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Transforming Sphingosine Kinase 1 Inhibitors into Dual and Sphingosine Kinase 2 Selective Inhibitors: Design, Synthesis, and *In Vivo* Activity

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KEYWORDS

Sphingosine, sphingosine 1-phosphate, sphingosine kinase, aminothiazole, structure-activity relationships.

ABSTRACT

Sphingosine 1-phosphate (S1P) is a pleiotropic signaling molecule that interacts with its five G-protein coupled receptors $S1P_{1-5}$ to regulate cell growth and survival and has been implicated in a

variety of diseases including cancer and sickle cell disease. As the key mediators in the synthesis of S1P, sphingosine kinase (SphK) isoforms 1 and 2 have attracted attention as viable targets for pharmaceutical inhibition. In this report, we describe the design, synthesis, and biological evaluation of aminothiazole-based guanidine inhibitors of SphK. Surprisingly, combining features of reported SphK1 inhibitors generated SphK1/2 dual inhibitor **20l** (SLC4011540) (hSphK1 K_i = 120 nM, hSphK2 K_i = 90 nM) and SphK2 inhibitor **20dd** (SLC4101431) (K_i = 90 nM, 100-fold SphK2 selectivity). These compounds effectively decrease S1P levels *in vitro*. *In vivo* administration of **20dd** validated that inhibition of SphK2 increases blood S1P levels.

INTRODUCTION

Sphingosine 1-phosphate (S1P) is a ubiquitous cellular signaling molecule that has been implicated in a variety of diseases including cancer,[1-4] fibrosis,[5-7] Alzheimer's,[8, 9] sickle cell disease,[10, 11] and viral infections such as Chikungunya virus.[12] S1P interacts with proteins both within and outside of the cell. As an extracellular ligand, S1P promotes cell migration and survival by binding to five G-protein coupled receptors, $S1P_{1\text{-}5}$.[13-16] Although its function as an intracellular ligand is less well defined, S1P is reported to control epigenetic modifications through regulation of HDAC 1/2 activity via sphingosine kinase isotype 2 (SphK2) and alter erythrocyte glycolysis to increase O_2 release under hypoxic conditions.[17-19] S1P is synthesized by the phosphorylation of sphingosine (Sph) by SphK, which exists as two isotypes – SphK1 and SphK2. SphK1 and SphK2 share approximately 50% sequence identity[20] but differ with respect to their function, in part due to their differing localization within the cell. SphK1 is a cytosolic enzyme that promotes cell survival and proliferation,[21, 22] whereas some SphK2 is found in the nucleus[17, 18] but can relocate to the cytosol on phosphorylation.[23, 24] Depending on this localization, SphK2 can promote either apoptosis[12,13] or cell proliferation.[17, 18, 25, 26] Although

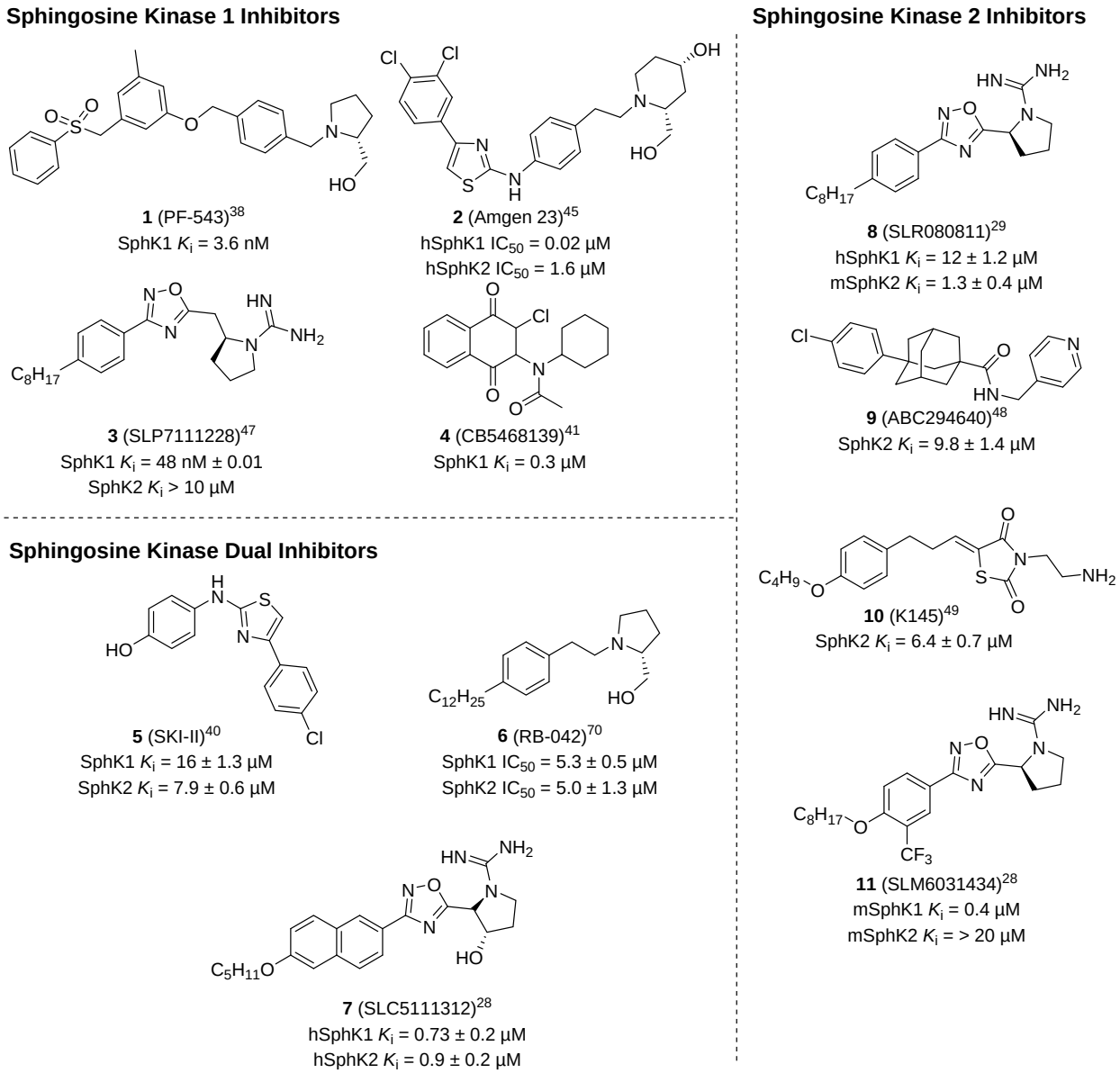
isotype-specific SphK null mice are viable, fertile, and phenotypically unremarkable,[27] SphK1-null mice have about a two-fold reduction in blood S1P levels while SphK2-null mice have 2-4 fold increased blood S1P levels.[28-32] However, ablation of both SphK isotype genes in the mouse is embryonically lethal in mid gestation as a consequence of complications during vascular and neurological development.[27, 32]

The therapeutic potential of drugging the S1P pathway was realized by the approval of Fingolimod by the Food and Drug Administration for the treatment of multiple sclerosis. [33, 34] Fingolimod is a pro-drug that is phosphorylated by SphK2 to act as a functional antagonist of S1P receptors, S1P1/3. Other approaches have also been employed to manipulate S1P activity including targeting SphKs to control S1P synthesis.[3, 35-37] There are currently multiple reports of potent SphK1-selective inhibitors and SphK1/SphK2-dual inhibitors (Figure 1). Inhibitors such as the SphK1-selective inhibitor **1** (PF-543)[38, 39] and the SphK1/SphK2-dual inhibitor **5** (SKI-II)[40-42] have been co-crystallized with SphK1 and have been useful in developing next generation inhibitors.[43, 44] Indeed, medicinal chemists at Amgen improved **5** to realize a selective SphK1 inhibitor, **2** (Amgen 23),[45] while preserving the aminothiazole region. While **5** is recently reported to have off-target activity against dihydroceramide desaturase,[46] **1** has shown promise for disease states such as sickle cell disease, where inflammation, cell sickling, and hemolysis were reduced in treated mouse models.[11]

In contrast with SphK1 inhibitors, highly potent SphK2-selective inhibitors are lacking. Early SphK2 inhibitors (**8** (SLR080811),[29, 47] **9** (ABC294640),[48] and **10** (K145)[49, 50]), which have low micromolar potency and are modestly selective vs. SphK1, are active in cultured cells as measured by lowering of cellular S1P levels. Among these, **9** has been deployed in a variety of animal disease models, including ulcerative colitis,[51] Crohns disease,[52] ischaemia/reperfusion

injury,[53] osteoarthritis,[54] and colon cancer.[55] However, **9** has recently been reported to have an off-target effect of acting as a tamoxifen-like molecule with the estrogen receptor.[56] The development of improved inhibitors that are SphK2 specific will help in understanding the physiological function of SphK2 *in vivo*. Recently, SphK2 was shown to play a role in endothelial cell barrier integrity as well as attenuation of kidney fibrosis through

Figure 1. Select SphK Inhibitors



interferon gamma using the azetidine analogue of **8**.[57, 58] In addition, an oncogenic role for SphK2 is emerging where high-level overexpression is associated with reduced cell survival and proliferation.[59]

The paucity of small molecule chemical biology tools for investigating SphK2 function prompted our interest in developing better selective SphK2 inhibitors. We previously reported two new guanidine-based inhibitors: the SphK1/SphK2 dual-inhibitor **7** (SLC5111312)[28, 60] and the SphK2-selective inhibitor **11** (SLM6031434)[28] (>50-fold selective). Treatment of mice with these inhibitors slows the clearance of mass-labeled S1P from the bloodstream, which implicates SphK2 in the disposal of circulating S1P. Although the mechanism whereby SphK2 influences S1P clearance from blood is currently unclear, these results highlight the need for more potent and selective SphK2 and SphK1/SphK2 dual inhibitors to explore this phenomenon further. Herein, we report the synthesis, structure-activity relationship study, and biological evaluation of guanidine-based aminothiazoles with *in vivo* activity as selective SphK2 inhibitors.

RESULTS AND DISCUSSION

Inhibitor Design and Development

Our group reported the synthesis of **3** (SLP7111228),[47] an SphK1-selective inhibitor with a K_i of 48 nM and >100-fold selectivity for SphK1 over SphK2 for both the rat and human enzymes. This compound was found to reduce S1P levels in both cultured human U937 leukemia cells and in the bloodstream of rats. The latter result recapitulates the phenotype of SphK1 null mice.[32, 47] In developing this molecule, the addition of a methylene unit between the 1,2,4-oxadiazole and pyrrolidine rings was key in converting a 10-fold SphK2-selective inhibitor (**8**) into a >100-fold SphK1-selective inhibitor. In this work, we sought to improve **3**'s potency and selectivity further by replacing the octyl chain with an aminothiazole group, as present in SphK1

inhibitors such as **2** (Figure 2). Docking of **2** into the binding pocket of a homology model of SphK2 and superimposition with **2**'s "aminothiazole tail" linked to an oxadiazole phenyl ring suggested binding interactions mimicking **2** (Figure 3). We hypothesized that these altered 'tail' groups, represented by the 14-18 carbon aliphatic groups of sphingoid bases, would create inhibitors that can adopt the necessary "j-shape" for strong binding interactions with the sphingosine binding pocket, as established by published co-crystal structures of SphK1 with the aminothiazole-based inhibitors **2** and **5**.[44, 45] Gustin *et al.* recently developed potent aminothiazole-based SphK1/SphK2-dual inhibitors derived from **5**, including **2**.[45] Although most compounds reported were dual-inhibitors, some compounds in their series show a bias towards SphK1 inhibition with attractive pharmacokinetic properties. Vogt and co-workers subsequently reported the synthesis of aminothiazole-based derivatives of **5** that are SphK1/SphK2-dual inhibitors with several inhibitors showing a slight bias for SphK2 selectivity.[61] However, these molecules show only micromolar potency, and extensive biological studies have yet to be reported. Aurelio *et al*. also recently reported the synthesis of derivatives of **5** that show limited success as SphK1/SphK2 dual inhibitors and SphK1- and SphK2-selective inhibitors.[62] Due to the prominence of aminothiazole moieties in SphK inhibitor scaffolds, we incorporated aminothiazole moieties into our guanidine-based scaffold, specifically SphK1-selective inhibitors.

Figure 2. Tail group modifications towards the development of new "j-shaped" SphK1 inhibitors.

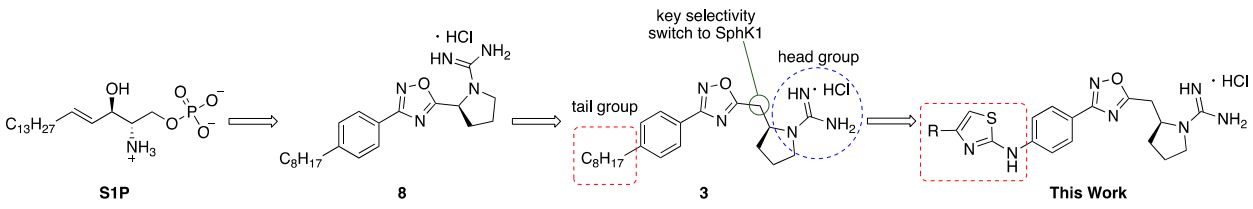
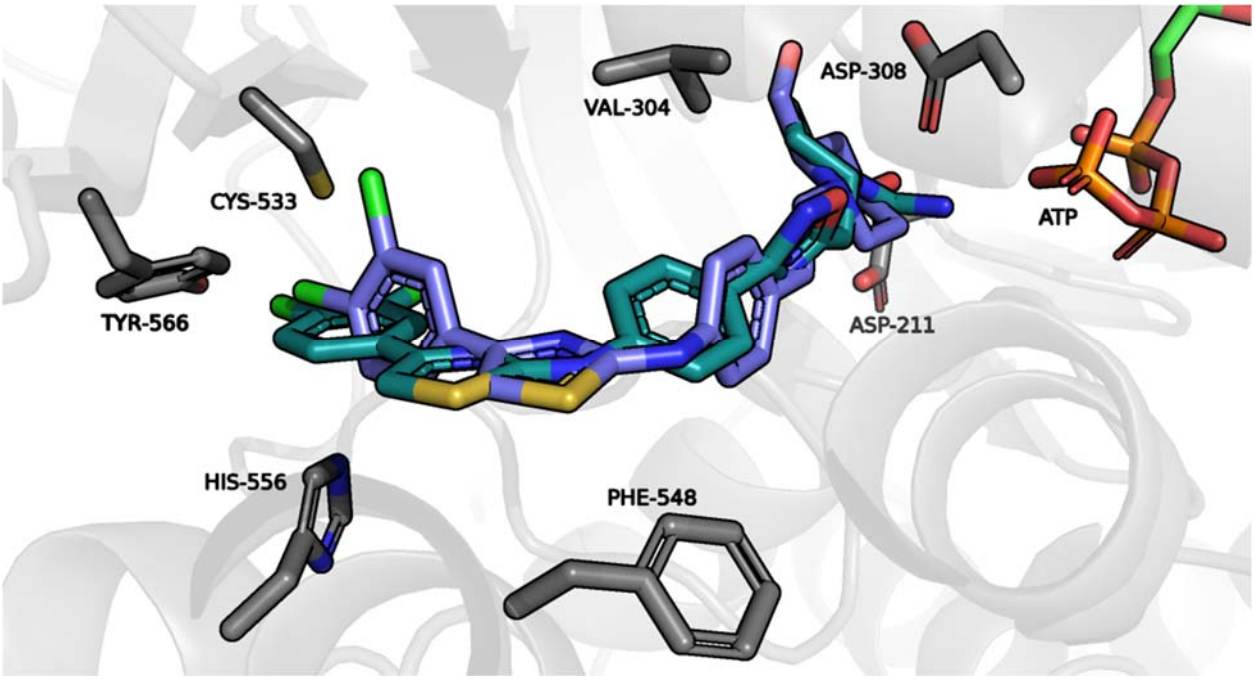


Figure 3. Superimposition of lowest energy docked poses of **2** (purple sticks, colored by atom) and aminothiazole analogue of **3** (teal stick, color by atom) in homology model of SphK2. Key residues in the binding cavity are shown as grey sticks, ATP is shown green colored by atom, and the overall protein structure is shown as grey cartoon for perspective.

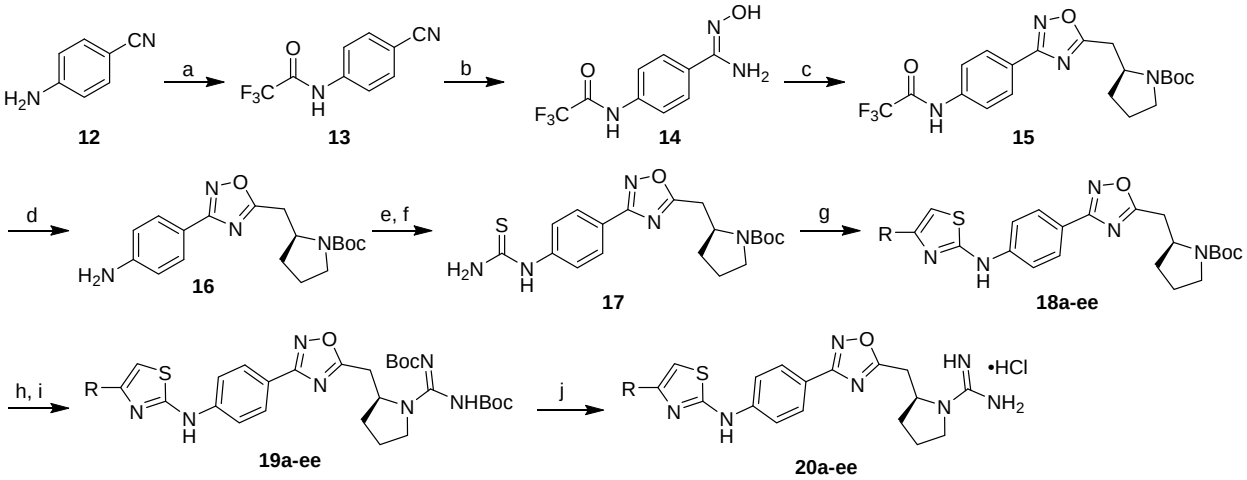


Inhibitor Synthesis

In prior studies,[47, 63] we established that the guanidine, 1,2,4-oxadiazole, and internal phenyl ring moieties were key features of the sphingosine kinase inhibitor scaffold. Therefore, we focused our attention on the 'tail' region by appending aminothiazoles decorated with diverse aryl structures. The synthesis of aryl-substituted aminothiazoles is shown in Scheme 1. 4-Trifluoromethylacetamide benzonitrile **13** was synthesized by the acetylation of 4-aminobenzonitrile **12** with trifluoroacetic anhydride. Benzonitrile **13** was then reacted with hydroxylamine hydrochloride and triethylamine in ethanol using a microwave reactor to yield amidoxime **14**, which was reacted with homoproline using HCTU and Hunig's base at 100 ºC to

afford the 1,2,4-oxadiazole **15**. The trifluoroacetate group was removed using lithium hydroxide to afford amine **16**. Treatment of **16** with thiocarbodiimidazole followed by ammonia provided the key intermediate thiourea **17**. Aminothiazoles **18a-ee** were produced by reacting the required

Scheme 1. Synthesis of aryl-substituted aminothiazole derivatives **20a-ee**.[a]



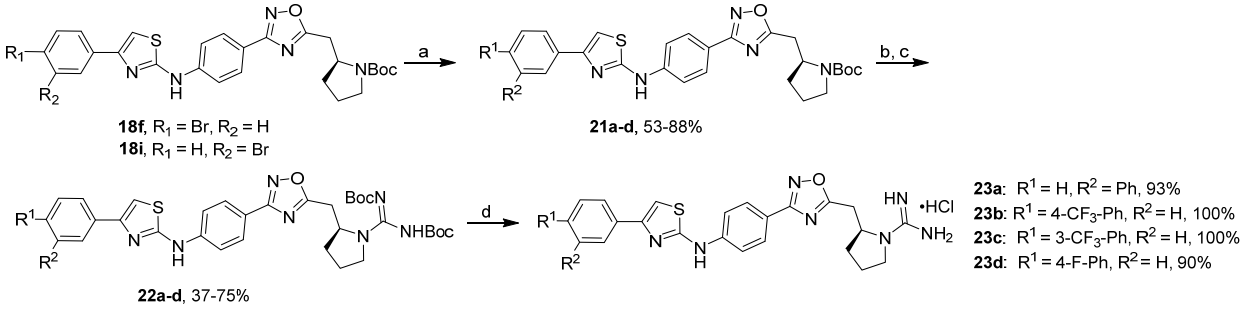
[a] Reagents and conditions: (a) trifluoroacetic anhydride, DCM, 0 ºC - rt, 19 h, 88%; (b) $NH_2OH{\cdot}HCl$, TEA, ACN, 150 ºC microwave, 6 min, 57%; (c) Boc-L-homoproline, HCTU, DIEA, DMF, rt - 100 ºC, 4 h, 67%; (d) 1:1 1M LiOH:MeOH, 100 ºC, 3 h, 82%; (e) Thio-CDI, THF, rt, 4 h; (f) NH_3(*g*), 1 min, 86%; (g) α-bromoketone, DIEA, EtOH, 100 ºC, microwave, 5 min, 30-90%; (h) 1:1 TFA:DCM (i) *N*, *N*'-di-Boc-1*H*-pyrazole-1-carboxamidine, DIEA, ACN, 50 ºC, microwave, 2 h, 26-87%; (j) HCl (*g*), MeOH, 90-100%.

α-bromoketone with thiourea **17** and Hunig's base in ethanol in a microwave reactor. The Boc group was removed with trifluoroacetic acid and immediately reacted with *N*,*N'*-di-Boc-1*H*-pyrazole-1-carboxamidine in a microwave reactor to afford the *bis*-Boc-protected guanidines **19a-ee**. Bubbling HCl gas subsequently provided the desired guanidine derivatives **20a-ee** (see Tables 1 and 2 for structures).

Biphenyl derivatives were synthesized as outlined in Scheme 2. Using either compound **18f** or **18i**, Suzuki-Miyaura cross-coupling with various aryl boronic acids yielded the biaryl

aminothiazoles **21a-d**. The standard synthetic sequence of deprotection, guanylation, and deprotection was then followed to yield the desired biaryl aminothiazole derivatives **23 a-d**.

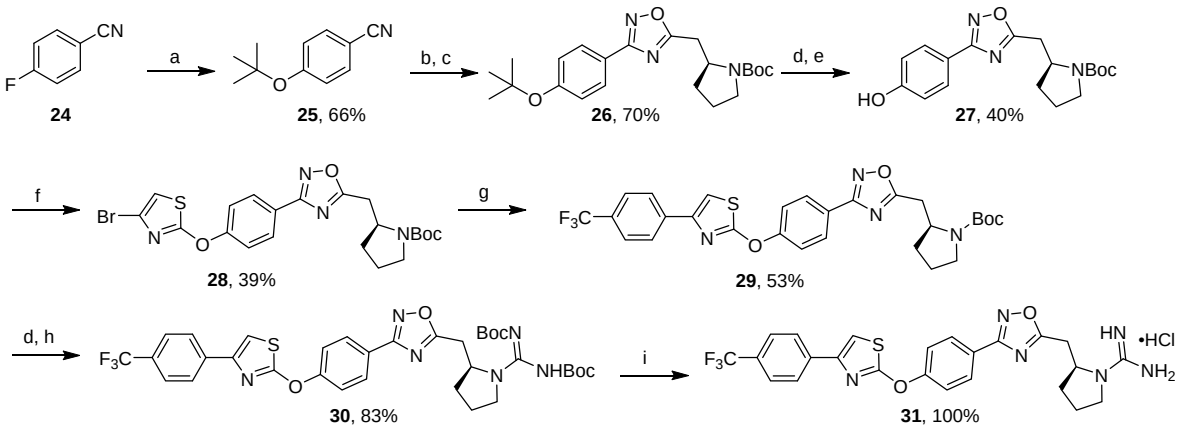
Scheme 2. Synthesis of biphenyl aminothiazole derivatives **23a-d**.[a]



[a]Reagents and conditions: (a) aryl boronic acid, $PdCl_2(dppf)$, Cs_2CO_3, DMF, 150 ºC microwave, 90 min; (b) 1:1 TFA:DCM; (c) *N*, *N*'-di-Boc-1*H*-pyrazole-1-carboxamidine, DIEA, ACN, 50 ºC, microwave, 2 h; (d) HCl (*g*), MeOH.

To assess the significance of the hydrogen bond effect in this series of aminothiazole, a comparison of activity between a representative aminothiazole example of the series (**20k**, Table 1) and its analogous oxathiazole was done. The corresponding oxathiazole derivative was synthesized as presented in Scheme 3. 4-*Tert*-butoxy benzonitrile **25** was synthesized via nucleophilic aromatic substitution of 4-fluorobenzonitrile **24** with 1 M potassium *tert*-butoxide. The benzonitrile **25** was then reacted with hydroxylamine hydrochloride and triethylamine in ethanol using a microwave reactor to yield its amidoxime that was then reacted with homoproline using HCTU and Hunig's base at 100 ºC to afford the 1,2,4-oxadiazole **26**. The phenol derivative **27** was achieved via treatment of 1,2,4-oxadiazole **26** with trifluoroacetic acid followed by reprotection with Boc-anhydride. Nucleophilic aromatic substitution with the phenol derivative **27** on 2,4-dibromothiazole afforded the oxathiazole **28**. Suzuki-Miyaura cross-coupling with 4-trifluoromethylphenylboronic acid yielded the desired oxathiazole **29**. The standard synthetic sequence of deprotection, guanylation, and deprotection was followed for compound **29** to yield the desired oxathiazole derivative **31**.

Scheme 3. Synthesis of the oxathiazole analogue of inhibitor **20k**.[a]



24

25, 66%

26, 70%

27, 40%

28, 39%

29, 53%

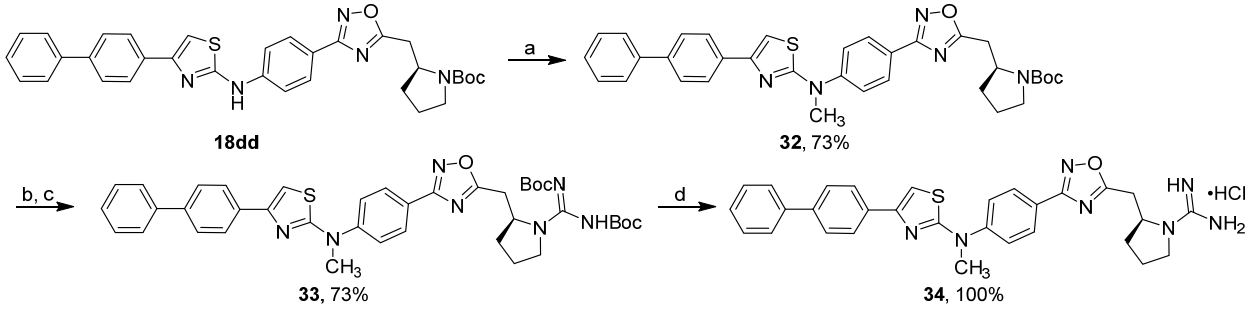
30, 83%

31, 100%

[a]Reagents and conditions: (a) 1M KO^{t}Bu; THF, reflux, 15 h; (b) $NH_2OH{\cdot}HCl$, TEA, EtOH, 150 ºC microwave, 6 min; (c) Boc-L-homoproline, HCTU, DIEA, DMF, rt - 100 ºC, 4 h; (d) 1:1 TFA:DCM (e) di-*tert*-butyl dicarbonate, TEA, dioxane, 0 ºC, 1 h; (f) 2, 5-dibromothiazole, K_2CO_3, DMF, 135 ºC, 1 h; (g) 4-trifluoromethylphenyl boronic acid, $PdCl_2$(dppf), Cs_2CO_3, DMF, 150 ºC, microwave, 90 min; (h) *N*, *N*'-di-Boc-1*H*-pyrazole-1-carboxamidine, DIEA, ACN, 50 ºC, microwave, 2 h; (i) HCl (*g*), MeOH.

To further probe the significance of the hydrogen bond effect of the amino moiety in **20dd**, its methylated derivative was synthesized as illustrated in Scheme 4. The biaryl aminothiazole **18dd** was methylated with methyl iodine in refluxing acetone to yield the **32**. The standard synthetic sequence of deprotection, guanylation, and deprotection was then followed to yield the desired methylated aminothiazole derivative **34**.

Scheme 4. Synthesis of the methylated analogue of **20dd**.[a]



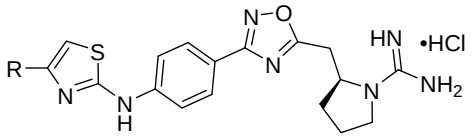
[a]Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux, 17 h; (b) 1:1 TFA:DCM; (c) *N*, *N*'-di-Boc-1*H*-pyrazole-1-carboxamidine, DIEA, ACN, 50 ºC, microwave, 2 h; (d) HCl (*g*), MeOH.

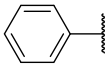
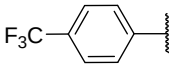
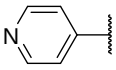
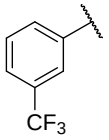
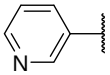
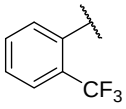
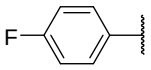
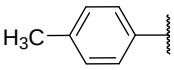
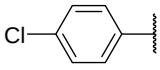
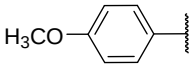
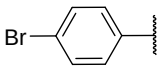
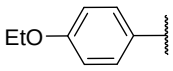
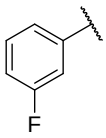
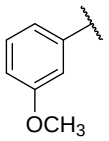
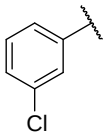
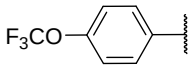
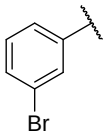
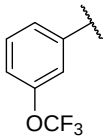
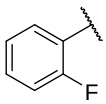
Structure-Activity Relationship Studies and Biological Evaluation of Derivatives

With the goal of defining the structure-activity profile of SphKs, a focused library of aminothiazoles bearing a guanidine group was synthesized. These analogues were assayed using a previously described protocol.[47, 64] In particular, synthesized inhibitors were tested at 0.3 μM with human recombinant enzymes (Tables 1 & 2). All aminothiazoles vary with respect to the number and type of substituents on the appended aryl ring as well as the substitution pattern on this ring.

As shown in Table 1, substituting the thiazole ring with an unsubstituted phenyl ring (**20a)** resulted in poor inhibition of either SphK isotype in our assay. Replacement of the phenyl ring with either a 4' (**20b**) or 3' (**20c**) pyridyl ring also produced compounds that were inactive with both SphK isotypes. Halogen substituents at the *para* position of the phenyl ring inhibited both enzymes but with slight selectivity for SphK2. The selectivity and potency for SphK2 was unanticipated because these compounds were expected to inhibit SphK1, as previous work from our laboratories demonstrated that the homologated guanidine-pyrrolidine head group[47] generates an SphK1 inhibitor when the 'tail' is an unsubstituted octyl group. Furthermore, aminothiazoles in the Amgen series are also selective for SphK1,[45] although their scaffold differed in other aspects also. The identity of the halogen atom – fluorine, chlorine, or bromine –

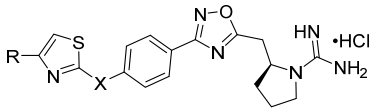
Table 1. SphK1 and SphK2 Inhibitory Activity for Mono-Substituted Aminothiazole Derivatives. [a]

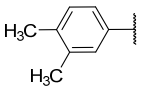
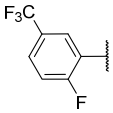
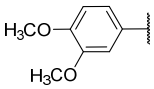
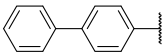
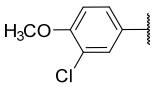
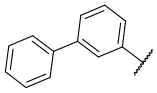
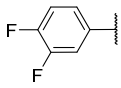
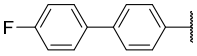
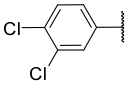
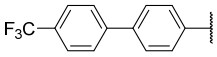
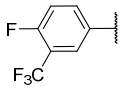
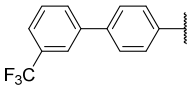
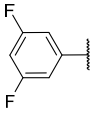
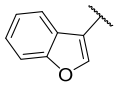
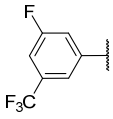
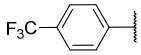
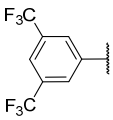
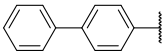


Compound	R	hSphK1	hSphK2	Compound	R	hSphK1	hSphK2
20a		100 ± 6	83 ± 4	**20k**		57 ± 0.4	36 ± 1
20b		100 ± 5	94 ± 4	**20l**		31 ± 12	28 ± 0.7
20c		95 ± 10	94 ± 7	**20m**		69 ± 4	72 ± 6
20d		100 ± 13	55 ± 1	**20n**		75 ± 0.2	80 ± 7
20e		70 ± 3	51 ± 0	**20o**		91± 2	100 ± 2
20f		88 ± 4	46 ± 6	**20p**		100 ± 9	84 ± 2
20g		60 ± 1	45 ± 2	**20q**		90 ± 1	100 ± 2
20h		64 ± 1	45 ± 10	**20r**		89 ± 0.7	44 ± 12
20i		79 ± 12	44 ± 8	**20s**		58 ± 4	82 ± 6
20j		50 ± 4	44 ± 9				

[a] SphK activity is presented as % control (no inhibitor added). Recombinant human SphK1 or SphK2 was isolated from a cell lysate, and enzyme activity was measured with 5 μM (SphK1) or 10 μM (SphK2) sphingosine and 250 μM γ-[^{32}P]ATP. Compounds were assayed at 0.3 μM in triplicate.

Table 2. SphK1 and SphK2 Inhibitory Activity for Di-Substituted and Bulky Aminothiazole Derivatives. [a]



Compound	R	X	hSphK1	hSphK2	Compound	R	X	hSphK1	hSphK2
20t		NH	91 ± 4	67 ± 12	**20cc**		NH	65 ± 2	48 ± 1
20u		NH	100 ± 7	100 ± 7	**20dd**		NH	100 ± 2	27 ± 12
20v		NH	100 ± 0.2	71 ± 11	**23a**		NH	92 ± 8	73 ± 7
20w		NH	51 ± 5	51 ± 5	**23b**		NH	82 ± 9	31 ± 7
20x		NH	51 ± 4	46 ± 11	**23c**		NH	100 ± 2	96 ± 1
20y		NH	58 ± 5	33 ± 5	**23d**		NH	99 ± 6	85 ± 3
20z		NH	68 ± 7	43 ± 8	**20ee**		NH	68 ± 7	67 ± 5
20aa		NH	51 ± 4	30 ± 15	**31**		O	62 ± 4	55 ± 2
20bb		NH	100 ± 4	63 ± 4	**34**		NCH_3	100 ± 5	100 ± 5

[a] SphK activity is presented as % control (no inhibitor added). Recombinant human SphK1 or SphK2 was isolated from a cell lysate, and enzyme activity was measured with 5 μM (SphK1) or 10 μM (SphK2) sphingosine and 250 μM γ-[^{32}P]ATP. Compounds were assayed at 0.3 μM in triplicate.

did not greatly affect the compounds' (**20d-f**) SphK2 potency, reducing the enzyme activity to ~ 50%. Moving the halogen group to the *meta* or *ortho* position (**20g-j**) resulted in a retention of SphK2 potency, but with a loss in SphK2 selectivity, producing only moderately SphK2 selective inhibitors.

Because of the SphK2 selectivity observed with halogen moieties at the *para* position, a bulkier electron-withdrawing trifluoromethyl group at the *para* position (**20k** (SLC4071411)) was synthesized. **20k** was more potent but less selective for SphK2. Interestingly, placement of the trifluoromethyl group at the *meta* position (**20l**) produced a more potent SphK inhibitor (28% inhibition). However, this molecule showed no selectivity for SphK1 vs. SphK2. The *ortho* trifluoromethyl analogue (**20m**) did not improve potency nor selectivity. These results suggest that the key binding interactions were lost with the *ortho*-substituted derivative likely due to a loss in CF_3 interactions with the residues Cys533, His556 and Tyr566 that are found at the end of the hydrophobic tunnel of the SphK2 binding pocket, which was shown[60] by our group to be important for strong inhibitor binding.

Replacement of the electron-withdrawing groups with electron-donating groups– methyl (**20n**), methyl ether (**20o**), and ethyl ether (**20p**) – at the *para* position markedly diminished SphK2 inhibition (<30%) (Table 1). Likewise, positioning the methyl ether to the *meta* position (**20q)** did not improve inhibitory activity at either enzyme isotype. A trifluoromethyl ether group was then tested at the *para* position for increased lipophilicity and to reestablish deactivating electronics[65, 66] to the aryl ring. The resulting molecule (**20r** (SLC4081418)) decreased SphK2 activity to ~40%, which is likely due to a reestablishment of the fluorine bonding interactions mentioned (*vide supra*). Good selectivity was also observed with this molecule, as SphK1 activity was only diminished by ~10%. However, shifting the trifluoromethyl ether moiety from

the *para* position to the *meta* position (**20s**) led to a switch in SphK potency and selectivity. Collectively, these results indicate that placement of electron-donating groups on the aryl ring is unfavorable for SphK2 inhibition.

The effects of di-substitution on the aryl ring of the aminothiazole were also explored (Table 2). Although poor inhibition activities were observed with mono-substituted aryl rings containing traditional electron-donating groups, we were curious about the effects of having di-substituted aryl rings. Compounds with either two methyl (**20t)** or two methyl ether moieties (**20u**) showed minimal activity. Placement of a methyl ether at the *para* position and the chlorine moiety at the *meta* position (**20v**) led to modest SphK2 activity (~70%) and no SphK1 inhibition. In contrast, di-substitution with electron-withdrawing groups reestablished SphK2 potency, particularly fluorines (**20w**, **20z**), chlorine (**20x**), or a combination of fluorine with a trifluoromethyl group (**20y (**SLC4091423**)**, **20aa** (SLC4091424), **20cc**). The substitution pattern for these molecules did not significantly affect their SphK2 potency; however, they did show SphK1/SphK2 dual inhibitor activity, affording good SphK2 inhibition (50-70%) and modest to good SphK1 inhibition (30-50%). Disubstitution of the aryl ring with two trifluoromethyl moieties (**20bb**) led to a loss in compound potency, but this loss in potency was met with a gain in selectivity, as it was inactive towards SphK1 at concentrations up to 1 μM. Together, these results reinforce the preference for electron deficient aryl ring.

Our previous studies[63, 67] suggest that the SphK2 lipid-binding pocket is larger than that of SphK1. To explore the effects of bulky moieties on the aminothiazole ring, biphenyl derivatives were synthesized and tested (Table 2). We discovered that the *para*-substituted biphenyl derivative (**20dd**) was not only potent towards SphK2 but also selective for SphK2. The *meta*-substituted biphenyl derivative (**23a**) essentially lost activity. However, a fluorine on the 4-

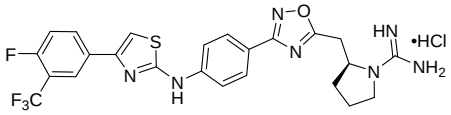
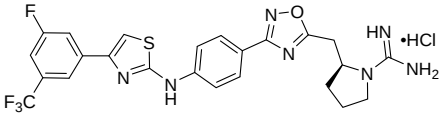
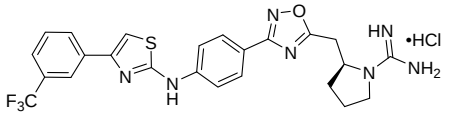
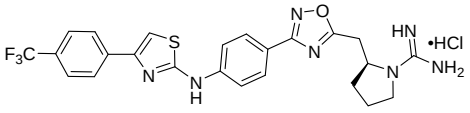
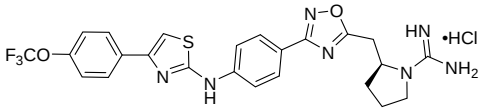
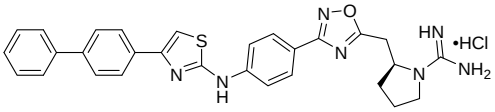
position (**23b**) maintained the potency and selectivity observed with **20dd**. Attempts to substitute **20dd** with a trifluoromethyl moiety at either the 4- (**23c**) or 3-position (**23d**) on the biphenyl ring led to compounds inactive in both SphKs, suggesting that the molecules may either be too large for the binding pocket or have poor solubility (clogP = 6.78). In an effort to introduce additional bulk onto the aminothiazole, a benzofuran moiety (**20ee**) was synthesized but was found to be ineffective as an inhibitor. Collectively, these results suggest that the biphenyl moiety has the optimal binding interaction as well as 'bend' to fit in the 'J-shaped' hydrophobic tunnel.

In addition to investigating the effects of various aryl groups on the aminothiazoles, we also explored the effects of modifying the exocyclic nitrogen of the aminothiazoles (Table 2). The co-crystal structure of SphK1 with **5** reported by Wang *et al.* notes a key hydrogen bonding interaction between the aminothiazole NH and SphK1 threonine-196.[44] Although our scaffold would most likely fit slightly deeper into the SphK1 binding pocket, we probed the significance of this hydrogen bonding capability by either replacing the NH with an ether linkage (**31**) or methylating (**34**) the amino group. The N-Me derivative **34** was found to be completely inactive in both SphKs up to 1 μM while the ether derivative **31** showed moderate activity towards both SphKs, decreasing SphK1 and SphK2 activity by ~ 45% at 0.3 μM. These results suggest that the amino moiety plays a key role in enzyme binding likely through hydrogen bonding (compare **34** with **20dd**) although we cannot rule out the loss in SphK2 potency may also be due to steric effects created from the methylation. Comparison of **31** with the amino moiety **20k** shows a loss in SphK2 potency with equipotent SphK1 inhibition, indicating that the molecules' hydrogen bonding role (donor vs. acceptor) at this position is more significant in SphK2 than SphK1.

To quantify the aminothiazoles' activity towards SphK1 and SphK2, we determined the inhibitory constant (K_i) of the most potent compounds in the library (Table 3). Consistent with

the results of the initial screen (Tables 1 & 2), fluoro and trifluoromethyl positional isomers of disubstituted aryls **20y** and **20aa** had good activity with both enzymes and partial selectivity towards SphK2 (~5 fold) (entries 1-2). Fortunately, monosubstitution with a *meta*-

Table 3. K_i and cLogP[a] values of Selected Inhibitors of SphK1 and SphK2.

Entry	Compound	Structure	hSphK1 K_i (μM)	hSphK2 K_i (μM)	hSphK2 Selectivity	cLogP
1	**20y**		0.7 ± 0.05	0.17 ± 0.15	4	5.33
2	**20aa**		0.8 ± 0.07	0.17 ± 0.17	5	5.33
3	**20l**		0.12 ± 0.04	0.09 ± 0.01	1	5.18
4	**20k**		0.82 ± 0.25	0.39 ± 0.09	2	5.18
5	**20r**		5 ± 0.22	0.25 ± 0.10	20	5.42
6	**20dd**		9 ± 2	0.09 ± 0.02	100	6.18

[a]cLogP was calculated for the protonated inhibitor with Chemdraw Professional 13.0.

trifluoromethyl group (**20l**) by removal of the fluorine atom from **20y** or **20aa** resulted in improved binding inhibition (entry 3). **20l** is a dual inhibitor with K_i of 120 nM and 90 nM with SphK1 and SphK2, respectively. Moving the trifluoromethyl group to the *para* position had a negative inhibitory effect as expected (entry 4). However, switching to a trifluoromethylether on the *para* position (**20r**) improved the K_i towards SphK2 (250 nM) while decreasing inhibitory

activity against SphK1 (K_i 5 μM), affording 20-fold selectivity towards SphK2 (entry 5). The introduction of a more lipophilic and larger substituent such as a phenyl ring on the *para* position (**20dd**) resulted in a potent and selective SphK2 inhibitor (K_i 90 nM). To the best of our knowledge, **20dd** is the most potent SphK2 reported to date; this compound is 100-fold selective towards SphK2 vs SphK1. In comparing compounds **20k**, **20r**, and **20dd**, it is interesting to note that as the steric bulk and lipophilicity of the molecules (cLogP 5.18, 5.42 and 6.18, respectively) increased, the inhibition constant and selectivity improved. These results are consistent with the observation that the hydrophobic binding pocket of SphK2 is larger than SphK1.

We selected the most potent, SphK2 selective (**20dd**) and SphK1/2 dual inhibitors (**20l**) towards their effect on S1P synthesis. U937 cells, a histiocytic lymphoma myeloid cell line that expresses both SphK isotypes, were incubated with either compound. Following incubation, the cells were lysed and sphingosine and S1P levels were determined by LC-MS-MS. Both inhibitors showed a concentration-dependent decrease in S1P levels (Figure 4A/C) while Sph levels remained constant (Figure 4B/D), indicating that the compounds are cell permeable and capable of inhibiting SphK activity in whole cells. Further, the selectivity of **20dd** towards SphK2 *in vitro* is observed as its effect on S1P level is lower than **20l**—S1P is still generated by functional SphK1. To assess the *in vivo* properties of **20dd**, C57BL/6 mice were treated with a single 10 mg/kg intraperitoneal dose. S1P concentration in blood was monitored over a course of 24 hours via LC-MS-MS. As shown in Figure 5, blood S1P levels increased on treatment with the SphK2 selective inhibitor **20dd** at two and a six-hour time points and returned to basal levels after 24 hours. Such an observation is in accordance with three SphK2 selective inhibitors[28, 29, 47] and supports the notion that SphK2 selective inhibitors drive elevated S1P levels in whole

blood.[28] To date, **20dd** is the most potent and selective SphK2 inhibitor reported with *in vivo*

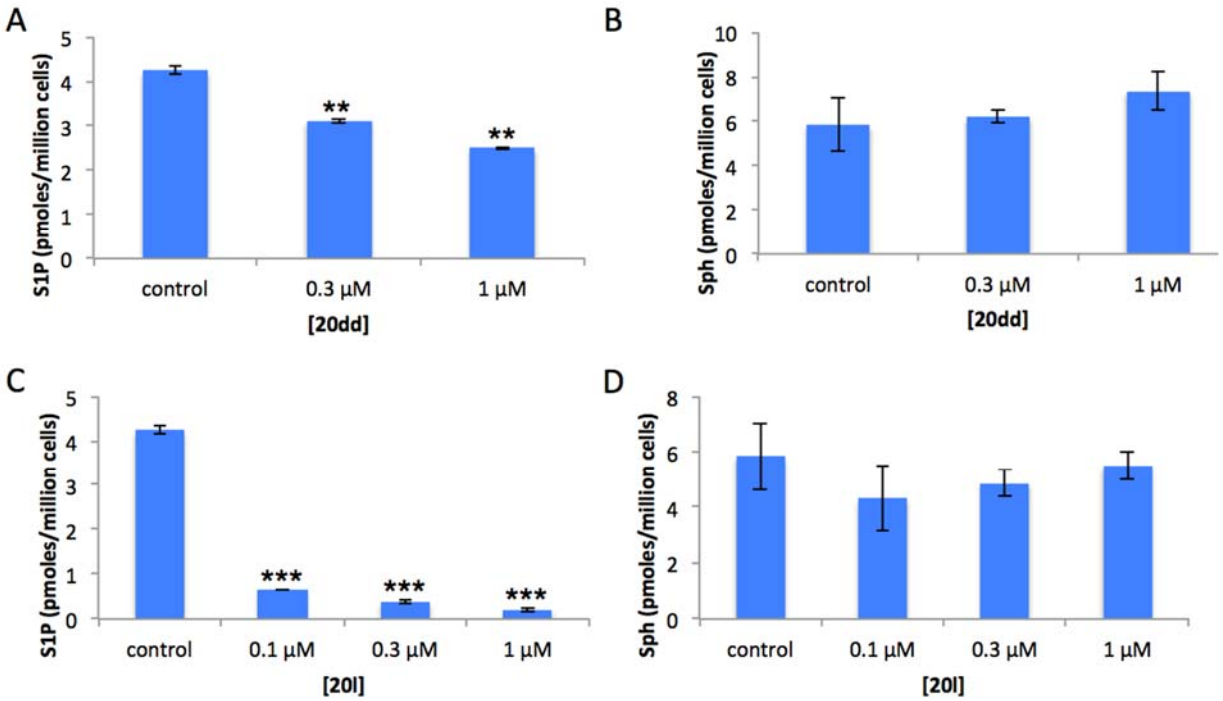


Figure 4. Effect of **20l** and **20dd** on sphingolipids in U937 cells. Following 2 h of incubations U937 cells were harvested by centrifugation, lysed, and levels of (A, C) S1P and (B, D) sphingosine were measured using LC-MS-MS. Amounts associated with cells are expressed as the number of pmoles per 10^6 cells. The experiment was performed in duplicate. The level of significance is indicated for each experiment (**P<0.005, ***P<0.001) using an unpaired t test (compared to control).

activity.

CONCLUSIONS

Herein, we disclose the discovery and development of the most potent and selective SphK2 inhibitor reported to date. The scaffold contains a guanidine head and aminothiazole 'tail' groups. A surprising result of our studies is that principles obtained from earlier SphK1

inhibitors – insertion of a methylene unit between the oxadiazole and pyrrolidine ring of **3** and aminothiazole from **2** – generated a potent and selective SphK2 inhibitor. Unfortunately, the X-ray crystal structure of SphK2 is not yet available. Thus, docking

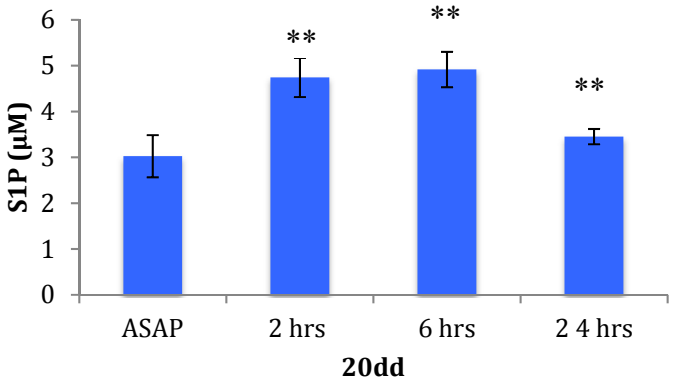


Figure 5. Detected S1P blood levels in mice following injection with **20dd**. Wild-type mice were treated with a single 10 mg/kg ip dose of **20dd** and blood samples were collected at the indicated time points. S1P levels from the blood samples were measured via LC-MS-MS. The standard deviations are values from a group of three to four mice. The level of significance is indicated for each experiment (**$P < 0.01$) using one-way analysis of variance with the Bonferroni multiple comparison test.

of inhibitors in the binding site using a validated homology model of SphK2 has been utilized to facilitate the development of inhibitors. Structure-activity relationship studies of these inhibitors indicate that potent inhibition of both SphK1 and SphK2 necessitates electron-deficient phenyl ring, but these substituents likely benefit from interacting with residues Cys533, His556 and Tyr566 at the end of the binding pocket. Our investigations also support the importance of hydrogen bonding with the exocyclic NH of the aminothiazole ring; removal of hydrogen bonding capacity resulted in significant loss in activity.

Biological analysis of the aminothiazole inhibitors **20l** and **20dd** effectively lower S1P levels in U937 cells. *In vivo* study of the SphK2 selective **20dd** caused elevated blood S1P levels in wildtype mice, recapitulating our previous findings[28, 29, 47, 60] with SphK2 selective inhibitors. Collectively, our work provides a novel chemical biology approach towards selective SphK2 and dual SphK inhibition. We expect that these studies will aid in elucidating the *in vivo* function of SphK2 as well as the development of improved SphK inhibitors.

EXPERIMENTAL SECTION

Sphingosine Kinase assays. The inhibitory activity of the synthesized compounds on human SphK1 and SphK2 was determined using a previously published method.[28, 47] Recombinant human SphK1 or SphK2 isolated from a cell lysate was briefly incubated with (0.3 μM) or without compound, sphingosine, and γ-[^{32}P]ATP. The radiolabeled sphingosine 1-phosphate was isolated via extraction and thin-layer chromatography and then quantified via scintillation counting.

Sample Preparation and LC-MS-MS Analysis. Sample preparation protocols were from our previous publication[29] with minor modifications. Cell pellets (2–3 × 10^6 cells), whole blood (10 μl) or plasma (10 μl) was mixed with 2 ml of a methanol:chloroform solution (3:1) and transferred to a capped glass vial. Suspensions were supplemented with 10 μl of internal standard solution containing 10 pmoles of deuterated (D7) S1P and deuterated (D7) sphingosine. The mixture was placed in a bath sonicator for 10 min and incubated at 48°C for 16 h. The mixture was then cooled to ambient temperature and mixed with 200 μl of 1M KOH in methanol. The samples were again sonicated and incubated a further 2 h at 37 °C. Samples were then neutralized by the addition of 20 μl of glacial acetic acid and transferred to 2 ml microcentrifuge tubes. Samples were then centrifuged at 12,000 x g for 12 min at 4 °C. The supernatant fluid was

collected in a separate glass vial and evaporated under a stream of nitrogen gas. Immediately prior to LC-MS analysis, the dried material was dissolved in 0.3 ml of methanol and centrifuged at 12,000 x g for 12 min at 4 °C. Fifty μL of the resulting supernatant fluid were analyzed by Liquid Chromatography-ESI Mass Spectrometry (LC-MS) using a triple quadrupole mass spectrometer (AB-Sciex 4000 Q-Trap) coupled to a Shimadzu LC-20AD LC system. A binary solvent gradient with a flow rate of 1 ml/min was used to separate sphingolipids and drugs by reverse phase chromatography using a Supelco Discovery C18 column (50 mm × 2.1 mm, 5 μm bead size). Mobile phase A consisted of water : methanol : formic acid (79:20:1) while mobile phase B was methanol : formic acid (99:1). The run started with 100% A for 0.5 minutes. Solvent B was then increased linearly to 100% B in 5.1 minutes and held at 100% for 4.3 min. The column was finally re-equilibrated to 100% A for 1 min. Natural sphingolipids were detected using multiple reaction monitoring (MRM) as follows: S1P (380.4 → 264.4); deuterated (D7)C_{18}S1P (387.4 → 271.3); sphingosine (300.5 → 264.4); deuterated (D7) sphingosine (307.5 → 271.3).

Pharmacokinetic Analysis. Mouse studies were conducted using a previously reported method.[47] **20dd** (10 mg/kg) and **20l** (3 mg/kg) were administered intraperitoneally to groups of 3 to 4 mice (strain: C57BL6/j) or an equal volume of vehicle (2% solution of hydroxypropyl-β-cyclodextrin (Cargill Cavitron 82004)). Blood samples were then collected at the specified time points (ASAP time points were collected 1-2 min following drug addition). The blood samples were analyzed via LC-MS, as described (*vide supra*). Animal protocols were approved prior to experimentation by the University of Virginia's School of Medicine Animal Care and Use Committee.

Molecular Docking. Molecular docking was performed using compounds (**2**, **20x**) to assess potential difference in position in the binding pocket of SphK2. The SphK2 model, with ATP and Mg^{2+} bound, was generated with Molecular Operating Environment (MOE) and energy minimized as previously described.[60] Marvin was used for drawing, displaying and characterizing chemical structures, substructures and reactions for preparation in docking programs, Marvin 17.3.13, 2017, ChemAxon (http://www.chemaxon.com). AutoDock Tools[68] was used to prepare the protein and ligand files, while AutoDock Vina[69] was used to perform the docking for pose prediction. The grid box was set to 20 x 20 x 28 Angstrom, with a 1.000 Å grid spacing was used. The center of the box was placed at the approximate center of the ligand-binding cavity, with a part of the ATP binding cavity included as previously performed[60] and to ensure coverage and interaction with key Asp residues. Up to ten docked poses were predicted for each compound. The number of predicted poses is dependent on the fitness of the sampled compound orientations. The lowest energy pose for each docked ligand in SphK2 was then used for analysis of interactions with key residues in the SphK2 binding pocket. Free energy of binding scores were cataloged for each docked compound and used as one level of comparison between compounds.

General Material and Synthetic Procedures

All reactions conducted in a microwave were conducted in a Discover SP microwave synthesizer (CEM Corporation). All solvents were dried using the PureSolv solvent purification system prior to use. All chemical reagents were purchased from commercial sources and used without further purification. Thin layer chromatography (TLC) was performed on aluminum-backed silica gel, 200 μm, F254, and column chromatography was performed on flash grade silica gel, 40-63 μm, using a Combiflash Rf purification system. ^{1}H NMR spectra were recorded at 500 or 400 MHz;

the corresponding ^{13}C NMR resonant frequencies were 126 and 101 MHz, respectively; the corresponding ^{19}F NMR resonant frequencies were 471 and 376 MHz, respectively. ^{1}H NMR chemical shifts are reported in ppm with the solvent resonance as an internal standard ($CDCl_3$: 7.26 ppm; CD_3OD: 4.87 ppm; acetone-d_6: 2.05 ppm). ^{13}C NMR, chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm; CD_3OD: 49.00 ppm; acetone-d_6: 206.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m= multiplet), coupling constants (Hz), and integration. Rotamers are denoted by an asterisk (*). High resolution mass spectroscopy (HRMS) was performed on an LC/MS time-of-flight mass spectrometer using electrospray ionization (ESI). HPLC analyses were performed with a Thermo Electron TSQ triple quadrupole mass spectrometer equipped with an ESI source. All compounds tested in biological assays are >95% pure by ^{1}H NMR and HPLC analyses unless noted otherwise.

General Procedure A: Synthesis of amide-oxime derivatives. TEA (2.7 equiv) was added to a solution of the appropriate benzonitrile (1 equiv) with hydroxylamine hydrochloride (2.6 equiv) in ethanol (0.47 M solution). The mixture was reacted in a microwave for 6 min at 150 ºC. The organic solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to yield the desired product.

General Procedure B: Coupling of amide-oxime derivatives with (*S*)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)acetic acid. DIEA (1.80 equiv) was added to a solution of the appropriate amidoxime (1 equiv) and (*S*)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)acetic acid in DMF (0.2 M solution). HCTU (1.5 equiv) was then added to the resulting mixture at rt and stirred at 100 ºC for 4 – 8 h. The reaction progress was followed by TLC. The solution was partitioned between EtOAc and LiBr aqueous solution. The aqueous solution was washed with

EtOAc three times, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *via* vacuum. The resulting residue was purified by silica gel column chromatography.

General Procedure C: Coupling of 6 with alpha-bromoketones. DIEA (2 equiv) was added to a solution of *tert*-butyl (*S*)-2-((3-(4-thioureidophenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate **6** (1 equiv) and alpha-bromoketone (1 equiv) in ethanol (0.2 M solution). The resulting reaction mixture was then reacted in a microwave at 100°C for 5 min. The organic solvent was removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography.

General Procedure D: Suzuki Coupling of aryl bromides with phenyl boronic acids. Cs_2CO_3 (2 equiv) was added to a solution of of *t*-Boc protected aryl bromide intermediate (1 equiv) and the appropriate phenyl boronic acid derivative (3 equiv) in DMF (0.045 M solution). The resulting mixture was degassed for 10 min by bubbling N_2 through the solution. $PdCl_2$(dppf) (0.03 equiv) was then added to the mixture, and heated in a microwave reactor at 150 ºC for 90 min. The solution was partitioned between EtOAc and LiBr aqueous solution. The aqueous solution was washed with EtOAc three times, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *via* vacuum. The resulting residue was purified by silica gel column chromatography.

General Procedure E: Deprotection of *t*-Boc protecting groups with TFA and guanylation of amines. To a solution of *t*-Boc protected intermediate in DCM, a 1N TFA solution in DCM was added. The reaction mixture was then stirred at rt for 4 h. At this time, TLC showed complete conversion of starting material. The organic solvent was removed under reduced pressure. The residue was then dissolved in ACN (0.02 M solution). Diisopropylethylamine (10

equiv) and (Z)-*tert*-butyl (((*tert*-butoxycarbonyl)imino)(1H-pyrazol-1-yl)methyl)carbamate (1.05 equiv) were added to the solution, and the resulting reaction mixture was reacted in a microwave reactor at 50° C for 2 h. The organic solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography.

General Procedure F: Deprotection of *t*-Boc protecting groups with HCl (*g*). Hydrochloric acid gas was bubbled through a solution of the *N*-Boc protected compound in methanol for 2-5 minutes, until complete consumption of starting material was observed by TLC. The reaction mixture was concentrated under reduced pressure and triturated with diethyl ether to yield the corresponding free amine hydrochloride salt.

N-(4-cyanophenyl)-2,2,2-trifluoroacetamide (**13**)**.** 4-aminobenzonitrile **12** (1.0 g, 8.46 mmol) was dissolved in DCM (8.5 mL) and cooled to 0°C. Triethylamine (1.3 mL, 9.31 mmol) was added dropwise and allowed to stir at 0°C for 10 min. Trifluoroacetic anhydride (1.8 mL, 9.31 mmol) was then added dropwise. The reaction mixture was allowed to warm up to rt and stirred for 19 h. The resulting reaction mixture was quenched with sat. aq. NH_4Cl, and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *via* vacuum. The residue was purified by silica gel column chromatography (30% EtOAc/ hexanes) to yield **13** (1.0 g, 88%) as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 157.14 (q, $^2J_{CF}$ = 38.4 Hz), 156.76 (q, $^2J_{CF}$ = 38.4 Hz), 142.17, 122.19, 121.26 (q, $^1J_{CF}$ = 281.3 Hz), 119.35, 118.57 (q, $^1J_{CF}$ = 281.3 Hz), 115.70 (q, $^1J_{CF}$ = 281.3 Hz), 112.85 (q, $^1J_{CF}$ = 281.3 Hz), 109.84; ^{19}F NMR (376 MHz, CD_3OD) δ -75.64 (s, 3F); HRMS (ESI-): Calcd for $C_9H_4F_3N_2O$ $[M-H]^-$: 213.0275, Found: 213.0273.

(Z)-2,2,2-trifluoro-N-(4-(N'-hydroxycarbamimidoyl)phenyl)acetamide (**14**). Synthesized by General Procedure A. 330 mg, 57% as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (101 MHz, acetone-d_6) δ 156.22 (q, $^{2}J_{CF}$ = 38.4 Hz), 155.85 (q, $^{2}J_{CF}$ = 38.4 Hz), 155.48 (q, $^{2}J_{CF}$ = 38.4 Hz), 155.11 (q, $^{2}J_{CF}$ = 38.4 Hz), 152.17, 138.14, 131.54, 127.11, 121.23, 120.91 (q, $^{1}J_{CF}$ = 280.2 Hz), 118.29 (q, $^{1}J_{CF}$ = 280.2 Hz), 115.42 (q, $^{1}J_{CF}$ = 280.2 Hz), 112.56 (q, $^{1}J_{CF}$ = 280.2 Hz); ^{19}F NMR (471 MHz, acetone-d_6) δ -76.14 (s, 3F); HRMS (ESI+): Calcd for $C_9H_8F_3N_3O_2$ $[M+H]^+$: 248.0659, Found: 248.1822.

tert-butyl (S)-2-((3-(4-(2,2,2-trifluoroacetamido)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**15**). Synthesized by General Procedure B. 454 mg, 67%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.12 – 7.93 (m, 2H), 7.75 (dd, *J* = 14.9, 8.2 Hz, 2H), 4.35 – 4.19 (m, 1H), 3.46 – 3.21 (m, 3H), 3.07 (dt, *J* = 15.3, 7.3 Hz, 1H), 2.06 (q, *J* = 8.0, 6.9 Hz, 1H), 1.94 – 1.73 (m, 3H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 177.39, 167.67, 155.56, 155.19 (q, $^{2}J_{CF}$ = 53.5 Hz), 154.79 (q, $^{2}J_{CF}$ = 53.5 Hz), 154.47 (q, $^{2}J_{CF}$ = 53.5 Hz), 153.94 (q, $^{2}J_{CF}$ = 53.5 Hz) 138.54, 128.45, 124.30, 120.89, 120.11 (q, $^{1}J_{CF}$ = 289.9 Hz), 117.24 (q, $^{1}J_{CF}$ = 289.9 Hz), 114.37 (q, $^{1}J_{CF}$ = 289.9 Hz), 111.51 (q, $^{1}J_{CF}$ = 289.9 Hz), 80.54*, 80.00*, 55.32*, 55.18*, 46.82*, 46.37*, 31.68*, 31.05*, 30.27, 28.47, 23.53*, 22.81*; ^{19}F NMR (470 MHz, $CDCl_3$) δ -74.47 (s, 3F); HRMS (ESI+): Calcd for $C_{20}H_{23}F_3N_4NaO_4$ $[M+Na]^+$: 463.1569, Found: 463.1546.

tert-butyl (S)-2-((3-(4-aminophenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**16**). (*S*)-*tert*-butyl-2-(3-(4-iodophenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **15** (54 mg, 0.123 mmol) was dissolved in MeOH (5 mL) and then 1 M LiOH (5 mL) was added. The reaction mixture was refluxed for 3 h. At this time, TLC showed complete conversion of starting material. The resulting product was extracted with EtOAc, and the combined organic layers were

washed with brine, dried over Na_2SO_4, filtered, and concentrated *via* vacuum to provide **16** (45 mg, 82%) as a clear solid without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.1 Hz, 2H), 4.34 – 4.17 (m, 1H), 4.04 (s, 2H), 3.49 – 3.19 (m, 3H), 3.13 – 2.90 (m, 1H), 2.02 (s, 1H), 1.93 – 1.69 (m, 3H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.14, 177.01, 168.62, 154.81, 154.59, 149.68, 129.26, 116.93, 116.78, 115.03, 114.71, 80.34*, 79.92*, 55.55, 47.11*, 46.70*, 32.16*, 31.35*, 31.14*, 30.38*, 28.85, 23.91*, 23.13*; HRMS (ESI+): Calcd for $C_{18}H_{24}N_4NaO_3$ $[M+Na]^+$: 367.1746, Found: 367.1743.

tert-butyl (S)-2-((3-(4-thioureidophenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**17**). *tert*-butyl (*S*)-2-((3-(4-aminophenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate **16** (100 mg, 0.290 mmol) was dissolved in THF (4 mL). Di(1*H*-imidazol-1-yl)methanethione (70 mg, 0.392 mmol) was added to the reaction mixture and allowed to stir at rt until TLC showed complete conversion of starting material. Ammonia gas was then passed through the solution for 1 min. The organic solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (35% -80% EtOAc/hexane) to yield **17** (101 mg, 86%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 13.6 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 2H), 7.42 – 7.32 (m, 2H), 6.33 (s, 2H), 4.29 (d, *J* = 30.3 Hz, 1H), 3.52 – 3.25 (m, 3H), 3.08 (t, *J* = 7.6 Hz, 1H), 2.07 (s, 0H), 1.93 – 1.76 (m, 3H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.73, 177.91, 167.46, 154.36, 151.61, 139.13, 129.40, 125.85, 124.54, 80.28*, 79.89*, 55.28, 46.88*, 46.53*, 31.90*, 31.15*, 30.34, 28.62, 23.69*, 22.92.*; HRMS (ESI+): Calcd for $C_{19}H_{25}N_5O_3S$ $[M+H]^+$: 404.1756, Found: 404.1751.

tert-butyl (S)-2-((3-(4-((4-phenylthiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18a**). Synthesized by General Procedure C. 42 mg, 56%,

yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.04 (m, 2H), 7.91 – 7.84 (m, 2H), 7.71 – 7.61 (m, 1H), 7.59 – 7.51 (m, 2H), 7.42 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.37 – 7.30 (m, 1H), 6.91 (s, 1H), 4.30 (m, 1H), 3.40 (m, 3H), 3.07 (m, 1H), 2.08 (m, 1H), 1.93 – 1.81 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.22, 168.00, 162.90, 154.37, 151.71, 142.84, 134.53, 128.96, 128.83, 128.19, 126.28, 120.75, 117.33, 102.84, 80.21, 55.28, 46.90*, 46.51*, 31.95*, 31.17*, 30.24*, 29.85*, 28.64, 23.72*, 22.93*; HRMS (ESI+): Calcd for $C_{27}H_{29}N_5O_3S$ $[M+H]^+$: 504.2069, Found: 504.2024.

tert-butyl (S)-2-((3-(4-((4-(pyridin-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18b**). Synthesized by General Procedure C. 25 mg, 39%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 2H), 8.09 (d, *J* = 8.3 Hz, 2H), 7.85 – 7.69 (m, 2H), 7.60 (t, *J* = 7.8 Hz, 2H), 7.15 (s, 1H), 4.41 – 4.21 (m, 1H), 3.51 – 3.27 (m, 3H), 3.15 – 2.99 (m, 1H), 2.15 – 2.01 (m, 1H), 1.96 – 1.78 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.33, 169.03, 167.92, 163.43, 150.29, 149.18, 142.56, 141.56, 131.98, 129.01, 121.16, 120.56, 117.59, 106.73, 80.22, 55.32, 46.90*, 46.53*, 31.94*, 31.18*, 30.28*, 29.85*, 28.65, 23.72*, 22.95*; HRMS (ESI+): Calcd for $C_{26}H_{29}N_6O_3S$ $[M+H]^+$: 505.2022, Found: 505.2016.

tert-butyl (S)-2-((3-(4-((4-(pyridin-3-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18c**). Synthesized by General Procedure C. 28 mg, 75%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 1.9 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.23 – 8.13 (m, 2H), 8.08 (d, *J* = 8.2 Hz, 2H), 7.65 – 7.54 (m, 2H), 7.36 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.00 (s, 1H), 4.40 – 4.21 (m, 1H), 3.52 – 3.26 (m, 3H), 3.15 – 2.98 (m, 1H), 2.13 – 2.01 (m, 1H), 1.95 – 1.75 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.24, 167.95, 163.59, 154.40, 148.85, 148.62, 147.73, 142.84, 133.54, 130.48, 128.98, 123.73, 120.88, 117.47, 104.04,

80.23*, 79.81*, 55.29, 46.91*, 46.50*, 31.92*, 31.15*, 30.23*, 29.85*, 28.63, 23.71*, 22.93*; HRMS (ESI+): Calcd for $C_{26}H_{29}N_6O_3S$ $[M+H]^+$: 505.2022, Found: 505.2012.

tert-butyl (S)-2-((3-(4-((4-(4-fluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18d**). Synthesized by General Procedure C. 21 mg, 66%, light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (ap t, J = 10, 2H), 7.95 (br s, 1H), 7.86 – 7.81 (m, 2H), 7.58 – 7.50 (m, 2H), 7.09 (ap t, J = 10, 2H), 6.82 (s, 1H), 4.38 – 4.23 (m, 1H), 3.50 – 3.26 (m, 3H), 3.14 - 3.00 (m, 1H), 2.12 – 2.00 (m, 1H), 1.94 – 1.77 (m, 3H), 1.48 (br s, 9H); ^{3}C NMR (101 MHz, $CDCl_3$) δ 177.23, 167.97, 164.00 (d,f $^1J_{CF}$ = 248.5 Hz), 163.13, 161.54 (d, $^1J_{CF}$ = 248.5 Hz), 158.61, 154.41, 151.31, 150.70, 142.80, 130.86 (d, $^4J_{CF}$ = 3.0), 130.83 (d, $^4J_{CF}$ = 3.0 Hz), 129.23, 128.95, 128.03 (d, $^3J_{CF}$ = 8.1 Hz), 127.95 (d, $^3J_{CF}$ = 8.1 Hz), 125.54, 120.95, 117.37, 115.83 (d, $^2J_{CF}$ = 22.2), 115.6 (d, $^2J_{CF}$ = 22.2 Hz), 102.34, 80.24*, 79.82*, 55.34, 46.90*, 46.52*, 31.94*, 31.17*, 31.01*, 30.26*, 28.64, 23.71*, 22.94*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.71 – -116.29 (m, 1F); HRMS (ESI+): Calcd for $C_{27}H_{28}FN_5O_3S$ $[M+H]^+$: 522.1975, Found: 522.1966.

tert-butyl (S)-2-((3-(4-((4-(4-chlorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18e**). Synthesized by General Procedure C. 30 mg, 77%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (ap t, J = 10 Hz, 2H), 7.98 (br s, 1H), 7.79 (dt, J = 10, 2.5 Hz, 2H), 7.59 – 7.50 (m, 2H), 7.37 (dt, J = 10, 2.5 Hz, 2H), 6.87 (s, 1H), 4.40 – 4.23 (m, 1H), 3.50 – 3.26 (m, 3H), 3.14 - 3.00 (m, 1H), 2.12 – 2.03 (m, 1H), 1.94 – 1.77 (m, 3H), 1.48 (br s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.05, 167.80, 162.99, 154.50, 150.34, 142.63, 133.70, 132.87, 128.80, 128.77, 127.34, 120.62, 117.23, 102.96, 80.10*, 79.67*, 55.14, 46.74*, 46.36*, 31.75*, 31.00*, 30.10*, 29.68*, 28.48, 23.54*, 22.76*; HRMS (ESI+): Calcd for $C_{27}H_{28}ClN_5NaO_3S$ $[M+Na]^+$: 560.1499, Found 560.1502.

tert-butyl (S)-2-((3-(4-((4-(4-bromophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18f**). Synthesized by General Procedure C. 73 mg, 84%, off-white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.77 – 7.70 (m, 2H), 7.53 (dd, *J* = 9.2, 2.7 Hz, 3H), 6.90 (s, 1H), 4.40 – 4.22 (m, 1H), 3.50-3.27 (m, 3H), 3.15 – 2.99 (m, 1H), 2.13 – 2.03 (m, 1H), 1.95-178 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.12, 168.01, 163.27, 154.44, 150.39, 142.98, 142.86, 133.45, 131.84, 128.82, 127.76, 121.95, 120.50, 117.35, 103.14, 80.33*, 79.87*, 55.34*, 55.22*, 46.86*, 46.51*, 31.84*, 31.13*, 31.05*, 30.99*, 30.25*, 29.80*, 28.61, 23.64*, 22.88*; HRMS (ESI+): Calcd for $C_{27}H_{28}BrN_5NaO_3S$ $[M+Na]^+$: 604.0993, Found: 604.0967.

tert-butyl (S)-2-((3-(4-((4-(3-fluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18g**). Synthesized by General Procedure C. 58 mg, 90%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.74 (br. s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.37 (td, *J* = 8.0, 5.9 Hz, 1H), 7.01 (q, *J* = 8.5, 1H), 6.92 (s, 1H), 4.40 – 4.40 – 4.21 (m, 1H), 3.3.57 – 3.26 (m, 3H), 3.16 – 2.96 (m, 1H), 2.15 – 2.01 (m, 1H), 1.94 – 1.78 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.28, 167.98, 164.52(d, $^{1}J_{CF}$ = 246.4 Hz), 163.06, 162.08 (d, $^{1}J_{CF}$ = 246.4 Hz), 154.42, 150.44, 142.71, 136.72 (d, $^{3}J_{CF}$ = 8.1 Hz), 136.64 (d, $^{3}J_{CF}$ = 8.1 Hz), 130.35 (d, $^{3}J_{CF}$ = 9.1 Hz), 130.26 (d, $^{3}J_{CF}$ = 9.1 Hz), 128.97, 121.80 (d, $^{4}J_{CF}$ = 2.0 Hz), 121.78 (d, $^{4}J_{CF}$ = 2.0 Hz), 121.11, 120.88 117.44, 115.05 (d, $^{2}J_{CF}$ = 21.2 Hz), 114.84 (d, $^{2}J_{CF}$ = 21.2 Hz), 113.36 (d, $^{2}J_{CF}$ = 23.2 Hz), 113.13 (d, $^{2}J_{CF}$ = 21.2 Hz), 103.77, 80.26*, 79.84*, 55.32, 46.91*, 46.52*, 31.94*, 31.16*, 30.27*, 29.85*, 28.64, 23.72*, 22.93*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.92 – -113.24 (m, 1F); HRMS (ESI+): Calcd for $C_{27}H_{28}FN_5NaO_3S$ $[M+Na]^+$: 544.1795, Found: 544.1784.

tert-butyl (S)-2-((3-(4-((4-(3-chlorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18h**). Synthesized by General Procedure C. 43 mg, 63%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.7 Hz, 3H), 7.90 – 7.79 (m, 1H), 7.76 – 7.68 (m, 1H), 7.56 (t, *J* = 9.6 Hz, 2H), 7.40 – 7.21 (m, 2H), 6.90 (s, 1H), 4.45 – 4.19 (m, 1H), 3.54 – 3.24 (m, 3H), 3.07 (ddd, *J* = 22.4, 14.7, 8.6 Hz, 1H), 2.16 – 1.99 (m, 1H), 1.87 (dd, *J* = 14.3, 7.1 Hz, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.19, 168.01, 163.18, 154.70, 154.44, 150.21, 142.87, 136.28, 134.76, 130.02, 128.90, 128.03, 126.36, 124.29, 120.69, 117.41, 103.78, 80.30*, 79.86*, 55.35*, 55.24*, 50.92*, 46.89*, 46.52*, 31.89*, 31.15*, 30.27*, 28.63*, 23.68*, 22.91*; HRMS (ESI+): Calcd for $C_{27}H_{28}ClN_5O_3S$ $[M+H]^+$: 538.1680, Found: 538.1679.

tert-butyl (S)-2-((3-(4-((4-(3-bromophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18i**). Synthesized by General Procedure C. 90 mg, 78%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.04 (m, 2H), 8.01 (d, *J* = 1.9 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.9 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.27 (d, *J* = 5.5 Hz, 1H), 6.91 (s, 1H), 4.30 – 4.22 (m, 1H), 3.40 – 3.16 – 2.98 (m, 3H), 3.07 (m, 1H), 2.20 – 1.97 (m, 1H), 1.97 – 1.77 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.22, 167.99, 163.11, 154.39, 150.10, 142.70, 136.48, 131.01, 130.33, 129.28, 128.96, 128.63, 124.75, 122.99, 120.83, 117.40, 103.84, 80.25*, 79.80*, 55.34, 46.90*, 46.51*, 31.92*, 31.16*, 30.24*, 28.64*, 23.71*, 22.92*; HRMS (ESI+): Calcd for $C_{27}H_{28}BrN_5NaO_3S$ $[M+Na]^+$: 604.0993, Found: 604.0988.

tert-butyl (S)-2-((3-(4-((4-(2-fluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18j**). Synthesized by General Procedure C. 25 mg, 56%, off-white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (td, *J* = 7.7, 2.0 Hz, 1H), 8.06 (d, *J* = 7.2 Hz, 2H), 7.75 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.32 – 7.18 (m, 3H), 7.13 (ddd, *J* = 12.0, 7.9, 1.5 Hz, 1H), 4.40 – 4.22 (m, 1H), 3.54 – 3.24 (m, 3H), 3.16 – 2.99 (m, 1H), 2.14 – 2.01 (m,

1H), 1.96 – 1.77 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.63, 177.19, 168.00, 161.95, 161.71 (d, $^1J_{CF}$ = 251.5 Hz), 159.22 (d, $^1J_{CF}$ = 251.5 Hz), 154.41, 145.30, 142.90, 130.07 (d, $^4J_{CF}$ = 3.0 Hz), 130.04 (d, $^4J_{CF}$ = 3.0 Hz), 129.17 (d, $^3J_{CF}$ = 9.1 Hz), 129.08 (d, $^3J_{CF}$ = 9.1 Hz), 128.92, 124.54, 124.50, 122.39 (d, $^3J_{CF}$ = 11.1 Hz), 122.28 (d, $^3J_{CF}$ = 11.1 Hz), 120.69, 117.34, 117.24, 116.15 (d, $^2J_{CF}$ = 22.2 Hz), 115.93 (d, $^2J_{CF}$ = 22.2 Hz), 108.05 (d, $^3J_{CF}$ = 16.2 Hz), 107.89 (d, $^3J_{CF}$ = 16.2 Hz), 80.25*, 79.80*, 55.35, 46.91*, 46.52*, 31.93*, 31.16*, 30.26, 28.65, 23.71*, 22.93*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.11 (s, 1F); HRMS (ESI+): Calcd for $C_{27}H_{28}FN_5NaO_3S$ $[M+Na]^+$: 544.1795, Found: 544.1782.

tert-butyl (S)-2-((3-(4-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18k**). Synthesized by General Procedure C. 83 mg, 70%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 8.10-8.00 (m, 2H), 7.96 (ap d, *J* = 8, 2H), 7.64 (ap d, *J* = 8, 2H), 7.62 – 7.53 (m, 2H), 6.98 (br s, 1H), 4.41 – 4.23 (m, 1H), 3.51 – 3.25 (m, 3H), 3.14 -3.01 (m, 1H), 2.14 – 2.02 (m, 1H), 1.95 – 1.78 (m, 3H), 1.48 (br s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.19, 167.99, 163.35, 154.44, 150.17, 142.83, 137.74, 130.26 (q, $^2J_{CF}$ = 32.3 Hz), 129.94 (q, $^2J_{CF}$ = 32.3 Hz), 129.62 (q, $^2J_{CF}$ = 32.3 Hz), 129.30 (q, $^2J_{CF}$ = 32.3 Hz), 128.89, 126.38, 125.82 (q, $^3J_{CF}$ = 4.0 Hz), 125.78 (q, $^3J_{CF}$ = 4.0 Hz), 125.74 (q, $^3J_{CF}$ = 4.0 Hz), 125.70 (q, $^3J_{CF}$ = 4.0 Hz), 122.97 (q, $^1J_{CF}$ = 224.2 Hz), 120.90, 120.75 (q, $^1J_{CF}$ = 224.2 Hz), 120.26, 117.44, 104.67, 104.65, 80.34*, 79.89*, 55.25, 46.89*, 46.53*, 31.86*, 31.13*, 30.27*, 29.84*, 28.62*, 23.67*, 22.90*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.49 (S, 3F); HRMS (ESI+): Calcd for $C_{28}H_{29}F_3N_5O_3S$ $[M+H]^+$: 572.1943, Found: 572.1958.

tert-butyl (S)-2-((3-(4-((4-(3-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18l**). Synthesized by General Procedure C. 45 mg, 79%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 12.3 Hz, 1H), 8.10

(s, 1H), 8.03 (dt, *J* = 14.0, 7.3 Hz, 3H), 7.54 (ddt, *J* = 23.4, 15.4, 8.1 Hz, 4H), 6.95 (s, 1H), 4.42 – 4.23 (m, 1H), 3.54 – 3.25 (m, 3H), 3.13 – 3.02 (m, 1H), 2.13 – 2.02 (m, 1H), 1.96 – 1.77 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.12, 168.02, 163.39, 154.49, 150.03, 142.94, 135.24, 131.58 (q, $^2J_{CF}$ = 32.3 Hz), 131.25 (q, $^2J_{CF}$ = 32.3 Hz), 130.93 (q, $^2J_{CF}$ = 32.3 Hz), 130.61 (q, $^2J_{CF}$ = 32.3 Hz), 129.32, 129.22, 128.82, 125.58 (q, $^1J_{CF}$ = 165.2 Hz), 124.56 (q, $^3J_{CF}$ = 4.0 Hz), 124.52(q, $^3J_{CF}$ = 4.0 Hz), 124.49 (q, $^3J_{CF}$ = 4.0 Hz; q, $^1J_{CF}$ = 165.2 Hz)), 124.45 (q, $^3J_{CF}$ = 4.0 Hz), 122.95, 122.91 (q, $^1J_{CF}$ = 165.2 Hz), 122.87, 120.65 (q, $^1J_{CF}$ = 165.2 Hz), 120.50, 117.37, 103.95, 80.40*, 79.90*, 55.35*, 55.20*, 46.86*, 46.51[8], 31.81*, 31.10*, 30.99*, 30.25*, 28.59, 23.62*, 22.86*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.71 (s, 3F). HRMS (ESI+): Calcd for $C_{28}H_{28}F_3N_5NaO_3S$ $[M+Na]^+$: 594.1763, Found: 594.1767.

tert-butyl (S)-2-((3-(4-((4-(2-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18m**). Synthesized by General Procedure C. 45 mg, 79%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.98 (d, *J* = 8.5 Hz, 2H), 7.78 – 7.73 (m, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.56 (td, *J* = 7.7, 1.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.76 (s, 1H), 4.38 – 4.22 (m, 1H), 3.49 – 3.27 (m, 3H), 3.16 – 2.97 (m, 1H), 2.13 – 2.00 (m, 1H), 1.95 – 1.77 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.63, 177.20, 167.97, 162.95, 154.38, 148.62, 142.83, 134.47, 132.09, 131.72, 129.01 (q, $^2J_{CF}$ = 30.3 Hz), 128.86, 128.71 (q, $^2J_{CF}$ = 30.3 Hz), 128.40, 128.38, 128.32 (q, $^2J_{CF}$ = 30.3 Hz), 128.10 (q, $^1J_{CF}$ = 275.7 Hz), 126.66 (q, $^3J_{CF}$ = 6.1 Hz), 126.60 (q, $^3J_{CF}$ = 6.1 Hz), 126.55 (q, $^3J_{CF}$ = 6.1 Hz), 126.49 (q, $^3J_{CF}$ = 6.1 Hz), 125.59 (q, $^1J_{CF}$ = 275.7 Hz), 122.87 (q, $^1J_{CF}$ = 275.7 Hz), 120.93, 120.73, 120.14 (q, $^1J_{CF}$ = 275.7 Hz), 117.48, 106.95, 106.91, 80.22*, 79.77*, 55.34, 46.90*, 46.51*, 31.95*, 31.16*, 30.98*, 30.23*, 29.84, 28.63*, 28.52*, 23.70*, 22.92*; ^{19}F

NMR (376 MHz, $CDCl_3$) δ -57.78 (s, 3F); HRMS (ESI+): Calcd for $C_{28}H_{28}F_3N_5NaO_3S$ $[M+H]^+$: 572.1943, Found: 572.1942.

tert-butyl (S)-2-((3-(4-((4-(p-tolyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18n**). Synthesized by General Procedure C. 30 mg, 47%, off-white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.58 – 7.47 (m, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.84 (s, 1H), 4.41 – 4.21 (m, 1H), 3.42 (t, *J* = 20.8 Hz, 3H), 3.18 – 2.97 (m, 1H), 2.38 (s, 3H), 2.16 – 2.01 (m, 1H), 1.87 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.30, 167.99, 162.98, 151.64, 142.84, 138.08, 131.75, 129.52, 128.96, 126.20, 120.69, 117.32, 102.00, 80.22*, 79.80*, 55.35, 46.91*, 46.51*, 31.97*, 31.17*, 30.24*, 29.85*, 28.64, 23.72*, 22.93*, 21.43; HRMS (ESI+): Calcd for $C_{28}H_{32}N_5O_3S$ $[M+H]^+$: 518.2226, Found: 518.2225.

tert-butyl (S)-2-((3-(4-((4-(4-methoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18o**). Synthesized by General Procedure C. 30 mg, 75%, clear amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 7.96 (m, 3H), 7.80 (d, 2H), 7.61 – 7.44 (m, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.75 (s, 1H), 4.40 – 4.20 (m, 1H), 3.83 (s, 3H), 3.50 – 3.24 (m, 3H), 3.21 – 2.97 (m, 1H), 2.13 – 1.99 (m, 1H), 1.96 – 1.76 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.14, 168.03, 162.96, 159.63, 154.64, 154.39, 151.36, 143.01, 128.85, 127.65, 127.55, 127.53, 120.60, 120.41, 117.23, 114.16, 100.95, 80.24*, 79.78*, 55.45*, 55.34, 55.21*, 46.88*, 46.50*, 31.89*, 31.13*, 30.96*, 30.21*, 28.62, 23.68*, 22.90*; HRMS (ESI+): Calcd for $C_{28}H_{32}N_5O_4S$ $[M+H]^+$: 534.2175, Found: 534.2160.

tert-butyl (S)-2-((3-(4-((4-(4-ethoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18p**). Synthesized by General Procedure C. 81 mg, 92%, light yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.82 (s,

1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.75 (s, 1H), 4.39 – 4.21 (m, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.51 – 3.26 (m, 3H), 3.07 (m, 1H), 2.13 – 2.02 (m, 1H), 1.95 – 1.78 (m, 4H), 1.48 (s, 9H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.09, 167.84, 162.73, 158.91, 154.25, 151.25, 142.74, 128.75, 127.38, 127.16, 120.41, 117.11, 114.58, 100.72, 80.06*, 79.63*, 63.49, 55.14, 46.72*, 46.34*, 31.77*, 30.99*, 30.05, 28.47, 23.54*, 22.75*, 14.80; HRMS (ESI+): Calcd for $C_{29}H_{34}N_5O_4S$ $[M+H]^+$: 548.2332, Found: 548.2308.

tert-butyl (S)-2-((3-(4-((4-(3-methoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18q**). Synthesized by General Procedure C. 28 mg, 70%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.97 (m, 3H), 7.58 – 7.51 (m, 2H), 7.49 – 7.40 (m, 2H), 7.32 (t, *J* = 8.1 Hz, 1H), 6.96 – 6.81 (m, 2H), 4.43 – 4.18 (m, 1H), 3.86 (s, 3H), 3.54 – 3.24 (m, 4H), 3.19 – 2.97 (m, 1H), 2.17 – 2.00 (m, 1H), 1.97 – 1.74 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.18, 167.97, 162.95, 160.02, 154.64, 154.40, 151.45, 142.89, 135.90, 129.82, 129.16, 128.88, 120.55, 118.71, 117.30, 113.91, 111.80, 103.11, 80.24*, 79.79*, 55.44*, 55.35*, 55.22*, 46.89*, 46.50*, 31.91*, 31.14*, 30.99*, 30.22*, 28.62, 23.69*, 22.91*; HRMS (ESI+): Calcd for $C_{28}H_{32}N_5O_4S$ $[M+H]^+$: 534.2175, Found: 534.2182.

tert-butyl (S)-2-((3-(4-((4-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18r**). Synthesized by General Procedure C. 27 mg, 30%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (ap. t, *J* = 7.5 Hz, 2H), 7.90 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.59 – 7.51 (m, 2H), 7.28 – 7.23 (m, 2H), 6.88 (s, 1H), 4.39 – 4.22 (m, 1H), 3.54 – 3.27 (m, 2H), 3.14 – 2.99 (m, 1H), 2.13 – 1.99 (m, 1H), 1.95 – 1.77 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.04, 167.73, 163.03, 154.22, 150.12, 148.80, 142.54, 133.08, 128.76, 127.46, 121.72 (q, $^1J_{CF}$ = 258.6 Hz), 121.09, 119.16 (q, $^1J_{CF}$ = 258.6 Hz), 117.22,

103.12, 80.09*, 79.64*, 55.18*, 55.06*, 46.73*, 46.34*, 31.73*, 30.98*, 30.83*, 30.06*, 29.68, 28.46*, 23.53*, 22.74*; ^{19}F NMR(376 MHZ, $CDCl_3$) δ -57.82 (s, 3F); HRMS (ESI+): Calcd for $C_{28}H_{28}F_3N_5O_4S$ $[M+H]^+$: 588.1892, Found: 588.1916.

tert-butyl (S)-2-((3-(4-((4-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18s**). Synthesized by General Procedure C. 27 mg, 30%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.78 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.73 (dt, *J* = 2.9, 1.4 Hz, 1H), 7.64 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.17 (ddt, *J* = 8.1, 2.3, 1.1 Hz, 1H), 6.95 (s, 1H), 4.40 – 4.20 (m, 1H), 3.51 – 3.25(m, 3H), 3.16 – 2.98 (m, 1H), 2.16 – 2.00 (m, 1H), 1.96 – 1.76 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.24, 167.96, 163.09, 154.40, 150.19, 149.84, 142.65, 136.56, 130.14, 128.98, 124.42, 121.97 (q, $^1J_{CF}$ = 156.6 Hz), 120.96, 120.32 (q, $^1J_{CF}$ = 156.6 Hz), 119.41, 118.87 (q, $^1J_{CF}$ = 156.6 Hz), 117.44, 104.04, 80.23*, 79.82*, 55.33, 46.89*, 46.52*, 31.94,* 31.17*, 30.26, 28.64, 23.71*, 22.93*; ^{19}F NMR(376 MHZ, $CDCl_3$) δ -57.82 (s, 3F); HRMS (ESI+): Calcd for $C_{28}H_{28}F_3N_5NaO_4S$ $[M+Na]^+$: 610.1712, Found: 610.1721.

tert-butyl (S)-2-((3-(4-((4-(3,4-dimethylphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18t**). Synthesized by General Procedure C. 30 mg, 75%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.08 (m, 1H), 8.03 (d, *J* = 8.1 Hz, 2H), 7.63 (s, 1H), 7.57 (d, *J* = 7.7, 2.1 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.82 (s, 1H), 4.30 (d, *J* = 29.1 Hz, 1H), 3.55 – 3.26 (m, 4H), 3.20 – 2.93 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 2.13 – 2.00 (m, 1H), 1.94 – 1.77 (m, 4H), 1.54 – 1.40 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.15, 168.03, 163.03, 154.64, 154.39, 151.76, 143.01, 136.92, 136.69, 132.19, 130.04, 128.84, 128.29, 127.48, 123.71, 120.40, 117.27, 101.87, 80.25*, 79.80*, 55.34*, 55.21*,

46.88*, 46.49*, 31.89*, 31.12*, 30.96*, 30.20*, 28.61, 23.67*, 22.89*, 20.07, 19.99, 19.72; HRMS (ESI+): Calcd for $C_{29}H_{34}N_5O_3S$ $[M+H]^+$: 532.2382, Found: 532.2398.

tert-butyl (S)-2-((3-(4-((4-(3,4-dimethoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18u**). Synthesized by General Procedure C. 25 mg, 63%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 7.98 (m, 3H), 7.58 – 7.48 (m, 2H), 7.46 – 7.37 (m, 2H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.78 (s, 1H), 4.30 (d, *J* = 30.3 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.53 – 3.25 (m, 3H), 3.19 – 2.95 (m, 1H), 2.15 – 1.99 (m, 1H), 1.97 – 1.75 (m, 3H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 177.18, 167.99, 162.95, 154.37, 151.37, 149.16, 149.11, 142.96, 128.87, 128.32, 127.78, 120.50, 118.79, 117.22, 111.36, 109.63, 101.28, 80.23*, 79.78*, 56.18, 56.08*, 56.06*, 56.02*, 55.31*, 46.87*, 46.48*, 31.91*, 31.13*, 30.98*, 30.20*, 28.61, 23.68*, 22.89*; HRMS (ESI+): Calcd for $C_{29}H_{34}N_5O_5S$ $[M+H]^+$: 564.2281, Found: 564.2271.

tert-butyl (S)-2-((3-(4-((4-(3-chloro-4-methoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18v**). Synthesized by General Procedure C. 83 mg, 91%, light yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 2H), 7.85 (d, *J* = 2.2 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.59 – 7.50 (m, 2H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.76 (s, 1H), 4.40 – 4.22 (m, 1H), 3.93 (s, 3H), 3.47 – 3.29 (m, 3H), 3.07 (ddd, *J* = 30.3, 14.3, 8.2 Hz, 1H), 2.14 – 2.02 (m, 1H), 1.94 – 1.78 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.24, 167.90, 163.26, 155.01, 149.42, 142.47, 128.97, 128.11, 127.80, 125.73, 122.84, 117.56, 112.20, 101.65, 80.23*, 79.79*, 56.38, 55.34*, 55.23*, 46.90*, 46.50*, 31.93*, 31.15*, 30.99*, 30.23*, 28.63, 23.72*, 22.92*; HRMS (ESI+): Calcd for $C_{28}H_{31}ClN_5O_4S$ $[M+H]^+$: 568.1785, Found: 568.1780.

tert-butyl (S)-2-((3-(4-((4-(3,4-difluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18w**). Synthesized by General Procedure C. 21 mg, 58%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.03 (m, 2H), 7.72 – 7.62 (m, 2H), 7.61 – 7.50 (m, 3H), 7.19 (dd, *J* = 10.1, 8.3 Hz, 1H), 6.84 (s, 1H), 4.29 (t, *J* = 18.7 Hz, 1H), 3.50 – 3.26 (m, 3H), 3.15 – 2.99 (m, 1H), 2.16 – 2.01 (m, 1H), 1.96 – 1.77 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.25, 167.94, 163.13, 154.42, 151.93 (dd, $^2J_{CF}$ = 36.4 Hz, $^3J_{CF}$ = 13.1 Hz), 151.80 (dd, $^2J_{CF}$ = 36.4 Hz, $^3J_{CF}$ = 13.1 Hz), 151.57 (dd, $^2J_{CF}$ = 36.4 Hz, $^3J_{CF}$ = 13.1 Hz), 151.45 (dd, $^2J_{CF}$ = 36.4 Hz, $^3J_{CF}$ = 13.1 Hz), 149.65, 149.47 (dd, $^2J_{CF}$ = 37.4 Hz, $^3J_{CF}$ = 13.1 Hz), 149.34 (dd, $^2J_{CF}$ = 37.4 Hz, $^3J_{CF}$ = 13.1 Hz), 149.10 (dd, $^2J_{CF}$ = 37.4 Hz, $^3J_{CF}$ = 13.1 Hz), 148.97 (dd, $^2J_{CF}$ = 37.4 Hz, $^3J_{CF}$ = 13.1 Hz), 142.64, 131.80 (d, $^3J_{CF}$ = 4.0 Hz), 131.76 (d, $^3J_{CF}$ = 4.0 Hz), 131.74 (d, $^3J_{CF}$ = 4.0 Hz), 131.70 (d, $^3J_{CF}$ = 4.0 Hz), 128.97, 122.21 (d, $^3J_{CF}$ = 4.0 Hz), 122.17 (d, $^3J_{CF}$ = 4.0 Hz), 122.15 (d, $^3J_{CF}$ = 4.0 Hz), 122.11 (d, $^3J_{CF}$ = 4.0 Hz), 120.97, 117.68 80 (dd, $^1J_{CF}$ = 227.8 Hz, $^2J_{CF}$ = 18.2 Hz), 117.50 (dd, $^1J_{CF}$ = 227.8 Hz, $^2J_{CF}$ = 18.2 Hz), 117.45, 115.43 (dd, $^1J_{CF}$ = 227.8 Hz, $^2J_{CF}$ = 19.2 Hz), 115.24 (dd, $^1J_{CF}$ = 227.8 Hz, $^2J_{CF}$ = 19.2 Hz), 103.26, 80.26*, 79.85*, 55.31, 46.91*, 46.53*, 31.93*, 31.17*, 30.28, 28.64, 23.71*, 22.94*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.57, -138.63; HRMS (ESI+): Calcd for $C_{27}H_{27}F_2N_5NaO_3S$ $[M+Na]^+$: 562.1695, Found: 562.1666.

tert-butyl (S)-2-((3-(4-((4-(3,4-dichlorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18x**). Synthesized by General Procedure C. 42 mg, 59%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.98 (m, 2H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.56 – 7.44 (m, 2H), 7.33 – 7.23 (m, 2H), 4.41 – 4.23 (m, 1H), 3.53 – 3.29 (m, 3H), 3.16 – 2.99 (m, 1H), 2.14 – 2.02 (m, 1H), 1.95 – 1.74 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.25, 167.95, 162.20, 154.67, 146.89, 142.77, 133.94, 132.53, 132.30, 131.74, 130.36, 128.90,

127.38, 117.45, 108.45, 80.27*, 79.84*, 55.34, 46.90*, 46.52*, 31.91*, 31.14*, 30.26, 28.64, 23.69*, 22.92*; HRMS (ESI+): Calcd for $C_{27}H_{28}Cl_2N_5O_3S$ $[M+H]^+$: 572.1290, Found: 572.1244.

tert-butyl (S)-2-((3-(4-((4-(4-fluoro-3-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18y**). Synthesized by General Procedure C. 21 mg, 24%, clear yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 7.98 (m, 4H), 7.82 (s, 1H), 7.60 – 7.51 (m, 2H), 7.31 – 7.17 (m, 1H), 6.90 (s, 1H), 4.40 – 4.23 (m, 1H), 3.52 – 3.27 (m, 3H), 3.15 – 3.01 (m, 1H), 2.14 – 2.03 (m, 1H), 1.94 – 1.81 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.27, 167.92, 163.40, 160.64 (d, $^1J_{CF}$ = 257.6 Hz), 158.09 (d, $^1J_{CF}$ = 257.6 Hz), 154.42, 149.25, 142.64, 131.46 (d, $^3J_{CF}$ = 8.1 Hz), 131.38 (d, $^3J_{CF}$ = 8.1 Hz), 131.14 (d, $^4J_{CF}$ = 4.0 Hz), 131.10 (d, $^4J_{CF}$ = 4.0 Hz), 128.96, 126.76 (q, $^1J_{CF}$ = 272.7 Hz), 125.04 (qd, $^3J_{CF}$ = 5.1 Hz, $^4J_{CF}$ = 1.0 Hz), 125.03 (qd, $^3J_{CF}$ = 5.1 Hz, $^4J_{CF}$ = 1.0 Hz), 125.00 (qd, $^3J_{CF}$ = 5.1 Hz, $^4J_{CF}$ = 1.0 Hz), 124.98 (qd, $^3J_{CF}$ = 5.1 Hz, $^4J_{CF}$ = 1.0 Hz), 124.95, 124.94, 124.05 (q, $^1J_{CF}$ = 272.7 Hz), 121.35 (q, $^1J_{CF}$ = 272.7 Hz), 120.99, 118.96 (d, $^3J_{CF}$ = 13.1 Hz), 118.83 (d, $^3J_{CF}$ = 13.1 Hz), 118.63 (q, $^1J_{CF}$ = 272.7 Hz), 118.50, 117.48, 117.43, 117.38, 117.22, 103.56, 80.30*, 79.88*, 55.33, 46.90*, 46.54*, 31.91*, 31.17*, 30.29, 28.63, 23.69*, 22.93*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.47 (d, J = 12.6 Hz 3F), -115.74 (br. s, 1F); HRMS (ESI+): Calcd for $C_{28}H_{27}F_4N_5NaO_3S$ $[M+Na]^+$: 612.1668, Found: 612.1663.

tert-butyl (S)-2-((3-(4-((4-(3,5-difluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18z**). Synthesized by General Procedure C. 37 mg, 76%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (t, J = 10.4 Hz, 2H), 7.94 (s, 1H), 7.62 – 7.52 (m, 2H), 7.40 – 7.32 (m, 1H), 6.92 (s, 1H), 6.75 (tt, J = 8.9, 2.5 Hz, 1H), 4.44 – 4.21 (m, 1H), 3.53 – 3.24 (m, 3H), 3.15 – 3.00 (m, 1H), 2.15 – 2.01 (m, 1H), 1.95 – 1.75 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.21, 168.01, 164.70 (dd, $^1J_{CF}$ = 248.5 Hz, $^3J_{CF}$ =

13.1 Hz), 164.57 (dd, $^{1}J_{CF}$ = 248.5 Hz, $^{3}J_{CF}$ = 13.1 Hz), 163.17, 162.24 (dd, $^{1}J_{CF}$ = 248.5 Hz, $^{3}J_{CF}$ = 13.1 Hz), 162.11 (dd, $^{1}J_{CF}$ = 248.5 Hz, $^{3}J_{CF}$ = 13.1 Hz), 154.47, 149.46, 149.42, 142.70, 137.75 (d, $^{2}J_{CF}$ = 20.2 Hz), 137.65, 137.55 (d, $^{2}J_{CF}$ = 20.2 Hz), 128.93, 120.87, 117.48, 109.16 (d, $^{2}J_{CF}$ = 27.3 Hz), 109.08 (d, $^{3}J_{CF}$ = 11.1 Hz), 108.97 (d, $^{3}J_{CF}$ = 11.1 Hz), 108.89 (d, $^{2}J_{CF}$ = 27.3 Hz), 104.66, 103.48 (d, $^{2}J_{CF}$ = 51.5 Hz), 103.23, 102.97 (d, $^{2}J_{CF}$ = 51.5 Hz), 80.34*, 79.89*, 55.34, 46.90*, 46.54*, 31.88*, 31.16*, 30.30, 28.74*, 28.63*, 23.68*, 22.92*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.78 (br. S, 2F); HRMS (ESI+): Calcd for $C_{27}H_{28}F_2N_5O_3S$ $[M+H]^+$: 540.1881, Found: 540.1845.

tert-butyl (S)-2-((3-(4-((4-(3-fluoro-5-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18aa**). Synthesized by General Procedure C. 39 mg, 44%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.02 (m, 2H), 7.91 (d, *J* = 12.9 Hz, 2H), 7.75 (d, *J* = 9.6 Hz, 0H), 7.64 – 7.51 (m, 2H), 7.28 – 7.23 (m, 1H), 7.00 (s, 1H), 4.41 – 4.23 (m, 1H), 3.52 – 3.27 (m, 3H), 3.14 – 3.01 (m, 1H), 2.14 – 2.02 (m, 1H), 1.97 – 1.75 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.24, 167.98, 164.16(d, $^{1}J_{CF}$ = 248.5 Hz), 163.39, 161.70 (d, $^{1}J_{CF}$ = 248.5 Hz), 154.47, 149.04, 142.61, 137.75 (d, $^{3}J_{CF}$ = 8.1 Hz), 137.67 (d, $^{3}J_{CF}$ = 8.1 Hz), 133.44 (qd, $^{2}J_{CF}$ = 33.3 Hz, $^{3}J_{CF}$ = 8.1 Hz), 133.36 (qd, $^{2}J_{CF}$ = 33.3 Hz, $^{3}J_{CF}$ = 8.1 Hz), 133.11(qd, $^{2}J_{CF}$ = 33.3 Hz, $^{3}J_{CF}$ = 8.1 Hz), 133.03, 132.78 (qd, $^{2}J_{CF}$ = 33.3 Hz, $^{3}J_{CF}$ = 8.1 Hz), 132.70 (qd, $^{2}J_{CF}$ = 33.3 Hz, $^{3}J_{CF}$ = 8.1 Hz), 132.45 (qd, $^{2}J_{CF}$ = 33.3 Hz, $^{3}J_{CF}$ = 8.1 Hz), 132.37 (qd, $^{2}J_{CF}$ = 33.3 Hz, $^{3}J_{CF}$ = 8.1 Hz), 128.96, 127.50 (q, $^{1}J_{CF}$ = 272.7 Hz), 124.81 (q, $^{1}J_{CF}$ = 272.7 Hz), 122.10 (q, $^{1}J_{CF}$ = 272.7 Hz), 121.00, 119.36 (q, $^{1}J_{CF}$ = 272.7 Hz),118.70, 118.66, 118.63, 117.53, 116.59 (d, $^{2}J_{CF}$ = 23.2 Hz), 116.36 (d, $^{2}J_{CF}$ = 23.2 Hz),, 112.11 (dq, $^{2}J_{CF}$ = 23.2 Hz, $^{3}J_{CF}$ = 4.0 Hz), 112.08 (dq, $^{2}J_{CF}$ = 23.2 Hz, $^{3}J_{CF}$ = 4.0 Hz), 111.87 (dq, $^{2}J_{CF}$ = 23.2 Hz, $^{3}J_{CF}$ = 4.0 Hz), 111.83 (dq, $^{2}J_{CF}$ = 23.2 Hz, $^{3}J_{CF}$ = 4.0 Hz), 105.06, 80.35*,

79.91*, 55.33, 46.90*, 46.54*, 31.89*, 31.16*, 30.31, 28.63, 23.69*, 22.93*; ^{19}F NMR (376 MHz, cdcl$_3$) δ ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.87 (s, 3F), -110.68 (q, *J* = 8.2, 7.6 Hz, 1F); HRMS (ESI+): Calcd for $C_{28}H_{28}F_4N_5O_3S$ $[M+H]^+$: 590.1849, Found: 590.1843.

tert-butyl (S)-2-((3-(4-((4-(3,5-bis(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18bb**). Synthesized by General Procedure C. 33 mg, 49%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 2H), 8.08 (dd, *J* = 13.4, 8.2 Hz, 2H), 7.89 (s, 1H), 7.80 (s, 1H), 7.57 (t, *J* = 9.0 Hz, 2H), 7.08 (s, 1H), 4.41 – 4.23 (m, 1H), 3.52 – 3.26 (m, 3H), 3.16 – 3.00 (m, 1H), 2.15 – 2.03 (m, 1H), 1.97 – 1.80 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.28, 167.93, 163.64, 154.46, 148.68, 142.53, 136.44, 132.65 (d, $^2J_{CF}$ = 33.3 Hz), 132.32 (q, $^2J_{CF}$ = 33.3 Hz), 131.99 (q, $^2J_{CF}$ = 33.3 Hz), 131.66 (d, $^2J_{CF}$ = 33.3 Hz), 129.00, 127.56 (q, $^1J_{CF}$ = 273.7 Hz), 126.12, 124.85 (q, $^1J_{CF}$ = 273.7 Hz), 122.14 (q, $^1J_{CF}$ = 273.7 Hz), 121.35, 119.42 (q, $^1J_{CF}$ = 273.7 Hz), 117.59, 105.45, 80.36*, 79.91*, 55.31, 46.90*, 46.55*, 31.91*, 31.18*, 30.32, 28.64, 23.69*, 22.94*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.96 (s, 6F); HRMS (ESI+): Calcd for $C_{29}H_{27}F_6N_5NaO_3S$ $[M+Na]^+$: 662.1636, Found: 662.1627.

tert-butyl (S)-2-((3-(4-((4-(2-fluoro-5-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18cc**). Synthesized by General Procedure C. 57 mg, 78%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 7.1, 2.5 Hz, 1H), 8.07 (ap. t, *J* = 9.6 Hz, 2H), 7.91 (s, 1H), 7.63 – 7.48 (m, 3H), 7.32 – 7.15 (m, 2H), 4.42 – 4.21 (m, 1H), 3.52 – 3.27 (m, 3H), 3.16 – 3.02 (m, 1H), 2.15 – 2.02 (m, 1H), 1.97 – 1.77 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.24, 167.94, 163.19 (d, $^1J_{CF}$ = 256.5 Hz), 162.29, 160.65 (d, $^1J_{CF}$ = 256.6 Hz), 154.46, 143.80, 142.71, 128.95, 128.00 (q, $^1J_{CF}$ = 272.7 Hz), 127.72, 127.67, 127.61, 127.38 (q, $^2J_{CF}$ = 33.3 Hz), 127.05 (q, $^2J_{CF}$ = 33.3 Hz), 126.72 (q, $^2J_{CF}$ =

33.3 Hz), 126.00, 125.30 (q, $^{1}J_{CF}$ = 272.7 Hz), 123.11 (d, $^{3}J_{CF}$ = 12.1 Hz), 122.99 (d, $^{3}J_{CF}$ = 12.1 Hz), 122.59 (q, $^{1}J_{CF}$ = 272.7 Hz), 120.89, 119.89 (q, $^{1}J_{CF}$ = 272.7 Hz), 117.43, 117.08, 116.81 (d, $^{2}J_{CF}$ = 24.2 Hz), 116.57 (d, $^{2}J_{CF}$ = 24.2 Hz), 109.27 (d, $^{2}J_{CF}$ = 16.2 Hz), 109.11 (d, $^{2}J_{CF}$ = 16.2 Hz), 80.34*, 79.88*, 55.31, 46.89*, 46.54*, 31.91*, 31.17*, 31.04*, 30.29*, 28.63, 23.69*, 22.92*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.08 (s, 3F), -109.18 (br. s, 1F); HRMS (ESI+): Calcd for $C_{28}H_{27}F_4N_5NaO_3S$ $[M+Na]^+$: 612.1668, Found: 612.1621.

tert-butyl (S)-2-((3-(4-((4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18dd**). Synthesized by General Procedure C. 13 mg, 19%, light yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.74 – 7.53 (m, 3H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 4.40 – 4.22 (m, 1H), 3.52 – 3.27 (m, 3H), 3.17 – 2.98 (m, 1H), 2.14 – 2.02 (m, 1H), 1.95 – 1.78 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.22, 167.98, 162.92, 154.64, 151.40, 142.85, 140.86, 140.81, 133.55, 129.00, 128.97, 128.95, 127.51, 127.31, 127.13, 126.67, 117.35, 102.90, 80.21*, 79.79*, 55.32, 46.52, 31.95*, 31.17*, 30.23, 28.65, 23.71*, 22.93*; HRMS (ESI+): Calcd for $C_{33}H_{34}N_5O_3S$ $[M+H]^+$: 580.2382, Found: 580.2377.

tert-butyl (S)-2-((3-(4-((4-(benzofuran-3-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**18ee**). Synthesized by General Procedure C. 24 mg, 71%, tan amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.99 – 7.93 (m, 1H), 7.77 (s, 1H), 7.61 – 7.51 (m, 3H), 7.40 – 7.31 (m, 2H), 6.94 (s, 1H), 4.40 – 4.22 (m, 1H), 3.53 – 3.27 (m, 3H), 3.17 – 2.98 (m, 1H), 2.15 – 2.01 (m, 1H), 1.97 – 1.77 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.25, 167.98, 163.02, 155.87, 154.39, 143.94, 143.76, 142.75, 128.96, 125.51, 124.82, 123.32, 120.99, 120.90, 117.43, 117.29, 117.13, 111.95,

103.23, 80.25*, 79.81*, 55.33, 46.90, 46.52, 31.94*, 31.18*, 31.02*, 30.26*, 28.65, 23.71*, 22.94*; HRMS (ESI+): Calcd for $C_{29}H_{29}N_5NaO_4S$ $[M+Na]^+$: 566.1838, Found: 566.1813.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-phenylthiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19a**). Synthesized by General Procedure E. 21 mg, 82%, off-white oily solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34 (dd, *J* = 7.4 Hz, 1H), 6.90 (s, 1H), 4.79 (dd, *J* = 8.3, 4.9 Hz, 1H), 3.72 – 3.61 (m, 2H), 3.50 (s, 1H), 3.14 (dd, *J* = 15.2, 8.5 Hz, 1H), 2.32 – 2.25 (m, 1H), 1.93 (dt, *J* = 10.2, 5.1 Hz, 1H), 1.82 (dd, *J* = 14.0, 7.5 Hz, 2H), 1.48 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.01, 167.91, 163.01, 154.20, 151.38, 142.61, 134.29, 129.06, 128.87, 128.28, 126.27, 117.38, 102.66, 77.73, 56.66, 50.25, 30.81, 30.45, 28.31; HRMS (ESI+): Calcd for $C_{33}H_{40}N_7O_5S$ $[M+H]^+$: 646.2812, Found: 646.2805.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(pyridin-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19b**). Synthesized by General Procedure E. 3 mg, 11%, off-white oily solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.65 (ap. s, 2H), 8.09 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 2H), 7.74 (ap. s, 2H), 7.60 (d, *J* = 7.9 Hz, 2H), 7.13 (s, 1H), 4.81 – 4.73 (s, 1H), 3.81 – 3.62 (m, 2H), 3.59 – 3.40 (m, 1H), 3.08 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.36 – 2.26 (m, 1H), 1.98 – 1.89 (m, 1H), 1.84 – 1.75 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.85, 167.83, 163.35, 162.48, 159.25, 156.79, 154.30, 150.41, 150.01, 149.24, 142.56, 141.49, 128.97, 127.21, 122.29, 121.09, 120.50, 117.42, 106.53, 82.01, 79.68, 56.60, 50.32, 30.94, 30.46, 28.32, 24.52; HRMS (ESI+): Calcd for $C_{32}H_{39}N_8O_5S$ $[M+H]^+$: 647.2764, Found: 647.2772.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(pyridin-3-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19c**). Synthesized by General Procedure E. 18 mg, 78%, yellow oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 9.18 (s, 1H), 8.90 (s, 1H), 8.56 (d, *J* = 4.8 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.35 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.96 (s, 1H), 4.81 – 4.71 (m, 1H), 3.85 – 3.62 (m, 2H), 3.59 – 3.42 (m, 1H), 3.04 (dd, *J* = 15.7, 9.0 Hz, 1H), 2.37 – 2.26 (m, 1H), 1.96 – 1.87 (m, 1H), 1.82 – 1.71 (m, 2H), 1.57 – 1.36 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.57, 167.78, 163.53, 162.51, 154.41, 148.70, 148.51, 147.62, 142.92, 133.59, 130.59, 128.80, 123.71, 120.40, 117.17, 103.81, 82.25, 79.85, 56.54, 50.41, 31.02, 30.43, 28.29, 24.64; HRMS (ESI+): Calcd for $C_{32}H_{38}N_8NaO_5S$ $[M+Na]^+$: 669.2584, Found: 669.2589.

tert-butyl (S,E)-(((tert-butoxycarbonyl)amino)(2-((3-(4-((4-(3-fluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methylene)carbamate (**19d**). Synthesized by General Procedure E. 10 mg, 43%, light yellow oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.88 – 7.81 (m, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.14 – 7.06 (m, 2H), 6.81 (s, 1H), 4.82 – 4.73 (m, 1H), 3.79 – 3.62 (m, 2H), 3.57 – 3.46 (m, 1H), 3.09 (dd, *J* = 15.5, 8.8 Hz, 1H), 2.35 – 2.25 (m, 1H), 1.96 – 1.88 (m, 1H), 1.85 – 1.74 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.79, 167.82, 163.97 (d, $^{1}J_{CF}$ = 247.5 Hz), 163.03, 161.52 (d, $^{1}J_{CF}$ = 247.5 Hz), 154.28, 150.72, 150.53, 142.67, 130.91, 130.76, 128.93, 128.00 (d, $^{3}J_{CF}$ = 8.1 Hz), 127.92 (d, $^{3}J_{CF}$ = 8.1 Hz), 120.72, 117.21, 115.83 (d, $^{2}J_{CF}$ = 21.2 Hz), 115.62 (d, $^{2}J_{CF}$ = 21.2 Hz), 102.16, 81.89, 79.74, 56.61, 50.34, 30.94, 30.44, 28.30; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.86 (p, *J* = 6.7 Hz, 1F); HRMS (ESI+): Calcd for $C_{33}H_{39}FN_7O_5S$ $[M+H]^+$: 664.2717, Found: 664.2710.

tert-butyl (S,E)-(((tert-butoxycarbonyl)amino)(2-((3-(4-((4-(4-chlorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methylene)carbamate (**19e**). Synthesized by General Procedure E. 16 mg, 57%, light yellow oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.85 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 6.88 (s, 1H), 4.77 (qd, *J* = 7.2, 3.9 Hz, 1H), 3.79 – 3.62 (m, 2H), 3.57 – 3.45 (m, 1H), 3.09 (dd, *J* = 15.5, 8.8 Hz, 1H), 2.31 (dt, *J* = 12.3, 6.5 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.86 – 1.74 (m, 1H), 1.72 – 1.59 (m, 1H), 1.48 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.84, 167.84, 163.03, 154.28, 153.95, 151.48, 150.56, 142.69, 133.84, 133.34, 133.10, 128.96, 127.52, 120.83, 117.25, 103.04, 102.80, 82.17, 81.67, 56.61, 50.28, 30.93, 30.46, 28.32; HRMS (ESI+): Calcd for $C_{33}H_{38}ClN_7O_5S$ $[M+H]^+$: 680.2422, Found: 680.2425.

tert-butyl (S,Z)-((2-((3-(4-((4-(4-bromophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)((tert-butoxycarbonyl)imino)methyl)carbamate (**19f**). Synthesized by General Procedure E. 10 mg, 83%, off-white oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 – 10.37 (m, 1H), 8.65 – 8.42 (m, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 6.86 (s, 1H), 4.75 (dq, *J* = 11.1, 6.7, 6.0 Hz, 1H), 3.90 – 3.72 (m, 1H), 3.72 – 3.61 (m, 1H), 3.57 – 3.43 (m, 1H), 3.00 (dd, *J* = 15.9, 9.2 Hz, 1H), 2.39 – 2.27 (m, 1H), 1.97 – 1.85 (m, 1H), 1.82 – 1.70 (m, 1H), 1.48 (d, *J* = 5.7 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.42, 167.73, 162.96, 154.49, 150.48, 142.82, 133.57, 131.86, 128.73, 127.78, 121.90, 120.23, 116.99, 102.96, 82.26, 79.99, 56.52, 50.47, 31.13, 30.44, 28.63, 28.29, 28.10, 24.60; HRMS (ESI+): Calcd for $C_{33}H_{39}BrN_7O_5S$ $[M+H]^+$: 724.1917, Found: 724.1912.

tert-butyl (S,E)-(((tert-butoxycarbonyl)amino)(2-((3-(4-((4-(3-fluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methylene)carbamate (**19g**). Synthesized by General Procedure E. 10 mg, 57%, yellow oily solid. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 10.43 (s, 1H), 8.21 – 8.04 (m, 0H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 3H), 7.37 (ap q, *J* = 8.0, 5.8 Hz, 1H), 7.01 (td, *J* = 8.5, 2.7 Hz, 1H), 6.91 (s, 1H), 4.81 – 4.72 (m, 1H), 3.82 – 3.63 (m, 2H), 3.57 – 3.44 (m, 1H), 3.06 (dd, *J* = 15.6, 8.9 Hz, 1H), 2.38 – 2.27 (m, 1H), 1.96 – 1.87 (m, 1H), 1.84 – 1.72 (m, 2H), 1.49 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.61, 167.80, 164.50 (d, $^1J_{CF}$ = 245.4 Hz), 162.93, 162.55, 162.07 (d, $^1J_{CF}$ = 245.4 Hz), 154.39, 150.44, 142.75, 136.84 (d, $^3J_{CF}$ = 8.1 Hz), 136.76 (d, $^3J_{CF}$ = 8.1Hz), 130.30 (d, $^3J_{CF}$ = 8.1 Hz), 130.22 (d, $^3J_{CF}$ = 8.1 Hz), 128.85, 121.76, 120.52, 117.11, 114.93 (d, $^2J_{CF}$ = 21.2 Hz), 114.72 (d, $^2J_{CF}$ = 21.2 Hz), 113.31 (d, $^2J_{CF}$ = 23.2 Hz), 113.08 (d, $^2J_{CF}$ = 23.2 Hz), 105.33, 103.58, 82.25, 79.80, 56.57, 50.45, 31.04, 30.43, 28.35, 28.25, 28.13; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.07 – -113.17 (m, 1F); HRMS (ESI+): Calcd for $C_{33}H_{39}FN_7O_5S$ $[M+H]^+$: 664.2717, Found: 664.2727.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3-chlorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19h**). Synthesized by General Procedure E. 37 mg, 77%, light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.35 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.86 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.24 (m, 2H), 6.89 (s, 1H), 4.80 – 4.71 (m, 1H), 3.86 – 3.73 (m, 1H), 3.72 – 3.62 (m, 1H), 3.57 – 3.45 (m, 1H), 3.02 (dd, *J* = 15.8, 9.1 Hz, 1H), 2.38 – 2.30 (m, 1H), 1.96 – 1.87 (m, 1H), 1.84 – 1.71 (m, 2H), 1.48 (ap d. rot, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.51, 167.78, 162.95, 162.52, 154.47, 150.43, 150.27, 142.77, 136.40, 134.73, 130.02, 128.80, 127.97, 126.32, 124.34, 120.42, 117.09, 103.61, 82.28, 79.89, 56.55, 50.43, 31.10, 30.46, 28.36, 28.25; HRMS (ESI+): Calcd for $C_{33}H_{38}ClN_7O_5S$ [M+H]+: 680.2422, Found: 680.2435.

tert-butyl (S,Z)-((2-((3-(4-((4-(3-bromophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)((tert-butoxycarbonyl)imino)methyl)carbamate (**19i**). Synthesized by General Procedure E. 21 mg, 57%, off-white oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.03 – 8.00 (m, 2H), 7.98 (s, 1H), 7.79 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.66 (s, 1H), 7.58 – 7.54 (m, 1H), 7.46 – 7.42 (m, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 6.90 (s, 1H), 4.82 – 4.73 (m, 1H), 3.79 – 3.62 (m, 2H), 3.58 – 3.46 (m, 1H), 3.07 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.37 – 2.26 (m, 1H), 1.97 – 1.87 (m, 1H), 1.86 – 1.73 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.60, 167.81, 163.23, 154.59, 154.32, 150.03, 142.82, 136.65, 130.91, 130.32, 129.23, 128.84, 124.80, 122.96, 120.53, 117.15, 103.57, 83.05, 56.54, 50.33, 31.02, 30.45, 28.30, 24.45; HRMS (ESI+): Calcd for $C_{33}H_{39}BrN_7O_5S$ $[M+H]^+$: 724.1917, Found: 724.1909.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(2-fluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19j**). Synthesized by General Procedure E. 25 mg, 86%, light yellow oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.18 (td, *J* = 7.8, 2.0 Hz, 1H), 8.09 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.63 – 7.56 (m, 2H), 7.25 – 7.18 (m, 2H), 7.17 – 7.09 (m, 1.5 Hz, 1H), 4.82 – 4.72 (m, 1H), 3.86 – 3.62 (m, 2H), 3.57 – 3.47 (d, *J* = 11.3 Hz, 1H), 3.04 (dd, *J* = 15.7, 9.0 Hz, 1H), 2.38 – 2.29 (m, 1H), 1.96 – 1.87 (m, 1H), 1.84 – 1.74 (m, 2H), 1.48 (ap. d., rot., 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.57, 167.83, 162.58, 161.80, 161.73 (d, $^1J_{CF}$ = 250.5 Hz), 159.25 (d, $^1J_{CF}$ = 250.5 Hz), 154.46, 150.45, 145.33 (d, $^4J_{CF}$ = 3.0 Hz), 145.30 (d, $^4J_{CF}$ = 3.0 Hz), 142.87, 130.15 (d, $^4J_{CF}$ = 4.0 Hz), 130.11 (d, $^4J_{CF}$ = 4.0 Hz), 129.05 (d, $^3J_{CF}$ = 8.1 Hz), 128.97 (d, $^3J_{CF}$ = 8.1 Hz), 128.83, 124.55, 124.52, 122.48 (d, $^3J_{CF}$ = 11.1 Hz), 122.37 (d, $^3J_{CF}$ = 11.1Hz), 120.46, 117.06, 116.11 (d, $^2J_{CF}$ = 23.2 Hz), 115.88 (d, $^2J_{CF}$ = 23.2 Hz), 107.92(d, $^3J_{CF}$ = 16.2 Hz), 107.76 (d, $^3J_{CF}$ = 16.2 Hz), 82.24, 79.79, 77.36, 56.56, 50.42, 31.07, 30.46, 28.38, 28.25, 28.13; ^{19}F NMR (376 MHz,

$CDCl_3$) δ - 114.04 – -114.17 (m, 1F); HRMS (ESI+): Calcd for $C_{33}H_{38}FN_7NaO_5S$ $[M+Na]^+$: 686.2537, Found: 686.2550.

tert-butyl (S,E)-(((tert-butoxycarbonyl)amino)(2-((3-(4-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methylene)carbamate (**19k**). Synthesized by General Procedure E. 52 mg, 45%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (br s, 1H), 8.54 (br s, 1H), 7.98 (d, *J*= 8 Hz, 2H), 7.93 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H), 7.61 (dt. *J* = 8, 4 Hz, 2H), 6.98 (br s. 1H), 4.81 – 4.72 (m, 1H), 3.85 – 3.62 (m, 2H), 3.58 – 3.43 (m, 1H). 3.02 (dd, *J* = 16, 8 Hz, 1H), 2.39 - 2.27 (m, 2H), 1.97 – 1.87 (m, 1H), 1.82 – 1.70 (m, 2H), 1.52-1.44 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.49, 167.75, 163.18, 154.41, 150.11, 149.03, 142.73, 137.81, 130.19 (q, $^2J_{CF}$ = 32.8 Hz), 129.86 (q, $^2J_{CF}$ = 32.8 Hz), 129.54 (q, $^2J_{CF}$ = 32.8 Hz), 129.22 (q, $^2J_{CF}$ = 32.8 Hz), 128.77, 128.39, 126.38, 125.80 (q, $^4J_{CF}$ = 4.0 Hz), 125.75 (q, $^4J_{CF}$ = 4.0 Hz), 125.71 (q, $^4J_{CF}$ = 4.0 Hz), 125.68 (q, $^4J_{CF}$ = 4.0 Hz), 122.98, 120.45, 117.13, 104.45, 83.52, 66.00, 56.54, 50.45, 31.08, 30.42, 28.28, 28.10; ^{19}F NMR(376 MHZ, $CDCl_3$) δ -62.53 (s, 3F); HRMS (ESI+): Calcd for $C_{34}H_{39}F_3N_7O_5S$ $[M+H]^+$: 714.2685, Found: 714.2703.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19l**). Synthesized by General Procedure E. 5 mg, 26%, off-white oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.60 (s, 1H), 8.11 (s, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.57 – 7.48 (m, 2H), 6.95 (s, 1H), 4.81 – 4.71 (m, 1H), 3.87 – 3.74 (m, 1H), 3.73 – 3.62 (m, 1H), 3.57 – 3.46 (m, 1H), 2.99 (dd, *J* = 16.0, 9.3 Hz, 1H), 2.41 – 2.30 (m, 1H), 1.96 – 1.86 (m, 1H), 1.82 – 1.71 (m, 2H), 1.48 (d, rot., *J* = 22.4 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.38, 167.74, 163.12, 162.49, 154.55, 150.41, 150.18, 142.79, 135.41,

131.61 (q, $^{2}J_{CF}$ = 32.3 Hz), 131.29 (q, $^{2}J_{CF}$ = 32.3 Hz), 130.97 (q, $^{2}J_{CF}$ = 32.3 Hz), 130.65 (q, $^{2}J_{CF}$ = 32.3 Hz), 129.45, 129.24, 128.88, 128.73, 125.66, 124.53 (q, $^{4}J_{CF}$ = 3.0 Hz), 124.48 (q, $^{4}J_{CF}$ = 3.0 Hz), 124.45 (q, $^{4}J_{CF}$ = 3.0 Hz), 124.41 (q, $^{4}J_{CF}$ = 3.0 Hz), 122.96 (q, $^{4}J_{CF}$ = 3.0 Hz), 122.92 (q, $^{4}J_{CF}$ = 3.0 Hz), 122.89 (q, $^{4}J_{CF}$ = 3.0 Hz), 122.85 (q, $^{4}J_{CF}$ = 3.0 Hz), 120.34, 117.04, 103.79, 82.32, 79.98, 56.50, 50.48, 31.17, 30.47, 28.35, 28.22, 28.09; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.66; HRMS (ESI+): Calcd for $C_{34}H_{39}F_3N_7O_5S$ $[M+H]^+$: 714.2685, Found: 714.2682.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(2-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19m**). Synthesized by General Procedure E. 10 mg, 37%, yellow oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.84 – 7.74 (m, 2H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.52 – 7.44 (m, 3H), 6.77 (s, 1H), 4.78 (qd, *J* = 7.3, 4.1 Hz, 1H), 3.74 – 3.61 (m, 2H), 3.56 – 3.44 (m, 1H), 3.12 (dd, *J* = 15.4, 8.5 Hz, 1H), 2.33 – 2.23 (m, 1H), 1.92 (dq, *J* = 10.4, 4.8 Hz, 1H), 1.87 – 1.75 (m, 2H), 1.48 (d, *J* = 9.0 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.61, 176.91, 167.90, 162.66 48 (q, $^{3}J_{CF}$ = 19.2 Hz), 162.47 48 (q, $^{2}J_{CF}$ = 319.2 Hz), 154.20, 150.48, 148.79, 142.69, 134.55 48 (q, $^{1}J_{CF}$ = 285.8 Hz), 132.10, 131.72 (q, $^{1}J_{CF}$ = 285.8 Hz), 128.97 48 (q, $^{1}J_{CF}$ = 285.8 Hz), 128.65, 128.32, 126.58 48 (q, $^{1}J_{CF}$ = 285.8 Hz), 120.91, 117.31, 107.12, 82.14, 79.54, 56.61, 50.27, 30.83, 30.46, 28.39*, 28.24*, 24.56; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.78 ; HRMS (ESI+): Calcd for $C_{34}H_{38}F_3N_7NaO_5S$ $[M+Na]^+$: 736.2505, Found: 714.2500.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(p-tolyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19n**).Synthesized by General Procedure E. 21 mg, 82%, off-white oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H),

6.83 (s, 1H), 4.81 – 4.73 (m, 1H), 3.80 – 3.60 (m, 2H), 3.56 – 3.45 (m, 1H), 3.08 (dd, *J* = 15.4, 8.8 Hz, 1H), 2.38 (s, 3H), 2.35 – 2.25 (m, 1H), 1.98 – 1.87 (m, 1H), 1.85 – 1.74 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.75, 167.87, 162.80, 154.28, 151.70, 142.87, 137.94, 131.88, 129.49, 129.22, 128.90, 126.16, 120.47, 117.09, 101.88, 81.88, 79.77, 56.61, 50.32, 30.93, 30.44, 29.81, 28.30, 24.53, 21.44; HRMS (ESI+): Calcd for $C_{34}H_{42}N_7O_5S$ [M+H]+: 660.2968, Found: 660.2991.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(4-methoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19o**). Synthesized by General Procedure E. 23 mg, 61%, clear oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.59 – 7.55 (m, 1H), 6.96 – 6.91 (m, 2H), 6.72 (s, 1H), 4.82 – 4.69 (m, 1H), 3.83 (s, 3H), 3.74 – 3.58 (m, 2H), 3.55 – 3.42 (m, 1H), 3.03 (dd, *J* = 15.7, 8.9 Hz, 1H), 2.36 – 2.23 (m, 1H), 1.96 – 1.83 (m, 1H), 1.81 – 1.71 (m, 1H), 1.58 – 1.35 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.75, 167.87, 162.80, 154.28, 151.70, 142.87, 137.94, 131.88, 129.49, 129.22, 128.90, 126.16, 120.47, 117.09, 101.88, 81.88, 79.77, 56.61, 50.32, 30.93, 30.44, 29.81, 28.30, 24.53, 21.44; HRMS (ESI+): Calcd for $C_{34}H_{42}N_7O_6S$ $[M+H]^+$: 676.2917, Found: 676.2903.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(4-ethoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19p**). Synthesized by General Procedure E. 67 mg, 68%, light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.74 (s, 1H), 4.82 – 4.73 (m, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 3.77 – 3.62 (m, 2H), 3.56 – 3.45 (m, 1H), 3.11 (dd, *J* = 15.4, 8.6 Hz, 1H), 2.34 – 2.24 (m, 1H), 1.97 – 1.88 (m, 2H), 1.86 – 1.75 (m, 2H), 1.52 – 1.40 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.96, 167.94,

162.78, 159.07, 153.98, 152.88, 151.53, 142.85, 134.03, 129.00, 127.54, 127.43, 117.19, 114.75, 105.35, 100.89, 83.18, 77.73, 63.67, 56.64, 50.25, 30.79, 30.45, 29.85, 28.31, 28.19, 15.00; HRMS (ESI+): Calcd for $C_{35}H_{44}N_7O_6S$ $[M+H]^+$: 690.3074, Found: 690.3084.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3-methoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19q**). Synthesized by General Procedure E. 18 mg, 51%, clear oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.63 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.48 – 7.41 (m, 2H), 7.32 (t, *J* = 8.0 Hz, 1H), 6.92 – 6.83 (m, 2H), 6.36 (s, 1H), 4.82 – 4.71 (m, 1H), 3.86 (s, 3H), 3.80 – 3.61 (m, 2H), 3.58 – 3.44 (m, 1H), 3.05 (dd, *J* = 15.6, 8.9 Hz, 1H), 2.39 – 2.22 (m, 0H), 1.97 – 1.87 (m, 1H), 1.84 – 1.70 (m, 2H), 1.55 – 1.39 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.65, 167.84, 163.00, 162.58, 160.02, 154.31, 153.02, 151.37, 150.40, 142.95, 136.02, 133.88, 129.80, 128.83, 120.35, 118.71, 117.07, 113.79, 111.79, 105.30, 102.87, 82.19, 79.75, 56.56, 55.45, 50.33, 30.96, 30.43, 29.83, 28.29, 28.10, 24.50; HRMS (ESI+): Calcd for $C_{34}H_{42}N_7O_6S$ $[M+H]^+$: 676.2917, Found: 676.2900.

tert-butyl (S,E)-(((tert-butoxycarbonyl)amino)(2-((3-(4-((4-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methylene)carbamate (**19r**). Synthesized by General Procedure E. 27 mg, 70%) as a yellow oily solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.85 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 6.88 (s, 1H), 4.81 – 4.71 (m, 1H), 3.79 – 3.61 (m, 2H), 3.56 – 3.44 (m, 1H), 3.14 – 3.04 (dd, *J* = 15.5, 8.6 Hz, 1H), 2.34 – 2.25 (m, 1H), 1.95 – 1.88 (m, 1H), 1.85 – 1.74 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.70, 168.89, 167.68, 162.92, 154.13, 150.83, 150.19, 148.84, 142.49, 133.15, 128.82, 127.48, 121.10, 120.75, 119.45, 117.11, 103.06, 81.60,

79.46, 56.46, 50.14, 30.75, 30.29, 29.67, 28.16, 24.33; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.82 (s, 3F); HRMS (ESI+): Calcd for $C_{34}H_{38}F_3N_7O_6S$ $[M+H]^+$: 730.2634, Found: 730.2672.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3-(trifluoromethoxy)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19s**). Synthesized by General Procedure E. 20 mg, 83%, yellow oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.04 – 8.00 (m, 2H), 7.80 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1H), 7.73 (dt, *J* = 2.5, 1.3 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.19 – 7.15 (m, 1H), 6.94 (s, 1H), 4.82 – 4.73 (m, 1H), 3.82 – 3.67 (m, 2H), 3.57 – 3.45 (m, 1H), 3.09 (dd, *J* = 15.5, 8.8 Hz, 1H), 2.32 (d, *J* = 11.6 Hz, 1H), 1.97 – 1.88 (m, 1H), 1.86 – 1.75 (m, 1H), 1.67 – 1.56 (m, 1H), 1.50 (s rot., 9H), 1.46 (s rot., 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.81, 163.00, 150.47 (q, $^3J_{CF}$ = 32.8 Hz), 150.20 (q, $^3J_{CF}$ = 32.8 Hz), 149.82 (q, $^3J_{CF}$ = 32.8 Hz), 142.60, 136.61, 130.13, 128.96, 124.46, 120.90, 120.28, 118.85, 117.26, 103.93, 82.20, 79.66, 56.59, 50.34, 30.95, 30.47, 28.38*, 28.24*, 28.14; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.66; HRMS (ESI+): Calcd for $C_{34}H_{38}F_3N_7O_6S$ $[M+H]^+$: 730.2634, Found: 730.2635.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3,4-dimethylphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19t**). Synthesized by General Procedure E. 35 mg, 92%, clear oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.67 – 7.51 (m, 6H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.81 (s, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 4.82 – 4.72 (m, 1H), 3.81 – 3.60 (m, 2H), 3.50 (s, 1H), 3.07 (dd, *J* = 15.5, 8.7 Hz, 1H), 2.30 (d, *J* = 11.3 Hz, 6H), 1.98 – 1.85 (m, 1H), 1.85 – 1.72 (m, 2H), 1.47 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.70, 167.88, 163.10, 162.57, 154.72, 154.24, 153.05, 151.67, 150.44, 143.05, 136.92, 136.63, 133.77, 132.34, 130.07, 128.85, 127.44, 123.69, 120.31,

117.05, 105.24, 101.66, 82.97, 82.15, 79.69, 56.57, 50.32, 30.90, 30.42, 28.29, 28.11, 24.55, 20.04, 19.74; HRMS (ESI+): Calcd for $C_{35}H_{44}N_7O_5S$ $[M+H]^+$: 674.3125, Found: 674.3134.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3,4-dimethoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19u**). Synthesized by General Procedure E. 25 mg, 78%, clear oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.56 – 8.24 (m, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.39 (m, 2H), 7.22 (s, 1H), 6.76 (s, 1H), 4.76 (dq, *J* = 11.7, 7.1, 5.1 Hz, 1H), 3.93 (d, *J* = 18.3 Hz, 6H), 3.83 – 3.60 (m, 3H), 3.56 – 3.43 (m, 1H), 3.04 (dd, *J* = 15.6, 9.0 Hz, 1H), 2.38 – 2.23 (m, 1H), 1.97 – 1.84 (m, 1H), 1.82 – 1.70 (m, 2H), 1.54 – 1.38 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.63, 167.81, 162.82, 162.56, 154.36, 151.37, 150.41, 149.11, 142.93, 128.79, 127.90, 120.32, 118.80, 117.01, 111.35, 109.61, 101.06, 83.08, 82.20, 79.74, 56.54, 56.08, 56.06, 50.36, 30.98, 30.46, 28.26, 28.09; HRMS (ESI+): Calcd for $C_{35}H_{44}N_7O_7S$ $[M+H]^+$: 706.3023, Found: 706.3028.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3-chloro-4-methoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19v**). Synthesized by General Procedure E. 17 mg, 34%, light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 2.2 Hz, 1H), 7.75 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.59 – 7.51 (m, 2H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.78 (s, 1H), 4.82 – 4.72 (m, 1H), 3.94 (s, 3H), 3.84 – 3.62 (m, 2H), 3.58 – 3.42 (m, 1H), 3.10 (dd, *J* = 15.4, 8.7 Hz, 1H), 2.36 – 2.23 (m, 1H), 1.97 – 1.87 (m, 1H), 1.88 – 1.74 (m, 1H), 1.74 – 1.56 (m, 1H), 1.54 – 1.40 (m, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.89, 167.87, 162.97, 154.91, 150.17, 142.71, 128.98, 128.46, 128.11, 125.70, 122.84, 117.23, 112.21, 101.84, 100.14, 83.18, 77.73, 56.62, 56.40, 30.88, 30.46, 29.85, 28.31, 28.18; HRMS (ESI+): Calcd for $C_{34}H_{41}ClN_7O_6S$ $[M+H]^+$: 710.2528, Found: 710.2542.

tert-butyl (*S*,*Z*)-(((*tert*-butoxycarbonyl)imino)(2-((3-(4-((4-(3,4-difluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19w**). Synthesized by General Procedure E. 10 mg, 43%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.96 – 7.87 (m, 1H), 7.74 – 7.65 (m, 1H), 7.62 – 7.52 (m, 3H), 7.23 – 7.15 (m, 1H), 6.84 (s, 1H), 4.81 – 4.72 (m, 1H), 3.86 – 3.61 (m, 2H), 3.57 – 3.43 (m, 1H), 3.07 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.38 – 2.26 (m, 1H), 1.97 – 1.88 (m, 1H), 1.84 – 1.72 (m, 2H), 1.48 (d, *J* = 17.1 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.74, 167.79, 162.99, 162.59, 150.44, 149.63, 142.58, 128.91, 122.12, 120.79, (dd, $^1J_{CF}$ = 228.3 Hz, $^3J_{CF}$ = 17.2 Hz), 117.49 (dd, $^1J_{CF}$ = 228.3 Hz, $^3J_{CF}$ = 17.2 Hz), 117.19, 115.40 (dd, $^1J_{CF}$ = 228.3 Hz, $^3J_{CF}$ = 17.2 Hz), 115.22 (dd, $^1J_{CF}$ = 228.3 Hz, $^3J_{CF}$ = 17.2 Hz), 103.12, 82.23, 79.74, 56.57, 50.43, 31.01, 30.44, 28.36, 28.24; ^{19}F NMR (376 MHz, $CDCl_3$) δ -137.54 – -137.74 (m, 1F), -138.64 – -138.84 (m, 1F); HRMS (ESI+): Calcd for $C_{33}H_{38}F_2N_7O_5S$ $[M+H]^+$: 682.2623, Found: 682.2590.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3,5-dichlorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19x**). Synthesized by General Procedure E. 20 mg, 45, clear yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 3H), 7.55 – 7.49 (m, 2H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.29 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.24 (s, 1H), 4.79 – 4.70 (m, 1H), 3.82 – 3.60 (m, 2H), 3.55 – 3.41 (m, 1H), 3.04 (dd, *J* = 15.6, 8.9 Hz, 1H), 2.33 – 2.23 (m, 1H), 1.95 – 1.85 (m, 1H), 1.82 – 1.68 (m, 2H), 1.48 (s, 12H), 1.44 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.68, 167.81, 162.57, 161.89, 150.45, 146.89, 142.75, 133.80, 132.44, 132.39, 131.76, 130.38, 128.87, 127.40, 120.65, 117.18, 108.44, 82.23, 79.76, 56.58, 50.34, 30.99, 30.45, 28.38, 28.24, 28.13; HRMS (ESI+): Calcd for $C_{33}H_{38}Cl_2N_7O_5S$ $[M+H]^+$: 714.2032, Found: 714.2042.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(4-fluoro-3-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19y**). Synthesized by General Procedure E. 12 mg, 48%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.13 – 7.91 (m, 5H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 9.4 Hz, 1H), 6.90 (s, 1H), 4.84 – 4.71 (m, 1H), 3.83 – 3.63 (m, 2H), 3.57 – 3.46 (m, 1H), 3.07 (dd, *J* = 15.6, 8.9 Hz, 1H), 2.37 – 2.27 (m, 1H), 1.98 – 1.88 (m, 1H), 1.85 – 1.72 (m, 2H), 1.55 – 1.42 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.79, 167.79, 163.28, 162.59, 160.66, 158.10, 154.35, 150.46, 149.30, 142.55, 140.47, 137.78, 131.52 (d, $^{3}J_{CF}$ = 9.1 Hz), 131.43 (d, $^{3}J_{CF}$ = 9.1 Hz), 131.19, 128.94, 126.81 (q, $^{1}J_{CF}$ = 273.7 Hz), 124.94, 124.09 (q, $^{1}J_{CF}$ = 273.7 Hz), 121.38 (q, $^{1}J_{CF}$ = 273.7 Hz), 120.93, 119.32, 118.64 (q, $^{1}J_{CF}$ = 273.7 Hz), 118.51, 117.43, 117.29, 117.22, 103.45, 82.24, 79.76, 56.58, 50.34, 30.99, 30.49, 28.36*, 28.26*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.44 (d, *J* = 12.7 Hz, 3F), -115.54 – -116.19 (m, 1F); HRMS (ESI+): Calcd for $C_{34}H_{38}F_4N_7O_5S$ $[M+H]^+$: 732.2591, Found: 732.2542.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3,5-difluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19z**). Synthesized by General Procedure E. 26 mg, 79%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 8.92 (s, 1H), 8.26 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.62 (s, 1H), 7.15 – 7.07 (m, 1H), 5.16 – 5.05 (m, 1H), 4.24 – 4.09 (m, 1H), 4.09 – 3.98 (m, 1H), 3.93 – 3.80 (m, 1H), 3.36 (dd, *J* = 15.9, 9.2 Hz, 1H), 2.78 – 2.65 (m, 1H), 2.34 – 2.23 (m, 1H), 2.18 – 2.05 (m, 2H), 1.92 – 1.74 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.41, 167.72, 164.69 (dd, $^{1}J_{CF}$ = 248.5 Hz, $^{3}J_{CF}$ = 13.1 Hz), 164.56 (dd, $^{1}J_{CF}$ = 248.5 Hz, $^{3}J_{CF}$ = 13.1 Hz), 162.95, 162.49, 162.23 (dd, $^{1}J_{CF}$ = 248.5 Hz, $^{3}J_{CF}$ = 13.1 Hz), 162.10 (dd, $^{1}J_{CF}$ = 248.5 Hz, $^{3}J_{CF}$ = 13.1 Hz), 154.55, 150.38, 149.46, 142.68, 137.86 (dd, $^{3}J_{CF}$ = 10.1 Hz), 137.76 (dd, $^{3}J_{CF}$ = 10.1

Hz), 137.66 (dd, $^{3}J_{CF}$ = 10.1 Hz), 128.77, 120.40, 117.07, 109.14 (dd, $^{3}J_{CF}$ = 19.2 Hz, $^{4}J_{CF}$ = 7.1 Hz), 109.07 (dd, $^{3}J_{CF}$ = 19.2 Hz, $^{4}J_{CF}$ = 7.1 Hz), 108.95 (dd, $^{3}J_{CF}$ = 19.2 Hz, $^{4}J_{CF}$ = 7.1 Hz), 108.88 (dd, $^{3}J_{CF}$ = 19.2 Hz, $^{4}J_{CF}$ = 7.1 Hz), 104.44, 103.40 (dd, $^{2}J_{CF}$ = 25.8 Hz), 103.14 (dd, $^{2}J_{CF}$ = 25.8 Hz), 102.89 (dd, $^{2}J_{CF}$ = 25.8 Hz), 82.33, 79.97, 56.53, 50.56, 31.17, 30.44, 28.34*, 28.24*, 24.68; ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.87 (t, *J* = 8.2 Hz, 2F); HRMS (ESI+): Calcd for $C_{33}H_{38}F_2N_7O_5S$ $[M+H]^+$: 682.2623, Found: 682.2615.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3-fluoro-5-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19aa**). Synthesized by General Procedure E. 22 mg, 51%, clear yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.34 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.89 (s, 1H), 7.78 (dt, *J* = 9.6, 1.9 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.25 (d, *J* = 6.2 Hz, 2H), 6.99 (s, 1H), 4.81 – 4.72 (m, 1H), 3.86 – 3.62 (m, 2H), 3.59 – 3.44 (m, 1H), 3.02 (dd, *J* = 15.7, 9.0 Hz, 1H), 2.41 – 2.29 (m, 1H), 1.98 – 1.87 (m, 1H), 1.83 – 1.71 (m, 2H), 1.51 (s, 8H), 1.45 (s, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.54, 167.74, 164.19 (d, $^{1}J_{CF}$ = 248.5 Hz), 163.20, 162.52, 161.73 (d, $^{1}J_{CF}$ = 248.5 Hz), 154.49, 150.43, 149.10, 142.57, 137.89 (q, $^{3}J_{CF}$ = 9.1 Hz), 137.80 (d, $^{3}J_{CF}$ = 9.1 Hz), 133.40 (qd, $^{2}J_{CF}$ = 34.3 Hz, $^{3}J_{CF}$ = 9.1 Hz), 133.32 (qd, $^{2}J_{CF}$ = 34.3 Hz, $^{3}J_{CF}$ = 9.1 Hz), 133.08 (qd, $^{2}J_{CF}$ = 34.3 Hz, $^{3}J_{CF}$ = 9.1 Hz), 132.99 (qd, $^{2}J_{CF}$ = 34.3 Hz, $^{3}J_{CF}$ = 9.1 Hz), 132.74 (qd, $^{2}J_{CF}$ = 34.3 Hz, $^{3}J_{CF}$ = 9.1 Hz), 132.66 (qd, $^{2}J_{CF}$ = 34.3 Hz, $^{3}J_{CF}$ = 9.1 Hz), 132.41 (qd, $^{2}J_{CF}$ = 34.3 Hz, $^{3}J_{CF}$ = 9.1 Hz), 132.33 (qd, $^{2}J_{CF}$ = 34.3 Hz, $^{3}J_{CF}$ = 9.1 Hz), 128.84, 127.56 (q, $^{1}J_{CF}$ = 274.7 Hz), 124.85 (q, $^{1}J_{CF}$ = 274.7 Hz), 122.13 (q, $^{1}J_{CF}$ = 274.7 Hz), 120.72, 119.41 (q, $^{1}J_{CF}$ = 274.7 Hz), 118.61, 117.20, 116.68 (d, $^{2}J_{CF}$ = 23.2 Hz), 116.45 (d, $^{2}J_{CF}$ = 23.2 Hz), 112.02 (d, $^{2}J_{CF}$ = 25.3 Hz), 111.77 (d, $^{2}J_{CF}$ = 25.3 Hz), 104.90, 82.32, 79.92, 56.54, 50.46, 31.13, 30.49, 28.37*,

28.24*, 24.62; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.84 (s, 3F) , -110.73 (t, *J* = 9.0 Hz, 1F); HRMS (ESI+): Calcd for $C_{34}H_{38}F_4N_7O_5S$ $[M+H]^+$: 732.2591, Found: 732.2602.

tert-butyl (S,Z)-((2-((3-(4-((4-(3,5-bis(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)((tert-butoxycarbonyl)imino)methyl)carbamate (**19bb**). Synthesized by General Procedure E. 31 mg, 84%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.30 (s, 2H), 8.11 (d, *J* = 19.0 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.80 (s, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.07 (s, 1H), 4.82 – 4.73 (m, 1H), 3.84 – 3.63 (m, 2H), 3.58 – 3.47 (m, 1H), 3.05 (dd, *J* = 15.6, 9.0 Hz, 1H), 2.39 – 2.28 (m, 1H), 1.99 – 1.88 (m, 1H), 1.85 – 1.74 (m, 2H), 1.48 (d, *J* = 18.2 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.75, 167.74, 163.51, 162.55, 150.45, 148.74, 142.42, 136.53, 132.64 (q, $^2J_{CF}$ = 33.3 Hz), 132.31 (q, $^2J_{CF}$ = 33.3 Hz), 131.98 (q, $^2J_{CF}$ = 33.3 Hz), 131.66 (q, $^2J_{CF}$ = 33.3 Hz), 128.94, 127.60(q, $^1J_{CF}$ = 274.7 Hz), 126.15, 124.88 (q, $^1J_{CF}$ = 274.7 Hz), 122.16 (q, $^1J_{CF}$ = 274.7 Hz), 121.35, 121.05, 119.45 (q, $^1J_{CF}$ = 274.7 Hz), 117.35, 105.34, 82.27, 79.83, 56.56, 50.40, 31.04, 30.53, 28.37*, 28.24*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.94 (s, 6F); HRMS (ESI+): Calcd for $C_{35}H_{38}F_6N_7O_5S$ $[M+H]^+$: 782.2559, Found: 782.2541.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(2-fluoro-5-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**19cc**). Synthesized by General Procedure E. 27 mg, 51%, clear yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.48 (dd, *J* = 7.1, 2.5 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 2H), 7.83 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 3H), 7.25 – 7.18 (m, 1H), 4.83 – 4.73 (m, 1H), 3.80 – 3.62 (m, 2H), 3.58 – 3.45 (m, 1H), 3.09 (dd, *J* = 16.9, 8.4 Hz, 1H), 2.36 – 2.24 (m, 1H), 1.99 – 1.89 (m, 1H), 1.86 – 1.72 (m, 2H), 1.49 (d, *J* = 9.5 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.91, 167.83, 163.22 (d, $^1J_{CF}$ = 256.5 Hz), 162.25, 160.68 (d, $^1J_{CF}$ = 256.5 Hz),

158.33, 154.26, 148.80, 143.85, 142.54, 129.01, 127.72, 126.04, 123.36, 123.26 (q, $^{3}J_{CF}$ = 12.1 Hz), 123.15 (q, $^{3}J_{CF}$ = 12.1 Hz), 123.03 (q, $^{3}J_{CF}$ = 12.1 Hz), 122.90 (q, $^{3}J_{CF}$ = 12.1 Hz), 122.61, 121.09, 117.33, 116.82, 116.58, 109.22 (d, $^{3}J_{CF}$ = 16.2 Hz), 109.06 (d, $^{3}J_{CF}$ = 16.2 Hz), 83.56, 56.61, 50.26, 30.92, 30.50, 29.85, 28.31, 28.14; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.05 (s,3F), -109.15 – -109.28 (m, 1F); HRMS (ESI+): Calcd for $C_{34}H_{38}F_4N_7O_5S$ $[M+H]^+$: 732.2591, Found: 732.2605.

tert-butyl (S,Z)-((2-((3-(4-((4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)((tert-butoxycarbonyl)imino)methyl)carbamate (**19dd**). Synthesized by General Procedure E. 7 mg, 83%, light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 – 10.31 (m, 1H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.99 – 7.92 (m, 2H), 7.79 – 7.69 (m, 1H), 7.65 (dd, *J* = 8.5, 6.9 Hz, 4H), 7.61 – 7.56 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 6.94 (s, 1H), 4.84 – 4.74 (m, 1H), 3.78 – 3.62 (m, 2H), 3.59 – 3.44 (m, 1H), 3.11 (dd, *J* = 15.5, 8.7 Hz, 1H), 2.36 – 2.25 (m, 1H), 1.97 – 1.88 (m, 1H), 1.87 – 1.75 (m, 2H), 1.53 – 1.44 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.82, 167.87, 162.83, 162.58, 154.31, 151.36, 150.33, 142.77, 140.80, 133.58, 128.95, 128.67, 127.49, 127.27, 127.12, 126.93, 126.65, 120.68, 117.18, 113.25, 102.79, 82.17, 79.67, 56.60, 50.33, 30.91, 30.45, 29.86, 28.31, 24.60; HRMS (ESI+): Calcd for $C_{39}H_{44}N_7O_5S$ $[M+H]^+$: 722.3125, Found: 722.3107.

tert-butyl (S,Z)-((2-((3-(4-((4-(benzofuran-2-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)((tert-butoxycarbonyl)imino)methyl)carbamate (**19ee**). Synthesized by General Procedure E. 18 mg, 69%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.13 (br. s, 2H), 8.05 – 7.92 (m, 3H), 7.62 – 7.50 (m, 3H), 7.40 – 7.31 (m, 2H), 6.92 (s, 1H), 4.83 – 4.73 (m, 1H), 3.83 – 3.62 (m, 1H), 3.57 – 3.45 (m, 1H), 3.08 (dd, *J* = 15.3, 8.6 Hz, 1H), 2.36 – 2.27 (m, 1H), 1.97 – 1.87 (m, 1H), 1.85 – 1.71 (m, 2H), 1.49* (ap. d, *J* = 5.9 Hz, 18H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 176.75, 167.84, 163.01, 155.88, 154.34, 148.93, 143.88, 143.82, 142.76, 128.91, 125.53, 124.78, 123.31, 120.92, 120.74, 117.26, 117.16, 111.95, 103.02, 83.55, 82.15, 79.75, 56.58, 50.33, 36.83, 30.97, 30.48, 29.85, 28.32, 28.13, 24.84, 24.61; HRMS (ESI+): Calcd for $C_{35}H_{40}N_7O_6S$ $[M+H]^+$: 686.2761, Found: 686.2760.

(S)-amino(2-((3-(4-((4-phenylthiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20a**). Synthesized by General Procedure E. 8 mg, 85%, yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.10 (d, *J* = 8.3 Hz, 2H), 7.85 (dd, *J* = 16.1, 8.0 Hz, 4H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.19 (s, 1H), 4.56 – 4.50 (m, 1H), 3.56 (ddd, *J* = 12.1, 10.3, 5.8 Hz, 1H), 3.51 – 3.42 (m, 1H), 3.33 (s, 2H), 2.33 – 2.24 (m, 1H), 2.17 – 1.97 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.97, 169.20, 166.40, 156.47, 144.36, 129.88, 129.72, 129.63, 127.27, 122.36, 119.87, 57.22, 31.61, 30.08, 23.59; HRMS (ESI+): Calcd for $C_{23}H_{24}N_7OS$ $[M+H]^+$: 446.1763, Found: 446.1755.

(S)-amino(2-((3-(4-((4-(pyridin-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium trifluoroacetate (**20b**). Synthesized by General Procedure E. 3 mg, 100%, yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (d, *J* = 6.0 Hz, 2H), 8.47 – 8.41 (m, 2H), 8.10 – 8.02 (m, 3H), 7.95 – 7.89 (m, 2H), 4.58 – 4.49 (m, 1H), 3.59 – 3.52 (m, 1H), 3.51 – 3.42 (m, 1H), 3.34 – 3.31 (m, 2H), 2.36 – 2.23 (m, 1H), 2.19 – 1.96 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 176.41, 167.86, 163.98, 155.01, 148.91, 146.25, 143.48, 142.84, 128.02, 122.18, 119.62, 117.04, 114.31, 55.77, 30.14, 28.63, 22.15; HRMS (ESI+): Calcd for $C_{22}H_{23}N_8OS$ $[M+H]^+$: 447.1716, Found: 447.1704. HPLC purity: 87%.

(S)-amino(2-((3-(4-((4-(pyridin-3-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20c**). Synthesized by General Procedure E. 8 mg, 85%, yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 9.31 (s, 1H), 8.96 (dt, *J* = 8.4, 1.7 Hz,

1H), 8.69 (d, *J* = 5.6 Hz, 1H), 8.05 – 7.97 (m, 3H), 7.91 – 7.82 (m, 2H), 7.66 (s, 1H), 4.55 – 4.48 (m, 1H), 3.57 – 3.50 (m, 1H), 3.48 – 3.40 (m, 1H), 3.31 – 3.29 (m, 1H), 2.33 – 2.21 (m, 1H), 2.17 – 1.95 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.82, 169.29, 165.60, 156.45, 145.97, 145.00, 142.24, 142.04, 141.36, 135.43, 129.44, 128.13, 120.86, 118.37, 109.98, 57.18, 31.57, 30.06, 23.58; HRMS (ESI+): Calcd for $C_{22}H_{23}N_8OS$ $[M+H]^+$: 447.1716, Found: 447.1698.

(S)-amino(2-((3-(4-((4-(4-fluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20d**). Synthesized by General Procedure E. 5 mg, 100%, yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.89 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.19 (t, *J* = 8.6 Hz, 2H), 7.15 (s, 1H), 4.57 – 4.51 (m, 1H), 3.60 – 3.51 (m, 1H), 3.51 – 3.41 (m, 1H), 3.36 – 3.33 (m, 2H), 2.29 (ddd, *J* = 18.0, 10.1, 5.4 Hz, 1H), 3.39 – 3.36 (m, 0H), 2.20 – 1.96 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 176.54, 167.77, 165.04, 163.86 (d, $^1J_{CF}$ = 199.0 Hz), 161.89 (d, $^1J_{CF}$ = 199.0 Hz), 155.04, 146.83, 142.85, 129.13, 128.29, 127.95 (d, $^4J_{CF}$ = 6.1 Hz), 127.89 (d, $^4J_{CF}$ = 6.1 Hz), 120.97, 118.47, 115.30 (d, $^3J_{CF}$ = 18.2 Hz), 115.12 (d, $^3J_{CF}$ = 18.2 Hz), 55.80, 36.84, 30.19, 28.67, 22.18; ^{19}F NMR (376 MHz, CD_3OD) δ -116.45 – -116.59 (m, 1F); HRMS (ESI+): Calcd for $C_{23}H_{23}FN_7OS$ $[M+H]^+$: 464.1669, Found: 464.1681.

(S)-amino(2-((3-(4-((4-(4-chlorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20e**). Synthesized by General Procedure E. 5 mg, 100%, off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.12 – 8.05 (m, 2H), 7.92 – 7.80 (m, 4H), 7.50 – 7.42 (m, 2H), 7.22 (d, *J* = 4.4 Hz, 1H), 4.55 (q, *J* = 6.6 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.52 – 3.43 (m, 1H), 2.35 – 2.24 (m, 1H), 2.19 – 1.98 (m, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 177.90, 169.24, 156.48, 148.86, 144.56, 135.11, 133.30, 129.92, 129.63, 128.72, 121.91, 119.47,

64.45, 57.24, 31.62, 30.10, 23.60; HRMS (ESI+): Calcd for $C_{23}H_{23}ClN_7OS$ $[M+H]^+$: 481.1452, Found: 481.1456.

(S)-amino(2-((3-(4-((4-(4-bromophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20f**). Synthesized by General Procedure E. 5 mg, 100% light yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 8.7 Hz, 2H), 7.84 (dd, J = 10.2, 8.6 Hz, 4H), 7.59 (d, J = 8.5 Hz, 2H), 7.22 (s, 1H), 4.59 – 4.50 (m, 1H), 3.59 – 3.51 (m, 1H), 3.51 – 3.43 (m, 1H), 3.30 – 3.28 (m, 2H), 2.35 – 2.23 (m, 1H), 2.19 – 1.98 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.71, 169.35, 164.59, 164.52, 156.43, 151.28, 151.16, 145.44, 135.19, 134.57, 132.73, 129.38, 128.78, 123.98, 122.39, 120.31, 118.08, 104.75, 57.20, 31.60, 30.06, 23.58; HRMS (ESI+): Calcd for $C_{23}H_{23}BrN_7OS$ $[M+H]^+$: 524.0868, Found: 524.0873.

(S)-amino(2-((3-(4-((4-(3-fluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**9g**). Synthesized by General Procedure E. 5 mg, 100%, yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.08 (d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 10.1 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.26 (s, 1H), 7.09 (td, J = 8.4, 2.1 Hz, 1H), 4.56 – 4.48 (m, 1H), 3.56 – 3.50 (m, 1H), 3.48 – 3.41 (m, 1H), 3.32 – 3.30 (m, 2H), 2.33 – 2.22 (m, 1H), 2.17 – 1.97 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.96, 169.19, 166.35, 165.52 (d, $^1J_{CF}$ = 195.9 Hz), 163.58 (d, $^1J_{CF}$ = 195.9 Hz), 156.46, 148.11, 144.28, 136.47 (d, $^4J_{CF}$ = 6.1 Hz), 136.41 (d, $^4J_{CF}$ = 6.1 Hz), 131.74 (d, $^4J_{CF}$ = 7.1 Hz), 131.67 (d, $^4J_{CF}$ = 7.1 Hz), 129.71, 123.04, 123.02, 122.35, 119.82, 116.20 (d, $^3J_{CF}$ = 17.2 Hz), 116.03 (d, $^3J_{CF}$ = 17.2 Hz), 114.06 (d, $^3J_{CF}$ = 18.2 Hz), 113.88 (d, $^3J_{CF}$ = 18.2 Hz), 105.55, 57.22, 31.62, 30.08, 23.60; ^{19}F NMR (376 MHz, CD_3OD) δ -77.20 (s, 1F); HRMS (ESI+): Calcd for $C_{23}H_{23}FN_7OS$ $[M+H]^+$: 465.1747, Found: 465.1724.

(S)-amino(2-((3-(4-((4-(3-chlorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20h**). Synthesized by General Procedure E. 26 mg, 100%, light yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, *J* = 8.2 Hz, 2H), 7.89 (s, 1H), 7.80 (t, *J* = 8.2 Hz, 3H), 7.51 – 7.39 (m, 2H), 7.31 (s, 1H), 4.61 – 4.52 (m, 1H), 3.63 – 3.53 (m, 1H), 3.53 – 3.44 (m, 1H), 2.37 – 2.25 (m, 1H), 2.20 – 2.00 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.03, 169.05, 167.18, 156.42, 143.65, 135.88, 135.09, 131.50, 129.81, 129.73, 127.24, 125.65, 123.22, 120.58, 57.19, 31.60, 30.09, 23.59; HRMS (ESI+): Calcd for $C_{23}H_{23}ClN_7OS$ $[M+H]^+$: 480.1373, Found: 480.1370.

(S)-amino(2-((3-(4-((4-(3-bromophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20i**). Synthesized by General Procedure E. 3 mg, 100%, off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 – 8.05 (m, 1H), 8.04 – 7.98 (m, 2H), 7.91 – 7.82 (m, 3H), 7.47 – 7.42 (m, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.21 (s, 1H), 4.56 – 4.48 (m, 1H), 3.58 – 3.50 (m, 1H), 3.48 – 3.40 (m, 1H), 3.29 – 3.27 (m, 2H), 2.33 – 2.21 (m, 1H), 2.16 – 1.97 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 180.23, 171.87, 167.12, 158.95, 153.37, 147.95, 140.81, 134.06, 133.94, 132.42, 131.90, 128.20, 126.20, 122.87, 120.59, 107.96, 59.72, 34.12, 32.58, 26.10; HRMS (ESI+): Calcd for $C_{23}H_{23}BrN_7OS$ $[M+H]^+$: 524.0868, Found: 524.0869.

(S)-amino(2-((3-(4-((4-(2-fluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20j**). Synthesized by General Procedure E. 14 mg, 100%, light yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 – 8.06 (m, 3H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.47 – 7.39 (m, 1H), 7.38 – 7.21 (m, 3H), 4.62 – 4.54 (m, 1H), 3.66 – 3.56 (m, 1H), 3.55 – 3.44 (m, 1H), 3.39 – 3.35 (m, 2H), 2.40 – 2.27 (m, 1H), 2.22 – 2.02 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.92, 169.20, 165.30, 162.76 (d, $^1J_{CF}$ = 250.5 Hz), 160.28 (d, $^1J_{CF}$

= 250.5 Hz), 156.45, 156.01, 152.88, 148.68, 144.41, 143.41, 131.07, 130.97, 130.93, 129.66, 125.73 (d, $^4J_{CF}$ = 3.0 Hz), 125.70 (d, $^4J_{CF}$ = 3.0 Hz), 122.10, 121.98, 119.61, 117.13 (d, $^2J_{CF}$ = 23.2 Hz), 116.90 (d, $^2J_{CF}$ = 23.2 Hz), 57.22, 31.62, 30.09, 23.60; ^{19}F NMR (471 MHz, CD_3OD) δ -116.05 – -116.22 (m, 1F); HRMS (ESI+): Calcd for $C_{23}H_{23}FN_7OS$ $[M+H]^+$: 464.1669, Found: 464.1658.

(S)-amino(2-((3-(4-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20k**). Synthesized by General Procedure E. 24 mg, 100%, yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.10 (d, *J* = 8.1 Hz, 2H), 8.06 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.37 (s, 1H), 4.57 – 4.50 (m, 1H), 3.60 – 3.51 (m, 1H), 3.51 – 3.42 (m, 1H), 3.32 (s, 1H), 2.34 – 2.24 (m, 1H), 2.19 – 1.98 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.81, 169.32, 165.27, 156.46, 149.94, 145.07, 139.07, 130.70 (q, $^2J_{CF}$ = 25.3 Hz), 130.45 (q, $^2J_{CF}$ = 25.3 Hz), 129.51, 127.53, 126.84, 126.70 (q, $^4J_{CF}$ = 3.0 Hz), 126.67 (q, $^4J_{CF}$ = 3.0 Hz), 126.64 (q, $^4J_{CF}$ = 3.0 Hz), 126.60 (q, $^4J_{CF}$ = 3.0 Hz), 124.69, 121.06, 118.72, 106.64, 57.24, 31.63, 30.09, 23.60; ^{19}F NMR (471 MHz, CD_3OD) δ -64.02 (s, 3F); HRMS (ESI+): Calcd for $C_{24}H_{23}F_3N_7OS$ $[M+H]^+$: 515.1715, Found: 515.1718.

(S)-amino(2-((3-(4-((4-(3-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20l**). Synthesized by General Procedure E. 3 mg, 100%, light yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 8.19 – 8.15 (m, 1H), 8.06 – 7.98 (m, 2H), 7.89 – 7.84 (m, 2H), 7.63 – 7.56 (m, 2H), 7.32 (s, 1H), 4.56 – 4.49 (m, 1H), 3.63 – 3.59 (m, 1H), 3.53 – 3.45 (m, 1H), 2.34 – 2.22 (m, 1H), 2.18 – 1.96 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.72, 169.34, 164.73, 156.46, 150.89, 145.42, 137.08, 134.58, 132.49 (q, $^2J_{CF}$ = 31.3 Hz), 132.17 (q, $^2J_{CF}$ = 31.3 Hz), 131.86 (q, $^2J_{CF}$ = 31.3 Hz), 131.54 (q, $^2J_{CF}$ = 31.3 Hz), 130.49, 130.43, 129.95, 129.80 (q, $^1J_{CF}$ = 272.7 Hz), 129.37, 127.10, 126.52 (q, $^1J_{CF}$ = 272.7

Hz), 125.14 (q, $^4J_{CF}$ = 4.0 Hz), 125.11 (q, $^4J_{CF}$ = 4.0 Hz), 125.06 (q, $^4J_{CF}$ = 4.0 Hz), 125.03 (q, $^4J_{CF}$ = 4.0 Hz), 124.40 (q, $^1J_{CF}$ = 272.7 Hz), 123.98, 123.59 (q, $^4J_{CF}$ = 4.0 Hz), 123.56 (q, $^4J_{CF}$ = 4.0 Hz), 123.51 (q, $^4J_{CF}$ = 4.0 Hz), 123.48 (q, $^4J_{CF}$ = 4.0 Hz), 121.70 (q, $^1J_{CF}$ = 272.7 Hz), 120.38, 118.08, 105.77, 57.22; ^{19}F NMR (376 MHz, CD_3OD) δ -64.27 (s, 3F); HRMS (ESI+): Calcd for $C_{24}H_{23}F_3N_7OS$ $[M+H]^+$: 514.1637, Found: 514.1625.

(S)-amino(2-((3-(4-((4-(2-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20m**). 5 mg, 93%, off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 – 8.09 (m, 2H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.83 – 7.65 (m, 5H), 7.04 (s, 1H), 4.61 – 4.53 (m, 1H), 3.62 – 3.55 (m, 1H), 3.54 – 3.46 (m, 1H), 3.40 – 3.35 (m, 2H), 2.37 – 2.26 (m, 1H), 2.21 – 2.00 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.06, 169.06, 166.70, 156.45, 148.60, 144.53, 143.47, 133.49, 133.34, 132.47, 130.78, 129.82, 129.34 (q, $^2J_{CF}$ = 29.3 Hz), 129.05 (q, $^2J_{CF}$ = 29.3 Hz), 127.68 (q, $^3J_{CF}$ = 5.1 Hz), 127.63 (q, $^4J_{CF}$ = 5.1 Hz), 127.57 (q, $^4J_{CF}$ = 5.1 Hz), 127.52 (q, $^4J_{CF}$ = 5.1 Hz), 123.47, 120.86, 108.89, 57.20, 31.60, 30.08, 23.59; ^{19}F NMR (376 MHz, CD_3OD) δ -59.48 (s, 3F); HRMS (ESI+): Calcd for $C_{24}H_{23}F_3N_7OS$ $[M+H]^+$: 515.1715, Found: 515.1663.

(S)-amino(2-((3-(4-((4-(p-tolyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20n**). Synthesized by General Procedure E. 6 mg, 85%, light yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.06 (s, 1H), 4.57 – 4.49 (m, 1H), 3.58 – 3.55 (m, 1H), 3.50 – 3.46 (m, 1H), 3.30 – 3.24 (m, 2H), 2.37 (s, 3H), 2.34 – 2.22 (m, 1H), 2.19 – 1.98 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.71, 169.39, 164.38, 156.44, 152.69, 145.64, 138.70, 133.46, 130.22, 129.38, 126.99, 120.16, 117.99, 103.13, 57.22, 31.61, 30.06, 23.59, 21.28; HRMS (ESI+): Calcd for $C_{24}H_{26}N_7OS$ $[M+H]^+$: 460.1920, Found: 460.1920.

(S)-amino(2-((3-(4-((4-(4-methoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20o**). Synthesized by General Procedure E. 15 mg, 100%, off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 – 7.97 (m, 2H), 7.90 – 7.79 (m, 4H), 6.99 – 6.93 (m, 3H), 4.57 – 4.46 (m, 1H), 3.83 (s, 3H), 3.58 – 3.50 (m, 1H), 3.50 – 3.40 (m, 1H), 3.29 (d, *J* = 3.7 Hz, 1H), 2.34 – 2.22 (m, 1H), 2.17 – 1.95 (m, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.23, 168.80, 168.62, 162.30, 156.38, 144.37, 142.34, 135.53, 131.81, 130.58, 130.11, 129.43, 128.98, 125.05, 123.38, 122.10, 118.64, 115.55, 114.71, 57.17, 56.02, 31.65, 30.14, 23.66; HRMS (ESI+): Calcd for $C_{24}H_{26}N_7O_2S^+$ $[M+H]^+$: 476.1869, Found: 476.1858. HPLC purity: 85%.

(S)-amino(2-((3-(4-((4-(4-ethoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20p**). Synthesized by General Procedure E. 26 mg, 76%, yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 8.2 Hz, 2H), 7.81 – 7.65 (m, 4H), 7.04 – 6.96 (m, 2H), 4.58 – 4.49 (m, 1H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.62 – 3.51 (m, 1H), 3.49 – 3.42 (m, 1H), 3.35 – 3.30 (m, 2H), 2.35 – 2.22 (m, 1H), 2.18 – 1.97 (m, 3H), 1.41 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.18, 174.32, 168.95, 161.43, 156.42, 130.58, 130.00, 129.43, 128.88, 121.55, 118.52, 115.95, 115.22, 81.41, 64.74, 57.18, 31.59, 30.06, 23.59, 15.09; HRMS (ESI+): Calcd for $C_{25}H_{28}N_7O_2S$ $[M+H]^+$: 490.2025, Found: 490.2024.

(S)-amino(2-((3-(4-((4-(3-methoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20q**). Synthesized by General Procedure E. 12 mg, 86%, yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.12 (d, *J* = 6.5 Hz, 2H), 7.78 – 7.66 (m, 2H), 7.40 – 7.27 (m, 3H), 6.97 (d, *J* = 7.1 Hz, 1H), 6.82 (s, 1H), 4.58 – 4.45 (m, 1H), 3.84 (s, 3H), 3.59 – 3.49 (m, 1H), 3.50 – 3.37 (m, 1H), 3.34 – 3.28 (m, 2H), 2.35 – 2.20 (m, 1H), 2.15 – 1.93 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.16, 168.87, 168.24, 161.59,

156.38, 145.44, 142.77, 132.82, 131.27, 130.05, 124.52, 121.75, 119.71, 116.02, 113.06, 57.21, 56.09, 31.69, 30.19, 23.69; HRMS (ESI+): Calcd for $C_{24}H_{26}N_7O_2S^+$ $[M+H]^+$: 476.1869, Found: 476.1847.

(S)-amino(2-((3-(4-((4-(4-(trifluoromethoxy)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20r**). Synthesized by General Procedure E. 9 mg, 90%, off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.06 (d, *J* = 8.3 Hz, 4H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.24 (s, 1H), 4.61 – 4.50 (m, 1H), 3.63 – 3.55 (m, 1H), 3.54 – 3.45 (m, 2H), 3.33 – 3.21 (m, 1H), 2.20 – 2.14 (m, 1H), 2.14 – 2.02 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.73, 169.41, 164.67, 156.47, 151.16, 149.87, 145.53, 135.35, 129.40, 128.63, 122.19, 120.33, 118.09, 104.99, 57.25, 31.62, 30.08, 23.59; ^{19}F NMR (470 MHz, CD_3OD) δ -59.47 (s, 3F); HRMS (ESI+): Calcd for $C_{24}H_{23}F_3N_7O_2S$ $[M+H]^+$: 531.1664, Found: 531.1672. HPLC purity: 81%.

(S)-amino(2-((3-(4-((4-(3-(trifluoromethoxy)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20s**). Synthesized by General Procedure E. 9 mg, 100%, light yellow solid. ^{1}H NMR (400 MHz, v) δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.96 – 7.83 (m, 4H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 7.25 – 7.19 (m, 1H), 4.58 – 4.50 (m, 1H), 3.60 – 3.52 (m, 1H), 3.51 – 3.43 (m, 1H), 2.34 – 2.23 (m, 1H), 2.19 – 1.99 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.75, 169.36, 164.61, 156.44, 150.98, 150.87, 145.47, 138.41, 131.34, 129.38, 125.52, 120.85, 120.37, 119.46, 118.07, 105.73, 57.23, 31.60, 30.07, 23.58; ^{19}F NMR (376 MHz, CD_3OD) δ -59.32 (s, 3F); HRMS (ESI+): Calcd for $C_{24}H_{23}F_3N_7O_2S$ $[M+H]^+$: 531.1664, Found: 531.1712.

(S)-amino(2-((3-(4-((4-(3,4-dimethylphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20t**). Synthesized by General Procedure E.

25 mg, 89%, yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.55 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 6.82 (s, 1H), 4.60 – 4.48 (m, 1H), 3.61 – 3.40 (m, 2H), 3.37 – 3.30 (m, 1H), 2.33 (s, 3H), 2.30 (s, 3H), 2.19 – 1.94 (m, 3H), 1.40 – 1.12 (m, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.21, 168.91, 168.29, 156.42, 145.71, 142.81, 139.57, 138.58, 135.47, 131.26, 130.04, 129.15, 128.37, 124.92, 124.60, 121.76, 57.18, 31.62, 30.10, 23.62, 19.89, 19.69; HRMS (ESI+): Calcd for $C_{25}H_{28}N_7O_3S^+$ $[M+H]^+$: 474.2076, Found: 474.2077.

(S)-amino(2-((3-(4-((4-(3,4-dimethoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20u**). Synthesized by General Procedure E. 19 mg, 100%, orange solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.33 (d, *J* = 6.9 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 1H), 4.58 – 4.49 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.60 – 3.51 (m, 1H), 3.49 – 3.42 (m, 1H), 3.33 (d, *J* = 6.0 Hz, 2H), 2.34 – 2.23 (m, 1H), 2.17 – 2.01 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.31, 168.99, 168.80, 156.42, 152.07, 150.90, 143.92, 142.18, 130.17, 129.46, 125.53, 123.36, 122.47, 120.66, 118.81, 113.03, 112.57, 111.17, 57.17, 56.76, 56.53, 31.60, 30.09, 23.60; HRMS (ESI+): Calcd for $C_{25}H_{28}N_7OS^+$ $[M+H]^+$: 506.1969, Found: 506.1948.

(S)-amino(2-((3-(4-((4-(3-chloro-4-methoxyphenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20v**). Synthesized by General Procedure E. 11 mg, 100%, off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.90 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.10 (s, 1H), 4.57 – 4.52 (m, 1H), 3.94 (s, 3H), 3.60 – 3.52 (m, 1H), 3.50 – 3.42 (m, 2H), 2.33 – 2.25 (m, 1H), 2.19 – 1.99 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.87, 169.26, 165.70, 156.49, 144.75,

129.59, 128.86, 128.54, 126.89, 123.76, 121.61, 119.20, 113.56, 57.24, 56.77, 31.63, 30.10, 23.60; HRMS (ESI+): Calcd for $C_{24}H_{25}ClN_7O_2S$ $[M+H]^+$: 510.1479, Found: 510.1495.

(S)-amino(2-((3-(4-((4-(3,4-difluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20w**). Synthesized by General Procedure E. 6 mg, 100%, yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, J = 8.2 Hz, 2H), 7.91 – 7.79 (m, 3H), 7.77 – 7.70 (m, 1H), 7.35 (q, J = 8.9 Hz, 1H), 7.24 (s, 1H), 4.63 – 4.53 (m, 1H), 3.64 – 3.56 (m, 1H), 3.56 – 3.46 (m, 1H), 2.40 – 2.24 (m, 1H), 2.23 – 2.03 (m, 3H^{13}C NMR (101 MHz, CD_3OD) δ 177.84, 169.26, 165.51, 156.44, 148.70, 144.82, 132.67, 129.56, 123.68 (dd, $^4J_{CF}$ = 4.0 Hz), 123.64 (dd, $^4J_{CF}$ = 4.0 Hz), 123.62 (dd, $^4J_{CF}$ = 4.0 Hz), 123.58 (dd, $^4J_{CF}$ = 4.0 Hz), 121.39, 118.99, 118.70 (d, $^2J_{CF}$ = 18.2 Hz), 118.52 (d, $^2J_{CF}$ = 18.2 Hz), 116.18 (d, $^2J_{CF}$ = 19.2 Hz), 115.99 (d, $^2J_{CF}$ = 19.2 Hz), 57.25, 31.66, 30.13, 23.63; ^{19}F NMR (376 MHz, CD_3OD) δ -140.17 – -140.55 (m, 1F), -141.28 – -141.63 (m, 1F); HRMS (ESI+): Calcd for $C_{23}H_{22}F_2N_7OS$ $[M+H]^+$: 482.1575, Found: 482.1571.

(S)-amino(2-((3-(4-((4-(3,4-dichlorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20x**). Synthesized by General Procedure E. 15 mg, 100%, white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.07 (d, J = 8.5 Hz, 2H), 7.90 (s, 1H), 7.83 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.10 (s, 1H), 4.57 – 4.52 (m, 1H), 3.56 – 3.49 (m, 1H), 3.48 – 3.39 (m, 1H), 2.33 – 2.25 (m, 1H), 2.19 – 1.99 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.85, 169.26, 156.45, 146.18, 144.76, 135.36, 133.91, 133.59, 132.58, 131.14, 129.55, 128.49, 121.49, 119.08, 57.23, 54.79, 31.62, 30.08, 23.59; HRMS (ESI+): Calcd for $C_{23}H_{22}Cl_2N_7OS$ $[M+H]^+$: 514.0984, Found: 514.0973.

(S)-amino(2-((3-(4-((4-(4-fluoro-3-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20y**). Synthesized by General

Procedure E. 9 mg, 100%, off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 – 8.10 (m, 2H), 8.04 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.39 (t, *J* = 9.4 Hz, 1H), 7.29 (s, 1H), 4.55 – 4.47 (m, 1H), 3.57 – 3.48 (m, 1H), 3.48 – 3.38 (m, 1H), 2.31 – 2.21 (m, 1H), 2.14 – 1.95 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.94, 169.17, 166.32, 161.64 (d, $^{1}J_{CF}$ = 205.0 Hz), 159.61 (d, $^{1}J_{CF}$ = 205.0 Hz), 156.44, 147.17, 144.34, 133.33 (d, $^{3}J_{CF}$ = 7.1 Hz), 133.26 (d, $^{3}J_{CF}$ = 7.1 Hz), 131.44 (d, $^{4}J_{CF}$ = 2.0 Hz), 131.42 (d, $^{4}J_{CF}$ = 2.0 Hz), 129.64, 127.31 (q, $^{1}J_{CF}$ = 218.2 Hz), 125.97 (q, $^{4}J_{CF}$ = 4.0 Hz), 125.93 (q, $^{4}J_{CF}$ = 4.0 Hz), 125.90 (q, $^{4}J_{CF}$ = 4.0 Hz), 125.86 (q, $^{4}J_{CF}$ = 4.0 Hz), 125.14 (q, $^{1}J_{CF}$ = 218.2 Hz), 122.98 (q, $^{1}J_{CF}$ = 218.2 Hz), 122.16, 120.82 (q, $^{1}J_{CF}$ = 218.2 Hz), 119.63, 119.36 (q, $^{3}J_{CF}$ = 11.1 Hz), 119.25 (q, $^{3}J_{CF}$ = 11.1 Hz), 118.67 (d, $^{3}J_{CF}$ = 17.2 Hz), 118.50 (d, $^{3}J_{CF}$ = 17.2 Hz), 57.22, 31.61, 30.10, 23.60; ^{19}F NMR (376 MHz, CD_3OD) δ -62.93 (d, *J* = 12.8 Hz, 3F), -117.55 – -117.83 (m, 1F); HRMS (ESI+): Calcd for $C_{24}H_{22}F_4N_7OS$ $[M+H]^+$: 532.1543, Found: 532.1538.

(S)-amino(2-((3-(4-((4-(3,5-difluorophenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20z**). Synthesized by General Procedure E. 8 mg, 100%, off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.48 (m, 2H), 7.31 (s, 1H), 6.91 – 6.83 (m, 1H), 4.59 – 4.48 (m, 1H), 3.71 (d, *J* = 2.8 Hz, 1H), 3.60 – 3.51 (m, 1H), 3.49 – 3.41 (m, 1H), 3.16 – 3.10 (m, 1H), 2.34 – 2.22 (m, 1H), 2.18 – 1.97 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.73, 169.35, 166.08 (dd, $^{1}J_{CF}$ = 246.5 Hz), 165.95 (dd, $^{1}J_{CF}$ = 246.5 Hz), 164.57, 163.63 (dd, $^{1}J_{CF}$ = 246.5 Hz), 163.50 (dd, $^{1}J_{CF}$ = 246.5 Hz), 156.44, 150.23 (d, $^{4}J_{CF}$ = 4.0 Hz), 150.19 (d, $^{4}J_{CF}$ = 4.0 Hz), 145.35, 139.76 (dd, $^{3}J_{CF}$ = 9.1 Hz), 139.66(dd, $^{3}J_{CF}$ = 9.1 Hz), 139.56 (dd, $^{3}J_{CF}$ = 9.1 Hz), 129.40, 120.43, 118.09, 109.79 (d, $^{2}J_{CF}$ = 27.3 Hz), 109.71 (d, $^{3}J_{CF}$ = 11.1 Hz), 109.59 (d, $^{3}J_{CF}$ = 11.1 Hz), 109.52 (d, $^{2}J_{CF}$ = 27.3 Hz), 106.65, 103.70 (dd, $^{2}J_{CF}$ = 26.3 Hz), 103.44 (dd, $^{3}J_{CF}$ = 26.3 Hz), 103.18 (dd, $^{2}J_{CF}$ = 26.3

Hz), 71.34*, 67.91*, 57.20, 40.56, 31.61, 30.05, 23.59; ^{19}F NMR (376 MHz, CD_3OD) δ -111.61 – -111.72 (m, 2F); HRMS (ESI+): Calcd for $C_{23}H_{22}F_2N_7OS$ $[M+H]^+$: 482.1575, Found: 482.1534.

(S)-amino(2-((3-(4-((4-(3-fluoro-5-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20aa**). Synthesized by General Procedure E. 6 mg, 100%, yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 – 8.10 (m, 2H), 8.04 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H), 7.39 (t, J = 9.4 Hz, 1H), 7.29 (s, 1H), 4.55 – 4.47 (m, 1H), 3.57 – 3.48 (m, 1H), 3.48 – 3.38 (m, 1H), 2.31 – 2.21 (m, 1H), 2.14 – 1.95 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.77, 169.32, 165.57, 164.91, 163.12, 156.44, 149.32, 145.21, 139.62, (d, $^3J_{CF}$ = 9.1 Hz) 139.53 (d, $^3J_{CF}$ = 9.1 Hz), 134.07 (d, $^3J_{CF}$ = 8.1 Hz), 133.99 (d, $^3J_{CF}$ = 8.1 Hz), 133.74 (d, $^3J_{CF}$ = 9.1 Hz), 133.65 (d, $^3J_{CF}$ = 9.1 Hz), 129.42, 126.24, 123.51, 120.70, 119.55 (q, $^4J_{CF}$ = 3.0 Hz), 119.52 (q, $^4J_{CF}$ = 3.0 Hz), 119.51 (q, $^4J_{CF}$ = 3.0 Hz), 119.48 (q, $^4J_{CF}$ = 3.0 Hz), 118.30, 117.37 (d, $^3J_{CF}$ = 17.2 Hz), 117.13 (d, $^3J_{CF}$ = 17.2 Hz), 112.44, 112.17, 107.28, 57.25, 31.64, 30.12, 23.61; ^{19}F NMR (376 MHz, CD_3OD) δ -64.34 (s, 1F) , -112.36 (t, J = 9.1 Hz, 1F); HRMS (ESI+): Calcd for $C_{24}H_{22}F_4N_7OS$ $[M+H]^+$: 532.1543, Found: 532.1520.

(S)-amino(2-((3-(4-((4-(3,5-bis(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20bb**). Synthesized by General Procedure E. 22 mg, 100%, white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 2H), 8.07 (d, J = 8.4 Hz, 2H), 7.93 – 7.86 (m, 3H), 7.60 (s, 1H), 4.62 – 4.54 (m, 1H), 3.64 – 3.55 (m, 1H), 3.55 – 3.46 (m, 1H), 2.39 – 2.27 (m, 1H), 2.21 – 2.03 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.12, 168.96, 167.94, 156.43, 145.08, 143.15, 133.46, 133.42, 132.82 (q, $^2J_{CF}$ = 32.3 Hz), 132.50 (q, $^2J_{CF}$ = 32.3 Hz), 132.18 (q, $^2J_{CF}$ = 32.3 Hz), 131.85 (q, $^2J_{CF}$ = 32.3 Hz), 131.02, 130.99, 129.91, 126.79, 126.64 (q, $^4J_{CF}$ = 3.0 Hz), 126.61 (q, $^4J_{CF}$ = 3.0 Hz), 126.57 (q, $^4J_{CF}$ = 3.0 Hz), 126.53 (q,

$^4J_{CF}$ = 3.0 Hz), 124.09, 124.06, 124.01, 123.98, 121.24, 57.18, 31.60, 30.09, 23.59; ^{19}F NMR (376 MHz, CD_3OD) δ -64.49; HRMS (ESI+): Calcd for $C_{25}H_{22}F_6N_7OS$ $[M+H]^+$: 582.1511, Found: 582.1516.

(S)-amino(2-((3-(4-((4-(2-fluoro-5-(trifluoromethyl)phenyl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20cc**). Synthesized by General Procedure E. 6 mg, 100%, yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 – 8.52 (m, 1H), 8.11 – 8.03 (m, 2H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.73 – 7.66 (m, 1H), 7.50 – 7.40 (m, 2H), 4.62 – 4.54 (m, 1H), 3.65 – 3.56 (m, 1H), 3.56 – 3.46 (m, 1H), 2.40 – 2.27 (m, 1H), 2.22 – 2.04 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 183.96, 177.78, 175.04, 169.33, 164.57 (d, $^1J_{CF}$ = 256.5 Hz), 164.00, 162.03 (d, $^1J_{CF}$ = 256.5 Hz), 156.45, 145.34, 144.51, 129.37, 128.20 (q, $^1J_{CF}$ = 112.1 Hz), 127.09 (q, $^1J_{CF}$ = 112.1 Hz), 124.59 (d, $^3J_{CF}$ = 12.1 Hz), 124.47 (d, $^3J_{CF}$ = 12.1 Hz), 124.32, 123.78, 120.62, 118.54, 118.20, 117.98, 110.58, 106.88, 103.88, 57.26, 31.61, 30.11, 23.58; ^{19}F NMR (376 MHz, CD_3OD) δ -63.69 (s, 3F), -110.28 – -110.99 (m, 1F); HRMS (ESI+): Calcd for $C_{24}H_{22}F_4N_7OS$ $[M+H]^+$: 532.1543, Found: 532.1520. HPLC purity: 85% pure.

(S)-(2-((3-(4-((4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)(amino)methaniminium chloride (**20dd**). Synthesized by General Procedure E. 5 mg, 100%, light yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, *J* = 8.5 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.73 (dd, *J* = 14.9, 7.9 Hz, 4H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.26 (s, 1H), 4.65 – 4.51 (m, 1H), 3.65 – 3.56 (m, 1H), 3.55 – 3.47 (m, 1H), 2.41 – 2.27 (m, 1H), 2.24 – 2.02 (m, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ 176.60, 167.69, 165.59, 155.03, 146.50, 142.48, 141.43, 140.13, 130.85, 128.55, 128.38, 127.30, 126.99, 126.46, 126.36, 121.61, 119.03, 55.78, 30.18, 28.66, 22.17; HRMS (ESI+): Calcd for $C_{29}H_{28}N_7OS$ $[M+H]^+$: 522.2076, Found: 522.2046.

(S)-amino(2-((3-(4-((4-(benzofuran-2-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**20ee**). Synthesized by General Procedure E. 13 mg, 100%, yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (d, *J* = 6.5 Hz, 1H), 7.98 (t, *J* = 7.7 Hz, 3H), 7.79 (d, *J* = 7.9 Hz, 2H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.37 – 7.25 (m, 2H), 4.52 – 4.42 (m, 1H), 3.52 – 3.44 (m, 1H), 3.43 – 3.35 (m, 2H), 2.30 – 2.13 (m, 1H), 2.13 – 1.90 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.93, 168.95, 166.98, 156.94, 156.73, 156.32, 145.31, 143.60, 139.64, 129.74, 126.42, 126.20, 126.02, 124.57, 123.13, 121.58, 120.62, 115.61, 112.61, 57.14, 31.56, 30.08, 23.56; HRMS (ESI+): Calcd for $C_{25}H_{24}N_7O_2S$ $[M+H]^+$: 486.1712, Found: 486.1683.

tert-butyl (S)-2-((3-(4-((4-([1,1'-biphenyl]-3-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**21a**). Synthesized by General Procedure D. 12 mg, 30%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.02 (m, 3H), 7.85 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.77 (s, 1H), 7.69 – 7.62 (m, 2H), 7.59 – 7.43 (m, 6H), 7.40 – 7.33 (m, 1H), 6.97 (s, 1H), 4.40 – 4.22 (m, 1H), 3.52 – 3.27 (m, 3H), 3.17 – 2.98 (m, 1H), 2.14 – 2.02 (m, 1H), 1.95 – 1.78 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.20, 167.90, 162.96, 154.37, 151.61, 142.82, 141.84, 141.22, 135.00, 129.26, 128.96, 128.92, 127.54, 127.37, 127.04, 125.21, 125.15, 120.66, 117.40, 117.29, 103.13, 80.23, 79.78*, 55.35, 55.22*, 46.90*, 46.50*, 31.93, 31.15*, 30.98*, 30.21*, 29.85*, 28.63, 23.71*, 22.91*; HRMS (ESI+): Calcd for $C_{33}H_{34}N_5O_3S$ $[M+H]^+$: 580.2382, Found: 580.2384.

tert-butyl (S)-2-((3-(4-((4-(4'-fluoro-[1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**21b**). Synthesized by General Procedure D. 14 mg, 34%, off-white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.70 – 7.65 (br s, 1H), 7.63 – 7.50 (m, 6H), 7.14 (t, *J* = 8.7 Hz, 2H),

6.95 (s, 1H), 4.39 – 4.22 (m, 1H), 3.50 – 3.27 (m, 3H), 3.15 – 2.97 (m, 1H), 2.13 – 2.01 (m, 1H), 1.95 – 1.79 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.22, 168.00, 163.88 (d, $^1J_{CF}$ = 247.5 Hz), 162.96, 161.43 (d, $^1J_{CF}$ = 247.5 Hz), 154.37, 151.25, 150.57, 142.75, 139.84, 136.93 (d, $^4J_{CF}$ = 3.0 Hz), 136.90 (d, $^4J_{CF}$ = 3.0 Hz), 133.53, 133.45, 131.92, 128.95, 128.84, 128.72 (d, $^3J_{CF}$ = 8.1 Hz), 128.64 (d, $^3J_{CF}$ = 8.1 Hz), 127.80, 127.35, 126.71, 122.07, 120.73, 117.39, 117.35, 115.92 (d, $^2J_{CF}$ = 21.2 Hz), 115.71 (d, $^2J_{CF}$ = 21.2 Hz), 103.27, 102.96, 80.23, 55.34, 46.90*, 46.51*, 31.93*, 31.15*, 31.00*, 30.23*, 29.85*, 28.64*, 23.71*, 22.92*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.71 – -116.15 (m, 1F); HRMS (ESI+): Calcd for $C_{33}H_{33}FN_5O_3S$ $[M+H]^+$: 598.2288, Found: 598.2234.

tert-butyl (S)-2-((3-(4-((4-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**21c**). Synthesized by General Procedure D. 11 mg, 37%, yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.2 Hz, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.54 (m, 8H), 6.98 (s, 1H), 4.40 – 4.21 (m, 1H), 3.52 – 3.27 (m, 3H), 3.17 – 2.97 (m, 1H), 2.13 – 2.00 (m, 1H), 1.96 – 1.78 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.41, 167.99, 163.01, 154.38, 151.06, 144.29, 142.73, 139.28, 134.41, 129.69 (q, $^2J_{CF}$ = 32.3 Hz), 129.37 (q, $^2J_{CF}$ = 32.3 Hz), 128.98, 128.83 (q, $^2J_{CF}$ = 32.3 Hz), 127.67, 127.54, 127.37, 127.23, 126.84, 125.91 (q, $^4J_{CF}$ = 4.0 Hz), 125.87 (q, $^4J_{CF}$ = 4.0 Hz), 125.79 (q, $^4J_{CF}$ = 4.0 Hz), 117.39, 103.40, 80.23*, 79.81*, 55.30, 46.90*, 46.50*, 31.93*, 31.15*, 30.23*, 29.83*, 28.63, 23.71*, 22.92*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.43 (s, 3F); HRMS (ESI+): Calcd for $C_{34}H_{32}F_3N_5NaO_3S$ $[M+H]^+$: 670.2075, Found: 670.2068.

tert-butyl (S)-2-((3-(4-((4-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**21d**). Synthesized by General Procedure D. 12 mg, 35%, tan amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.03 (m, 2H), 7.98

(d, J = 7.9 Hz, 2H), 7.88 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.70 – 7.51 (m, 6H), 6.98 (s, 1H), 4.39 – 4.23 (m, 1H), 3.52 – 3.27 (m, 3H), 3.15 – 2.96 (m, 1H), 2.13 – 2.01 (m, 1H), 1.95 – 1.79 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.08, 167.78, 162.84, 154.24, 150.90, 142.60, 141.42, 139.12, 134.10, 131.77, 131.65, 131.34 (q, $^2J_{CF}$ = 30.3 Hz), 131.02 (q, $^2J_{CF}$ = 30.3 Hz), 130.22, 129.27, 128.81, 128.68, 127.64 (q, $^1J_{CF}$ = 155.5 Hz), 127.41, 126.69, 126.10 (q, $^1J_{CF}$ = 155.5 Hz), 125.51, 123.99 (q, $^2J_{CF}$ = 30.3 Hz), 123.69 (q, $^2J_{CF}$ = 30.3 Hz), 122.81, 120.63, 117.20, 103.18, 80.10, 55.15, 46.74*, 46.35*, 31.75*, 30.98*, 30.07*, 28.47, 23.54*, 22.76*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.60 (s, 3F); HRMS (ESI+): Calcd for $C_{34}H_{33}F_3N_5O_3S$ $[M+H]^+$: 648.2256, Found: 648.2209.

tert-butyl (S,Z)-((2-((3-(4-((4-([1,1'-biphenyl]-3-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)((tert-butoxycarbonyl)imino)methyl)carbamate (**22a**). Synthesized by General Procedure E. 13mg, 68%, off-white oily solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.09 (s, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.4 Hz, 2H), 7.59 – 7.53 (m, 4H), 7.52 – 7.44 (m, 3H), 7.37 (t, J = 7.3 Hz, 1H), 6.96 (s, 1H), 4.82 – 4.72 (m, 1H), 3.81 – 3.62 (m, 3H), 3.57 – 3.43 (m, 1H), 3.09 (dd, 1H), 2.36 – 2.26 (m, 1H), 1.95 – 1.87 (m, 1H), 1.85 – 1.73 (m, 2H), 1.48 (d, J = 14.1 Hz, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.87, 167.90, 162.91, 162.64, 154.28, 151.66, 150.48, 142.80, 141.84, 141.27, 135.10, 129.26, 128.95, 127.54, 127.38, 127.00, 125.26, 125.12, 120.74, 117.20, 103.03, 82.17, 79.61, 56.62, 50.29, 30.88, 30.47, 28.38, 28.25, 24.51; HRMS (ESI+): Calcd for $C_{39}H_{44}N_7O_5S$ $[M+H]^+$: 722.3125, Found: 722.3107.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(4'-fluoro-[1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**22b**). Synthesized by General Procedure E. 25 mg, 50%, off-white oily solid. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 10.39 (s, 1H), 8.03 (d, *J* = 8.1 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.89 – 7.78 (m, 1H), 7.65 – 7.55 (m, 5H), 7.13 (t, *J* = 8.5 Hz, 2H), 6.94 (s, 1H), 4.84 – 4.71 (m, 1H), 3.81 – 3.61 (m, 2H), 3.58 – 3.43 (m, 1H), 3.09 (dd, *J* = 15.4, 8.7 Hz, 1H), 2.37 – 2.24 (m, 1H), 1.96 – 1.87 (m, 1H), 1.86 – 1.72 (m, 2H), 1.54 – 1.41 (m, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.85, 167.88, 163.65 (d, $^1J_{CF}$ = 100 Hz), 162.89, 162.65 (d, $^1J_{CF}$ = 100 Hz), 154.31, 151.29, 150.51, 142.78, 139.81, 136.97, 133.61, 131.92, 128.97, 128.71 (d, $^4J_{CF}$ = 7.1 Hz), 128.64 (d, $^4J_{CF}$ = 7.1 Hz), 127.82, 127.35 (d, $^2J_{CF}$ = 63.6 Hz), 126.72 (d, $^2J_{CF}$ = 63.6 Hz), 120.77, 117.23, 115.91 (d, $^3J_{CF}$ = 17.2 Hz), 115.74 (d, $^3J_{CF}$ = 17.2 Hz), 103.17, 102.86, 82.17, 79.64, 56.61, 50.31, 30.92, 30.46, 29.85, 28.32, 28.17, 24.56; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.56 – -115.66 (m, 1F); HRMS (ESI+): Calcd for $C_{39}H_{43}FN_7O_5S$ $[M+H]^+$: 740.3030, Found: 740.2979.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**22c**). Synthesized by General Procedure E. 10 mg, 75%, off-white oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.09 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 7.9 Hz, 2H), 7.81 – 7.63 (m, 6H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.46 (s, 1H), 6.98 (s, 1H), 4.79 (dt, *J* = 11.9, 5.8 Hz, 1H), 3.79 – 3.62 (m, 2H), 3.57 – 3.44 (m, 1H), 3.15 (dd, *J* = 15.4, 8.3 Hz, 1H), 2.33 – 2.22 (m, 1H), 1.98 – 1.91 (m, 1H), 1.89 – 1.74 (m, 2H), 1.53 – 1.44 (m, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.80, 167.74, 162.82, 162.54, 154.05, 150.95, 148.99, 144.17, 142.55, 139.09, 134.34, 129.52, 128.86, 127.50, 127.21, 126.69, 125.78 (q, $^4J_{CF}$ = 2.0 Hz), 125.75 (q, $^4J_{CF}$ = 2.0 Hz), 125.73 (q, $^4J_{CF}$ = 2.0 Hz), 125.70 (q, $^4J_{CF}$ = 2.0 Hz), 121.05 (q, $^4J_{CF}$ = 2.0 Hz), 120.79, 117.15, 103.17, 101.06, 83.41, 81.99, 56.47, 50.10, 30.69, 30.30, 29.69, 28.15, 27.98; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.44 (s, 3F); HRMS (ESI+): Calcd for $C_{40}H_{43}F_3N_7O_5S$ $[M+H]^+$: 790.2998, Found: 790.2989.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**22d**). Synthesized by General Procedure E. 7 mg, 37%, off-white oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.06 – 7.94 (m, 4H), 7.87 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.68 – 7.52 (m, 6H), 6.96 (s, 1H), 4.82 – 4.73 (m, 1H), 3.82 – 3.62 (m, 2H), 3.57 – 3.45 (m, 1H), 3.09 (dd, *J* = 15.5, 8.8 Hz, 1H), 2.31 (dt, *J* = 11.5, 6.7 Hz, 1H), 1.97 – 1.88 (m, 1H), 1.84 – 1.75 (m, 1H), 1.71 – 1.62 (m, 2H), 1.55 – 1.42 (m, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.83, 167.87, 163.01, 151.07, 150.47, 142.78, 141.61, 139.21, 134.37, 131.91, 131.75 (q, $^2J_{CF}$ = 25.3 Hz), 131.49 (q, $^2J_{CF}$ = 25.3 Hz), 131.24 (q, $^2J_{CF}$ = 25.3 Hz), 130.98 (q, $^2J_{CF}$ = 25.3 Hz), 130.36, 129.42, 128.96, 128.81 (q, $^1J_{CF}$ = 100.0 Hz), 127.81 (q, $^1J_{CF}$ = 100.0 Hz), 127.55, 126.86, 126.26, 125.41, 124.17 (q, $^4J_{CF}$ = 3.0 Hz), 124.14 (q, $^4J_{CF}$ = 3.0 Hz), 124.11 (q, $^4J_{CF}$ = 3.0 Hz), 124.09 (q, $^4J_{CF}$ = 3.0 Hz), 123.90 (q, $^4J_{CF}$ = 3.0 Hz), 123.87 (q, $^4J_{CF}$ = 3.0 Hz), 123.84 (q, $^4J_{CF}$ = 3.0 Hz), 123.81 (q, $^4J_{CF}$ = 3.0 Hz), 123.25, 120.75, 117.24, 117.16, 105.35, 103.20, 82.19, 79.67, 56.61, 50.32, 30.92, 30.45, 28.36, 28.28, 28.16; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.63; HRMS (ESI+): Calcd for $C_{40}H_{43}F_3N_7O_5S$ $[M+H]^+$: 790.2998, Found: 790.2997.

(S)-(2-((3-(4-((4-([1,1'-biphenyl]-3-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)(amino)methaniminium chloride (**23a**). Synthesized by General Procedure E. 5 mg, 93%, light yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 – 8.14 (m, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 7.95 – 7.86 (m, 3H), 7.73 – 7.66 (m, 2H), 7.60 – 7.55 (m, 1H), 7.53 – 7.44 (m, 3H), 7.40 – 7.33 (m, 1H), 7.25 (s, 1H), 7.22 (s, 1H), 4.57 – 4.50 (m, 1H), 3.55 (ddd, *J* = 9.8, 8.0, 4.2 Hz, 1H), 3.51 – 3.41 (m, 1H), 2.36 – 2.19 (m, 1H), 2.19 – 1.97 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.73, 169.37, 164.53, 156.44, 152.44, 145.59, 142.93, 142.47, 136.66, 130.19, 129.92, 129.40, 128.48, 128.08, 127.47, 126.06, 125.64, 120.26, 118.04, 104.46, 57.23,

31.60, 30.07, 23.58; HRMS (ESI+): Calcd for $C_{29}H_{28}N_7OS$ $[M+H]^+$: 522.2076, Found: 522.2072. HPLC purity: 88%.

(S)-amino(2-((3-(4-((4-(4'-fluoro-[1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**23b**). Synthesized by General Procedure E. 8 mg, 90%, off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.09 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 7.8 Hz, 2H), 7.84 (d, J = 8.5 Hz, 3H), 7.72 – 7.63 (m, 3H), 7.23 (s, 1H), 7.22 – 7.15 (m, 2H), 4.57 – 4.49 (m, 1H), 3.58 – 3.50 (m, 1H), 3.49 – 3.42 (m, 1H), 3.33 – 3.31 (m, 2H), 2.35 – 2.22 (m, 1H), 2.18 – 1.97 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.96, 169.20, 167.04, 166.33 (d, $^1J_{CF}$ = 128.3 Hz), 165.06 (d, $^1J_{CF}$ = 128.3 Hz), 156.46, 149.01, 144.38, 141.46, 138.03, 132.86, 129.76, 129.70, 129.54, 128.90, 128.26 (d, $^2J_{CF}$ = 49.5 Hz), 127.77 (d, $^2J_{CF}$ = 49.5 Hz), 119.81, 118.95, 116.73 (d, $^3J_{CF}$ = 17.3 Hz), 116.56 (d, $^3J_{CF}$ = 17.3 Hz), 57.22, 31.62, 30.08, 28.13, 23.59; ^{19}F NMR (376 MHz, CD_3OD) δ --117.18 – -117.54 (m, 1F); HRMS (ESI+): Calcd for $C_{29}H_{27}FN_7OS$ $[M+H]^+$: 540.1982, Found: 540.1978.

(S)-amino(2-((3-(4-((4-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**23c**). Synthesized by General Procedure E. 2 mg, 100%, off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.11 – 7.99 (m, 3H), 7.96 – 7.83 (m, 4H), 7.80 – 7.73 (m, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.28 – 7.18 (m, 2H), 4.58 – 4.51 (m, 1H), 3.59 – 3.51 (m, 1H), 3.51 – 3.45 (m, 1H), 2.36 – 2.25 (m, 1H), 2.19 – 1.99 (m, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.72, 169.41, 156.48, 152.04, 151.44, 145.62, 145.54, 139.94, 136.20, 135.32, 132.74, 131.64, 129.40, 128.80, 128.45, 128.38, 127.72, 126.84 (q, $^4J_{CF}$ = 3.0 Hz), 126.81 (q, $^4J_{CF}$ = 3.0 Hz), 126.78 (q, $^4J_{CF}$ = 3.0 Hz), 126.75 (q, $^4J_{CF}$ = 3.0 Hz), 122.39, 120.29, 118.08, 104.78, 57.26, 31.63, 30.09, 23.60; ^{19}F NMR (376 MHz, CD_3OD) δ -63.98 (s, 3F): Calcd for $C_{30}H_{27}F_3N_7OS$ $[M+H]^+$: 590.1950, Found: 590.1954.

(S)-amino(2-((3-(4-((4-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**23d**). Synthesized by General Procedure E. 5 mg, 100%, off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 – 8.03 (m, 2H), 8.02 – 7.97 (m, 1H), 7.94 (d, J = 4.1 Hz, 2H), 7.88 – 7.82 (m, 2H), 7.79 – 7.75 (m, 2H), 7.68 – 7.65 (m, 2H), 4.57 – 4.50 (m, 1H), 3.60 – 3.50 (m, 1H), 3.50 – 3.41 (m, 1H), 3.34 – 3.31 (m, 1H), 2.34 – 2.22 (m, 1H), 2.17 – 2.00 (m, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ 177.96, 169.17, 166.36, 156.43, 148.71, 144.30, 142.73, 140.75, 133.87, 132.47, 131.64, 130.89, 129.70, 128.53, 127.96, 127.34, 127.06, 125.26 (q, $^{4}J_{CF}$ = 4.0 Hz), 125.22 (q, J_{CF} = 4.0 Hz), 125.18 (q, J_{CF} = 4.0 Hz), 125.14 (q, J_{CF} = 4.0 Hz), 124.41, 124.37, 122.32, 119.83, 57.20, 31.60, 30.07, 23.59; ^{19}F NMR (376 MHz, CD_3OD) δ -64.14 (s, 3F); HRMS (ESI+): Calcd for $C_{30}H_{27}F_3N_7OS$ $[M+H]^+$: 590.1950, Found: 590.1949.

N-(4-cyanophenyl)-2,2,2-trifluoroacetamide (**25**). 4-Fluorobenzonitrile (0.5 g, 4.13 mmol) was dissolved in THF (20.6 mL) and 1 M potassium *tert*-butoxide in THF (10.3 mL, 10.32 mmol) was then added. The reaction mixture was refluxed for 4 h, after which the organic solvent was removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography (5% EtOAc/ hexanes) to yield **2** (207 mg, 29%) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.90, 133.36, 122.94, 119.11, 105.58, 80.17, 28.80; HRMS (ESI+): Calcd for $C_{11}H_{14}NO$ $[M+H]^+$: 176.1075, Found: 176.1083.

(Z)-4-(tert-butoxy)-N'-hydroxybenzimidamide. Synthesized by General Procedure A. 215 mg, 87% as white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.11 (s, 1H), 7.64 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 1H), 5.48 (s, 2H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 157.36,

151.95, 128.89, 126.94, 123.92, 78.87, 28.95; HRMS (ESI+): Calcd for $C_{11}H_{17}N_2O_2$ $[M+H]^+$: 209.1290, Found: 209.1290.

tert-butyl (S)-2-((3-(4-(tert-butoxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**26**). Synthesized by General Procedure B. 214 mg, 52%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 4.35 – 4.18 (m, 1H), 3.46 – 3.23 (m, 3H), 3.04 (ddd, *J* = 37.3, 14.5, 8.7 Hz, 1H), 2.04 (q, *J* = 6.4, 4.4 Hz, 1H), 1.91 – 1.74 (m, 3H), 1.44 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.30, 168.09, 158.39, 154.24, 128.43, 123.86, 121.52, 80.05, 79.37, 55.26, 46.82, 46.41, 31.83, 31.03, 30.86, 30.10, 28.97, 28.54, 23.63, 22.84; HRMS (ESI+): Calcd for $C_{22}H_{32}N_3O_4$ $[M+H]^+$: 402.2393, Found: 402.2407.

tert-butyl (S)-2-((3-(4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**27**). **26** (212 mg, 0.529 mmol) was dissolved in DCM (2 mL) and then 1 N TFA (2 mL) was added. The reaction mixture was stirred for 4 h. At this time, TLC showed complete conversion of starting material. Organic solvent was removed under reduced pressure. The resulting product was then dissolved in dioxane (1 mL), and a mixture of di-*tert*-butyl dicarbonate (0.146 mL, 0.635 mmol) and TEA (0.192 mL, 1.38 mmol) was added dropwise to the solution. The reaction mixture was stirred for 1 h, after which the organic solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (30% EtOAc/hexane) to provide **27**(73 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.92 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.29 – 4.20 (m, 1H), 3.41 – 3.25 (m, 2H), 3.13 (dd, *J* = 14.6, 8.2 Hz, 1H), 2.95 (s, 1H), 2.15 – 2.06 (m, 1H), 1.95 – 1.80 (m, 3H), 1.47 – 1.39 (m, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.74, 169.35, 161.71, 156.09, 130.01, 118.99, 116.75, 81.52, 81.01, 56.89*, 56.53*, 47.81*, 47.31*, 32.38*, 32.10*, 31.53*, 31.16*, 28.73*, 28.59*, 24.33*, 23.51*; HRMS (ESI+): Calcd for $C_{18}H_{22}N_3O_4$ $[M-H]^-$: 344.1610, Found: 344.1620.

tert-butyl (S)-2-((3-(4-((4-bromothiazol-2-yl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**28**). 2, 4-dibromothiazole (0.025 g, 0.101 mmol) was added to a mixture of **27** (0.035 g, 0.101 mmol) and K_2CO_3 (0.017 g, 0.122 mmol) in DMF (1 mL). The reaction mixture was refluxed for 17 h, after which the solution was partitioned between EtOAc and LiBr aqueous solution. The aqueous solution was washed with EtOAc three times, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *via* vacuum. The resulting residue was purified by silica gel column chromatography (30% EtOAc/ hexane) to yield **28** (20 mg, 39%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.78 (s, 1H), 4.38 – 4.21 (m, 1H), 3.49 – 3.28 (m, 3H), 3.27 – 2.98 (m, 1H), 2.13 – 2.01 (m, 1H), 1.93 – 1.77 (m, 3H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.64, 172.10, 167.55, 156.88, 154.30, 129.48, 129.19, 124.79, 120.39, 120.10, 119.76, 110.97, 80.18*, 79.77*, 55.27*, 55.20*, 46.88*, 46.49*, 31.95*, 31.16*, 31.01*, 30.24*, 28.62, 23.71*, 22.92*; HRMS (ESI+): Calcd for $C_{21}H_{23}BrN_4NaO_4S$ $[M+Na]^+$: 529.0466, Found: 529.0493.

tert-butyl (S)-2-((3-(4-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**29**). Synthesized by General Procedure D. 30 mg, 45%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.17 (s, 1H), 4.39 – 4.21 (m, 1H), 3.51 – 3.30 (m, 3H), 3.17 – 3.00 (m, 1H), 2.14 – 2.03 (m, 1H), 1.94 – 1.80 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.78, 172.08, 167.71, 157.42, 148.58, 137.36, 129.50, 129.41, 126.27, 125.83, 124.50, 120.36, 110.97, 108.87, 80.20*, 79.80*, 55.29, 46.89*, 46.52*, 31.96*, 31.17*, 30.27*, 28.64, 23.73*, 22.94*; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.61 (s, 3F); HRMS (ESI+): Calcd for $C_{21}H_{23}BrN_4NaO_4S$ $[M+Na]^+$: 529.0466, Found: 529.0493.

tert-butyl (S,Z)-(((tert-butoxycarbonyl)imino)(2-((3-(4-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methyl)carbamate (**30**). Synthesized by General Procedure E. 10 mg, 83%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.21 – 8.13 (m, 2H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.45 (m, 2H), 7.42 – 7.37 (m, 1H), 7.17 (s, 1H), 4.85 – 4.75 (m, 1H), 3.74 – 3.61 (m, 2H), 3.56 – 3.43 (m, 1H), 3.20 (dd, *J* = 15.2, 8.2 Hz, 1H), 2.32 – 2.23 (m, 1H), 1.97 – 1.89 (m, 1H), 1.88 – 1.76 (m, 2H), 1.47 (d, *J* = 7.6 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.49, 172.13, 167.61, 162.67, 157.36, 156.85, 154.23, 150.45, 148.55, 137.35, 130.41, 130.24, 129.92, 129.58, 129.49, 126.26, 125.89 (q, $^{4}J_{CF}$ = 3.5 Hz), 125.85 (q, $^{4}J_{CF}$ = 3.5 Hz), 125.81 (q, $^{4}J_{CF}$ = 3.5 Hz), 125.77 (q, $^{4}J_{CF}$ = 3.5 Hz), 124.69, 121.91, 120.41, 120.35, 119.78, 110.93, 108.84, 82.12, 79.45, 56.61, 50.28, 30.76, 30.45, 28.36, 28.23, 24.54; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.62 (s, 3F); HRMS (ESI+): Calcd for $C_{34}H_{38}F_3N_6O_6S$ $[M+H]^+$: 715.2526, Found: 715.2499.

(S)-amino(2-((3-(4-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride (**31**). Synthesized by General Procedure E. 6 mg, 100%, yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 – 8.15 (m, 2H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.63 (s, 1H), 7.61 – 7.53 (m, 2H), 4.59 – 4.51 (m, 1H), 3.61 – 3.52 (m, 1H), 3.53 – 3.43 (m, 1H), 3.38 – 3.34 (m, 2H), 2.38 – 2.25 (m, 1H), 2.21 – 2.01 (m, 3H); ^{13}C NMR (101 MHz, cd$_3$od) δ 178.31, 173.59, 168.87, 159.02, 156.45, 149.34, 138.97, 130.41, 130.32, 127.36, 126.75 (q, $^{4}J_{CF}$ = 4.0 Hz), 126.71 (q, $^{4}J_{CF}$ = 4.0 Hz), 126.67 (q, $^{4}J_{CF}$ = 4.0 Hz), 126.64 (q, $^{4}J_{CF}$ = 4.0 Hz), 125.48, 121.77, 121.60, 113.12, 111.34, 57.17, 31.60, 30.05, 23.58; ^{19}F NMR (376 MHz, CD_3OD) δ -64.16 (s, 3F); HRMS (ESI+): Calcd for $C_{24}H_{22}F_3N_6O_2S$ $[M+H]^+$: 515.1477, Found: 515.1445.

tert-butyl (S)-2-((3-(4-((4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)(methyl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate (**32**). To a solution of *tert*-butyl (*S*)-2-((3-(4-**18dd** (0.025 g, 0.043 mmol) in acetone (1 mL) was added K_2CO_3 (0.024 g, 0.172 mmol) and methyl iodide (0.061 g, 0.431 mmol). The reaction mixture was refluxed for 17 h. The organic solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (30% EtOAc/ hexane) to yield **32** (15 mg, 73%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.3 Hz, 2H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 5H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 6.85 (s, 1H), 4.40 – 4.22 (m, 1H), 3.68 (s, 3H), 3.52 – 3.28 (, 3H), 3.20 – 2.99 (m, 1H), 2.16 – 2.02 (m, 1H), 1.97 – 1.78 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.62, 168.41, 154.64, 151.48, 148.51, 140.96, 140.54, 134.00, 128.93, 128.79, 127.43, 127.40, 127.33, 127.12, 126.59, 123.52, 102.76, 80.17, 55.29, 46.92*, 46.53*, 40.39, 31.98*, 31.13*, 30.25*, 29.85*, 28.65, 23.74*, 22.94*; HRMS (ESI+): Calcd for $C_{34}H_{36}N_5O_3S$ $[M+H]^+$: 594.2538, Found: 594.2553

tert-butyl (S,Z)-((2-((3-(4-((4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)(methyl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)((tert-butoxycarbonyl)imino)methyl)carbamate (**33**). Synthesized by General Procedure E. 15 mg, 73%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.15 (d, *J* = 8.2 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.62 (dd, *J* = 10.9, 8.2 Hz, 6H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 6.84 (s, 1H), 4.84 – 4.76 (m, 1H), 3.73 – 3.61 (m, 5H), 3.55 – 3.48 (m, 1H), 3.19 (dd, *J* = 15.2, 8.2 Hz, 1H), 2.32 – 2.24 (m, 1H), 1.98 – 1.90 (m, 1H), 1.89 – 1.76 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.30, 168.44, 167.82, 158.56, 155.56, 154.18, 151.41, 148.46, 140.94, 140.50, 133.98, 128.91, 128.85, 128.71, 127.39, 127.11, 126.57, 123.65, 123.55, 102.70, 81.99, 79.53, 56.63, 50.23, 40.37, 30.76, 30.48,

28.30, 28.12, 24.54; HRMS (ESI+): Calcd for $C_{40}H_{46}N_7O_5S$ $[M+H]^+$: 736.3281, Found: 736.3274.

(S)-(2-((3-(4-((4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)amino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)(amino)methaniminium chloride (**34**). Synthesized by General Procedure F. 5mg, 100% yield, off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.13 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.66 – 7.59 (m, 5H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.10 (s, 1H), 4.58 – 4.50 (m, 1H), 3.66 (s, 3H), 3.55 (td, *J* = 9.2, 8.5, 3.9 Hz, 1H), 3.49 – 3.42 (m, 1H), 3.33 – 3.31 (m, 2H), 2.34 – 2.22 (m, 1H), 2.17 – 2.12 (m, 1H), 2.11 – 1.97 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 178.12, 169.97, 169.08, 156.47, 152.27, 150.03, 141.96, 141.78, 135.08, 129.89, 129.60, 128.41, 128.07, 127.81, 127.58, 124.81, 124.41, 57.20, 40.80, 31.61, 30.09, 23.59; HRMS (ESI+): Calcd for $C_{30}H_{30}N_7OS$ $[M^*]^+$: 536.2233, Found: 536.2230.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the

ACS Publications website at DOI:

^{1}H, ^{13}C and ^{19}F NMR spectra of intermediates and final products.

Molecular formula strings

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Author Contributions

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ABBREVIATIONS
Sph, sphingosine; S1P, sphingosine-1-phosphate; SphK, sphingosine kinase; HCTU, O-(1H-6-Chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

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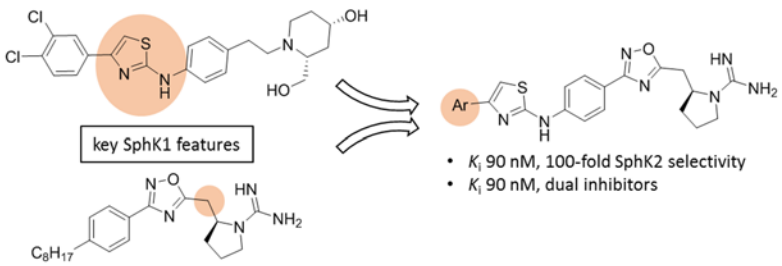
key SphK1 features
Ar
• K_i 90 nM, 100-fold SphK2 selectivity
• K_i 90 nM, dual inhibitors