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Design and Synthesis of Potent HIV-1 Protease Inhibitors Containing Bicyclic Oxazolidinone Scaffold as the P2 Ligands: Structure–Activity Studies and Biological and X-ray Structural Studies

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Abstract

We have designed, synthesized, and evaluated a new class of potent HIV-1 protease inhibitors with novel bicyclic oxazolidinone derivatives as the P2 ligand. We have developed an enantioselective synthesis of these bicyclic oxazolidinones utilizing a key *o*-iodoxybenzoic acid mediated cyclization. Several inhibitors displayed good to excellent activity toward HIV-1 protease and significant antiviral activity in MT-4 cells. Compound **4k** has shown an enzyme K_i of 40 pM and antiviral IC_{50} of 31 nM. Inhibitors **4k** and **4l** were evaluated against a panel of highly resistant multidrug-resistant HIV-1 variants, and their fold-changes in antiviral activity were similar to those observed with darunavir. Additionally, two X-ray crystal structures of the related inhibitors

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ASSOCIATED CONTENT

Supporting Information

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Full NMR spectroscopic data for all final compounds and X-ray structural data for inhibitors **4a** and **4e**-bound HIV-1 protease (PDF) Molecular formula strings and some data (CSV)

Accession Codes

The PDB accession codes for inhibitor **4a**-bound HIV-1 protease and inhibitor **4e**-bound HIV-1 protease X-ray structures are 6E9A and 6E7J. Authors will release the atomic coordinates and experimental data upon article publication.

The authors declare no competing financial interest.

4a and **4e** bound to HIV-1 protease were determined at 1.22 and 1.30 Å resolution, respectively, and revealed important interactions in the active site that have not yet been explored.

Graphical Abstract

INTRODUCTION

The development of combined antiretroviral therapy (cART) has dramatically improved the treatment of human immune-deficiency virus type 1 (HIV-1) infections and acquired immunity deficiency syndrome (AIDS).^{1,2} HIV-1 protease inhibitors (PIs) are a critically important class of antiretroviral medications in cART.^{3,4} HIV-1 protease plays an essential role in the HIV life cycle and is a primary target for HIV/AIDS treatment.^{5,6} PIs block the ability of HIV-1 protease to cleave polyproteins and prevent the formation of mature virions.^{7,8} While cART drastically improved the course of HIV management and reduced the mortality and morbidity rates of HIV-1 infected individuals, the early FDA-approved PIs suffer from the traditional problems of peptide-like drugs including poor absorption, metabolic instability, and a number of other debilitating side effects.^{9,10} Perhaps the most alarming problem is the emergence of drug resistance which renders these therapies ineffective.^{11,12} Darunavir (DRV) is the latest FDA-approved PI and is the only PI-drug recommended as a first-line therapy.^{13,14} DRV exhibits a high genetic barrier to resistance and is used for both treatment-experienced and treatment-naïve patients with HIV-1 infection and AIDS.^{15,16} DRV exhibits a dual mechanism of action as (1) an inhibitor of catalytically important dimeric HIV-1 protease and (2) an inhibitor of the dimerization of protease monomers.^{17,18} The present first-line cART with boosted PI-based drugs and integrase-inhibitor bound regimens are effective against developing multidrug-resistant HIV-1 variants over an extended period of time. However, there are limitations with regard to drug related side effects, toxicity, and rapid emergence of drug-resistant variants for some patient groups. Therefore, potent and more effective HIV-1 protease inhibitors are necessary for the long-term success of cART.

DRV incorporates a privileged P2 ligand, 3(*R*),3a(*S*),6a(*R*)-bis-tetrahydrofuranyurethane (bis-THF), on an (*R*)-(hydroxyethylamino)sulfonamide isostere (**1**, Figure 1).^{19,20} The X-ray structural studies of DRV-bound HIV-1 protease revealed a network of hydrogen bonds with backbone atoms like a molecular crab throughout the S2 and S2' subsites.^{21,22} In particular, both oxygens on the bis-THF P2 ligand formed a pair of strong hydrogen bonds with the backbone amide NHs of Asp30 and Asp29. Furthermore, the 4-aminobenzene-sulfonamide P2' ligand also formed a strong hydrogen bond with the Asp30 backbone amide NH. These ligand-binding site interactions are responsible for DRV's superb antiviral and drug-

resistance properties. Further modulation of ligand-binding site interactions in the active site of HIV-1 protease led us to develop a range of very potent PIs effective against multidrug-resistant HIV-1 variants.^{23,24} In particular, we have designed inhibitor **3** containing a cyclopentanyltetrahydrofuran (Cp-THF) as the P2 ligand. Upon the basis of the X-ray structure of DRV-bound HIV-1 protease, we now speculate that a bicyclic oxazolidinone derivative can mimic the hydrogen-bonding interactions as well as the van der Waals interactions of the bis-THF and Cp-THF ligands in PIs **1–3** in the S2 subsite. We describe here the design and synthesis of a new class of HIV-1 protease inhibitors that incorporate stereochemically defined bicyclic oxazolidinone scaffolds as the P2 ligands.

CHEMISTRY

For initial investigation, we planned to synthesize an unsubstituted oxazolidinone ligand as represented in inhibitor **4a**. The synthesis of the requisite bicyclic oxazolidinone ligand in inhibitor **4a** in the optically active form is shown in Scheme 1. Multigram quantities of optically active (1*R*,4*S*)-*cis*-4-acetoxy-2-cyclopenten-1-ol (—)-**5** were prepared from cyclopentadiene using procedures described previously.^{25,26} We utilized a 2-iodoxybenzoic acid (IBX) mediated cyclization protocol developed by Nicolaou and Baran for the synthesis of the bicyclic oxazolidine ligand.²⁷ Thus, monoacetate **5** was treated with phenyl isocyanate or 4-methoxyphenyl isocyanate and a catalytic amount (10 mol %) of DBU in CH₂Cl₂ at 23 °C for 4 h to provide carbamate derivatives **6a** and **6b**, respectively, in 81% yield. Treatment of these aryl carbamates with IBX in a mixture (10:1) of THF and DMSO at 90 °C for 24 h afforded oxazolidinones **7a** and **7b**, respectively, in 37–65% yields. Both *N*-aryl oxazolidinones were obtained as a single isomer (by ¹H NMR analysis). The cleavage of the *p*-methoxyphenyl group on **7b** was accomplished by treatment with ceric ammonium nitrate (CAN) in a mixture (5:1) of acetonitrile and water at 23 °C for 1 h to afford the acetate derivative **8** in 71% yield. Removal of the acetate group in **8** with K₂CO₃ in methanol provided the optically active 5-hydroxyhexahydro-2*H*-cyclopenta[*d*]oxazol-2-one **9** in near quantitative yield. To investigate the stereochemical effect on the ligand-binding site interactions, we have also prepared the corresponding enantiomeric oxazolidinone, *ent*-**9**. This was prepared from the known optically active (1*S*,4*R*)-*cis*-4-acetoxy-2-cyclopenten-1-ol, *ent*-**5** using the steps as described for compound **9**.

For the structure–activity relationship studies, we have prepared a number of substituted oxazolidinone derivatives. Upon the basis of our initial X-ray structure of DRV-bound HIV-1 protease-based models, it appeared that (3*aS*,5*R*,6*aR*)-5-hydroxyhexahydro-2*H*-cyclopenta[*d*]oxazol-2-one stereochemistry would be well-accommodated by the HIV-1 protease active site.²¹ Our preliminary studies of the unsubstituted oxazolidinone-derived inhibitors revealed the preference for the (3*aS*,5*R*,6*aR*)-oxazolidinone stereochemistry as in inhibitor **4a** over the enantiomeric ligand in compound **4b**. The synthesis of various substituted oxazolidinone derivatives is shown in Scheme 2. For the synthesis of *N*-phenyl and substituted phenyl oxazolidinones, optically active (1*R*,4*S*)-*cis*-4-acetoxy-2-cyclopenten-1-ol **5** was reacted with various aryl isocyanates in the presence of DBU to provide the respective carbamates. IBX-mediated cyclization of these carbamates at 90 °C in a mixture (10:1) of THF and DMSO provided the corresponding bicyclic oxazolidinone

derivatives.²⁷ Removal of the acetate group by exposure to K_2CO_3 in methanol at 23 °C afforded the phenyl-substituted oxazolidinone ligand alcohols **10a–d**. For the synthesis of various aliphatic *N*-alkyl derivatives, acetoxy oxazolidinone derivative **8** was alkylated with various alkyl halides. As shown, oxazolidinone **8** was reacted with KHMDS in CH_3CN at 0 °C and the resulting anion was treated with MeI and the reaction mixture was warmed to 23 °C for 1 h to provide the *N*-Me derivative **10e** in 80% isolated yield. Saponification of the resulting ester afforded *N*-Me ligand alcohol **10e** in near quantitative yield. The corresponding enantiomeric *N*-Me derivative *ent*-**10** was prepared from *ent*-**9**. Similarly, *N*-alkylation with allyl iodide followed by removal of the acetate group furnished *N*-allyl derivative **10f** in 60% yield over two steps. Catalytic hydrogenation of **10f** in the presence of catalytic amount of 10% Pd–C in methanol under a hydrogen-filled balloon furnished the *N*-propyl derivative **10g** in 86% yield. Similarly, alkylation of **8** with 3-bromo-2-methylpropene followed by removal of the acetate provided ligand alcohol **10h** in 84% yield. Catalytic hydrogenation of **10h** furnished saturated ligand alcohol **10i** in 92% yield. For the introduction of the methoxymethyl side chain in ligand alcohol, oxazolidinone **8** was alkylated with KHMDS and chloromethyl methyl ether in THF at 0–23 °C for 1 h, providing the corresponding alkylated product. Removal of acetate group gave ligand alcohol **10j** in 33% yield over two steps.

The diverse optically active ligand alcohols **9**, *ent*-**9**, **10a–j**, and *ent*-**10e** were converted to the corresponding activated mixed carbonates.²⁸ As shown in Scheme 3, treatment of ligand alcohols with 4-nitrophenyl chloroformate and 4-methylmorpholine in CH_2Cl_2 at 0 °C for 12 h provided carbonates **11a–m** in good to excellent yields (30–97%).

The syntheses of various inhibitors containing hydroxyethylaminesulfonamide isosteres with 4-methoxysulfonamide as the P2' ligands are shown in Scheme 4. Reaction of known amine **12**²⁸ with activated carbonate **11a** provided inhibitor **4a** in good yield. Similarly, reaction of carbonates **11b–m** and amine **12** provided inhibitors **4b–m**. Inhibitor **4n** was prepared by reaction of known amine **13**²⁹ and carbonate **11b** as described above.

RESULTS AND DISCUSSION

We first evaluated all new inhibitors in an HIV-1 protease inhibitory assay according to the protocol described by Toth and Marshall.³⁰ Inhibitors that displayed potent K_i values (<1 nM), were then selected for further evaluation in an antiviral assay in MT-4 human T-lymphocytes exposed to HIV-1_{NL4-3}, and the antiviral assay was carried out as described previously.¹⁵ Inhibitor structures and biological results are shown in Tables 1 and 2. As can be seen in Table 1, inhibitor **4a** with (3a*S*,5*R*,6a*R*)-2-oxohexahydro-2*H*-cyclopenta[*d*]-5-oxazolyl urethane as the P2 ligand exhibited very potent enzyme inhibitory and antiviral activity. The corresponding enantiomeric ligand in inhibitor **4b** showed an over 1000-fold reduction of enzyme inhibitory activity. Also, this inhibitor did not exhibit any appreciable antiviral activity. We then examined the effect of an *N*-alkyl group and stereochemical effects on potency. Inhibitor **4c** containing (3a*S*,5*R*,6a*R*)-oxazolidinone with an *N*-Me group showed an enzyme inhibitory K_i of 0.03 nM. This inhibitor showed slight improvement of antiviral activity (36 nM, entry 3). Inhibitor **4d**, containing the enantiomeric *N*-Me oxazolidinone derivative, displayed substantial reduction of enzyme inhibitory as well as

antiviral activity. This result is consistent with activity observed for the unsubstituted ligand in inhibitor **4b** (entry 2). The stereochemical preference for (3a*S*,5*R*,6a*R*)-oxazolidinone is also consistent with our preliminary models. All further SAR studies were carried out with (3a*S*,5*R*,6a*R*)-oxazolidinone derived compounds. We then examined the effect of steric bulk on the oxazolidinone nitrogen. Incorporation of an *N*-phenyl derivative in inhibitor **4e** (entry 5) resulted in significant loss of enzyme inhibitory activity. This inhibitor also displayed no appreciable antiviral activity. To promote hydrogen bonding interactions in the S2 subsite of HIV-1 protease, we incorporated a methoxy substituent on the *N*-phenyl ring. As shown, both *p*-methoxy and *m*-methoxy derivatives show reduction of enzymatic K_i values, particularly for inhibitor **4g** (entry 7). Inhibitor **4h** with a 2-methoxy substituent on the *N*-phenyl ring, showed an improvement in enzyme inhibitory and antiviral activity (entry 8).

We then investigated the effect of a sterically demanding alkyl chain on the oxazolidinone ring. The results are shown in Table 2. Inhibitor **4i** with an *N*-allyl oxazolidinone as the P2 ligand showed a comparable enzyme inhibitory K_i as the *N*-methyl derivative **4c** (entry 3). However, there is a 10-fold reduction of antiviral activity compared to the corresponding *N*-methyl derivative **4c**. The corresponding inhibitor **4j** with *N*-propyl side chain showed a 10-fold reduction of HIV-1 protease inhibitory activity compared to *N*-allyl derivative **4i**. There was a slight reduction of antiviral activity as well. Incorporation of a sterically demanding branched chain *N*-methylallyl group in inhibitor **4k** resulted in good enzyme inhibitory activity as well as antiviral activity with an IC_{50} value of 31 nM (entry 3). Inhibitor **4l** with a saturated isobutyl side chain resulted in slight reduction of both enzyme K_i and antiviral activity compared to inhibitor **4k** (entry 4). We have introduced an *N*-methoxymethyl side chain in an effort to promote hydrogen bonding with the methoxyl oxygen in the S2 subsite. Inhibitor **4m** showed very potent enzyme inhibitory activity. We recently demonstrated the potency enhancing effect of the cyclopropylaminobenzothiazole group as a P2' ligand as it forms additional hydrogen bonding and van der Waals interactions in the S2' subsite. We, therefore, synthesized inhibitor **4n** with a *N*-methyloxazolidinone as the P2 ligand and cyclopropylaminobenzothiazole as the P2' ligand. However, there was no significant change in potency for this inhibitor compared to inhibitor **4c** (entry 3, Table 1) with a 4-methoxyphenylsulfonamide as the P2' ligand.

PIs continue to be an important in current ART regimens, and in particular, they are extensively used for the treatment of naive and experienced HIV/AIDS patients. However, heavily ART regimen-experienced HIV/AIDS patients show drug failure with current PIs including DRV.^{31,32} Therefore, one of the main design objectives is to develop new PIs that maintain potency against a variety of existing multi-PI-resistant HIV-1 variants. In preliminary studies, we examined the activity of two potent oxazolidinone containing PIs **4k** and **4l** against a panel of HIV-1 variants that had been selected in vitro with three widely used FDA-approved PIs, ATV, LPV, and APV. Each of these HIV-1 variants was selected in vitro by propagating HIV-1_{NL4-3} in the presence of increasing concentrations of each PI (up to 5 μ M) in MT-4 cells as described by us previously.^{31,33}

The viruses used in the present work were obtained, propagated, and titrated as described by us previously.³⁴ Also, the IC_{50} values were determined as previously described and the names of HIV-1 strains used are described in the very left column of Table 3.³⁴ The results

are shown in Table 3. As can be seen, PI APV lost significant activity against all multidrug-resistant HIV-1 variants. LPV also lost activity against the three HIV-1 variants. DRV showed relatively better results; however, it too failed to block replication of each of these three variants very effectively. DRV exhibited an IC_{50} value fold-change ranging from 5- to 86-fold. While both oxazolidinone-based new PIs **4k** and **4l** are significantly less potent than DRV, both PIs maintained good activity against all three HIV-1 variants compared to wild-type HIV_{NL4-3}. Inhibitor **4l** showed antiviral activity with IC_{50} values ranging from 33 nM to 615 nM. In particular, its fold-changes in activity are better than any other PIs examined. Both PIs **4k** and **4l** maintained full antiviral activity against highly ATV-resistant HIV-1 variants. While DRV was relatively less potent against HIV-1_{DRV^RP20} with an IC_{50} value of 169 nM, both oxazolidinone-derived inhibitors **4k** and **4l** failed to block the replication of a highly DRV-resistant HIV-1 variants. In general, oxazolidinone-derived inhibitors showed low cytotoxicity (CC_{50}) values in MT-4 cells. The CC_{50} values were determined as previously described.³⁴ The selectivity index of selected inhibitors is shown in Table 4. In general, our detailed X-ray crystallo-graphic studies of structurally related inhibitor **4e**-bound HIV-1 protease provided molecular insight into the binding features responsible for its properties.³⁵

The X-ray structures of wild-type HIV-1 protease cocrystallized with inhibitors **4a** (GRL-034-17A) and **4e** (GRL-042-17A) were refined to resolutions of 1.22 and 1.30 Å resolution with R/R_{free} of 15.5/18.8 and 15.0/18.2%, respectively. The protease dimer complexed with **4a** bound two alternative orientations of inhibitor in the active site cavity with 0.7/0.3 relative occupancy, while the other protease structure contained a single conformation of the inhibitor **4e**. The overall backbones of the two protease dimers were very similar to that of the PR/DRV complex with a RMSD of 0.20 and 0.24 Å for 198 equivalent C α atoms in the complexes with **4a** and **4e**, respectively.^{21,36} The **4a**-bound protease showed the largest shift of approximately 1.0 Å for flap residue Phe53, which may result from the hydrogen bond between the urethane nitrogen of P2 ligand and the carbonyl oxygen of Gly48 in the adjacent β strand of the flap. In contrast, the largest disparity of approximately 0.8 Å at Gly48 in the **4e**-bound protease is likely caused by steric hindrance of the additional phenyl group of P2. The key interactions of inhibitors **4a** and **4e** with HIV-1 protease are highlighted in a stereoview of the active sites in Figures 2 and 3, respectively. Both inhibitors form a water-mediated tetracoordinated hydrogen bonding interaction involving the inhibitor carbonyl oxygen and one of the oxygens of the sulfonamide functionality with amides of Ile50 and Ile50' in the flaps. Such interactions have been observed for many other HIV-1 protease inhibitors.^{3,21,22} With the exception of the P2 ligand, the inhibitors retain the majority of hydrogen bonds observed between DRV and the main chain atoms of the protease. The oxazolidin-2-one P2 group of both inhibitors is embedded between the amide of Asp29 and the carbonyl oxygen of Gly48. The two oxygens of the oxazolidinone group form good hydrogen bond interactions with the amide NH of Asp29 at 3.1–3.2 Å and 2.8–2.9 Å distances for the ring oxygen and the carbonyl oxygen, respectively. The P2 urethane NH of the major conformation of inhibitor **4a** forms a good hydrogen bond with the main chain carbonyl oxygen of Gly48 with distance of 3.0 Å, although the distance lengthened to 3.5 Å, for the minor conformation.

The larger P2 group of **4e** exhibits hydrophobic, C–H... π , and hydrogen bond interactions with the protease (Figure 4). The phenyl group is sandwiched between the carbonyl oxygen atom of Gly48 and the guanidinium group of Arg8' and forms several C–H... π interactions with shortest interatomic distances of 2.8 and 3.5 Å with Gly48 and Arg8', respectively. These short hydrophobic interactions of **4e** are associated with a shift of Gly48 and may be responsible for the higher K_i of this inhibitor compared to that of **4a**. The cyclopentoxazol group of both inhibitors has van der Waals contacts with Val32, Ile47, Ile50', and Ile84 similar to those seen for the bis-THF P2 ligand of DRV.^{21,22} A comparison of the ligand binding interactions of the bis-THF ligand of darunavir and the oxazolidinone ligand of inhibitor **4a** in the HIV-1 protease active site is shown in the stereoview of Figure 3. The figure was created based upon the X-ray structures of DRV-bound and **4a**-bound HIV-1 protease. It appears that the bis-THF ligand in DRV makes additional hydrogen bonding interactions with the backbone amide NH of Asp30. However, van der Waals interactions of both bicyclic scaffolds are comparable. The bicyclic oxazolidinone moiety for both inhibitors **4a** and **4e** make similar hydrogen bonding interactions in the active site. These interactions contribute to the high enzyme affinity and antiviral activity of the majority of the oxazolidinone-derived inhibitors in our current studies.

CONCLUSION

In summary, we have designed and synthesized a new class of HIV-1 protease inhibitors incorporating bicyclic oxazolidinone as the P2 ligand. We demonstrated that the ligand stereochemistry is very important for potency. Inhibitor **4a** with (3a*S*,5*R*,6a*R*)-oxazolidinone stereochemistry is significantly more potent than the corresponding inhibitor with the enantiomeric ligand. We have examined various *N*-aryl and *N*-alkyl oxazolidinone derivatives to improve potency. It turns out that *N*-alkyl oxazolidinones with small aliphatic alkyl groups can be accommodated by the active site. The *N*-methyl, *N*-isobutenyl, and *N*-isobutyl derivatives **4c**, **4k**, and **4l**, respectively, have shown excellent enzyme inhibitory and antiviral activity. Inhibitors **4k** and **4l** were evaluated against a panel of multidrug-resistant HIV-1 variants. While both compounds are less potent than darunavir, its fold-changes in activity were similar to those observed with other approved PIs. Both inhibitors **4k** and **4l** maintained near full antiviral potency against ATV-resistant HIV-1 variants. However, these PIs failed to block the replication of highly DRV-resistant HIV-1 variants. The bicyclic oxazolidinones contain three asymmetric centers, and various ligands were synthesized efficiently from readily available, optically active *cis*-4-acetoxycyclopenten-1-ol by formation of the aryl carbamate followed by an IBX-mediated cyclization reaction developed by Nicolaou and Baran. Our X-ray structural studies of inhibitor **4a**- and **4e**-bound HIV-1 protease provided molecular insight into their ligand-binding site interactions. As it turns out, the oxazolidinone oxygen forms a strong hydrogen bonding interaction with Asp29 backbone amide NH. The bicyclic scaffold and the *N*-phenyl ring form van der Waals interactions with residues in the S2 site. The preliminary results of these oxazolidinone-derived inhibitors are very encouraging, and we plan to carry out optimization of ligand-binding site interactions and improve inhibitor potency. Further structural modifications are in progress in our laboratories.

EXPERIMENTAL METHODS

All moisture-sensitive reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise stated. Anhydrous solvents were obtained as follows: Tetrahydrofuran was distilled from sodium metal/benzophenone under argon. Dichloromethane was distilled from calcium hydride under argon. All other solvents were reagent grade. Column chromatography was performed using Silicycle SiliaFlash F60 230–400 mesh silica gel. Thin layer chromatography was carried out using EMD Millipore TLC silica gel 60 F254 plates. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-III-400, Bruker DRX500, or Bruker AV-III-800. Low-resolution mass spectra were collected on an LCMS. High-resolution mass spectra were collected by the Purdue University Campus-Wide Mass Spectrometry Center. HPLC analysis and purification were done on an Agilent 1100 series instrument using a YMC Pack ODS-A column of 4.6 mm i.d. for analysis and either 10 mm i.d. or 20 mm i.d. for purification. The purity of all test compounds was determined by HPLC analysis to be 95% pure.

(3a*S*,5*R*,6a*R*)-2-Oxohehexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)-sulfonamido)-1-phenylbutan-2-yl)carbamate (4a).

To a stirred solution of activated carbonate **11a** (16 mg, 0.05 mmol) in dry acetonitrile (1.5 mL) were added *N,N*-diisopropylethylamine (56 μL , 0.3 mmol) and isostere amine **12** (23 mg, 0.06 mmol) at 23 °C under argon atmosphere. The reaction mixture was stirred for 48 h. Upon completion, solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (80% EtOAc in hexane) to afford **4a** (13 mg, 44%): ^1H NMR (500 MHz, CD_3OD) δ 7.77 (d, J = 8.8 Hz, 2H), 7.24 (dd, J = 8.9, 6.1 Hz, 4H), 7.19–7.14 (m, 1H), 7.08 (d, J = 8.9 Hz, 2H), 5.12 (t, J = 6.7 Hz, 1H), 5.03–4.96 (m, 1H), 4.33–4.27 (m, 1H), 3.87 (s, 3H), 3.78–3.68 (m, 2H), 3.48–3.37 (m, 1H), 3.03 (ddd, J = 20.0, 13.1, 9.7 Hz, 3H), 2.98–2.83 (m, 2H), 2.57 (dd, J = 13.7, 10.4 Hz, 1H), 2.09–1.94 (m, 3H), 1.90–1.82 (m, 2H), 1.16 (dd, J = 10.7, 6.3 Hz, 1H), 0.95–0.80 (m, 7H). ^{13}C NMR (201 MHz, CDCl_3) δ 162.9, 158.8, 155.5, 138.4, 137.5, 129.6, 128.4, 126.3, 114.3, 81.4, 81.2, 72.8, 58.6, 57.9, 55.6, 54.8, 52.2, 40.0, 39.2, 36.4, 35.9, 29.7, 27.2, 27.1, 20.2, 19.9. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 576.2. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd $\text{C}_{28}\text{H}_{37}\text{N}_3\text{O}_8\text{SNa}$ 598.2194; found 598.2185.

(3a*R*,5*S*,6a*S*)-2-Oxohehexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)-sulfonamido)-1-phenylbutan-2-yl)carbamate (4b).

Compound **11c** (4.8 mg, 0.02 mmol) was treated with isostere amine **12** (7 mg, 0.02 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4b** (5.3 mg, 60%): ^1H NMR (800 MHz, CD_3OD) δ 7.77 (d, J = 8.9 Hz, 2H), 7.29–7.21 (m, 4H), 7.16 (tt, J = 7.0, 1.7 Hz, 1H), 7.08 (d, J = 8.9 Hz, 2H), 5.16–5.11 (m, 1H), 4.99 (t, J = 4.5 Hz, 1H), 4.35 (t, J = 7.1 Hz, 1H), 3.87 (s, 3H), 3.80–3.72 (m, 1H), 3.65 (ddd, J = 10.5, 6.8, 3.6 Hz, 1H), 3.44 (dd, J = 15.0, 3.0 Hz, 1H), 3.34 (d, J = 10.8 Hz, 1H), 3.10–3.02 (m, 2H), 2.93 (dd, J = 15.0, 8.6 Hz, 1H), 2.87 (dd, J = 13.6, 7.1 Hz, 1H), 2.55 (dd, J = 13.7, 10.6 Hz, 1H), 2.09–1.96 (m, 3H), 1.96–1.88 (m, 2H), 1.29 (s, 2H), 0.91 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H). ^{13}C NMR (201 MHz, CD_3OD) δ 163.1, 160.7, 156.3, 138.7, 130.8, 129.4, 129.3, 129.2, 128.0, 125.6, 114.0, 82.1, 76.4, 72.6, 57.3, 56.6, 56.2, 54.8, 52.3, 39.3, 39.1, 35.8,

26.6, 19.1, 19.0. LRMS (ESI) m/z : $[M + H]^+$ 576.2. HRMS (ESI) m/z : $[M + Na]^+$ calcd $C_{28}H_{37}N_3O_8SNa$ 598.2194; found 598.2189.

(3a*S*,5*R*,6a*R*)-3-Methyl-2-oxohexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4c).

Compound **11b** (7.5 mg, 0.02 mmol) was treated with isostere amine **12** (10.4 mg, 0.03 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4c** (3.5 mg, 88%): 1H NMR (800 MHz, $CDCl_3$) δ 7.80–7.74 (m, 2H), 7.35–7.24 (m, 4H), 7.23–7.16 (m, 1H), 7.04–6.95 (m, 2H), 5.04 (t, J = 4.3 Hz, 1H), 4.95 (q, J = 9.3, 6.9 Hz, 1H), 4.20–4.12 (m, 1H), 3.96 (dq, J = 9.8, 4.4 Hz, 1H), 3.89 (s, 3H), 3.79 (q, J = 17.3, 10.2 Hz, 1H), 3.22 (dd, J = 14.4, 4.2 Hz, 1H), 3.14 (dd, J = 14.9, 8.3 Hz, 2H), 3.00 (dd, J = 13.5, 8.0 Hz, 1H), 2.94 (dd, J = 13.5, 7.1 Hz, 1H), 2.75 (dd, J = 14.2, 10.1 Hz, 2H), 2.57 (s, 3H), 2.39–2.32 (m, 1H), 2.18 (dd, J = 15.1, 3.0 Hz, 1H), 1.97 (p, J = 6.7 Hz, 1H), 1.90 (dt, J = 15.7, 5.5 Hz, 1H), 1.63 (ddd, J = 15.5, 6.6, 4.0 Hz, 1H), 0.92 (t, J = 6.9 Hz, 6H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 162.8, 157.6, 155.3, 138.0, 130.5, 129.5, 129.4, 128.4, 126.2, 114.3, 77.7, 75.7, 71.9, 61.3, 58.3, 55.6, 54.7, 54.6, 53.1, 39.4, 35.4, 34.9, 29.7, 28.8, 27.2, 20.2, 19.9. LRMS (ESI) m/z : $[M + H]^+$ 590.3. HRMS (ESI) m/z : $[M + H]^+$ calcd $C_{29}H_{40}N_3O_8S$ 590.2531; found 590.2525.

(3a*R*,5*S*,6a*S*)-3-Methyl-2-oxohexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4d).

Compound **11d** (4.9 mg, 0.02 mmol) was treated with isostere amine **12** (6.8 mg, 0.02 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4d** (6.1 mg, 68%): 1H NMR (800 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.35–7.19 (m, 5H), 7.01 (d, J = 8.8 Hz, 2H), 5.08 (s, 1H), 4.99 (t, J = 6.7 Hz, 1H), 4.89 (d, J = 8.8 Hz, 1H), 4.23–4.18 (m, 1H), 3.90 (s, 3H), 3.82 (d, J = 19.1 Hz, 1H), 3.64 (s, 1H), 3.38 (s, 1H), 3.16 (dd, J = 15.0, 9.1 Hz, 1H), 3.05–2.96 (m, 2H), 2.82 (dd, J = 13.6, 7.6 Hz, 1H), 2.79 (s, 3H), 2.30 (d, J = 15.4 Hz, 1H), 2.19 (d, J = 15.9 Hz, 1H), 1.91 (dd, J = 15.5, 5.4 Hz, 1H), 1.88–1.82 (m, 1H), 1.74–1.69 (m, 1H), 1.67 (s, 2H), 0.92 (dd, J = 35.7, 6.6 Hz, 6H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 163.0, 157.4, 155.4, 137.7, 130.1, 129.6, 129.5, 128.6, 128.3, 126.4, 114.3, 77.6, 75.8, 72.1, 61.4, 58.6, 56.0, 55.6, 55.6, 53.4, 39.8, 35.8, 35.3, 29.7, 29.2, 29.0, 27.3, 27.0, 20.2, 19.9. LRMS (ESI) m/z : $[M + H]^+$ 590.6. HRMS (ESI) m/z : $[M + Na]^+$ calcd $C_{29}H_{39}N_3O_8SNa$ 612.2350; found 612.2358.

(3a*S*,5*R*,6a*R*)-2-Oxo-3-phenylhexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4e).

Compound **11e** (8 mg, 0.02 mmol) was treated with isostere amine **12** (9.3 mg, 0.02 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4e** (6.1 mg, 45%): 1H NMR (800 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.54–7.46 (m, 2H), 7.44–7.35 (m, 2H), 7.15 (dt, J = 16.1, 5.6 Hz, 6H), 6.99 (d, J = 8.4 Hz, 2H), 5.12 (q, J = 3.5 Hz, 1H), 5.09 (t, J = 6.7 Hz, 1H), 4.91–4.82 (m, 2H), 3.87 (s, 3H), 3.78 (s, 2H), 3.70 (s, 1H), 3.14 (dd, J = 14.9, 8.1 Hz, 1H), 3.06–3.00 (m, 1H), 2.97 (dd, J = 14.4, 6.8 Hz, 2H), 2.82 (dd, J = 13.4, 6.8 Hz, 1H), 2.77 (dd, J = 13.9, 8.2 Hz, 1H), 2.48–2.41 (m, 1H), 2.21–2.14 (m, 1H), 1.99 (d, J = 15.8 Hz, 1H), 1.63 (s, 2H), 0.89 (dd, J = 29.2, 6.4 Hz, 6H). ^{13}C NMR (201 MHz, $CDCl_3$) δ

162.9, 155.3, 154.6, 137.5, 137.3, 130.3, 129.5, 129.4, 129.3, 128.4, 126.4, 124.5, 120.3, 119.8, 114.3, 75.6, 72.0, 60.7, 58.5, 55.6, 55.3, 53.3, 39.7, 37.5, 35.8, 29.7, 27.2, 20.2, 19.9. LRMS (ESI) m/z : $[M + Na]^+$ 674.2. HRMS (ESI) m/z : $[M + Na]^+$ calcd $C_{34}H_{41}N_3O_8SNa$ 674.2507; found 674.2497.

(3a*S*,5*R*,6a*R*)-3-(4-Methoxyphenyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4*f*).

Compound **11f** (3.9 mg, 0.01 mmol) was treated with isostere amine **12** (4.2 mg, 0.01 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4f** (2.7 mg, 47%): 1H NMR (800 MHz, $CDCl_3$) δ 7.72 (dd, $J = 33.8$, 8.5 Hz, 2H), 7.34 (d, $J = 9.2$ Hz, 2H), 7.20 (dd, $J = 24.4$, 7.4 Hz, 4H), 6.97 (dd, $J = 22.4$, 8.5 Hz, 3H), 6.90 (t, $J = 7.9$ Hz, 2H), 5.12 (s, 1H), 5.11–5.06 (m, 2H), 4.97 (d, $J = 9.2$ Hz, 1H), 4.76 (t, $J = 7.5$ Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.15 (dd, $J = 15.0$, 8.7 Hz, 1H), 3.06 (d, $J = 15.0$ Hz, 1H), 3.02–2.88 (m, 2H), 2.82 (ddd, $J = 34.6$, 16.1, 8.6 Hz, 2H), 2.43 (d, $J = 15.9$ Hz, 1H), 2.22 (s, 1H), 2.16 (d, $J = 15.3$ Hz, 1H), 1.96 (tt, $J = 15.8, 4.6$ Hz, 2H), 1.91–1.78 (m, 2H), 0.95–0.85 (m, 6H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 162.9, 157.1, 155.2, 137.6, 130.3, 130.1, 129.5, 129.4, 128.5, 126.5, 123.0, 114.6, 114.3, 77.4, 77.2, 77.0, 76.9, 75.8, 72.0, 61.5, 58.5, 55.6, 55.5, 55.2, 53.3, 39.8, 37.2, 35.8, 27.2, 20.2, 19.9. LRMS (ESI) m/z : $[M + H]^+$ 682.2. HRMS (ESI) m/z : $[M + H]^+$ calcd $C_{35}H_{44}N_3O_9SNa$ 682.2793; found 682.2800.

(3a*S*,5*R*,6a*R*)-3-(3-Methoxyphenyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4*g*).

Compound **11g** (13.6 mg, 0.03 mmol) was treated with isostere amine **12** (14.7 mg, 0.04 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4g** (13.1 mg, 58%): 1H NMR (800 MHz, CD_3OD) δ 7.77 (d, $J = 7.9$ Hz, 2H), 7.35 (t, $J = 7.7$ Hz, 1H), 7.26 (dd, $J = 14.5$, 7.2 Hz, 4H), 7.16 (dd, $J = 22.0$, 7.2 Hz, 2H), 7.09 (t, $J = 7.2$ Hz, 3H), 6.91 (s, 1H), 5.23–5.17 (m, 1H), 5.10 (s, 1H), 4.85–4.80 (m, 1H), 3.89–3.85 (m, 6H), 3.84 (s, 1H), 3.82–3.75 (m, 2H), 3.38 (d, $J = 15.2$ Hz, 1H), 3.12 (d, $J = 14.3$ Hz, 1H), 3.04 (dt, $J = 13.1$, 7.2 Hz, 2H), 2.91 (dd, $J = 13.4$, 7.0 Hz, 1H), 2.72–2.65 (m, 1H), 2.26 (d, $J = 15.8$ Hz, 1H), 2.10 (d, $J = 15.9$ Hz, 1H), 2.05–1.96 (m, 1H), 1.89 (d, $J = 15.3$ Hz, 1H), 1.74 (dd, $J = 13.9$, 7.0 Hz, 1H), 0.89 (dd, $J = 21.6$, 6.2 Hz, 6H). ^{13}C NMR (201 MHz, CD_3OD) δ 163.1, 157.8, 156.3, 155.4, 138.7, 130.8, 130.0, 129.3, 129.0, 128.0, 125.9, 124.3, 120.5, 114.0, 111.9, 79.5, 76.2, 72.2, 61.8, 57.3, 55.9, 54.8, 54.8, 52.3, 39.5, 36.2, 35.4, 26.6, 19.1, 19.1. LRMS (ESI) m/z : $[M + H]^+$ 682.2. HRMS (ESI) m/z : $[M + H]^+$ calcd $C_{35}H_{44}N_3O_9SNa$ 682.2793; found 682.2787.

(3a*S*,5*R*,6a*R*)-3-(2-Methoxyphenyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4*h*).

Compound **11h** (14.5 mg, 0.03 mmol) was treated with isostere amine **12** (15.6 mg, 0.04 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4h** (12.2 mg, 51%): 1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, $J = 8.5$ Hz, 2H), 7.37–7.08 (m, 7H), 7.08–6.92 (m, 3H), 6.70 (d, $J = 8.2$ Hz, 1H), 5.18–5.02 (m, 2H), 4.83 (dd, $J = 15.7$, 5.4 Hz, 2H), 3.86 (s, 3H), 3.78 (dt, $J = 13.8$, 3.5 Hz, 5H), 3.68 (s, 1H), 3.14 (dd, $J = 15.1$, 8.7 Hz, 1H), 3.06–2.90 (m, 3H), 2.78 (ddd, $J = 22.2$, 13.4, 7.2 Hz, 2H), 2.43 (d, $J = 15.9$ Hz, 1H),

2.19 (d, J = 15.5 Hz, 1H), 2.02–1.79 (m, 3H), 0.88 (d, J = 6.8 Hz, 6H). ^{13}C NMR (201 MHz, CD_3OD) δ 163.1, 160.5, 156.1, 155.8, 138.6, 130.8, 129.6, 129.3, 128.9, 127.8, 125.6, 114.0, 112.2, 109.5, 106.6, 78.7, 75.9, 72.1, 61.2, 57.4, 56.1, 54.8, 54.5, 52.4, 39.1, 37.2, 35.7, 26.7, 19.1, 19.0. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 682.2. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd $\text{C}_{35}\text{H}_{43}\text{N}_3\text{O}_9\text{SNa}$ 704.2612; found 704.2602.

(3a*S*,5*R*,6a*R*)-3-Allyl-2-oxohexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4i).

Compound **11i** (17 mg, 0.05 mmol) was treated with isostere amine **12** (22 mg, 0.06 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4i** (23 mg, 76%): ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, J = 8.9 Hz, 2H), 7.39–7.22 (m, 4H), 7.22–7.11 (m, 1H), 7.04–6.86 (m, 2H), 5.68–5.52 (m, 1H), 5.46 (d, J = 8.8 Hz, 1H), 5.20–5.09 (m, 2H), 4.97 (d, J = 4.1 Hz, 1H), 4.92 (t, J = 6.8 Hz, 1H), 4.16 (t, J = 7.0 Hz, 1H), 4.02–3.89 (m, 2H), 3.86 (s, 3H), 3.83–3.70 (m, 2H), 3.29 (dd, J = 14.8, 5.1 Hz, 1H), 3.22–2.87 (m, 5H), 2.71 (dd, J = 14.2, 10.1 Hz, 1H), 2.32 (d, J = 15.9 Hz, 1H), 2.15 (d, J = 15.3 Hz, 1H), 2.02–1.93 (m, 1H), 1.85 (dd, J = 15.0, 9.7 Hz, 1H), 1.54 (ddd, J = 15.4, 6.7, 4.1 Hz, 1H), 0.88 (dd, J = 16.0, 6.6 Hz, 6H). ^{13}C NMR (201 MHz, CDCl_3) δ 162.8, 157.4, 155.2, 138.2, 131.9, 130.6, 129.5, 129.4, 128.4, 126.2, 118.6, 114.3, 78.1, 75.6, 71.6, 58.8, 58.2, 55.6, 54.6, 54.5, 52.9, 44.7, 39.4, 35.6, 34.5, 29.7, 27.1, 20.2, 20.0. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 616.2. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd $\text{C}_{31}\text{H}_{41}\text{N}_3\text{O}_8\text{SNa}$ 638.2507; found 638.2498.

(3a*S*,5*R*,6a*R*)-2-Oxo-3-propylhexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4j).

Compound **11j** (3.7 mg, 0.01 mmol) was treated with isostere amine **12** (4.7 mg, 0.01 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4j** (4 mg, 62%): ^1H NMR (800 MHz, CDCl_3) δ 7.78–7.70 (m, 2H), 7.33–7.22 (m, 4H), 7.20 (s, 1H), 7.02–6.93 (m, 2H), 5.08–5.02 (m, 1H), 4.98 (s, 1H), 4.94 (s, 1H), 4.22 (d, J = 7.7 Hz, 1H), 3.87 (d, J = 2.7 Hz, 3H), 3.79 (s, 1H), 3.74 (s, 1H), 3.33–3.25 (m, 1H), 3.14 (ddd, J = 17.8, 8.9, 4.7 Hz, 2H), 3.07 (d, J = 14.3 Hz, 1H), 2.97 (dd, J = 13.6, 8.2 Hz, 1H), 2.93–2.86 (m, 1H), 2.75 (t, J = 12.2 Hz, 1H), 2.67 (d, J = 8.7 Hz, 1H), 2.33 (d, J = 16.0 Hz, 1H), 2.13 (d, J = 15.2 Hz, 1H), 1.89 (dt, J = 13.2, 6.2 Hz, 2H), 1.60–1.50 (m, 3H), 1.48 (d, J = 7.2 Hz, 1H), 1.02–0.76 (m, 9H). ^{13}C NMR (201 MHz, CDCl_3) δ 162.9, 157.5, 155.4, 137.8, 130.4, 129.5, 129.4, 128.5, 126.4, 114.3, 77.7, 75.7, 72.1, 59.0, 58.4, 55.6, 54.9, 53.2, 43.7, 39.6, 35.8, 35.4, 29.7, 27.2, 20.3, 20.2, 19.9, 11.2. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 618.2. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd $\text{C}_{31}\text{H}_{43}\text{N}_3\text{O}_8\text{SNa}$ 640.2663; found 640.2669.

(3a*S*,5*R*,6a*R*)-3-(2-Methylallyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4k).

Compound **11k** (6.1 mg, 0.02 mmol) was treated with isostere amine **12** (7.5 mg, 0.02 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4k** (8 mg, 75%): ^1H NMR (800 MHz, CDCl_3) δ 7.77 (d, J = 8.8 Hz, 2H), 7.36–7.25 (m, 4H), 7.24–7.15 (m, 1H), 7.00 (d, J = 8.9 Hz, 2H), 5.19 (s, 1H), 5.03 (s, 1H), 4.96 (t, J = 6.9 Hz, 1H), 4.92 (s, 1H), 4.82 (s, 1H), 4.12 (t, J = 7.1 Hz, 1H), 4.01–3.95 (m, 1H), 3.93–3.87 (m, 4H), 3.85–3.76 (m, 2H), 3.24 (dd, J = 15.1, 4.5 Hz, 1H), 3.14 (dd, J = 14.8, 8.4 Hz, 2H), 3.06 (d, J

=15.4 Hz, 1H), 3.01 (dd, J = 13.6, 8.0 Hz, 1H), 2.96 (dd, J = 13.6, 7.2 Hz, 1H), 2.76 (dd, J = 14.3, 10.1 Hz, 1H), 2.36 (d, J = 15.6 Hz, 1H), 2.16 (d, J = 15.1 Hz, 1H), 1.98 (dt, J = 13.1, 6.5 Hz, 1H), 1.90 (dt, J = 15.4, 4.8 Hz, 1H), 1.68 (s, 3H), 1.59 (ddd, J = 15.3, 6.7, 4.2 Hz, 1H), 0.92 (dd, J = 13.5, 6.6 Hz, 6H). ^{13}C NMR (201 MHz, CDCl_3) δ 162.9, 157.6, 155.3, 139.4, 138.1, 130.6, 129.5, 129.4, 128.5, 126.3, 114.3, 114.0, 78.0, 75.7, 71.8, 58.6, 58.3, 55.6, 54.7, 53.1, 48.1, 39.5, 35.5, 34.8, 29.7, 27.2, 20.3, 20.0, 19.9. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 630.6. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd $\text{C}_{32}\text{H}_{43}\text{N}_3\text{O}_8\text{SNa}$ 652.2663; found 652.2666.

(3a*S*,5*R*,6a*R*)-3-Isobutyl-2-oxohexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4l).

Compound **11l** (9 mg, 0.02 mmol) was treated with isostere amine **12** (11 mg, 0.03 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4l** (10 mg, 65%): ^1H NMR (800 MHz, CDCl_3) δ 7.80–7.75 (m, 2H), 7.30 (d, J = 23.2 Hz, 4H), 7.21 (t, J = 7.3 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 5.17–5.11 (m, 1H), 5.04 (t, J = 4.2 Hz, 1H), 4.97 (t, J = 6.8 Hz, 1H), 4.23 (t, J = 6.9 Hz, 1H), 3.98–3.92 (m, 1H), 3.89 (s, 4H), 3.82 (s, 1H), 3.23 (d, J = 12.5 Hz, 1H), 3.19–3.04 (m, 3H), 3.04–2.91 (m, 2H), 2.81–2.73 (m, 1H), 2.52 (d, J = 13.9 Hz, 1H), 2.37 (d, J = 15.6 Hz, 1H), 2.18 (d, J = 15.0 Hz, 1H), 2.01–1.94 (m, 1H), 1.94–1.82 (m, 2H), 1.71 (s, 1H), 1.64 (d, J = 14.7 Hz, 1H), 0.92 (dq, J = 19.3, 6.4 Hz, 12H). ^{13}C NMR (201 MHz, CDCl_3) δ 162.9, 157.8, 155.3, 138.0, 130.6, 129.5, 129.4, 128.5, 126.3, 114.3, 77.8, 75.7, 71.8, 59.3, 58.3, 55.6, 54.8, 53.1, 49.4, 39.5, 35.6, 34.9, 29.7, 27.2, 26.2, 20.3, 20.0, 19.8. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 630.6. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd $\text{C}_{32}\text{H}_{45}\text{N}_3\text{O}_8\text{SNa}$ 654.2820; found 654.2815.

(3a*S*,5*R*,6a*R*)-3-(Methoxymethyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl ((2*S*,3*R*)-3-Hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (4m).

Compound **11m** (3.2 mg, 0.01 mmol) was treated with isostere amine **12** (4.1 mg, 0.01 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4m** (3.4 mg, 60%): ^1H NMR (800 MHz, CD_3OD) δ 7.76 (d, J = 8.8 Hz, 2H), 7.28–7.19 (m, 4H), 7.19–7.15 (m, 1H), 7.10–7.05 (m, 2H), 5.12 (s, 1H), 5.06 (t, J = 6.9 Hz, 1H), 5.02 (t, J = 4.6 Hz, 1H), 4.58 (d, J = 11.0 Hz, 1H), 4.40–4.33 (m, 2H), 3.88 (s, 3H), 3.75 (ddd, J = 14.9, 10.4, 5.1 Hz, 1H), 3.40–3.32 (m, 4H), 3.22 (s, 2H), 3.18 (s, 1H), 3.09 (dd, J = 14.2, 3.5 Hz, 1H), 3.05 (dd, J = 13.6, 7.9 Hz, 1H), 2.99 (dd, J = 14.9, 8.1 Hz, 1H), 2.89 (dd, J = 13.6, 7.0 Hz, 1H), 2.57 (dd, J = 14.2, 10.2 Hz, 1H), 2.26–2.17 (m, 1H), 2.10 (dd, J = 15.2, 2.8 Hz, 1H), 2.08–2.02 (m, 1H), 1.82 (ddd, J = 15.4, 6.9, 4.7 Hz, 1H), 0.97–0.82 (m, 6H). ^{13}C NMR (201 MHz, CD_3OD) δ 163.1, 158.6, 156.2, 138.7, 130.8, 129.3, 128.9, 127.9, 125.8, 114.0, 79.5, 76.9, 76.2, 74.7, 72.5, 59.0, 57.3, 55.5, 54.8, 52.4, 38.9, 36.3, 35.2, 31.6, 29.3, 29.0, 26.6, 19.0. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 620.2. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd $\text{C}_{30}\text{H}_{41}\text{N}_3\text{O}_9\text{SNa}$ 642.2456; found 642.2454.

(3a*S*,5*R*,6a*R*)-3-Methyl-2-oxohexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl ((2*S*,3*R*)-4-((2-(Cyclopropylamino)-*N*-isobutylbenzo[*d*]thiazole)-6-sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate (4n).

Compound **11b** (7.1 mg, 0.02 mmol) was treated with isostere amine **13** (12 mg, 0.02 mmol) by following the same procedure outlined for inhibitor **4a** to give inhibitor **4n** (10 mg, 69%):

¹H NMR (400 MHz, CDCl₃) δ 8.17–8.07 (m, 1H), 7.72 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 2.8 Hz, 5H), 7.19 (dd, *J* = 6.7, 2.3 Hz, 1H), 5.10 (d, *J* = 10.3 Hz, 1H), 5.02 (s, 1H), 4.91 (t, *J* = 6.9 Hz, 1H), 3.89 (dd, *J* = 34.2, 5.3 Hz, 3H), 3.34 (s, 1H), 3.28–3.07 (m, 3H), 3.07–2.88 (m, 2H), 2.74 (td, *J* = 9.7, 6.4 Hz, 3H), 2.57 (s, 3H), 2.30 (d, *J* = 15.8 Hz, 1H), 2.15 (dd, *J* = 15.2, 2.9 Hz, 1H), 2.00–1.80 (m, 2H), 1.60 (ddd, *J* = 15.3, 6.5, 4.1 Hz, 1H), 0.91 (dd, *J* = 13.9, 5.7 Hz, 9H), 0.78 (t, *J* = 1.8 Hz, 2H). ¹³C NMR (201 MHz, CD₃OD) δ 158.6, 156.3, 155.4, 138.8, 131.4, 130.8, 129.6, 129.0, 127.9, 127.7, 125.7, 125.3, 121.0, 120.7, 117.5, 78.9, 76.0, 72.5, 61.7, 57.4, 55.6, 52.5, 39.2, 35.3, 34.9, 27.9, 26.7, 25.9, 19.1, 19.1, 19.1, 6.5. LRMS (ESI) *m/z*: [M + H]⁺ 672.3. HRMS (ESI) *m/z*: [M + Na]⁺ calcd C₃₂H₄₂N₅O₇S₂Na 672.2520; found 672.2512.

(1*S*,4*R*)-4-(((4-Methoxyphenyl)carbamoyl)oxy)cyclopent-2-en-1-yl Acetate (6a).

To a stirring solution of (1*R*,4*S*)-*cis*-4-acetoxy-2-cyclopenten-1-ol **5** (49 mg, 0.34 mmol) in dry dichloromethane were added phenyl isocyanate (45 mg, 0.38 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.3 mg, 0.03 mmol) all under an argon atmosphere. Reaction was stirred at 23 °C for 1 h. After this period, the reaction was quenched with in saturated solution of NaHCO₃ and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (20% EtOAc in hexane) to afford the known²⁷ carbamate derivative **6a** (73 mg, 81%).

(1*S*,4*R*)-4-(((4-Methoxyphenyl)carbamoyl)oxy)cyclopent-2-en-1-yl Acetate (6b).

To a stirring solution of (1*R*,4*S*)-*cis*-4-acetoxy-2-cyclopenten-1-ol **5** (0.6 g, 4.2 mmol) in dry dichloromethane were added 4-methoxyphenyl isocyanate (0.7 g, 4.6 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (64 mg, 0.42 mmol) all under an argon atmosphere. Reaction was stirred at 23 °C for 1 h. Upon completion, the residue was taken up in saturated solution of NaHCO₃ and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (20% EtOAc in hexane) to afford **6b** (1 g, 81%): ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.22 (m, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.57 (s, 1H), 6.12 (dddd, *J* = 20.7, 5.6, 2.1, 1.1 Hz, 2H), 5.58 (qd, *J* = 6.1, 3.5, 2.1 Hz, 2H), 3.77 (s, 3H), 2.90 (qt, *J* = 15.1, 7.5 Hz, 1H), 2.06 (s, 3H), 1.80 (dt, *J* = 15.0, 3.7 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 170.6, 156.0, 153.3, 134.9, 134.5, 130.7, 120.6, 114.2, 77.3, 77.0, 76.6, 55.4, 37.2, 21.0. LRMS (ESI) *m/z*: [M + Na]⁺ 314.0.

(3*aS*,5*R*,6*aR*)-2-Oxo-3-phenylhexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl Acetate (7a).

In a sealed tube, phenyl carbamate **6a** (60 mg, 0.2 mmol) was dissolved in dry tetrahydrofuran (8.4 mL) followed by the addition of freshly distilled dimethyl sulfoxide (0.84 mL). Freshly made 2-iodoxybenzoic acid (0.13 g, 0.46 mmol) was added all at once. The reaction vessel was heated for 8 h at 90 °C. Another portion of 2-iodoxybenzoic acid (0.13 g, 0.5 mmol) was added, and the reaction was heated for an additional 8 h. Upon completion, the residue was taken up in 5% saturated solution of NaHCO₃ and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was purified by silica gel

column chromatography (60% EtOAc in hexane) to afford **7a** (23 mg, 37%): ^1H NMR (800 MHz, CDCl_3) δ 7.54 (d, $J = 7.7$ Hz, 2H), 7.42–7.38 (m, 2H), 7.18 (t, $J = 7.4$ Hz, 1H), 5.30 (t, $J = 4.5$ Hz, 1H), 5.18 (t, $J = 7.0$ Hz, 1H), 4.95 (t, $J = 7.2$ Hz, 1H), 2.53 (dd, $J = 16.0, 3.1$ Hz, 1H), 2.30 (dd, $J = 15.5, 3.0$ Hz, 1H), 2.12 (ddd, $J = 16.0, 6.5, 4.5$ Hz, 1H), 2.03 (s, 3H), 1.98 (ddd, $J = 15.4, 6.8, 4.5$ Hz, 1H). ^{13}C NMR (201 MHz, CDCl_3) δ 170.6, 154.6, 137.3, 129.3, 124.6, 120.2, 77.4, 77.2, 77.1, 76.9, 75.0, 60.7, 42.7, 39.9, 37.0, 21.2. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 262.1.

(3a*S*,5*R*,6a*R*)-3-(4-Methoxyphenyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl Acetate (7b).

In a sealed tube, *p*-methoxyphenyl carbamate **6b** (0.8 g, 2.5 mmol) was dissolved in dry tetrahydrofuran (46 mL) followed by the addition of freshly distilled dimethyl sulfoxide (4.6 mL). Freshly made 2-iodoxybenzoic acid (1.4 g, 5 mmol) was added all at once. The reaction vessel was heated for 8 h at 90 °C. Another portion of 2-iodoxybenzoic acid (1.4 g, 5 mmol) was added, and the reaction was heated for an additional 8 h. Upon completion, the residue was taken up in 5% saturated solution of NaHCO_3 and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na_2SO_4 , and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **7b** (0.48 g, 65%): ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.34 (m, 2H), 6.94–6.88 (m, 2H), 5.27 (t, $J = 4.5$ Hz, 1H), 5.14 (t, $J = 7.2, 6.7$ Hz, 1H), 4.84 (t, $J = 7.0$ Hz, 1H), 3.80 (s, 3H), 2.49 (dd, $J = 15.9, 2.5$ Hz, 1H), 2.24 (dd, $J = 15.4, 3.0$ Hz, 1H), 2.08 (ddd, $J = 15.9, 6.4, 4.6$ Hz, 1H), 2.03 (s, 3H), 1.88 (ddd, $J = 15.4, 6.6, 4.6$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.4, 156.8, 154.8, 130.0, 122.8, 114.5, 77.2, 76.9, 76.6, 74.9, 61.3, 55.4, 39.9, 36.7, 21.1. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 292.0.

(3a*S*,5*R*,6a*R*)-3-(3-Methoxyphenyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl Acetate (7c).

In a sealed tube, *m*-methoxyphenyl carbamate **6c** (57 mg, 0.2 mmol) was dissolved in dry tetrahydrofuran (7.1 mL) followed by the addition of freshly distilled dimethyl sulfoxide (0.7 mL). Freshly made 2-iodoxybenzoic acid (0.11 g, 0.4 mmol) was added all at once. The reaction vessel was heated for 8 h at 90 °C. Another portion of 2-iodoxybenzoic acid (0.11 g, 0.4 mmol) was added, and the reaction was heated for an additional 8 h. Upon completion, the residue was taken up in 5% saturated solution of NaHCO_3 and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na_2SO_4 , and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **7c** (24 mg, 42%): ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.23 (m, 1H), 7.21 (t, $J = 2.3$ Hz, 1H), 7.03 (ddd, $J = 8.2, 2.1, 0.9$ Hz, 1H), 6.70 (ddd, $J = 8.3, 2.5, 0.8$ Hz, 1H), 5.27 (t, $J = 4.5$ Hz, 1H), 5.14 (t, $J = 7.1, 6.6$ Hz, 1H), 4.88 (t, $J = 7.1$ Hz, 1H), 3.81 (s, 3H), 2.50 (dd, $J = 15.9, 2.6$ Hz, 1H), 2.31 (dd, $J = 15.4, 3.0$ Hz, 1H), 2.09 (ddd, $J = 15.9, 6.2, 4.6$ Hz, 1H), 2.00 (s, 3H), 1.99–1.90 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.4, 160.2, 154.3, 138.4, 129.8, 112.0, 109.6, 106.3, 77.3, 77.2, 76.9, 76.6, 74.8, 60.6, 55.3, 39.7, 37.0, 21.1. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 292.0.

(3a*S*,5*R*,6a*R*)-3-(2-Methoxyphenyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl Acetate (7*d*).

In a sealed tube, *o*-methoxyphenyl carbamate **6d** (17 mg, 0.06 mmol) was dissolved in dry tetrahydrofuran (2.1 mL) followed by the addition of freshly distilled dimethyl sulfoxide (0.2 mL). Freshly made 2-iodoxybenzoic acid (33 mg, 0.1 mmol) was added all at once. The reaction vessel was heated for 8 h at 90 °C. Another portion of 2-iodoxybenzoic acid (33 mg, 0.1 mmol) was added, and the reaction was heated for an additional 8 h. Upon completion, the residue was taken up in 5% saturated solution of NaHCO₃ and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **7d** (11 mg, 65%): ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.26 (m, 2H), 7.03–6.93 (m, 2H), 5.28 (t, *J* = 4.5 Hz, 1H), 5.19 (t, *J* = 7.4, 5.7 Hz, 1H), 4.96 (t, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 2.49 (dd, *J* = 16.0, 2.6 Hz, 1H), 2.13 (s, 3H), 2.11–2.01 (m, 2H), 1.78–1.63 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 156.2, 154.8, 129.6, 128.8, 124.7, 120.9, 111.9, 78.2, 77.2, 76.9, 76.6, 75.3, 61.0, 55.5, 42.6, 39.9, 36.6, 21.3. LRMS (ESI) *m/z*: [M + H]⁺ 292.0.

(3a*S*,5*R*,6a*R*)-2-Oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl Acetate (8).

To a stirring solution of cyclic *p*-methoxyphenyl carbamate **7b** (0.14 g, 0.5 mmol) in acetonitrile (4.7 mL) and water (0.9 mL) was added cerium ammonium nitrate (1.3 g, 2.4 mmol) at 0 °C. Reaction was stirred for 30 min. Upon completion, the residue was taken up in 5% saturated solution of NaHCO₃ and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (80% EtOAc in hexane) to afford **8** (62 mg, 71%): ¹H NMR (400 MHz, CDCl₃) δ 5.53 (s, 1H), 5.28 (t, *J* = 4.5 Hz, 1H), 5.17 (t, *J* = 7.0 Hz, 1H), 4.39 (t, *J* = 7.0 Hz, 1H), 2.44 (dd, *J* = 15.9, 2.9 Hz, 1H), 2.12 (dd, *J* = 15.4, 2.9 Hz, 1H), 2.03 (s, 3H), 1.95 (tdd, *J* = 15.8, 6.5, 4.6 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 170.6, 158.7, 81.3, 77.2, 77.12, 76.9, 76.6, 75.3, 55.9, 40.1, 39.3, 21.1. LRMS (ESI) *m/z*: [M + H]⁺ 186.1.

(3a*R*,5*S*,6a*S*)-2-Oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl Acetate (*ent*-8).

To a stirring solution of cyclic *p*-methoxyphenyl carbamate *ent*-**7b** (20 mg, 0.07 mmol) in acetonitrile (0.7 mL) and water (0.2 mL) was added cerium ammonium nitrate (0.2 g, 0.3 mmol) at 0 °C. Reaction was stirred for 30 min. Upon completion, the residue was taken up in 5% saturated solution of NaHCO₃ and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (80% EtOAc in hexane) to afford *ent*-**8** (7.7 mg, 61%): NMR (800 MHz, CDCl₃) δ 5.36 (s, 1H), 5.31 (t, *J* = 4.2 Hz, 1H), 5.20 (t, *J* = 6.8 Hz, 1H), 4.41 (t, *J* = 6.9 Hz, 1H), 2.47 (dd, *J* = 15.9, 2.2 Hz, 1H), 2.15 (dd, *J* = 15.3, 2.9 Hz, 1H), 2.07 (s, 3H), 1.99 (dddd, *J* = 30.4, 15.3, 6.6, 4.5 Hz, 2H). ¹³C NMR (201 MHz, CDCl₃) δ 170.8, 158.7, 81.4, 77.2, 77.0, 76.9, 75.4, 56.0, 40.3, 39.4, 21.2. LRMS (ESI) *m/z*: [M + H]⁺ 185.9.

(3a*S*,5*R*,6a*R*)-5-Hydroxyhexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (9).

To a stirring solution of protected oxazolidinone **8** (6 mg, 0.03 mmol) in methanol (1 mL) was added potassium carbonate (5.5 mg, 0.04 mmol). Reaction was stirred at 23 °C for 4 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (80% EtOAc in hexane) to afford **9** (4.6 mg, 99%). $[\alpha]_D^{20} + 20.0$ (*c* 1.0, MeOH). ^1H NMR (800 MHz, CD_3OD) δ 5.14 (t, *J* = 7.0 Hz, 1H), 4.41 (t, *J* = 4.4 Hz, 1H), 4.33 (t, *J* = 7.3 Hz, 1H), 2.18 (d, *J* = 15.2 Hz, 1H), 1.99–1.94 (m, 2H), 1.88 (ddd, *J* = 14.5, 6.9, 4.4 Hz, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 160.5, 82.4, 72.1, 56.6, 47.9, 47.8, 47.7, 47.6, 47.5, 47.4, 47.3, 41.6, 41.2. LRMS (ESI) *m/z*: $[\text{M} + \text{H}]^+$ 144.1. HRMS (ESI) *m/z*: $[\text{M} + \text{H}]^+$ calcd $\text{C}_6\text{H}_{10}\text{NO}_3$ 144.0655; found 144.0653.

(3a*R*,5*S*,6a*S*)-5-Hydroxyhexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (*ent*-9).

To a stirring solution of protected oxazolidinone *ent*-**8** (8 mg, 0.04 mmol) in methanol (1.4 mL) was added potassium carbonate (7.2 mg, 0.05 mmol). Reaction was stirred at 23 °C for 4 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (80% EtOAc in hexane) to afford *ent*-**9** (5.9 mg, 95%). $[\alpha]_D^{20} - 7.65$ (*c* 1.35, MeOH). ^1H NMR (800 MHz, CD_3OD) δ 5.14 (t, *J* = 7.0 Hz, 1H), 4.41 (t, *J* = 4.3 Hz, 1H), 4.33 (t, *J* = 7.2 Hz, 1H), 2.18 (d, *J* = 15.2 Hz, 1H), 1.99–1.94 (m, 2H), 1.88 (ddd, *J* = 14.5, 6.9, 4.5 Hz, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 160.5, 82.4, 72.1, 56.6, 47.9, 47.8, 47.7, 47.6, 47.5, 47.4, 47.3, 41.6, 41.2. LRMS (ESI) *m/z*: $[\text{M} + \text{H}]^+$ 144.1. HRMS (ESI) *m/z*: $[\text{M} + \text{H}]^+$ calcd $\text{C}_6\text{H}_{10}\text{NO}_3$ 144.0655; found 144.0653.

(3a*S*,5*R*,6a*R*)-5-Hydroxy-3-phenylhexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (10a).

To a stirring solution of cyclic phenyl carbamate **7a** (22 mg, 0.08 mmol) in methanol (2.8 mL) was added potassium carbonate (14 mg, 0.1 mmol). Reaction was stirred at 23 °C for 12 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **10a** (14 mg, 73%). $[\alpha]_D^{20} + 87.6$ (*c* 1.90, MeOH). ^1H NMR (800 MHz, CDCl_3) δ 7.56 (dt, *J* = 8.6, 1.2 Hz, 2H), 7.39 (ddt, *J* = 8.7, 7.3, 1.7 Hz, 2H), 7.16 (td, *J* = 7.3, 1.3 Hz, 1H), 5.15 (t, *J* = 7.0 Hz, 1H), 4.88 (t, *J* = 7.3 Hz, 1H), 4.53 (t, *J* = 4.4 Hz, 1H), 2.41 (dd, *J* = 15.6, 3.0 Hz, 1H), 2.20 (ddd, *J* = 14.9, 3.0, 1.5 Hz, 1H), 2.06 (ddd, *J* = 15.5, 6.3, 4.3 Hz, 1H), 1.90 (ddd, *J* = 15.0, 7.0, 4.4 Hz, 1H), 1.84 (s, 1H). ^{13}C NMR (201 MHz, CDCl_3) δ 154.9, 137.6, 129.2, 124.4, 120.4, 78.0, 77.2, 77.0, 76.9, 72.6, 61.1, 42.6, 39.5. LRMS (ESI) *m/z*: $[\text{M} + \text{H}]^+$ 220.1. HRMS (ESI) *m/z*: $[\text{M} + \text{Na}]^+$ calcd $\text{C}_{12}\text{H}_{13}\text{NO}_3\text{Na}$ 242.0788; found 242.0786.

(3a*S*,5*R*,6a*R*)-5-Hydroxy-3-(4-methoxyphenyl)hexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (10b).

To a stirring solution of cyclic *p*-methoxyphenyl carbamate **7b** (46 mg, 0.2 mmol) in methanol (6 mL) was added potassium carbonate (26 mg, 0.2 mmol). Reaction was stirred at 23 °C for 12 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **10b** (38 mg, 96%). $[\alpha]_D^{20} + 75.5$ (*c* 2.00, MeOH). ^1H NMR (400 MHz,

CDCl₃) δ 7.45–7.36 (m, 2H), 6.95–6.87 (m, 2H), 5.13 (dd, J = 7.8, 5.2 Hz, 1H), 4.78 (t, J = 7.2 Hz, 1H), 4.54–4.46 (m, 1H), 3.80 (s, 3H), 2.41–2.31 (m, 1H), 2.14 (ddt, J = 14.9, 2.8, 1.2 Hz, 1H), 2.03 (ddd, J = 15.4, 6.4, 4.2 Hz, 1H), 1.78 (ddd, J = 14.9, 6.9, 4.3 Hz, 1H), 1.71 (d, J = 2.4 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 156.8, 155.2, 130.3, 123.3, 114.4, 77.9, 77.2, 76.9, 76.6, 72.6, 61.7, 55.4, 42.7, 39.0. LRMS (ESI) m/z : [M + H]⁺ 250.0. HRMS (ESI) m/z : [M + Na]⁺ calcd C₁₃H₁₅NO₄Na 272.0893; found 272.0895.

(3a*S*,5*R*,6a*R*)-5-Hydroxy-3-(3-methoxyphenyl)hexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (10c).

To a stirring solution of cyclic *m*-methoxyphenyl carbamate **7c** (24 mg, 0.08 mmol) in methanol (6.7 mL) was added potassium carbonate (17 mg, 0.1 mmol). Reaction was stirred at 23 °C for 12 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **10c** (20 mg, 97%). $[\alpha]_D^{20}$ + 98.2 (*c* 2, MeOH). ¹H NMR (800 MHz, CDCl₃) δ 7.32–7.26 (m, 2H), 7.07 (ddd, J = 8.2, 2.1, 0.9 Hz, 1H), 6.71 (ddd, J = 8.3, 2.5, 0.8 Hz, 1H), 5.14 (t, J = 7.0 Hz, 1H), 4.85 (t, J = 7.3 Hz, 1H), 4.54 (t, J = 4.3 Hz, 1H), 3.84 (s, 3H), 2.40 (dd, J = 15.5, 2.2 Hz, 1H), 2.23 (dd, J = 14.9, 2.9 Hz, 1H), 2.10–2.02 (m, 1H), 1.92 (dddd, J = 15.0, 7.1, 4.4, 0.6 Hz, 1H), 1.71 (s, 1H). ¹³C NMR (201 MHz, CDCl₃) δ 160.3, 154.7, 138.8, 129.8, 112.2, 109.8, 106.3, 77.9, 77.2, 77.0, 76.9, 72.6, 61.1, 55.4, 42.5, 39.7. LRMS (ESI) m/z : [M + H]⁺ 250.1. HRMS (ESI) m/z : [M + Na]⁺ calcd C₁₃H₁₅NO₄Na 272.0893; found 272.0895.

(3a*S*,5*R*,6a*R*)-5-Hydroxy-3-(2-methoxyphenyl)hexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (10d).

To a stirring solution of cyclic *o*-methoxyphenyl carbamate **7d** (20 mg, 0.1 mmol) in methanol (5.5 mL) was added potassium carbonate (17 mg, 0.1 mmol). Reaction was stirred at 23 °C for 12 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **10d** (17 mg, 96%) $[\alpha]_D^{20}$ + 71.2 (*c* 2.67, MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.38 (dd, J = 7.7, 1.7 Hz, 1H), 7.30 (ddd, J = 8.3, 7.5, 1.7 Hz, 1H), 7.05–6.96 (m, 2H), 5.19 (t, J = 7.2 Hz, 1H), 4.82 (t, J = 7.3 Hz, 1H), 4.47 (t, J = 4.4 Hz, 1H), 3.87 (s, 3H), 2.39 (ddd, J = 15.5, 3.1, 0.9 Hz, 2H), 2.10–1.87 (m, 3H), 1.63 (dddd, J = 15.1, 6.7, 4.5, 0.6 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 156.1, 155.1, 129.8, 129.0, 125.0, 121.3, 112.1, 79.0, 77.2, 77.1, 76.9, 76.6, 72.7, 62.1, 55.7, 43.0, 38.8, 29.6. LRMS (ESI) m/z : [M + H]⁺ 250.0. HRMS (ESI) m/z : [M + H]⁺ calcd C₁₃H₁₆NO₄ 250.1074; found 250.1072.

(3a*S*,5*R*,6a*R*)-5-Hydroxy-3-methylhexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (10e).

Protected oxazolidinone **8** (21 mg, 0.1 mmol) was dissolved with dry acetonitrile (1.4 mL) and was placed under an argon atmosphere. Reaction mixture was cooled to 0 °C, and potassium bis(trimethylsilyl)amide (0.5 M solution) (0.25 mL, 0.1 mmol) was added dropwise. The reaction stirred for 30 min. Iodomethane (18 mg, 0.1 mmol) was then added dropwise, and the reaction mixture was allowed to warm up to 23 °C for 1 h. Upon completion, the residue was taken up in DI water and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na₂SO₄, and the solvent was removed under

reduced pressure. The crude product was taken up in methanol (3 mL) and followed the addition of potassium carbonate (19 mg, 0.14 mmol). The reaction was stirred at 23 °C for 12 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **10e** (14 mg, 80%). $[\alpha]_D^{20} + 31.2$ (*c* 2.20, MeOH). ^1H NMR (400 MHz, CDCl_3) δ 4.98 (t, *J* = 7.0 Hz, 1H), 4.48 (t, *J* = 4.2 Hz, 1H), 4.17 (t, *J* = 7.2 Hz, 1H), 2.85 (s, 3H), 2.38 (s, 1H), 2.23 (ddd, *J* = 34.7, 15.9, 1.9 Hz, 2H), 1.94 (dddd, *J* = 15.4, 6.6, 4.3, 0.6 Hz, 1H), 1.66 (dddd, *J* = 14.8, 6.8, 4.3, 0.6 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.6, 78.4, 77.3, 76.9, 76.6, 72.4, 61.9, 42.4, 37.6, 29.2. LRMS (ESI) *m/z*: $[\text{M} + \text{H}]^+$ 158.0. HRMS (ESI) *m/z*: $[\text{M} + \text{Na}]^+ \text{ calcd } \text{C}_7\text{H}_{11}\text{NO}_3\text{Na } 180.0631$; found 180.0630.

(3a*R*,5*S*,6a*S*)-5-Hydroxy-3-methylhexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (*ent*-10e).

Protected oxazolidinone *ent*-**8** (20 mg, 0.1 mmol) was dissolved with freshly distilled dimethylformamide (2.1 mL) and was placed under an argon atmosphere. Reaction mixture was cooled to 0 °C, and sodium hydride (0.1 mmol) was added all at once. Reaction stirred for 20 min, and then iodomethane (21 mg, 0.2 mmol) was added dropwise. Reaction was allowed to warm up to 23 °C for 1 h. Upon completion, the residue was taken up in water and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na_2SO_4 , and the solvent was removed under reduced pressure. The crude product was taken up in methanol (2.1 mL) and followed the addition of potassium carbonate (17 mg, 0.1 mmol). Reaction was stirred at 23 °C for 12 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford *ent*-**10e** (10 mg, 60%). $[\alpha]_D^{20} - 16.0$ (*c* 1.00, MeOH). ^1H NMR (800 MHz, CD_3OD) δ 5.04 (t, *J* = 8.0, 7.0 Hz, 1H), 4.40 (t, *J* = 4.3 Hz, 1H), 4.27 (t, *J* = 7.2 Hz, 1H), 2.85 (s, 3H), 2.20–2.13 (m, 2H), 2.03–1.96 (m, 2H), 1.77–1.71 (m, 2H). ^{13}C NMR (201 MHz, CD_3OD) δ 158.6, 79.2, 71.8, 62.1, 47.9, 47.9, 47.8, 47.7, 47.6, 47.5, 47.4, 47.3, 41.3, 36.9, 27.9. LRMS (ESI) *m/z*: $[\text{M} + \text{H}]^+$ 158.0. HRMS (ESI) *m/z*: $[\text{M} + \text{H}]^+ \text{ calcd } \text{C}_7\text{H}_{12}\text{NO}_3 \text{ 158.0812}$; found 158.0810.

(3a*S*,5*R*,6a*R*)-3-Allyl-5-hydroxyhexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (10f**).**

Protected oxazolidinone **8** (17 mg, 0.1 mmol) was dissolved with dry acetonitrile (4 mL) and was placed under an argon atmosphere. Reaction mixture was cooled to 0 °C, and potassium bis(trimethylsilyl)amide (0.5 M solution, 0.2 mL, 0.1 mmol) was added dropwise. The reaction stirred for 30 min. Allyl iodide (17 mg, 0.1 mmol) was then added dropwise, and the reaction mixture was allowed to warm up to 23 °C for 1 h. Upon completion, the residue was taken up in DI water and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na_2SO_4 , and the solvent was removed under reduced pressure. The crude product was taken up in methanol (2 mL) and followed the addition of potassium carbonate (15 mg, 0.11 mmol). Reaction was stirred at 23 °C for 12 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (80% EtOAc in hexane) to afford **10f** (10 mg, 60%). $[\alpha]_D^{20} + 19$ (*c* 2.0, MeOH). ^1H NMR (800 MHz, CD_3OD) δ 5.76 (dddd, *J* = 17.2, 10.2, 7.1, 4.9 Hz, 1H), 5.22 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.16 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.96 (t, *J* = 7.1

Hz, 1H), 4.31 (dq, $J = 4.3, 2.1, 1.6$ Hz, 1H), 4.24 (t, $J = 7.3$ Hz, 1H), 4.04 (ddt, $J = 15.8, 5.0, 1.7$ Hz, 1H), 3.58 (ddt, $J = 15.8, 7.1, 1.3$ Hz, 1H), 2.07 (dd, $J = 28.0, 15.3$ Hz, 2H), 1.92 (ddd, $J = 15.1, 6.5, 4.3$ Hz, 1H), 1.63 (ddd, $J = 14.7, 6.9, 4.3$ Hz, 1H). ^{13}C NMR (201 MHz, CD_3OD) δ 159.7, 133.7, 118.5, 80.9, 73.2, 61.1, 49.1, 49.0, 48.9, 46.1, 42.7, 38.7. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 183.9. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd $\text{C}_9\text{H}_{14}\text{NO}_3$ 184.0968; found 184.0967.

(3a*S*,5*R*,6a*R*)-5-Hydroxy-3-propylhexahydro-2*H*-cyclopenta-[*d*]oxazol-2-one (10g).

To a stirred reaction of alcohol **10f** (4.5 mg, 0.02 mmol) in dry methanol (1 mL) under an argon atmosphere were added Pd/C (10 wt %) and a hydrogen balloon. Reaction mixture was stirred at 23 °C for 12 h. Upon completion, the residue was filtered over Celite and rinsed with dichloromethane. The solvent collected was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **10g** (3.9 mg, 86%). $[\alpha]_{\text{D}}^{20} + 14.3$ (c 0.77, MeOH). ^1H NMR (800 MHz, CDCl_3) δ 5.02 (t, $J = 7.0$ Hz, 1H), 4.51 (t, $J = 4.4$ Hz, 1H), 4.28 (t, $J = 7.2$ Hz, 1H), 3.51 (ddd, $J = 14.1, 8.7, 7.3$ Hz, 1H), 3.04 (ddd, $J = 13.9, 8.6, 5.2$ Hz, 1H), 2.30–2.26 (m, 1H), 2.20–2.16 (m, 1H), 2.03 (ddd, $J = 15.5, 6.5, 4.4$ Hz, 1H), 1.75 (ddd, $J = 14.9, 6.9, 4.5$ Hz, 1H), 1.69–1.64 (m, 1H), 1.61 (ddd, $J = 13.5, 8.0, 6.6$ Hz, 1H), 0.97 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (201 MHz, CDCl_3) δ 157.3, 78.3, 77.2, 77.0, 76.9, 72.8, 59.5, 44.2, 42.7, 38.3, 29.7, 20.5, 11.2. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 186.0. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd $\text{C}_9\text{H}_{15}\text{NO}_3\text{Na}$ 208.0944; found 208.0942.

(3a*S*,5*R*,6a*R*)-5-Hydroxy-3-(2-methylallyl)hexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (10h).

Protected oxazolidinone **8** (10 mg, 0.06 mmol) was dissolved with dry acetonitrile (1 mL) and was placed under an argon atmosphere. Reaction mixture was cooled to 0 °C, and potassium bis(trimethylsilyl)amide (0.5 M solution, 0.13 mL, 0.07 mmol) was added dropwise. The reaction stirred for 30 min. 3-Bromo-2-methylprop-1-ene (8.8 mg, 0.06 mmol) was then added dropwise, and the reaction mixture was allowed to warm up to 23 °C for 1 h. Upon completion, the residue was taken up in DI water and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was taken up in methanol (0.6 mL) and followed the addition of potassium carbonate (4.6 mg, 0.02 mmol).

Reaction was stirred at 23 °C for 12 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (80% EtOAc in hexane) to afford **10h** (3.2 mg, 84%). $[\alpha]_{\text{D}}^{20} + 22.9$ (c 0.67, MeOH). ^1H NMR (800 MHz, CDCl_3) δ 5.03 (t, $J = 7.0$ Hz, 1H), 4.95 (d, $J = 20.5$ Hz, 2H), 4.51 (s, 1H), 4.19 (t, $J = 7.3$ Hz, 1H), 4.15 (d, $J = 15.2$ Hz, 1H), 3.58 (d, $J = 15.3$ Hz, 1H), 2.30 (dd, $J = 15.5, 2.9$ Hz, 1H), 2.19 (dt, $J = 14.8, 1.8$ Hz, 1H), 2.01 (ddd, $J = 15.4, 6.4, 4.3$ Hz, 1H), 1.77 (s, 2H), 1.69 (ddt, $J = 19.2, 7.0, 3.7$ Hz, 2H). ^{13}C NMR (201 MHz, CDCl_3) δ 157.5, 140.1, 113.8, 78.5, 77.2, 77.0, 76.9, 72.7, 59.3, 48.9, 42.7, 38.0, 19.9. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 198.0. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd $\text{C}_{10}\text{H}_{14}\text{NO}_3$ 198.1125; found 198.1126.

(3a*S*,5*R*,6a*R*)-5-Hydroxy-3-isobutylhexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (10i).

To a stirred reaction of alcohol **10h** (16 mg, 0.07 mmol) in dry methanol (2.2 mL) under an argon atmosphere were added of Pd/C (10 wt %) and a hydrogen balloon. Reaction mixture was stirred at 23 °C for 12 h. Upon completion, the residue was filtered over Celite and rinsed with dichloromethane. The solvent collected was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **10i** (15 mg, 92%). $[\alpha]_D^{20} + 65.2$ (*c* 2.00, MeOH). ¹H NMR (800 MHz, CDO₃) δ 5.02 (t, *J* = 6.9 Hz, 1H), 4.51 (s, 1H), 4.26 (t, *J* = 7.4 Hz, 1H), 3.33 (t, *J* = 12.5, 11.0 Hz, 1H), 2.89 (ddd, *J* = 14.1, 6.2, 2.3 Hz, 1H), 2.29 (d, *J* = 15.4 Hz, 1H), 2.19 (d, *J* = 14.7 Hz, 1H), 2.05–1.91 (m, 2H), 1.78–1.67 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H). ¹³C NMR (201 MHz, CDCl₃) δ 157.7, 78.38, 77.2, 77.0, 76.9, 72.7, 59.9, 50.0, 42.7, 38.0, 26.4, 20.2, 19.8. LRMS (ESI) *m/z*: [M + H]⁺ 200.1. HRMS (ESI) *m/z*: [M + H]⁺ calcd C₁₀H₁₈NO₃ 200.1281; found 200.1280.

(3a*S*,5*R*,6a*R*)-5-Hydroxy-3-(methoxymethyl)hexahydro-2*H*-cyclopenta[*d*]oxazol-2-one (10j).

Protected oxazolidinone **8** (8 mg, 0.04 mmol) was dissolved with dry tetrahydrofuran (2.7 mL) and was placed under an argon atmosphere. Reaction mixture was cooled to 0 °C, and potassium bis(trimethylsilyl)amide (0.5 M solution, 0.13 mL, 0.07 mmol) was added dropwise. The reaction stirred for 30 min. Chloromethyl methyl ether (5.7 mg, 0.07 mmol) was then added dropwise, and the reaction mixture was allowed to warm up to 23 °C for 1 h. Upon completion, the residue was taken up in DI water, and the aqueous phase was extracted with EtOAc. The organic extracts were dried with Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was taken up in methanol (1 mL) and followed the addition of potassium carbonate (8 mg, 0.06 mmol). Reaction was stirred at 23 °C for 12 h. Upon completion, the residue solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (60% EtOAc in hexane) to afford **10j** (2.7 mg, 33%). $[\alpha]_D^{20} + 9.87$ (*c* 2.60, MeOH). ¹H NMR (800 MHz, CD₃OD) δ 5.09 (t, *J* = 7.1 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.45–4.40 (m, 2H), 3.35 (s, 3H), 2.20 (dd, *J* = 14.9, 1.4 Hz, 2H), 2.04–1.98 (m, 1H), 1.83–1.76 (m, 1H). ¹³C NMR (201 MHz, CD₃OD) δ 158.7, 79.9, 74.8, 71.9, 59.4, 54.8, 47.9, 47.9, 47.8, 47.7, 47.6, 47.5, 47.4, 47.3, 41.1, 38.3. LRMS (ESI) *m/z*: [M + Na]⁺ 209.9. HRMS (ESI) *m/z*: [M + Na]⁺ calcd C₁₈H₁₃NO₃Na 210.0737; found 210.0736.

4-Nitro phenyl ((3a*S*,5*R*,6a*R*)-2-Oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl)carbonate (11a).

To a stirred solution of alcohol **9** (10 mg, 0.07 mmol) in dry dichloromethane (2 mL) were added 4-methylmorpholine (23 μL, 0.2 mmol) and 4-nitrophenyl chloroformate (42 mg, 0.2 mmol) at 0 °C under an argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 12 h. Upon completion, solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (80% EtOAc in hexane) to afford **11a** (18 mg, 83%): ¹H NMR (800 MHz, CDCl₃) δ 8.29 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H), 5.36 (t, *J* = 4.6 Hz, 1H), 5.29 (s, 1H), 5.26 (t, *J* = 6.9 Hz, 1H), 4.49 (t, *J* = 7.2 Hz, 1H), 2.67 (dd, *J* = 16.3, 3.0 Hz, 1H), 2.34 (dd, *J* = 15.6, 3.0 Hz, 1H), 2.16 (ddd, *J* = 16.2, 6.4, 4.6 Hz, 1H), 2.10 (ddd, *J* = 15.6, 6.8, 4.7 Hz, 1H). ¹³C NMR (201 MHz, CDCl₃) δ 158.1,

155.4, 151.9, 145.5, 125.3, 121.9, 81.0, 80.7, 77.2, 77.0, 76.9, 55.9, 40.2, 39.5, 29.7. LRMS (ESI) m/z : $[M + H]^+$ 309.0.

(3a*S*,5*R*,6a*R*)-3-Methyl-2-oxohexahydro-2*H*-cyclopenta[*d*]-oxazol-5-yl (4-Nitrophenyl) Carbonate (11b).

Alcohol **10e** (13 mg, 0.08 mmol) was treated with 4-methylmorpholine (27 μ L, 0.3 mmol) and 4-nitrophenyl chloroformate (50 mg, 0.3 mmol) by following the procedure outline for activated alcohol **11a** to afford **11b** (15 mg, 56%): ^1H NMR (500 MHz, CDCl_3) δ 8.26 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 9.2 Hz, 2H), 5.32–5.28 (m, 1H), 5.07 (t, J = 7.1 Hz, 1H), 4.28 (t, J = 7.1 Hz, 1H), 2.89 (s, 3H), 2.59 (dd, J = 16.3, 2.7 Hz, 1H), 2.44 (dd, J = 15.7, 3.1 Hz, 1H), 2.21–2.13 (m, 1H), 1.98–1.88 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 156.9, 155.3, 151.9, 145.5, 125.3, 121.9, 80.5, 77.3, 77.0, 76.8, 61.5, 39.7, 35.6, 29.3. LRMS (ESI) m/z : $[M + H]^+$ 323.0

4-Nitrophenyl ((3a*R*,5*S*,6a*S*)-2-Oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl)carbonate (11c).

Alcohol *ent*-**9** (6.3 mg, 0.04 mmol) was treated with 4-methylmorpholine (15 μ L, 0.1 mmol) and 4-nitrophenyl chloroformate (27 mg, 0.1 mmol) by following the procedure outline for activated alcohol **11a** to afford **11c** (4.8 mg, 35%): ^1H NMR (800 MHz, CDCl_3) δ 8.29 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 5.36 (t, J = 4.8 Hz, 1H), 5.26 (t, J = 7.0 Hz, 1H), 5.19 (s, 1H), 4.49 (t, J = 7.2 Hz, 1H), 2.67 (d, J = 15.9 Hz, 1H), 2.34 (d, J = 15.5 Hz, 1H), 2.15 (dt, J = 16.3, 5.5 Hz, 1H), 2.10 (dt, J = 15.6, 5.8 Hz, 1H). ^{13}C NMR (201 MHz, CDCl_3) δ 158.1, 155.4, 151.9, 145.5, 125.3, 121.9, 81.0, 80.7, 77.2, 77.0, 76.9, 55.9, 40.2, 39.5. LRMS (ESI) m/z : $[M + H]^+$ 309.0.

4-Nitrophenyl ((3a*R*,5*S*,6a*S*)-2-Oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl)carbonate (11d).

Alcohol *ent*-**10e** (5.7 mg, 0.04 mmol) was treated with 4-methylmorpholine (12 μ L, 0.1 mmol) and 4-nitrophenyl chloroformate (22 mg, 0.1 mmol) by following the procedure outline for activated alcohol **11a** to afford **11d** (11 mg, 94%): ^1H NMR (500 MHz, CDCl_3) δ 8.27 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 9.2 Hz, 2H), 5.30 (t, J = 4.6 Hz, 1H), 5.07 (t, J = 7.0 Hz, 1H), 4.28 (t, J = 7.1 Hz, 1H), 2.89 (s, 3H), 2.45 (dd, J = 15.6, 3.0 Hz, 1H), 2.20–2.13 (m, 1H), 1.96–1.89 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 156.9, 155.3, 151.9, 145.5, 125.3, 121.9, 80.5, 77.3, 77.2, 77.0, 76.8, 61.5, 39.7, 35.6, 29.3. LRMS (ESI) m/z : $[M + H]^+$ 323.0.

4-Nitrophenyl ((3a*R*,5*S*,6a*S*)-2-Oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl)carbonate (11e).

Alcohol **10a** (14 mg, 0.06 mmol) was treated with 4-methylmorpholine (20 μ L, 0.2 mmol) and 4-nitrophenyl chloroformate (37 mg, 0.2 mmol) by following the procedure outline for activated alcohol **11a** to afford **11e** (19 mg, 78%): ^1H NMR (800 MHz, CDCl_3) δ 8.27 (dd, J = 9.0, 1.8 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.44–7.38 (m, 2H), 7.33–7.26 (m, 3H), 7.21 (t, J = 7.4 Hz, 1H), 5.33 (t, J = 4.6 Hz, 1H), 5.25 (t, J = 7.0 Hz, 1H), 5.02 (t, J = 7.1 Hz, 1H), 2.72 (dd, J = 16.3, 3.2 Hz, 1H), 2.49 (dd, J = 15.7, 3.2 Hz, 1H), 2.27 (dddd, J = 16.2, 6.4, 4.5, 1.6 Hz, 1H), 2.09 (dddd, J = 15.8, 6.5, 4.4, 1.5 Hz, 1H). ^{13}C NMR (201 MHz, CDCl_3) δ 155.3, 154.3, 151.8, 145.5, 137.0, 129.3, 125.3, 124.9, 121.9, 120.7, 80.4, 77.2, 77.0, 76.9, 60.6, 39.9, 36.9. LRMS (ESI) m/z : $[M + H]^+$ 385.0.

(3a*S*,5*R*,6a*R*)-3-(4-Methoxyphenyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl (4-Nitrophenyl) Carbonate (11f).

Alcohol **10b** (6.8 mg, 0.03 mmol) was treated with 4-methylmorpholine (9.0 μ L, 0.08 mmol) and 4-nitrophenyl chloroformate (17 mg, 0.08 mmol) by following the procedure outline for activated alcohol **11a** to afford **11f** (11 mg, 97%): ^1H NMR (500 MHz, CDCl_3) δ 8.27 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 9.1 Hz, 2H), 7.32 (d, J = 9.2 Hz, 2H), 6.92 (d, J = 9.1 Hz, 2H), 5.31 (t, J = 4.5 Hz, 1H), 5.22 (t, J = 7.1 Hz, 1H), 4.92 (t, J = 7.0 Hz, 1H), 3.81 (s, 3H), 2.69 (dd, J = 16.3, 2.8 Hz, 1H), 2.43 (dd, J = 15.7, 3.1 Hz, 1H), 2.27–2.19 (m, 1H), 2.03–1.95 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 157.2, 155.3, 154.7, 151.9, 145.5, 129.8, 125.3, 123.5, 121.9, 114.6, 80.5, 77.3, 77.0, 76.8, 61.3, 55.6, 40.0, 36.7. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 415.0.

(3a*S*,5*R*,6a*R*)-3-(3-Methoxyphenyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl (4-Nitrophenyl) Carbonate (11 g).

Alcohol **10c** (20 mg, 0.08 mmol) was treated with 4-methylmorpholine (26 μ L, 0.2 mmol) and 4-nitrophenyl chloroformate (48 mg, 0.2 mmol) by following the procedure outline for activated alcohol **11a** to afford **11g** (13 mg, 60%): ^1H NMR (800 MHz, CDCl_3) δ 8.27 (d, J = 9.2 Hz, 2H), 7.32–7.29 (m, 3H), 7.22 (t, J = 2.3 Hz, 1H), 7.05 (dd, J = 8.0, 1.7 Hz, 1H), 6.75 (dd, J = 8.3, 2.3 Hz, 1H), 5.32 (t, J = 4.5 Hz, 1H), 5.24 (t, J = 7.0 Hz, 1H), 4.98 (t, J = 7.1 Hz, 1H), 3.81 (s, 3H), 2.71 (dd, J = 16.2, 3.1 Hz, 1H), 2.52 (dd, J = 15.8, 3.1 Hz, 1H), 2.26 (ddd, J = 16.2, 6.6, 4.6 Hz, 1H), 2.09 (ddd, J = 15.8, 6.8, 4.5 Hz, 1H). ^{13}C NMR (201 MHz, CDCl_3) δ 160.4, 155.3, 154.1, 151.8, 145.5, 138.2, 130.0, 125.3, 121.9, 112.6, 109.9, 107.3, 80.4, 77.2, 77.0, 76.9, 60.6, 55.4, 39.9, 37.0. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 415.0.

(3a*S*,5*R*,6a*R*)-3-(2-Methoxyphenyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl (4-Nitrophenyl) Carbonate (11h).

Alcohol **10d** (21 mg, 0.08 mmol) was treated with 4-methylmorpholine (28 μ L, 0.3 mmol) and 4-nitrophenyl chloroformate (51 mg, 0.3 mmol) by following the procedure outline for activated alcohol **11a** to afford **11h** (15 mg, 42%): ^1H NMR (800 MHz, CDCl_3) δ 8.32 (d, J = 9.0 Hz, 2H), 7.42 (t, J = 8.0 Hz, 3H), 7.33 (t, J = 7.8 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 5.33 (t, J = 4.3 Hz, 1H), 5.28 (t, J = 7.2 Hz, 1H), 5.09 (t, J = 7.2 Hz, 1H), 3.90 (s, 3H), 2.71 (dd, J = 16.2, 3.1 Hz, 2H), 2.28–2.21 (m, 3H), 1.85 (ddd, J = 15.8, 6.8, 4.6 Hz, 2H). ^{13}C NMR (201 MHz, CDCl_3) δ 156.0, 155.4, 154.9, 152.0, 145.5, 129.8, 129.0, 125.4, 124.6, 121.9, 121.1, 112.0, 80.8, 77.9, 77.2, 77.0, 76.9, 60.8, 55.7, 40.1, 36.7. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ 415.1.

(3a*S*,5*R*,6a*R*)-3-Allyl-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl (4-Nitrophenyl) Carbonate (11i).

Alcohol **10f** (14 mg, 0.08 mmol) was treated with 4-methylmorpholine (25 μ L, 0.2 mmol) and 4-nitrophenyl chloroformate (46 mg, 0.2 mmol) by following the procedure outline for activated alcohol **11a** to afford **11i** (17 mg, 66%): ^1H NMR (800 MHz, CDCl_3) δ 8.30 (d, J = 9.2 Hz, 2H), 7.39 (d, J = 9.2 Hz, 2H), 5.83 (dddd, J = 17.2, 10.1, 7.1, 5.4 Hz, 1H), 5.34–5.27 (m, 3H), 5.10 (t, J = 7.1 Hz, 1H), 4.37 (t, J = 7.2 Hz, 1H), 4.20 (ddt, J = 15.5, 5.4, 1.6 Hz, 1H), 3.69 (ddt, J = 15.5, 7.1, 1.2 Hz, 1H), 2.63 (dd, J = 16.2, 2.5 Hz, 1H), 2.48 (dd, J = 15.7,

3.0 Hz, 1H), 2.18 (dddd, J = 16.2, 6.6, 4.6, 0.7 Hz, 1H), 1.92 (dddd, J = 15.6, 6.8, 4.7, 0.7 Hz, 1H). ^{13}C NMR (201 MHz, CDCl_3) δ 156.6, 155.3, 151.9, 145.5, 132.3, 125.3, 121.9, 118.9, 80.5, 77.6, 77.2, 77.2, 77.0, 73.9, 59.3, 45.6, 39.7, 36.0. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+ 349.0$.

4-Nitrophenyl ((3a*S*,5*R*,6a*R*)-2-oxo-3-propylhexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl)carbonate (11j).

Alcohol **10g** (7 mg, 0.04 mmol) was treated with 4-methylmorpholine (12 μL , 0.1 mmol) and 4-nitrophenyl chloroformate (23 mg, 0.1 mmol) by following the procedure outline for activated alcohol **11a** to afford **11j** (4 mg, 30%): ^1H NMR (500 MHz, CDCl_3) δ 8.27 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 9.2 Hz, 2H), 5.29 (t, J = 4.6 Hz, 1H), 5.07 (t, J = 7.0 Hz, 1H), 4.35 (t, J = 7.2 Hz, 1H), 3.47 (ddd, J = 14.0, 8.8, 7.1 Hz, 1H), 3.02 (ddd, J = 14.0, 8.6, 5.2 Hz, 1H), 2.60 (ddd, J = 16.3, 3.0, 1.0 Hz, 1H), 2.43 (dd, J = 15.7, 3.0 Hz, 1H), 2.16 (dddd, J = 16.1, 6.5, 4.7, 0.7 Hz, 1H), 1.94 (dddd, J = 15.6, 6.8, 4.7, 0.7 Hz, 1H), 1.73–1.57 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 156.9, 155.3, 151.9, 145.5, 125.3, 121.9, 80.5, 77.3, 77.0, 76.8, 59.4, 44.3, 39.7, 36.2, 29.7, 20.7, 11.2. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+ 351.0$.

(3a*S*,5*R*,6a*R*)-3-(2-Methylallyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl (4-Nitrophenyl) Carbonate (11k).

Alcohol **10h** (6 mg, 0.03 mmol) was treated with 4-methylmorpholine (10 μL , 0.09 mmol) and 4-nitrophenyl chloroformate (19 mg, 0.09 mmol) by following the procedure outline for activated alcohol **11a** to afford **11k** (7.2 mg, 66%): ^1H NMR (500 MHz, CDCl_3) δ 8.27 (d, J = 9.3 Hz, 2H), 7.36 (d, J = 9.2 Hz, 2H), 5.30 (t, J = 4.6 Hz, 1H), 5.08 (t, J = 7.0 Hz, 1H), 4.95 (d, J = 17.9 Hz, 2H), 4.26 (t, J = 7.2 Hz, 1H), 4.09 (d, J = 15.2 Hz, 1H), 3.59 (d, J = 15.2 Hz, 1H), 2.61 (dd, J = 16.4, 2.7 Hz, 1H), 2.43 (dd, J = 15.7, 3.0 Hz, 1H), 2.15 (dddd, J = 16.2, 6.5, 4.6, 0.7 Hz, 1H), 1.89 (dddd, J = 15.8, 7.0, 4.8, 0.7 Hz, 1H), 1.76 (t, J = 0.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 157.0, 155.3, 151.9, 145.5, 139.9, 125.3, 121.9, 114.2, 80.5, 77.6, 77.3, 77.0, 76.8, 59.3, 49.2, 39.7, 35.9, 19.9. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+ 363.0$.

(3a*S*,5*R*,6a*R*)-3-Isobutyl-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl (4-Nitrophenyl) Carbonate (11l).

Alcohol **10i** (11 mg, 0.05 mmol) was treated with 4-methylmorpholine (18 μL , 0.2 mmol) and 4-nitrophenyl chloroformate (33 mg, 0.2 mmol) by following the procedure outline for activated alcohol **11a** to afford **11l** (15 mg, 77%): ^1H NMR (800 MHz, CDCl_3) δ 8.29 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 9.2 Hz, 2H), 5.32 (t, J = 4.7 Hz, 1H), 5.10 (t, J = 7.0 Hz, 1H), 4.36 (t, J = 7.2 Hz, 1H), 3.33 (dd, J = 14.0, 8.9 Hz, 1H), 2.88 (dd, J = 14.0, 6.3 Hz, 1H), 2.63 (dd, J = 16.2, 2.6 Hz, 1H), 2.45 (dd, J = 15.7, 3.0 Hz, 1H), 2.20–2.15 (m, 1H), 2.01–1.93 (m, 2H), 1.00 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H). ^{13}C NMR (201 MHz, CDCl_3) δ 157.2, 155.3, 151.9, 145.5, 125.3, 121.9, 80.5, 77.4, 77.2, 77.0, 76.9, 59.7, 50.2, 39.7, 36.0, 26.5, 20.2, 19.8. LRMS (ESI) m/z : $[\text{M} + \text{H}]^+ 365.0$.

(3a*S*,5*R*,6a*R*)-3-(Methoxymethyl)-2-oxohexahydro-2*H*-cyclopenta[*d*]oxazol-5-yl (4-Nitrophenyl) Carbonate (11*m*).

Alcohol **10j** (5 mg, 0.03 mmol) was treated with 4-methylmorpholine (9.0 μ L, 0.08 mmol) and 4-nitrophenyl chloroformate (16 mg, 0.08 mmol) by following the procedure outline for activated alcohol **11a** to afford **11m** (7 mg, 74%): ^1H NMR (800 MHz, CDCl_3) δ 8.29 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 9.2 Hz, 2H), 5.35 (t, J = 4.6 Hz, 1H), 5.14 (t, J = 7.1 Hz, 1H), 4.79 (d, J = 0.6 Hz, 2H), 4.48 (t, J = 7.1 Hz, 1H), 3.41 (s, 3H), 2.70–2.59 (m, 2H), 2.18 (dddd, J = 16.2, 6.6, 4.6, 0.7 Hz, 1H), 2.02 (dddd, J = 15.7, 6.9, 4.7, 0.7 Hz, 1H). ^{13}C NMR (201 MHz, CDCl_3) δ 157.1, 155.3, 151.9, 145.5, 125.3, 121.8, 80.6, 78.0, 77.2, 77.2, 77.0, 76.9, 75.8, 59.4, 56.2, 39.5, 37.4. LRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ 375.0.

Determination of X-ray Structures of HIV-1 Protease–Inhibitor Complexes.

HIV-1 protease was expressed and purified as described.³⁷ The protease complexes with inhibitors **4a** and **4e** were crystallized using the hanging drop vapor diffusion method with well solutions of 1.0 M NaCl, 0.1 M sodium acetate, pH 4.8 for **4a**, and 1.4 M NaCl, 0.1 M sodium acetate, pH 5.5 for **4e**. X-ray diffraction data were collected on a single crystal cooled to 90 K at SER-CAT (22-ID beamline), Advanced Photon Source, Argonne National Lab (Chicago, IL, USA) with X-ray wavelength of 1.0 Å. X-ray data were processed by HKL-2000³⁸ to give R_{merge} values of 9.9% for **4a**-bound protease and 8.2% for **4e**-bound protease. The crystal structures were solved by PHASER³⁹ in CCP4i Suite^{40–42} using one of the previously reported isomorphous structures⁴³ as the initial model, and refined using both SHELX-2014^{44,45} and Refmac⁵⁴⁶ with X-ray data at 1.22 and 1.30 Å resolution for **4a** and **4e** complexes, respectively. PRODRG-2⁴⁸ was used to construct the inhibitors and geometric restraints for refinement. COOT⁴⁷⁴⁹ was used for modification of the models. Alternative conformations were modeled, and isotropic atomic displacement parameters (B factors) were applied for all atoms including solvent molecules. The final refined solvent structure comprised two Na^+ ions, two Cl^- ions, one formic acid, and 190 waters for **4a**-bound protease and two Na^+ ions, four Cl^- ions, and 155 water molecules for the **4e**-bound protease structure. The crystallographic data collection and refinement statistics are listed in Table 1 of Supporting Information. The coordinates and structure factors of the HIV-1 protease structures have been deposited in the Protein Data Bank⁴⁹ with accession code of 6E9A for **4a**-bound protease and 6E7J for **4e**-bound protease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS USED

APV	amprenavir
ART	antiretroviral therapy
ATV	atazanavir
bis-THF	bis-tetrahydrofuran
DIPEA,<i>N</i>	<i>N</i> -diisopropyl-ethylamine
DRV	darunavir
LPV	lopinavir
PI	protease inhibitor
TFA	trifluoroacetic acid
Cp-THF	cyclopentanyl-tetrahydrofuran
IBX	<i>O</i> -iodoxybenzoic acid

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Figure 1.
Structures of HIV-1 protease inhibitors **1–4**.

Figure 2. Stereoview of the X-ray crystal structure of inhibitor **4a** (turquoise) in the active site of HIV-1 protease (PDB code 6E9A). The oxazolidinone P2 ligand makes hydrogen-bonding and van der Waals interactions in the S2 subsite. All key hydrogen bonds are shown as black dotted lines.

Figure 3.

Stereoview of the overlay of X-ray crystal structures of inhibitor **4a** (green) and DRV (magenta) in the active site of HIV-1 protease (PDB code 6E9A for **4a** and PDB code 2IEN for DRV). Both P2 and P2' ligands make strong hydrogen bonds in the S2 subsite. All key hydrogen bonds are shown as black dotted lines for **4a** and orange dotted lines for DRV.

Figure 4. Stereoview of the X-ray crystal structure of inhibitor **4e** (green) in the active site of HIV-1 protease (PDB code 6E7J). The oxazolinone P2 ligand makes hydrogen-bonding and van der Waals interactions in the S2 subsite. All key hydrogen bonds are shown as black dotted lines.

Scheme 1.
Synthesis of Bicyclic Oxazolidinone Ligands 9

Scheme 2.

Synthesis of Substituted Oxazolidinone Ligand Alcohols

Scheme 3.
Synthesis of Activated Carbonates of Oxazolidinone Ligands

Scheme 4.
Synthesis of HIV-1 Protease Inhibitors 4a–n

Table 1.

HIV-1 Protease Inhibitory and Antiviral Activity of PIs 4a–h

Entry	Inhibitor	K_i (nM) ^a	IC ₅₀ (nM) ^b
1.		0.0012	48.3
2.		1.33	>1000
3.		0.03	36
4.		0.16	436
5.		0.33	>1000
6.		0.63	>1000
7.		92.8	>1000
8.		0.08	251

^a K_i values represents at least four data points. Standard error in all cases was less than 7%. Darunavir exhibited K_i = 16 pM.

^b Values are the mean of at least three experiments. Standard error in all cases was less than 5%. Darunavir exhibited antiviral IC₅₀ = 3.2 nM, saquinavir IC₅₀ = 21 nM.

Table 2.

HIV-1 Protease Inhibitory and Antiviral Activity of PIs 4i–n

Entry	Inhibitor	K_i (nM) ^a	IC ₅₀ (nM) ^b
1.		0.016	369
2.		0.14	447
3.		0.04	31
4.		0.16	41
5.		0.016	84
6.		0.19	84

^a K_i values represents at least four data points. Standard error in all cases was less than 7%. Darunavir exhibited $K_i = 16$ pM.

^b Values are the mean of at least three experiments. Standard error in all cases was less than 5%. Darunavir exhibited antiviral IC₅₀ = 3.2 nM, saquinavir IC₅₀ = 21 nM.

Table 3.
Comparison of the Antiviral Activity of 4k and 4l and Other PIs against Highly PI-Resistant HIV-1 Variants

virus ^a	mean IC ₅₀ ± SD (nM) ^b					
	LPV	APV	DRV	4k	4l	
HIV-1 _{NL4-3}	6.0 ± 0.09	431 ± 3	0.89 ± 0.02	3.5 ± 0.09	23 ± 0.1	40 ± 1
HIV-1 _{ATV} ^R _{5μM}	311 ± 6	>1000	>1000	19 ± 2 (5)	36 ± 2 (1)	33 ± 2 (1)
HIV-1 _{LPV} ^R _{5μM}	>1000	>1000	293 ± 4	301 ± 0.2 (86)	>1000	615 ± 8 (15)
HIV-1 _{APV} ^R _{5μM}	218 ± 1	>1000	2.0 ± 0.08	129 ± 3 (37)	261 ± 15 (11)	309 ± 4 (7)
HIV-1 _{DRV} ^R _{P20}	>1000	>1000	>1000	169 ± 15	>1000	>1000
HIV-1 _{DRV} ^R _{P30}	>1000	>1000	>1000	426 ± 26	>1000	>1000
HIV-1 _{DRV} ^R _{P51}	>1000	>1000	>1000	>1000	>1000	>1000

^aThe amino acid substitutions identified in the protease-encoding region compared to the wild-type HIV-1_{NL4-3} were L23I, E34Q, K43I, M46I, I50L, G51A, L63P, A71V, V82A, T91A in HIV-1_{ATV}^R_{5μM}; L10F, M46I, I54V, V82A in HIV-1_{LPV}^R_{5μM}; or L10F, M46I, I50V, I85V in HIV-1_{APV}^R_{5μM}.

^bThe IC₅₀ (50% effective concentration) values were determined by using MT-4 cells as target cells. MT-4 cells (10⁵/mL) were exposed to 100 TCID₅₀ values of each HIV-1, and the inhibition of p24 Gag protein production by each drug was used as an end point. All assays were conducted in duplicate, and the data shown represent mean values (±SD) derived from the results of two independent experiments.

Table 4.Selectivity Index for Selected Inhibitors^a

inhibitor	CC ₅₀ (μM)	selectivity index ^a
4a	>100	>2070
4c	>100	>2778
4d	>100	>229
4k	>100	>3226
4l	>100	>2439
4n	43	1536

^a Each selectivity index denotes a ratio of CC₅₀ to IC₅₀.