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Structural optimization of cyclic sulfonamide based novel HIV-1 protease inhibitors to picomolar affinities guided by X-ray crystallographic analysis

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ABSTRACT

Synthesis and HIV-1 protease inhibitory activity of compound **5** based on the structure of a novel cyclic sulfonamide pharmacophore has been recently disclosed from our group. X-ray crystallographic structure of **5** when bound to the HIV-1 protease defined its binding mode. The importance of the geometry of the substitution at C4–Me (*S* configuration) was emphasized. In the present paper we wish to disclose the design of novel inhibitors **47** and **48** based on the X-ray structure of compound **5** bound to the HIV-1 protease, their synthesis and activity against HIV-1 protease. By making changes at the C4 position and the carbamate linkage the above compounds **47** and **48** were found to be approximately one hundred fold more active compared to **5** and their K_i values are in the picomolar range. An unusual observation regarding the activity and geometry was made with compounds **51** and **52**. X-ray results demonstrate that **48** and **52** bind to the same binding pocket with simultaneous change in the conformation of the cyclic sulfonamide ring.

1. Introduction

In our previous publication[1a] we have disclosed the synthesis of a novel class of HIV-1 protease inhibitors represented by structure **1**. These inhibitors were designed based on a novel pharmacophore containing conformationally restricted sulfonamides. Our expectation is that the cyclic sulfonamides would assume fewer conformations when bound to the HIV-1 protease compared with the corresponding open chain sulfonamides,[2–4] which might also translate into advantages in potency and possibly pharmacokinetic properties. An unusual radical cyclisation[1b] process yielded the above novel cyclic sulfonamides. In HIV-1 protease assay, our initial lead compound **2** was found to have K_i value of 470 nM (Fig. 1). In order to optimize the potency we decided to suitably substitute both the aliphatic and aromatic rings in compound **2**. Following the sequence of steps as in our earlier publication, the diastereoisomers **3** and **4** were synthesized. The HIV-1 protease inhibitory activities of the diastereoisomers showed that compound **3** was significantly more potent with a K_i of 29 nM. Indeed for optimal potency it is important that the C4–Me group has (*S*) configuration (compound **3**) as the diastereoisomer with C4–Me with (*R*) configuration was found to be essentially inactive with K_i of 1000 nM (compound **4**).

We have synthesized several analogs to establish the structure–activity relationship and found that compound **5** was the most potent in this series with a K_i of 20 nM (Fig. 1). The X-ray crystallographic analysis of compound **5** bound to the HIV-1 protease[1a] revealed that compound **5** binds to the same cavity as the clinical drug darunavir and that it makes hydrogen bonding to the catalytic aspartic acid residues Asp 25 and Asp 25′ through the 2′ hydroxyl group. The sulfonamide and the carbamate carbonyl form hydrogen bonds with a structural water molecule, which in turn hydrogen-bonds with Ile50 and Ile50′ of the protease backbone. In addition to these favorable interactions, C4–Me (*S* configuration) fits into a hydrophobic pocket containing Val82, Leu23, Ile84. Furthermore, C4–Me (*S* configuration) in compound **5** is 2.9 Å away from the carbonyl oxygen of Gly27′. If the C4–Me configuration is changed to (*R*) instead of (*S*), an unfavorable repulsion would be created between the C4–Me and the Gly27′ carbonyl group and the interactions to the hydrophobic pocket would be lost. These are the

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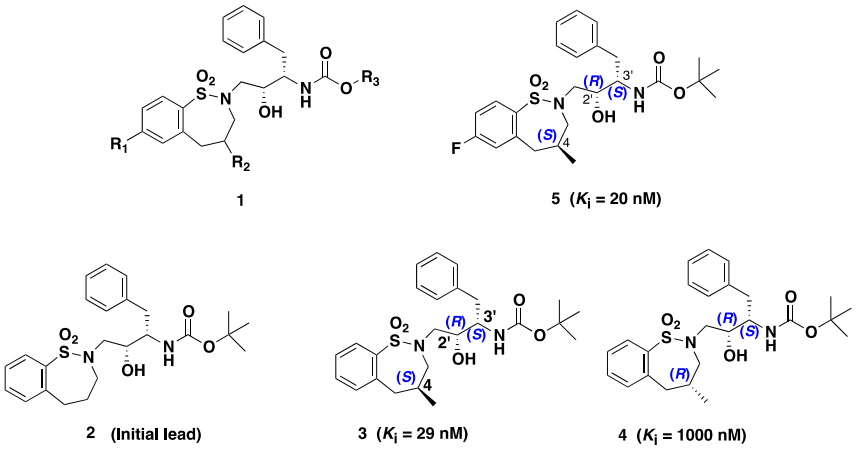


Fig. 1. Novel HIV-1 protease inhibitors.

reasons for the improved activity of compound **5** when compared with the initial lead compound **2**.

2. Present study

The X-ray crystallographic analysis of compound **5** also suggested that C4–Me group could be further extended in order to maximize the interactions with the hydrophobic pocket, thus enhancing potency. Hence we decided to study the effect of various alkyl groups on the cyclic sulfonamide ring for their activities against HIV-1 protease. In addition, the molecular modeling suggested that the tetrahydrofuran carbamates similar to amprenavir and different than darunavir would provide stronger binding to the protease backbone through hydrogen bonding of Asp 29′ and Asp30′. In our earlier publication we noted that fluorine substitution of the aromatic sulphonamide ring was optimum for activity. Thus we synthesized compounds represented by the structure **6** (Fig. 2) incorporating all the above ideas. As predicted

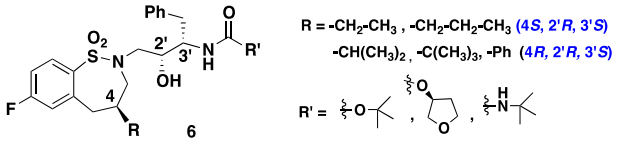


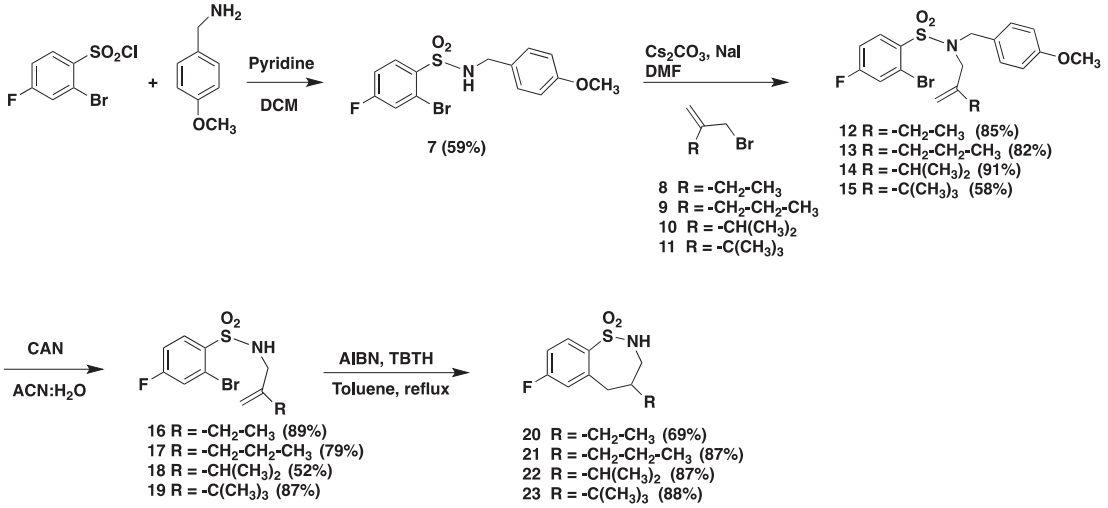
Fig. 2. Novel cyclic sulfonamides.

the compounds possessing tetrahydrofuran carbamate moiety were more potent in the HIV-1 protease inhibitory activity when compared with compounds possessing *t*-butyl carbamate. In addition the molecular modeling studies also suggested that a phenyl group could be accommodated at the C4 position, although not as tightly as the alkyl groups in the same pocket. As a test case we synthesized compound **49** and found that it had good activity although it was not as active as the alkyl substituted compounds.

Thus in the present study we identified compounds **47** and **48** as the most potent inhibitors with K_i values of 360 pM and 260 pM, respectively, which are approximately a hundred fold more potent than compound **5** described in our earlier paper. As discussed above in the C4–Me series only the diastereoisomers with (*S*) stereochemistry at this center were active and it was also true when the methyl group was displaced with ethyl and *n*-propyl groups. However when the methyl group was replaced with isopropyl or tertiary butyl groups both the distereoisomers were active. Thus **51** and **52** were active although much less so when compared with **47** and **48**, respectively. X-ray crystallographic analysis of **52** bound to the HIV-1 protease provided a clue to this unexpected result, which is described later in the paper.

2.1. Synthesis of C4-substituted derivatives

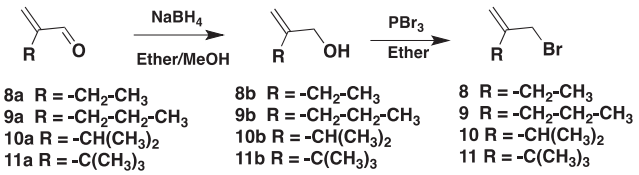
Synthesis of newer analogs is summarized in Scheme 1. It involves steps we have disclosed in our earlier publication, however it



Scheme 1. Synthesis of cyclic sulfonamides **20**–**23**.

has been modified to incorporate novel structural features in the molecules disclosed in the present study. Thus the treatment of 2-bromo-4 fluorobenzenesulfonyl chloride with 4-methoxybenzyl amine gave the sulfonamide **7**.

Allylation of **7** with substituted bromo compounds **8**–**11** using sodium iodide and cesium carbonate in DMF as solvent yielded the *N*-allyl sulfonamides **12**–**15**, respectively. Removal of the 4-methoxybenzyl group in the presence of ceric ammonium nitrate and acetonitrile:water (5:1) as solvent provided the radical precursors **16**–**19**. Radical cyclization of compounds **16**–**19** with tributyltin hydride (TBTH) and azobisisobutyronitrile (AIBN) as radical initiator in toluene under reflux conditions gave the radical cyclized products **20**–**23**, respectively. The bromo intermediates **8**–**11**, in turn were synthesized following Scheme 2.[5] Thus substituted acroleins **8a**–**11a** were reduced by sodium borohydride in presence of methanol and ether to give the corresponding alcohols **8b**–**11b**, which were then converted to the desired bromo intermediates using phosphorous tribromide in ether at 0 °C.



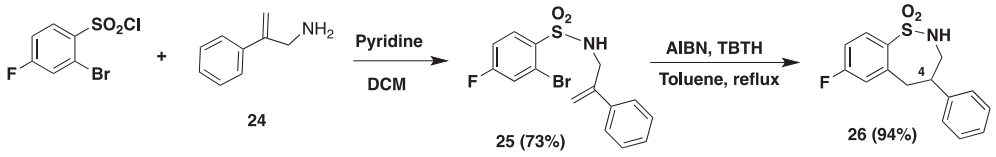
Scheme 2. Synthesis of bromo intermediates **8**–**11**.

The C4-phenyl substituted sulfonamide was prepared following Scheme 3. Treatment of 2-bromo-4 fluorobenzenesulfonyl chloride with 2-phenylallylamine (**24**)[6] in the presence of pyridine yielded the radical precursor **25**, which when treated with AIBN, TBTH in toluene under reflux provided the desired compound **26**.

respectively with (*S*)-2,5-dioxopyrrolidin-1-yl (tetrahydrofuran-3-yl) carbonate (**46**)[7] and triethylamine in dichloromethane yielded **47**–**49**. Treatment of **40** with *tert*-butyl isocyanate in the presence of magnesium bromide using 1,4-dioxane as solvent gave the urea **50**. Although the less polar diastereoisomers were inactive in previous cases,[1a] compounds **35** and **36**, when converted into tetrahydrofuran carbamates, **51** and **52**, respectively, were found to be active. It should be noted that in every case studied, it is the more polar diastereoisomeric amines when converted to the carbamates show activity.

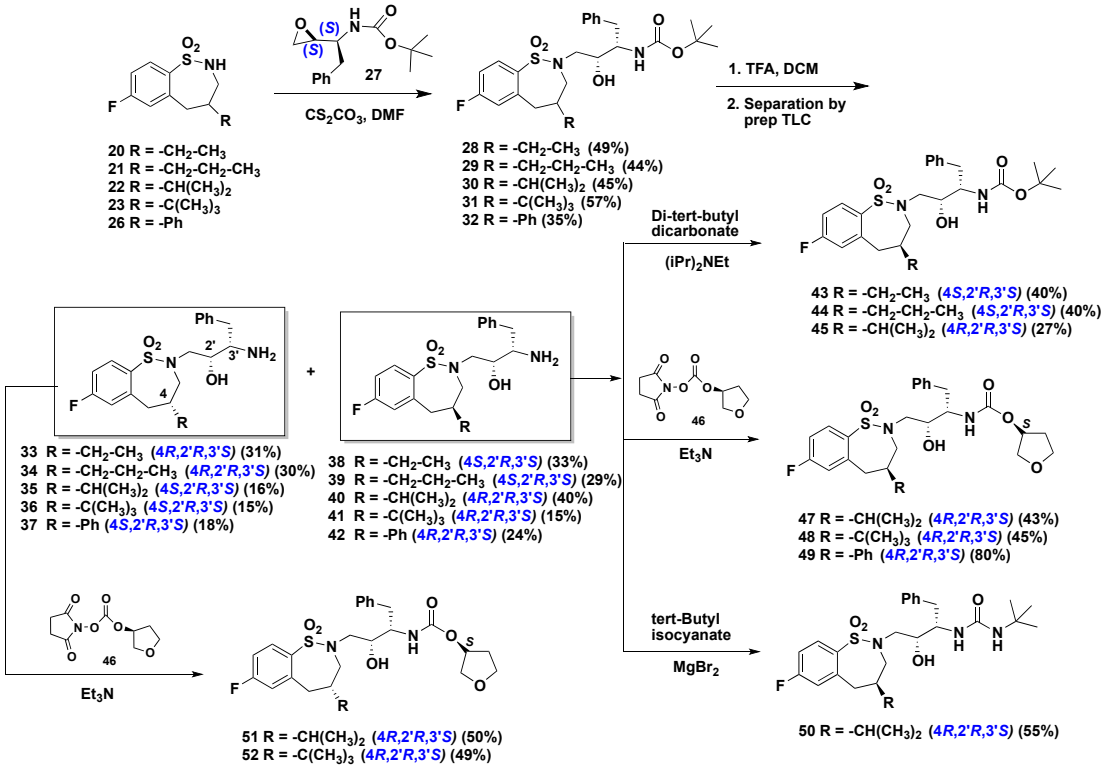
2.2. HIV-1 protease activity and X-ray crystallographic analysis

The results of HIV-1 protease inhibitory assay of compounds **43**–**45**, **47**–**52** are summarized in Table 1. Compound **43** with C4–Et (*S*) on the cyclic sulfonamide ring was found to have the K_i value of 11 nM, which was a slight improvement in potency when compared with C4–Me (*S*) substitution as in compound **5**. C4-Pr (*S*) compound **44** had the K_i value of 28 nM. With the introduction of C4–^{i}Pr (*R*) group in compound **45** there was nearly 6-fold increase in the potency with K_i of 2.8 nM when compared to compound **5**. The urea derivative **50** was also found to be active with a K_i of 6.4 nM. The activity improved significantly in compound **47** when the tetrahydrofuran carbamate was made with a K_i of 360 pM. With the introduction of C4–*t*-butyl (*R*) group as in compound **48** there was further increase in activity when compared with compound **47**. Indeed compound **48** is the most potent analog in this series of cyclic sulfonamides with a K_i of 260 pM. We have also made the diastereoisomers **51** and **52** and to our surprise found them to be also active with a K_i value of 19 nM and 14 nM, respectively. Although **51** was considerably less active than **47** and **52** much less active than **48**, however, when these results are compared with the activities of the C4–Me diastereoisomers, in which case (*S*) diastereoisomer was active and the (*R*) diastereoisomer was essentially inactive, the above observations were surprising. The potent



Scheme 3. Synthesis of C4-phenyl sulfonamide **26**.

Treatment of **20**–**23**, **26** with the commercially available chiral epoxide **27** in the presence of cesium carbonate and DMF yielded mixtures of diastereoisomers **28**–**32**, respectively, which could not be separated (Scheme 4). However, **28** on treatment with trifluoroacetic acid in dichloromethane yielded the diastereoisomers **33** and **38**, which could be separated using preparatory TLC. Similarly, **29** gave **34** and **39**, **30** gave **35**, and **40**, **31** gave **36** and **41**, **32** gave **37** and **42**. The absolute configuration in the C4–Me (*S*) diastereoisomer series was established by X-ray crystallography of the corresponding amine and corroborated further by X-ray crystal structure of compound **5** bound to the protease as disclosed in our previous publication.[1a] The more polar (6% Methanol in Chloroform) diastereoisomers **38**–**40** were treated with di-*tert*-butyl dicarbonate and diisopropylethylamine to give the final products **43**–**45**, respectively, which showed potent activity as HIV-1 protease inhibitors. The corresponding derivatives obtained from the less polar diastereoisomers **33**, and **34** were inactive and not reported in the paper. Treatment of the diastereoisomers **40**–**42**, activity of **51** and **52** were indeed unexpected and needed an explanation. X-ray analysis of **48** and **52** when bound to the HIV-1 protease unequivocally demonstrated that both these compounds bind to the same hydrophobic pocket as the C4–Me (*S*) diastereoisomer and have similar interactions involving Asp 25, Asp 25′, Ile50, and Ile50′. X-ray results also demonstrated that **48** and **52** assume different conformations of the seven membered sulfonamide rings (Fig. 5). The same explanation we suspect holds good for **47** and **51**. Although the inactive C4–Me (*R*) diastereoisomer could not be soaked into HIV protease apo crystals, molecular modeling suggests that the methyl group in this case was pushed away from the important hydrophobic binding site. The above X-ray crystallography results also confirmed the absolute stereochemistry of **47**, **48**, **51**, and **52**. Perhaps it should also be noted that the absolute stereochemistry at C2′ and C3′ were derived from the absolute stereochemistry of the epoxide **27** and the remaining asymmetric center was defined from compound **46** used in the preparation of the carbamate.



Scheme 4. Synthesis of novel HIV-1 protease inhibitors **43**–**45**, **47**–**52**.

Table 1
Summary of biological activity in HIV-1 protease assay

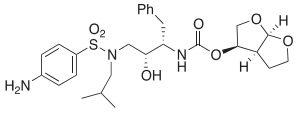
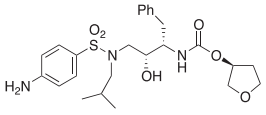
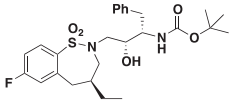
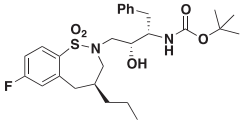
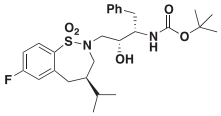
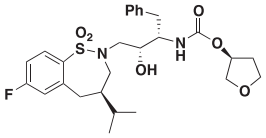
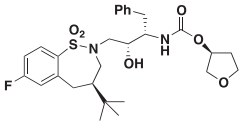
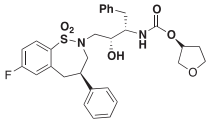
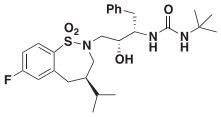
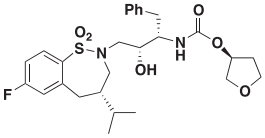
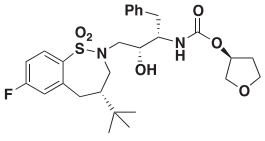
Compound	Structure	K_i (nM)
Darunavir		<0.02
Amprenavir		0.08±0.02
43		11±1.1
44		28±6
45		2.8±1.9 3[a]
47		0.36±0.1 0.43[a]

Table 1 (*continued*)

Compound	Structure	K_i (nM)
48		0.26±0.05
49		34±5.1
50		6.4±1
51		19±1.6
52		14±0.6

[a] Replicate of HIV-1 assay at a different time.

The X-ray crystal structure of compound **47** bound to the HIV-1 protease is shown in Fig. 3. It was found that in addition to the binding interactions shown by compound **5**, the tetrahydrofuran group in compound **47** forms a hydrogen bond with Asp 29′ and Asp30′. The isopropyl group extends deeper into the hydrophobic pocket of Val82, Leu23, Ile84. It is partially disordered by rotation of the isopropyl group placing the two methyl groups at three positions. The additional interactions are responsible for much improved activity of **47**. The *t*-butyl group in compound **48** eliminates the disorder of compound **47** and further maximizes the interactions with the hydrophobic pocket, which makes it the most potent analog in this series of compounds. Fig. 4 shows overlay of compounds **47**, **50**, and **5**. Fig. 5 shows the overlay of **48** and **52**.

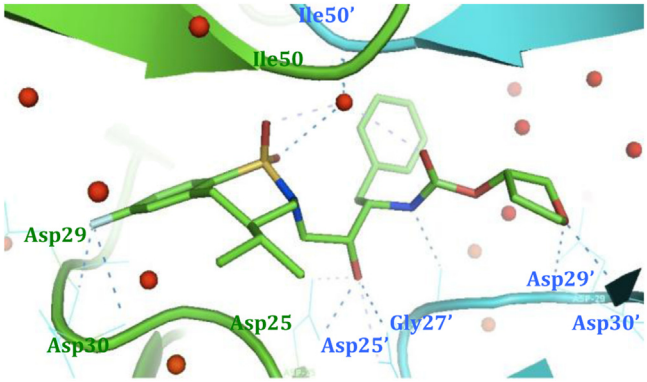


Fig. 3. X-ray crystal structure of compound **47** bound to HIV-1 protease.

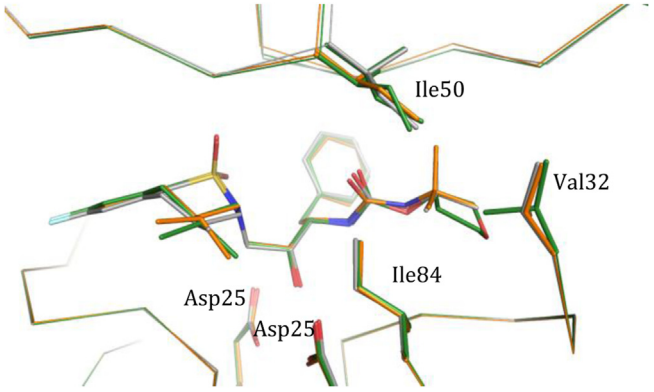


Fig. 4. Overlay of X-ray crystallographic structures of compound **5** (gray), compound **47** (green), and compound **50** (orange).

3. Conclusion

In conclusion, the compounds with C4-alkyl substitution, i.e., isopropyl or *t*-butyl groups were found to be significantly more active than the C4-phenyl substitution. The X-ray crystallographic analysis of compound **47** bound to the HIV-1 protease revealed that it binds to the same cavity as the C4–Me (*S*) diastereoisomer and that it makes hydrogen bonding to the catalytic aspartic acid residues Asp 25 and Asp 25′ through the 2′ hydroxyl group. The sulfonamide and the carbamate carbonyl form hydrogen bonds with a structural water molecule, which in turn hydrogen-bonds with Ile50 and Ile50′ of the protease backbone. In addition to these favorable interactions, the tetrahydrofuran group in compound **47** shows hydrogen-bonding interactions with Asp 29′ and Asp30′ of the protease backbone. The isopropyl group extends deeper into the hydrophobic pocket of Val82, Leu23, and Ile84. These factors contribute to the picomolar activity of compound **47** and we believe that in the case of the t-butyl group at C4 position as in compound **48** the hydrophobic interactions are further maximized. In HIV-1 protease assay compound **47** showed K_i of 360 pM and compound **48** showed K_i of 260 pM, which were a hundred fold more active than our previously reported compound **5**. To our greatest surprise we have found that both the C4–^{i}Pr (*S*), C4–*t*-butyl (*S*), **51** and, **52** diastereoisomers were active although much less so when compared to the corresponding (*R*) isomers. X-ray studies demonstrated that when bound to the HIV-1 protease they occupy the same pocket as the C4–Me (*S*) diastereoisomer, excepting that in the case of **51** and **52** the seven membered sulfonamide rings assume different conformations. In spite of our best effort we have not been able to get our compounds screened against resistant organisms. Once we are successful we shall report the results in a future publication.

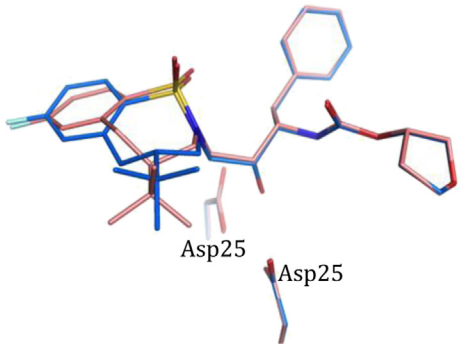


Fig. 5. Overlay of X-ray crystallographic structures of compounds **48** (red) and **52** (blue).

4. Experimental section

4.1. General

All the reactions were performed under a nitrogen atmosphere with magnetic stirring. Air and moisture-sensitive reagents were transferred via disposable syringes. Anhydrous solvents and commercially available chemicals were used without further drying. TLC was performed on Analtech silica gel glass plates (250 μ) and visualized with a UV lamp. NMR spectra were recorded with Varian 400 MHz spectrometer using $CDCl_3$ as solvent unless otherwise noted. The purity of the compounds was established using various chromatographic techniques including HPLC and were judged to be >95%.

4.2. A general procedure for sulfonamide formation (7) and (25)

2-Bromo-4-fluoro-*N*-(4-methoxybenzyl)benzenesulfonamide (**7**). To a solution of 4-methoxybenzylamine (1.0 g, 3.66 mmol) in dichloromethane (DCM) (5 mL) were added, pyridine (0.59 mL, 7.32 mmol) followed by a solution of 4-fluoro-2-bromobenzenesulfonyl chloride (0.52 mL, 4.02 mmol) in DCM (2 mL). The reaction mixture was stirred at room temperature for 8–10 h. TLC was monitored to check the progress of the reaction.

After the reaction was complete, the reaction mixture was diluted with DCM and washed with 15% HCl (2×10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to yield the crude compound, which was purified by column chromatography using 15% ethyl acetate in hexane to yield the pure compound. Crystals were obtained from DCM and hexane (1:4). Yield: 59%. Mp 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.17–8.03 (m, 1H), 7.41 (d, J=7.9 Hz, 1H), 7.16–7.05 (m, 3H), 6.76 (d, J=8.3 Hz, 2H), 5.32 (t, J=5.7 Hz, 1H), 4.04 (d, J=6.1 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.38, 162.80, 159.36, 135.26, 133.63, 133.55, 129.37, 127.46, 122.46, 122.20, 120.97, 120.86, 114.93, 114.73, 55.26, 47.02. HRMS calcd for $C_{14}H_{14}BrFNO_3S$ $[M+H]^+$ 371.9700; found 371.9690.

*4.2.1. 2-Bromo-4-fluoro-N-(2-phenylallyl)benzenesulfonamide (**25**).* The title compound was prepared starting from **24**[6] and 2-bromo-4-fluorobenzenesulfonyl chloride following the general procedure for sulfonamide formation. Yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (dd, J=8.8, 5.8 Hz, 1H), 7.35 (dd, J=7.9, 2.5 Hz, 1H), 7.31–7.24 (m, 3H), 7.24–7.10 (m, 3H), 5.34 (s, 1H), 5.21 (b, 2H), 4.04 (d, J=6.1 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.40, 162.83, 142.58, 137.48, 135.38, 133.45, 128.72, 128.32, 125.95, 125.88, 122.48, 122.23, 121.26, 121.16, 115.79, 114.86, 114.65, 47.36. HRMS calcd for $C_{15}H_{14}BrFNO_2S$ $[M+H]^+$ 369.9907; found 369.9902.

4.3. A general procedure for *N*-allylation 12–15

To a solution of compound **7** (1.35 g, 3.62 mmol) in *N*,*N*-dimethyl formamide (DMF) (3 mL) were added sodium iodide (1.08 g, 7.24 mmol) and cesium carbonate (2.35 g, 7.24 mmol), followed by substituted allyl bromides, **8**–**11** (1.18 g, 7.24 mmol). The reaction mixture was allowed to stir for 10–12 h at room temperature under nitrogen. TLC was checked to monitor the progress of the reaction. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to yield crude product, which was purified by column chromatography in 15% ethyl acetate in hexane to yield the pure compound.

*4.3.1. 2-Bromo-4-fluoro-N-(4-methoxybenzyl)-N-(2-methylenebutyl)benzenesulfonamide (**12**).* The title compound was prepared following the general procedure for N-allylation using compound **7** and 2-(bromomethyl)but-1-ene (**8**). Crystals were obtained from DCM and hexane (1:5). Yield: 85%. Mp 50–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (td, J=9.3, 4.7 Hz, 1H), 7.46 (td, J=8.0, 3.0 Hz, 1H), 7.11 (ddd, J=9.1, 7.7, 2.5 Hz, 1H), 7.03 (d, J=8.7 Hz, 2H), 6.78 (d, J=8.6 Hz, 2H), 4.92 (s, 1H), 4.87 (s, 1H), 4.39 (s, 2H), 3.81 (s, 2H), 3.78 (s, 3H), 1.87 (q, J=7.3 Hz, 2H), 0.90 (t, J=7.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.27, 162.69, 159.19, 145.05, 134.37, 130.09, 129.96, 127.32, 122.87, 122.62, 121.88, 114.62, 113.80, 112.87, 55.24, 51.67, 49.64, 25.78, 11.78. HRMS calcd for $C_{19}H_{22}BrFNO_3S$ $[M+H]^+$ 442.0482; found 442.0474.

*4.3.2. 2-Bromo-4-fluoro-N-(4-methoxybenzyl)-N-(2-methylenepentyl)benzenesulfonamide (**13**).* The title compound was prepared following the general procedure for N-allylation using compound **7** and 2-(bromomethyl)pent-1-ene (**9**). Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.16 (dd, J=8.9, 5.9 Hz, 1H), 7.47 (dd, J=8.0, 2.5 Hz, 1H), 7.15–7.08 (m, 1H), 7.06 (d, J=8.5 Hz, 2H), 6.79 (d, J=8.5 Hz, 2H), 4.91 (s, 1H), 4.86 (s, 1H), 4.42 (s, 2H), 3.78 (s, 3H), 3.76 (s, 2H), 1.81 (t, J=7.5 Hz, 2H), 1.24 (dd, J=14.9, 7.4 Hz, 2H), 0.80 (t, J=7.3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.24, 162.67, 159.15, 143.23, 136.28, 134.33, 134.24, 130.06, 127.35, 122.85, 122.60, 121.99, 121.89, 114.57, 114.36, 114.00, 113.78, 55.18, 51.26, 49.65, 35.01, 20.45, 13.69. HRMS calcd for $C_{20}H_{24}BrFNO_3S$ $[M+H]^+$ 456.0639; found 456.0628.

*4.3.3. 2-Bromo-4-fluoro-N-(4-methoxybenzyl)-N-(3-methyl-2-methylenebutyl)benzene sulfonamide (**14**).* The title compound was prepared following the general procedure for N-allylation using compound **7** and 2-(bromomethyl)-3-methylbut-1-ene (**10**). Crystals were obtained from DCM and hexane (1:4). Yield: 91%. Mp 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (dd, J=8.9, 5.9 Hz, 1H), 7.46 (dd, J=8.0, 2.6 Hz, 1H), 7.10 (ddd, J=8.9, 7.5, 2.6 Hz, 1H), 7.03 (d, J=8.7 Hz, 2H), 6.78 (d, J=8.7 Hz, 2H), 4.91 (s, 1H), 4.86 (s, 1H), 4.40 (s, 2H), 3.84 (s, 2H), 3.77 (s, 3H), 2.08 (m, 1H), 0.89 (d, J=6.8 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.28, 162.70, 159.22, 149.40, 134.40, 134.31, 130.10, 127.39, 122.89, 122.64, 121.97, 121.87, 114.63, 114.42, 113.82, 111.01, 55.22, 50.67, 49.80, 30.38, 21.43. HRMS calcd for $C_{20}H_{24}BrFNO_3S$ $[M+H]^+$ 456.0639; found 456.0627.

*4.3.4. 2-Bromo-N-(3,3-dimethyl-2-methylenebutyl)-4-fluoro-N-(4-methoxybenzyl)benzene sulfonamide (**15**).* The title compound was prepared following the general procedure for N-allylation using compound **7** and 2-(bromomethyl)-3,3-dimethylbut-1-ene (**11**). Crystals were obtained from DCM and hexane (1:4). Yield: 58%. Mp 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.14 (dd, J=8.9, 5.8 Hz, 1H), 7.46 (dd, J=8.0, 2.5 Hz, 1H), 7.13–7.06 (m, 1H), 6.99 (d, J=8.6 Hz, 2H), 6.77 (d, J=8.6 Hz, 2H), 4.94 (s, 1H), 4.86 (s, 1H), 4.43 (s, 2H), 3.96 (s, 2H), 3.77 (s, 3H), 0.96 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.18, 162.61, 159.27, 150.23, 136.43, 136.39, 134.27, 134.17, 130.05, 127.27, 122.86, 122.61, 114.62, 114.41, 113.81, 107.48, 55.22, 49.79, 47.63, 34.99, 29.02. HRMS calcd for $C_{21}H_{26}BrFNO_3S$ $[M+H]^+$ 470.0795; found 470.0781.

4.4. A general procedure for synthesis of substituted allyl bromides 8–11[5]

Substituted acroleins **8a**–**11a** (1.0 g, 11.89 mmol) were dissolved in a solution of diethyl ether and methanol (8 mL:2 mL) and cooled to 0 °C. Sodium borohydride (0.44 g, 11.89 mmol) was added portion wise, and the reaction was stirred at 0 °C for 1 h and at room temperature 3–4 h. TLC showed the disappearance of starting material. The reaction mixture was diluted with diethyl ether and washed with water. The organic layer was dried over sodium sulfate, filtered, and evaporated to 1/4 volume to yield the substituted allyl alcohols **8b**–**11b**, which were used for the next step without further purification.

To a solution of compounds **8b**–**11b** (1.02 g, 11.89 mmol) in diethyl ether (10 mL) was added phosphorus tribromide (0.82 mL, 8.76 mmol) drop wise at 0 °C. Then the reaction mixture was stirred at room temperature for 8–10 h. The reaction mixture was cooled to 0 °C and quenched with ice water. The organic layer was then washed sequentially with water, saturated sodium bicarbonate, and brine solution. The combined organic layer was dried over sodium sulfate, filtered, and evaporated to 1/4 volume to yield substituted allyl bromides **8**–**11**. These crude products were used for N-allylation reaction without further purification.

4.5. A general procedure for ceric ammonium nitrate reaction (CAN) reaction 16–19

Compound **12** (0.84 g, 1.89 mmol) was dissolved in an acetonitrile:water solution (5 mL : 1 mL) to which ceric ammonium nitrate (4.16 g, 7.59 mmol) was added portion wise (3 portions) with intervals of 10 min. The reaction mixture was allowed to stir at room temperature for 10–12 h. TLC was monitored to check the progress of the reaction. The reaction mixture was quenched with 10% aq sodium bicarbonate (5 mL) solution and extracted with ethyl

acetate. The combined organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to yield the crude mixture, which was purified by column chromatography using 15% ethyl acetate in hexane to yield the product (0.80 g). According to NMR data, the product at this stage contained *p*-methoxybenzaldehyde as a byproduct. The product mixture (0.80 g, 5.87 mmol) was dissolved in methanol and cooled to 0 °C. To this mixture sodium borohydride (0.33 g, 8.81 mmol) was added slowly. The reaction was allowed to stir for 4–6 h at room temperature under nitrogen. TLC was used to monitor the progress of the reaction. The reaction mixture was quenched with water and extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to yield the crude mixture, which was purified by column chromatography using 15% ethyl acetate in hexane to yield the pure product **16** (0.54 g) and *p*-methoxybenzyl alcohol as a byproduct.

*4.5.1. 2-Bromo-4-fluoro-N-(2-methylenebutyl)benzenesulfonamide (**16**).* The title compound was prepared from compound **12** following the general procedure for CAN reaction. Yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (dd, J=8.8, 5.7 Hz, 1H), 7.48–7.36 (m, 1H), 7.17–7.09 (m, 1H), 5.09 (s, 1H), 4.88–4.79 (m, 2H), 3.48 (d, J=6.4 Hz, 2H), 2.01 (q, J=7.7 Hz, 2H), 0.987 (t, J=7.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.40, 162.33, 152.42, 134.98, 133.66, 133.55, 122.61, 120.93, 120.83, 115.05, 114.83, 110.07, 48.11, 26.38, 11.81. HRMS calcd for $C_{11}H_{14}BrFNO_2S$ $[M+H]^+$ 321.9907; found 321.9896.

*4.5.2. 2-Bromo-4-fluoro-N-(2-methylenepentyl)benzenesulfonamide (**17**).* The title compound was prepared from compound **13** following the general procedure for CAN reaction. Yield: 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (dd, J=8.6, 5.9 Hz, 1H), 7.48 (dd, J=7.9, 2.2 Hz, 1H), 7.21–7.12 (m, 1H), 5.09 (t, J=5.2 Hz, 1H), 4.93 (s, 1H), 4.84 (s, 1H), 3.46 (d, J=6.4 Hz, 2H), 1.96 (t, J=7.5 Hz, 2H), 1.45–1.30 (m, 2H), 0.86 (t, J=7.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.48, 162.90, 143.99, 133.64, 133.55, 122.58, 122.33, 120.99, 120.89, 115.04, 114.82, 112.60, 47.99, 35.63, 20.52, 13.65. HRMS calcd for $C_{12}H_{16}BrFNO_2S$ $[M+H]^+$ 336.0064; found 336.0056.

*4.5.3. 2-Bromo-4-fluoro-N-(3-methyl-2-methylenebutyl)benzenesulfonamide (**18**).* The title compound was prepared from compound **14** following the general procedure for CAN reaction. Yield: 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.14 (dd, J=8.8, 5.8 Hz, 1H), 7.47 (dd, J=7.9, 2.5 Hz, 1H), 7.16 (ddd, J=8.8, 7.6, 2.5 Hz, 1H), 5.07–4.87 (m, 1H), 4.88 (d, J=16.1, 2H), 3.50 (d, J=6.3, 2H), 2.24–2.14 (m, 1H), 0.982 (d, J=6.9 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.47, 162.89, 150.17, 135.21, 135.17, 133.64, 133.55, 122.58, 122.32, 120.97, 115.04, 114.82, 110.38, 46.95, 31.42, 21.39. HRMS calcd for $C_{12}H_{16}BrFNO_2S$ $[M+H]^+$ 336.0064; found 336.0055.

*4.5.4. 2-Bromo-N-(3,3-dimethyl-2-methylenebutyl)-4-fluorobenzenesulfonamide (**19**).* The title compound was prepared from compound **15** following the general procedure for CAN reaction. Crystals were obtained from DCM and hexane (1:4). Yield: 87%. Mp 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (dd, J=8.8, 5.8 Hz, 1H), 7.48 (dd, J=7.9, 2.5 Hz, 1H), 7.22–7.14 (m, 1H), 5.04 (t, J=5.6 Hz, 1H), 4.98 (d, J=11.1 Hz, 2H), 3.52 (d, J=6.1 Hz, 2H), 1.02 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.45, 162.87, 152.42, 134.98, 134.95, 133.64, 133.55, 122.61, 122.35, 120.93, 115.05, 114.83, 110.07, 44.36, 35.35, 28.98. HRMS calcd for $C_{13}H_{18}BrFNO_2S$ $[M+H]^+$ 350.0220; found 350.0205.

4.6. A general procedure for radical reaction 20–23 and 26

Compound **16** (180 mg, 0.55 mmol) was dissolved in toluene (12 mL) and to it was added azobisisobutyronitrile (AIBN) (18.39 mg, 0.11 mmol). The above solution was heated to about 60–70 °C and then tributyltin hydride (TBTH) (0.16 mL, 0.61 mmol) was added slowly under nitrogen. After the addition was complete, the reaction mixture was refluxed for 4–6 h. Upon completion (followed by TLC), the reaction mixture was evaporated to dryness. The residue was extracted with DCM and washed with water. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to yield the crude compound, which was further purified by column chromatography using ethyl acetate and hexane to yield the pure compound **20** (93 mg).

*4.6.1. 4-Ethyl-7-fluoro-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**20**).* The title compound was prepared starting from **16** following the general procedure for radical reaction. Crystals were obtained from DCM and hexane (1:4). Yield: 69%. Mp 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.88 (m, 1H), 6.95–6.84 (m, 2H), 4.57 (s, 1H), 3.42–3.10 (m, 2H), 1.61–6.52 (m, 2H), 1.35–1.25 (m, 1H), 1.27–1.14 (m, 2H), 0.960 (t, J=7.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.72, 163.20, 138.53, 129.60, 129.51, 128.56, 126.99, 119.23, 119.01, 113.21, 112.99, 49.47, 40.20, 33.01, 26.25, 11.46. HRMS calcd for $C_{11}H_{15}FNO_2S$ $[M+H]^+$ 244.0802; found 244.0796.

*4.6.2. 7-Fluoro-4-propyl-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**21**).* The title compound was prepared starting from **17** following the general procedure for radical reaction. Crystals were obtained from DCM and hexane (1:4). Yield: 87%. Mp 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (dd, J=8.50, 6.08 Hz, 1H), 7.02–6.90 (m, 2H), 4.51 (t, J=6.0 Hz, 1H), 3.79–2.91 (m, 4H), 1.84–1.68 (m, 1H), 1.45–1.27 (m, 2H), 1.25–1.05 (m, 2H), 0.89 (t, J=7.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.90, 163.38, 138.51, 129.64, 129.54, 119.19, 118.98, 113.23, 113.02, 49.73, 40.48, 32.78, 26.75, 20.01, 14.02. HRMS calcd for $C_{12}H_{17}FNO_2S$ $[M+H]^+$ 258.0959; found 258.0953.

*4.6.3. 7-Fluoro-4-isopropyl-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**22**).* The title compound was prepared starting from **18** following the general procedure for radical reaction. Crystals were obtained from DCM and hexane (1:4). Yield: 87%. Mp 158–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (dd, J=8.3, 5.8 Hz, 1H), 6.96 (dd, J=12.8, 4.5 Hz, 2H), 4.46 (t, J=6.5 Hz, 1H), 3.64–3.51 (m, 1H), 3.16–3.03 (m, 3H), 1.54–1.43 (m, 2H), 0.955 (d, J=6.6 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.72, 163.20, 138.46, 138.43, 129.69, 129.59, 118.91, 118.69, 113.11, 112.90, 48.16, 43.33, 38.25, 19.65, 19.19. HRMS calcd for $C_{12}H_{17}FNO_2S$ $[M+H]^+$ 258.0959; found 258.0954.

*4.6.4. 4-(tert-Butyl)-7-fluoro-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**23**).* The title compound was prepared starting from **19** following the general procedure for radical reaction. Crystals were obtained from DCM and hexane (1:4). Yield: 88%. Mp 196–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.94 (dd, J=8.3, 5.8 Hz, 1H), 6.96 (dd, J=10.8, 4.5 Hz, 2H), 4.38–4.21 (m, 1H), 3.71–3.61 (m, 1H), 3.59–3.40 (m, 2H), 2.95–2.85 (m, 1H), 1.41–1.1.38 (m, 1H), 0.98 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.83, 163.31, 142.98, 129.59, 129.50, 118.27, 118.05, 113.09, 112.88, 48.27, 47.35, 36.88, 33.07, 27.35. HRMS calcd for $C_{13}H_{19}FNO_2S$ $[M+H]^+$ 272.1115; found 272.1110.

*4.6.5. 7-Fluoro-4-phenyl-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**26**).* The title compound was prepared starting from **25** following the general procedure for radical reaction. Yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.96 (dd, J=8.6, 5.6 Hz, 1H), 7.36 (m, 2H), 7.29 (t, J=6.8 Hz, 1H), 7.21 (d, J=7.6 Hz, 2H), 7.07–6.90 (m, 2H), 4.69 (dd, J=9.1, 4.4 Hz, 1H), 4.10 (dd, J=13.7, 11.9 Hz, 1H), 4.03–3.86 (m, 1H), 3.41 (d, J=14.7 Hz, 1H), 3.03 (d, J=14.7 Hz, 1H), 2.91 (dt, J=11.3, 3.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.82,

163.29, 142.55, 141.55, 141.46, 138.64, 138.61, 129.79, 129.04, 127.35, 126.80, 119.11, 118.89, 113.43, 113.22, 51.41, 44.48, 42.10. HRMS calcd for $C_{15}H_{15}FNO_2S$ $[M+H]^+$ 292.0802; found 292.0797.

4.7. A general procedure for epoxide reaction 28–32

To a solution of compound **20** (182 mg, 0.70 mmol) in *N*,*N*-dimethyl formamide (DMF) (2 mL) was added (2*S*,3*S*)-1,2-epoxy-3-(Bocamino)-4-phenylbutane (**27**) (186 mg, 0.70 mmol) followed by the addition of cesium carbonate (461 mg, 1.41 mmol). The reaction mixture was stirred for 10–12 h at room temperature under nitrogen. TLC was checked to monitor the progress of the reaction. The reaction mixture was filtered, diluted with ethyl acetate, and then washed with water. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to yield the crude compound, which was purified by column chromatography using 25% ethyl acetate in hexane to yield the product (180 mg).

*4.7.1. tert-Butyl ((2S,3R)-4-(4-ethyl-7-fluoro-1,1-dioxido-4,5-dihydrobenzo[1,2-f]thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**28**).* The title compound was prepared starting from **20** following the general procedure for epoxide reaction. Yield: 49%. Mixture of diastereoisomers. NMR data were consistent with the proposed structure.

*4.7.2. tert-Butyl((2S,3R)-4-(7-fluoro-1,1-dioxido-4-propyl-4,5-dihydrobenzo[1,2-f] thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**29**).* The title compound was prepared starting from **21** following the general procedure for epoxide reaction. Yield: 44%. Mixture of diastereoisomers. NMR data were consistent with the proposed structure.

*4.7.3. tert-Butyl((2S,3R)-4-(7-fluoro-4-isopropyl-1,1-dioxido-4,5-dihydrobenzo[1,2-f] thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**30**).* The title compound was prepared starting from **22** following the general procedure for epoxide reaction. Yield: 45%. Mixture of diastereoisomers. NMR data were consistent with the proposed structure.

*4.7.4. tert-Butyl ((2S,3R)-4-(4-(tert-butyl)-7-fluoro-1,1-dioxido-4,5-dihydrobenzo[1,2-f]thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**31**).* The title compound was prepared starting from **23** following the general procedure for epoxide reaction. Yield: 57%. Mixture of diastereoisomers. NMR data were consistent with the proposed structure.

*4.7.5. tert-Butyl ((2S,3R)-4-(7-fluoro-1,1-dioxido-4-phenyl-4,5-dihydrobenzo[1,2-f] thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**32**).* The title compound was prepared starting from **26** following the general procedure for epoxide reaction. Yield 76%. Mixture of diastereoisomers. NMR data were consistent with the structure.

4.8. A general procedure for TFA reaction 33–42

Compound **28** (87 mg, 0.17 mmol) was dissolved in a mixture of DCM and trifluoroacetic acid (TFA) (5 mL:1 mL) and stirred at room temperature under nitrogen for 3–4 h. TLC was checked to monitor the progress of the reaction. After the reaction was complete, the reaction mixture was basified with sodium hydroxide solution (50%) and extracted with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate and evaporated to yield the crude compound. Compounds **33** (22 mg) and **38** (23 mg) were separated by preparative TLC (6% methanol in chloroform).

*4.8.1. (R)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenylbutyl)-4-ethyl-7-fluoro-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**33**) and (S)-2-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-4-ethyl-7-fluoro-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**38**).* The title compounds were prepared following general procedure for TFA reaction starting from compound **28**. Compound **33** is less polar than compound **38**.

Compound **33**. Yield: 31%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.92 (dd, J=8.9, 5.3 Hz, 1H), 7.30–7.15 (m, 5H), 7.00–6.96 (m, 2H), 3.91–3.81 (m, 1H), 3.65–3.40 (m, 1H), 3.52–3.28 (m, 1H), 3.23–3.03 (m, 3H), 2.98–2.84 (m, 3H), 2.95–2.53 (m, 1H), 2.59–2.48 (m, 1H), 2.16–1.97 (m, 2H), 1.85–1.69 (m, 1H), 1.41–1.26 (m, 2H), 0.99 (t, J=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.98, 163.46, 138.73, 135.08, 131.59, 131.50, 129.33, 129.23, 128.58, 126.45, 119.07, 118.84, 113.16, 112.95, 73.59, 56.67, 55.14, 49.84, 40.74, 38.47, 34.53, 26.89, 11.27. HRMS calcd for $C_{21}H_{28}FN_2O_3S$ $[M+H]^+$ 407.1799; found 407.1795.

Compound **38**. Yield: 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.94 (dd, J=8.9, 5.3 Hz, 1H), 7.29–7.07 (m, 5H), 6.94–6.80 (m, 2H), 4.01–3.87 (m, 1H), 3.89–3.71 (m, 1H), 3.53–3.40 (m, 2H), 3.13 (d, J=11.2 Hz, 2H), 2.97 (d, J=12.5 Hz, 1H), 2.89–2.72 (m, 2H), 2.41 (m, 1H), 2.99–2.87 (m, 2H), 1.80–1.70 (m, 1H), 1.41–1.29 (m, 3H), 0.99 (t, J=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.99, 163.46, 138.75, 135.10, 131.60, 131.50, 129.34, 129.30, 128.60, 126.45, 119.09, 118.86, 113.17, 112.96, 73.61, 56.65, 55.14, 49.84, 40.72, 38.44, 34.51, 26.89, 11.27. HRMS calcd for $C_{21}H_{28}FN_2O_3S$ $[M+H]^+$ 407.1799; found 407.1792.

*4.8.2. (R)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenylbutyl)-7-fluoro-4-propyl-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**34**) and (S)-2-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-7-fluoro-4-propyl-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**39**).* The title compounds were prepared following general procedure for TFA reaction starting from compound **29**. Compound **34** is less polar than compound **39**.

Compound **34**. Yield: 30%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.93 (dd, J=9.3, 5.5 Hz, 1H), 7.31–7.19 (m, 5H), 7.12–6.91 (m, 2H), 4.09–4.79 (m, 2H), 3.61–3.32 (m, 2H), 3.19–3.01 (m, 2H), 2.99–2.89 (m, 1H), 2.75–2.61 (m, 2H), 2.43–2.31 (m, 1H), 2.12–1.82 (m, 3H), 1.91–1.74 (m, 1H), 1.51–1.35 (m, 2H), 1.32–1.20 (m, 2H), 0.99 (t, J=7.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.95, 163.41, 138.69, 135.08, 131.52, 129.29, 129.18, 128.56, 126.42, 119.06, 118.83, 113.09, 112.93, 73.60, 55.15, 49.87, 41.14, 38.41, 36.11, 34.15, 32.78, 19.87, 14.05. HRMS calcd for $C_{22}H_{30}FN_2O_3S$ $[M+H]^+$ 421.1956; found 421.1944.

Compound **39**. Yield: 29%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.93 (dd, J=9.3, 5.5 Hz, 1H), 7.31–7.19 (m, 5H), 7.12–6.91 (m, 2H), 4.09–4.79 (m, 2H), 3.61–3.32 (m, 2H), 3.19–3.01 (m, 2H), 2.99–2.89 (m, 1H), 2.75–2.61 (m, 2H), 2.43–2.31 (m, 1H), 2.12–1.82 (m, 3H), 1.91–1.74 (m, 1H), 1.51–1.35 (m, 2H), 1.32–1.20 (m, 2H), 0.99 (t, J=7.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.96, 163.43, 138.72, 135.08, 131.55, 129.32, 129.21, 128.56, 126.42, 119.06, 118.83, 113.14, 112.93, 73.62, 55.15, 49.87, 41.11, 38.42, 36.08, 34.20, 32.78, 19.90, 14.07. HRMS calcd for $C_{22}H_{30}FN_2O_3S$ $[M+H]^+$ 421.1956; found 421.1950.

*4.8.3. (S)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenylbutyl)-7-fluoro-4-isopropyl-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**35**) and (R)-2-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-7-fluoro-4-isopropyl-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**40**).* The title compounds were prepared following general procedure for TFA reaction starting from compound **30**. Compound **35** is less polar than compound **40**.

Compound **35**. Isolated yield: 16%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (dd, J=9.2, 5.6 Hz, 1H), 7.33–7.25 (m, 2H), 7.23–7.14 (m, 3H), 7.03–6.93 (m, 2H), 4.09–4.00 (m, 1H), 3.65–3.47 (m, 2H),

3.27–3.02 (m, 3H), 2.89 (dd, *J*=13.8, 4.3 Hz, 2H), 2.67 (d, *J*=14.2 Hz, 1H), 2.51 (dd, *J*=13.5, 9.4 Hz, 1H), 2.17–1.80 (m, 3H), 1.78–1.57 (m, 2H), 1.00 (d, *J*=6.8 Hz, 3H), 0.93 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.95, 163.42, 143.14, 143.06, 138.43, 134.86, 131.56, 131.47, 129.16, 128.55, 126.43, 118.83, 118.61, 113.16, 112.94, 72.21, 54.85, 53.34, 49.56, 39.45, 37.88, 31.69, 19.26, 18.45. HRMS calcd for $C_{22}H_{30}FN_2O_3S$ $[M+H]^+$ 421.1956; found 421.1953.

Compound **40**. Yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.93 (dd, *J*=9.3, 5.5 Hz, 1H), 7.31–7.19 (m, 5H), 7.12–6.91 (m, 2H), 4.19–4.01 (m, 1H), 3.83–3.71 (m, 1H), 3.65–3.51 (m, 1H), 3.49–3.35 (m, 1H), 3.21–3.10 (m, 2H), 3.05–2.89 (m, 1H), 2.90–2.81 (m, 1H), 2.74–2.62 (m, 1H), 2.51–2.40 (m, 1H), 1.61–1.50 (m, 5H), 0.98 (dd, *J*=21.7, 6.8 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.95, 163.42, 143.36, 143.28, 138.78, 134.94, 134.91, 131.64, 131.55, 129.32, 128.55, 126.39, 118.80, 118.58, 113.03, 73.68, 55.27, 55.19, 49.68, 38.47, 37.86, 31.72, 19.40, 18.30. HRMS calcd for $C_{22}H_{30}FN_2O_3S$ $[M+H]^+$ 421.1956; found 421.1946.

*4.8.4. (S)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenylbutyl)-4-(tert-butyl)-7-fluoro-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**36**) and (R)-2-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-4-(tert-butyl)-7-fluoro-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**41**).* The title compounds were prepared following general procedure for TFA reaction starting from compound **31**. Compound **36** is less polar than compound **41**.

Compound **36**. Isolated yield: 15%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98–7.84 (m, 1H), 7.33–7.14 (m, 5H), 6.97 (d, *J*=8.4 Hz, 2H), 4.01 (t, *J*=13.3 Hz, 1H), 3.66–3.41 (m, 4H), 3.22–3.05 (m, 3H), 2.97–2.83 (m, 3H), 2.48 (dd, *J*=13.0, 10.2 Hz, 1H), 1.47 (t, *J*=11.0 Hz, 1H), 1.30–1.22 (m, 1H), 1.04–0.92 (m, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 166.25, 163.72, 143.77, 143.69, 138.69, 135.29, 135.26, 131.62, 129.42, 128.83, 126.71, 118.92, 118.69, 113.40, 113.19, 72.73, 55.16, 52.55, 49.85, 42.30, 39.75, 37.02, 33.00, 27.64. HRMS calcd for $C_{23}H_{32}FN_2O_3S$ $[M+H]^+$ 435.2112; found 435.2109.

Compound **41**. Isolated yield: 15%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.95–7.87 (m, 1H), 7.34–7.15 (m, 5H), 6.97 (d, *J*=9.2 Hz, 2H), 4.09–3.97 (m, 1H), 3.82–3.74 (m, 1H), 3.67 (d, *J*=14.1 Hz, 1H), 3.58–3.44 (m, 3H), 3.11 (d, *J*=13.0 Hz, 2H), 2.99 (d, *J*=13.7 Hz, 1H), 2.87 (d, *J*=14.4 Hz, 1H), 2.83–2.73 (m, 2H), 2.48–2.36 (m, 1H), 1.53–1.37 (m, 1H), 0.99 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 166.41, 163.51, 143.75, 143.69, 138.70, 135.29, 135.21, 131.62, 129.39, 128.83, 126.69, 118.92, 118.69, 113.43, 113.19, 72.73, 55.16, 52.53, 49.85, 42.30, 39.75, 37.05, 33.07, 27.61. HRMS calcd for $C_{23}H_{32}FN_2O_3S$ $[M+H]^+$ 435.2112; found 435.2109.

*4.8.5. (S)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenylbutyl)-7-fluoro-4-phenyl-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**37**) and (R)-2-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-7-fluoro-4-phenyl-2,3,4,5-tetrahydrobenzo[1,2-f]thiazepine 1,1-dioxide (**42**).* The title compounds were prepared starting from **32** following the general procedure for TFA reaction.

Compound **37**. Isolated yield: 18%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98 (dd, *J*=8.5, 5.6 Hz, 1H), 7.45–7.11 (m, 11H), 7.03 (m, 2H), 4.35–4.25 (m, 1H), 4.18 (dd, *J*=14.1, 11.6 Hz, 1H), 3.78–3.43 (m, 1H), 3.05 (m, 8H), 2.54 (dd, *J*=13.6, 9.3 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 166.03, 163.49, 142.27, 141.98, 141.89, 138.30, 135.16, 135.13, 131.70, 131.61, 129.16, 129.06, 128.58, 127.37, 126.83, 126.47, 119.36, 113.6, 113.42, 72.27, 56.31, 54.91, 49.94, 41.98, 39.73, 38.92. HRMS calcd for $C_{25}H_{28}FN_2O_3S$ $[M+H]^+$ 455.1799; found 455.1796.

Compound **42**. Isolated yield: 24%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.99 (dd, *J*=8.6, 5.6 Hz, 1H), 7.44–7.12 (m, 11H), 7.11–6.96 (m, 2H), 4.39–4.24 (m, 1H), 4.17 (dd, *J*=14.1, 11.9 Hz, 1H), 3.83–3.74 (m, 1H), 3.51 (d, *J*=14.9 Hz, 1H), 3.24 (dd, *J*=14.8, 3.4 Hz, 1H), 3.19–2.87 (m, 6H), 2.42 (dd, *J*=13.3, 10.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.99, 163.45, 142.49, 142.11, 142.03, 138.71, 135.11, 135.08, 131.80, 131.70, 129.28, 129.05, 128.96, 128.55, 126.89, 126.40, 119.33, 113.47, 113.26, 73.82, 57.85, 55.15, 49.66, 42.01, 39.21, 38.66. HRMS calcd for $C_{25}H_{28}FN_2O_3S$ $[M+H]^+$ 455.1799; found 455.1797.

4.9. A general procedure for *t*-Boc carbamate formation 43–45

To an ice cold solution of compound **38** (20 mg, 0.05 mmol) in THF (2 mL), diisopropylethylamine (DIPEA) (10.73 mg, 0.05 mmol) was added followed by the addition of di-*tert*-butyl dicarbonate (0.01 mL, 0.05 mmol) in THF (1 mL). The reaction mixture was slowly allowed to reach room temperature and stirring was continued for 10–12 h under nitrogen. The progress of the reaction was monitored by TLC. When the reaction was complete, the reaction mixture was diluted with water and extracted with chloroform. The combined organic layer was dried over anhydrous sodium sulfate and evaporated to yield the crude compound. The crude compound was purified by column chromatography using ethyl acetate and hexane.

*4.9.1. tert-Butyl((2S,3R)-4-((S)-4-ethyl-7-fluoro-1,1-dioxido-4,5-dihydrobenzo[1,2-f] thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**43**).* The title compound was prepared following the general procedure for *t*-Boc carbamate formation starting from compound **38**. Yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (dd, *J*=5.6, 9.3 Hz, 1H), 7.34–7.14 (m, 5H), 7.03–6.94 (m, 2H), 4.70–4.64 (m, 1H), 4.11–4.03 (m, 1H), 3.86–3.75 (m, 3H), 3.51–3.27 (m, 2H), 3.11–2.90 (m, 4H), 2.76–2.64 (m, 2H), 1.71–1.52 (m, 2H), 1.35 (s, 9H), 0.98 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.78, 163.42, 143.19, 137.99, 134.75, 131.66, 129.52, 128.44, 126.46, 118.81, 118.62, 113.07, 112.83, 107.90, 72.87, 67.66, 55.14, 54.84, 36.99, 34.91, 32.12, 29.06, 28.18, 19.42, 12.01. HRMS calcd for $C_{26}H_{36}FN_2O_5S$ $[M+H]^+$ 507.2323; found 507.2322.

*4.9.2. tert-Butyl ((2S,3R)-4-((S)-7-fluoro-1,1-dioxido-4-propyl-4,5-dihydrobenzo[1,2-f]thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**44**).* The title compound was prepared following the general procedure for *t*-Boc carbamate formation starting from compound **39**. Yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91 (dd, *J*=5.6, 9.3 Hz, 1H), 7.32–7.14 (m, 5H), 7.05–6.93 (m, 2H), 5.58 (dd, *J*=1.1, 5.5 Hz, 1H), 4.68 (d, *J*=6.9 Hz, 1H), 4.30–4.00 (m, 1H), 3.98–3.71 (m, 2H), 3.52–3.21 (m, 1H), 3.12–2.89 (m, 3H), 2.72–2.65 (m, 2H), 2.09–1.92 (m, 2H), 1.93–1.80 (m, 2H), 1.77–1.70 (m, 2H), 1.34 (s, 9H), 0.98 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.94, 163.44, 143.20, 137.89, 134.77, 131.66, 129.51, 128.42, 126.49, 118.82, 118.60, 113.05, 112.87, 107.94, 72.87, 67.65, 55.09, 49.75, 37.72, 34.92, 32.78, 29.09, 28.18, 19.93, 14.04. HRMS calcd for $C_{27}H_{38}FN_2O_5S$ $[M+H]^+$ 521.2480; found 521.2477.

*4.9.3. tert-Butyl((2S,3R)-4-((R)-7-fluoro-4-isopropyl-1,1-dioxido-4,5-dihydrobenzo[1,2-f] thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**45**).* The title compound was prepared following the general procedure for *t*-Boc carbamate formation starting from compound **40**. Yield: 27%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (dd, *J*=5.6, 9.3 Hz, 1H), 7.35–7.20 (m, 5H), 7.01–6.92 (m, 2H), 5.58 (dd, *J*=1.1, 5.5 Hz, 1H), 4.69 (d, *J*=6.9 Hz, 1H), 4.17–4.00 (m, 1H), 3.99–3.90 (m, 1H), 3.87–3.76 (m, 1H), 3.53 (dd, *J*=11.2, 13.9 Hz, 1H), 3.24 (d, *J*=15.2 Hz, 1H), 3.15–2.87 (m, 2H), 2.70–2.59 (m, 1H), 2.09–1.96 (m, 1H), 1.95–1.81 (m, 1H), 1.80–1.65 (m, 2H), 1.34 (s, 9H), 0.98 (d, *J*=6.6 Hz, 3H), 0.92 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.99, 163.46, 158.62, 143.24, 137.89, 134.77, 131.66, 129.53, 128.42, 126.46, 118.82, 118.60, 113.05, 112.83, 107.90, 72.87, 67.65, 55.14, 49.75, 37.71, 31.68, 29.09, 28.18, 23.88, 19.42, 18.26. HRMS calcd for $C_{27}H_{38}FN_2O_5S$ $[M+H]^+$ 521.2480; found 521.2479.

4.10. A general procedure for urea formation. 1-(*tert*-Butyl)-3-((2*S*,3*R*)-4-((*R*)-7-fluoro-4-isopropyl-1,1-dioxido-4,5-dihydrobenzo[1,2-*f*]thiazepin-2(3*H*)-yl)-3-hydroxy-1-phenylbutan-2-yl)urea (50)

To a solution of 2-isocyanato-2-methylpropane (0.005 mL, 0.05 mmol) in 1,4-dioxane (1 mL), was added magnesium bromide (0.87 mg, 0.005 mmol) followed by compound **40** (20 mg, 0.05 mmol) in 1,4 dioxane (1 mL). The reaction mixture was stirred at room temperature for 10–12 h under nitrogen. TLC was checked to monitor the progress of the reaction. The reaction mixture was evaporated to dryness. The residue was extracted with DCM and washed with water. The combined organic layer was dried over sodium sulfate, filtered, and evaporated to dryness to yield the crude compound, which was purified by column chromatography using 15% ethyl acetate in hexane to give the title compound **50**. Yield 55%. ^{1}H NMR (400 MHz) δ ppm 7.89 (dd, 1H, J=5.4, 9.1 Hz, 1H), 7.32–7.16 (m, 5H), 7.01–6.93 (m, 2H), 5.39 (s, 1H), 4.69–4.60 (m, 1H), 4.37–4.33 (m, 1H), 4.04–3.92 (m, 2H), 3.85–3.49 (m, 1H), 3.54–3.46 (m, 1H), 3.26–3.04 (m, 2H), 2.98–2.90 (m, 2H), 2.69–2.56 (m, 2H), 1.76–1.64 (m, 2H), 1.25 (s, 9H), 0.99 (d, J=6.5 Hz, 3H), 0.92 (d, J=6.6 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 166.01, 163.47, 158.68, 143.32, 143.24, 138.48, 134.78, 131.39, 131.31, 129.39, 129.24, 128.48, 126.41, 118.85, 113.13, 112.92, 72.29, 56.32, 53.71, 50.53, 48.87, 37.62, 37.03, 35.40, 31.68, 29.31, 19.44, 18.22. HRMS calcd for $C_{27}H_{39}FN_3O_4S$ $[M+H]^+$ 520.2640; found 520.2636.

4.11. A general procedure for tetrahydrofuran (THF) carbamate formation 47–49 and 51–52

To a solution of (*S*)-2,5-dioxopyrrolidin-1-yl (tetrahydrofuran-3-yl) carbonate (12.6 mg, 0.06 mmol) and triethylamine (0.01 mL, 0.1 mmol) in DCM (2 mL), was added compound **40** (20 mg, 0.05 mmol) dissolved in DCM (1 mL). The reaction mixture was stirred at room temperature for 10–12 h under nitrogen. After the completion of the reaction, monitored by TLC, the reaction mixture was diluted with DCM, and washed with saturated aq sodium bicarbonate solution. The aqueous layer was again extracted with DCM. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to give the crude compound, which was purified by column chromatography using 20% ethyl acetate in hexane to give the pure compound **47** (11 mg).

*4.11.1. (S)-Tetrahydrofuran-3-yl((2S,3R)-4-((R)-7-fluoro-4-isopropyl-1,1-dioxido-4,5-dihydrobenzo[1,2-f]thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**47**).* The title compound was prepared following the general procedure for THF carbamate starting from compound **40**. Yield: 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (dd, J=9.3, 5.6 Hz, 1H), 7.25 (m, 5H), 6.98 (m, 2H), 5.12 (m, 1H), 4.89 (m, 1H), 4.08 (m, 1H), 3.86 (m, 5H), 3.68 (m, 1H), 3.53 (m, 1H), 3.22 (m, 1H), 3.05 (m, 1H), 2.84 (m, 1H), 2.64 (m, 2H), 2.09 (m, 1H), 1.90 (m, 1H), 1.72 (m, 1H), 1.58 (m, 2H), 1.28 (m, 1H), 0.99 (d, J=6.9 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 166.06, 163.53, 156.69, 143.25, 137.61, 134.68, 131.70, 129.46, 128.54, 126.62, 118.93, 118.70, 114.68, 113.10, 112.89, 75.58, 73.10, 72.64, 66.87, 55.43, 54.92, 49.90, 37.81, 35.03, 32.78, 25.44, 19.40, 18.34. HRMS calcd for $C_{27}H_{36}FN_2O_6S$ $[M+H]^+$ 535.2273; found 535.2265.

*4.11.2. (S)-Tetrahydrofuran-3-yl((2S,3R)-4-((R)-4-(tert-butyl)-7-fluoro-1,1-dioxido-4,5-dihydrobenzo[1,2-f]thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**48**).* The title compound was prepared following the general procedure for THF carbamate starting from compound **41**. Yield: 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98–7.81 (m, 1H), 7.38–7.15 (m, 5H), 7.06–6.89 (m, 2H), 5.15–5.07 (m, 1H), 4.95–4.83 (m, 1H), 4.13–3.96 (m, 1H), 3.96–3.58 (m, 7H), 3.59–3.40 (m, 2H), 3.13–2.98 (m, 2H), 2.95–2.80 (m, 2H), 2.67–2.57 (m, 1H), 2.13–2.05 (m, 1H), 1.98–1.81 (m, 1H), 1.47–1.36 (m, 1H), 0.98 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 166.03, 163.50, 156.56, 143.65, 143.57, 137.56, 137.19, 134.82, 131.41, 129.44, 128.49, 126.57, 118.70, 118.48, 113.02, 112.80, 75.48, 73.09, 72.73, 66.85, 55.29, 49.94, 36.81, 36.73, 35.10, 32.74, 32.69, 22.61, 14.09. HRMS calcd for $C_{28}H_{38}FN_2O_6S$ $[M+H]^+$ 549.2429; found 549.2422.

*4.11.3. (S)-Tetrahydrofuran-3-yl((2S,3R)-4-((R)-4-(4-fluorophenyl)-1,1-dioxido-4,5-dihydrobenzo[1,2-f]thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**49**).* The title compounds were prepared starting from **42** following the general procedure for THF carbamate formation. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.96 (dd, J=8.6, 5.6 Hz, 1H), 7.42–7.15 (m, 10H), 7.10–6.95 (m, 2H), 5.13–5.06 (m, 1H), 5.03–4.79 (m, 1H), 4.41–4.26 (m, 1H), 4.13 (m, 2H), 3.95–3.62 (m, 5H), 3.40–3.27 (m, 1H), 3.22–3.12 (m, 1H), 3.07–2.73 (m, 5H), 2.19–2.05 (m, 1H), 2.04 (m, 1H), 1.87 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 166.09, 163.55, 156.67, 142.24, 142.10, 142.02, 137.57, 134.92, 134.90, 131.80, 129.41, 129.05, 128.54, 127.39, 126.87, 126.62, 119.44, 119.22, 113.52, 113.30, 75.58, 73.04, 72.74, 66.84, 57.47, 55.42, 50.04, 42.04, 39.09, 34.85, 32.78. HRMS calcd for $C_{30}H_{34}FN_2O_6S$ $[M+H]^+$ 569.2116; found 569.2113.

*4.11.4. (S)-Tetrahydrofuran-3-yl((2S,3R)-4-((S)-7-fluoro-4-isopropyl-1,1-dioxido-4,5-dihydrobenzo[1,2-f]thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**51**).* The title compound was prepared following the general procedure for THF carbamate starting from compound **35**. Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87 (dd, J=9.2, 5.6 Hz, 1H), 7.31–7.12 (m, 5H), 7.10–6.93 (m, 2H), 5.15–5.02 (m, 1H), 5.01–4.94 (m, 1H), 4.06–3.95 (m, 1H), 3.79–3.60 (m, 5H), 3.62–3.42 (m, 3H), 3.15–3.01 (m, 1H), 2.97–2.86 (m, 3H), 2.71–2.60 (m, 2H), 2.07–2.00 (m, 1H), 1.91–1.79 (m, 1H), 1.70–1.65 (m, 1H), 1.57–1.50 (m, 1H), 0.97 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 166.00, 163.47, 155.86, 143.09, 143.00, 137.29, 134.61, 131.55, 131.45, 129.36, 128.42, 126.50, 118.92, 118.69, 113.21, 112.99, 75.23, 73.10, 71.45, 66.78, 54.56, 53.74, 50.74, 37.75, 35.46, 32.64, 31.61, 19.25, 18.34. HRMS calcd for $C_{27}H_{36}FN_2O_6S$ $[M+H]^+$ 535.2273; found 535.2251.

*4.11.5. (S)-Tetrahydrofuran-3-yl((2S,3R)-4-((S)-4-(tert-butyl)-7-fluoro-1,1-dioxido-4,5-dihydrobenzo[1,2- f]thiazepin-2(3H)-yl)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**52**).* The title compound was prepared following the general procedure for THF carbamate starting from compound **36**. Yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.99–7.82 (m, 1H), 7.32–7.14 (m, 5H), 7.05–6.92 (m, 2H), 5.13–5.05 (m, 1H), 4.91–4.83 (m, 1H), 4.15–4.08 (m, 1H), 4.02–3.93 (m, 1H), 3.87–3.66 (m, 4H), 3.59 (d, J=10.4 Hz, 1H), 3.53–3.42 (m, 2H), 3.36 (d, J=14.3 Hz, 1H), 2.99–2.82 (m, 4H), 2.76–2.65 (m, 1H), 2.14–2.02 (m, 1H), 1.95–1.81 (m, 1H), 1.42–1.29 (m, 1H), 0.96 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 166.09, 163.55, 155.89, 143.50, 143.41, 137.18, 134.75, 131.50, 131.40, 129.46, 128.50, 126.59, 118.79, 118.57, 113.24, 113.03, 75.28, 73.20, 71.70, 66.84, 54.52, 52.87, 51.01, 42.39, 36.73, 35.63, 32.70, 27.38, 18.34. HRMS calcd for $C_{28}H_{38}FN_2O_6S$ $[M+H]^+$ 549.2429; found 549.2421.

4.12. In vitro HIV-1 protease assay

Compounds were evaluated for the ability to inhibit the enzymatic activity of HIV-1 protease in an in vitro assay modified for product quantitation with use of mass spectrometric analysis.[8] Protease activity was assessed in reactions catalyzed by purified HIV-1 protease at 20 pM in buffer (50 mM sodium acetate, pH 5.5, 100 mM NaCl, 1 mg/mL bovine serum albumin) using a peptide substrate with sequence Val-Ser-Gln-Asn-(β-naphthylalanine)-Pro-Ile-Val at 450 μM in a final volume of 25 μL. Compounds in DMSO stock were added to a final DMSO concentration of 2.5% and

preincubated with enzyme prior to the initiation of the reaction by addition of substrate. Inhibitor dose titrations were used to determine IC_{50} values. Reactions were incubated at 30 °C for 60 min and were then quenched by the addition of 30 μL of 0.04% formic acid and 250 nM indinavir as an internal standard. The amount of product formed was determined using high performance liquid chromatography with a Zorbax Eclipse XDB-C18 column and mass spectrometric detection of product on an Agilent API4000 mass spectrometer. Percent inhibition was determined relative to control samples without inhibitor, and IC_{50} values were determined using a standard four parameter fit to the inhibition data. K_i values were determined from Eq. 1 for competitive inhibitors,

$$IC_{50} = K_i(1 + [S]/K_M) \quad (1)$$

with a K_M of 90 μM.

4.13. X-ray crystallography

The triple mutant Q7K L33I L63I was used because of its higher stability against autoproteolysis. HIV-1 protease crystals were grown by the hanging-drop vapor diffusion method against 0.7 M NaCl, acetate buffer, pH 5.5. Plate-shaped crystals belong to space group P21212 with unit cell dimensions of a=58.6 Å, b=85.9 Å, c=46.2 Å and one dimer per asymmetric unit. Crystals were soaked in the reservoir solution in the presence of 1 mM inhibitor. 25% glycerol was added for cryoprotection, and crystals were flash-frozen in liquid nitrogen. High resolution limits lay between 1.18 and 1.56 Å. Data sets with atleast 97% completeness were collected at the APS beamline ID17 (Argonne, IL) and processed using autoProc. Rmerge and I/σ were atleast 6.9% and 15.9 for the whole data set and were 63.4% and 2.5 for the highest resolution shell, respectively. The structures were refined using Buster and manually refitted using Coot, resulting in final Rwork (Rfree) of 20.0% (20.7%) and excellent geometry. Figures were generated using Pymol.

4.14. Accession codes

The X-ray crystal structure of inhibitors **47**, **48**, **50**, and **52** bound to HIV-1 protease have been deposited within the Protein Databank with access code 4mc9, 4mc6, 4mc2, and 4mc1, respectively.

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