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Graphical Abstract

Design, Synthesis, and X-Ray Studies of Potent HIV-1 Protease Inhibitors incorporating amino-thiochromane and aminotetrahydronaphthalene carboxamide derivatives as the P2 ligands.

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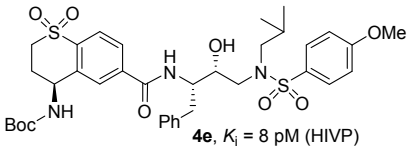

4e, K_i = 8 pM (HIVP)
IC_{50} = 47 nM (antiviral)

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Design, Synthesis, and X-Ray Studies of Potent HIV-1 Protease Inhibitors incorporating aminothiochromane and aminotetrahydronaphthalene carboxamide derivatives as the P2 ligands.

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ABSTRACT

We describe the design, synthesis, and biological evaluation of a series of novel HIV-1 protease inhibitors with carboxamide derivatives as the P2 ligands. We have specifically designed aminothiochromane and aminotetrahydronaphthalene-based carboxamide ligands to promote hydrogen bonding and van der Waals interactions in the active site of HIV-1 protease. Inhibitors **4e** and **4j** have shown potent enzyme inhibitory and antiviral activity. High resolution X-ray crystal structures of **4d-** and **4k**-bound HIV-1 protease revealed molecular insights into the ligand-binding site interactions.

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1. Introduction

Design and development of HIV-1 protease inhibitors and their introduction in combination therapy represent a major innovation for the treatment of HIV-1 infection and AIDS.[1,2] These combination antiretroviral therapies (ART) significantly improve the life expectancy of HIV-1 infected patients.[3,4] The mortality rates for HIV/AIDS patients who are treated with ART, have become close to those of the general population.[5,6] However, the majority of approved protease inhibitors in ART have limitations due to rapid occurrence of resistant strains, high pill burdens and other side effects.[7,8] The last FDA approved protease inhibitor, darunavir (**1**, Figure 1), has significantly improved properties.[9,10] Darunavir has been shown to maintain excellent potency against a broad-spectrum of highly multidrug-resistant HIV-1 variants.[11,12] Darunavir and related derivative TMC126 (**2**) were specifically designed to promote extensive hydrogen-bonding interactions with HIV-1 protease backbone atoms.[13,14] Indeed, the X-ray structure of darunavir-bound HIV-1 protease revealed these critical ligand-binding site interactions which are now further utilized in our molecular design.[15,16] The design of protease inhibitors continue to be an important area of research. There are recent reports of novel PIs incorporating P2/P2' ligands.[17-20] PIs were also designed with new P1 and P2' ligands.[21,22] Recently, a new class of piperazine derived non-peptide inhibitors have been reported.[23,24]

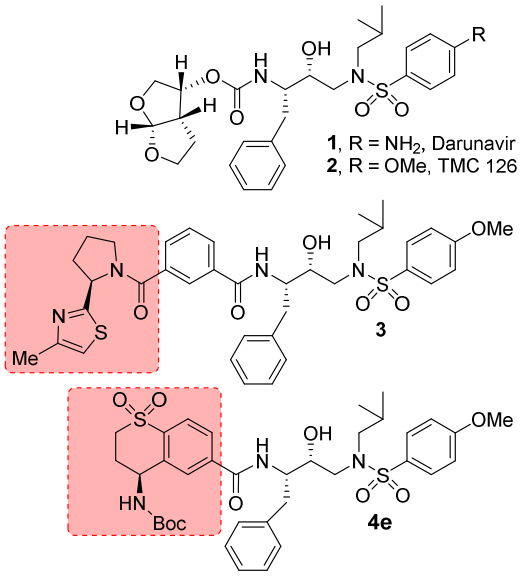


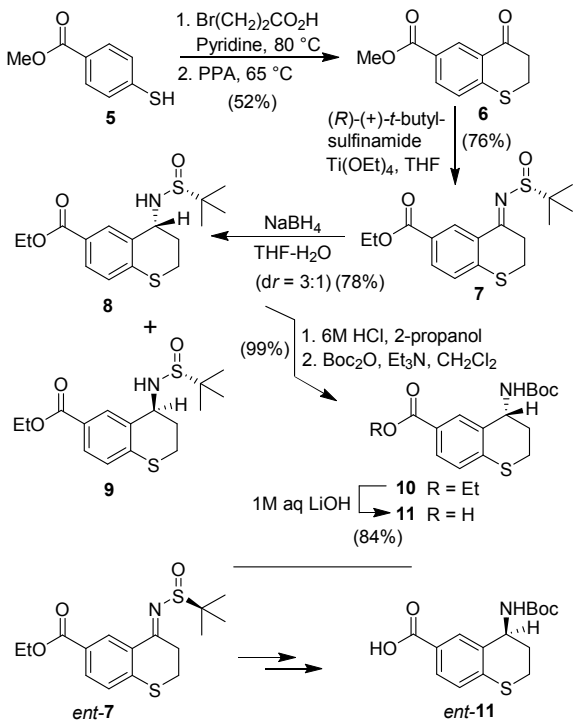
Figure 1. Structure of protease inhibitors **1-3, 4e**.

In our continuing studies towards the design and synthesis of new class of PIs, we have structure-based designed a range of exceptionally potent PIs with intriguing molecular features including, GRL-6579, GRL-02031, GRL-0519, and more recently GRL-0142.[14,25-28] These inhibitors exhibit broad-spectrum antiviral activity against highly multidrug-resistant HIV-1 mutant strains and also show high genetic barrier to resistance.[27,29] In these inhibitors, we incorporated a variety of cyclic ether-derived templates as the P2-ligand attached to the hydroxyethylamine sulfonamide isostere with a urethane functionality.[30] The major design concept behind these PIs is to promote extensive hydrogen bonding with the HIV-1 protease active site backbone atoms like a molecular crab.[13,14] Recently, we and others reported a variety of protease inhibitors with benzoic acid amide derivatives as the P2-ligands.[31-34] These inhibitors were designed based upon the X-ray structures of FDA approved inhibitors darunavir and nelfinavir-bound to HIV-1 protease.[15,16,35] Our efforts led to very potent inhibitors with picomolar enzyme inhibitory activity and low nanomolar antiviral activity. The X-ray structural studies of a number of these inhibitors provided structural insights into the ligand and HIV-1 protease interactions, particularly in the active site of the enzyme.[15,35] We have now further explored these molecular insights and we report the design, synthesis, biological evaluation, and X-ray structural studies of a new series of protease inhibitors incorporating stereochemically defined aminothiochromane and aminotetrahydronaphthalene carboxamide derivatives as the P2 ligands.

2. Results and discussion

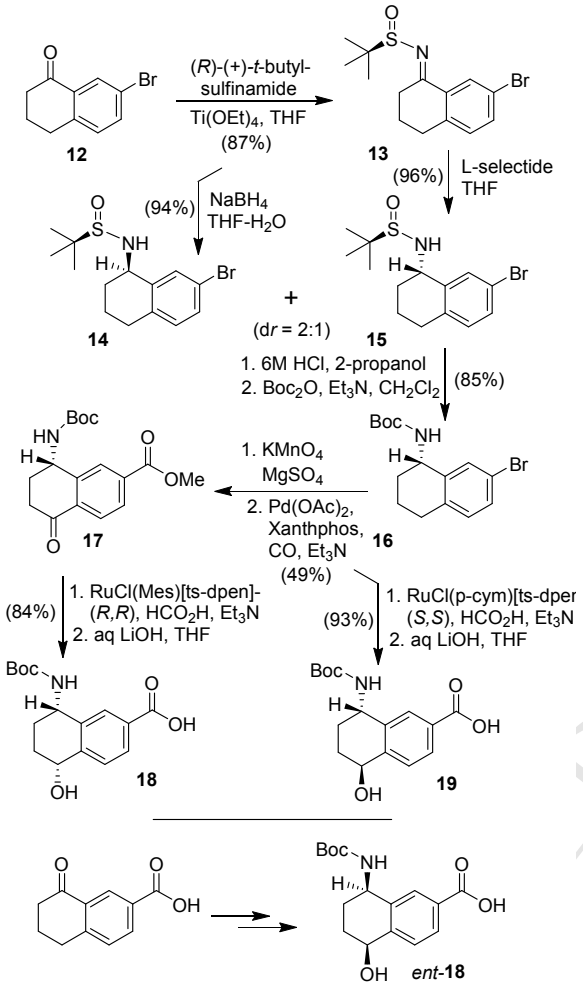
2.1 Chemistry

Based upon the X-ray structures of darunavir-bound HIV-1 protease and nelfinavir-bound HIV-1 protease, we designed 4-aminothiochromane and 4-aminotetrahydronaphthalene carboxamide derivatives as the P2 ligand. The synthesis of 4-aminothiochromane-6-carboxylic acid in optically active form is shown in Scheme 1. Reaction of 4-mercaptobenzoic acid methyl ester **5** with 3-bromopropionic acid in the presence of pyridine at 80 °C for 1 h provided the corresponding alkylated product. The resulting acid was reacted with polyphosphoric acid (PPA) at 65 °C for 6 h to afford 4-oxothiochromane derivative **6**.[36] Reaction of ketone **6** with commercially available (*R*)-(+)-2-methyl-2-propane sulfinamide in the presence of $Ti(OEt)_4$ in THF at 70 °C furnished sulfinyl imins **7**.[37,38] Imine derivative **7** was reduced with $NaBH_4$ in a mixture of THF and water at -50 °C to afford a mixture (3:1) of diastereomeric sulfonamides **8** and **9** in 78% combined yield. The diastereomers were separated by silica gel chromatography to



Scheme 1. 4-Aminothiochromane-6-carboxylic acid.

provide *R*-sulfinyl inamide **8** as the major product. Sulfinamide **8** was treated with HCl (6 M solution in isopropanol) in methanol at 23 °C for 1 h to provide the corresponding amine hydrochloride salt. Reaction of this amine salt in CH_2Cl_2 with Boc_2O in the presence of triethylamine afforded Boc- protected amine derivative **10**. Saponification of the ethyl ester with aqueous LiOH provided carboxylic acid **11**. For the synthesis of the enantiomeric amine

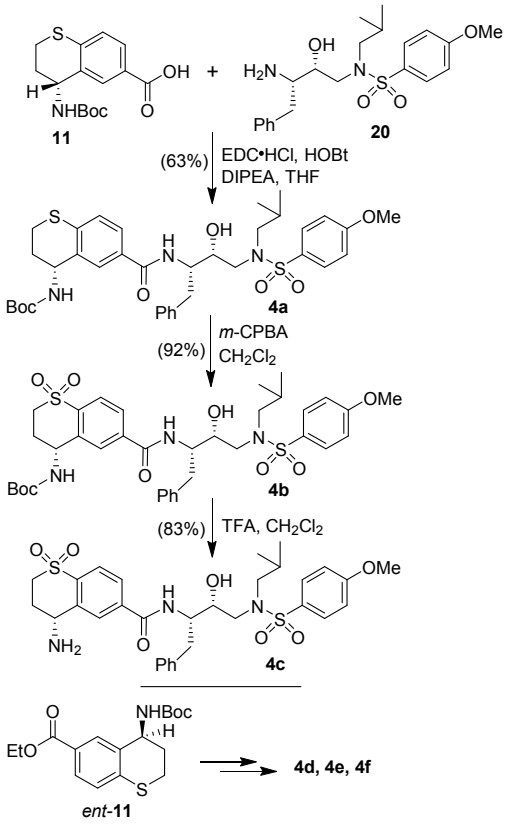


Scheme 2. Synthesis of 8-amino-5-hydroxy-tetrahydronaphthalene-2-carboxylic acid.

derivative *ent*-**11** (enantiomer of compound **11**), 4-oxochromane derivative **6** was reacted with commercially available (*S*)-(-)-2-methyl-2-propane sulfinamide to obtain the corresponding imine which was reduced with $NaBH_4$ to provide mixture of diastereomers. Separation of diastereomers followed by reaction of the major isomers with 6 M HCl, and protection of amine as a *Boc*-derivative, and aqueous LiOH hydrolysis as described above resulted in enantiomeric acid *ent*-**11**.

The synthesis of optically active amino-hydroxytetrahydronaphthalene carboxylic acids is shown in Scheme 2. Commercially available bromotetralone **12** was reacted with (*R*)-(+)-2-methyl-2-propane sulfinamide in the presence of $Ti(OEt)_4$ in THF at 66 °C for 10 h to provide sulfinyl imine **13** in 87% yield. Reduction of **13** with $NaBH_4$ in a mixture of (98:2) THF and water at -50 °C to 23 °C for 3 h provided **14** and **15** in 2:1 ratio in 94% combined yield. The diastereomeric sulfinamides were separated by silica gel chromatography using 30% ethyl acetate in hexanes as the eluent. Reduction of **13** with L-selectride at 0 °C to 23 °C for 3 h afforded only disatereomer **15** in 96% yield.

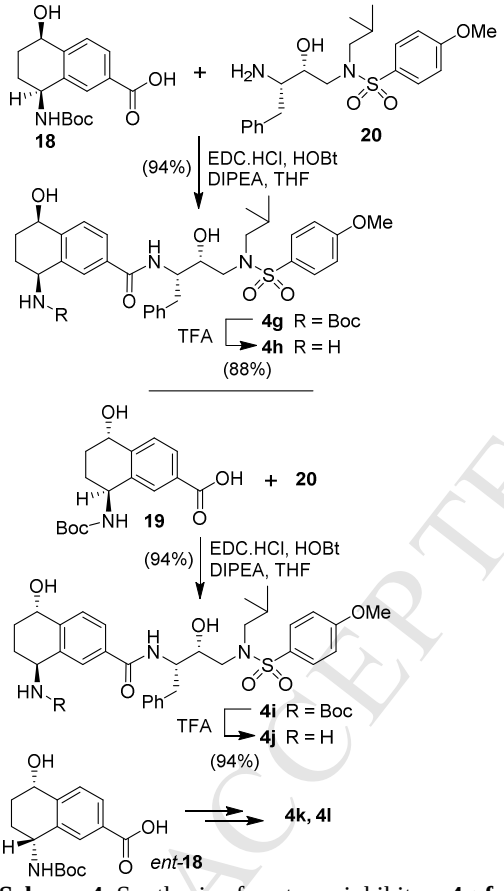
Treatment of sulfinamide **15** with HCl (6M solution in isopropanol) in methanol at 23 °C for 2.5 h afforded the corresponding amine which was reacted with Boc_2O in the presence of Et_3N in CH_2Cl_2 at 0 °C to 23 °C for 12 h to provide optically active Boc-derivative **16** in 85% yield over two-steps. For introduction of the 5-hydroxyl group, Boc-amine derivative **16** was oxidized using $KMnO_4$ in the presence of $MgSO_4$ in acetone at 0 °C to 23 °C for 8 h to furnish the corresponding bromoketone derivative in 61% yield. Treatment of the resulting bromoketone in methanol in the presence of catalytic amount $Pd(OAc)_2$, (2 mol%) xantphos (4 mol%) and excess of Et_3N under a CO-filled balloon at 70 °C for 3.5 h provided methyl ester derivative **17** in 80% yield.[39] Ketoester **17** was converted to the corresponding Boc-aminoalcohol derivative by a catalytic transfer hydrogenation reaction using the Noyori catalyst RuCl(*Mes*)[*R*,*R*-ts-dpen] in DMF in the presence of formic acid and Et_3N at 60 °C for 12 h to afford the corresponding alcohol as a single diastereomer in 94% yield.[40,41] Saponification of the resulting methyl ester with 1N aqueous LiOH in THF in the presence of a few drops of MeOH at 23 °C for 12 h afforded carboxylic acid **18** in 89% yield. Furthermore, reduction of ketoester **17** with RuCl(*p*-Cym)[*S*,*S*-ts-dpen] under the same reaction conditions mentioned above, provided the diastereomeric alcohol as a single diastereomer in 93% yield. Basic ester hydrolysis furnished ligand acid **19**. The synthesis of enantiomeric ligand carboxylic acid *ent*-**18** was carried out from commercially available methyl 8-oxo-5,6,7,8-tetrahydronaphthalene-2-



Scheme 3. Synthesis of protease inhibitors **4a-f**.

carboxylate and (*S*)-*t*-butyl sulfinamide to provide imine which was reduced with $NaBH_4$ to obtain a mixture (2:1) of diastereomers. The major diastereomer was was treated with 6 M HCl to provide the corresponding amine. Protection of the resulting amine as Boc-derivative. This was converted to carboxylic acid *ent*-**18** by following the same sequence of reactions as described above.

The synthesis of various inhibitors containing the (*R*)-hydroxyethylaminesulfonamide isostere and various thiochromane derivatives as the P2-ligand is shown in Scheme 3. Optically active thiochromane carboxylic acid **11** with the known aminoalcohol **20**[25,26] was reacted with EDC and HOBt in the presence of diisopropyl-ethylamine (DIPEA) in THF at 23 °C for 8 h to furnish inhibitor **4a** in 63% yield. Oxidation of thiochromane derivative **4a** with mCPBA in CH_2Cl_2 at 0 °C to 23 °C for 6 h afforded sulfone derivative **4b** in 92% yield. Treatment of **4b** with trifluoroacetic acid (TFA) in CH_2Cl_2 at 23 °C for 3 h furnished the amine derivative **4c** in 83% yield. Enantiomeric ligand acid *ent*-**11** was converted to inhibitors **4d-f** as described above. The full structures of these inhibitors are shown in Table 1.



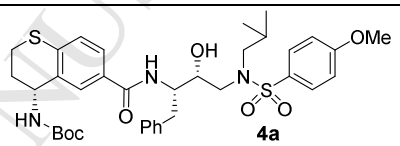
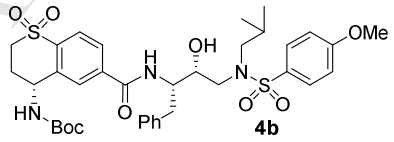
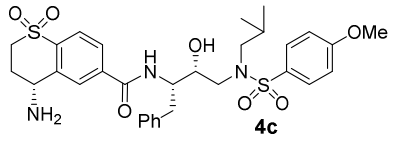
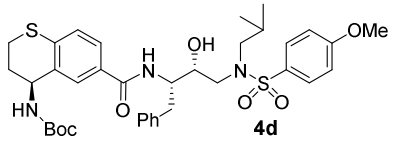
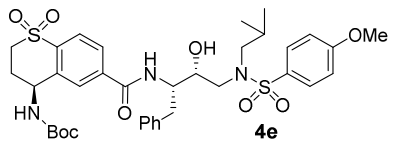
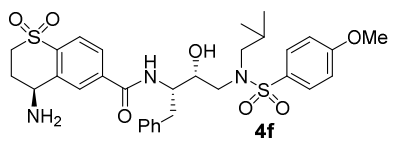
Scheme 4. Synthesis of protease inhibitors **4g-f**.

The synthesis of various aminotetrahydronapthalene derivatives as the P2 ligands is shown in Scheme 4. Coupling of acid containing Boc-aminoalcohol derivative **18** with amine **20** using EDCI and HOBt in the presence of DIPEA in THF to provide inhibitor **4g**. Removal of Boc-group by exposure to TFA in CH_2Cl_2 at 23 °C for 3 h provided inhibitor **4h** with aminoalcohol functionalities. Coupling of diastereomeric ligand acid **19** with amine **20** under similar coupling conditions afforded inhibitor **4i**. Removal of the Boc group with TFA provided inhibitor **4j**. The corresponding enantiomeric ligand *ent*-**19** was then converted to inhibitors **4k** and **4l** as described above. The full structures of these inhibitors are shown in Table 2.

2.2 HIV-1 Protease inhibitory and antiviral activity

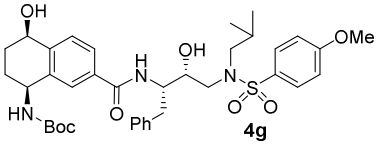
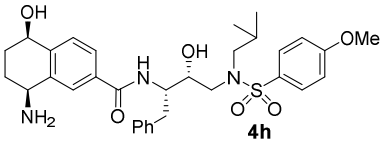
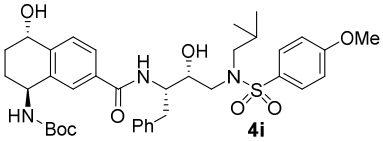
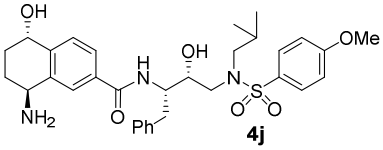
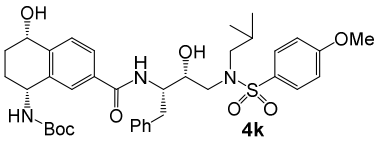
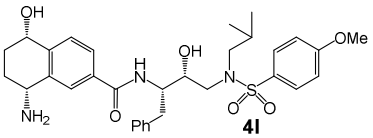
Our preliminary model of inhibitor **4a** that we created in the Nelfinavir-bound HIV-1 protease active site,[35] indicated that the thiochroman heterocycle with (*S*)-Boc-amine functionality can interact with Asp29 and Asp30 backbone NHs in the S2 subsite, while the thiochroman moiety would fill the hydrophobic pocket. The results of HIV-1 protease inhibitory K_i and antiviral IC_{50} values are shown in Table 1. The assay protocol for HIV-1 protease activity is similar to the report of Toth and Marshall.[42] Antiviral activity was determined in MT-4 human T-lymphoid cells exposed to HIV-1_{NL4-3} (subtype B) as described by us previously.[11] We chose to utilize a hydroxyethylaminesulfonamide isostere with 4-methoxybenzene sulfonamide as the P2' ligand as in inhibitor **2**. As can be seen, inhibitor **4a** with 4-(*R*)-aminothiochroman carboxamide as the P2 ligand, showed a HIV-1 protease inhibitory K_i of 26.7 nM, but did not show any appreciable antiviral activity

Table 1. Structures and potency of inhibitors **4a-f**.[a,b]

Entry	Inhibitor Structure	K_i (nM)	IC_{50} (nM)
1	 **4a**	26.7	>1000
2	 **4b**	0.10	476
3	 **4c**	18	>1000
4	 **4d**	0.38	>1000
5	 **4e**	0.008	47
6	 **4f**	15.8	>1000

[a] All antiviral assays were performed using MT-4 cells and HIV_{NL4-3} (subtype B). Values are the mean value of at least two experiments. [b]The IC_{50} values of amprenavir (APV), saquinavir (SQV), indinavir (IDV), and darunavir (DRV) were 0.03, 0.015, 0.03, and 0.003 μM, respectively.

Table 2. Structures and potency of inhibitors **4g-l**.[a,b]

Entry	Inhibitor Structure	K_i (nM)	IC_{50} (nM)
1	 **4g**	0.3	>1000
2	 **4h**	17	>1000
3	 **4i**	0.14	254
4	 **4j**	0.06	232
5	 **4k**	1.63	>1000
6	 **4l**	1.10	>1000

[a] All antiviral assays were performed using MT-4 cells and HIV_{NL4-3} (subtype B). [b] The IC_{50} values of amprenavir (APV), saquinavir (SQV), indinavir (IDV), and darunavir (DRV) were 0.03, 0.015, 0.03, and 0.003 μM, respectively.

(IC_{50} > 1 μM). Since sulfone oxygens are known[43,44] to form strong bonding interactions, we oxidized the ring sulfur to its sulfone derivative. The resulting inhibitor **4b** showed improvement of potency, exhibiting enzyme K_i of 0.1 nM. It also exhibited improvement of antiviral activity with an IC_{50} value of 476 nM (entry 2). The removal of the Boc-group provided 4-amine derivative **4c** which displayed significant loss of activity (entry 3). We then examined stereochemical effect and inhibitor **4d** with a 4-(*S*)-aminothiochroman carboxamide as the P2 ligand showed potent enzyme inhibitory activity with a K_i of 0.38 nM. However, inhibitor **4d** did not exhibit appreciable antiviral activity (IC_{50} > 1 μM). We oxidized the ring sulfur to its sulfone derivative **4e**. This led to significant improvement of enzyme inhibitory activity with a K_i of 8 pM (entry 5). Inhibitor **4e** also showed very good antiviral activity (IC_{50} = 47 nM). We presume that the improvement of activity is due to formation of a hydrogen bond through one of the sulfone oxygens of the P2 ligand. Removal of the Boc-group provided inhibitor **4f**, which showed substantial loss of enzyme inhibitory and antiviral activity similar to inhibitor **4c** (entries 3 and 6). In general, this series of inhibitors showed low cytotoxicity (CC_{50}) values in MT4 cells. The selectivity index of selected inhibitors are shown in Table 3.

Table 3. Selectivity Index for selected inhibitors.[a]

Inhibitor	CC_{50} (μM)	Selectivity Index[a]
4b	>100	>210
4e	>100	>2128
4i	33.3	131
4j	35.1	151

[a] Each selectivity index denotes a ratio of CC_{50} to IC_{50}.

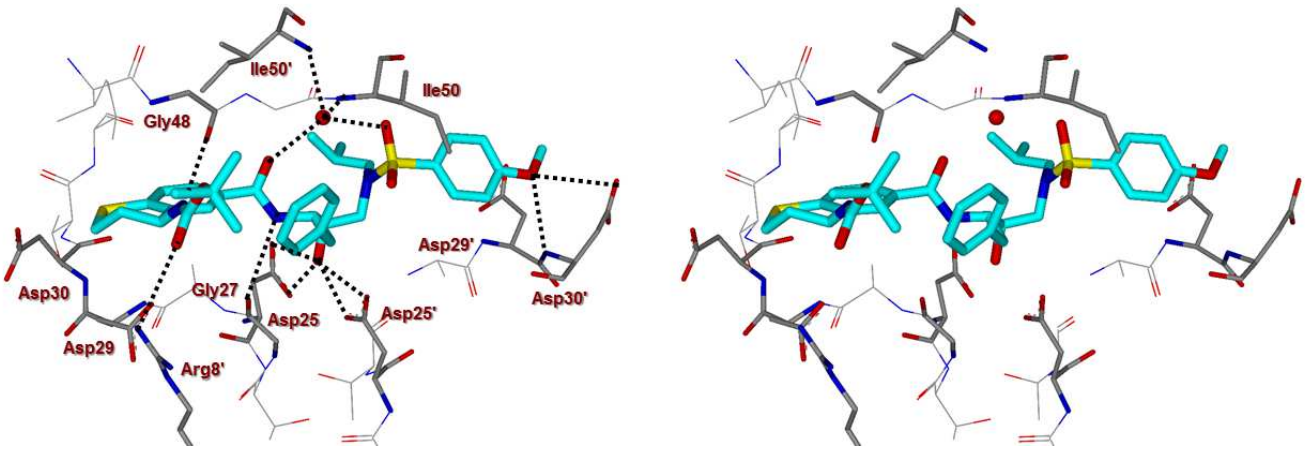


Figure 2. Stereoview of the X-ray structure of inhibitor **4d** (turquoise)-bound HIV-1 protease (PDB code: 6DV0). All strong active site hydrogen bonding interactions of inhibitor **4d** with HIV-1 protease are shown as dotted lines.

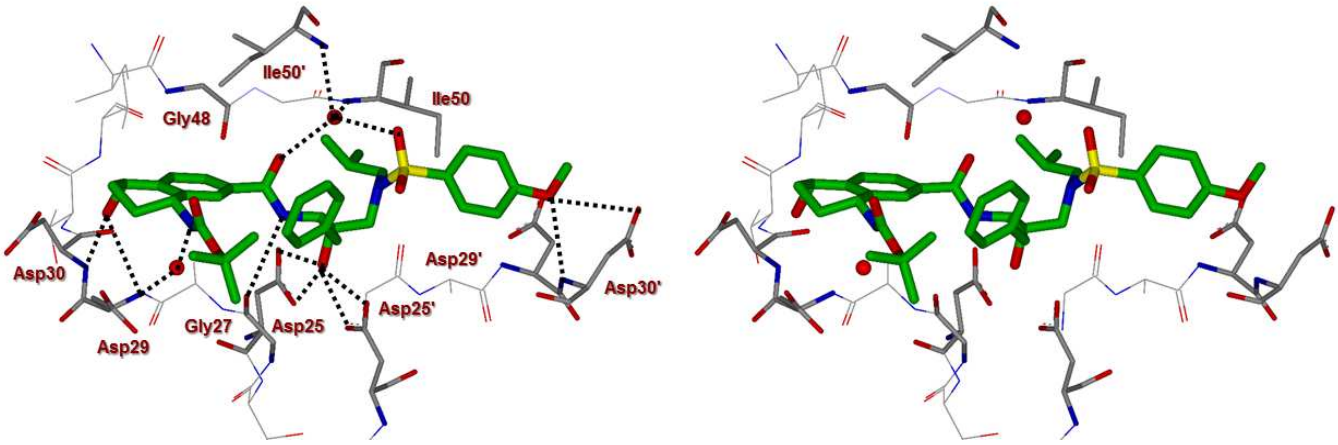


Figure 3. Stereoview of the X-ray structure of inhibitor **4k** (green)-bound HIV-1 protease (PDB code: 6DV4). All strong active site hydrogen bonding interactions of inhibitor **4k** with HIV-1 protease are shown as dotted lines.

Since both sulfone derivatives **4b** and **4e** are significantly more potent than the corresponding sulfides **4a** and **4d**, we speculated that one of the sulfone oxygens may have formed hydrogen bonding interactions with a residue in the active site. We, therefore, designed tetrahydronapthalene carboxamide derivatives with aminoalcohol substitution on the ring to mimic the interactions of Boc-amine and sulfone functionalities of inhibitor **4e**. The results are shown in Table 2. Inhibitor **4g** with a (*R*)-hydroxy derivative as the P2 ligand showed good enzyme activity, but antiviral activity was > 1 μM. The corresponding amine derivative **4h** is significantly less potent (entry 2). The 4(*S*)-hydroxy derivative **4i** showed improvement of both enzyme inhibitory and antiviral activity with an IC_{50} value of 254 nM. The corresponding aminoalcohol derivative **4j** exhibited 1-fold improvement in enzyme activity, but showed comparable antiviral activity to its Boc-derivative **4i**. We also examined the stereochemical effect of the Boc derivative **4k** and the corresponding amine derivative **4l**. Both compounds were less potent.

2.3 X-Ray Crystal structure of inhibitor-bound HIV-1 protease

To obtain molecular insight into the ligand-binding site interactions, we set up co-crystallization experiments with several inhibitors and HIV-1 protease.[45] The X-ray structures were obtained for the wild-type HIV-1 protease co-crystallized independently with inhibitors **4d** (GRL-02815A) and **4k (**GRL-04315A) and were refined to a resolution of 1.20 Å and 1.14 Å, respectively. The protease dimer structures were very similar to the darunavir-bound HIV-1 protease complex[15] with a RMSD of 0.15 Å for 198 equivalent Cα atoms, and the largest disparity of around 0.4-0.6 Å. In both structures, the active site of the protease dimer was occupied by two alternate conformations of inhibitor related by 180º rotation with a relative occupancy of 0.60/0.40. The two inhibitor conformations show similar interactions with the protease, hence details are given for the major conformation. With the exception of the P2 ligand, both inhibitors retain the hydrogen bonds observed between darunavir and the main chain atoms of protease. These inhibitors have distinctly different P2 ligands from the bis-tetrahydrofuran in darunavir. Inhibitor **4d** contains a thiochroman heterocycle with (*S*)-Boc-amine functionality as the P2 ligand and a stereoview of the active site interactions is shown in **Figure 2**. Inhibitor **4k**, on the other hand, contains a tetrahydronaphthalene carboxamide with (*R*)-Boc-amine and (*S*)-hydroxyl functionalities as the P2 ligand and a stereoview of the active site interactions is shown in **Figure 3**.

In inhibitor **4d**-bound HIV-1 protease structure, the bulky sulfur atom in the thiochroman group provides hydrophobic interactions with the side chains of Asp29, Asp30 and Ile47. The amide of the carbamate group forms a hydrogen bond of 2.6 Å length with the carbonyl oxygen atom of Gly48 in the flap, and carbonyl oxygen forms a hydrogen bond of 3.4 Å with NH_2 moiety of guanidinium side chain of Arg8'. As can be seen from the X-ray structure of **4d**, the significant improvement of enzyme inhibitory and antiviral activity of the corresponding sulfone derivative **4e** could be due to formation of hydrogen bonding interactions of the sulfone oxygens with the backbone NH's of Asp29 and Asp30 located in the S2 subsite. The *t*-butyl group forms van der Waals interactions with the hydrophobic side chains of Pro81, Val82 and Phe53. In the inhibitor **4k**-HIV-1 protease complex, the hydroxyl oxygen on the cyclohexane ring is in an equivalent location to the methoxy oxygen of the P2′ ligand and forms similar hydrogen bonds with the main chain amides of Asp29 and Asp30 with bond lengths of 3.5 Å and 3.1 Å, respectively, and a 2.8 Å-long hydrogen bond with the carboxylate oxygen of the Asp30 side chain. The different chiral orientation relative to inhibitor **4d** shifts the carbamate away from the flap residue Gly48. The carbamate amide and carbonyl oxygen can only form hydrogen bonds via one or two water intermediates to the amide atom of Asp29 and main chain oxygen and amide of Gly49, respectively. The terminal *t*-butyl group embeds between the side chains of Arg8', Pro81 and Val82, forming a C-H...π interaction with the guanidinium group of Arg8' and van der Waals interactions with Pro81 and Val82. These differences in the P2 group may contribute to the inhibitor potency against HIV-1 protease.

3. Conclusion

In summary, we have reported the structure-based design and synthesis of a series of HIV-1 protease inhibitors incorporating stereochemically defined amino-thiochroman and aminotetrahydronaphthalene carboxamide derivatives as the P2 ligands. We have investigated various stereoisomers in order to promote effective hydrogen bonding interactions with backbone atoms in the S2 subsite. These functionalized ligands were

synthesized stereoselectively in optically active form by reduction of chiral sulfinamide derivatives. Also, Noyori transfer hydrogenation using chiral ruthenium catalyst provided selective reduction of the 8-amino-5-tetralone derivatives to the corresponding 5-hydroxy-naphthalene derivatives. Amide derivatives of these ligands on a hydroxyethylamine sulfonamide isostere provided potent inhibitors. Inhibitors **4e** and **4j** exhibited very potent enzyme inhibitory activity in the picomolar range. These inhibitors have also shown very good antiviral activity. To obtain molecular insights into the ligand-binding site interactions, we determined high resolution X-ray crystal structures of related inhibitors **4d** and **4k**-bound HIV-1 protease. The structures show key interactions of amino-thiochroman and amino-tetrahydronaphthalene ligands in the S2 subsite. Both amine functionalities formed strong hydrogen bonds with the Asp30 backbone NH. This may explain the high enzyme inhibitory activity of these inhibitors. Further design and ligand optimization using X-ray structural insights are currently underway in our laboratories.

4. Experimental Section

4.1. General experimental conditions

All moisture-sensitive reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise stated. Anhydrous solvents were obtained as follows: Diethyl ether and tetrahydrofuran were distilled from sodium metal/benzophenone under argon. Toluene and dichloromethane were 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 F_{254} plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA300, Bruker ARX400, Bruker DRX500, or Bruker AV-III-500-HD. Low-resolution mass spectra were collected on a Waters 600 LCMS or by the Purdue University Campus-Wide Mass Spectrometry Center. High-resolution mass spectra were collected by the Purdue University Campus-Wide Mass Spectrometry Center. HPLC analysis and purification was done an on Agilent 1100 series instrument using a YMC Pack ODS-A column of 4.6 mm ID for analysis and either 10 mm ID or 20 mm ID for purification. The purity of all test compounds was determined by HPLC analysis to be ≥95% pure.

4.2 Synthesis of inhibitors

Methyl 4-oxothiochromane-6-carboxylate (6)

A mixture of 3-bromopropionic acid (0.91 g, 5.95 mmol) and *p*-(carbomethoxy)thio-phenol (1 g, 5.95 mmol) was placed in a round-bottom flask. The flask was heated slowly with the aid of an oil bath. When the mixture melted, giving a homogeneous solution, pyridine (0.96 mL, 11.90 mmol) was added and the reaction was allowed to proceed under an atmosphere of nitrogen at 80 ^{o}C for 1 h. After this period, the product was dissolved in ethyl acetate and extracted repeatedly with aqueous bicarbonate. Acidification of the bicarbonate layer afforded 3-((4-(methoxycarbonyl)phenyl)thio)propanoic acid (982 mg, 69%) as an amorphous crystals. LRMS-ESI *(m/z)*: 241 $[M+H]^+$.

To the above 3-((4-(methoxycarbonyl)phenyl)-thio)propanoic acid (200 mg, 0.832 mmol), 1.5 g of polyphosphoric acid was added and the resulting mixture was stirred at 65 °C for 6 h. After this period, the reaction mixture was allowed to cool to room temperature and quenched by the addition of cold water and extracted with ethyl acetate (3×25 mL). The organic layer was washed with saturated aq. $NaHCO_3$ solution, water, saturated aq. NaCl solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give **6** (141 mg, 76 %) as a yellow solid. R_f = 0.4 (30% EtOAc/hexanes). LRMS-ESI *(m/z)*: 223 $[M+H]^+$.

Ethyl (*S*,*E*)-4-((*tert*-butylsulfinyl)imino)thiochromane-6-carboxylate (7)

To a stirred solution of **6** (435 mg, 1.92 mmol) in THF (18 mL) was added $Ti(OEt)_4$ (1.0 mL, 4.805 mmol). The solution was stirred at ambient temperature for 5 min before addition of (*R*)-(+)-2-methyl-2-propanesulfinamide (291 mg, 2.4 mmol). Then reaction mixture refluxed for 12 h. The reaction mixture was cooled to room temperature and concentrated in *vacuo*, diluted with EtOAc (35 mL). Saturated $NaHCO_3$ (17 mL) was added under vigourous stirring and the slurry was filtered through a pad of celite. The organic phase was separated, dried over Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography (30% EtOAc/hexanes) to furnish **7** (500 mg, 76%). R_f = 0.3 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 2.0 Hz, 1H), 7.91 (dt, *J* = 8.3, 2.0 Hz, 1H), 7.28 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.77 – 3.61 (m, 1H), 3.50 (ddd, *J* = 16.9, 6.7, 5.5 Hz, 1H), 3.14 (dd, *J* = 7.1, 5.6 Hz, 2H), 1.38 (t, *J* = 7.3 Hz, 3H), 1.35 (s, 9H); LRMS-ESI *(m/z)*: 340 $[M+H]^+$.

Ethyl (*R*)-4-(((*R*)-*tert*-butylsulfinyl)amino)thiochromane-6-carboxylate (8) and Ethyl (*S*)-4-(((*R*)-*tert*-butylsulfinyl)amino)thiochromane-6-carboxylate (9)

To a srirred solution of **7** (400 mg, 1.22 mmol) in THF/H_2O (4 mL, 98:2) was added $NaBH_4$ (139 mg, 3.68 mmol) at -50 ^{o}C. The resulting solution was warmed to room temperature over 3 h. The solvent was then removed in *vacuo* and the resulting residue was triturated with CH_2Cl_2. The solution was dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo* to furnish a crude product. The crude product was purified by flash column chromatography over silica gel (30% ethyl acetate/hexanes) to furnish **8** (250 mg, 60%) and **9** (76 mg, 18%).

Compound 8

R_f = 0.4 (50% EtOAc/hexanes); $[\alpha]_D^{23}$ = -14.4 (*c* 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 1.9 Hz, 1H), 7.77 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 4.56 (dt, *J* = 10.2, 5.5 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.49 (d, *J* = 9.2 Hz, 1H), 3.21 – 3.06 (m, 2H), 2.43 (qd, *J* = 6.2, 5.4, 2.7 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.27 (s, 9H); LRMS-ESI *(m/z)*: 342 $[M+H]^+$.

Compound 9

R_f = 0.3 (50% EtOAc/hexanes); $[\alpha]_D^{23}$ = +32.2 (c 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.9 Hz, 1H), 7.81 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 4.69 (d, *J* = 4.7 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.34 (td, *J* = 12.7, 3.0 Hz, 1H), 3.17 (s, 1H), 2.85 (dt, *J* = 12.4, 4.0 Hz, 1H), 2.58 (dq, *J* = 14.5, 3.9 Hz, 1H), 2.07 – 1.93 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 9H). LRMS-ESI *(m/z)*: 342 $[M+H]^+$.

Ethyl (*R*)-4-((*tert*-butoxycarbonyl)amino)thiochromane-6-carboxylate (10)

To a solution of **8** (350 mg, 1.02 mmol) in MeOH (10 mL) was

added 6 M HCl in Isopropanol (4mL) at 23 °C under argon atmosphere. The reaction mixture was stirred at 23 °C for 1 h. After this period, the solvent was removed under reduced pressure to afford the desired amine salt. Thus obtained amine salt and Et_3N (0.46 mL, 3.20 mmol) were dissolved in CH_2Cl_2 (5 mL), cooled to 0 °C and di-*tert*-butyldicarbonate (349 mg, 1.60 mmol) was added and allowed to warm to 23 °C. After stirring for 12 h, the reaction was diluted with CH_2Cl_2 and washed with water, brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford **10** (347 mg, 99% over two steps). R_f = 0.3 (10% EtOAc/hexanes); $[\alpha]_D^{23}$ = +36.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.9 Hz, 1H), 7.77 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 4.89 (s, 1H), 4.75 (s, 1H), 4.35 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.13 (td, *J* = 11.8, 10.6, 3.1 Hz, 1H), 3.07 – 2.98 (m, 1H), 2.39 (s, 1H), 2.09 (td, *J* = 10.5, 3.5 Hz, 1H), 1.49 (s, 10H), 1.38 (t, *J* = 7.1 Hz, 3H). LRMS-ESI *(m/z)*: 355 $[M+NH_4]^+$.

(*R*)-4-((*tert*-Butoxycarbonyl)amino)thiochromane-6-carboxylic acid (11)

A solution of **10** (364 mg, 1.08 mmol) in THF: MeOH (6 mL, 2:1) was treated with 1N LiOH solution (1.62 mL, 1.62 mmol). The resulting mixture was stirred for 12 h, and then concentrated under reduced pressure. The residue was dissolved in water and acidified with citric acid then extracted with ethyl acetate (3×20 mL). The combined ethyl acetate layer was dried over Na_2SO_4, filtered, and concentrated to give carboxylic acid **11** (280 mg, 84%). R_f = 0.5 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = +33.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.82 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 4.91 (s, 1H), 4.78 (s, 1H), 3.14 (t, *J* = 11.5 Hz, 1H), 3.04 (ddd, *J* = 12.7, 6.5, 3.6 Hz, 1H), 2.39 (s, 1H), 2.18 – 2.06 (m, 1H), 1.49 (s, 9H). LRMS-ESI *(m/z)*: 332 $[M+Na]^+$.

Ethyl (*S*)-4-((*tert*-butoxycarbonyl)amino)thiochromane-6-carboxylate (*ent*-10)

Compound *ent*-**10** (50 mg, 68%) was synthesized from *ent*-**8** (75 mg, 0.21 mmol) by following the procedure outlined for compound **10**. R_f = 0.2 (10% EtOAc/hexanes); $[\alpha]_D^{23}$ = -37.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.9 Hz, 1H), 7.77 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 4.89 (s, 1H), 4.75 (s, 1H), 4.35 (q, *J* = 7.1, 1.4 Hz, 2H), 3.12 (td, *J* = 11.8, 10.6, 3.2 Hz, 1H), 3.06 – 2.97 (m, 1H), 2.38 (s, 1H), 2.18 – 2.03 (m, 1H), 1.48 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H). LRMS-ESI *(m/z)*: 360 $[M+Na]^+$.

(*S*)-4-((*tert*-Butoxycarbonyl)amino)thiochromane-6-carboxylic acid (*ent*-11)

Compound *ent*-**10** (120 mg, 0.37 mmol) was treated with 1N LiOH (0.55 mL, 0.55 mmol) by following the procedure outlined for compound **11** to give compound *ent*-**11** (75 mg, 66%). R_f = 0.5 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = -36.6 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.81 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 4.91 (s, 1H), 4.77 (s, 1H), 3.12 (d, *J* = 11.2 Hz, 1H), 3.07 – 2.98 (m, 1H), 2.39 (s, 1H), 2.18 – 2.06 (m, 1H), 1.49 (s, 9H); LRMS-ESI *(m/z)*: 332 $[M+Na]^+$.

***tert*-Butyl ((*R*)-6-(((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamoyl)thiochroman-4-yl)carbamate (4a)**

To a solution of **11** (85 mg, 0.27 mmol) and HOBt (56 mg, 0.41 mmol) in anhydrous THF (5 mL) at 0 °C was added EDC.HCl (58 mg, 0.30 mmol) and stirred at 23 °C for 1 h. An isostere amine **20** (112 mg, 0.27 mmol) and DIPEA (0.1 mL, 0.54 mmol) in THF (3 mL) was added and resulting mixture was stirred for 8 h at 23 °C. The reaction mixture was extracted with ethyl acetate and successively washed with 5% citric acid, sat $NaHCO_3$, brine solution, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography over silica gel (30% EtOAc/hexanes) to afford inhibitor **4a** (120 mg, 63%). R_f = 0.3 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ = +22.0 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 6.7 Hz, 2H), 7.57 (d, *J* = 5.4 Hz, 1H), 7.29 (m, 4H), 7.21 (m, 1H), 7.10 – 7.05 (m, 1H), 6.93 (t, *J* = 7.5 Hz, 2H), 6.48 (d, *J* = 8.6 Hz, 1H), 4.79 (m, 2H), 4.40 – 4.17 (m, 2H), 3.98 (s, 1H), 3.85 (s, 3H), 3.24 – 2.90 (m, 6H), 2.89 – 2.73 (m, 2H), 2.35 (d, *J* = 9.5 Hz, 1H), 2.04 (d, *J* = 12.3 Hz, 1H), 1.91 – 1.67 (m, 2H), 1.51 – 1.34 (m, 9H), 0.85 (t, *J* = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.52, 163.14, 154.95, 138.99, 137.99, 133.15, 129.92, 129.52, 129.00, 128.79, 126.88, 126.79, 126.08, 114.46, 80.15, 73.00, 58.93, 55.75, 54.86, 53.60, 48.10, 35.15, 28.52, 28.25, 27.34, 22.99, 20.24, 20.14; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{48}N_3O_7S_2$, 698.2928; found 698.2925.

***tert*-Butyl ((*R*)-6-(((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamoyl)-1,1-dioxidothiochroman-4-yl)carbamate (4b)**

To a solution of inhibitor **4a** (50 mg, 0.07 mmol) in dichloromethane (1 mL), 3- chloroperbenzoic acid (26 mg, 0.15 mmol) was added slowly at 0 °C under argon atmosphere. The reaction was stirred for 6 h at 23 °C. The reaction mixture was diluted with dichloromethane and washed with sat. Na_2CO_3 solution and brine. The organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude residue was purified by flash column chromatography over silica gel to afford inhibitor **4b** (48 mg, 92%). R_f = 0.3 (60% EtOAc/hexanes); $[\alpha]_D^{23}$ = -11.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.70 (m, 2H), 7.70 – 7.62 (m, 2H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.29– 7.26 (m, 4H), 7.20 (m, 1H), 7.00 – 6.91 (m, 3H), 5.20 (d, *J* = 8.5 Hz, 1H), 4.98 (s, 1H), 4.42 (s, 1H), 4.06 (dt, *J* = 12.0, 4.8 Hz, 1H), 3.86 (s, 3H), 3.50 (t, *J* = 11.5 Hz, 1H), 3.37 (t, *J* = 10.9 Hz, 1H), 3.11 (dt, *J* = 21.0, 7.4 Hz, 4H), 2.87 (dt, *J* = 10.1, 5.2 Hz, 2H), 2.70 – 2.47 (m, 2H), 1.87 (m, 1H), 1.47 (s, 9H), 0.86 (dd, *J* = 6.7, 3.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.26, 163.24, 155.10, 138.40, 137.88, 137.05, 130.25, 129.84, 129.54, 129.42, 128.79, 128.27, 127.44, 126.86, 124.18, 114.54, 80.64, 72.86, 60.54, 58.92, 55.79, 54.92, 53.42, 48.15, 47.72, 35.03, 28.46, 27.84, 27.33, 21.19, 20.24, 20.13, 14.32; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{48}N_3O_9S_2$, 730.2827; found 730.2824.

(*S*)-4-Amino-*N*-((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)thiochromane-6-carboxamide 1,1-dioxide (4c)

To a stirred solution of inhibitor **4b** (25 mg, 0.034 mmol) in dichloromethane (1.0 mL) was added TFA (0.1 mL) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred at for 3 h. Upon completion, solvent was removed under reduced pressure. The residue was extracted with dichloromethane and washed with sat. NaHCO3 solution, brine, dried over Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by column chromatography over silica gel to give inhibitor **4c** (18 mg, 83%) as an amorphous solid. R_f = 0.2 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = -13.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.74 (m,

2H), 7.69 – 7.63 (m, 2H), 7.56 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.29 – 7.23 (m, 4H), 7.19 (m, 1H), 6.95 (dd, *J* = 8.4, 5.4 Hz, 3H), 4.40 (tt, *J* = 9.4, 5.0 Hz, 1H), 4.15 (dd, *J* = 7.1, 4.3 Hz, 1H), 4.05 (dt, *J* = 8.3, 4.3 Hz, 1H), 3.85 (s, 3H), 3.67 (ddd, *J* = 13.4, 9.8, 3.0 Hz, 1H), 3.37 – 3.24 (m, 1H), 3.22 – 2.99 (m, 4H), 2.87 (d, *J* = 7.5 Hz, 2H), 2.65 (dt, *J* = 20.3, 6.8 Hz, 1H), 2.38 – 2.26 (m, 2H), 1.87 (m, 1H), 0.85 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.71, 163.13, 142.56, 138.11, 137.26, 130.04, 129.54, 129.47, 128.68, 126.71, 114.46, 72.90, 60.51, 58.73, 55.75, 54.95, 53.48, 48.12, 44.11, 34.91, 28.56, 28.47, 27.28, 22.25, 21.73, 20.24, 20.13; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{40}N_3O_7S_2$, 630.2302; found 630.2298.

tert-Butyl ((*S*)-6-(((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamoyl)thiochroman-4-yl)carbamate (4d)

Compound *ent*-**11** (65 mg, 0.21 mmol) was treated with isostere amine **20** (85 mg, 0.21 mmol) by following the procedure outlined for inhibitor **4a** to give inhibitor **4d** (117 mg, 80%) as an amorphous solid. R_f = 0.2 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ = -6.5 (*c* 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.54 (s, 1H), 7.27 (d, *J* = 4.6 Hz, 3H), 7.24 (s, 1H), 7.19 (m, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.43 (d, *J* = 8.4 Hz, 1H), 4.78 (s, 2H), 4.32 (m, 1H), 3.96 (s, 1H), 3.84 (s, 3H), 3.22 – 2.91 (m, 6H), 2.85 (d, *J* = 7.5 Hz, 1H), 2.33 (s, 1H), 2.03 (d, *J* = 9.7 Hz, 1H), 1.83 (m, 1H), 1.72 (m, 1H), 1.45 (s, 9H), 0.84 (t, *J* = 5.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.80, 163.44, 155.25, 139.27, 138.28, 133.42, 130.32, 129.88, 129.10, 127.21, 127.13, 126.50, 114.78, 80.51, 73.21, 59.24, 56.08, 55.04, 53.96, 48.40, 35.43, 28.87, 28.53, 27.67, 23.27, 20.56, 20.44; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{48}N_3O_7S_2$, 698.2928; found 698.2920.

tert-Butyl ((*S*)-6-(((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamoyl)-1,1-dioxidothiochroman-4-yl)carbamate (4e)

Inhibitor **4d** (25 mg, 0.035 mmol) was treated with *m*CPBA (13 mg, 0.075 mmol) by following the procedure outlined for compound **4b** to give compound inhibitor **4e** (26 mg, 96%) as an amorphous solid. R_f = 0.2 (60% EtOAc/hexanes); $[\alpha]_D^{23}$ = -8.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.58 (dd, *J* = 15.8, 8.3 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.30 – 7.26 (m, 4H), 7.19 (m, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.34 (s, 1H), 4.97 (s, 1H), 4.40 (dq, *J* = 9.6, 4.8 Hz, 1H), 4.06 (dt, *J* = 8.3, 4.6 Hz, 1H), 3.85 (s, 3H), 3.53 (ddd, *J* = 12.5, 8.8, 3.2 Hz, 1H), 3.36 (dd, *J* = 13.3, 8.0 Hz, 1H), 3.18 – 3.01 (m, 4H), 2.89 (dd, *J* = 7.7, 2.1 Hz, 2H), 2.70 – 2.49 (m, 3H), 1.88 (m, 1H), 1.49 (d, *J* = 5.0 Hz, 9H), 0.86 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.24, 163.21, 155.40, 141.03, 138.30, 137.96, 137.02, 133.68, 129.95, 129.56, 129.50, 128.75, 128.29, 127.45, 126.90, 124.00, 114.52, 80.96, 77.43 72.86, 58.84, 55.79, 54.85, 53.49, 48.04, 47.58, 34.94, 28.51, 27.32, 20.26, 20.11; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{36}H_{48}N_3O_9S_2$, 730.2827; found 730.2822.

(*S*)-4-Amino-*N*-((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)thiochromane-6-carboxamide 1,1-dioxide (4f)

Inhibitor **4f** (20 mg, 0.027 mmol) was treated with TFA (0.1 mL) by following the procedure outlined for inbitor **4c** to give inhibitor **4f** (16 mg, 93%) as an amorphous solid; R_f = 0.1 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = +13.7 (*c* 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.71 – 7.63 (m, 2H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 4.4 Hz, 4H), 7.20 (m, 1H), 6.99 – 6.91 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.46 – 4.33 (m, 1H), 4.16 (s, 1H), 4.05 (dt, *J* = 8.4, 4.2 Hz, 1H), 3.86 (s, 3H), 3.68 (ddd, *J* = 13.5, 9.6, 3.0 Hz, 1H), 3.38 – 3.24 (m, 1H), 3.13 (m, 4H), 2.88 (d, *J* = 7.5 Hz, 2H), 2.65 (t, *J* = 12.8 Hz, 1H), 2.41 – 2.28 (m, 1H), 1.87 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.45, 163.24, 140.49, 138.15, 137.92, 129.84, 129.56, 129.49, 128.79, 128.09, 126.93, 126.85, 124.19, 114.54, 77.41, 72.81, 58.89, 55.80, 54.84, 53.51, 48.12, 47.53, 35.00, 30.58, 27.31, 20.24, 20.15; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{40}N_3O_7S_2$, 630.2302; found 630.2294.

(*R*,*E*)-*N*-(7-Bromo-3,4-dihydronaphthalen-1(2*H*)-ylidene)-2-methylpropane-2-sulfinamide (13)

A mixture of 5-bromo-1-tetralone **12** (1.5 g, 6.66 mmol), (*R*)-(+)-2-methyl-2 propanesulfinamide (1.21 g, 9.99 mmol) and titanium (IV) ethoxide (3.01 g, 13.32 mmol) were dissolved in anhydrous THF (15 mL) and stirred at 66 °C for 10 h under argon atmosphere. The reaction mixture was cooled to 23 °C and ethyl acetate and aq sodium bicarbonate was added. The mixture was filtered through a pad of celite and the aqueous layer was extracted with ethyl acetate. The combined organic phase were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel (5% EtOAc/hexanes) to afford **13** (1.9 g, 87%). R_f = 0.5 (40% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.2 Hz, 1H), 7.48 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 3.27 (ddd, *J* = 17.6, 9.3, 4.8 Hz, 1H), 3.05 (ddd, *J* = 17.6, 7.5, 4.5 Hz, 1H), 2.81 (t, *J* = 6.2 Hz, 2H), 1.99 – 1.87 (m, 2H), 1.33 (d, *J* = 2.3 Hz, 9H).

(*R*)-*N*-((*R*)-7-Bromo-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methylpropane-2-sulfinamide (14)

Compound **13** (175 mg, 0.53 mmol) was dissolved in THF/H_2O (2 mL, 98:2) and cooled to -50 °C. To the mixture was then added $NaBH_4$ (61 mg, 1.59 mmol), and the resulting solution was warmed to 23 °C over a period of 3 h. The solvent was then removed in *vacuo*, and the resulting residue was triturated with dichloromethane, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.The crude product was purified by column chromatography over silica gel (30% EtOAc/hexanes) to afford **14** (110 mg, 63%) and **15** (55 mg, 31%). R_f = 0.4 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.1 Hz, 1H), 7.30 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 4.52 (q, *J* = 4.2 Hz, 1H), 3.21 (d, *J* = 3.7 Hz, 1H), 2.76 (dt, *J* = 17.0, 5.2 Hz, 1H), 2.70 – 2.57 (m, 1H), 2.08 – 1.97 (m, 1H), 1.96 – 1.81 (m, 2H), 1.79 – 1.70 (m, 1H), 1.22 (s, 9H).

(*R*)-*N*-((*S*)-7-Bromo-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methylpropane-2-sulfinamide (15)

Compound **13** (275 mg, 0.83 mmol) was dissolved in anhydrous THF (3 mL) and cooled to 0 °C. To this solution was then added L-Selectride (2.5 mL, 1.0 M in THF, 2.51 mmol) and the resulting solution was allowed to warm to 23 °C over period of 3 h. The solution was then concentrated under *vacuo* to furnish crude product. The crude residue was purified by column chromatography over silica gel (30% EtOAc/hexanes) to give **15** (265 mg, 96%). R_f = 0.3 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.1 Hz, 1H), 7.28 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 4.42 (q, *J* = 8.0, 7.4 Hz, 1H), 3.36 (d, *J* = 10.1 Hz, 1H), 2.80 – 2.56 (m, 2H), 2.40 – 2.24 (m, 1H), 1.96 –

1.73 (m, 3H), 1.28 (s, 9H).

***tert*-Butyl (*S*)-(7-bromo-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (16)**

A solution of **15** (1.2 g, 3.63 mmol) in MeOH (20 mL) was treated with 6 N HCl in isopropanol (5 mL). After 2.5 h, solvent was removed in *vacuo*, and the residue was co-evaporated with ethyl acetate. The residue obtained was dried under high vacuum to provide (*S*)-7-bromo-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride (0.94 g).

To a stirred solution of above amine hydrochloride (0.94 g, 3.6 mmol) in CH_2Cl_2 (30 mL) was consecutively added triethylamine (1.5 mL, 10.89 mmol) and di-*tert*-butyl-dicarbonate (1.17 g, 5.44 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 12 h. The reaction mixture was then diluted with CH_2Cl_2 and washed with water and brine solution, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography over silica gel (20% EtOAc/hexanes) to give **16** (1.0 g, 85% over two steps) as an amorphous solid. R_f = 0.7 (20% EtOAc/hexanes); $[\alpha]_D^{23}$ = -9.32 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.39 (m, 1H), 7.33 – 7.09 (m, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 4.78 (q, *J* = 10.6, 8.8 Hz, 2H), 2.88 – 2.50 (m, 2H), 2.02 (td, *J* = 10.9, 9.9, 4.9 Hz, 1H), 1.78 (ddp, *J* = 23.3, 11.4, 4.2 Hz, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.55, 139.66, 136.43, 131.38, 130.84, 130.31, 119.73, 79.77, 48.67, 30.45, 28.89, 28.57, 20.05.

Methyl (*S*)-8-((*tert*-butoxycarbonyl)amino)-5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (17)

Boc-amine derivative **16** (950 mg, 2.91 mmol) was dissolved in acetone (55 mL) and cooled to 0 °C. $MgSO_4$ (837 mg, 6.99 mmol) and water (23 mL) were added to the solution. $KMnO_4$ (2.38 g, 15.15 mmol) was added to this mixture in small portions over 1 h and stirred for 8 h at 23 °C. The solid was filtered off and the filtrate was treated with a saturated solution of sodium sulfite. The resulting mixture was filtered and the acetone was removed from the filtrate in *vacuo*. The remaining aqueous residue was extracted with dichloromethane. The combined organic phases were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel (20% EtOAc/hexanes) to afford bromo ketone derivative (600 mg, 61%) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.62 (s, 1H), 7.53 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.03 (s, 1H), 4.82 (d, *J* = 9.0 Hz, 1H), 2.81 (dt, *J* = 17.4, 5.3 Hz, 1H), 2.66 (ddd, *J* = 17.1, 11.5, 4.7 Hz, 1H), 2.49 – 2.32 (m, 1H), 2.18 – 1.99 (m, 2H), 1.51 (s, 9H).

A solution of above bromo ketone (600 mg, 1.76 mmol) in triethylamine (5.3 mL) and methanol (1 mL) was degassed with argon and palladium (II) acetate (8.0 mg, 0.035 mmol) and Xantphos (41 mg, 0.070 mmol) were added. The solution was degassed again and CO gas was bubbled through the solution for approximately 2 min. The reaction flask was fitted with a condenser and a CO balloon and the reaction mixture was heated at 70 °C for 3.5 h. The reaction mixture was cooled to 23 °C, diluted with EtOAc and filtered through a pad of celite. The filtrate was evaporated and the residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford titled compound **17** (450 mg, 80 %). R_f = 0.3 (20% EtOAc/hexanes); $[\alpha]_D^{23}$ = -10.7 (*c* 1.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 5.09 (s, 1H), 4.83 (s, 1H), 3.95 (s, 3H), 2.87 (dt, *J* = 17.4, 5.0 Hz, 1H), 2.71 (ddd, *J* = 16.9, 11.4, 4.7 Hz, 1H), 2.50 – 2.32 (m, 1H), 2.22 – 2.03 (m, 1H), 1.52 (s, 9H); LRMS-ESI *(m/z)*: 342 $[M+Na]^+$.

(5*R*,8*S*)-8-((*tert*-Butoxycarbonyl)amino)-5-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (18)

Argon was bubbled through a solution of **17** (150 mg, 0.46 mmol) and RuCl[(*R*,*R*)-TsDPEN](mesitylene) (9.0 mg, 0.014 mmol) in dry DMF (2 mL) for 10 min. A premixed combination of formic acid (35 µL, 0.938 mmol) and Et_3N (135 µL, 0.938 mmol) was added and the mixture stirred at 60 °C for 12 h. The mixture was cooled to 23 °C and diluted with CH_2Cl_2 and successively washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* to give the crude product. The crude residue was purified by column chromatography over silica gel (30% EtOAc/hexanes) to afford the desired alcohol (142 mg, 94%) as an amorphous white solid. R_f = 0.3 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 4.85 (s, 1H), 4.77 (m, 2H), 3.91 (s, 3H), 2.09 – 1.93 (m, 5H), 1.49 (s, 9H); LRMS-ESI *(m/z)*: 643 $[2M+H]^+$.

To a solution of above methyl ester (80 mg, 0.248 mmol) in THF: MeOH (1.5 mL, (2:1) was added 1N LiOH (0.37 mL, 0.373 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 12 h. Solvent was removed under reduced pressure, acidified with aq. saturated citric acid to pH 3-4 and the product was extracted with ethyl acetate, dried over Na_2SO_4 and concentrated to afford **18** (68 mg, 89 %) as an amorphous solid. R_f = 0.3 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = -38.6 (*c* 0.29, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.89 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 9.1 Hz, 1H), 4.71 (s, 2H), 2.05 – 1.89 (m, 4H), 1.50 (d, *J* = 4.7 Hz, 9H); LRMS-ESI *(m/z)*: 615 $[2M+H]^+$.

(5*S*,8*S*)-8-((*tert*-Butoxycarbonyl)amino)-5-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (19)

Argon was bubbled through a solution of **17** (150 mg, 0.469 mmol) and RuCl(p-cymene)[(*S*,*S*)-Ts-DPEN] (9.0 mg, 0.014 mmol) in dry DMF (1.5 mL) for 10 min. A premixed combination of formic acid (35 µL, 0.938 mmol) and Et_3N (135 µL, 0.938 mmol) was added and the mixture was stirred at 60 °C for 12 h. The mixture was cooled to 23 °C and diluted with CH_2Cl_2 and successively washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* to give the crude product. The crude product was purified by column chromatography over silica gel (30% EtOAc/ hexanes) to give the desired alcohol (140 mg, 93%) as an amorphous white solid. R_f = 0.3 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.94 – 7.88 (m, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 4.88 (s, 1H), 4.83 – 4.59 (m, 2H), 3.90 (s, 3H), 2.38 – 2.16 (m, 2H), 2.07 – 1.94 (m, 1H), 1.89 – 1.66 (m, 2H), 1.49 (s, 9H); LRMS-ESI *(m/z)*: 643 $[2M+H]^+$.

Above methyl ester (75 mg, 0.233 mmol) was treated with 1N LiOH (0.46 mL, 0.466 mmol) by following the procedure outlined for **18** to give the titled compound **19** (60 mg, 85%) as an amorphous solid; R_f = 0.3 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = -6.0 (*c* 0.5, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.85 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 4.79 – 4.67 (m, 2H), 2.24 – 2.11 (m, 3H), 1.74 (td, *J* = 12.1, 8.8 Hz, 2H), 1.46 (s, 9H); LRMS-ESI *(m/z)*: 615 $[2M+H]^+$.

(5*S*,8*R*)-8-((*tert*-Butoxycarbonyl)amino)-5-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (*ent*-18)

Argon was bubbled through a solution of ethyl (*R*)-8-((*tert*-butoxycarbonyl)amino)-5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (100 mg, 0.299 mmol) and RuCl(p-cymene)[(*S*,*S*)-Ts-DPEN] (6.0 mg, 0.0089 mmol) in dry DMF (1.0 mL) for 10 min. A

premixed combination of formic acid (22 µL, 0.598 mmol) and Et_3N (83 µL, 0.598 mmol) was added and the mixture stirred at 60 °C for 12 h. The mixture was cooled to room temperature and diluted with CH_2Cl_2 and successively washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* to give the crude product. The crude product was purified by column chromatography over silica gel (30% EtOAc/ hexanes) to give desired alcohol (87 mg, 86%) as an amorphous white solid. R_f = 0.3 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 4.90 (s, 1H), 4.84 – 4.67 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.46 – 2.12 (m, 2H), 1.90 – 1.67 (m, 3H), 1.50 (s, 9H), 1.39 (t, *J* = 7.2 Hz, 3H). LRMS-ESI *(m/z)*: 353 $[M+NH_4]^+$.

Above ethyl ester (47 mg, 0.11 mmol) was treated with 1N LiOH (0.2 mL, 0.21 mmol) by following the procedure outlined for **18** to give the titled compound *ent*-**18** (40 mg, 89%) as an amorphous solid. R_f = 0.3 (10% MeOH/CH_2Cl_2); LRMS-ESI *(m/z)*: 615 $[2M+H]^+$.

tert-Butyl ((1*S*,4*R*)-4-hydroxy-7-(((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamoyl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (4g)

Carboxylic acid **18** (40 mg, 0.130 mmol) was treated with isostere amine **20** (68 mg, 0.130 mmol) by following the procedure outlined for inhibitor **4a** to give inhibitor **4g** (85 mg, 94%) as an amorphous white solid. R_f = 0.5 (80% EtOAc/hexanes); $[\alpha]_D^{23}$ = -3.2 (*c* 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 17.2 Hz, 1H), 7.40 (m, 1H), 7.31 – 7.18 (m, 4H), 7.18 – 7.07 (m, 2H), 6.952 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.35 – 5.24 (m, 1H), 4.66 (m, 1H), 4.56 (m, 1H), 4.35 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 1H), 3.97 (s, 1H), 3.83 (s, 3H), 3.27 – 2.93 (m, 5H), 2.85 (d, *J* = 7.6 Hz, 2H), 1.89 (m, 2H), 1.46 (s, 9H), 0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.75, 163.09, 155.79, 142.78, 138.07, 137.74, 133.70, 129.94, 129.52, 128.86, 128.65, 126.90, 126.65, 126.10, 114.44, 79.83, 73.00, 67.38, 58.70, 55.73, 54.57, 53.53, 48.80, 35.08, 29.79, 29.20, 28.56, 27.24, 25.96, 20.21, 20.06; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{37}H_{49}N_3O_8SNa$, 718.3133; found 718.3124.

(5*R*,8*S*)-8-Amino-5-hydroxy-*N*-((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide (4h)

To a solution of **4g** (80 mg, 0.114 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.3 mL) and resulting solution was stirred at 23 °C for 3 h. Then reaction mixture concentrated under *vacuo* and extracted with ethyl acetate and washed with sat. $NaHCO_3$, water, brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography over silica gel (10% MeOH/NH_3 in CH_2Cl_2) to give inhibitor **4h** (60 mg, 88%) as an amorphous white solid. R_f = 0.15 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = +12.2 (*c* 0.63, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 9.1, 2.8 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.36 – 7.29 (m, 1H), 7.29 – 7.24 (m, 3H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.17 – 7.07 (m, 2H), 6.91 (dd, *J* = 9.5, 2.6 Hz, 2H), 4.54 (d, *J* = 5.3 Hz, 1H), 4.38 (dp, *J* = 9.2, 4.8 Hz, 2H), 4.03 (dt, *J* = 8.4, 4.2 Hz, 2H), 3.86 (d, *J* = 6.0 Hz, 1H), 3.82 (s, 3H), 3.23 (dd, *J* = 15.1, 4.0 Hz, 1H), 3.15 – 2.96 (m, 4H), 2.88 (td, *J* = 13.9, 6.9 Hz, 3H), 1.97 – 1.61 (m, 6H), 0.83 (t, *J* = 5.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.11, 163.05, 143.02, 140.41, 138.27, 133.62, 130.06, 129.51, 128.60, 128.46, 126.94, 126.56, 125.91, 114.41, 77.48, 72.92, 67.88, 58.60, 55.71, 54.61, 53.42, 49.18, 34.97, 28.64, 28.50, 27.18, 20.20, 20.11; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{42}N_3O_6S$, 596.2789; found 596.2785.

tert-Butyl ((1*S*,4*S*)-4-hydroxy-7-(((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamoyl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (4i)

Carboxylic acid **19** (40 mg, 0.13 mmol) was treated with isostere amine **20** (68 mg, 0.13 mmol) by following the procedure outlined for inhibitor **4a** to give inhibitor **4i** (85mg, 94%) as an amorphous solid. R_f = 0.5 (80% EtOAc/hexanes); $[\alpha]_D^{23}$ = +15.0 (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.9 Hz, 2H), 7.53 (s, 1H), 7.46 – 7.43 (m, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.25 – 7.20 (m, 4H), 7.15 (td, *J* = 6.2, 2.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.03 (d, *J* = 8.9 Hz, 1H), 4.68 (dd, *J* = 16.6, 10.3 Hz, 2H), 4.28 (d, *J* = 20.1 Hz, 1H), 3.96 (dt, *J* = 8.6, 4.3 Hz, 1H), 3.82 (s, 3H), 3.22 – 2.92 (m, 4H), 2.84 (h, *J* = 7.6, 6.8 Hz, 2H), 2.22 (m, 6H), 1.86 (dt, *J* = 13.6, 6.7 Hz, 1H), 1.77 – 1.55 (m, 2H), 1.46 (s, 9H), 0.83 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.13, 163.05, 156.10, 143.27, 138.26, 137.31, 133.64, 129.93, 129.49, 128.58, 128.46, 126.57, 114.40, 80.15, 72.86, 67.63, 58.61, 55.70, 54.74, 53.42, 49.80, 49.58, 49.37, 49.03, 34.94, 30.22, 28.49, 27.73, 27.18, 20.11, 20.03; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{50}F_2N_3O_8S$, 696.3313; found 696.3305.

(5*S*,8*S*)-8-Amino-5-hydroxy-*N*-((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphnyl)sulfonamido)-1-phenylbutan-2-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide (4j)

Inhibitor **4i** (50 mg, 0.071 mmol) was treated with TFA (0.2 mL) by following the procedure outlined for inbitor **4h** to give compound inhibitor **4j** (40 mg, 94%) as an amorphous solid. R_f = 0.15 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = +35.6 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.62 (s, 1H), 7.38 – 7.31 (m, 2H), 7.30 – 7.24 (m, 4H), 7.22 – 7.14 (m, 1H), 6.98 – 6.86 (m, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 4.68 (dd, *J* = 7.6, 4.3 Hz, 1H), 4.37 (dd, *J* = 9.4, 4.9 Hz, 1H), 4.04 (m, 1H), 3.84 (s, 3H), 3.23 (dd, *J* = 15.0, 4.2 Hz, 1H), 3.16 – 2.97 (m, 4H), 2.87 (m 3H), 2.26 – 2.10 (m, 2H), 1.87 (dq, *J* = 13.8, 6.8 Hz, 2H), 1.69 (q, *J* = 9.6, 8.2 Hz, 2H), 1.52 (q, *J* = 11.3, 9.9 Hz, 1H), 0.84 (dd, *J* = 6.6, 2.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.10, 163.09, 142.51, 140.87, 138.30, 133.51, 130.08, 129.55, 128.68, 128.33, 126.68, 125.50, 114.44, 72.92, 68.03, 58.72, 55.74, 54.77, 53.50, 49.34, 35.00, 31.05, 30.20, 29.89, 27.22, 20.22, 20.14; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{42}N_3O_6S$, 596.2789; found 596.2784.

tert-Butyl ((1*R*,4*S*)-4-hydroxy-7-(((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamoyl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (4k)

Carboxylic acid *ent*-**18** (41 mg, 0.10 mmol) was treated with isostere amine **20** (52 mg, 0.10 mmol) by following the procedure outlined for compound **4a** to give compound inhibitor **4k** (75 mg, 94%) as an amorphous solid. R_f = 0.5 (80% EtOAc/hexanes); $[\alpha]_D^{23}$ = +5.9 (*c* 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.5, 6.4 Hz, 3H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.28 (m, 4H), 7.23 – 7.15 (m, 1H), 6.99 – 6.87 (m, 2H), 6.70 (d, *J* = 8.7 Hz, 1H), 5.06 (d, *J* = 8.9 Hz, 1H), 4.71 (m, 1H), 4.64 (m, 1H), 4.47 – 4.27 (m, 2H), 3.99 (s, 1H), 3.85 (s, 3H), 3.21 – 2.99 (m, 4H), 2.85 (d, *J* = 7.5 Hz, 2H), 2.62 (s, 1H), 1.97 (m, 3H), 1.86 (m, 3H), 1.47 (s, 9H), 0.85 (dd, *J* = 6.6, 3.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.89,

163.15, 155.72, 142.88, 138.06, 137.88, 133.87, 129.95, 129.55, 128.96, 128.76, 127.01, 126.75, 126.08, 114.47, 79.93, 73.04, 67.50, 58.87, 55.76, 54.87, 53.62, 48.89, 35.02, 29.83, 29.33, 28.57, 27.34, 26.07, 20.24, 20.13; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{37}H_{50}N_3O_8S$, 696.3313; found 696.3310.

(5*S*,8*R*)-8-Amino-5-hydroxy-*N*-((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide (4l)

Inhibitor **4k** (30 mg, 0.043 mmol) was treated with TFA (0.1 mL) by following the procedure outlined for inbitor **4h** to give inhibitor **4l** (23 mg, 89%) as an amorphous solid. R_f = 0.15 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = -9.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.59 (m, 3H), 7.48 – 7.40 (m, 1H), 7.38 – 7.25 (m, 4H), 7.19 (t, *J* = 7.0 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 1H), 4.66 (t, *J* = 4.7 Hz, 1H), 4.38 (d, *J* = 8.7 Hz, 1H), 4.01 (dt, *J* = 10.4, 4.5 Hz, 2H), 3.85 (s, 3H), 3.22 (dd, *J* = 15.0, 4.3 Hz, 1H), 3.14 – 3.01 (m, 4H), 2.85 (dt, *J* = 13.5, 7.4 Hz, 2H), 1.96 – 1.76 (m, 6H), 0.85 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.03, 163.12, 143.32, 140.01, 138.25, 133.71, 130.09, 130.08, 129.56, 128.69, 126.82, 126.68, 126.30, 114.45, 73.02, 68.02, 58.67, 55.75, 54.85, 53.40, 49.38, 35.05, 29.83, 28.66, 28.09, 27.24, 20.23, 20.15; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{42}N_3O_6S$, 596.2789; found 596.2786.

4.3 Determination of X-ray structure of HIV-1 protease inhibitor complexes.

For X-ray crystallographic studies, HIV-1 protease was expressed and purified as described.[45] The protease-inhibitor complex was crystallized by the hanging drop vapor diffusion method with well solutions of 0.9M NaCl, 0.1M Sodium Cacodylate, pH 6.4 for PR/GRL-02815A (**4d**) complex, and 0.95M NaCl, 0.1M Sodium Acetate, pH 5.5 for PR/GRL-043-15A (**4k**) complex. 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, USA) with X-ray wavelength of 1.0 Å. X-ray data were processed by HKL-2000[46] to give Rmerge values of 8.5% and 7.8% for inhibitors 4d- and 4k-bound HIV-1 protease complexes, respectively. The crystal structures were solved by PHASER[47] in CCP4i Suite[48-50] using one of the previously reported isomorphous structures[51] as the initial model, and refined by SHELX-2014[52,53] with X-ray data at 1.20 Å resolution for inhibitor **4d** and HIV-1 protease complex and 1.14 Å for inhibitor **4k** and HIV-1 protease complex. PRODRG-2[54] was used to construct the inhibitor and geometric restraints for refinement. COOT[55,56] was used for modification of the model. 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 one Na^+ ion, two Cl^- ions, one glycerol molecules and 209 water molecules for inhibitor **4d** and HIV-1 protease complex and Na^+ ion, two Cl^- ions, one acetate ion, one glycerol molecules and 142 water molecules for for inhibitor **4k** and HIV-1 protease complex. The crystallographic statistics are listed in Table 1 (Please see, supporting information). The coordinates and structure factors of the protease complexes with inhibitors **4d** and **4k** have been deposited in the Protein Data Bank[57] with accession codes of 6DV0 and 6DV4, respectively.

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Highlights

- Design and synthesis of novel HIV-1 protease inhibitors are reported
- Aminothiochromane and aminotetrahydronaphthalene derivatives were synthesized
- The synthesis of ligands utilized reduction of chiral sulfinamide derivatives
- The X-ray crystal structures of inhibitor-bound HIV-1 protease were determined
- Hydrogen bonding and van der Waals interactions were observed in the active site