# Discovery of HIV-1 Protease Inhibitors with Picomolar Affinities Incorporating *N*-Aryl-oxazolidinone-5-carboxamides as Novel P2 Ligands

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Here, we describe the design, synthesis, and biological evaluation of novel HIV-1 protease inhibitors incorporating *N*-phenyloxazolidinone-5-carboxamides into the (hydroxyethylamino)sulfonamide scaffold as P2 ligands. Series of inhibitors with variations at the P2 phenyloxazolidinone and the P2′ phenylsulfonamide moieties were synthesized. Compounds with the (*S*)-enantiomer of substituted phenyloxazolidinones at P2 show highly potent inhibitory activities against HIV-1 protease. The inhibitors possessing 3-acetyl, 4-acetyl, and 3-trifluoromethyl groups at the phenyl ring of the oxazolidinone fragment are the most potent in each series, with $K_i$ values in the low picomolar (pM) range. The electron-donating groups 4-methoxy and 1,3-dioxolane are preferred at P2′ phenyl ring, as compounds with other substitutions show lower binding affinities. Attempts to replace the isobutyl group at P1′ with small cyclic moieties caused significant loss of affinities in the resulting compounds. Crystal structure analysis of the two most potent inhibitors in complex with the HIV-1 protease provided valuable information on the interactions between the inhibitor and the protease enzyme. In both inhibitor−enzyme complexes, the carbonyl group of the oxazolidinone ring makes hydrogen-bond interactions with relatively conserved Asp29 residue of the protease. Potent inhibitors from each series incorporating various phenyloxazolidinone based P2 ligands were selected and their activities against a panel of multidrug-resistant (MDR) protease variants were determined. Interestingly, the most potent protease inhibitor starts out with extremely tight affinity for the wild-type enzyme ($K_i$ = 0.8 pM), and even against the MDR variants it retains picomolar to low nanomolar $K_i$, which is highly comparable with the best FDA-approved protease inhibitors.

## Introduction

Human immunodeficiency virus type 1 (HIV-1) protease plays a critical role in the virus life cycle by processing the viral Gag and Gag-Pol polyproteins into structural and functional proteins essential for viral maturation. Inhibition of HIV-1 protease leads to the production of noninfectious virus particles and hence is a promising therapeutic target for antiviral therapy in AIDS patients. In fact, HIV-1 protease inhibitors represent the most potent anti-AIDS drugs reported to date and are essential components of highly active antiretroviral therapy (HAART).[1,2] In the past decade, structure-based drug design has led to the discovery of nine FDA-approved drugs and several others in advanced clinical trials. Currently marketed HIV-1 protease inhibitors, saquinavir,[3] indinavir,[4] ritonavir,[5] nelfinavir,[6] amprenavir,[7] lopinavir,[8] atazanavir,[9] tipranavir,[10] and darunavir (TMC-114),[11] are all competitive inhibitors that bind in the active site of the enzyme. Except the newly approved drug tipranavir, all approved inhibitors have been developed on the basis of the transition state mimetic concept and contain various noncleavable dipeptide isosteres as core scaffolds to mimic the transition state of HIV-1 protease substrates. The development and clinical introduction of anti-AIDS HIV-1 protease inhibitors is regarded as a major success of structure-based drug design.[12]

Anti-AIDS chemotherapy based on HIV-1 protease and reverse-transcriptase inhibitors has been remarkably successful in decreasing the mortality rate in HIV-1-infected patients. However, the emergence of HIV-1 mutants that are resistant to current drug regimens is a critical factor in the clinical failure of antiviral therapy. For most of the currently approved protease inhibitors, the emergence of multidrug-resistant (MDR) protease variants poses a great challenge to the efficacy of these drugs.[13,14] Development of next-generation HIV-1 protease inhibitors active against MDR virus has been the focus of intense research efforts in recent years.[11,15] Thus, there is an increasing need to discover new classes of protease inhibitors that possess favorable pharmacological profiles and are less susceptible to drug resistance with an emphasis on broad spectrum activity against MDR variants.

One possible strategy to reduce the probability of drug resistance is to design inhibitors that interact with the same residues of HIV-1 protease that are necessary to recognize the substrate.[16,17] Analysis of the crystal structures of HIV-1 protease in complex with substrate peptides suggests that substrate specificity for HIV-1 protease is based not on a particular amino acid sequence but on a conserved shape ("substrate envelope").[18] Comparison of the substrate structures with protease inhibitor structures reveals critical differences between inhibitor and substrate binding to the enzyme. In the case of substrates, most of the conserved hydrogen bonds occur primarily between the backbone of the protease and the backbone of the substrate. Thus, it is important that the inhibitors are designed to form hydrogen bonds with relatively conserved residues and preferably with the backbone atoms of the protease rather than the side chain atoms. Among the approved protease inhibitors, amprenavir (APV, **1**; Figure 1) fits reasonably well within the substrate envelope. It has been suggested that the inhibitors designed on the APV template may be less susceptible to drug

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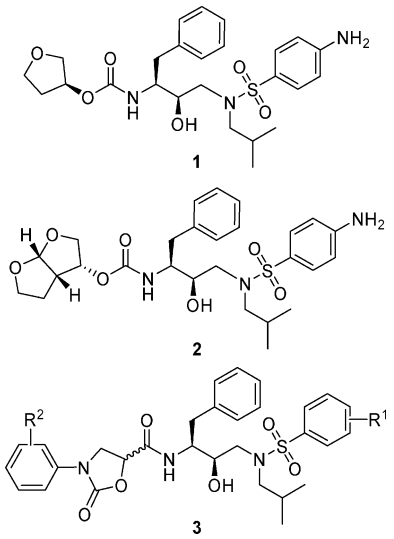


**Figure 1.** Chemical structures of APV (**1**), DRV (**2**), and designed inhibitors (**3**).

resistance.[19] Recently approved protease inhibitor darunavir (DRV, **2**), structurally similar to **1**, has been shown to possess very potent in vitro and in vivo antiviral activity against wild-type as well as MDR variants. Compared to the THF moiety in **1**, the additional interactions of the bis-THF moiety in **2** with the backbone atoms of fairly conserved Asp29 and Asp30 residues in protease explains its potent and broad spectrum activity against MDR variants.[19,20]

In an effort to discover new classes of HIV-1 protease inhibitors that target ensembles of HIV-1 protease and exhibit broad spectrum activity against MDR variants, we have designed inhibitors based on the (*R*)-(hydroxyethylamino)sulfonamide isostere present in **1** and **2**. We envisioned that a small heterocyclic moiety with multiple polar atoms located at the P2 position would mimic the critical interactions of the THF/bis-THF moieties present in APV/DRV. Since the oxygen atom of the carbamate linking THF/bis-THF moieties to the hydroxyethylamine core in **1** and **2** does not make any hydrogen-bond contacts with the protease, we decided to attach the heterocyclic moiety to the core isostere via an amide linkage. Previous reports of inhibitors with heteroaryl and other polar heterocyclic groups as P2 ligands directly linked to the (hydroxyethylamino)-sulfonamide fragment did not show promising activities.[21] However, inhibitors incorporating substituted hydroxybenzamides as P2 ligands have shown potent inhibitory activities against HIV-1 protease.[22,23] Recently, protease inhibitors incorporating 2,3-dihydroxybenzoic acid derived macrocyclic P1−P2 ligands have been reported to exhibit low nanomolar protease inhibitory activities.[24]

Among possible five-membered heterocyclic structures, we selected *N*-phenyloxazolidinone-5-carboxamides to be utilized as P2 ligands in HIV-1 protease inhibitors. The oxazolidinones represent a class of synthetic antimicrobial agents that are highly stable and exhibit exceptional bioavailability profiles.[25] Linezolid is an FDA-approved antibacterial drug that contains *N*-phenyloxazolidinone nucleus.[26] Recently, *N*-phenyloxazolidinone-5-carboxamides have been reported to possess better antibacterial activities compared to linezolid with enhanced solubility and bioavailability properties.[27] We reasoned that the carbonyl group of the oxazolidinone ring would mimic critical hydrogen-bond interactions of THF/bis-THF moieties of APV and DRV in the S2 binding pocket of the protease active site. The phenyl group at the ring nitrogen can be utilized to introduce functional groups to make additional contacts with the protease. In addition, the selected heterocyclic moiety can be linked to the (hydroxyethylamino)sulfonamide isostere in a stereochemically defined manner using either the (*R*)- or (*S*)-enantiomer of *N*-phenyloxazolidinone-5-carboxylic acids.

The *N*-phenyloxazolidinone-based cyclic carbamate ligands have not been utilized previously in protease inhibitors. However, there are reports of inhibitors containing other cyclic carbamate ligands, but with poor protease inhibitory activities.[28] On the other hand, cyclic urea based ligands have been widely used in protease inhibitors; approved drug lopinavir (LPV) contains cyclic urea at the P3 position.[8] Substituted imidazolidines have been incorporated as cyclic P1−P2 scaffolds in protease inhibitors based on hydroxyethylene and hydroxyethylamine isosteres. These conformationally restricted molecules displayed potent inhibitory activities against HIV-1 protease with $K_i$ values in the nanomolar range.[29] Recently, potent oximinoarylsulfonamide-based HIV-1 protease inhibitors that contain *N*-substituted five-membered cyclic urea moiety linked to the hydroxyethylamine core analogous to the LPV P3 side chain have been reported.[30]

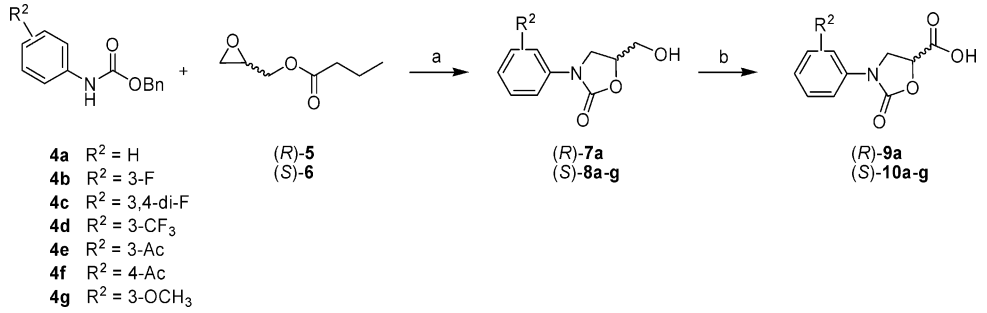
Herein, we report the synthesis and biological evaluation of novel series of HIV-1 protease inhibitors incorporating *N*-phenyloxazolidinone-5-carboxamides as P2 ligands. Preliminary structure−activity relationship (SAR) studies with variations at the P2, P2′, and P1′ positions resulted in the discovery of highly potent inhibitors of HIV-1 protease. In addition to activities against wild-type protease, we also report the inhibitory activities of several new inhibitors against a panel of MDR variants of HIV-1 protease. The crystal structures of the two most potent new inhibitors in complex with wild-type HIV-1 protease are also discussed.

## Chemistry

Chiral *N*-phenyloxazolidinone-5-carboxylic acids **9** and **10** used in the synthesis of designed inhibitors were prepared following the literature procedure as outlined in Scheme 1.[26,27,31] The intermediate chiral alcohols, 5-(hydroxymethyl)-3-aryloxazolidine-2-ones **7** and **8**, were obtained from substituted anilines in two steps. The reaction of CBZ-protected anilines **4a**−**g** with either the (*R*)- or the (*S*)-enantiomer of glycidyl butyrate promoted by n-BuLi provided chiral alcohols **7a** and **8a**−**g**. This one-pot, three-step cascade reaction involves the initial ring opening of chiral epoxide with *N*-lithium species followed by an intramolecular cyclization and finally an in situ ester hydrolysis.[26] Oxidation of the resulting chiral alcohols using catalytic ruthenium chloride provided the desired *N*-phenyloxazolidinone-5-carboxylic acids **9a** and **10a**−**g** (Scheme 1). In the case of the unsubstituted phenyloxazolidinones, both (*R*)- and (*S*)-enantiomers, **9a** and **10a**, respectively, were prepared from the corresponding chiral epoxide. All other compounds with a substituted phenyl ring, **10b**−**g**, were prepared only as (*S*)-enantiomers.

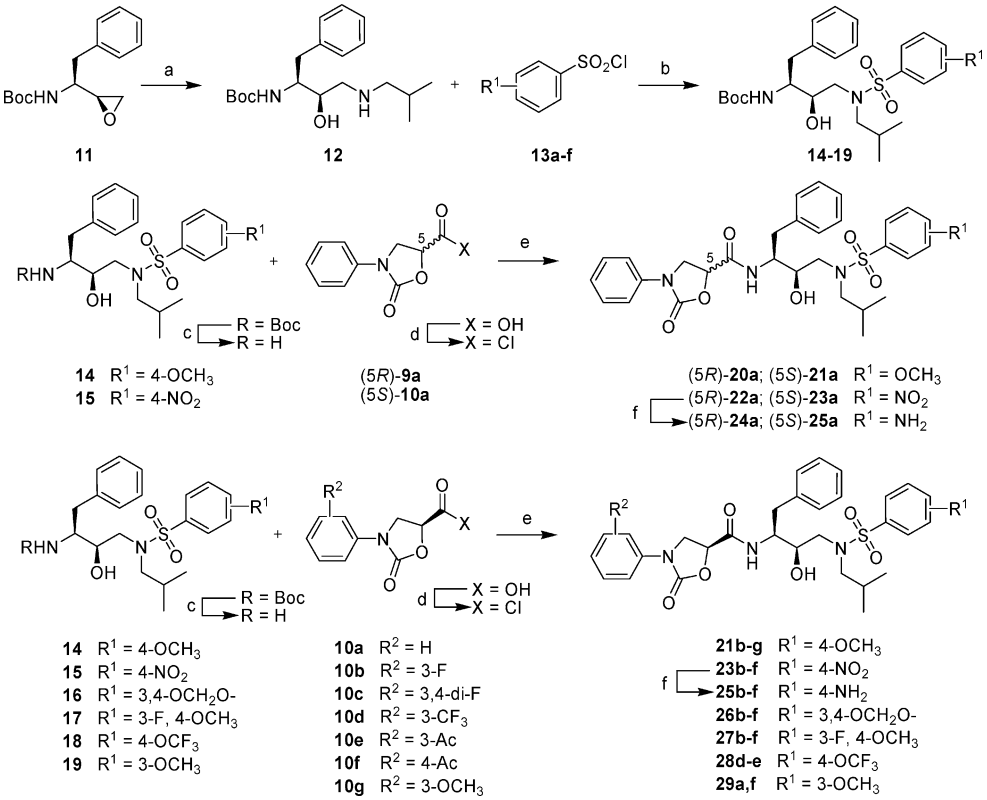
The synthetic route applied for the preparation of designed protease inhibitors is illustrated in Scheme 2. The Boc-protected intermediate (*R*)-(hydroxyethylamino)sulfonamides **14**−**19** were prepared following a literature procedure.[11] Briefly, ring opening of commercially available chiral epoxide (1*S*,2*S*)-(1-oxiranyl-2-phenylethyl)carbamic acid *tert*-butyl ester (**11**) with isobutylamine provided the amino alcohol **12**. Reactions of substituted phenylsulfonyl chlorides with **12** afforded the sulfonamides **14**−**19** that were coupled with phenyloxazolidinone fragments. Initially, four compounds were synthesized using either unsubstituted (*R*)- or (*S*)-3-phenyloxazolidinone-5-carboxylic acid **9a**

**Scheme 1.** Synthesis of Intermediates *N*-Phenyloxazolidinone-5-carboxylic Acids **9** and **10**[a]




[a] (a) n-BuLi, THF, −78 °C to rt overnight; (b) $NaIO_4$, $RuCl_3 \cdot H_2O$, $CH_3CN-CCl_4-H_2O$ (2:2:3), 0 °C to rt 4−10 h.

**Scheme 2.** Synthesis of Designed Protease Inhibitors **20**−**29**[a]



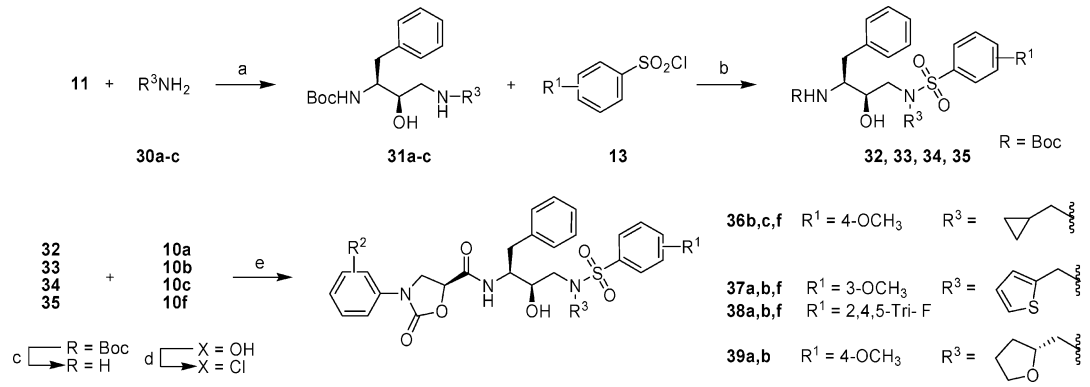

[a] (a) *i*$BuNH_2$, EtOH, 80 °C, 3−4 h; (b) aq $Na_2CO_3$, $CH_2Cl_2$, 0 °C to rt, 4−8 h; (c) TFA, $CH_2Cl_2$, 1 h; (d) $(COCl)_2$, rt, overnight; (e) $Et_3N$, THF, 0 °C to rt, 4−8 h; (f) $SnCl_2 \cdot 2H_2O$, EtOAc, 70 °C, 2 h.

or **10a** attached to the (*R*)-(hydroxyethylamino)sulfonamide isostere at the P2 position. The previously optimized phenylsulfonamides 4-methoxyphenylsulfonamide and 4-aminophenylsulfonamide were utilized as P2′ ligands. Thus, removal of the Boc protection of sulfonamides **14** and **15** followed by the reactions of the resulting amino alcohols with either the (*R*)- or the (*S*)-enantiomer of the activated carboxylic acids **9a** or **10a** provided the target compounds **20a**−**23a** (Scheme 2). In the case of compounds **22a** and **23a**, the nitro group was reduced using tin chloride to afford the corresponding amino derivatives **24a** and **25a**. It has to be noted that attempts to use the standard amide coupling conditions EDCI/HOBt/DIEA were not very successful and resulted in poor yields, mainly because of very slow reactions even with DMF as solvent. In all subsequent reactions the carboxylic acids **9** and **10** were converted to the corresponding acid chlorides using oxalyl chloride.

Series of inhibitors were synthesized using substituted (*S*)-phenyloxazolidinones at P2 and different phenylsulfonamide groups at the P2′ position for structure−activity relationship (SAR) studies. Following the deprotection of sulfonamide intermediates **14**−**19**, the resulting amines were reacted with (*S*)-*N*-phenyloxazolidinone-5-carbonyl chlorides obtained by the activation of the corresponding carboxylic acids **10b**−**g** to afford the target compounds **21** and **25**−**29** (Scheme 2). The compounds **23b**−**f** containing 4-nitrophenylsulfonamide group at P2′ position were transformed to the corresponding 4-aminophenylsulfonamide derivatives **25b**−**f** by the reduction of the nitro group.

In addition to the compounds described above, series of compounds were prepared with variations at three different positions. The isobutyl group at the P1′ position was replaced with three cyclic primary amines. Again, starting from commercially available chiral epoxide **11**, the target compounds were synthesized using an analogous synthetic route (Scheme 3). In brief, ring opening of epoxide **11** with primary amines **30a**−**c** provided amino alcohols **31a**−**c**. Reactions of various substituted phenylsulfonyl chlorides with **31a**−**c** provided sulfonamides **32**−**35**. After deprotection of intermediate compounds **32**−**35**, the resulting amines were reacted with (*S*)-*N*-phenyloxazolidinone-5-carbonyl chlorides prepared from the corresponding

**Scheme 3.** Synthesis of Inhibitors **36**−**39**[a]




[a] (a) *i*PrOH or EtOH, 80 °C, 3−4 h; (b) aq $Na_2CO_3$, $CH_2Cl_2$, 0 °C to rt, 4−8 h; (c) TFA, $CH_2Cl_2$, 1 h; (d) $(COCl)_2$, rt, overnight; (e) $Et_3N$, THF, 0 °C to rt, 4−8 h.

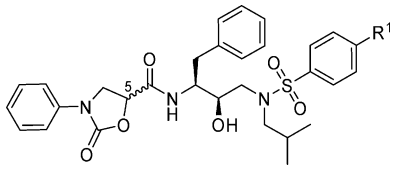
carboxylic acids **10** to afford the target compounds **36**−**39** (Scheme 3).

### Biological Evaluation of Inhibitors

HIV protease inhibitor activities were determined by the fluorescence resonance energy transfer (FRET) method.[32] Protease substrate [Arg-Glu(EDANS)-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-Lys(DABCYL)-Arg] was labeled with the energy transfer donor (EDANS) and acceptor (DABCYL) dyes at its two ends to perform FRET. The inhibitor binding dissociation constant ($K_i$ value) was obtained by nonlinear regression fitting to the plot of initial velocity as a function of inhibitor concentration.[33] The activities of all the synthesized inhibitors against wild-type HIV-1 protease (Q7K) were determined in triplicate. Chemical structures of inhibitors and their inhibitory activities ($K_i$ values) are presented in Table 1. A small set of protease inhibitors with potent activities against wild-type protease was studied against a panel of MDR variants of HIV-1 protease each representing different paradigms of resistance. The mutant variants were selected by examining the Stanford HIV-1 Drug Resistance Database (http://hivdb.stanford.edu), which contains sequences of HIV-1 isolates from HIV-1-infected persons. The three selected protease variants represent the pattern of resistance mutations that occur under the selective pressure of three or more currently prescribed protease inhibitors.[34] These MDR variants are L10I, G48V, I54V, L63P, V82A (M1); D30N, L63P, N88D (M2); and L10I, L63P, A71V, G73S, I84V, L90M (M3). The inhibitory activities of selected protease inhibitors against M1−M3 mutant HIV-1 proteases were examined. For comparison, two currently marketed drugs, APV and LPV, were also studied against the selected panel of mutant proteases.

### Results and Discussion

To test the design concept, protease inhibitors based on the hydroxyethylamine isostere incorporating unsubstituted *N*-phenyloxazolidinone-5-carboxamide were prepared and their inhibitory activities against the wild-type HIV-1 protease were determined. It was also critical to determine which stereoisomer of phenyloxazolidinone-based P2 ligand will bind more favorably to the protease. For these preliminary investigations, two pairs of compounds containing either (*R*)- or (*S*)-*N*-phenyloxazolidinone-5-carboxylic acid [(5*R*)-**9a** or (5*S*)-**10a**] and two phenylsulfonamide groups, 4-methoxy- and 4-aminophenylsulfonamide, were prepared and tested (Figure 2). The inhibitors **20a** and **24a** containing (5*R*)-**9a** attached at P2 and both 4-methoxy- and 4-amino-substituted phenylsulfonamides at the P2′ position exhibited nanomolar inhibitory activities against




(5*R*)-**20a** ($R^1$ = $OCH_3$) Ki = 10.7 nM
(5*S*)-**21a** ($R^1$ = $OCH_3$) Ki = 0.10 nM
(5*R*)-**24a** ($R^1$ = $NH_2$) Ki = 37.4 nM
(5*S*)-**25a** ($R^1$ = $NH_2$) Ki = 0.53 nM

**Figure 2.** Structure and inhibitory activities of new protease inhibitors.

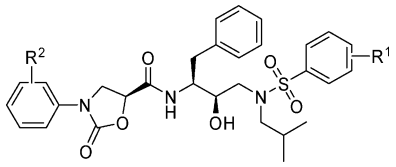
wild-type HIV-1 protease with $K_i$ = 10.7 and 37.4 nM, respectively. When (5*S*)-**10a** was attached at the P2 position, there was significant improvement in the inhibitory activities with both phenylsulfonamide groups. Interestingly, the compound **21a** with 4-methoxybenzenesulfonamide as P2′ ligand was more potent ($K_i$ = 0.1 nM) than the 4-aminobenzenesulfonamide analogue **25a** ($K_i$ = 0.53 nM). The protease inhibitory activities of compounds **21a** and **25a** are comparable to that of structurally related drug APV (**1**) with $K_i$ = 0.10 nM in our assay.

These results clearly show that hydroxyethylamine isostere based inhibitors incorporating *N*-phenyloxazolidinone-5-carboxamides as P2 ligands exhibit potent HIV-1 protease inhibitory activities. These studies also suggest that compounds containing (5*S*)-*N*-phenyloxazolidinone-5-carboxamides are more potent inhibitors of HIV-1 protease compared to the corresponding (5*R*)-inhibitors. Thus, in subsequent SAR studies, only (*S*)-*N*-phenyloxazolidinone-5-carboxylic acids **10a**−**g** were used.

**Structure**−**Activity Relationship Studies.** To explore the possibilities of enhancing the potency of **21a** and **25a**, we synthesized and tested series of analogues with variations at both the P2 and P2′ positions. The inhibitor series **21** and **25**−**29** were prepared using a small set of mainly substituted (*S*)-*N*-phenyloxazolidinone-5-carboxylic acids **10b**−**g** linked to the (*R*)-(hydroxyethylamino)sulfonamides **14**−**19** as P2 ligands (Scheme 2). All the compounds were evaluated for their activities against wild-type HIV-1 protease, and $K_i$ values are presented in Table 1, where the $K_i$ values of **21a** and **25a** are also included. The inhibitory activities of APV and LPV were also determined using the same assay conditions, and $K_i$ data are included in Table 1 for comparison.

In the first series of inhibitors, the 4-methoxybenzenesulfonamide group at P2′ was kept constant, and substituted *N*-phenyloxazolidinones **10b**−**g** were attached to the (*R*)-(hydroxyethylamino)sulfonamide isostere **14** as P2 ligands. Compared to **21a**, all the compounds with a substituted phenyl ring (**21b**−

**Table 1.** Inhibitory Activities of Compounds against Wild-type HIV-1 Protease



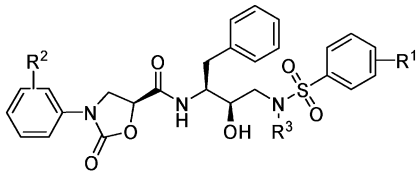
| compd | $R^1$ | $R^2$ | $K_i$ (nM) |
|---|---|---|---|
| **21a** | 4-$OCH_3$ | H | 0.10 |
| **21b** | 4-$OCH_3$ | 3-F | 0.083 |
| **21c** | 4-$OCH_3$ | 3,4-di-F | 0.066 |
| **21d** | 4-$OCH_3$ | 3-$CF_3$ | 0.006 |
| **21e** | 4-$OCH_3$ | 3-Ac | 0.0008 |
| **21f** | 4-$OCH_3$ | 4-Ac | 0.004 |
| **21g** | 4-$OCH_3$ | 3-$OCH_3$ | 0.045 |
| **25a** | 4-$NH_2$ | H | 0.530 |
| **25b** | 4-$NH_2$ | 3-F | 0.170 |
| **25c** | 4-$NH_2$ | 3,4-di-F | 0.230 |
| **25d** | 4-$NH_2$ | 3-$CF_3$ | 0.042 |
| **25e** | 4-$NH_2$ | 3-Ac | 0.032 |
| **25f** | 4-$NH_2$ | 4-Ac | 0.184 |
| **26b** | 3,4-$OCH_2O$- | 3-F | 0.107 |
| **26c** | 3,4-$OCH_2O$- | 3,4-di-F | 0.085 |
| **26d** | 3,4-$OCH_2O$- | 3-$CF_3$ | 0.016 |
| **26e** | 3,4-$OCH_2O$- | 3-Ac | 0.006 |
| **26f** | 3,4-$OCH_2O$- | 4-Ac | 0.016 |
| **27b** | 3-F, 4-$OCH_3$ | 3-F | 0.070 |
| **27c** | 3-F, 4-$OCH_3$ | 3,4-di-F | 0.343 |
| **27d** | 3-F, 4-$OCH_3$ | 3-$CF_3$ | 0.072 |
| **27e** | 3-F, 4-$OCH_3$ | 3-Ac | 0.133 |
| **27f** | 3-F, 4-$OCH_3$ | 4-Ac | 0.080 |
| **28d** | 4-$OCF_3$ | 3-$CF_3$ | 10.0 |
| **28e** | 4-$OCF_3$ | 3-Ac | 2.0 |
| **29a** | 3-$OCH_3$ | H | 3.80 |
| **29f** | 3-$OCH_3$ | 4-Ac | 0.84 |
| APV | | | 0.10 |
| LPV | | | 0.005 |

**g**) exhibited improved inhibitory activities against HIV-1 protease (Table 1, entries 1−7). For the inhibitors with 3-fluoro and 3,4-difluoro groups on the phenyl ring, **21b** and **21c**, the improvement was relatively minor; $K_i$ values of **21b** and **21c** are 80 and 66 pM, respectively. Introduction of polar groups trifluoromethyl, acetyl, and methoxy at positions 3 and 4 of the phenyl ring resulted in a significant increase in the potency of the inhibitors. The $K_i$ value of compound **21d** with a 3-trifluoromethyl group is 6 pM and the 3-methoxy analogue **21g** showed a $K_i$ value of 45 pM. Inhibitors **21e** and **21f** with 3- and 4-acetyl groups are the most potent HIV-1 protease inhibitors discovered in our studies, with $K_i$ values of 0.8 and 4 pM, respectively.

The protease inhibitors **25b**−**f** with 4-aminobenzenesulfonamide at P2′ did not show much improvement in the protease inhibitory activities, as was observed in the corresponding 4-methoxy analogues **21**. Only the inhibitors with a 3-trifluoromethyl- and 3-acetyl-substituted phenyl ring, **25d** ($K_i$ = 42 pM) and **25e** ($K_i$ = 32 pM), exhibited a significant increase in potency compared to the unsubstituted analogue **25a**. Inhibitors with 3-fluoro (**25b**), 3,4-difluoro (**25c**), and 4-acetyl (**25f**) groups at the phenyl ring showed relatively small improvement in activities compared to **25a** (Table 1, entries 9, 10, and 13). Compounds **26b**−**f** with another commonly used P2′ ligand, 1,3-benzodioxolane sulfonamide, also showed very potent inhibitory activities. Again, inhibitors with 3-trifluoromethyl (**26d**), 3-acetyl (**26e**) and 4-acetyl (**26f**) groups at the phenyl ring of oxazolidinone were the most potent against HIV-1 protease, with $K_i$ values of 16, 6, and 16 pM, respectively.

The introduction of disubstituted 3-fluoro-4-methoxyphenylsulfonamide at P2′ (**27b**−**f**) showed mixed results with different substituted phenyloxazolidinones at P2. It appears that the addition of a 3-fluoro group on the phenyl ring at P2′ is not well tolerated. Relatively low $K_i$ values were observed for derivatives with 3-fluoro (**27b**, $K_i$ = 70 pM), 3-trifluoromethyl (**27d**, $K_i$ = 72 pM), and 4-acetyl (**27f**, $K_i$ = 80 pM) groups compared to derivatives with 3,4-difluoro (**27c**, $K_i$ = 343 pM) and 3-acetyl (**27e**, $K_i$ = 133 pM) groups. The replacement of 4-methoxyphenyl with 4-trifluoromethoxyphenyl resulted in substantial loss of activity (inhibitors **28d**−**e**). Changing the position of the methoxy group from the 4- to the 3-position in **29a** and **29f** also resulted in significant loss of protease inhibitory activity (Table 1, entries 26 and 27). These results suggest that inhibitors with the electron-donating substituents methoxy, dioxolane, and amino at the P2′ phenylsulfonamide group exhibit potent HIV-1 protease inhibitory activities. Other substitutions and modifications are not well tolerated and could result in significant loss of protease inhibitory activity.

**Table 2.** Inhibitory Activities of Compounds against Wild-type HIV-1 Protease



| Compd | $R^1$ | $R^2$ | $R^3$ | *K*i (nM) |
|---|---|---|---|---|
| **36b** | 4-$OCH_3$ | 3-F |  | 0.257 |
| **36c** | 4-$OCH_3$ | 3,4-di-F |  | 0.58 |
| **36f** | 4-$OCH_3$ | 4-Ac |  | 0.80 |
| **37a** | 3-$OCH_3$ | H |  | 238.7 |
| **37b** | 3-$OCH_3$ | 3-F |  | 188.8 |
| **37f** | 3-$OCH_3$ | 4-Ac |  | 29.5 |
| **38a** | 2,4,5-tri-F | H |  | 170.2 |
| **38b** | 2,4,5-tri-F | 3-F |  | 160.2 |
| **38f** | 2,4,5-tri-F | 4-Ac |  | 167.7 |
| **39a** | 3-$OCH_3$ | H |  | 42.0 |
| **39b** | 3-$OCH_3$ | 3-F |  | 150.0 |

In addition to the variations at the P2 and P2′ positions, the SAR effort was extended to replace the isobutyl group at P1′ with cyclic groups. Selected primary amines **30a**−**c** include a small hydrophobic group, cyclopropylmethylamine, as well as polar saturated (*S*)-(2-tetrahydrofuranyl)methylamine and unsaturated 2-(thiophenyl)methylamine heterocyclic groups. Again, sulfonyl chlorides utilized at the $R^1$ position are all substituted benzene derivatives containing functional groups at various positions. A small set of compounds with variations at all three $R^1$, $R^2$, and $R^3$ positions, corresponding to P2′, P2, and P1′, were prepared and tested (Table 2). To our surprise, replacing the isobutyl group at P1′ with cyclopropylmethyl resulted in significantly lower inhibitory activities. The $K_i$ values of **36b** (257 pM), **36c** (580 pM), and **36f** (800 pM) are about 3-, 9-, and 200-fold higher than the corresponding inhibitors with isobutyl group at the P1′ position. Inhibitors **37**−**39** with (2-thiophenyl)methyl and (*S*)-(2-tetrahydrofuranyl)methyl groups at the P1′ position all showed very weak inhibitory activities against HIV-1 protease (Table 2, entries 4−11).

**Table 3.** X-ray Crystallographic Data Collection and Refinement Statistics for Complexes of **21e** and **21f** with the Wild-type HIV-1 Protease

| | **21e** | **21f** |
|---|---|---|
| resolution (Å) | 1.95 | 1.8 |
| temperature (°C) | -80 | -80 |
| space group | $P2_12_12_1$ | $P2_12_12_1$ |
| *a* (Å) | 50.78 | 50.77 |
| *b* (Å) | 58.31 | 57.65 |
| *c* (Å) | 61.69 | 61.89 |
| *Z* | 4 | 4 |
| $R_{merge}$ (%) | 4.7 | 5.0 |
| completeness (%) | 95.3 | 95.6 |
| total no. of reflections | 65 161 | 107 046 |
| no. of unique reflections | 13 238 | 16 632 |
| $R_{free}$ (%) | 21.6 | 18.5 |
| $R_{factor}$ (%) | 16.6 | 16.0 |
| RMSD[a] | | |
| bond length (Å) | 0.008 | 0.007 |
| bond angle (deg) | 1.294 | 1.232 |
| no. of crystallographic waters | 159 | 174 |
| PDB code[b] | 2I0D | 2I0A |

[a] RMSD, root-mean-square deviation. [b] PDB, Protein Data Bank.

**Crystal Structures of HIV-1 Protease Complexes.** Crystal structures of the two most potent inhibitors, **21e** and **21f**, in complex with wild-type HIV-1 protease have been determined to a resolution of 1.95 and 1.8 Å, respectively.[35] Both compounds are similar except for the position of the acetyl group on the phenyl ring attached to the oxazolidinone moiety at P2. The refinement statistics are presented in Table 3. The high resolution of the structures combined with the unambiguous density for the inhibitors and the active site residues allow for a detailed analysis of the intermolecular interactions present in the complexes. The backbone atoms in the two structures superimpose within 0.16 Å. The inhibitors also superimpose well on each other in the crystal structures, and the inhibitor−protease contacts are almost similar except at the substituted phenyloxazolidinone moiety, where the position of the acetyl group is different in **21e** and **21f**. Figure 3 shows the inhibitor−protease hydrogen bonds in the **21e** and **21f** complexes, including those mediated by water. Table 4 shows the hydrogen-bond distances observed in the crystal structures. Except for one hydrogen bond in **21f**, the hydrogen-bonding pattern is almost the same in both the structures. As observed with other protease inhibitors, a water molecule tetrahedrally coordinated the backbone nitrogen atoms in Ile50 of both monomers of the protease at the tips of the flaps to the sulfonyl and carbonyl groups of the inhibitors. The central hydroxyl group forms hydrogen bonds with the carboxylate groups of the catalytic aspartic acids of the protease, Asp25 and Asp25′, located in the floor of the active site. The amide nitrogen of the inhibitors forms a hydrogen bond with the main chain carbonyl of Gly27. The central skeleton of **21e** and **21f** is similar to that of APV (**1**) and DRV (**2**). All the hydrogen bonds mentioned above are also observed in the crystal structures of **1** and **2**.

The methoxy group at the P2′ end of the inhibitors **21e**/**21f** forms a hydrogen bond with the backbone nitrogen of the protease residue Asp30′ with a distance of 3.4/3.3 Å. The 4-acetyl group on the other end of the **21f** does not form any hydrogen bond with the protease but extends beyond the protease into the solvent. The carbonyl of the 3-acetyl group in **21e** forms van der Waals (VDW) contacts with the residues Gly48, Gly49, and Pro81′ of the protease. The methyl group of the acetyl moiety forms VDW contacts with the phenyl ring of Phe53 in the flap region in both the structures. This interaction pattern involving Phe53 has not been seen in other FDA-approved protease inhibitors.

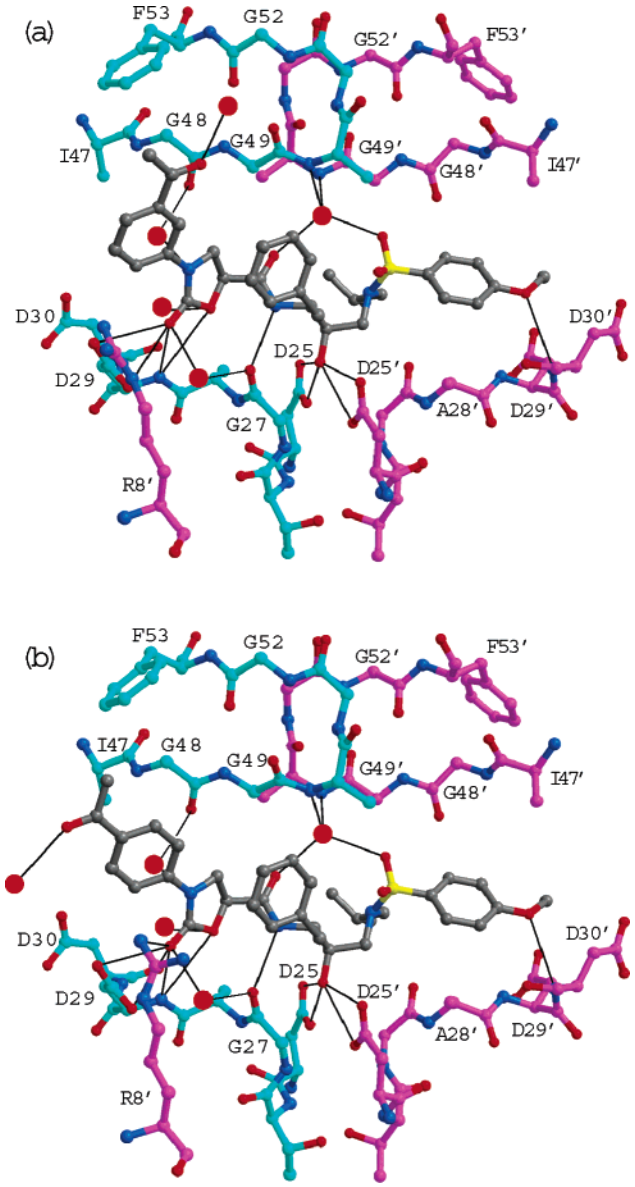
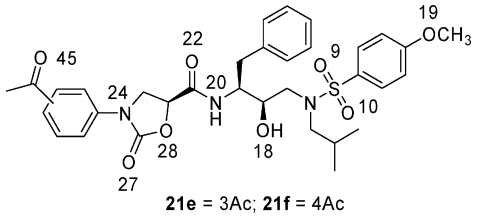



**Figure 3.** Hydrogen bonds, shown as black lines, observed in the protease complexes of (a) **21e** and (b) **21f**. The two monomers and the inhibitor are shown in cyan, magenta, and gray, respectively. Nitrogen, oxygen, and sulfur atoms are in blue, red, and yellow, respectively.

The carbonyl group of the oxazolidinone ring of both **21e** and **21f** forms hydrogen bonds with the backbone nitrogen and side chain oxygen atoms of Asp29. This carbonyl group also forms a weak hydrogen bond (3.5 Å) with the side chain of Arg8′ in **21f**, whereas the Arg8′ in **21e** points away from the carbonyl group. This is one of the major differences between the two structures. A water molecule bridges this carbonyl group with the oxygen atom of the Gly27 at the bottom of the active site through hydrogen bonds. The oxazolidinone ring in both the structures forms VDW contacts with the residues Gly48 and Gly49 in the upper region of the active site and with the residues Gly27, Ala28, and Asp29 in the lower region of the active site. In addition, it forms VDW contacts with Arg8′ in **21f**. A water molecule connects the nitrogen atom of the oxazolidinone ring to the oxygen atom of Gly48 in the flap through hydrogen bonding, and another water molecule connects the oxygen atom in the oxazolidinone ring to the backbone nitrogen of Asp30 in both the structures.

The protease inhibitors incorporating phenyloxazolidinones as P2 ligands form many interesting hydrogen bonds, some

**Table 4.** Hydrogen-Bonding Distances between Protease and Inhibitor Atoms in the Crystal Structures of **21e** and **21f**




**21e** = 3Ac; **21f** = 4Ac

| protease atom | inhibitor atom | distance (Å) | |
|---|---|---|---|
| | | **21e** | **21f** |
| Asp 29 N | O27 | 3.0 | 3.0 |
| Asp 29 OD1 | O27 | 3.2 | 3.1 |
| Asp 29 OD2 | O27 | 3.3 | 3.2 |
| water | O27 | 3.0 (W3)[a] | 3.0 (W82) |
| Arg 8′ NH2 | O27 | | 3.5 |
| Asp 29 N | O28 | 3.6 | 3.6 |
| water | O28 | 3.1 (W10) | 3.1 (W88) |
| Gly 27 O | N20 | 3.1 | 3.2 |
| water | O45 | 2.8 (W152) | 3.5 (W64) |
| water | N24 | 3.4 (W124) | 3.3 (W47) |
| Asp 25 OD1 | O18 | 2.5 | 2.6 |
| Asp 25 OD2 | O18 | 3.3 | 3.3 |
| Asp 25′ OD1 | O18 | 2.5 | 2.5 |
| Asp 25′ OD2 | O18 | 2.9 | 2.9 |
| flap water | O22 | 2.7 (W12) | 2.7 (W17) |
| flap water | O9 | 2.7 (W12) | 2.8 (W17) |
| Asp 30′ N | O19 | 3.4 | 3.3 |

[a] The corresponding water number is in parentheses.

**Table 5.** Inhibitory Activities of Compounds against MDR Variants of HIV-1 Protease[a]

| compd | $K_i$ (nM) | | | |
|---|---|---|---|---|
| | Wt | M1 | M2 | M3 |
| **21b** | 0.083 | 3.56 | 0.080 | 4.94 |
| **21c** | 0.066 | 1.18 | 0.152 | 8.69 |
| **21e** | 0.0008 | 0.16 | 0.039 | 3.36 |
| **21f** | 0.004 | 0.78 | 0.179 | 1.94 |
| **25a** | 0.53 | 2.08 | 0.92 | 10.3 |
| **25d** | 0.042 | 4.42 | 0.36 | 12.3 |
| **26e** | 0.006 | 0.72 | 0.235 | 3.51 |
| APV | 0.10 | 0.15 | 0.21 | 1.40 |
| LPV | 0.005 | 6.10 | 0.04 | 0.90 |

[a] Wt: Q7K. M1: L10I, G48V, I54V, L63P, V82A. M2: D30N, L63P, N88D. M3: L10I, L63P, A71V, G73S, I84V, L90M.

directly with the protease and some bridging through the water molecules to the protease. The side chain of Asp30 near the oxazolidinone ring does not participate in direct hydrogen bonding with the inhibitor in both the structures. The structural knowledge obtained from the two crystal structures can be utilized to design new compounds of high binding affinity by varying substituents on the phenyloxazolidinone ring so as to form hydrogen bonds with Asp30.

**Inhibitor Activities against MDR Variants.** Selected inhibitors that exhibited potent activities against wild-type HIV-1 protease were further evaluated for their activities against a panel of MDR protease variants that represent different paradigms of resistance found in HIV-1-infected persons.[34] At least one compound was selected from each of the series incorporating different phenyloxazolidinone-based P2 ligands. In some cases, different functional group variations on the benzenesulfonamide fragment were selected in preference to compounds with the lowest $K_i$ values in that series. The $K_i$ values of selected inhibitors against M1−M3 MDR variants of protease are presented in Table 5. Two known drugs, APV and LPV, were also studied for comparisons. The data show that all protease inhibitors lose affinity against mutant variants compared to the wild-type protease. However, the relative loss of activity is different in different class of inhibitors. While LPV significantly loses activity against protease variants M1 and M3, it still retains high affinity against the M2 variant. In the case of APV, the relative loss of activity is not that significant against all mutants, but its $K_i$ value for wild-type is also relatively high. The protease inhibitors with *N*-phenyloxazolidinone at P2 showed some loss of activities against M1 variant and significant loss against M3 variant but still retained potent inhibitory activities against M2 variant. These data are consistent with an analysis of the crystal structures. The M1 and M3 variants are more severely drug resistant, with M1 having the active site mutations V82A and G48V and M3 having I84V and L90M, whereas M2 is more representative of nelfinavir resistance with D30N. G48V could potentially cause a van der Waals clash with the acetyl group in **21e**, while V82A and I84V would potentially cause a loss of van der Waals contacts. As no group is making an ionic interaction with the side chain of D30, the D30N mutation in M2 should have minimal effect on the $K_i$, as is observed. Interestingly, the most potent protease inhibitor, **21e**, starts out with extremely tight affinity for the wild-type enzyme ($K_i$ = 0.8 pM), and even against the resistant variants it retains picomolar to low nanomolar $K_i$, which is highly comparable with the best FDA-approved protease inhibitors.

## Conclusions

In summary, we have discovered novel and highly potent HIV-1 protease inhibitors based on the (hydroxyethylamino)-sulfonamide isostere incorporating *N*-phenyloxazolidinone-5-carboxamides as P2 ligands. The inhibitors with the (*S*)-enantiomer of *N*-phenyloxazolidinone-5-carboxylic acid attached at P2 are significantly more potent compared to the corresponding compounds with the (*R*)-enantiomer. Preliminary SAR studies suggest that both electron-donating and -withdrawing groups are well-tolerated on the phenyl ring of the oxazolidinone fragment at P2 position. The addition of any functionality on the phenyl ring results in significantly increased inhibitory activities against HIV-1 protease. On the P2′ side, inhibitors with electron-donating substituents at phenylsulfonamide group exhibited highly potent HIV-1 protease inhibitory activities. Other substitutions and modifications are not well tolerated and result in significant loss of protease inhibitory activity. In current SAR studies, only *N*-phenyloxazolidinone moieties with the phenyl group substituted at various positions were used. The structural knowledge obtained from the two crystal structures of the drug-enzyme complexes in this series can be utilized to design new protease inhibitors that may interact with relatively conserved residues in the protease active site. A variety of *N*-aryl-, heteroaryl-, acyl-, and alkyloxazolidinone derivatives could be utilized as potential P2 ligands, thus vastly expanding the possibilities of finding new potent inhibitors in future SARs. Several new inhibitors exhibiting low picomolar inhibitory activities against wild-type protease were evaluated for their activity against a panel of MDR proteases. The most potent protease inhibitor, **21e**, with a $K_i$ value of 0.8 pM against wild-type HIV-1 protease, also showed potent activity against MDR enzymes. In future studies, the bioavailability and antiviral activities of these inhibitors will be investigated.

## Experimental Section

**General.** $^1$H and $^{13}$C NMR spectra were recorded on a Varian 400 MHz NMR spectrometer, operating at 400 MHz for $^1$H and 100 MHz for $^{13}$C. Chemical shifts are reported in ppm relative to the solvent signal, and coupling constant (*J*) values are reported in hertz (Hz). Thin-layer chromatography (TLC) was performed on

E. Merck silica gel 60-F-254 plates, and spots were visualized with UV light. Flash column chromatography was performed using 230−400 mesh silica gels (E-Merck). High-resolution mass spectra (HRMS) were recorded on a Waters Q-TOF Premier mass spectrometer by direct infusion of solutions of each compound using electrospray ionization (ESI) in positive mode. Low-resolution mass spectra were obtained using a Waters Alliance HT/Micromass ZQ system (ESI). Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Anhydrous dichloromethane, *N*,*N*-dimethylformamide (DMF), benzene, and toluene were purchased from Aldrich and used as such. All reagents and chemicals were purchased from commercial vendors and used as received. Analytical reversed-phase high performance liquid chromatography (HPLC) was performed on a Waters Separation Module 2695 system equipped with an autosampler and a Waters 996 photodiode array detector. Purity of the final compounds was determined using two different chromatographic systems. First system: column, Waters Nova-Pak RP-C18 (4 $\mu$m, 3.9 mm × 150 mm); mobile phase A, 10 mM ammonium acetate in water; mobile phase B, acetonitrile; flow rate of 0.8 mL/min, gradient elution was performed from 50% B to 100% B over 10 min. Second system: column, Agilent Zorbax 300SB-C8 (5 $\mu$m, 4.6 mm × 250 mm); mobile phase A, 0.1% trifluoroacetic acid (TFA) in water; mobile phase B, 0.1% TFA in acetonitrile; gradient elution was performed from 50% B to 100% B over 10 min at a flow rate of 1 mL/min. A table containing the retention time and purity of each final compound is in Supporting Information.

**Synthesis of Designed Protease Inhibitors.** General experimental procedures for the synthesis of intermediates phenyloxazolidinones (**9** and **10**) and (*R*)-(hydroxyethylamino)sulfonamides (**14**−**19** and **32**−**35**) and for the coupling reactions to provide the target compounds (**20**−**29** and **36**−**39**) are provided in the Supporting Information.

**(5*R*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl[(4-methoxyphenyl)sulfonyl]amino]propyl]-2-oxo-3-phenyloxazolidine-5-carboxamide (20a):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (d, $J$ = 8.8 Hz, 2H), 7.46 (d, $J$ = 8.4 Hz, 2H), 7.35 (t, $J$ = 7.6 Hz, 2H), 7.24−7.13 (m, 6H), 6.92 (d, $J$ = 8.8 Hz, 2H), 6.75 (d, $J$ = 8.4 Hz, 1H), 4.71 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.17 (m, 2H), 4.07 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.91 (m, 1H), 3.84 (m, 1H), 3.82 (s, 3H), 3.10−2.77 (m, 6H), 1.76 (m, 1H), 0.84 (d, $J$ = 6.4 Hz, 3H), 0.79 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.98, 163.23, 153.06, 137.49, 137.46, 129.91, 129.67 (2C), 129.44 (2C), 129.41 (2C), 128.79 (2C), 126.96, 124.95, 118.55 (2C), 114.54 (2C), 72.28, 70.03, 58.90, 55.80, 54.41, 53.56, 48.19, 35.05, 27.46 20.25, 20.11; HRMS (ESI) *m/z* $C_{31}H_{38}N_3O_7S$ $(M + H)^+$ calcd 596.2430, found 596.2421.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl[(4-methoxyphenyl)sulfonyl]amino]propyl]-2-oxo-3-phenyloxazolidine-5-carboxamide (21a):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 8.8 Hz, 2H), 7.45−7.38 (m, 4H), 7.19 (t, $J$ = 7.2 Hz, 1H), 7.12 (d, $J$ = 7.2 Hz, 2H), 7.04−6.98 (m, 4H), 6.89 (t, $J$ = 7.6 Hz, 1H), 6.69 (d, $J$ = 9.6 Hz, 1H), 4.77 (dd, $J$ = 9.6, 5.6 Hz, 1H), 4.22 (m, 1H), 4.04 (t, $J$ = 9.6 Hz, 1H), 3.90 (m, 1H), 3.87 (s, 3H), 3.78 (d, $J$ = 2.4 Hz, 1H), 3.36 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.23 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.11 (dd, $J$ = 13.6, 4.4 Hz, 1H), 3.02 (dd, $J$ = 13.6, 8.8 Hz, 1H), 2.96 (dd, $J$ = 15.2, 2.8 Hz, 1H), 2.81 (dd, $J$ = 13.6, 6.8 Hz, 1H), 2.73 (dd, $J$ = 14.0, 10.8 Hz, 1H), 1.84 (m, 1H), 0.96 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.86, 163.25, 153.12, 137.52, 137.49, 129.94, 129.68 (2C), 129.50 (2C), 129.26 (2C), 128.50 (2C), 126.61, 124.76, 118.47 (2C), 114.56 (2C), 72.46, 69.87, 58.91, 55.79, 53.78, 53.52, 48.29, 35.64, 27.44, 20.31, 20.07; HRMS (ESI) *m/z* $C_{31}H_{38}N_3O_7S$ $(M + H)^+$ calcd 596.2430, found 596.2438.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl[(4-methoxyphenyl)sulfonyl]amino]propyl]-3-(3-fluorophenyl)-2-oxooxazolidine-5-carboxamide (21b):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 8.8 Hz, 2H), 7.39−7.33 (m, 2H), 7.10 (m, 3H), 7.04−6.98 (m, 4H), 6.93−6.85 (m, 2H), 6.68 (d, $J$ = 9.6 Hz, 1H), 4.78 (dd, $J$ = 10.2, 6.0 Hz, 1H), 4.23 (m, 1H), 4.01 (t, $J$ = 9.6 Hz, 1H), 3.91 (m, 1H), 3.88 (s, 3H), 3.68 (br s, 1H), 3.32 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.23 (dd, $J$ = 14.8, 9.2 Hz, 1H), 3.10 (dd, $J$ = 13.6, 4.4 Hz, 1H), 3.03 (dd, $J$ = 13.2, 8.8 Hz, 1H), 2.97 (dd, $J$ = 15.2, 2.4 Hz, 1H), 2.81 (dd, $J$ = 13.6, 6.8 Hz, 1H), 2.73 (dd, $J$ = 14.0, 10.4 Hz, 1H), 1.84 (m, 1H), 0.96 (d, $J$ = 6.4 Hz, 3H), 0.90 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.60, 163.29, 163.18 (d, $J$ = 244.2 Hz), 152.82, 138.98 (d, $J$ = 10.6 Hz), 137.48, 130.48 (d, $J$ = 9.1 Hz), 129.91, 129.70 (2C), 129.50 (2C), 128.49 (2C), 126.60, 114.58 (2C), 113.52 (d, $J$ = 2.3 Hz), 111.49 (d, $J$ = 21.2 Hz), 106.06 (d, $J$ = 27.3 Hz), 72.47, 69.82, 58.95, 55.82, 53.79, 53.44, 48.20, 35.56, 27.46, 20.31, 20.08; HRMS (ESI) *m/z* $C_{31}H_{37}FN_3O_7S$ $(M + H)^+$ calcd 614.2336, found 614.2357.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl[(4-methoxyphenyl)sulfonyl]amino]propyl]-3-(3,4-difluorophenyl)-2-oxooxazolidinone5-carboxamide (21c):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (m, 2H), 7.54−7.48 (m, 1H), 7.19 (dd, $J$ = 18.4, 8.8 Hz, 1H), 7.12 (d, $J$ = 6.8 Hz, 2H), 7.05−6.97 (m, 5H), 6.89 (t, $J$ = 7.6 Hz, 1H), 6.75 (d, $J$ = 10.0 Hz, 1H), 4.78 (dd, $J$ = 9.6, 5.6 Hz, 1H), 4.25 (m, 1H), 3.99 (t, $J$ = 9.2 Hz, 1H), 3.92 (m, 1H), 3.87 (s, 3H), 3.69 (d, $J$ = 3.2 Hz, 1H), 3.31 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.22 (dd, $J$ = 15.2, 9.6 Hz, 1H), 3.12−2.97 (m, 3H), 2.82 (dd, $J$ = 13.2, 6.8 Hz, 1H), 2.74 (dd, $J$ = 14.0, 11.2 Hz, 1H), 1.84 (m, 1H), 0.95 (d, $J$ = 6.4 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.45, 163.35, 152.78, 150.49 (dd, $J$ = 246.4, 13.6 Hz), 147.41 (dd, $J$ = 245.0, 12.1 Hz), 137.46, 134.03 (m), 129.87, 129.72 (2C), 129.55 (2C), 128.53 (2C), 126.61, 117.62 (d, $J$ = 18.2 Hz), 114.62 (2C), 113.85 (q, $J$ = 3.0 Hz), 108.37 (dd, $J$ = 22.8 Hz), 72.47, 69.70, 59.05, 55.84, 53.86, 53.39, 48.25, 35.51, 27.54, 20.34, 20.08; HRMS (ESI) *m/z* $C_{31}H_{36}F_2N_3O_7S$ $(M + H)^+$ calcd 632.2242, found 632.2251.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl[(4-methoxyphenyl)sulfonyl]amino]propyl]-2-oxo-3-[(3-trifluoromethyl)phenyl]-oxazolidine-5-carboxamide (21d):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (dd, $J$ = 10.0, 2.4 Hz, 2H), 7.70 (dd, $J$ = 8.8, 1.6 Hz, 1H), 7.64 (s, 1H), 7.54 (t, $J$ = 8.0 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.12 (dd, $J$ = 8.4, 1.6 Hz, 2H), 7.01−6.96 (m, 4H), 6.83 (t, $J$ = 7.2 Hz, 1H), 6.79 (d, $J$ = 10.0 Hz, 1H), 4.81 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.27 (m, 1H), 4.04 (t, $J$ = 9.6 Hz, 1H), 3.94 (m, 1H), 3.87 (s, 3H), 3.69 (br s, 1H), 3.33 (dd, $J$ = 9.2, 5.6 Hz, 1H), 3.22 (dd, $J$ = 15.6, 9.6 Hz, 1H), 3.10 (dd, $J$ = 14.0, 4.4 Hz, 1H), 3.04−2.98 (m, 2H), 2.83 (dd, $J$ = 13.2, 6.8 Hz, 1H), 2.74 (dd, $J$ = 14.0, 10.8 Hz, 1H), 1.85 (m, 1H), 0.95 (d, $J$ = 6.4 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.49, 163.34, 152.83, 138.19, 137.43, 131.76 (d, $J$ = 32.6 Hz), 129.93, 129.87, 129.72 (2C), 129.53 (2C), 128.52 (2C), 126.58, 121.40, 121.24 (q, $J$ = 3.8 Hz), 115.02 (q, $J$ = 3.8 Hz), 114.61 (2C), 72.50, 69.86, 59.03, 55.83, 53.84, 53.36, 48.10, 35.56, 27.52, 20.34, 20.08; HRMS (ESI) *m/z* $C_{32}H_{37}F_3N_3O_7S$ $(M + H)^+$ calcd 664.2304, found 664.2316.

**(5*S*)-3-(3-Acetylphenyl)-*N*-[(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[isobutyl[(4-methoxyphenyl)sulfonyl]amino]propyl]-2-oxooxazolidine-5-carboxamide (21e):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (t, $J$ = 1.6 Hz, 1H), 7.80−7.74 (m, 2H), 7.71 (d, $J$ = 9.2 Hz, 2H), 7.50 (t, $J$ = 8.0 Hz, 1H), 7.10 (d, $J$ = 7.2 Hz, 2H), 6.98 (m, 4H), 6.83 (m, 2H), 4.78 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.23 (m, 1H), 4.05 (t, $J$ = 9.6 Hz, 1H), 3.93 (m, 1H), 3.84 (s, 3H), 3.46 (s, 1H), 3.36 (dd, $J$ = 9.2, 5.6 Hz, 1H), 3.19 (dd, $J$ = 15.2, 9.6 Hz, 1H), 3.09 (dd, $J$ = 14.0, 4.4 Hz, 1H), 3.01−2.95 (m, 2H), 2.82 (dd, $J$ = 13.2, 6.8 Hz, 1H), 2.73 (dd, $J$ = 14.0, 10.8 Hz, 1H), 2.63 (s, 3H), 1.84 (m, 1H), 0.92 (d, $J$ = 6.4 Hz, 3H), 0.88 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.59, 168.59, 163.31, 153.07, 138.10, 138.04, 137.52, 129.91, 129.71 (2C), 129.65, 129.55 (2C), 128.53 (2C), 126.62, 124.71, 123.01, 117.58, 114.60 (2C), 72.54, 69.93, 59.01, 55.82, 53.85, 53.44, 48.23, 35.63, 27.50, 26.90, 20.33, 20.08; HRMS (ESI) *m/z* $C_{33}H_{40}N_3O_8S$ $(M + H)^+$ calcd 638.2536, found 638.2544.

**(5*S*)-3-(4-Acetylphenyl)-*N*-[(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[isobutyl[(4-methoxyphenyl)sulfonyl]amino]propyl]-2-oxooxazolidine-5-carboxamide (21f):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.99 (d, $J$ = 9.2 Hz, 2H), 7.72 (d, $J$ = 8.8 Hz, 2H), 7.53 (d, $J$ = 9.2 Hz, 2H), 7.10 (d, $J$ = 7.2 Hz, 2H), 6.98−6.93 (m, 4H), 6.86 (d, $J$ = 10.0 Hz, 1H), 6.80 (t, $J$ = 7.6 Hz, 1H), 4.80 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.24 (m, 1H), 4.05 (t, $J$ = 9.6 Hz, 1H), 3.95 (m, 1H), 3.85 (s, 3H), 3.33 (dd, $J$ = 9.6, 6.0 Hz, 1H), 3.19 (dd, $J$ = 14.8, 8.8 Hz, 1H),

3.10−2.94 (m, 3H), 2.83 (dd, $J$ = 13.2, 6.4 Hz, 1H), 2.73 (dd, $J$ = 14.0, 11.2 Hz, 1H), 2.60 (s, 3H), 1.84 (m, 1H), 0.92 (d, $J$ = 6.4 Hz, 3H), 0.88 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.99, 168.46, 163.29, 152.75, 141.55, 137.51, 133.13, 129.86, 129.78 (2C), 129.68 (2C), 129.52 (2C), 128.44 (2C), 126.58, 117.57 (2C), 114.58 (2C), 72.47, 69.85, 58.95, 55.81, 53.78, 53.43, 48.0, 35.49, 27.46, 26.65, 20.31, 20.07; HRMS (ESI) *m/z* $C_{33}H_{40}N_3O_8S$ $(M + H)^+$ calcd 638.2536, found 638.2545.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl[(4-methoxyphenyl)sulfonyl]amino]propyl]-3-(3-methoxyphenyl)-2-oxooxazolidine-5-carboxamide (21g):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (m, 2H), 7.29 (t, $J$ = 8.8 Hz, 1H), 7.14 (d, $J$ = 2 Hz, 1H), 7.11 (m, 2H), 7.03 (t, $J$ = 7.2 Hz, 2H), 6.98 (m, 2H), 6.92−6.88 (m, 2H), 6.73 (ddd, $J$ = 8.4, 2.8, 0.8 Hz, 1H), 6.70 (d, $J$ = 9.6 Hz, 1H), 4.75 (dd, $J$ = 10.4, 6.4 Hz, 1H), 4.21 (m, 1H), 4.01 (t, $J$ = 9.6 Hz, 1H), 3.89 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.68 (br s, 1H), 3.32 (dd, $J$ = 9.6, 6.4 Hz, 1H), 3.21 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.10 (dd, $J$ = 14.0, 4.8 Hz, 1H), 3.01 (dd, $J$ = 13.2, 8.8 Hz, 1H), 2.96 (dd, $J$ = 15.2, 2.4 Hz, 1H), 2.80 (dd, $J$ = 13.6, 6.4 Hz, 1H), 2.73 (dd, $J$ = 13.6, 10.4 Hz, 1H), 1.83 (m, 1H), 0.95 (d, $J$ = 6.4 Hz, 3H), 0.89 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.86, 163.37, 160.45, 152.94, 138.72, 137.39, 130.08, 129.87, 129.76 (2C), 129.55 (2C), 128.65 (2C), 126.79, 114.66 (2C), 110.61, 110.33, 104.73, 72.49, 69.77, 59.12, 55.89, 55.65, 53.97, 53.52, 48.41, 35.76, 27.60, 20.40, 20.11; HRMS (ESI) *m/z* $C_{32}H_{40}N_3O_8S$ $(M + H)^+$ calcd 626.2536, found 626.2546.

**(5*R*)-*N*-[(1*S*,2*R*)-3-[[(4-Aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropyl]-2-oxo-3-phenyloxazolidine-5-carboxamide (24a):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52−7.47 (m, 4H), 7.38 (t, $J$ = 8.4 Hz, 2H), 7.24−7.15 (m, 7H), 6.86 (d, $J$ = 8.8 Hz, 1H), 6.61 (d, $J$ = 8.8 Hz, 2H), 4.72 (dd, $J$ = 9.6, 6.4 Hz, 1H), 4.23−4.11 (m, 2H), 4.05 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.95 (m, 1H), 3.87 (br s, 1H), 3.14−2.96 (m, 3H), 2.89−2.80 (m, 3H), 1.78 (m, 1H), 0.86 (d, $J$ = 6.8 Hz, 3H), 0.82 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.79, 153.29, 150.81, 137.68, 137.56, 129.61 (2C), 129.43 (2C), 129.34 (2C), 128.65 (2C), 126.79, 126.20, 124.83, 118.61 (2C), 114.32 (2C), 72.29, 70.12, 58.80, 54.30, 53.53, 48.18, 35.19, 27.33, 20.23, 20.12; HRMS (ESI) *m/z* $C_{30}H_{37}N_4O_6S$ $(M + H)^+$ calcd 581.2434, found 581.2430.

**(5*S*)-*N*-[(1*S*,2*R*)-3-[[(4-Aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropyl]-2-oxo-3-phenyloxazolidine-5-carboxamide (25a):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.4 Hz, 2H), 7.43−7.37 (m, 5H), 7.18 (t, $J$ = 6.8 Hz, 1H), 7.10 (d, $J$ = 7.6 Hz, 2H), 6.98 (m, 3H), 6.87 (t, $J$ = 7.6 Hz, 1H), 6.69 (d, $J$ = 8.0 Hz, 2H), 4.77 (dd, $J$ = 9.6, 6.0 Hz, 1H), 4.23 (m, 1H), 4.02 (t, $J$ = 9.6 Hz, 1H), 3.93 (m, 1H), 3.31 (dd, $J$ = 9.2, 6.4 Hz, 1H), 3.19−3.0 (m, 3H), 2.93 (dd, $J$ = 13.6, 8.8 Hz, 1H), 2.82 (dd, $J$ = 13.2, 6.8 Hz, 1H), 2.71 (t, $J$ = 13.2 Hz, 1H), 1.83 (m, 1H), 0.91 (d, $J$ = 6.4 Hz, 3H), 0.88 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.82, 153.25, 150.64, 137.60, 137.47, 129.68 (2C), 129.51 (2C), 129.26 (2C), 128.46 (2C), 126.55, 126.41, 124.77, 118.49 (2C), 114.57 (2C), 72.45, 69.91, 58.89, 53.74, 53.50, 48.32, 35.63, 27.42, 20.32, 20.10; HRMS (ESI) *m/z* $C_{30}H_{37}N_4O_6S$ $(M + H)^+$ calcd 581.2434, found 581.2438.

**(5*S*)-*N*-[(1*S*,2*R*)-3-[[(4-Aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropyl]-3-(3-fluorophenyl)-2-oxooxazolidine-5-carboxamide (25b):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (d, $J$ = 8.8 Hz, 2H), 7.38−7.33 (m, 2H), 7.12−7.08 (m, 3H), 7.01 (t, $J$ = 8.0 Hz, 2H), 6.93−6.85 (m, 2H), 6.70 (d, $J$ = 8.8 Hz, 3H), 4.78 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.22 (m, 2H), 4.01 (t, $J$ = 9.2 Hz, 1H), 3.91 (m, 1H), 3.73 (br s, 1H), 3.30 (dd, $J$ = 9.2, 5.6 Hz, 1H), 3.22 (dd, $J$ = 14.8, 9.2 Hz, 1H), 3.07 (dd, $J$ = 13.6, 4.4 Hz, 1H), 3.0 (dd, $J$ = 13.6, 8.8 Hz, 1H), 2.95 (dd, $J$ = 14.8, 2.4 Hz, 1H), 2.79 (dd, $J$ = 13.6, 6.8 Hz, 1H), 2.72 (dd, $J$ = 14.0, 10.8 Hz, 1H), 1.83 (m, 1H), 1.60 (br s, 1H), 0.95 (d, $J$ = 6.4 Hz, 3H), 0.89 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.51, 163.22 (d, $J$ = 244.2 Hz), 152.72, 150.92, 139.0 (d, $J$ = 10.6 Hz), 137.43, 130.50 (d, $J$ = 9.10 Hz), 129.77 (2C), 129.53 (2C), 128.54 (2C), 126.64, 126.33, 114.37 (2C), 113.50 (d, $J$ = 3.0 Hz), 111.52 (d, $J$ = 21.2 Hz), 106.06 (d, $J$ = 27.3 Hz), 72.46, 69.75, 59.11, 53.92, 53.40, 48.17, 35.62, 27.58, 20.38, 20.10; HRMS (ESI) *m/z* $C_{30}H_{36}FN_4O_6S$ $(M + H)^+$ calcd 599.2339, found 599.2340.

**(5*S*)-*N*-[(1*S*,2*R*)-3-[[(4-Aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropyl]-3-(3,4-difluorophenyl)-2-oxooxazolidine-5-carboxamide (25c):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.4 Hz, 2H), 7.54−7.48 (m, 1H), 7.19 (q, $J$ = 9.2 Hz, 1H), 7.11 (d, $J$ = 7.6 Hz, 2H), 7.02−6.96 (m, 3H), 6.90−6.85 (m, 2H), 6.68 (d, $J$ = 8.8 Hz, 2H), 4.78 (dd, $J$ = 10.0, 5.6 Hz, 1H), 4.28−4.21 (m, 2H), 3.98 (t, $J$ = 9.6 Hz, 1H), 3.94 (m, 1H), 3.76 (br s, 1H), 3.27 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.17 (dd, $J$ = 15.2, 8.8 Hz, 1H), 3.08 (dd, $J$ = 14.0, 4.4 Hz, 1H), 2.99 (dd, $J$ = 14.8, 2.4 Hz, 1H), 2.95 (dd, $J$ = 13.6, 8.4 Hz, 1H), 2.81 (dd, $J$ = 13.2, 6.8 Hz, 1H), 2.73 (dd, $J$ = 14.0, 10.8 Hz, 1H), 1.83 (m, 1H), 0.92 (d, $J$ = 6.4 Hz, 3H), 0.89 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.41, 152.92, 151.02, 150.44 (dd, $J$ = 246.5, 13.6 Hz), 147.36 (dd, $J$ = 245.0, 12.4 Hz), 137.59, 134.06 (m), 129.72 (2C), 129.55 (2C), 128.45 (2C), 126.52, 126.14, 117.59 (d, $J$ = 18.2 Hz), 114.32 (2C), 113.88 (q, $J$ = 3.8 Hz), 108.36 (d, $J$ = 22.0 Hz), 72.491, 69.75, 59.01, 53.81, 53.36, 48.27, 35.48, 27.48, 20.34, 20.10; HRMS (ESI) *m/z* $C_{30}H_{35}F_2N_4O_6S$ $(M + H)^+$ calcd 617.2245, found 617.2246.

**(5*S*)-*N*-[(1*S*,2*R*)-3-[[(4-Aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropyl]-2-oxo-3-[(3-trifluoromethyl)phenyl]-oxazolidine-5-carboxamide (25d):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (d, $J$ = 8.0 Hz, 1H), 7.61 (s, 1H), 7.55 (d, $J$ = 8.8 Hz, 2H), 7.52 (t, $J$ = 8.0 Hz, 1H), 7.45 (d, $J$ = 7.6 Hz, 1H), 7.09 (d, $J$ = 7.2 Hz, 2H), 6.96 (t, $J$ = 7.6 Hz, 2H), 6.81 (t, $J$ = 7.6 Hz, 1H), 6.77 (d, $J$ = 10.4 Hz, 1H), 6.67 (d, $J$ = 8.8 Hz, 2H), 4.78 (dd, $J$ = 10.4, 6.0 Hz, 1H), 4.24 (m, 1H), 4.16 (br s, 1H), 4.02 (t, $J$ = 9.6 Hz, 1H), 3.91 (m, 1H), 3.73 (br s, 1H), 3.30 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.19 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.07 (dd, $J$ = 14.0, 4.4 Hz, 1H), 3.0−2.93 (m, 2H), 2.78 (dd, $J$ = 13.2, 6.8 Hz, 1H), 2.70 (dd, $J$ = 13.6, 10.8 Hz, 1H), 1.82 (m, 1H), 0.93 (d, $J$ = 6.8 Hz, 3H), 0.88 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.44, 152.86, 150.98, 138.13, 137.50, 131.77 (d, $J$ = 32.6 Hz), 129.94, 129.77 (2C), 129.55 (2C), 128.50 (2C), 126.55, 126.24, 121.40, 121.23 (q, $J$ = 3.8 Hz), 115.02 (q, $J$ = 3.8 Hz), 114.35 (2C), 72.50, 69.85, 59.09, 53.89, 53.32, 51.06, 48.10, 35.57, 27.56, 20.37, 20.11; HRMS (ESI) *m/z* $C_{31}H_{36}F_3N_4O_6S$ $(M + H)^+$ calcd 649.2307, found 649.2291.

**(5*S*)-3-(3-Acetylphenyl)-*N*-[(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropyl]-2-oxooxazolidine-5-carboxamide (25e):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.91 (t, $J$ = 2.0 Hz, 1H), 7.80−7.74 (m, 2H), 7.54 (d, $J$ = 8.8 Hz, 2H), 7.50 (t, $J$ = 7.6 Hz, 1H), 7.10 (d, $J$ = 7.2 Hz, 2H), 6.97 (t, $J$ = 7.2 Hz, 2H), 6.92 (d, $J$ = 10.0 Hz, 1H), 6.83 (t, $J$ = 7.2 Hz, 1H), 6.65 (d, $J$ = 8.8 Hz, 2H), 4.78 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.22 (m, 2H), 4.03 (t, $J$ = 9.6 Hz, 1H), 3.94 (m, 1H), 3.79 (br s, 1H), 3.34 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.15 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.08 (dd, $J$ = 14.0, 4.4 Hz, 1H), 3.01−2.90 (m, 2H), 2.80 (dd, $J$ = 13.6, 6.8 Hz, 1H), 2.72 (dd, $J$ = 13.6, 11.2 Hz, 1H), 2.62 (s, 3H), 1.82 (m, 1H), 0.91 (d, $J$ = 6.4 Hz, 3H), 0.87 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.64, 168.54, 153.15, 151.03, 138.12, 138.01, 137.62, 129.72 (2C), 129.63, 129.56 (2C), 128.47 (2C), 126.55, 126.14, 124.69, 123.0, 117.61, 114.30 (2C), 72.55, 69.94, 59.02, 53.84, 53.41, 48.23, 35.65, 27.47, 26.90, 20.34, 20.10; HRMS (ESI) *m/z* $C_{32}H_{39}N_4O_7S$ $(M + H)^+$ calcd 623.2539, found 623.2543.

**(5*S*)-3-(4-Acetylphenyl)-*N*-[(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropyl]-2-oxooxazolidine-5-carboxamide (25f):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.04−8.01 (m, 2H), 7.59−7.53 (m, 4H), 7.11 (d, $J$ = 6.8 Hz, 2H), 6.98 (t, $J$ = 7.6 Hz, 2H), 6.81 (t, $J$ = 7.2 Hz, 1H), 6.72−6.66 (m, 3H), 4.80 (dd, $J$ = 9.6, 5.6 Hz, 1H), 4.24 (m, 1H), 4.16 (br s, 2H), 4.06 (t, $J$ = 9.6 Hz, 1H), 3.91 (m, 1H), 3.74 (br s, 1H), 3.35 (dd, $J$ = 9.6, 6.4 Hz, 1H), 3.24 (dd, $J$ = 15.2, 9.6 Hz, 1H), 3.08 (dd, $J$ = 14.0, 4.8 Hz, 1H), 3.01 (dd, $J$ = 13.6, 8.8 Hz, 1H), 2.94 (dd, $J$ = 14.8, 2.4 Hz, 1H), 2.79 (dd, $J$ = 13.2, 6.0 Hz, 1H), 2.73 (dd, $J$ = 14.0, 11.2 Hz, 1H), 2.63 (s, 3H), 1.83 (m, 1H), 0.96 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.0, 168.39, 152.73, 151.0, 141.58, 137.52, 133.17, 129.81-

(2C), 129.75 (2C), 129.55 (2C), 128.46 (2C), 126.60, 126.22, 117.58 (2C), 114.34 (2C), 72.47, 69.84, 59.08, 53.88, 53.40, 48.0, 35.54, 27.55, 26.68, 20.37, 20.11; HRMS (ESI) *m/z* $C_{32}H_{39}N_4O_7S$ $(M + H)^+$ calcd 623.2539, found 623.2532.

**(5*S*)-*N*-[(1*S*,2*R*)-3-[[(Benzo[1,3]dioxole-5-sulfonyl)](isobutyl)-amino]-1-benzyl-2-hydroxypropyl]-3-(3-fluorophenyl)-2-oxooxazolidine-5-carboxamide (26b):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.30 (m, 3H), 7.20 (s, 1H), 7.13−7.08 (m, 3H), 7.02 (t, $J$ = 8.0 Hz, 2H), 6.92−6.86 (m, 3H), 6.75 (d, $J$ = 9.6 Hz, 1H), 6.09 (s, 2H), 4.78 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.23 (m, 1H), 4.02 (t, $J$ = 9.6 Hz, 1H), 3.93 (m, 1H), 3.64 (br s, 1H), 3.32 (dd, $J$ = 8.8, 5.6 Hz, 1H), 3.20 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.10 (dd, $J$ = 14.0, 4.4 Hz, 1H), 3.03−2.98 (m, 2H), 2.83 (dd, $J$ = 13.6, 6.4 Hz, 1H), 2.74 (dd, $J$ = 14.0, 10.8 Hz, 1H), 1.85 (m, 1H), 0.96 (d, $J$ = 6.8 Hz, 3H), 0.91 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.63, 163.19 (d, $J$ = 243.4 Hz), 152.81, 151.77, 148.56, 139.01 (d, $J$ = 10.6 Hz), 137.45, 131.57, 130.48 (d, $J$ = 9.1 Hz), 129.49 (2C), 128.52 (2C), 126.63, 123.35, 113.52 (d, $J$ = 3.1 Hz), 111.50 (d, $J$ = 21.3 Hz), 108.58, 107.71, 106.06 (d, $J$ = 27.3 Hz), 102.56, 72.52, 69.81, 59.04, 53.87, 53.47, 48.20, 35.58, 27.48, 20.31, 20.07; HRMS (ESI) *m/z* $C_{31}H_{35}FN_3O_8S$ $(M + H)^+$ calcd 628.2129, found 628.2127.

**(5*S*)-*N*-[(1*S*,2*R*)-3-[[(Benzo[1,3]dioxole-5-sulfonyl)](isobutyl)-amino]-1-benzyl-2-hydroxypropyl]-3-(3,4-difluorophenyl)-2-oxooxazolidine-5-carboxamide (26c):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.54−7.48 (m. 1H), 7.36 (dd, $J$ = 8.0, 1.6 Hz, 1H), 7.22−7.11 (m, 4H), 7.04−6.98 (m, 3H), 6.89 (t, $J$ = 4.0 Hz, 2H), 6.81 (d, $J$ = 9.6 Hz, 1H), 6.08 (s, 2H), 4.79 (dd, $J$ = 10.0, 5.6 Hz, 1H), 4.25 (m, 1H), 4.0 (t, $J$ = 9.6 Hz, 1H), 3.95 (m, 1H), 3.64 (br s, 1H), 3.30 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.17 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.10 (dd, $J$ = 13.6, 4.4 Hz, 1H), 3.05−2.95 (m, 2H), 2.85 (dd, $J$ = 13.6, 6.4 Hz, 1H), 2.74 (dd, $J$ = 13.6, 10.8 Hz, 1H), 1.85 (m, 1H), 0.94 (d, $J$ = 6.0 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.49, 152.84, 151.79, 150.45 (dd, $J$ = 246.3, 12.9 Hz), 148.57, 147.39 (dd, $J$ = 245.0, 12.9 Hz), 137.49, 134.05 (m), 131.53, 129.53 (2C), 128.51 (2C), 126.59, 123.36, 117.60 (d, $J$ = 18.2 Hz), 113.86 (d, $J$ = 3.8 Hz), 108.59, 108.37 (d, $J$ = 22.0 Hz), 107.71, 102.58, 72.54, 69.74, 59.07, 53.87, 53.42, 48.26, 35.50, 27.49, 20.31, 20.07; HRMS (ESI) *m/z* $C_{31}H_{34}F_2N_3O_8S$ $(M + H)^+$ calcd 646.2034, found 646.2037.

**(5*S*)-*N*-[(1*S*,2*R*)-3-[[(Benzo[1,3]dioxole-5-sulfonyl)](isobutyl)-amino]-1-benzyl-2-hydroxypropyl]-2-oxo-3-[(3-trifluoromethyl)-phenyl]oxazolidine-5-carboxamide (26d):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.70 (dd, $J$ = 8.0, 1.2 Hz, 1H), 7.63 (s, 1H), 7.54 (t, $J$ = 8.4 Hz, 1H), 7.46 (d, $J$ = 7.6 Hz, 1H), 7.37 (dd, $J$ = 8.4, 2.0 Hz, 2H), 7.20 (d, $J$ = 2.0 Hz, 1H), 7.11 (dd, $J$ = 8.4, 1.6 Hz, 1H), 6.99 (t, $J$ = 7.2 Hz, 2H), 6.90 (d, $J$ = 8.0 Hz, 1H), 6.85−6.80 (m, 2H), 6.09 (s, 2H), 4.81 (dd, $J$ = 10.0, 5.6 Hz, 1H), 4.26 (m, 1H), 4.05 (t, $J$ = 9.6 Hz, 1H), 3.94 (m, 1H), 3.65 (br s, 1H), 3.34 (dd, $J$ = 9.6, 6.4 Hz, 1H), 3.20 (dd, $J$ = 14.8, 8.8 Hz, 1H), 3.11 (dd, $J$ = 13.6, 4.4 Hz, 1H), 3.04−2.97 (m, 2H), 2.84 (dd, $J$ = 13.6, 7.2 Hz, 1H), 2.73 (dd, $J$ = 13.6, 11.2 Hz, 1H), 1.86 (m, 1H), 0.95 (d, $J$ = 6.8 Hz, 3H), 0.91 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.54, 152.83, 151.82, 148.60, 138.11, 137.42, 131.78 (d, $J$ = 32.6 Hz), 131.52, 129.94, 129.52 (2C), 129.54 (2C), 126.61, 123.38, 121.40, 121.27 (q, $J$ = 3.8 Hz), 115.02 (q, $J$ = 3.8 Hz), 108.62, 107.73, 102.59, 72.57, 69.86, 59.14, 53.94, 53.39, 51.05, 48.11, 35.58, 27.54, 20.34, 20.08; HRMS (ESI) *m/z* $C_{32}H_{35}F_3N_3O_8S$ $(M + H)^+$ calcd 678.2097, found 678.2101.

**(5*S*)-3-(3-Acetylphenyl)-*N*-[(1*S*,2*R*)-3-[[(benzo[1,3]dioxole-5-sulfonyl)](isobutyl)amino]-1-benzyl-2-hydroxypropyl]-2-oxooxazolidine-5-carboxamide (26e):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (s, 1H), 7.77 (dd, $J$ = 7.6, 1.6 Hz, 2H), 7.52 (t, $J$ = 8.0 Hz, 1H), 7.36 (dd, $J$ = 8.0, 2.0 Hz, 1H), 7.19 (d, $J$ = 2.0 Hz, 1H), 7.13 (d, $J$ = 6.8 Hz, 2H), 6.99 (t, $J$ = 7.6 Hz, 3H), 6.89−6.83 (m, 2H), 6.07 (d, $J$ = 2 Hz, 2H), 4.82 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.24 (m, 1H), 4.07 (t, $J$ = 9.6 Hz, 1H), 3.98 (m, 1H), 3.77 (br s, 1H), 3.38 (dd, $J$ = 9.2, 6.4 Hz, 1H), 3.20−3.11 (m, 2H), 3.06 (dd, $J$ = 15.2, 4.6 Hz, 1H), 2.97 (dd, $J$ = 13.2, 8.0 Hz, 1H), 2.87 (dd, $J$ = 13.2, 6.8 Hz, 1H), 2.75 (dd, $J$ = 14.0, 11.0 Hz, 1H), 2.64 (s, 3H), 1.87 (m, 1H), 0.93 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.64, 168.68, 153.16, 151.72, 148.52, 138.10, 138.01, 137.61, 131.59, 129.62, 129.54 (2C), 128.50 (2C), 126.58, 124.71, 123.33, 123.0, 117.64, 108.56, 107.72, 102.55, 72.65, 69.96, 59.02, 53.86, 53.49, 48.25, 35.67, 27.44, 26.89, 20.29, 20.08; HRMS (ESI) *m/z* $C_{33}H_{38}N_3O_9S$ $(M + H)^+$ calcd 652.2329, found 652.2324.

**(5*S*)-3-(4-Acetylphenyl)-*N*-[(1*S*,2*R*)-3-[[(benzo[1,3]dioxole-5-sulfonyl)](isobutyl)amino]-1-benzyl-2-hydroxypropyl]-2-oxooxazolidine-5-carboxamide (26f):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J$ = 8.8 Hz, 2H), 7.54 (d, $J$ = 8.8 Hz, 2H), 7.36 (dd, $J$ = 8.4, 2.0 Hz, 1H), 7.19 (d, $J$ = 1.6 Hz, 1H), 7.11 (d, $J$ = 7.2 Hz, 2H), 6.98 (t, $J$ = 7.6 Hz, 2H), 6.89 (d, $J$ = 8.0 Hz, 1H), 6.83−6.79 (m, 2H), 6.08 (s, 2H), 4.81 (dd, $J$ = 9.6, 5.6 Hz, 1H), 4.24 (m, 1H), 4.07 (t, $J$ = 9.6 Hz, 1H), 3.95 (m, 1H), 3.64 (br s, 1H), 3.35 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.19 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.10 (dd, $J$ = 13.6, 4.4 Hz, 1H), 3.05−2.96 (m, 2H), 2.84 (dd, $J$ = 13.2, 6.4 Hz, 1H), 2.73 (dd, $J$ = 13.6, 10.8 Hz, 1H), 2.62 (s, 3H), 1.86 (m, 1H), 0.94 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.97, 168.48, 152.71, 151.79, 148.57, 141.55, 137.46, 133.17, 131.53, 129.80 (2C), 129.52 (2C), 128.49 (2C), 126.64, 123.36, 117.58 (2C), 108.60, 107.71, 102.58, 72.53, 69.84, 59.09, 53.90, 53.46, 48.0, 35.53, 27.51, 26.66, 20.32, 20.08; HRMS (ESI) *m/z* $C_{33}H_{38}N_3O_9S$ $(M + H)^+$ calcd 652.2329, found 652.2325.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-3-[[(3-fluoro-4-methoxyphenyl)sulfonyl](isobutyl)amino]-2-hydroxypropyl]-3-(3-fluorophenyl)-2-oxooxazolidine-5-carboxamide (27b):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (m, 1H), 7.51 (dd, $J$ = 10.4, 2.4 Hz, 1H), 7.38−7.32 (m, 2H), 7.13−7.05 (m, 4H), 7.02 (t, $J$ = 7.6 Hz, 2H), 6.92−6.86 (m, 2H), 6.83 (d, $J$ = 10.0 Hz, 1H), 4.80 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.24 (m, 1H), 4.03 (t, $J$ = 9.6 Hz, 1H), 3.95 (s, 3H, overlapping signal), 3.94 (m, 1H, overlapping signal), 3.61 (d, $J$ = 3.2 Hz, 1H), 3.32 (dd, $J$ = 9.6, 6.0 Hz, 1H), 3.20 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.11 (dd, $J$ = 13.6, 4.4 Hz, 1H), 3.05 (dd, $J$ = 15.2, 2.8 Hz, 1H), 2.99 (dd, $J$ = 13.2, 8.4 Hz, 1H), 2.86 (dd, $J$ = 13.2, 6.4 Hz, 1H), 2.74 (dd, $J$ = 14.0, 10.8 Hz, 1H), 1.86 (m, 1H), 0.93 (d, $J$ = 6.4 Hz, 3H), 0.90 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.67, 163. 21 (d, $J$ = 244.2 Hz), 152.80, 151.95 (d, $J$ = 250.2 Hz), 151.83 (d, $J$ = 9.8 Hz), 139.0 (d, $J$ = 10.6 Hz), 137.37, 130.51 (d, $J$ = 9.1 Hz), 130.34 (d, $J$ = 4.5 Hz), 129.49 (2C), 128.56 (2C), 126.69, 124.89 (d, $J$ = 3.8 Hz), 115.60 (d, $J$ = 20.5 Hz), 113.53 (d, $J$ = 3 Hz), 113.19, 111.54 (d, $J$ = 21.2 Hz), 106.08 (d, $J$ = 26.6 Hz), 72.48, 69.81, 58.91, 56.63, 53.78, 53.50, 48.21, 35.59, 27.46, 20.29, 20.06; HRMS (ESI) *m/z* $C_{31}H_{36}F_2N_3O_7S$ $(M + H)^+$ calcd 632.2242, found 632.2258.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-3-[[(3-fluoro-4-methoxyphenyl)sulfonyl](isobutyl)amino]-2-hydroxypropyl]-3-(3,4-difluorophenyl)-2-oxooxazolidine-5-carboxamide (27c):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59−7.55 (m, 1H), 7.54−7.48 (m, 2H), 7.18 (q, $J$ = 9.2 Hz, 1H), 7.12 (d, $J$ = 7.2 Hz, 2H), 7.07−6.97 (m, 4H), 6.90 (t, $J$ = 7.2 Hz, 1H), 6.86 (d, $J$ = 10.0 Hz, 1H), 4.80 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.26 (m, 1H), 4.0 (t, $J$ = 9.2 Hz, 1H), 3.96 (m, 1H, overlapping signal), 3.95 (s, 3H), 3.62 (d, $J$ = 3.6 Hz, 1H), 3.31 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.18 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.21−3.04 (m, 2H), 2.97 (dd, $J$ = 13.6, 8.0 Hz, 1H), 2.87 (dd, $J$ = 13.6, 6.8 Hz, 1H), 2.74 (dd, $J$ = 13.6, 10.8 Hz, 1H), 1.86 (m, 1H), 0.92 (d, $J$ = 6.4 Hz, 3H), 0.89 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.55, 152.88, 151.92 (d, $J$ = 250.2 Hz), 151.82 (d, $J$ = 10.6 Hz), 150.45 (dd, $J$ = 246.4, 12.9 Hz), 147.39 (dd, $J$ = 245.7, 12.9 Hz), 137.46, 134.03 (m), 130.32 (d, $J$ = 3.8 Hz), 129.51 (2C), 128.52 (2C), 126.61, 124.88 (d, $J$ = 3.8 Hz), 117.61 (d, $J$ = 18.2 Hz), 115.58 (d, $J$ = 21.2 Hz), 113.88 (q, $J$ = 3.8 Hz), 113.18, 108.37 (d, $J$ = 22.0 Hz), 72.50, 69.76, 58.86, 56.62, 53.72, 53.47, 48.28, 35.49, 27.42, 20.27, 20.06; HRMS (ESI) *m/z* $C_{31}H_{35}F_3N_3O_7S$ $(M + H)^+$ calcd 650.2148, found 650.2151.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-3-[[(3-fluoro-4-methoxyphenyl)-sulfonyl](isobutyl)amino]-2-hydroxypropyl]-2-oxo-3-[(3-trifluoromethyl)phenyl)]oxazolidine-5-carboxamide (27d):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69 (d, $J$ = 8 Hz, 1H), 7.64 (br s, 1H), 7.59−7.49 (m 3H), 7.45 (d, $J$ = 7.6 Hz, 1H), 7.12 (d, $J$ = 6.8 Hz, 2H), 7.05 (t, $J$ = 8.4 Hz, 1H), 6.99 (t, $J$ = 7.6 Hz, 2H), 6.87−6.82 (m,

2H), 4.81 (dd, $J$ = 10.0, 5.6 Hz, 1H), 4.27 (m, 1H), 4.06 (t, $J$ = 10.0 Hz, 1H), 3.96 (m, 1H, overlapping signal), 3.95 (s, 3H), 3.61 (br s, 1H), 3.35 (dd, $J$ = 9.2, 5.6 Hz, 1H), 3.20 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.11 (dd, $J$ = 14.0, 4.4 Hz, 1H), 3.05 (dd, $J$ = 15.2, 3.2 Hz, 1H), 2.98 (dd, $J$ = 13.2, 8.0 Hz, 1H), 2.87 (dd, $J$ = 13.2, 6.8 Hz, 1H), 2.74 (dd, $J$ = 14, 10.8 Hz, 1H), 1.87 (m, 1H), 0.94 (d, $J$ = 6.4 Hz, 3H), 0.90 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.59, 152.88, 151.95 (d, $J$ = 250.9 Hz), 151.84 (d, $J$ = 10.7 Hz), 138.09, 137.40, 131.76 (d, $J$ = 32.5 Hz), 130.30, 129.94, 129.50 (2C), 128.54 (2C), 126.62, 124.89 (d, $J$ = 3.8 Hz), 121.40, 121.25 (q, $J$ = 3.8 Hz), 115.60 (d, $J$ = 20.5 Hz), 115.04 (q, $J$ = 3.8 Hz), 113.19, 72.53, 69.88, 58.92, 56.63, 53.78, 53.43, 48.13, 35.56, 27.46, 20.29, 20.06; HRMS (ESI) *m/z* $C_{32}H_{36}F_4N_3O_7S$ $(M + H)^+$ calcd 682.2210, found 682.2203.

**(*S*)-3-(3-Acetylphenyl)-*N*-[(1*S*,2*R*)-1-benzyl-3-[[(3-fluoro-4-methoxyphenyl)sulfonyl](isobutyl)amino]-2-hydroxypropyl]-2-oxooxazolidine-5-carboxamide (27e):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (m, 1H), 7.78−7.73 (m, 2H), 7.59−7.48 (m, 3H), 7.13 (d, $J$ = 7.2 Hz, 2H), 7.07−6.98 (m, 4H), 6.85 (t, $J$ = 8.0 Hz, 1H), 4.82 (dd, $J$ = 9.6, 5.6 Hz, 1H), 4.25 (m, 1H), 4.07 (t, $J$ = 9.6 Hz, 1H), 3.99 (br s, 1H), 3.94 (s, 3H), 3.75 (m, 1H), 3.41−3.37 (m, 1H), 3.21−3.06 (m, 3H), 3.0−2.86 (m, 2H), 2.76 (dd, $J$ = 14.0, 11.2 Hz, 1H), 2.64 (s, 3H), 1.88 (m, 1H), 0.92 (d, $J$ = 6.8 Hz, 3H), 0.89 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.65, 168.71, 153.18, 151.90 (d, $J$ = 251.0 Hz), 151.74 (d, $J$ = 9.9 Hz), 138.09, 138.01, 137.59, 130.46 (d, $J$ = 4.5 Hz), 129.62, 129.53 (2C), 128.51 (2C), 126.61, 124.86 (d, $J$ = 3.8 Hz), 124.74, 122.98, 117.64, 115.58 (d, $J$ = 20.4 Hz), 113.17, 72.60, 69.98, 58.82, 56.60, 53.69, 53.55, 48.26, 35.68, 27.38, 26.88, 20.25, 20.06; HRMS (ESI) *m/z* $C_{33}H_{39}FN_3O_8S$ $(M + H)^+$ calcd 656.2442, found 656.2441.

**(*S*)-3-(4-Acetylphenyl)-*N*-[(1*S*,2*R*)-1-Benzyl-3-[[(3-fluoro-4-methoxyphenyl)sulfonyl](isobutyl)amino]-2-hydroxypropyl]-2-oxooxazolidine-5-carboxamide (27f):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J$ = 8.8 Hz, 2H), 7.58−7.52 (m, 3H), 7.50 (dd, $J$ = 10.4, 2.4 Hz, 1H), 7.11 (d, $J$ = 8.0 Hz, 2H), 7.04 (t, $J$ = 8.4 Hz, 1H), 6.97 (t, $J$ = 7.6 Hz, 2H), 6.92 (d, $J$ = 9.6 Hz, 1H), 6.82 (t, $J$ = 7.2 Hz, 1H), 4.82 (dd, $J$ = 9.6, 5.6 Hz, 1H), 4.26 (m, 1H), 4.08 (t, $J$ = 10.0 Hz, 1H), 3.98 (m, 1H), 3.94 (s, 3H), 3.68 (br s, 1H), 3.35 (dd, $J$ = 9.6, 6.4 Hz, 1H), 3.18 (dd, $J$ = 15.2, 8.8 Hz, 1H), 3.13−3.06 (m, 2H), 2.97 (dd, $J$ = 13.2, 8.0 Hz, 1H), 2.89 (dd, $J$ = 13.6, 6.8 Hz, 1H), 2.74 (dd, $J$ = 14.0, 11.2 Hz, 1H), 2.61 (s, 3H), 1.87 (m, 1H), 0.91 (d, $J$ = 6.4 Hz, 3H), 0.89 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.0, 168.55, 152.78, 151.90 (d, $J$ = 251.0 Hz), 151.78 (d, $J$ = 10.7 Hz), 141.54, 137.46, 133.15, 130.31, 129.78 (2C), 129.50 (2C), 128.47 (2C), 126.63, 124.86 (d, $J$ = 3.0 Hz), 117.58 (2C), 115.56 (d, $J$ = 20.5 Hz), 113.18, 72.49, 69.88, 58.83, 56.60, 53.69, 53.50, 48.01, 35.49, 27.39, 26.64, 20.26, 20.06; HRMS (ESI) *m/z* $C_{33}H_{39}FN_3O_8S$ $(M + H)^+$ calcd 656.2442, found 656.2448.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl[[(4-trifluoromethoxy)phenyl]sulfonyl]amino]propyl]-2-oxo-3-[(3-trifluoromethyl)phenyl]oxazolidine-5-carboxamide (28d):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.88−7.85 (m, 2H), 7.70 (d, $J$ = 8.0 Hz, 1H), 7.63 (s, 1H), 7.54 (dt, $J$ = 8.0, 2.4 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.37 (dd, $J$ = 7.6, 1.2 Hz, 2H), 7.12 (dd, $J$ = 7.6, 1.2 Hz, 2H), 7.03−6.98 (m, 2H), 6.85 (dt, $J$ = 8.0, 2.4 Hz, 1H), 6.70 (d, $J$ = 8.0 Hz, 1H), 4.81 (dd, $J$ = 9.6, 6.0 Hz, 1H), 4.26 (m, 1H), 4.06 (t, $J$ = 10.0 Hz, 1H), 3.94 (m, 1H), 3.54 (br s, 1H), 3.37 (dd, $J$ = 10.0, 6.0 Hz, 1H), 3.25 (dd, $J$ = 15.6, 9.2 Hz, 1H), 3.13−3.02 (m, 3H), 2.87 (dd, $J$ = 13.6, 6.0 Hz, 1H), 2.71 (dd, $J$ = 13.6, 9.6 Hz, 1H), 1.87 (m, 1H), 0.96 (d, $J$ = 6.4 Hz, 3H), 0.91 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.61, 152.78, 152.57, 138.06, 137.26, 136.82, 131.81 (d, $J$ = 32.6 Hz), 129.96 129.71 (2C), 129.48 (2C), 128.61 (2C), 126.69, 121.40, 121.33, 121.27 (2C), 115.02 (m), 72.50, 69.84, 58.90, 53.79, 53.47, 51.07, 48.10, 35.56, 27.49, 20.28, 20.02; HRMS (ESI) *m/z* $C_{32}H_{34}F_6N_3O_7S$ $(M + H)^+$ calcd 718.2021, found 718.2028.

**(5*S*)-3-(3-Acetylphenyl)-*N*-[(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[isobutyl[[(4-trifluoromethoxy)phenyl]sulfonyl]amino]propyl]-2-oxooxazolidine-5-carboxamide (28e):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90−7.77 (m, 5H), 7.53 (t, $J$ = 8.0 Hz, 1H), 7.36 (d, $J$ = 8.8 Hz, 2H), 7.13 (d, $J$ = 8.0 Hz, 2H), 7.03 (t, $J$ = 8.0 Hz, 2H), 6.87 (t, $J$ = 7.6 Hz, 1H), 6.83 (d, $J$ = 9.6 Hz, 1H), 4.82 (dd, $J$ = 9.6, 5.6 Hz, 1H), 4.25 (m, 1H), 4.09 (t, $J$ = 10.0 Hz, 1H), 3.94 (m, 1H), 3.59 (d, $J$ = 3.2 Hz, 1H), 3.42 (dd, $J$ = 9.6, 6.0 Hz, 1H), 3.25 (dd, $J$ = 15.2, 9.2 Hz, 1H), 3.13 (dd, $J$ = 14.4, 4.8 Hz, 1H), 3.07−3.02 (m, 2H), 2.88 (dd, $J$ = 13.2, 6.4 Hz, 1H), 2.75 (dd, $J$ = 13.6, 10.8 Hz, 1H), 2.65 (s, 3H), 1.87 (m, 1H), 0.95 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.53, 168.68, 152.95, 152.55, 138.06, 137.27, 136.85, 129.72 (2C), 129.68, 129.50 (2C), 128.65 (2C), 126.77, 124.79, 123.01, 121.27 (2C), 117.53, 72.52, 69.89, 58.93, 53.84, 53.54, 48.21, 35.65, 27.51, 26.90, 20.29, 20.03; HRMS (ESI) *m/z* $C_{33}H_{37}F_3N_3O_8S$ $(M + H)^+$ calcd 692.2253, found 692.2244.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl[(3-methoxyphenyl)sulfonyl]amino]propyl]-2-oxo-3-phenyloxazolidine-5-carboxamide (29a):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46−7.36 (m, 6H), 7.31 (t, $J$ = 2.8 Hz, 1H), 7.20 (m, 1H), 7.12 (m, 3H), 7.02 (t, $J$ = 7.2 Hz, 2H), 6.88 (t, $J$ = 7.6 Hz, 1H), 6.77 (d, $J$ = 10 Hz, 1H), 4.78 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.22 (m, 1H), 4.04 (t, $J$ = 9.6 Hz, 1H), 3.93 (m, 1H), 3.86 (s, 3H), 3.64 (br s, 1H), 3.36 (dd, $J$ = 8.8, 5.6 Hz, 1H), 3.25 (dd, $J$ = 15.6, 9.6 Hz, 1H), 3.12 (dd, $J$ = 14.0, 4.4 Hz, 1H), 3.07−3.01 (m, 2H), 2.87 (dd, $J$ = 13.6, 6.4 Hz, 1H), 2.73 (dd, $J$ = 14.0, 10.8 Hz, 1H), 1.86 (m, 1H), 0.96 (d, $J$ = 6.4 Hz, 3H), 0.90 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.89, 160.23, 153.02, 139.53, 137.49, 137.37, 130.51, 129.49 (2C), 129.31 (2C), 128.59 (2C), 126.71, 124.82, 119.65, 119.16, 118.47 (2C), 112.65, 72.47, 69.82, 59.03, 55.91, 53.91, 53.56, 48.29, 35.70, 27.53, 20.31, 20.06; HRMS (ESI) *m/z* $C_{31}H_{38}N_3O_7S$ $(M + H)^+$ calcd 596.2430, found 596.2435.

**(5*S*)-3-(4-Acetylphenyl)-*N*-[(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[isobutyl[(3-methoxyphenyl)sulfonyl]amino]propyl]-2-oxooxazolidine-5-carboxamide (29f):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.0 (d, $J$ = 8.8 Hz, 2H), 7.54 (d, $J$ = 8.8 Hz, 2H), 7.43 (t, $J$ = 7.6 Hz, 1H), 7.36 (d, $J$ = 8.8 Hz, 1H), 7.30 (t, $J$ = 2.4 Hz, 1H), 7.10 (d, $J$ = 7.6 Hz, 3H), 6.97 (t, $J$ = 7.6 Hz, 2H), 6.85 (d, $J$ = 10.0 Hz, 1H), 6.80 (t, $J$ = 7.6 Hz, 1H), 4.81 (dd, $J$ = 9.6, 5.6 Hz, 1H), 4.25 (m, 1H), 4.06 (t, $J$ = 9.6 Hz, 1H), 3.96 (m, 1H), 3.85 (s, 3H), 3.68 (br s, 1H), 3.34 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.23 (dd, $J$ = 15.4, 9.2 Hz, 1H), 3.12−3.05 (m, 2H), 3.02 (dd, $J$ = 13.6, 8.4 Hz, 1H), 2.89 (dd, $J$ = 13.6, 7.2 Hz, 1H), 2.74 (dd, $J$ = 14.0, 11.2 Hz, 1H), 2.61 (s, 3H), 1.87 (m, 1H), 0.93 (d, $J$ = 6.4 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.97, 168.49, 160.19, 152.72, 141.54, 139.49, 137.46, 133.14, 130.50, 129.78 (2C), 129.50 (2C), 128.46 (2C), 126.61, 119.61, 119.06, 117.57 (2C), 112.70, 72.47, 69.84, 58.97, 55.89, 53.81, 53.47, 47.99, 35.49, 27.46, 26.65, 20.28, 20.05; HRMS (ESI) *m/z* $C_{33}H_{40}N_3O_8S$ $(M + H)^+$ calcd 638.2536, found 638.2538.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-3-[(cyclopropylmethyl)[(3-methoxyphenyl)sulfonyl]amino]-2-hydroxypropyl]-3-(3-fluorophenyl)-2-oxooxazolidine-5-carboxamide (36b):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 9.2 Hz, 2H), 7.38−7.32 (m, 1H), 7.13 (d, $J$ = 6.8 Hz, 2H), 7.09 (dd, $J$ = 8.8, 2.0 Hz, 1H), 7.04−6.97 (m, 4H), 6.92−6.86 (m, 2H), 6.80 (d, $J$ = 10.0 Hz, 1H), 4.79 (dd, $J$ = 10.0, 5.6 Hz, 1H), 4.28 (m, 1H), 4.02 (t, $J$ = 9.2 Hz, 2H), 3.87 (s, 3H), 3.62 (br s, 1H), 3.36−3.10 (m, 5H), 2.96 (dd, $J$ = 14.0, 7.2 Hz, 1H), 2.78 (dd, $J$ = 14.0, 11.2 Hz, 1H), 0.87 (m, 1H), 0.56−0.53 (m, 2H), 0.18 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.63, 163.26, 163.20 (d, $J$ = 244.2 Hz), 152.77, 139.03 (d, $J$ = 10.6 Hz), 137.49, 130.53, 130.44, 129.57 (2C), 129.51 (2C), 128.54 (2C), 126.63, 114.61 (2C), 113.52 (d, $J$ = 3.1 Hz), 111.51 (d, $J$ = 21.2 Hz), 106.07 (d, $J$ = 27.3 Hz), 72.36, 69.81, 55.82, 55.04, 53.40, 52.15, 48.21, 35.57, 10.07, 4.72, 4.26; HRMS (ESI) *m/z* $C_{31}H_{35}FN_3O_7S$ $(M + H)^+$ calcd 612.2179, found 612.2180.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-3-[(cyclopropylmethyl)[(3-methoxyphenyl)sulfonyl]amino]-2-hydroxypropyl]-3-(3,4-difluorophenyl)-2-oxooxazolidine-5-carboxamide (36c):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 8.8 Hz, 2H), 7.54−7.48 (m, 1H), 7.19 (q, $J$ = 9.6 Hz, 1H), 7.13 (d, $J$ = 7.6 Hz, 2H), 7.05−6.96 (m, 5H), 6.90 (t, $J$ = 7.6 Hz, 1H), 6.82 (d, $J$ = 10.0 Hz, 1H), 4.80 (dd, $J$ = 10.0, 5.6 Hz, 1H), 4.29 (m, 1H), 4.04 (m, 1H), 4.0 (t, $J$ = 9.2 Hz, 1H), 3.87

(s, 3H), 3.60 (br s, 1H) 3.35−3.24 (m, 3H), 3.21−3.10 (m, 2H), 2.96 (dd, $J$ = 14.4, 7.6 Hz, 1H), 2.79 (dd, $J$ = 14.0, 10.8 Hz, 1H), 0.91−0.83 (m, 1H), 0.54 (m, 2H), 0.18 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.51, 163.27, 152.83, 150.46 (d, $J$ = 246.4 Hz), 147.38 (d, $J$ = 245.6 Hz), 137.57, 134.05 (m), 130.42, 129.56 (2C), 129.55 (2C), 128.51 (2C), 126.57, 117.59 (d, $J$ = 17.4 Hz), 114.60 (2C), 113.87 (d, $J$ = 3.8 Hz), 108.38 (d, $J$ = 22.7 Hz), 72.38, 69.76, 55.82, 55.03, 53.37, 52.12, 48.28, 35.48, 10.05, 4.71, 4.26; HRMS (ESI) *m/z* $C_{31}H_{34}F_2N_3O_7S$ $(M + H)^+$ calcd 630.2086, found 630.2077.

**(5*S*)-3-(4-Acetylphenyl)-*N*-[(1*S*,2*R*)-1-Benzyl-3-[(cyclopropylmethyl)[(3-methoxyphenyl)sulfonyl]amino]-2-hydroxypropyl]-2-oxooxazolidine-5-carboxamide (36f):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J$ = 9.2 Hz, 2H), 7.74 (d, $J$ = 8.8 Hz, 2H), 7.55 (d, $J$ = 8.8 Hz, 2H), 7.12 (d, $J$ = 7.6 Hz, 2H), 7.02−6.97 (m, 4H), 6.83 (t, $J$ = 6.8 Hz, 1H), 6.69 (d, $J$ = 9.6 Hz, 1H), 4.81 (dd, $J$ = 10.4, 6.0 Hz, 1H), 4.28 (m, 1H), 4.08 (t, $J$ = 9.6 Hz, 1H), 4.02 (m, 1H), 3.87 (s, 3H), 3.54 (d, $J$ = 2.4 Hz, 1H), 3.39 (dd, $J$ = 9.2, 5.6 Hz, 1H), 3.30 (dd, $J$ = 15.2, 8.8 Hz, 1H), 3.23−3.18 (m, 2H), 3.12 (dd, $J$ = 14.4, 4.8 Hz, 1H), 2.94 (dd, $J$ = 14.0, 7.2 Hz, 1H), 2.78 (dd, $J$ = 13.6, 10.4 Hz, 1H), 2.62 (s, 3H), 0.88 (m, 1H), 0.56 (d, $J$ = 7.6 Hz, 2H), 0.23−0.15 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.97, 168.50, 163.24, 152.74, 141.57, 137.58, 133.13, 130.44, 129.78 (2C), 129.54 (4C), 128.46 (2C), 126.58, 117.58 (2C), 114.59 (2C), 72.38, 69.89, 55.80, 55.0, 53.40, 52.09, 48.01, 35.49, 26.65, 10.02, 4.69, 4.26; HRMS (ESI) *m/z* $C_{33}H_{38}N_3O_8S$ $(M + H)^+$ calcd 636.2379, found 636.2369.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[[(3-methoxyphenyl)-sulfonyl](2-thiophenylmethyl)]amino]propyl]-2-oxo-3-phenyloxazolidine-5-carboxamide (37a):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45−7.38 (m, 6H), 7.32 (d, $J$ = 2.0 Hz, 1H), 7.22−7.17 (m, 2H), 7.13 (m, 1H), 7.08 (d, $J$ = 8.0 Hz, 2H), 7.02 (t, $J$ = 7.6 Hz, 2H), 6.93−6.88 (m, 3H), 6.57 (d, $J$ = 9.6 Hz, 1H), 4.72 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.65 (AB, d, $J$ = 15.6 Hz, 1H), 4.59 (AB, d, $J$ = 15.6 Hz, 1H), 4.10 (m, 1H), 4.05 (t, $J$ = 9.6 Hz, 1H), 3.85 (s, 3H), 3.66 (dd, $J$ = 11.2, 6.4 Hz, 1H), 3.48 (br s, 1H), 3.43 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.24 (m, 2H), 3.04 (dd, $J$ = 14.0, 4.0 Hz, 1H), 2.68 (dd, $J$ = 14.0, 10.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.97, 160.30, 153.01, 139.91, 138.26, 137.49, 137.29, 130.59, 129.50 (2C), 129.31 (2C), 128.59 (2C), 128.34, 127.21, 127.07, 126.67, 124.82, 119.68, 119.59, 118.47 (2C), 112.34, 71.96, 69.78, 55.91, 53.36, 51.68, 48.27, 48.20, 35.61; HRMS (ESI) *m/z* $C_{32}H_{34}N_3O_7S_2$ $(M + H)^+$ calcd 636.1838, found 636.1864.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[[(3-methoxyphenyl)-sulfonyl](2-thiophenylmethyl)]amino]propyl]-3-(3-fluorophenyl)-2-oxooxazolidine-5-carboxamide (37b):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.47−7.34 (m, 4H), 7.32 (t, $J$ = 2.0 Hz, 1H), 7.24 (t, $J$ = 3.2 Hz, 1H), 7.14 (m, 1H), 7.10−7.01 (m, 5H), 6.93−6.87 (m, 4H), 6.43 (d, $J$ = 9.2 Hz, 1H), 4.72 (dd, $J$ = 10.0, 5.6 Hz, 1H), 4.65 (AB d, $J$ = 15.6 Hz, 1H), 4.58 (AB d, $J$ = 15.6 Hz, 1H), 4.11 (m, 1H), 4.02 (t, $J$ = 10.0 Hz, 1H), 3.86 (s, 3H), 3.63 (m, 1H), 3.38 (dd, $J$ = 9.2, 5.6 Hz, 1H), 3.29−3.17 (m, 2H), 3.04 (dd, $J$ = 14.0, 4.4, Hz, 1H), 2.67 (dd, $J$ = 13.6, 10.4, Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.70, 163.19 (d, $J$ = 244.1 Hz), 160.28, 152.76, 139.91, 139.01 (d, $J$ = 10.6 Hz), 138.24, 137.32, 130.59, 130.51 (d, $J$ = 9.8 Hz), 129.49 (2C), 128.53 (2C), 128.35, 127.18, 127.04, 126.62, 119.66, 119.56, 113.51 (d, $J$ = 2.2 Hz), 112.37, 111.52 (d, $J$ = 21.3 Hz), 106.05 (d, $J$ = 26.5 Hz), 72.04, 69.74, 55.91, 53.30, 51.58, 48.16, 48.15, 35.56; HRMS (ESI) *m/z* $C_{32}H_{33}FN_3O_7S_2$ $(M + H)^+$ calcd 654.1744, found 654.1766.

**(*S*)-3-(4-Acetylphenyl)-*N*-[(2*S*,3*R*)-1-benzyl-2-hydroxy-3-[[(3-methoxyphenyl)sulfonyl](2-thiophenylmethyl)]amino]propyl]-2-oxooxazolidine-5-carboxamide (37f):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J$ = 8.8 Hz, 2H), 7.55 (d, $J$ = 9.2 Hz, 2H), 7.45 (t, $J$ = 7.6 Hz, 1H), 7.40 (d, $J$ = 7.6 Hz, 1H), 7.32 (t, $J$ = 2.4 Hz, 1H), 7.23 (dd, $J$ = 4.4, 2.8 Hz, 1H), 7.13 (m, 1H), 7.07 (d, $J$ = 7.2 Hz, 2H), 6.99 (t, $J$ = 7.6 Hz, 2H), 6.91 (m, 2H), 6.84 (t, $J$ = 7.6 Hz, 1H), 6.54 (d, $J$ = 9.6 Hz, 1H), 4.76 (dd, $J$ = 10.0, 6.0 Hz, 1H), 4.65 (AB d, $J$ = 15.2 Hz, 1H), 4.59 (AB d, $J$ = 15.2 Hz, 1H), 4.14 (m, 1H), 4.07 (t, $J$ = 9.6 Hz, 1H), 3.85 (s, 3H), 3.68 (m, 1H), 3.41 (m, 2H), 3.24 (m, 2H), 3.04 (dd, $J$ = 14.0, 4.4, Hz, 1H), 2.67 (dd, $J$ = 13.6, 10.4, Hz, 1H), 2.62 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.98, 168.56, 160.31, 152.63, 141.54, 139.81, 138.25, 137.27, 133.20, 130.63, 129.84 (2C), 129.51 (2C), 128.52 (2C), 128.34, 127.22, 127.10, 126.66, 119.67, 119.58, 117.57 (2C), 112.41, 72.01, 69.75, 55.93, 53.28, 51.73, 48.29, 47.97, 35.58, 26.68; HRMS (ESI) *m/z* $C_{34}H_{36}N_3O_8S_2$ $(M + H)^+$ calcd 678.1944, found 678.1953.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[(2-thiophenylmethyl)-[(2,4,5-trifluorophenyl)sulfonyl]amino]propyl]-2-oxo-3-phenyloxazolidine-5-carboxamide (38a):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76−7.70 (m, 1H), 7.43−7.36 (m, 4H), 7.19−7.16 (m, 2H), 7.08−7.01 (m, 5H), 6.93−6.86 (m, 3H), 6.67 (d, $J$ = 9.2 Hz, 1H), 4.79−4.67 (m, 3H), 4.12 (m, 1H), 4.06 (t, $J$ = 9.6 Hz, 1H), 3.79 (m, 1H), 3.49−3.33 (m, 4H), 3.02 (dd, $J$ = 14.0, 4.4 Hz, 1H), 2.69 (dd, $J$ = 14.0, 10.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.21, 154.8 (dd, $J$ = 253.2, 10.6 Hz), 153.45 (dt, $J$ = 257.0, 13.6 Hz), 153.05, 146.48 (dd, $J$ = 253.2, 13.2 Hz), 137.57, 137.44, 137.14, 129.43 (2C), 129.34 (2C), 128.68 (2C), 127.20, 127.14, 126.81, 124.89, 119.64 (d, $J$ = 22.0 Hz), 118.51 (2C), 107.72 (dd, $J$ = 27.3, 21.2 Hz), 72.10, 69.81, 53.78, 51.05, 51.02, 48.29, 47.63, 35.45, 29.88; HRMS (ESI) *m/z* $C_{31}H_{29}F_3N_3O_6S_2$ $(M + H)^+$ calcd 660.1450, found 660.1462.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[(2-thiophenylmethyl)-[(2,4,5-trifluorophenyl)sulfonyl]amino]propyl]-3-(3-fluorophenyl)-2-oxooxazolidine-5-carboxamide (38b):** $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.78−7.72 (m, 1H), 7.39−7.32 (m, 2H), 7.22 (d, $J$ = 4.8, 1.2 Hz, 1H), 7.11−7.03 (m, 6H), 6.95−6.87 (m, 4H), 6.55 (d, $J$ = 9.2 Hz, 1H), 4.79−4.69 (m, 3H), 4.14 (m, 1H), 4.05 (t, $J$ = 9.6 Hz, 1H), 3.78 (m, 1H), 3.47−3.35 (m, 3H), 3.18 (d, $J$ = 4.0 Hz, 1H), 3.04 (dd, $J$ = 14.0, 4.8 Hz, 1H), 2.72 (dd, $J$ = 14.0, 11.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.94, 164.42, 161.98, 154.75 (dd, $J$ = 250.0, 10.6 Hz), 153.43 (dt, $J$ = 248.0, 10.4 Hz)), 152.83, 146.32 (dd, $J$ = 248.2, 10.4 Hz), 138.97 (d, $J$ = 10.6 Hz), 137.51, 137.21, 130.52 (d, $J$ = 9.5 Hz), 129.43 (2C), 128.72, 128.62 (2C), 127.17, 127.09, 126.74, 119.61 (d, $J$ = 22.0 Hz), 113.55, 111.58 (d, $J$ = 21.2 Hz), 107.69 (dd, $J$ = 27.3, 21.3 Hz), 106.10 (d, $J$ = 27.3 Hz), 72.24, 69.81, 53.71, 50.94, 48.21, 47.55, 35.40; HRMS (ESI) *m/z* $C_{31}H_{28}F_4N_3O_6S_2$ $(M + H)^+$ calcd 678.1355, found 678.1377.

**(*S*)-3-(4-Acetylphenyl)-*N*-[(2*S*,3*R*)-1-Benzyl-2-hydroxy-3-[(2-thiophenylmethyl)[(2,4,5-trifluorophenyl)sulfonyl]amino]propyl]-2-oxooxazolidine-5-carboxamide (38f):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J$ = 9.2 Hz, 2H), 7.78−7.72 (m, 1H), 7.55 (d, $J$ = 9.2 Hz, 2H), 7.21 (dd, $J$ = 5.2, 1.2 Hz, 1H), 7.10−6.99 (m, 5H), 6.93−6.85 (m, 3H), 6.67 (d, $J$ = 8.8 Hz, 1H), 4.82−4.70 (m, 3H), 4.17 (m, 1H), 4.10 (t, $J$ = 10 Hz, 1H), 3.84 (m, 1H), 3.50−3.36 (m, 3H), 3.30 (d, $J$ = 4.0 Hz, 1H), 3.04 (dd, $J$ = 14.0, 4.4 Hz, 1H), 2.71 (dd, $J$ = 14.0, 10.8 Hz, 1H), 2.62 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.97, 168.80, 154.50 (dd, $J$ = 252.3, 10.8 Hz), 153.4 (dt, $J$ = 255.6, 12.2 Hz), 152.68, 146.28 (dd, $J$ = 252.4, 10.5 Hz), 141.51, 137.53, 137.17, 133.25, 129.84 (2C), 129.45 (2C), 128.71, 128.62 (2C), 127.21, 127.16, 126.78, 119.76 (d, $J$ = 22.0 Hz), 117.61 (2C), 107.74 (dd, $J$ = 27.3, 21.2 Hz), 72.22, 69.81, 53.69, 51.09, 51.06, 48.0, 47.66, 35.43, 26.67; HRMS (ESI) *m/z* $C_{33}H_{31}F_3N_3O_7S_2$ $(M + H)^+$ calcd 702.1555, found 702.1561.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[[(3-methoxyphenyl)-sulfonyl][(*R*)-(tetrahydro-2-furanyl)methyl]amino]propyl]-2-oxo-3-phenyloxazolidine-5-carboxamide (39a):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.47−7.38 (m, 5H), 7.35 (d, $J$ = 7.6 Hz, 1H), 7.29 (d, $J$ = 1.8 Hz, 1H), 7.19 (t, $J$ = 7.2 Hz, 2H), 7.11 (m, 3H), 7.0 (t, $J$ = 7.6 Hz, 2H), 6.89 (t, $J$ = 7.6 Hz, 1H), 6.83 (d, $J$ = 10 Hz, 1H), 5.27 (br s, 1H), 4.81 (dd, $J$ = 10.4, 6.0 Hz, 1H), 4.31−4.18 (m, 2H), 4.05 (t, $J$ = 9.6 Hz, 1H), 4.0 (t, $J$ = 10.0 Hz, 1H), 3.92−3.80 (m, 2H, overlapping signal), 3.88 (s, 3H, overlapping signal), 3.66 (dt, $J$ = 15.2, 2.4 Hz, 1H), 3.43 (dd, $J$ = 9.2, 6.0 Hz, 1H), 3.05 (dd, $J$ = 14.0, 4.4 Hz, 1H), 2.88 (dd, $J$ = 9.2, 4.8 Hz, 1H), 2.84 (dd, $J$ = 9.6, 4.8 Hz, 1H), 2.72 (dd, $J$ = 13.2, 10.0 Hz, 1H), 2.04 (m, 1H), 1.92 (m, 2H), 1.47 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.53, 160.22, 153.13, 139.78, 137.65, 137.57, 130.53, 129.67 (2C), 129.28 (2C), 128.44 (2C), 126.55, 124.67, 119.45, 119.02, 118.44 (2C), 112.68, 80.49, 73.81, 69.87, 68.48,

56.48, 56.27, 55.91, 52.90, 48.29, 35.96, 29.22, 25.46; HRMS (ESI) *m/z* $C_{32}H_{38}N_3O_8S$ $(M + H)^+$ calcd 624.2379, found 624.2390.

**(5*S*)-*N*-[(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[[(3-methoxyphenyl)-sulfonyl][(*R*)-(tetrahydro-2-furanyl)methyl]amino]propyl]-3-(3-fluorophenyl)-2-oxooxazolidine-5-carboxamide (39b):** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42 (t, $J = 7.6$ Hz, 1H), 7.38−7.32 (m, 2H), 7.28 (t, $J = 2.4$ Hz, 1H), 7.11 (m, 4H), 7.0 (t, $J = 7.2$ Hz, 2H), 6.91−6.86 (m, 2H), 6.84 (d, $J = 9.6$ Hz, 1H), 5.28 (d, $J = 2.8$ Hz, 1H), 4.82 (dd, $J = 10.0$, 5.6 Hz, 1H), 4.31−4.19 (m, 2H), 4.02 (m, 2H), 3.92−3.80 (m, 2H, overlapping signal), 3.85 (s, 3H, overlapping signal), 3.69−3.64 (m, 2H), 3.39 (dd, $J = 9.2$, 5.6 Hz, 1H), 3.05 (dd, $J = 14.0$, 4.4 Hz, 1H), 2.89−2.82 (m, 2H), 2.71 (dd, $J = 14.0$, 10.4 Hz, 1H), 2.04 (m, 1H), 1.92 (m, 2H), 1.46 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.29, 163.21 (d, $J = 243.4$ Hz), 160.22, 152.86, 139.75, 139.17 (d, $J = 10.6$ Hz), 137.59, 130.54, 130.46 (d, $J = 9.1$ Hz), 129.67 (2C), 128.40 (2C), 126.50, 119.43, 118.99, 113.48 (d, $J = 3.1$ Hz), 112.71, 111.38 (d, $J = 20.4$ Hz), 106.03 (d, $J = 27.3$ Hz), 80.51, 73.85, 69.84, 68.49, 56.53, 56.31, 55.90, 52.87, 48.20, 35.92, 29.23, 25.46; HRMS (ESI) *m/z* $C_{32}H_{37}FN_3O_8S$ $(M + H)^+$ calcd 642.2285, found 642.2289.

**Biological Evaluation of HIV-1 Protease Inhibitors.** HIV-1 protease inhibitor activities were determined by the fluorescence resonance energy transfer (FRET) method.[32] Protease substrate [Arg-Glu(EDANS)-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-Lys(DABCYL)-Arg] was purchased from Molecular Probe. The energy transfer donor (EDANS) and acceptor (DABCYL) were labeled at its two ends respectively to perform FRET. Fluorescence measurements were carried out on a PTI fluorescence spectrophotometer (Photon Technology International) at 30 °C. Excitation and emission wavelengths were set at 340 and 490 nm, respectively. Each reaction was recorded for about 10 min. Wide-type HIV-1 protease (Q7K) and its MDR variants M1 (L10I, G48V, I54V, L63P, V82A), M2 (D30N, L63P, N88D), and M3 (L10I, L63P, A71V, G73S, I84V, L90M) were desalted through PD-10 columns (Amersham Biosciences). Sodium acetate (20 mM, pH 5) was used as elution buffer. Apparent protease concentrations were around 50 nM as estimated by UV spectrophotometer (Shimadzu) at 280 nm. All inhibitors were dissolved in DMSO and diluted to appropriate concentrations. Protease (2 $\mu$L) and inhibitor (2 $\mu$L) or DMSO were mixed and the solution incubated for 20−30 min at room temperature before initializing the substrate cleavage reaction. Throughout this work, 150 $\mu$L of 1 $\mu$M substrate was used. Substrate buffer is a composite of 0.1 M sodium acetate, 1 M sodium chloride, 1 mM ethylenediaminetetraacetic acid (EDTA), 1 mM dithiothreitol (DTT), 2% dimethyl sulfoxide (DMSO), and 1 mg/mL bovine serum albumin (BSA) with an adjusted pH 4.7. Inhibitor binding dissociation constant ($K_i$) was obtained by nonlinear regression fitting (GraFit 5, Erithacus software) to the plot of initial velocity as a function of inhibitor concentrations based on Morrison equation.[33] The initial velocities were derived from the linear range of reaction curves.

**Protein Crystallography.** Protein expression, isolation, and purification were carried out as previously described.[36] The protein used for crystallizing **21e** and **21f** was further purified using a Pharmacia Superdex 75 FPLC column. Crystals were set up with a 3−5-fold molar excess of inhibitors to protease of 1−1.5 mg/mL concentration. The hanging drop vapor diffusion method was used for crystallization as previously described.[17] The reservoir solution consisted of 126 mM phosphate buffer at pH 6.2, 63 mM sodium citrate, and 24−29% ammonium sulfate. Intensity data were collected on an in-house Rigaku X-ray generator equipped with an R-axis IV image plate system. Data were collected at −80 °C and the data processing was carried out using the programs DENZO and ScalePack, respectively.[37,38] Data collection statistics are listed in Table 3.

The CCP4i interface to the CCP4 suite[39] was used to refine the structures. Structure solution was obtained with the molecular replacement package AMoRe,[40] with 1F7A[41] as the starting model. The molecular replacement phases were further improved using ARP/wARP[42] by building solvent molecules into the unaccounted regions of electron density. Model building was performed using the interactive graphics program O.[43] Conjugate gradient refinement using Refmac5[44] was performed by incorporating Schomaker and Trueblood tensor formulation of TLS (translation, libration, screw-rotation) parameters.[45−47] The working $R$ ($R_{factor}$) and its cross-validation ($R_{free}$) were monitored throughout the refinement. The refinement statistics are also shown in Table 1. Figures were made using MIDASPlus.[48] The structures of **21e**− and **21f**−protease complexes were deposited in the PDB with accession codes 2I0D and 2I0A, respectively.

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**Supporting Information Available:** Detailed experimental procedures for the synthesis of intermediate and target compounds, characterization data of intermediate compounds **7**−**10**, and results of HPLC analysis of final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Bartlett, J. A.; DeMasi, R.; Quinn, J.; Moxham, C.; Rousseau, F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS* **2001**, *15*, 1369−1377.

(2) Gulick, R. M.; Mellors, J. W.; Havlir, D.; Eron, J. J.; Meibohm, A.; Condra, J. H.; Valentine, F. T.; McMahon, D.; Gonzalez, C.; Jonas, L.; Emini, E. A.; Chodakewitz, J. A.; Isaacs, R.; Richman, D. D. 3-Year suppression of HIV viremia with indinavir, zidovudine, and lamivudine. *Ann. Intern. Med.* **2000**, *133*, 35−39.

(3) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A. Rational design of peptide-based HIV proteinase inhibitors. *Science* **1990**, *248*, 358−361.

(4) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. L-735,524: The design of a potent and orally bioavailable HIV protease inhibitor. *J. Med. Chem.* **1994**, *37*, 3443−3451.

(5) Kempf, D. J.; Marsh, K. C.; Denissen, J. F.; McDonald, E.; Vasavanonda, S.; Flentge, C. A.; Green, B. E.; Fino, L.; Park, C. H.; Kong, X. P.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H. L.; Robins, T.; Stewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard, J. M.; Norbeck, D. W. ABT-538 is a potent inhibitor of human immunodeficiency virus protease and has high oral bioavailability in humans. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2484−2488.

(6) Kaldor, S. W.; Kalish, V. J.; Davies, J. F.; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. Viracept (Nelfinavir Mesylate, AG1343): A potent, orally bioavailable inhibitor of HIV-1 protease. *J. Med. Chem.* **1997**, *40*, 3979−3985.

(7) Kim, E. E.; Baker, C. T.; Dwyer, M. D.; Murcko, M. A.; Rao, B. G.; Tung, R. D.; Navia, M. A. Crystal structure of HIV-1 protease in complex with VX-478, a potent and orally bioavailable inhibitor of the enzyme. *J. Am. Chem. Soc.* **1995**, *117*, 1181−1182.

(8) Sham, H. L.; Kempf, D. J.; Molla, A.; Marsh, K. C.; Kumar, G. N.; Chen, C. M.; Kati, W.; Stewart, K.; Lal, R.; Hsu, A.; Betebenner, D.; Korneyeva, M.; Vasavanonda, S.; McDonald, E.; Saldivar, A.; Wideburg, N.; Chen, X.; Niu, P.; Park, C.; Jayanti, V.; Grabowski, B.; Granneman, G. R.; Sun, E.; Japour, A. J.; Norbeck, D. W. ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease. *Antimicrob. Agents Chemother.* **1998**, *42*, 3218−3224.

(9) Robinson, B. S.; Riccardi, K. A.; Gong, Y. F.; Guo, Q.; Stock, D. A.; Blair, W. S.; Terry, B. J.; Deminie, C. A.; Djang, F.; Colonno, R. J.; Lin, P. F. BMS-232632, a highly potent human immunodeficiency virus protease inhibitor that can be used in combination with other available antiretroviral agents. *Antimicrob. Agents Chemother.* **2000**, *44*, 2093−2099.

(10) Turner, S. R.; Strohbach, J. W.; Tommasi, R. A.; Aristoff, P. A.; Johnson, P. D.; Skulnick, H. I.; Dolak, L. A.; Seest, E. P.; Tomich, P. K.; Bohanon, M. J.; Horng, M. M.; Lynn, J. C.; Chong, K. T.; Hinshaw, R. R.; Watenpaugh, K. D.; Janakiraman, M. N.; Thaisrivongs, S. Tipranavir (PNU-140690): A potent, orally bioavailable nonpeptidic HIV protease inhibitor of the 5,6-dihydro-4-hydroxy-2-pyrone sulfonamide class. *J. Med. Chem.* **1998**, *41*, 3467−3476.

(11) (a) Koh, Y.; Nakata, H.; Maeda, K.; Ogata, H.; Bilcer, G.; Devasamudram, T.; Kincaid, J. F.; Boross, P.; Wang, Y.-F.; Tie, Y.; Volarath, P.; Gaddis, L.; Harrison, R. W.; Weber, I. T.; Ghosh, A. K.; Mitsuya, H. Novel bis-tetrahydrofuranylurethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC114) with potent activity against multi-PI-resistant human immunodeficiency virus in vitro. *Antimicrob. Agents Chemother.* **2003**, *47*, 3123−3129. (b) Surleraux, D. L. N. G.; Tahri, A.; Verschueren, W. G.; Pille, G. M. E.; deKock, H. A.; Jonckers, T. H. M.; Peeters, A.; DeMeyer, S.; Azijn, H.; Pauwels, R.; deBethune, M.-P.; King, N. M.; Prabu-Jeyabalan, M.; Schiffer, C. A.; Wigerinck, P. B. T. P. Discovery and selection of TMC114, a next generation HIV-1 protease inhibitor. *J. Med. Chem.* **2005**, *48*, 1813−1822. (c) De Meyer, S.; Azijn, H.; Surleraux, D.; Jochmans, D.; Tahri, A.; Pauwels, R.; Wigerinck, P.; de Bethune, M. P. TMC114, A novel human immunodeficiency virus type 1 protease inhibitor active against protease inhibitor-resistant viruses, including a broad range of clinical isolates. *Antimicrob. Agents Chemother.* **2005**, *49*, 2314−2321.

(12) Wlodawer, A.; Vondrasek, J. Inhibitors of HIV-1 protease: A major success of structure-assisted drug design. *Annu. Rev. Biophys. Biomol. Struct.* **1998**, *27*, 249−284.

(13) Condra, J. H.; Schleif, W. A.; Blahy, O. M.; Gabryelski, L. J.; Graham, D. J.; Quintero, J. C.; Rhodes, A.; Robbins, H. L.; Roth, E.; Shivaprakash, M. In vivo emergence of HIV-1 variants resistant to multiple protease inhibitors. *Nature (London)* **1995**, *374*, 569−571.

(14) Clavel, F.; Hance, A. J. HIV drug resistance. Structural and thermodynamic basis of resistance to HIV-1 protease inhibition: Implications for inhibitor design. *N. Engl. J. Med.* **2004**, *350*, 1023−1035.

(15) (a) Surleraux, D. L. N. G.; deKock, H. A.; Verschueren, W. G.; Pille, G. M. E.; Maes, L. J. R.; Peeters, A.; Vendeville, S.; DeMeyer, S.; Azijn, H.; Pauwels, R.; deBethune, M.-P.; King, N. M.; Prabu-Jeyabalan, M.; Schiffer, C. A.; Wigerinck, P. B. T. P. Design of HIV-1 protease inhibitors active on multidrug-resistant virus. *J. Med. Chem.* **2005**, *48*, 1965−1973. (b) Miller, J. F.; Andrews, C. W.; Brieger, M.; Furfine, E. S.; Hale, M. R.; Hanlon, M. H.; Hazen, R. J.; Kaldor, I.; McLean, E. W.; Reynolds, D., Ultra-potent P1 modified arylsulfonamide HIV protease inhibitors: The discovery of GW0385. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1788−1794. (c) Ghosh, A. K.; Sridhar, P. R.; Leshchenko, S.; Hussain, A. K.; Li, J.; Kovalevsky, A. Y.; Walters, D. E.; Wedekind, J. E.; Grum-Tokars, V.; Das, D.; Koh, Y.; Maeda, K.; Gatanaga, H.; Weber, I. T.; Mitsuya, H. Structure-based design of novel HIV-1 protease inhibitors to combat drug resistance. *J. Med. Chem.* **2006**, *49*, 5252−5261.

(16) King, N. M.; Prabu-Jeyabalan, M.; Nalivaika, E. A.; Schiffer, C. A. Combating susceptibility to drug resistance: Lessons from HIV-1 protease. *Chem. Biol.* **2004**, *11*, 1333−1338.

(17) Prabu-Jeyabalan, M.; Nalivaika, E. A.; King. N. M.; Schiffer, C. A. Viability of a drug resistant HIV-1 protease variant: Structural insights for better anti-viral therapy. *J. Virol.* **2003**, *77*, 1306−1315.

(18) Prabu-Jeyabalan, M.; Nalivaika, E. A.; Schiffer, C. A. Substrate shape determines specificity of recognition for HIV-1 protease: Analysis of crystal structures of six substrate complexes. *Structure* **2002**, *10*, 369−381.

(19) King, N. M.; Prabu-Jeyabalan, M.; Nalivaika, E. A.; Wigerinck, P.; deBethune, M.-P.; Schiffer, C. A. Structural and thermodynamic basis for the binding of TMC114, a next generation human immunodeficiency virus type 1 protease inhibitor. *J. Virol.* **2004**, *78*, 12012−12021.

(20) Kovalevsky, A. Y.; Tie, Y.; Liu, F.; Boross, P. I.; Wang, Y. F.; Leshchenko, S.; Ghosh, A. K.; Harrison, R. W.; Weber, I. T., Effectiveness of nonpeptide clinical inhibitor TMC-114 on HIV-1 protease with highly drug resistant mutations D30N, I50V, and L90M. *J. Med. Chem.* **2006**, *49*, 1379−1387.

(21) (a) Ghosh, A. K.; Krishnan, K.; Eric Walters, D.; Cho, W.; Cho, H.; Koo, Y.; Trevino, J.; Holland, L.; Buthod, J. Structure based design: Novel spirocyclic ethers as nonpeptidal P2-ligands for HIV protease inhibitors. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 979−982. (b) Ghosh, A. K.; Shin, D.; Swanson, L.; Krishnan, K.; Cho, H.; Hussain, K. A.; Walters, D. E.; Holland, L.; Buthod, J. Structure-based design of non-peptide HIV protease inhibitors. *Farmaco* **2001**, *56*, 29−32.

(22) (a) Freskos, J. N.; Bertenshaw, D. E.; Getman, D. P.; Heintz, R. M.; Mischke, B. V.; Blystone, L. W.; Bryant, M. L.; Funckes-Shippy, C.; Houseman, K. A.; Kishore, N. N. (Hydroxyethyl) sulfonamide HIV-1 protease inhibitors: Identification of the 2-methylbenzoyl moiety at P-2. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 445−450.; (b) Cheng, T.-J.; Brik, A.; Wong, C.-H.; Kan, C.-C. Model system for high-throughput screening of novel human immunodeficiency virus protease inhibitors in *Escherichia coli*. *Antimicrob. Agents Chemother.* **2004**, *48*, 2437−2447.

(23) (a) Nagarajan, S. R.; De Crescenzo, G. A.; Getman, D. P.; Lu, H.-F.; Sikorski, J. A.; Walker, J. L.; McDonald, J. J.; Houseman, K. A.; Kocan, G. P.; Kishore, N. Discovery of novel benzothiazole-sulfonamides as potent inhibitors of HIV-1 protease. *Bioorg. Med. Chem.* **2003**, *11*, 4769−4777. (b) Vazquez, M. L.; Mueller, R. A.; Talley, J. J.; Getman, D. P.; Decrescenzo, G. A.; Freskos, J. N.; Bertebshaw, D. E.; Heintz, R. M. Preparation of hydroxyethylamino sulfonamides useful as retroviral protease inhibitors. US Patant, 6046190, 2000.

(24) Ghosh, A. K.; Swanson, L. M.; Cho, H.; Leshchenko, S.; Hussain, K. A.; Kay, S.; Walters, D. E.; Koh, Y.; Mitsuya, H. Structure-based design: Synthesis and biological evaluation of a series of novel cycloamide-derived HIV-1 protease inhibitors. *J. Med. Chem.* **2005**, *48*, 3576−3585.

(25) Barbachyn, M. R.; Ford, C. W. Oxazolidine structure−activity relationships leading to linezolid. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010−2023.

(26) (a) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. Synthesis and antibacterial activity of U-100592 and U-100766, two oxazolidinone antibacterial agents for the potential treatment of multidrug-resistant gram-positive bacterial infections. *J. Med. Chem.* **1996**, *39*, 673−679.

(27) (a) Hester, J. B. Preparation of Amide-containing oxazolidines having improved solubility and bioavailability. PCT Int. Appl. WO 2003/006440, **2003**; (b) Thomas, R. C.; Poel, T.-J.; Barbachyn, M. R.; Gordeev, M. F.; Luehr, G. W.; Renslo, A.; Singh, U. Preparation of 3-aryl-2-oxo-5-oxazolidinecarboxamides and analogs as antibacterial agents. PCT Int. Appl. WO 2003/072553, **2003**.

(28) Salituro, F. G.; Baker, C. T.; Court, J. J.; Deininger, D. D.; Kim, E. E.; Li, B.; Novak, P. M.; Rao, B. G.; Pazhanisamy, S.; Porter, M. D.; Schairer, W. C.; Tung, R. D. Design and synthesis of novel conformationally restricted HIV protease inhibitors. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3637−3642.

(29) Kazmierski, W. M.; Furfine, E.; Gray-Nunez, Y.; Spaltenstein, A.; Wright, L. Potent inhibitors of the HIV-1 protease incorporating cyclic urea P1−P2 scaffold. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5685−5687.

(30) (a) Yeung, C. M.; Klein, L. L.; Flentge, C. A.; Randolph, J. T.; Zhao, C.; Sun, M.; Dekhtyar, T.; Stoll, V. S.; Kempf, D. A. Oximinoarylsulfonamides as potent HIV-1 protease inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2275−2278. (b) Randolph, J. T.; Huang, P. P.; Flosi, W. J.; DeGoey, D.; Klein, L. L.; Yeung, C. M.; Flentge, C.; Sun, M.; Zhao, C.; Dekhtyar, T. Synthesis, antiviral activity, and pharmacokinetic evaluation of P3 pyridylmethyl analogs of oximinoarylsulfonyl HIV-1 protease inhibitors. *Bioorg. Med. Chem.* **2006**, *14*, 4035−4046.

(31) Manninen, P. R.; Brickner, S. J. Preparation of *N*-aryl-5*R*-hydroxymethyl-2-oxazolidinones from *N*-aryl carbamates: *N*-Phenyl-(5*R*)-hydroxymethyl-2-oxazolidinone. *Org. Synth.* **2005**, *81*, 112−120.

(32) Matayoshi, E. D.; Wang, G. T.; Krafft, G. A.; Erickson, J. Novel fluorogenic substrates for assaying retroviral proteases by resonance energy transfer. *Science* **1990**, *247*, 954−958.

(33) Greco, W. R.; Hakala, M. T. Evaluation of methods for estimating the dissociation constant of tight binding enzyme inhibitors. *J. Biol. Chem.* **1979**, *254*, 12104−12109.

(34) Wu, T. D.; Schiffer, C. A.; Gonzales, M. J.; Taylor, J.; Kantor, R.; Chou, S.; Israelski, D.; Zolopa, A. R.; Fessel, W. J.; Shafer, R. W. Mutation patterns and structural correlates in human immunodeficiency virus type 1 protease following different protease inhibitor treatments. *J. Virol.* **2003**, *77*, 4836−4847.

(35) The crystal structures of **21e**− and **21f**−protease complexes have been deposited in the Proten Data Bank (PDB) with the accession codes 2I0D and 2I0A, respectively.

(36) King, N. M.; Melnick, L.; Prabu-Jeyabalan, M.; Nalivaika, E. A.; Yang, S. S.; Gao, Y.; Nie, X.; Zepp, C.; Heefner, D. L.; Schiffer, C. A. Lack of synergy for inhibitors targeting a multi-drug-resistant HIV-1 protease. *Protein Sci.* **2002**, *11*, 418−429.

(37) Minor, W. *XDISPLAYF* (program); Purdue University: West Lafayette, IN, 1993.

(38) Otwinowski, Z.; Minor, W. Processing of X-ray diffraction data collected in oscillation mode. *Macromolecular Crystallography Part A*; Academic Press: New York, 1997; pp 307−326.

(39) Collaborative-Computational-Project, N. The CCP4 suite: Programs for protein crystallography. *Acta Crystallogr.* **1994**, *D50*, 760−763.

(40) Navaza, J. AMoRe: An automated package for molecular replacement. *Acta Crystallogr.* **1994**, *A50*, 157−163.

(41) Prabu-Jeyabalan, M.; Nalivaika, E.; Schiffer, C. A. How does a symmetric dimer recognize an asymmetric substrate? A substrate complex of HIV-1 protease. *J. Mol. Biol.* **2000**, *301*, 1207−1220.

(42) Morris, R. J.; Perrakis, A.; Lamzin, V. S. ARP/wARP's model-building algorithms. I. The main chain. *Acta Crystallogr.* **2002**, *D58*, 968−975.

(43) Jones, T. A.; Bergdoll, M.; Kjeldgaard, M. O: A Macromolecular Modeling Environment. In *Crystallographic and Modeling Methods in Molecular Design*. Bugg, C.; Ealick, S., Eds.; Springer-Verlag Press: Berlin, Germany, 1990; pp 189−195.
(44) Murshudov, G. N.; Vagin, A. A.; Dodson, E. J. Refinement of macromolecular structures by the maximum-likelihood method. *Acta Crystallogr*. **1997**, *D53*, 240−255.
(45) Kuriyan, J.; Weis, W. I. Rigid protein motion as a model for crystallographic temperature factors. *Proc. Natl. Acad. Sci. U. S. A.* **1991**, *88*, 2773−2777.
(46) Schomaker, V.; Trueblood, K. N. *Acta Crystallogr*. **1968**, *B24*, 63−76.
(47) Tickle, I. J.; Moss, D. S. Presented at the IUCr99 Computing School, London, 1999.
(48) Ferrin, T. E.; Huang, C. C.; Jarvis, L. E.; Langridge, R. The MIDAS display system. *J. Mol. Graph*. **1988**, *6*, 13−27.

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