 mg (71%) of product **48p**. HRMS calcd for $C_{37}H_{52}N_6O_6$ ($M^+ + H$) 677.4026, found 677.3999.

**(4*S*)-5-{4-[(Hexyloxy)carbonyl]piperazin-1-yl}-4-[({4-[4-(methoxymethyl)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (48s).** General procedure J afforded 110 mg (48%) of product **48s**. HRMS calcd for $C_{35}H_{49}N_5O_7$ ($M^+ + H$) 652.3705, found 652.3706.

**(4*S*)-4-[({4-[4-(Aminomethyl)piperidin-1-yl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-{4-[(hexyloxy)carbonyl]piperazin-1-yl}-5-oxopentanoic Acid (48u).** General procedure J afforded 150.3 mg (66%) of product **48u**. HRMS calcd for $C_{34}H_{48}N_6O_6$ ($M^+ + H$) 637.3708, found 637.3723.

**General Procedure K. Alkylation of the 4-Hydroxypyridine Intermediates 39−42.** To a 2 dram vial with 4-hydroxypyridine intermediates **39**−**42** (0.20 mmol) dissolved in dimethylformamide (1 mL) were added cesium carbonate (0.13 g, 0.4 mmol), a catalytic amount of potassium iodide, and electrophile **49** (0.40 mmol). The mixtures were stirred at 50−100 °C for 1−16 h until judged complete. The mixtures were filtered, dried in vacuo, and purified by HPLC if necessary.

**Deprotection of the *tert*-Butyl Ester Group**. A solution of 10% trifluoroacetic acid/dichloromethane solution (2.0 mL) was added to the *tert*-butyl ester (∼0.20 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The products were purified by HPLC to afford pure products **50**−**53**.

**General Procedure L. Mitsunobu Reaction with 4-Hydroxypyridines 39−42.** To a 2 dram vial with 4-hydroxypyridine intermediates **39**−**42** (0.5 mmol) dissolved in anhydrous tetrahydrofuran (2 mL) were added the alcohol **24** (1.0 mmol) and triphenylphosphine (0.26 g, 1.0 mmol). The mixtures were chilled to 5 °C, and diethylazodicarboxylate (158 $\mu$L, 1.0 mmol) was added dropwise. The mixtures were stirred at ambient temperature for 1−24 h, solvents were evaporated, and the residue was purified by HPLC if necessary.

**Deprotection of the *tert*-Butyl Ester Group**. A solution of 10% trifluoroacetic acid/dichloromethane solution (2.0 mL) was added to the *tert*-butyl ester (∼0.20 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The crude products were purified by HPLC to afford pure products **50**−**53**.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-{[(4-hydroxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (50a).** General procedure B afforded 57 mg (55%) of product **50a**. HRMS calcd for $C_{24}H_{28}N_4O_7$ ($M^+ + H$) 485.2031, found 485.1991.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-{[(4-methoxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (50b).** General procedure K afforded 78 mg (73%) of product **50b**. HRMS calcd for $C_{25}H_{30}N_4O_7$ ($M^+ + H$) 499.2187, found 499.2198.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-{[(4-ethoxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (50c).** General procedure K afforded 89 mg (81%) of product **50c**. HRMS calcd for $C_{26}H_{32}N_4O_7$ ($M^+ + H$) 513.2344, found 513.2350.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-{[(6-phenyl-4-propoxypyridin-2-yl)carbonyl]amino}pentanoic Acid (50d).** General procedure K afforded 90 mg (95%) of product **50d**. HRMS calcd for $C_{27}H_{34}N_4O_7$ ($M^+ + H$) 527.2500, found 527.2460.

**(4*S*)-4-{[(4-Butoxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-[4-(ethoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (50e).** General procedure K afforded 52 mg (93%) of product **50e**. HRMS calcd for $C_{28}H_{36}N_4O_7$ ($M^+ + H$) 541.2657, found 541.2635.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-({[4-(2-hydroxyethoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (50f).** General procedure K afforded 93 mg (82%) of product **50f**. HRMS calcd for $C_{26}H_{32}N_4O_8$ ($M^+ + H$) 529.2293, found 529.2271.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-({[4-(3-hydroxypropoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (50g).** General procedure K afforded 65 mg (56%) of product **50g**. HRMS calcd for $C_{27}H_{34}N_4O_8$ ($M^+ + H$) 543.2449, found 543.2431.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-({[4-(4-hydroxybutoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (50h).** General procedure K afforded 49 mg (96%) of product **50h**. HRMS calcd for $C_{28}H_{36}N_4O_8$ ($M^+ + H$) 557.2606, found 557.2585.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-({[4-(2-methoxyethoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (50i).** General procedure K afforded 86 mg (74%) of product **50i**. HRMS calcd for $C_{27}H_{34}N_4O_8$ ($M^+ + H$) 543.2449, found 543.2476.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-4-({[4-(3-methoxypropoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (50j).** General procedure K afforded 80 mg (96%) of product **50j**. HRMS calcd for $C_{28}H_{36}N_4O_8$ ($M^+ + H$) 557.2606, found 557.2592.

**(4*S*)-4-({[4-(2-Aminoethoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-[4-(ethoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (50m).** General procedure K afforded 95 mg (91%) of product **50m**. HRMS calcd for $C_{26}H_{33}N_5O_7$ ($M^+ + H$) 528.2453, found 528.2497.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(piperidin-4-yloxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (50n).** General procedure K afforded 29 mg (91%) of product **50n**. HRMS calcd for $C_{29}H_{37}N_5O_7$ ($M^+ + H$) 568.2766, found 568.2727.

**(4*S*)-5-[4-(Ethoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(piperidin-4-ylmethoxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (50q).** General procedure K afforded 99 mg (88%) of product **50q**. HRMS calcd for $C_{30}H_{39}N_5O_7$ ($M^+ + H$) 582.2922, found 582.2894.

**(4*S*)-4-({[4-(Benzyloxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-[4-(ethoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (50w).** General procedure K afforded 99 mg (99%) of product **50w**. HRMS calcd for $C_{31}H_{34}N_4O_7$ ($M^+ + H$) 575.2500, found 575.2496.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-hydroxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (51a).** General procedure B afforded 41 mg (80%) of product **51a**. HRMS calcd for $C_{26}H_{33}N_4O_7$ ($M^+ + H$) 513.2344, found 513.2318.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-butoxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (51e).** General procedure K afforded 86 mg (71%) of product **51e**. HRMS calcd for $C_{30}H_{40}N_4O_7$ ($M^+ + H$) 569.2970, found 569.2990.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-({[4-(2-hydroxyethoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (51f).** General procedure K afforded 53 mg (100%) of product **51f**. HRMS calcd for $C_{28}H_{36}N_4O_8$ ($M^+ + H$) 557.2606, found 557.2600.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-({[4-(3-hydroxypropoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (51g).** General procedure K afforded 38.1 mg (31%) of product **51g**. HRMS calcd for $C_{29}H_{38}N_4O_8$ ($M^+ + H$) 571.2762, found 571.2798.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-({[4-(4-hydroxybutoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (51h).** General procedure K afforded 31.6 mg (25%) of product **51h**. HRMS calcd for $C_{30}H_{40}N_4O_8$ ($M^+ + H$) 585.2919, found 585.2952.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-({[4-(2-methoxyethoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (51i).** General procedure K afforded 17 mg (70%) of product **51i**. HRMS calcd for $C_{29}H_{38}N_4O_8$ ($M^+ + H$) 571.2762, found 571.2728.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-({[4-(3-methoxypropoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (51j).** General procedure K afforded 95.4 mg (55%) of product **51j**. HRMS calcd for $C_{30}H_{40}N_4O_8$ ($M^+ + H$) 585.2919, found 585.2922.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(tetrahydro-2*H*-pyran-4-yloxy)pyridin-2-yl]carbonyl}amino)-pentanoic Acid (51k).** General procedure L afforded 85 mg (100%) of product **51k**. HRMS calcd for $C_{31}H_{40}N_4O_8$ ($M^+ + H$) 597.2919, found 597.2925.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(tetrahydro-2*H*-pyran-4-ylmethoxy)pyridin-2-yl]carbonyl}-amino)pentanoic Acid (51l).** General procedure L afforded 84 mg (100%) of product **51l**. HRMS calcd for $C_{32}H_{42}N_4O_8$ ($M^+ + H$) 611.3081, found 611.3052.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(piperidin-4-yloxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (51n).** General procedure K afforded 34 mg (58%) of product **51n**. HRMS calcd for $C_{31}H_{41}N_5O_7$ ($M^+ + H$) 596.3079, found 596.3246.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(piperidin-3-yloxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (51o).** General procedure L afforded 63 mg (100%) of product **51o**. HRMS calcd for $C_{31}H_{41}N_5O_7$ ($M^+ + H$) 596.3082, found 596.3075.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(pyrrolidin-3-yloxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (51p).** General procedure L afforded 33 mg (35%) of product **51p**. HRMS calcd for $C_{30}H_{39}N_5O_7$ ($M^+ + H$) 582.2922, found 582.2921.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(piperidin-4-ylmethoxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (51q).** General procedure K afforded 109.2 mg (85%) of product **51q**. HRMS calcd for $C_{32}H_{43}N_5O_7$ ($M^+ + H$) 610.3235, found 610.3191.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(piperidin-3-ylmethoxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (51r).** General procedure L afforded 118 mg (100%) of product **51r**. HRMS calcd for $C_{32}H_{43}N_5O_7$ ($M^+ + H$) 610.3240, found 610.3259.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(piperidin-2-ylmethoxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (51s).** General procedure L afforded 14.7 mg (81%) of product **51s**. HRMS calcd for $C_{32}H_{43}N_5O_7$ ($M^+ + H$) 610.3240, found 610.3226.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(2-piperidin-4-ylethoxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (51t).** General procedure L afforded 119 mg (100%) of product **51t**. HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+ + H$) 624.3397, found 624.3410.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(2-piperidin-3-ylethoxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (51u).** General procedure L afforded 107 mg (100%) of product **51u**. HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+ + H$) 624.3392, found 624.3389.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-({[6-phenyl-4-(2-piperidin-2-ylethoxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (51v).** General procedure L afforded 112 mg (100%) of product **51v**. HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+ + H$) 624.3392, found 624.3401.

**(4*S*)-4-{[(4-Hydroxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (52a).** General procedure B afforded 52 mg (92%) of product **52a**. HRMS calcd for $C_{27}H_{34}N_4O_7$ ($M^+ + H$) 527.2500, found 527.25500.

**(4*S*)-4-{[(4-Ethoxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (52c).** General procedure K afforded 38 mg (32%) of product **52c**. HRMS calcd for $C_{29}H_{38}N_4O_7$ ($M^+ + H$) 555.2813, found 555.2801.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-{[(6-phenyl-4-propoxypyridin-2-yl)carbonyl]amino}pentanoic Acid (52d).** General procedure K afforded 102.6 mg (85%) of product **52d**. HRMS calcd for $C_{30}H_{40}N_4O_7$ ($M^+ + H$) 569.2970, found 569.2970.

**(4*S*)-4-{[(4-Butoxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (52e).** General procedure K afforded 39.0 mg (95%) of product **52e**. HRMS calcd for $C_{31}H_{42}N_4O_7$ ($M^+ + H$) 583.3126, found 583.3118.

**(4*S*)-4-({[4-(2-Hydroxyethoxy)-6-phenylpyridin-2-yl]carbonyl}-amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (52f).** General procedure K afforded 64 mg (70%) of product **52f**. HRMS calcd for $C_{29}H_{38}N_4O_8$ ($M^+ + H$) 571.2762, found 571.2790.

**(4*S*)-4-({[4-(2-Methoxyethoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (52i).** General procedure K afforded 63 mg (68%) of product **52i**. HRMS calcd for $C_{30}H_{40}N_4O_8$ ($M^+ + H$) 585.2919, found 585.2880.

**(4*S*)-4-({[4-(2-Aminoethoxy)-6-phenylpyridin-2-yl]carbonyl}-amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (52m).** General procedure K afforded 90.1 mg (74%) of product **52m**. HRMS calcd for $C_{29}H_{39}N_5O_7$ ($M^+ + H$) 570.2922, found 570.2887.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-({[6-phenyl-4-(piperidin-4-yloxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (52n).** General procedure K afforded 26 mg (62%) of product **52n**. HRMS calcd for $C_{32}H_{43}N_5O_7$ ($M^+ + H$) 610.3235, found 610.3180.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-({[6-phenyl-4-(piperidin-4-ylmethoxy)pyridin-2-yl]carbonyl}amino)-pentanoic Acid (52q).** General procedure K afforded 133.5 mg (100%) of product **52q**. HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+ + H$) 624.3392, found 624.3355.

**(4*S*)-5-{4-[(Hexyloxy)carbonyl]piperazin-1-yl}-4-{[(4-hydroxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (53a).** General procedure B afforded 45 mg (79%) of product **53a**. HRMS calcd for $C_{28}H_{36}N_4O_7$ ($M^+ + H$) 541.2657, found 541.2660.

**(4*S*)-4-{[(4-Butoxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-{4-[(hexyloxy)carbonyl]piperazin-1-yl}-5-oxopentanoic Acid (53e).** General procedure K afforded 35 mg (43%) of product **53e**. HRMS calcd for $C_{32}H_{44}N_4O_7$ ($M^+ + H$) 597.3283, found 597.3283.

**(4*S*)-5-{4-[(Hexyloxy)carbonyl]piperazin-1-yl}-4-({[4-(2-hydroxyethoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (53f).** General procedure K afforded 46 mg (99%) of product **53f**. HRMS calcd for $C_{30}H_{40}N_4O_8$ ($M^+ + H$) 585.2919, found 585.2900.

**(4*S*)-5-{4-[(Hexyloxy)carbonyl]piperazin-1-yl}-4-({[4-(2-methoxyethoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (53i).** General procedure K afforded 13 mg (100%) of product **53i**. HRMS calcd for $C_{31}H_{42}N_4O_8$ ($M^+ + H$) 599.3075, found 599.3040.

**(4*S*)-4-({[4-(2-Aminoethoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-{4-[(hexyloxy)carbonyl]piperazin-1-yl}-5-oxopentanoic Acid (53m).** General procedure K afforded 92.9 mg (75%) of product **53m**. HRMS calcd for $C_{30}H_{41}N_5O_7$ ($M^+ + H$) 584.3079, found 584.3101.

**(4*S*)-5-{4-[(Hexyloxy)carbonyl]piperazin-1-yl}-5-oxo-4-({[6-phenyl-4-(piperidin-4-yloxy)pyridin-2-yl]carbonyl}amino)pentanoic Acid (53n).** General procedure K afforded 22 mg (36%) of product **53n**. HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+ + H$) 624.3392, found 624.3356.

**(4*S*)-5-{4-[(Hexyloxy)carbonyl]piperazin-1-yl}-5-oxo-4-({[6-phenyl-4-(piperidin-4-ylmethoxy)pyridin-2-yl]carbonyl}amino)-pentanoic Acid (53q).** General procedure K afforded 73.9 mg (55%) of product **53q**. HRMS calcd for $C_{34}H_{47}N_5O_7$ ($M^+ + H$) 638.3548, found 638.3539.

**General Procedure M. Method A: Preparation of 4-Pyridine-carbamates 56 and 57.** To a 2 dram vial with carbamoyl chlorides **54** (0.40 mmol) were added the 4-hydroxypyridine intermediate **40** or **41** (0.5 M in dichloromethane) (3 mL, 0.15 mmol) and triethylamine (112 uL, 0.80 mmol). The mixtures were stirred at room temperature for 18 h. If judged incomplete, the mixture continued to be stirred at 35 °C until complete. The solvents were evaporated, and if necessary the residue was purified by HPLC.

**Deprotection of the *tert*-Butyl Ester Group**. A solution of 10% trifluoroacetic acid/dichloromethane solution (2.0 mL) was added to the *tert*-butyl ester (~0.15 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The products were purified by HPLC to afford the pure products **56**−**57**.

**General Procedure M. Method B: Preparation of 4-Carbamates 56 and 57.** To a mixture of 4-hydroxypyridine intermediate **40** or **41** (2.79 g, 4.8 mmol) and triethylamine (2.04 mL, 27.8 mmol) in dichloromethane (48 mL) was added 4-nitrophenyl chloroformate **55** (1.06 g, 5.3 mmol). The mixture was stirred at room temperature for 1 h. An aliquot of the 4-nitrophenylcarbonate intermediate (0.1 M reaction mixture) (2 mL, ~0.2 mmol) was added to a 2 dram vial with amine **44** (0.60 mmol). The mixture was stirred at ambient temperature for 1 h, solvents were evaporated, and the residue was purified by HPLC if necessary.

**Deprotection of the *tert*-Butyl Ester Group**. A solution of 10% trifluoroacetic acid/dichloromethane solution (2.0 mL) was added to the *tert*-butyl ester (~0.22 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The products were purified by HPLC to afford the pure products **56** and **57**.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[(dimethylamino)carbonyl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (56a).** General procedure M, method B, afforded 12.6 mg (13%) of product **56a**. HRMS calcd for $C_{29}H_{37}N_5O_8$ ($M^+ + H$) 584.2715, found 584.2720.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-({[4-({[methyl(tetrahydro-2H-pyran-4-ylmethyl)amino]carbonyl}oxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (56b).** General procedure M, method B, afforded 41.1 mg (38%) of product **56b**. HRMS calcd for $C_{34}H_{45}N_5O_9$ ($M^+ + H$) 668.3290, found 668.3319.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-({[4-({[methyl(tetrahydrofuran-3-yl)amino]carbonyl}oxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (56c).** General procedure M, method B, afforded 42.8 mg (41%) of product **56c**. HRMS calcd for $C_{32}H_{41}N_5O_9$ ($M^+ + H$) 640.2977, found 640.2940.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-[({4-[(morpholin-4-ylcarbonyl)oxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (56f).** General procedure M, method B, afforded 19.4 mg (19%) of product **56f**. HRMS calcd for $C_{31}H_{39}N_5O_9$ ($M^+ + H$) 626.2821, found 626.2820.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-({[4-({[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl}oxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxopentanoic Acid (56g).** General procedure M, method B, afforded 27.8 mg (26%) of product **56g**. HRMS calcd for $C_{32}H_{41}N_5O_9$ ($M^+ + H$) 640.2977, found 640.2971.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[(4-ethoxypiperidin-1-yl)carbonyl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (56h).** General procedure M, method B, afforded 37.6 mg (34%) of product **56h**. HRMS calcd for $C_{34}H_{45}N_5O_9$ ($M^+ + H$) 668.3290, found 668.3249.

**(4*S*)-4-{[(4-{[(Dimethylamino)carbonyl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (57a).** General procedure M, method A, afforded 23.6 mg (17%) of product **57a**. HRMS calcd for $C_{30}H_{39}N_5O_8$ ($M^+ + H$) 598.2871, found 598.2846.

**(4*S*)-4-({[4-({[Methyl(tetrahydro-2*H*-pyran-4-ylmethyl)amino]carbonyl}oxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (57b).** General procedure M, method B, afforded 36.3 mg (30%) of product **57b**. HRMS calcd for $C_{35}H_{47}N_5O_9$ ($M^+ + H$) 682.3447, found 382.3448.

**(4*S*)-4-({[4-({[Methyl(tetrahydrofuran-3-yl)amino]carbonyl}oxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (57c).** General procedure M, method B, afforded 48.8 mg (42%) of product **57c**. HRMS calcd for $C_{33}H_{43}N_5O_9$ ($M^+ + H$) 654.3134, found 654.3130.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-[({6-phenyl-4-[(pyrrolidin-1-ylcarbonyl)oxy]pyridin-2-yl}carbonyl)amino]pentanoic Acid (57d).** General procedure M, method A, afforded 60.9 mg (41%) of product **57d**. HRMS calcd for $C_{32}H_{41}N_5O_8$ ($M^+ + H$) 624.3028, found 624.3063.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-[({6-phenyl-4-[(piperidin-1-ylcarbonyl)oxy]pyridin-2-yl}carbonyl)amino]-pentanoic Acid (57e).** General procedure M, method A, afforded 46.2 mg (31%) of product **57e**. HRMS calcd for $C_{33}H_{43}N_5O_8$ ($M^+ + H$) 638.3184, found 631.3191.

**(4*S*)-4-[({4-[(Morpholin-4-ylcarbonyl)oxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (57f).** General procedure M, method A, afforded 83.9 mg (56%) of product **57f**. HRMS calcd for $C_{32}H_{41}N_5O_9$ ($M^+ + H$) 640.2977, found 640.2988.

**(4*S*)-4-({[4-({[(3*S*)-3-Methoxypyrrolidin-1-yl]carbonyl}oxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)-carbonyl]piperazin-1-yl}pentanoic Acid (57g).** General procedure M, method A, afforded 37.1 mg (32%) of product **57g**. HRMS calcd for $C_{33}H_{43}N_5O_9$ ($M^+ + H$) 654.3134, found 654.3114.

**(4*S*)-4-{[(4-{[(4-Ethoxypiperidin-1-yl)carbonyl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]-piperazin-1-yl}pentanoic Acid (57h).** General procedure M, method B, afforded 27.3 mg (23%) of product **57h**. HRMS calcd for $C_{35}H_{47}N_5O_9$ ($M^+ + H$) 682.3447, found 682.3453.

**Butyl 4-[(2*S*)-2-({[4-({1-[(Benzyloxy)carbonyl]piperidin-4-yl}oxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate (60).** General procedure L afforded 1.5 g (77%) of product **60**. MS (ESI+) *m*/*z* 786 (M + H).

**Pentyl 4-[(2*S*)-2-({[4-({1-[(Benzyloxy)carbonyl]piperidin-4-yl}oxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate (61).** General procedure L afforded 287 mg (72%) of product **61**. HRMS calcd for $C_{44}H_{57}N_5O_9$ ($M^+ + H$) 800.4227, found 800.4224.

**Butyl 4-[(2*S*)-2-({[4-({1-[(Benzyloxy)carbonyl]piperidin-4-yl}methoxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate (62).** General procedure L afforded 1.0 g (52%) of product **62.** MS (ESI+) *m*/*z* 800 (M + H).

**Pentyl 4-[(2*S*)-2-({[4-({1-[(Benzyloxy)carbonyl]piperidin-4-yl}oxy)-6-phenylpyridin-2-yl]carbonyl}amino)-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate (63).** General procedure L afforded 1.33 g (77%) of product **63**. HRMS calcd for $C_{45}H_{59}N_5O_9$ ($M^+ + H$) 814.4386, found 814.4393.

**Butyl 4-[(2*S*)-5-*tert*-Butoxy-5-oxo-2-({[6-phenyl-4-(piperidin-4-yloxy)pyridin-2-yl]carbonyl}amino)pentanoyl]piperazine-1-carboxylate (64).** General procedure H afforded 1.2 g (98%) of product **64**. MS (ESI+) *m*/*z* 652 (M + H).

**Pentyl 4-[(2*S*)-5-*tert*-Butoxy-5-oxo-2-({[6-phenyl-4-(piperidin-4-yloxy)pyridin-2-yl]carbonyl}amino)pentanoyl]piperazine-1-carboxylate (65).** General procedure H afforded 196 mg (82%) of product **65**. HRMS calcd for $C_{36}H_{51}N_5O_7$ ($M^+ + H$) 666.3861, found 666.3881.

**Butyl 4-[(2*S*)-5-*tert*-Butoxy-5-oxo-2-({[6-phenyl-4-(piperidin-4-ylmethoxy)pyridin-2-yl]carbonyl}amino)pentanoyl]piperazine-1-carboxylate (66).** General procedure H afforded 830 mg (100%) of product **66.** MS (ESI+) *m*/*z* 666 (M + H).

**Pentyl 4-[(2*S*)-5-*tert*-Butoxy-5-oxo-2-({[6-phenyl-4-(piperidin-4-ylmethoxy)pyridin-2-yl]carbonyl}amino)pentanoyl]piperazine-1-carboxylate (67).** General procedure H afforded 507 mg (55%) of product **67**. HRMS calcd for $C_{37}H_{53}N_5O_7$ ($M^+ + H$) 680.4018, found 680.4305.

**General Procedure N. Reaction of Amines 64−67 with Electrophiles 68 To Afford Products 69−72.** A solution of the amine **64−67** (0.15 M in dichloromethane or dimethylformamide) (1 mL, 0.15 mmol) was added to each reaction well containing the electrophile **68** (0.30 mmol) (which included alkyl halides, chloroformates, acid chlorides, and sulfonyl chlorides). Triethylamine or *N*-methylmorpholine (0.75 mmol) and dichloromethane or dimethyl formamide (2 mL) were added to each reaction well. Mixtures in dichloromethane were agitated for 1 to several hours. Mixtures in dimethylformamide were heated to 75 °C and agitated for 1 to several hours. The product mixtures were evaporated to afford the *tert*-butyl ester product.

**Deprotection of the *tert*-Butyl Ester Group**. A solution of 10% trifluoroacetic acid/dichloromethane solution (1.5 mL) was added to the *tert*-butyl ester (∼0.15 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The products were purified by HPLC to afford pure products **69−72**.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-[({4-[(1-methylpiperidin-4-yl)oxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (69a).** General procedure N afforded 90 mg (92%) of product **69a**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.89 (t, 3H, $J$ = 7.50 Hz), 1.25−1.40 (m, 3H), 1.48−1.61 (m, 3H), 1.77−2.39 (m, 13H), 2.79 (s, 3H), 3.40−3.73 (m, 6H), 5.04 (s, 1H), 7.38−7.65 (m, 4H), 7.73 (d, 1H, $J$ = 16.84 Hz), 8.20 (d, 2H, $J$ = 7.32 Hz), 8.97 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{32}H_{43}N_5O_7$ ($M^+ +$ H) 610.3240, found 610.3195.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-[({4-[(1-isopropylpiperidin-4-yl)oxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (69b).** General procedure N afforded 28 mg (72%) of product **69b**. HRMS calcd for $C_{34}H_{47}N_5O_7$ ($M^+ + H$) 638.3548, found 638.3507.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (69c).** General procedure N afforded 41 mg (83%) of product **69c**. HRMS calcd for $C_{34}H_{47}N_5O_8$ ($M^+ + H$) 654.3497, found 654.3498.

**(4*S*)-4-[({4-[(1-Acetylpiperidin-4-yl)oxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-[4-(butoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (69d).** General procedure N afforded 113 mg (100%) of product **69d**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.88 (t, 3H, $J$ = 7.32 Hz), 1.26−1.41 (m, 2H) 1.47−1.76 (m, 6H), 1.76−2.13 (m, 9H), 2.24−2.39 (m, 2H), 3.36−3.76 (m, 8H), 3.84 (s, 1H), 5.03 (s, 1H), 7.41−7.64 (m, 4H), 7.70 (s, 1H), 8.20 (d, 2H, $J$ = 8.05 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{33}H_{43}N_5O_8$ ($M^+ + H$) 638.3190, found 638.3174.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-{[(6-phenyl-4-{[1-(trifluoroacetyl)piperidin-4-yl]oxy}pyridin-2-yl)carbonyl]amino}pentanoic Acid (69e).** General procedure N afforded 101 mg (100%) of product **69e**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.89 (t, 3H, $J$ = 7.32 Hz), 1.26−1.40 (m, 2H), 1.48−1.61 (m, 3H), 1.69−1.95 (m, 4H), 2.07 (d, 4H, $J$ = 9.52 Hz), 2.23−2.39 (m, 2H), 3.36−3.92 (m, 1 H), 4.01 (t, H, $J$ = 6.41 Hz), 4.92−5.22 (m, 1H), 7.37−7.66 (m, 4H), 7.72 (d, 1H, $J$ = 1.83 Hz), 8.20 (d, 2H, $J$ = 7.32 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{33}H_{40}F_3N_5O_8$ ($M^+ + H$) 692.2907, found 692.2881.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[1-(methoxyacetyl)piperidin-4-yl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (69f).** General procedure N afforded 86 mg (100%) of product **69f**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.88 (t, 3H, $J$ = 7.32 Hz), 1.26−1.42 (m, 3H), 1.48−1.77 (m, 7H), 1.79−2.15 (m, 7H), 2.23−2.40 (m, 3H), 3.36−3.73 (m, 7H), 3.78−3.93 (m, 1H), 4.01 (t, 2H, $J$ = 6.59 Hz), 4.10 (s, 3H), 5.04 (s, 1H), 7.39−7.63 (m, 4H), 7.71 (s, 1H), 8.20 (d, 2H, $J$ = 7.69 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{34}H_{45}N_5O_9$ ($M^+ + H$) 668.3290, found 668.3272.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[1-(ethoxycarbonyl)piperidin-4-yl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (69g).** General procedure N afforded 121 mg (100%) of product **69g**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.89 (t, 3H, $J$ = 7.32 Hz), 1.19 (t, 3H, $J$ = 7.14 Hz), 1.26−1.44 (m, 2H), 1.49−1.72 (m, 6H), 1.76−2.16 (m, 6H), 2.22−2.41 (m, 3H), 3.37−3.82 (m, 8H), 3.95−4.12 (m, 4H), 4.90−5.14 (m, 1H), 7.37−7.60 (m, 4H), 7.70 (d, 1H, $J$ = 2.20 Hz), 8.20 (d, 2H, $J$ = 7.32 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{34}H_{45}N_5O_9$ ($M^+ + H$) 668.3295, found 668.3322.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[1-(ethylsulfonyl)piperidin-4-yl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (69h).** General procedure N afforded 82 mg (100%) of product **69h**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.89 (t, 3H, $J$ = 7.32 Hz), 1.15−1.42 (m, 6H), 1.50−1.61 (m, 3H), 1.66−2.17 (m, 8H), 2.2 −2.41 (m, 3H), 3.09 (q, 2H, $J$ = 7.32 Hz), 3.36−3.78 (m, 8H), 4.01 (t, 2H, $J$ = 6.41 Hz), 4.89−5.13 (m, 1H), 7.35−7.61 (m, 4H), 7.71 (d, 1H, $J$ = 1.83 Hz), 8.20 (d, 2H, $J$ = 7.32 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{33}H_{45}N_5O_9S$ ($M^+ + H$) 688.3016, found 688.3040.

**(4*S*)-4-[({4-[(1-Methylpiperidin-4-yl)oxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (70a).** General procedure N afforded 36 mg (88%) of product **70a**. HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+ + H$) 624.3392, found 624.3416.

**(4*S*)-4-[({4-[(1-Isopropylpiperidin-4-yl)oxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (70b).** General procedure N afforded 43 mg (83%) of product **70b**. HRMS calcd for $C_{35}H_{49}N_5O_7$ ($M^+ + H$) 652.3705, found 652.3724.

**(4*S*)-4-{[(4-{[1-(2-Methoxyethyl)piperidin-4-yl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]-piperazin-1-yl}pentanoic Acid (70c).** General procedure N afforded 19 mg (79%) of product **70c**. HRMS calcd for $C_{35}H_{50}N_5O_8$ ($M^+ + H$) 668.3654, found 668.3632.

**(4*S*)-4-[({4-[(1-Acetylpiperidin-4-yl)oxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (70d).** General procedure N afforded 20 mg (18%) of product **70d**. HRMS calcd for $C_{34}H_{45}N_5O_8$ ($M^+ + H$) 652.3341, found 652.3336.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-{[(6-phenyl-4-{[1-(trifluoroacetyl)piperidin-4-yl]oxy}pyridin-2-yl)carbonyl]amino}pentanoic Acid (70e).** General procedure N afforded 85 mg (100%) of product **70e**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.87 (t, 3H, $J$ = 6.77 Hz), 1.19−1.37 (m, 5H), 1.50−1.64 (m, 2H), 1.67−1.94 (m, 4H), 1.99−2.18 (m, 4H), 2.22−2.40 (m, 2H), 3.36−3.72 (m, 8H), 3.86 (s, 2H), 4.00 (t, 2H, $J$ = 6.41 Hz), 4.94−5.21 (m, 1H), 7.41−7.66 (m, 4H), 7.72 (d, 1H, $J$ = 1.83

Hz), 8.20 (d, 2H, $J$ = 6.95 Hz), 8.97 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{34}H_{42}F_3N_5O_8$ ($M^+$ + H) 706.3063, found 706.3056.

**(4*S*)-4-{[(4-{[1-(Methoxyacetyl)piperidin-4-yl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (70f).** General procedure N afforded 80 mg (91%) of product **70f**. HRMS calcd for $C_{35}H_{47}N_5O_9$ ($M^+$ + H) 682.3447, found 682.3485.

**(4*S*)-4-{[(4-{[1-(Ethoxycarbonyl)piperidin-4-yl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (70g).** General procedure N afforded 120 mg (90%) of product **70g**. HRMS calcd for $C_{35}H_{47}N_5O_9$ ($M^+$ + H) 682.3447, found 682.3430.

**(4*S*)-4-{[(4-{[1-(Ethylsulfonyl)piperidin-4-yl]oxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (70h).** General procedure N afforded 113 mg (100%) of product **70h**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.86 (t, 3H, $J$ = 6.41 Hz), 1.13−1.36 (m, 9H), 1.49−1.64 (m, 3H), 1.68−1.94 (m, 5H), 2.06 (d, 5H, $J$ = 7.69 Hz), 2.21−2.37 (m, 4H), 3.08 (q, 1H, $J$ = 7.32 Hz), 3.36−3.73 (m, 5H), 4.00 (t, 2H, $J$ = 6.59 Hz), 4.90−5.11 (m, 1H), 7.36−7.61 (m, 4H), 7.71 (s, 1H), 8.20 (d, 2H, $J$ = 7.69 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{34}H_{47}N_5O_9S$ ($M^+$ + H) 702.3167, found 702.3152.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-[({4-[(1-methylpiperidin-4-yl)methoxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (71a).** General procedure N afforded 61 mg (87%) of product **71a**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.88 (t, 3H, $J$ = 7.32 Hz), 1.24−1.43 (m, 2H), 1.45−1.71 (m, 6H), 1.74−2.18 (m, 7H), 2.21−2.42 (m, 3H), 2.73 (s, 3H), 2.97 (s, 1H), 3.37−3.76 (m, 5H), 4.01 (t, 2H, $J$ = 6.59 Hz), 4.09−4.40 (m, 3H), 4.98−5.16 (m, 1H), 7.39−7.61 (m, 4H), 7.68 (s, 1H), 8.20 (d, 2H, $J$ = 7.69 Hz), 8.97 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+$ + H) 624.3392, found 624.3365.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-[({4-[(1-isopropylpiperidin-4-yl)methoxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxopentanoic Acid (71b).** General procedure N afforded 18 mg (93%) of product **71b**. HRMS calcd for $C_{35}H_{49}N_5O_7$ ($M^+$ + H) 652.3705, found 652.3701.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[1-(2-methoxyethyl)piperidin-4-yl]methoxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (71c).** General procedure N afforded 25 mg (93%) of product **71c**. HRMS calcd for $C_{35}H_{49}N_5O_8$ ($M^+$ + H) 668.3654, found 668.3653.

**(4*S*)-4-[({4-[(1-Acetylpiperidin-4-yl)methoxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-[4-(butoxycarbonyl)piperazin-1-yl]-5-oxopentanoic Acid (71d).** General procedure N afforded 49 mg (89%) of product **71d**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.89 (t, 3H, $J$ = 7.32 Hz), 1.06−1.44 (m, 6H), 1.46−1.69 (m, 2H), 1.68−2.17 (m, 9H), 2.24−2.42 (m, 2H), 2.58 (s, 1H), 3.07 (s, 1H), 3.36−3.73 (m, 5H), 3.83 (s, 1H), 4.01 (t, 2H, $J$ = 6.59 Hz), 4.12 (d, 2H, $J$ = 6.59 Hz), 4.40 (d, 1H, $J$ = 12.08 Hz), 4.95−5.13 (m, 1H), 7.39−7.60 (m, 4H), 7.68 (d, 1H, $J$ = 2.20 Hz), 8.21 (d, 2, H, $J$ = 6.96 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{34}H_{45}N_5O_8$ ($M^+$ + H) 652.3347, found 652.3367.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-5-oxo-4-{[(6-phenyl-4-{[1-(trifluoroacetyl)piperidin-4-yl]methoxy}pyridin-2-yl)carbonyl]amino}pentanoic Acid (71e).** General procedure N afforded 86 mg (100%) of product **71e**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.88 (t, 3H, $J$ = 7.50 Hz), 1.12−1.44 (m, 6H), 1.42−1.65 (m, 2H), 1.68−2.41 (m, 10H), 2.84−3.08 (m, 1H), 3.37−3.76 (m, 4H), 3.79−4.09 (m, 3H), 4.15 (d, 2H, $J$ = 6.22 Hz), 4.94−5.11 (m, 1H), 7.42−7.59 (m, 4H), 7.68 (s, 1H), 8.20 (d, 2H, $J$ = 7.69 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{34}H_{42}F_3N_5O_8$ ($M^+$ + H) 706.3058, found 706.3070.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (71f).** General procedure N afforded 78 mg (100%) of product **71f**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.88 (t, 3H, $J$ = 7.50 Hz), 1.00−1.40 (m, 7H), 1.43−1.65 (m, 2H), 1.66−1.92 (m, 5H), 1.95−2.17 (m, 2H), 2.18−2.39 (m, 3H), 2.63 (s, 1H), 3.01 (s, 1H), 3.35−3.71 (m, 4H), 3.79 (s, 1H), 3.85−4.23 (m, 7H), 4.34 (s, 1H), 5.03 (d, 1H, $J$ = 3.29 Hz), 7.35−7.61 (m, 4H), 7.68 (s, 1H), 8.20 (d, 2H, $J$ = 7.69 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{35}H_{47}N_5O_9$ ($M^+$ + H) 682.3452, found 682.3430.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[1-(ethoxycarbonyl)piperidin-4-yl]methoxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (71g).** General procedure N afforded 97 mg (96%) of product **71g**. 1H NMR (DMSO-$d_6$) $\delta$ 0.89 (t, 3H, $J$ = 7.32 Hz), 1.08−1.45 (m, 6H), 1.44−1.63 (m, 2H), 1.68−2.43 (m, 10H), 2.71−2.90 (m, 1H), 2.91−3.06 (m, 1 H), 3.36−3.77 (m, 5H), 3.89 (s, 1H), 3.95−4.08 (m, 4H), 4.07−4.22 (m, 3H), 4.33 (d, 1H, $J$ = 13.18 Hz), 4.96−5.12 (m, 1H), 7.40−7.60 (m, 4H), 7.68 (s, 1H), 8.20 (d, 2H, $J$ = 7.32 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{35}H_{47}N_5O_9$ ($M^+$ + H) 682.3452, found 682.3433.

**(4*S*)-5-[4-(Butoxycarbonyl)piperazin-1-yl]-4-{[(4-{[1-(ethylsulfonyl)piperidin-4-yl]methoxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoic Acid (71h).** General procedure N afforded 52 mg (100%) of product **71h**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.89 (t, 3H, $J$ = 7.32 Hz), 1.21 (t, 4H, $J$ = 7.50 Hz), 1.26−1.46 (m, 6H), 1.49−1.64 (m, 2H), 1.78−2.17 (m, 6H), 2.23−2.40 (m, 2H), 2.85 (t, 2H, $J$ = 11.16 Hz), 3.03 (q, 2H, $J$ = 7.32 Hz), 3.37−3.78 (m, 6H), 4.01 (t, 2H, $J$ = 6.41 Hz), 4.15 (d, 2H, $J$ = 6.22 Hz), 4.94−5.19 (m, 1H), 7.42−7.57 (m, 4H), 7.68 (d, 1H, $J$ = 1.83 Hz), 8.21 (d, 2H, $J$ = 6.95 Hz), 8.97 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{34}H_{47}N_5O_9S$ ($M^+$ + H) 702.3173, found 702.3176.

**(4*S*)-4-[({4-[(1-Methylpiperidin-4-yl)methoxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (72a).** General procedure N afforded 26 mg (19%) of product **72a**. HRMS calcd for $C_{34}H47N_5O_7$ ($M^+$ + H) 638.3548, found 638.3530.

**(4*S*)-4-[({4-[(1-Isopropylpiperidin-4-yl)methoxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (72b).** General procedure N afforded 52 mg (93%) of product **72b**. HRMS calcd for $C_{36}H_{52}N_5O_7$ ($M^+$ + H) 666.3861, found 666.3864.

**(4*S*)-4-{[(4-{[1-(2-Methoxyethyl)piperidin-4-yl]methoxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (72c).** General procedure N afforded 53 mg (91%) of product **72c**. HRMS calcd for $C_{36}H_{52}N_5O_8$ ($M^+$ + H) 682.3810, found 682.3833.

**(4*S*)-4-[({4-[(1-Acetylpiperidin-4-yl)methoxy]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (72d).** General procedure N afforded 53 mg (84%) of product **72d**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.87 (t, 3H, $J$ = 6.77 Hz), 1.04−1.39 (m, 8H), 1.49−1.64 (m, 3H), 1.73−1.94 (m, 4H), 1.95−2.15 (m, 5H), 2.24−2.40 (m, 2H), 2.55−2.67 (m, 1H), 3.07 (s, 1H), 3.65 (s, 4H), 3.85 (d, 1H, $J$ = 13.91 Hz), 4.00 (t, 2H, $J$ = 6.59 Hz), 4.13 (d, 2H, $J$ = 6.59 Hz), 4.40 (d, 1H, $J$ = 12.45 Hz), 4.95−5.12 (m, 1H), 7.37−7.62 (m, 4H), 7.68 (d, 1H, $J$ = 2.20 Hz), 8.21 (d, 2H, $J$ = 6.96 Hz), 8.97 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{35}H_{47}N_5O_8$ ($M^+$ + H) 666.3503, found 666.3560.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-{[(6-phenyl-4-{[1-(trifluoroacetyl)piperidin-4-yl]methoxy}pyridin-2-yl)carbonyl]amino}pentanoic Acid (72e).** General procedure N afforded 39 mg (74%) of product **72e**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.87 (t, 3H, $J$ = 6.77 Hz), 1.20−1.45 (m, 8H), 1.49−1.66 (m, 3H), 1.78−2.40 (m, 9H), 2.97 (s, 1H), 3.65 (s, 4H), 3.91 (d, 1H, $J$ = 13.18 Hz), 4.00 (t, 2H, $J$ = 6.59 Hz), 4.15 (d, 2H, $J$ = 6.22 Hz), 4.33 (d, 1H, $J$ = 12.81 Hz), 4.94−5.14 (m, 1H), 7.41−7.62 (m, 4H), 7.68 (d, 1H, $J$ = 2.20 Hz), 8.21 (d, 2H, $J$ = 6.96 Hz), 8.97 (d, 1H, $J$ = 8.42 Hz); HRMS calcd for $C_{35}H_{44}F_3N_5O_8$ ($M^+$ + H) 720.3220, found 720.3201.

**(4*S*)-4-{[(4-{[1-(Methoxyacetyl)piperidin-4-yl]methoxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (72f).** General procedure N afforded 88 mg (100%) of product **72f**. HRMS calcd for $C_{36}H_{50}N_5O_9$ ($M^+$ + H) 696.3603, found 696.3631.

**(4*S*)-4-{[(4-{[1-(Ethoxycarbonyl)piperidin-4-yl]methoxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (72g).** General procedure N afforded 104 mg (100%) of product **72g**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.87 (t, 3H, $J$ = 6.59 Hz), 1.09−1.38 (m, 11H), 1.50−1.64 (m, 2H), 1.70−2.14 (m, 7H), 2.24−2.39 (m, 2H), 2.83 (s, 2H), 3.40−3.71 (m, 4H), 3.94−4.22 (m, 8H), 4.92−5.15 (m, 1H), 7.36−7.59 (m, 4H), 7.67 (d, 1H, $J$ = 2.20 Hz), 8.20 (d, 2H, $J$ = 7.32 Hz), 8.96 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{36}H_{49}N_5O_9$ ($M^+$ + H) 696.3608, found 696.3634.

**(4*S*)-4-{[(4-{[1-(Ethylsulfonyl)piperidin-4-yl]methoxy}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]-piperazin-1-yl}pentanoic Acid (72h).** General procedure N afforded 86 mg (100%) of product **72h**. $^1$H NMR (DMSO-$d_6$) $\delta$ 0.87 (t, 3H, $J$ = 6.59 Hz), 1.08−1.44 (m, 11H), 1.46−1.65 (m, 2H), 1.70−2.13 (m, 7H), 2.20−2.40 (m, 2H), 2.85 (t, 2H, $J$ = 11.35 Hz), 3.03 (q, 2H, $J$ = 7.32 Hz), 3.36−3.77 (m, 7H), 4.00 (t, 2H, $J$ = 6.41 Hz), 4.15 (d, 2H, $J$ = 6.59 Hz), 4.88−5.18 (m, 1H), 7.38−7.59 (m, 4H), 7.68 (d, 1H, $J$ = 2.20 Hz), 8.21 (d, 2H, $J$ = 7.32 Hz), 8.97 (d, 1H, $J$ = 8.05 Hz); HRMS calcd for $C_{35}H_{49}N_5O_9S$ ($M^+$ + H) 716.3329, found 716.3333.

**Pentyl 4-[(2*S*)-2-{[(4-Amino-6-phenylpyridin-2-yl)carbonyl]-amino}-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate (73).** To a mixture of 4-azido-6-phenylpyridine-2-carboxylic acid **31** (4.79 g, 19.9 mmol), hydroxybenzotriazole (2.90 g, 21.5 mmol), and *N*-methylmorpholine (6.36 mL, 57.8 mmol) dissolved in DMF (160 mL) were added pentyl (*S*)-4-(2-amino-4-*tert*-butoxycarbonylbutyryl)piperazine-1-carboxylate **38c** (7.67 g, 19.9 mmol) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (5.8 g, 30.2 mmol). The mixture was stirred at room temperature for 23 h and then diluted with ethyl acetate (140 mL) and water (140 mL). The aqueous phase was extracted with ethyl acetate (1 × 100 mL) and the combined organics were washed with aqueous saturated $NaHCO_3$ (1 × 100 mL), brine (1 × 75 mL), dried over magnesium sulfate, filtered, and concentrated to provide the crude product. The residue was dissolved in methanol (250 mL), and the reaction vessel was flushed with $N_{2(g)}$. Then 10% Pd/C (50% water-wet, 2.07 g, 0.97 mmol) was added to the solution, and the reaction vessel was flushed with $N_{2(g)}$ and then $H_{2(g)}$. The mixture was stirred for 19 h under a balloon of $H_{2(g)}$. The mixture was filtered through a pad of Celite, and the filtrate and cake rinses were dried in vacuo. The crude residue was purified on silica gel (50−80% ethyl acetate:hexanes) to afford 7.26 g (55% yield) of product **73**. $^1$H NMR ($CDCl_3$) $\delta$ 0.86−0.97 (m, 3H), 1.28−1.41 (m, 4H), 1.45 (s, 9H), 1.57−1.71 (m, 2H), 1.86−2.01 (m, 1H), 2.09−2.24 (m, 1H), 2.27−2.51 (m, 2H), 3.37−3.81 (m, 8H), 4.10 (t, 2H, $J$ = 6.71 Hz), 4.44 (s, 2H), 5.15−5.26 (m, 1H), 7.06 (d, 1H, $J$ = 2.15 Hz), 7.37−7.53 (m, 4H), 7.97−8.03 (m, 2H), 8.92 (d, 1H, $J$ = 8.86 Hz); HRMS calcd for $C_{31}H_{44}N_5O_6$ ($M^+$ + H) 582.3286, found 582.3273.

**General Procedure O. Preparation of 4-Amide Pyridine Products 75.** To a solution of pentyl 4-[(2*S*)-2-{[(4-amino-6-phenylpyridin-2-yl)carbonyl]amino}-5-*tert*-butoxy-5-oxopentanoyl]-piperazine-1-carboxylate **73** (116 mg, 0.20 mmol) in ethyl acetate (1.5 mL) were added the carboxylic acid **74** (0.28 mmol), 1-methylimidazole (128 $\mu$L, 1.56 mmol), and propylphosphonic anhydride (50% in EtOAc) (298 $\mu$L, 0.5 mmol). The mixtures were stirred at 55 °C for 1−16 h, cooled to room temperature, and diluted with water (1 mL) and dichloromethane (2 mL). The phases were partitioned, the organic solvents were evaporated, and if necessary, the residue was purified by HPLC.

**Deprotection of the *tert*-Butyl Ester Group**. A solution of 10% trifluoroacetic acid/dichloromethane solution (1.5 mL) was added to the *tert*-butyl ester (~0.20 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The products were purified by HPLC to afford pure products **75**.

**General Procedure P. Preparation of 4-Urea and 4-Carbamate Pyridine Products 76 and 77.** A solution of pentyl 4-[(2*S*)-2-{[(4-amino-6-phenylpyridin-2-yl)carbonyl]amino}-5-*tert*-butoxy-5-oxopentanoyl]piperazine-1-carboxylate **73** (58 mg, 0.10 mmol) and pyridine (91 uL, 1.12 mmol) in dichloromethane (2.0 mL) was chilled to 0 °C. Bis(trichloromethyl)carbonate **22** (0.1 M in DCM) (1 mL, 0.1 mmol) was added, the mixture was stirred for 1 min, and the reaction mixture was added to a chilled solution of amine **44** or alcohol **24** (0.75 mmol) in dichloromethane (1.0 mL). The mixtures were stirred at ambient temperature for 0.5−16 h, the solvents were evaporated, and if necessary, the residue was purified by HPLC.

**Deprotection of the *tert*-Butyl Ester Group**. A solution of 10% trifluoroacetic acid/dichloromethane solution (1.5 mL) was added to the *tert*-butyl ester (~0.10 mmol) and agitated on an orbital shaker or stirred at room temperature for 1−24 h. Evaporation of the solvents afforded the crude products. The products were purified by HPLC to afford pure products **76** or **77**.

**Pentyl 4-[(2*S*)-5-*tert*-Butoxy-5-oxo-2-{[(6-phenyl-4-{[(trifluoromethyl)sulfonyl]oxy}pyridin-2-yl)carbonyl]amino}pentanoyl]piperazine-1-carboxylate (78).** A solution of pentyl 4-((2*S*)-5-*tert*-butoxy-2-{[(4-hydroxy-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxopentanoyl)piperazine-1-carboxylate **43c** (13.0 g, 22.3 mmol) was dissolved in pyridine (90 mL), and the solution was chilled in an ice bath. Triflic anhydride (11.55 mL, 68.6 mmol) was added slowly, keeping the temperature below 20 °C. The solvent was reduced in vacuo and the residue dissolved in ethyl acetate. The solids were removed by vacuum filtration, and the filtrate was purified on silica gel (30−70% ethyl acetate:hexanes) to afford 12.4 g (78%) of product **78**. $^1$H NMR ($CDCl_3$) $\delta$ 0.85−0.95 (m, 3H), 1.28−1.39 (m, 4H), 1.43 (s, 9H), 1.57−1.70 (m, 2H), 1.84−1.99 (m, 1H), 2.09−2.23 (m, 1H), 2.27−2.48 (m, 2H), 3.38−3.79 (m, 8H) 4.09 (t, 2H, $J$ = 6.71 Hz), 5.14−5.28 (m, 1H), 7.48−7.57 (m, 3H), 7.75 (d, 1H, $J$ = 2.42 Hz), 8.00 (d, 1H, $J$ = 2.15 Hz), 8.05 (dd, 2H, $J$ = 7.79, 1.61 Hz), 8.87 (d, 1H, $J$ = 8.32 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ ppm −73.08 (s).

**2-((4-Carboxy-1-oxo-1-(4-(pentyloxycarbonyl)piperazin-1-yl)-butan-2-yl)carbamoyl)-6-phenylisonicotinic Acid (79).** A solution of pentyl 4-[(2*S*)-5-*tert*-butoxy-5-oxo-2-{[(6-phenyl-4-{[(trifluoromethyl)sulfonyl]oxy}pyridin-2-yl)carbonyl]amino}-pentanoyl]piperazine-1-carboxylate **78** (~9.4 mmol) in DMSO (100 mL) was added to $Pd(PPh_3)_4$ (2.68 g, 2.3 mmol) and triethylamine (9.16 mL, 66 mmol) under an inert atmosphere. The reaction solution was evacuated and flushed with $N_{2(g)}$ and then with $CO_{(g)}$. The mixture was stirred under a $CO_{(g)}$ balloon at 60 °C for 27 h and then was diluted with dichloromethane (200 mL) and washed with HCl (1 N in water) (1 × 200 mL). The aqueous phase was extracted with dichloromethane (150 mL) and the combined organics were washed with brine (200 mL), dried over $MgSO_4$, filtered, concentrated, and purified by reverse-phase HPLC (30−95% acetonitrile/water gradient with 0.1% TFA modifier) to afford 4.58 g (53% yield) of 75% pure product **79**. $^1$H NMR ($CDCl_3$) $\delta$ 0.87−0.98 (m, 3H), 1.29−1.43 (m, 4H), 1.45 (s, 9H), 1.60−1.72 (m, 2H), 1.93−2.08 (m, 1H), 2.15−2.28 (m, 1H), 2.33−2.56 (m, 2H), 3.42−3.90 (m, 8H), 4.13 (t, 2H, $J$ = 6.71 Hz), 5.25−5.37 (m, 1H), 7.41−7.54 (m, 3H), 8.03−8.11 (m, 2H), 8.36 (d, 1H, $J$ = 1.34 Hz), 8.62 (d, 1H, $J$ = 1.34 Hz), 8.96 (d, 1H, $J$ = 8.32 Hz); HRMS calcd for $C_{32}H_{43}N_4O_8$ ($M^+$ + H) 611.3075, found 611.3089.

**General Procedure Q. Preparation of 4-Carboxamide Pyridine Compounds 80.** A solution of 2-((4-carboxy-1-oxo-1-(4-(pentyloxycarbonyl)piperazin-1-yl)butan-2-yl)carbamoyl)-6-phenylisonicotinic acid **79** (3.6 g, 6 mmol), 1-hydroxybenzotriazole (0.2 g, 1.48 mmol), and *N*-methylmorpholine (1.8 mL, 18 mmol) in dichloromethane (96 mL) was aliquoted (1 mL per well) between 96 1-dram vials containing PS-carbodiimide **6** (~0.10 mmol per well). The mixtures were agitated for 10 min, and then amines **44** (0.09 mmol) were added to the vials. The mixtures were agitated at room temperature for 12−72 h. The reaction mixtures were

filtered and filtrates evaporated to afford the *tert*-butyl ester intermediates.

**Deprotection of the *tert*-Butyl Ester Group.** A solution of 15% trifluoroacetic acid/dichloromethane (0.65 mL) was added to each *tert*-butyl ester (~0.063 mmol) and agitated on an orbital shaker or stirred at room temperature for 16 h. Purification by HPLC provided the desired pure products **80**.

**(4*S*)-4-({[4-(Aminocarbonyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80a).** General procedure Q afforded 15.5 mg (14%) of product **80a**. HRMS calcd for $C_{28}H_{35}N_5O_7$ ($M^+ + H$) 554.2615, found 554.2606.

**(4*S*)-4-[({4-[(Methylamino)carbonyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80b).** General procedure Q afforded 42 mg (37%) of product **80b**. HRMS calcd for $C_{29}H_{37}N_5O_7$ ($M^+ + H$) 568.2771, found 568.2775.

**(4*S*)-4-[({4-[(Ethylamino)carbonyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80c).** General procedure Q afforded 18.3 mg (16%) of product **80c**. HRMS calcd for $C_{30}H_{39}N_5O_7$ ($M^+ + H$) 582.2928, found 582.2953.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-[({6-phenyl-4-[(propylamino)carbonyl]pyridin-2-yl}carbonyl)amino]pentanoic Acid (80d).** General procedure Q afforded 22.7 mg (45%) of product **80d**. HRMS calcd for $C_{31}H_{41}N_5O_7$ ($M^+ + H$) 596.3084, found 596.3115.

**(4*S*)-4-[({4-[(Dimethylamino)carbonyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80e).** General procedure Q afforded 50.1 mg (43%) of product **80e**. HRMS calcd for $C_{30}H_{39}N_5O_7$ ($M^+ + H$) 582.2928, found 582.2913.

**(4*S*)-4-{[(4-{[Ethyl(methyl)amino]carbonyl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80f).** General procedure Q afforded 25.7 mg (42%) of product **80f**. HRMS calcd for $C_{31}H_{41}N_5O_7$ ($M^+ + H$) 596.3084, found 596.3046.

**(4*S*)-4-{[(4-{[Butyl(methyl)amino]carbonyl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80g).** General procedure Q afforded 19.5 mg (52%) of product **80g**. HRMS calcd for $C_{33}H_{45}N_5O_7$ ($M^+ + H$) 624.3397, found 624.3412.

**(4*S*)-4-{[(4-{[(2-Methoxyethyl)amino]carbonyl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80h).** General procedure Q afforded 25.4 mg (39%) of product **80h**. HRMS calcd for $C_{31}H_{41}N_5O_8$ ($M^+ + H$) 612.3033, found 612.3063.

**(4*S*)-4-{[(4-{[(3-Methoxypropyl)amino]carbonyl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80i).** General procedure Q afforded 19.3 mg (31%) of product **80i**. HRMS calcd for $C_{32}H_{43}N_5O_8$ ($M^+ + H$) 626.3190, found 626.3193.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-[({6-phenyl-4-[(tetrahydro-2*H*-pyran-4-ylamino)carbonyl]pyridin-2-yl}carbonyl)amino]pentanoic Acid (80j).** General procedure Q afforded 15.5 mg (42%) of product **80j**. HRMS calcd for $C_{33}H_{43}N_5O_8$ ($M^+ + H$) 638.3190, found 638.3191.

**(4*S*)-4-{[(4-{[(3-Methoxypropyl)(methyl)amino]carbonyl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80k).** General procedure Q afforded 23.3 mg (42%) of product **80k**. HRMS calcd for $C_{33}H_{45}N_5O_8$ ($M^+ + H$) 640.3347, found 640.3323.

**(4*S*)-4-({[4-({[3-(Dimethylamino)propyl](methyl)amino}carbonyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80l).** General procedure Q afforded 31 mg (55%) of product **80l**. HRMS calcd for $C_{34}H_{48}N_6O_7$ ($M^+ + H$) 653.3663, found 653.3646.

**(4*S*)-4-{[(4-{[Methyl(1-methylpiperidin-4-yl)amino]carbonyl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80m).** General procedure Q afforded 22.6 mg (36%) of product **80m**. HRMS calcd for $C_{35}H_{48}N_6O_7$ ($M^+ + H$) 665.3663, found 665.3654.

**(4*S*)-5-Oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}-4-({[6-phenyl-4-(piperidin-1-ylcarbonyl)pyridin-2-yl]carbonyl}amino)pentanoic Acid (80n).** General procedure Q afforded 13.7 mg (21%) of product **80n**. HRMS calcd for $C_{33}H_{43}N_5O_7$ ($M^+ + H$) 622.3240, found 622.3239.

**(4*S*)-4-({[4-(Morpholin-4-ylcarbonyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80o).** General procedure Q afforded 22.1 mg (34%) of product **80o**. HRMS calcd for $C_{32}H_{41}N_5O_8$ ($M^+ + H$) 624.3033, found 624.3050.

**(4*S*)-4-[({4-[(4-Methoxypiperidin-1-yl)carbonyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80p).** General procedure Q afforded 25.1 mg (44%) of product **80p**. HRMS calcd for $C_{34}H_{45}N_5O_8$ ($M^+ + H$) 652.3347, found 652.3327.

**(4*S*)-4-{[(4-{[4-(Dimethylamino)piperidin-1-yl]carbonyl}-6-phenylpyridin-2-yl)carbonyl]amino}-5-oxo-5-{4-[(pentyloxy)carbonyl]-piperazin-1-yl}pentanoic Acid (80q).** General procedure Q afforded 10 mg (15%) of product **80q**. HRMS calcd for $C_{35}H_{48}N_6O_7$ ($M^+ + H$) 665.3663, found 665.3665.

**(4*S*)-4-[({4-[(4-Methylpiperazin-1-yl)carbonyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80r).** General procedure Q afforded 44.7 mg (36%) of product **80r**. HRMS calcd for $C_{33}H_{44}N_6O_7$ ($M^+ + H$) 637.3350, found 637.3352.

**(4*S*)-4-[({4-[(4-Acetylpiperazin-1-yl)carbonyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (80s).** General procedure Q afforded 13.4 mg (17%) of product **80s**. HRMS calcd for $C_{34}H_{44}N_6O_8$ ($M^+ + H$) 665.3293, found 665.3292.

**General Procedure R. Method A (Heck Coupling): Preparation of 4-Aliphatic Pyridine Compounds 83.** To a solution of pentyl 4-[(2*S*)-5-*tert*-butoxy-5-oxo-2-{[(6-phenyl-4-{[(trifluoromethyl)-sulfonyl]oxy}pyridin-2-yl)carbonyl]amino}pentanoyl]piperazine-1-carboxylate **78** (250 mg, 0.35 mmol), *trans*-dichlorobis-(triphenylphosphine)Pd(II) (12.6 mg, 0.018 mmol), and LiBr (97.2 mg, 1.12 mmol) in DMF (3.5 mL) was added alkene **81** (1.0−1.4 mmol). The mixtures were stirred at 100 °C for 1 h, then cooled to room temperature. Triethylamine (54 uL, 0.49 mmol) was added, and the mixtures were stirred at 100 °C for 1.5−18 h. The crude reaction solution was diluted with α,α,α-trifluorotoluene (4 mL) and washed with water (4 mL). The organic phase was isolated, and the aqueous phase was extracted with α,α,α-trifluorotoluene (4 mL). The combined organics were dried in vacuo to afford the *tert*-butyl ester products.

**Deprotection of the *tert*-Butyl Ester Group**. A solution of 15% trifluoroacetic acid/dichloromethane (3.5 mL) was added to the *tert*-butyl ester (~0.35 mmol) agitated on an orbital shaker or stirred at room temperature for 12−60 h. Evaporation of the solvents and purification by reverse-phase HPLC afforded the pure alkene intermediates.

**Reduction of the Alkene**. The alkenes (~0.35 mmol) were dissolved in EtOAc (2.5 mL), and the reaction vessel was flushed with $N_{2(g)}$. A slurry of 10% Pd/C (0.016 mmol) in EtOAc (0.5 mL) was added to the solution, and the reaction vessels were flushed with $N_{2(g)}$ and then $H_{2(g)}$. The mixtures were stirred for 2−18 h under a balloon of $H_{2(g)}$ and then filtered through a pad of Celite. The filtrate and cake rinses were dried in vacuo, and the residues were purified by HPLC to afford pure products **83**.

**General Procedure R. Method B (Sonogashira): Preparation of 4-Aliphatic Pyridine Compounds 83.** A solution of pentyl 4-[(2*S*)-5-*tert*-butoxy-5-oxo-2-{[(6-phenyl-4-{[(trifluoromethyl)sulfonyl]-oxy}pyridin-2-yl)carbonyl]amino}pentanoyl]piperazine-1-carboxylate **78** (386 mg, 0.54 mmol), CuI (23 mg, 0.12 mmol), $Pd(PPh_3)_4$ (39 mg, 0.034 mmol), and diethylamine (165 μL, 1.6 mmol) in THF (5.4 mL) was added to each alkyne **82** (1.5 mmol). The mixtures were agitated at room temperature for 2−48 h and then diluted with α,α,α-trifluorotoluene (4 mL) and aqueous saturated $NH_4Cl$

(4 mL). The organic phase was isolated and evaporated to afford the *tert*-butyl ester intermediates.

**Deprotection of the *tert*-Butyl Ester Group**. A solution of 15% trifluoroacetic acid/dichloromethane (2.2 mL) was added to the *tert*-butyl ester (~0.27 mmol) agitated on an orbital shaker or stirred at room temperature for 24 h. Evaporation of the solvents and purification by reverse-phase HPLC afforded the pure alkyne intermediates.

**Reduction of the Alkyne**. The alkynes (~0.25 mmol) were dissolved in EtOAc (2 mL), and the reaction vessel was flushed with $N_{2(g)}$. A slurry of 10% Pd/C (0.025 mmol) in EtOAc (0.4 mL) was added to the reaction solution, and the reaction vessels were flushed with $N_{2(g)}$ and then $H_{2(g)}$. The mixtures were stirred for 1.5 h under a balloon of $H_{2(g)}$ and then filtered through a pad of Celite. The filtrate and cake rinses were dried in vacuo, and the residues were purified by HPLC to afford products **83**.

**(4*S*)-4-({[4-(Cyclohexylmethyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83a).** General procedure R, method A, afforded 48.4 mg (19%) of product **83a**. HRMS calcd for $C_{34}H_{46}N_4O_6$ ($M^+ + H$) 607.3495, found 607.3529.

**(4*S*)-4-({[4-(3-Hydroxypropyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83b).** General procedure R, method B, afforded 8.3 mg (5%) of product **83b**. HRMS calcd for $C_{30}H_{40}N_4O_7$ ($M^+ + H$) 569.2970, found 569.2971.

**(4*S*)-4-({[4-(4-Hydroxybutyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83c).** General procedure R, method B, afforded 28 mg (17%) of product **83c**. HRMS calcd for $C_{31}H_{42}N_4O_7$ ($M^+ + H$) 583.3126, found 583.3102.

**(4*S*)-4-({[4-(5-Hydroxypentyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83d).** General procedure R, method B, afforded 49.3 mg (28%) of product **83d**. HRMS calcd for $C_{32}H_{44}N_4O_7$ ($M^+ + H$) 619.3102, found 619.3073.

**(4*S*)-4-({[4-(3-Methoxypropyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83e).** General procedure R, method B, afforded 81 mg (45%) of product **83e**. HRMS calcd for $C_{31}H_{42}N_4O_7$ ($M^+ + H$) 583.2126, found 583.3124.

**(4*S*)-4-({[4-(4-Methoxybutyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83f).** General procedure R, method B, afforded 20.4 mg (11%) of product **83f**. HRMS calcd for $C_{32}H_{44}N_4O_7$ ($M^+ + H$) 597.3283, found 597.3270.

**(4*S*)-4-[({4-[3-(Isobutylamino)propyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83g).** General procedure R, method B, afforded 22 mg (13%) of product **83g**. HRMS calcd for $C_{34}H_{49}N_5O_6$ ($M^+ + H$) 624.3756, found 624.3728.

**(4*S*)-4-[({4-[3-(Dimethylamino)propyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83h).** General procedure R, method B, afforded 58 mg (34%) of product **83h**. HRMS calcd for $C_{32}H_{45}N_5O_6$ ($M^+ + H$) 596.3443, found 596.3481.

**(4*S*)-4-[({4-[3-(Diethylamino)propyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83i).** General procedure R, method B, afforded 40 mg (23%) of product **83i**. HRMS calcd for $C_{34}H_{49}N_5O_6$ ($M^+ + H$) 624.3756, found 624.3732.

**(4*S*)-4-[({4-[4-(Dimethylamino)butyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83j).** General procedure R, method A, afforded 62.4 mg (24%) of product **83j**. HRMS calcd for $C_{33}H_{47}N_5O_6$ ($M^+ + H$) 610.3605, found 610.3608.

**(4*S*)-4-[({4-[3-(Dimethylamino)-3-oxopropyl]-6-phenylpyridin-2-yl}carbonyl)amino]-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83k).** General procedure R, method A, afforded 88.4 mg (35%) of product **83k**. HRMS calcd for $C_{32}H_{43}N_5O_7$ ($M^+ + H$) 610.3240, found 610.3248.

**(4*S*)-4-({[4-(3-Morpholin-4-yl-3-oxopropyl)-6-phenylpyridin-2-yl]carbonyl}amino)-5-oxo-5-{4-[(pentyloxy)carbonyl]piperazin-1-yl}pentanoic Acid (83l).** General procedure R, method A, afforded 49 mg (18%) of product **83l**. HRMS calcd for $C_{34}H_{45}N_5O_8$ ($M^+ + H$) 652.3347, found 652.3336.

**Biology. $P2Y_{12}$ Radioligand Binding Assay.** CHO (Chinese hamster ovary) cells transfected with a synthetic human $P2Y_{12}$ gene were cultured in α-MEM containing 10% dialyzed FBS, 0.05% Geneticin, 1× GlutaMAX, and 1× penicillin−streptomycin. Washed membranes prepared from near confluent cells were stored at −80 °C. Binding reactions were conducted in polypropylene assay plates in a volume of 150 μL of assay buffer (50 mM Tris, 100 mM NaCl, 1 mM EDTA) including 0.3 μg/well membrane protein, 0.2 nM $^{33}$P-MeSADP, and serial dilutions of test compounds, vehicle, or 300 nM 2-MeSADP for the definition of nonspecific binding. Dry compounds were prepared as 10 mM DMSO stocks and were diluted in seven-point, 3-fold dilution series in assay buffer with 0.02% BSA. Each concentration was run in triplicate beginning at 10 mM, final concentration in the assay.

Binding reactions were incubated at room temperature for 1 h and stopped by dilution and transfer/aspiration of the mixture onto GF/B UniFilter 96-well plates (Perkin-Elmer) and washed 3× with ice-cold 50 mM Tris, pH 7.4, aspirating between each wash. The filter plates were counted on a Top Count (Perkin-Elmer), and data were analyzed using GraphPad Prism using a single site binding equation.

**Blood Donors and Draws.** The donors consisted of males and females of 18−65 years, and those with sickle cell anemia were excluded. Blood donors were asked to abstain from aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) usage 7−10 days prior to donation, but fasting was not required. A total of 100 mL each per donor (×4 donors) was collected into five individual 20 mL syringes (Terumo brand, VWR, St. Louis, MO) filled with 2 mL of 0.105 M buffered sodium citrate anticoagulant (Sigma, St. Louis, MO) using a 19 gauge butterfly needle.

**Chemicals and Agonists.** Dilutions were prepared in analytical grade (ACS) reagents such as PBS (Gibco, Carlsbad, CA), DMSO, and human albumin serum (Sigma). Stocks of a 1 mM adenosine diphosphate (ADP) (Chrono-Log, Havertown, PA) were prepared in PBS for a final agonist concentration of 20 μM in assay per 96 reaction well.

**Human Platelet-Rich Plasma Preparation.** Platelet-rich plasma (PRP) was prepared from whole blood by diluting prepared PRP with prepared platelet poor plasma (PPP) to achieve a final concentration of 330 000 platelets per microliter for use in assay. All centrifugation steps were performed at room temperature in a Beckman Allegra X-12 benchtop centrifuge using rotor SX4750A. Whole blood collected from syringes was transferred into 50 mL VWR conical tubes. Any whole blood with evidence of clotting was excluded from preparation. Whole blood samples containing an acutely dense appearance of lipemia were also excluded from PRP preparations, but minor lipemic conditions were allowed. PRP was obtained by a two-step centrifugation process: Centrifugation at 910*g* (average) for 10 s was immediately followed by centrifugation at 220*g* (average) for 15 min. The upper layer was collected using a 10 mL pipet, into a polypropylene bottle (Corning, Acton, MA), leaving a 5 mL layer of liquid behind to avoid disturbing the buffy coat and red blood cells layers in the conical tubes. For platelet poor plasma, the lower phase and remaining PRP in the conicals was centrifuged at 2380*g* for 15 min. The upper layer was collected again, taking care not to disturb the RBC layer, into a clean polypropylene bottle. PRP platelets counts were determined using a Z1 Coulter particle counter (Beckman Coulter, Fullerton, CA), and PRP was adjusted to 330 000 cells per microliter by dilution with PPP.

**ADP-Induced Human PRP Aggregation Assay.** Platelet aggregation was measured with a microplate spectrophotometer

(SpectraMax Plus 384, SoftMax Pro software, Molecular Devices, Sunnyvale, CA). First, a dilution plate at 5% DMSO/4.2% HSA in PBS was prepared by 2-fold serial dilution of DMSO stocks of test compounds to yield 7 concentrations per 96-well plate (500−7.813 $\mu$M). The last plate row contains buffer alone for effect control purposes. Next, assay plates are prepared from the dilution plate by pipetting 18 $\mu$L ($^1/_{10}$ of 180 $\mu$L total assay reaction volume) in duplicate columns on an empty assay plate. Final assay dose response concentrations for test compound and reference control AZD-6140 were 10, 5, 2.5, 1.25, 0.625, 0.313, 0.156 $\mu$M at 0.5% DMSO. The reference compound AZD-6140 was included on every plate for normalization purposes to minimize donor-to-donor variability. For preincubation of PRP and vehicle or vehicle plus compound, 144 $\mu$L of PRP was added to the assay plate containing diluted analogues, then mixed 30 s on titer plate shaker (setting 3), then warmed for 5 min at 37 °C on heater block. Reverse pipetting (Rainin LTS multichannel pipet) prevented the formation of air bubbles on the surface of plasma that otherwise would obscure reader function, giving rise to false values. Aggregation was then initiated by addition of 18 $\mu$L of 200 $\mu$M ADP (20 $\mu$M final concentration in assay) to assay plate. The last row on each plate containing PRP plus vehicle was divided by half, so the first six wells represented 100% effect aggregation to which 18 $\mu$L of ADP was added and the last six wells represented 0% effect aggregation to which 18 $\mu$L of PBS was added. Immediately, aggregation response was measured by kinetic readings of the optical density at 626 nm at 37 °C for 15 min using a SpectraMax Plus spectrophotometer. The kinetic program was set for automix function (oscillatory bidirectional motion) for 45 s between the 1 min reading intervals during the 15 min duration. Assay plate preincubations and incubations were staggered in order to have one plate at the end point read while another plate was ready for kinetic read. Concentration−response data from the 15 min end point read were analyzed using BioAssay Solver to afford $IC_{50}$ values. Final volume and concentration of assay were as follows: total volume per well 180 $\mu$L, 0.5% final DMSO, 20 $\mu$M ADP, $4.752 \times 10^7$ platelets/well, and 50 or 10 $\mu$M test compounds.

**Supporting Information Available:** Biological and characterization data for compounds **20**, **75**, **76**, and **77**. This material is available free of charge via the Internet at http://pubs.acs.org.

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