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FULL PAPER

A Structure–Activity Relationship Study of Novel Hydroxamic Acid Inhibitors around the S1 Subsite of Human Aminopeptidase N

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Abstract: Aminopeptidase N (APN/CD13) is a zinc-dependent ubiquitous transmembrane ectoenzyme that is widely present in different types of cells. APN is one of the most extensively studied metalloaminopeptidases as an anti-cancer target due to its significant role in the regulation of metastasis and angiogenesis. Previously we identified a potent and selective APN inhibitor, *N*-(2-(hydroxyamino)-2-oxo-1-(3',4',5'-trifluoro-[1,1'-biphenyl]-4-yl)ethyl)-4-(methylsulfonamido)benzamide (**3**). Herein, we report the further modifications performed to explore SAR around the S1 subsite of APN and to improve the physicochemical properties. A series of hydroxamic acid analogues were synthesised, and the pharmacological activities were evaluated *in vitro*. *N*-(1-(3'-fluoro-[1,1'-biphenyl]-4-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide (**6f**) was found to display an extremely potent inhibitory activity in the sub-nanomolar range.

Introduction

Cancer is one of the most concerning public health problems worldwide. According to the GLOBOCAN 2018 studies, more than 18 million new cancer cases and 9 million cancer related deaths were estimated.[1] Although there has been a promising increase in cancer survival rates and reduced rates of cancer mortality, cancer still ranks the first or the second most common cause of death in many countries.[1] Unfortunately, many cancer drugs are associated with undesirable side effects, primarily due to their non-selective activity towards non-cancerous cells.[2] Furthermore, the chronic use of anti-cancer medications inevitably accompanies drug resistance which reduces its efficacy.[3] Therefore, the development of novel anti-cancer drugs with less toxicity, improved efficacy, and higher selectivity continues to be critically important. With the ever-growing interests in the discovery of less toxic and more selective anti-cancer agents, extensive research has been conducted to identify and characterise therapeutic targets for cancer at the molecular level.[4]

Aminopeptidase N (APN/CD13; EC 3.4.11.2) is one of the most studied metalloaminopeptidases associated with cancer.[5] A strong correlation between the level of APN expression of a cell and its invasive characteristics has been established through multiple studies.[6] Dysregulation of APN has been found to evolve in almost all types of human malignancies.[7] Over-expression of APN has been observed in various cancers including small cell lung carcinoma,[8] thyroid carcinoma,[9] acute myeloid leukaemia,[10] colon carcinoma[11] and prostate carcinoma.[12] Selective expression of APN has also been found on the surface of angiogenic blood vessels that are mostly absent in normal blood vessels.[13] In addition, APN activity affects metastasis, a complex biological process that contributes to more than 90% of cancer related deaths, by promoting cell adhesion, cell motility, angiogenesis and extracellular matrix (ECM) degradation.[14, 15]

As a member of M1 aminopeptidase enzyme superfamily, APN contains a catalytic zinc ion in the active site and is responsible for the cleavage of amino acids from the N-terminus of polypeptide substrates.[5] APN displays an identical gene sequence to the human lymphocyte surface cluster of differentiation CD13 antigen; therefore, APN is also called as CD13.[7, 16] APN possesses a $HEXXHX_{18}E$ zinc-binding motif and GXMEN substrate-recognition motif that can be found across M1 aminopeptidases.[17] The enzyme is involved in various biological responses with different roles, therefore it is often known as a "moonlighting" enzyme.[18] Many peptides, including angiotensin III and IV, neuropeptides and chemokines are processed by APN.[19] Moreover, APN acts as a signalling molecule for cell adhesion and endocytosis and is also a receptor for coronavirus.[18, 20]

Amongst the APN inhibitors developed previously, bestatin (**1**) is the most extensively investigated competitive APN inhibitor (Figure 1).[7, 21] Bestatin is a natural dipeptide, originally isolated from *Streptomyces olivoreticuli* as an immunomodulating agent.[22] Later clinical trials proved the therapeutic activity of

bestatin against lung cancer, gastric cancer, and acute myeloid leukaemia, and it is currently available in Japan as adjuvant therapy for acute non-lymphatic leukaemia.[23] Another well-known APN inhibitor is Tosedostat (**2**), which is an orally bioavailable prodrug that is converted to a pharmacologically active drug intracellularly.[24] Tosedostat exhibited anti-leukemic activity in phase II clinical trials of acute myeloid leukaemia.[25]

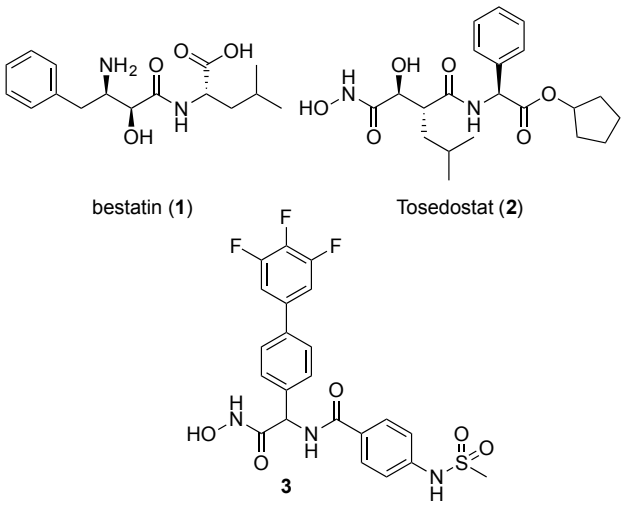


Figure 1. Structures of APN inhibitors.

We previously synthesised a series of hydroxamic acid analogues to optimise the binding interactions around and beyond the S1′ subsite of APN. We discovered that the sulfonamide compound (**3**) showed the most potent inhibition against APN ($K_i^{(app)}$ = 4.8 nM), which was a 500-fold improved activity compared to bestatin ($K_i^{(app)}$ = 2.4 μM).[26] Despite its potent activity and promising pharmacokinetic properties, compound **3** possessed sub-optimal aqueous solubility (12.5 – 25 μg/mL in pH 2.0 and 6.0)[26] which could potentially lead to a limited absorption and low efficacy in the cellular environment.

In this study, we proposed further modifications to compound **3** not only to improve aqueous solubility but also to maintain or improve the potent inhibitory activity by replacing the hydrophobic 3,4,5-trifluorophenyl moiety that is positioned at the S1 binding site of APN. The 3,4,5-trifluorophenyl group was derived from the SAR studies and structure-guided optimisation of the parasitic homologue *Pf*A-M1.[29a] However, there was a limited exploration of the S1 subsite of APN to probe binding interactions.

Results and Discussion

Chemistry

Compound Design. A set of target compounds were designed to investigate the binding interactions at the S1 pocket of APN as well as to achieve favourable aqueous solubility (Figure 2). According to the previous molecular modelling studies, the 3,4,5-trifluorophenyl ring formed various hydrophobic interactions, creating a stable binding site for the inhibitors within the S1 subsite of APN.[26] Therefore, the complete removal of the trifluorophenyl group would allow us to investigate if the biphenyl system is essential for obtaining potency against APN. In addition, replacing the hydrophobic 3,4,5-trifluorophenyl to various isosteric heteroaromatic groups such as pyridyl and pyrimidyl moieties may improve both the solubility and binding interactions.

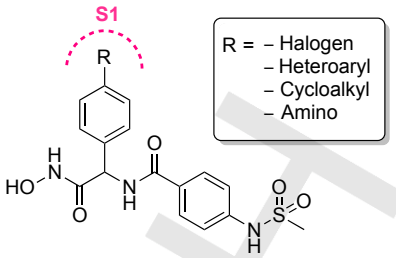


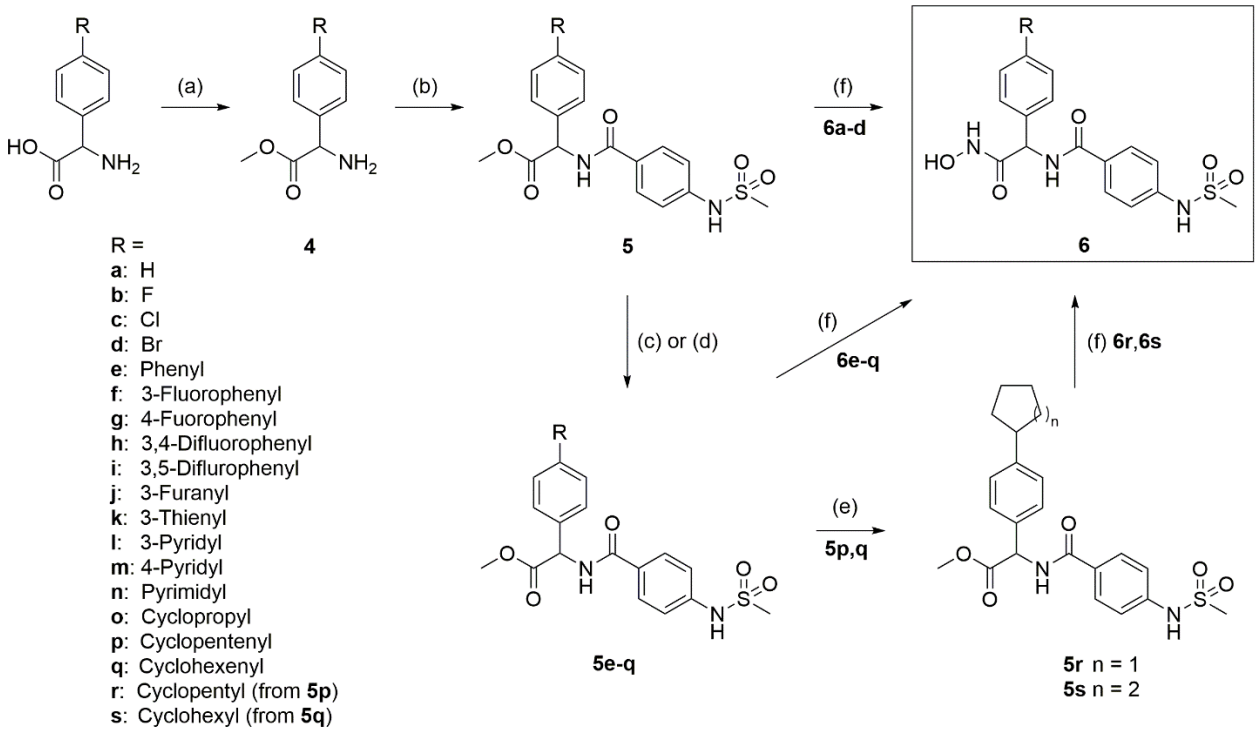
Figure 2. Structures of designed hydroxamic acid analogues

The molecular sizes of pyridine and pyrimidine are comparable to that of benzene. The designed analogues would retain the biphenyl core scaffold so that the compounds could engage in π-stacking hydrophobic interactions with the phenylalanine residues of domain IV as described in earlier studies.[26] Introducing additional polar atoms into the molecule increases the hydrogen bonding capacity, which may also enhance binding interactions with APN. Moreover, incorporating nitrogen-containing heteroaromatics may change the physicochemical properties significantly due to lowered LogP/LogD and increased polar surface area, which would also assist in improving aqueous solubility and other aspects of the pharmacokinetic profile.[27]

Apart from six-membered heteroaromatic, it was thought that five-membered heteroaryl groups such as furan and thiophene would be worthy of investigation. Furan bears an electronegative oxygen atom which is capable of capturing additional hydrogen bonding interactions with the nearby residues. Thiophene is one of the most widely exploited sulfur-containing heteroaromatics in medicinal chemistry due to its unique electropositive properties that allow interactions with electronegative atoms.[28]

Earlier studies heavily focussed on the biaryl or 4-haloaryl units.[26, 29] Therefore, incorporating sp^3-rich groups as replacements of the 3,4,5-trifluorophenyl moiety may create new chemical scaffolds to probe the activities around the S1 pocket of APN. Moreover, the installation of sp^3-groups has been used as effective strategies to enhance solubility by changing the crystal polymorphs.[30] Therefore, introducing cycloalkyl groups such as cyclohexyl and cyclopropyl may remove the aromaticity and symmetry of the biphenyl scaffold to reach an ideal balance between solubility and hydrophobicity, which is essential for optimal oral bioavailability.[30] Piperidine and piperazine derivatives may have advantages in two-fold because they are not only sp^3-rich but also contain additional ionisable nitrogen atom(s).

Synthesis. The synthesis of monoaryl, biaryl, and cycloalkyl compounds **6a**–**s** was achieved as described in Scheme 1. Commercially available phenylglycine derivatives were protected by acid-catalysed esterification, followed by EDCI/DMAP amide coupling with (methylsulfonamido)benzoic acid to produce methyl ester intermediates **5a**-**d** successfully. The aryl bromide **5d** was used as the key intermediate to generate biaryl compounds **5e**-**n** through microwave-assisted Suzuki-Miyaura coupling reactions in the presence of K_3PO_4 and $Pd(PPh_3)_2Cl_2$ under anhydrous conditions.

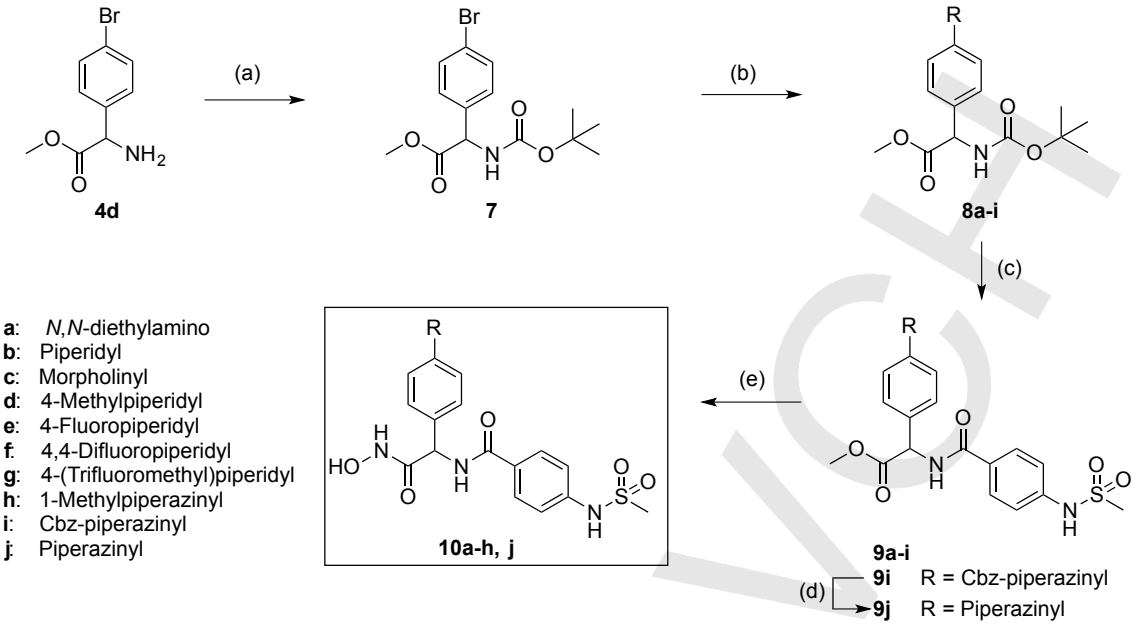


Scheme 1. *Reagents and conditions*: (a) conc. H_2SO_4, MeOH, reflux, overnight, 75–90%; (b) 4-(methylsulfonamido)benzoic acid, EDCI, DMAP, DCM, rt, overnight, 61–92%; (c) arylboronic acid, K_3PO_4, anhydrous DMF, $Pd(PPh_3)_2Cl_2$, 100 °C, microwave, 1–20 h, 33–95%; (d) alkylboronic acid, K_2CO_3, anhydrous THF, $Pd(dppf)Cl_2$, reflux, overnight, 78–94%; (e) EtOH or MeOH, 10% Pd/C, NH_4HCO_2, reflux, 2–16 h, 80–83%; (f) $NH_2OH{\cdot}HCl$, 5 M KOH/MeOH, anhydrous MeOH, rt, overnight, 5–78%.

The coupling reaction between **5d** and cyclopropylboronic acid under the same conditions only resulted in a minimal conversion to the desired product. Cross-coupling reactions of alkylboronic acids remain challenging because of several serious issues such as decomposition of palladium-alkyl intermediate via β-elimination, slow transmetallation, and formation of side products.[31] Molander *et al*. reported successful coupling reactions of alkylboronic acids with electron-deficient and electron-excessive aryl bromides in the presence of $Pd(dppf)Cl_2$, K_2CO_3, and biphasic solvent THF/water.[32] It was also noted that $Pd(dppf)Cl_2$ was commonly used catalyst for coupling reactions with alkylboronic acids which usually required for forcing conditions.[33] Therefore, the modified reaction conditions reported by Molander *et al*. were attempted in the absence of water to avoid hydrolysis of methyl ester, which formed the cyclopropyl **5o** in an excellent yield of 94%.

Unfortunately, the reaction conditions applied for the cyclopropyl **5o** failed to produce the cyclopentyl **5r** and cyclohexyl **5s** analogues. Minimal conversion to the desired product was observed, and the starting material **5d** was mostly recovered. While cyclopropylboronic acid derivatives are widely explored as a competent nucleophile in Suzuki-Miyaura coupling reactions[32-33], there is limited evidence of other secondary alkylboronic acids due to slow transmetallation rates.[33-34] A strategy applied to accelerate the transmetallation step involved was the use of silver(II) oxide (Ag_2O) as an additive.[33, 35] However, when this approach was applied to couple the aryl bromide **5d** with cyclopentylboronic acid, a complete debromination of **5d** was observed. Therefore, cyclopentenyl and cyclohexenylboronic acids were used as alternative substrates because sp^2 vinylboronic acids are known to undergo Suzuki-Miyaura couplings more readily than their sp^3 alkylboronic acid pairs. The reaction outcome was significantly improved and generated cyclopentenyl and cyclohexenyl analogues **5p** and **5q** in yields of 87% and 78%, respectively. The C=C bonds present in **5p** and **5q** were reduced by a transfer catalytic hydrogenation to afford fully saturated cyclopentyl and cyclohexyl analogues **5r** and **5s** in good yields (80% and 83%, respectively).

In order to synthesise analogues containing piperidine and piperazine derivatives, a study was conducted to optimise Buchwald-Hartwig amination reaction of **5d** with 1-methylpiperazine and 4-methylpiperidine. Different combinations of commonly used catalyst $Pd_2(dba)_3$, ligands (XPhos and BINAP), and bases (NaO*t*Bu, K_3PO_4, and Cs_2CO_3) were assessed. Despite substantial efforts to optimise the Buchwald-Hartwig aminations, we were not able to generate the desired compounds successfully. Debromination of the aryl bromide **5d** was prevalent and minimal conversion to the desired product was observed. As such, an alternative synthetic pathway was established, which involved the use of relatively simple molecule methyl 2-(4-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)acetate (**7**) as the key aryl bromide intermediate (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) **4d**, Boc_2O, sat. $NaHCO_3$, water, THF, rt, overnight; 75%; (b) amines, Cs_2CO_3, $Pd_2(dba)_3$, XPhos, anhydrous toluene, reflux, overnight, 50–99%; (c) (i) 20% TFA/DCM, rt, 3 h, quantitative; (ii) HCTU, DIPEA, 4-(methylsulfonamido)benzoic acid, rt, overnight, 41–70%; (d) MeOH, 10% Pd/C, NH_4HCO_2, reflux, 4 h, 59%; (e) $NH_2OH{\cdot}HCl$, 5 M KOH/MeOH, anhydrous MeOH, rt, overnight, 35–73%.

The intermediate **7** was synthesised by Boc protection of the amino acid derivative **4d**. A total of 10 alkyl amines were coupled with **7** smoothly in the presence of $Pd_2(dba)_3$, XPhos, and Cs_2CO_3. The installation of *N,N*-diethyl moiety resulted in modest yield (42%) because of the higher volatility of *N,N*-diethylamine (b.p. = 56 °C) compared to other piperidine derivatives, which quickly evaporated at a high reaction temperature of 120 °C. This problem was easily rectified by increasing the amount of *N,N*-diethylamine and by heating the reaction mixture in a closed microwave vessel, which significantly improved the yield to 84%. The Boc group of intermediates **8a–i** was cleaved by acid hydrolysis with 20% TFA in DCM to give the corresponding free amines as TFA salts. The subsequent amide coupling reaction was performed in the presence of excess DIPEA, HCTU, and 4-(methylsulfonamido)benzoic acid to produce methyl ester intermediates **9a-i**. Synthesis of the piperazinyl analogue **9j** required additional deprotection of the mono-benzyl carbamate (Cbz) group of compound **9i** which was removed by a transfer catalytic hydrogenation with ammonium formate and 10% Pd/C. Finally, the methyl ester intermediates **9a-h** and **9j** were converted to the corresponding hydroxamic acids **10a-h** and **10j** via direct aminolysis.

Biology

A total of 28 novel hydroxamic acid analogues were successfully synthesised (**6a**–**s**, 1**0a**–**h,** and **10j**). The inhibitory activities of hydroxamic acid analogues were evaluated by a fluorescence-based assay using recombinant human APN in the presence of L-Leucine-7-amido-4-methylcoumarin hydrochloride as a competitive substrate (Table 1).[26] The measured inhibition constants ($K_i^{(app)}$) were compared between different analogues comprehensively based on their structural variations to determine which groups successfully replaced the 3,4,5-trifluorophenyl group without sacrificing activity. In addition, as a measure of solubility, partition coefficient cLogP, which reflects the partitioning of a molecule between lipophilic and aqueous layers, was calculated *in silico* by ChemAxon Instant JChem software 16.9.12.0. (Table 1). While there was no striking trend between the inhibitory activity and cLogP observed, all the hydroxamic acid analogues displayed smaller cLogP values than the lead compound **3** (cLogP = 2.10), suggesting that this series of analogues could potentially have improved solubility than compound **3**.

Considering phenylglycine analogues **6a**–**d**, it was noted that complete removal of the 3,4,5-trifluorophenyl group resulted in a significant loss in the activity from $K_i^{(app)}$ = 4.90 nM (**3**) to $K_i^{(app)}$ = 116 nM (**6a**). However, inhibitory activity was regained once halogen groups were introduced in the descending order of Cl > Br > F, indicating dipole-induced interactions play a role in improving potency. The result also suggested that biphenyl was the preferred scaffold over phenylglycines; the phenyl analogue **6e** ($K_i^{(app)}$ = 4.1 nM) was comparable to that of the lead compound **3** but more potent than the bromophenylglycine analogue **6d** ($K_i^{(app)}$ = 9.47 nM) which contained bromo group as a bioisostere of phenyl.

The fluorine substituted phenyl compounds **6f**–**i** were well tolerated. For example, the 3-fluorophenyl analogue **6f** was determined to be the most potent inhibitor of the series with a $K_i^{(app)}$ value of 0.66 nM. A decrease in potency was observed when fluorine was substituted at the 4-position. For instance, the 4-fluorophenyl analogue **6g** showed a reduced inhibitory activity of $K_i^{(app)}$ = 9.54 nM. Similarly, the 3,4-difluorophenyl analogue **6h** possessed a $K_i^{(app)}$ = 6.15 nM, which was approximately 6-fold less potent than the 3,5-difluorophenyl analogue **6i** ($K_i^{(app)}$ = 1.19 nM). Based on these results, it was proposed that substituents at the 3-position were preferred to 4-position and trifluoro group was not essential for achieving the potent inhibitory activity.

Table 1. Inhibition activities ($K_i^{(app)}$) of synthesised compounds against APN.

Cpd	R	$K_i^{(app)}$ ± SEM / nM[a]	cLogP
3	3,4,5-Trifluorophenyl	4.90 ± 0.80	2.10
6a	H	166 ± 15	0.02
6b	F	48.6 ± 1.3	0.17
6c	Cl	7.38 ± 0.17	0.63
6d	Br	9.47 ± 0.17	0.79
6e	Phenyl	4.15 ± 0.24	1.67
6f	3-Fluorophenyl	0.66 ± 0.06	1.81
6g	4-Fluorophenyl	9.54 ± 0.97	1.81
6h	3,4-Difluorophenyl	6.15 ± 0.29	1.96
6i	3,5-Difluorophenyl	1.19 ± 0.13	1.96
6j	3-Furan	34.6 ± 1.2	0.81
6k	3-Thiophene	10.2 ± 1.0	1.45
6l	3-Pyridyl	9.77 ± 0.19	0.45
6m	4-Pyridyl	2.41 ± 0.30	0.45
6n	Pyrimidyl	49.0 ± 4.4	-0.25
6o	Cyclopropyl	9.74 ± 0.62	0.81
6p	1-Cyclopentenyl	90.6 ± 4.1	1.43
6q	1-Cyclohexenyl	343 ± 5	1.87
6r	Cyclopentyl	11.4 ± 1.2	1.70
6s	Cyclohexyl	4.87 ± 0.34	2.14
10a	*N,N*-Diethylamino	54.8 ± 4.1	0.85
10b	Piperidyl	151 ± 13	0.98
10c	Morpholine	224 ± 6	-0.09
10d	4-Methylpiperidyl	212 ± 9	1.27
10e	4-Fluoropiperidyl	54.8 ± 4.6	0.34
10f	4,4-Difluoropiperidyl	63.5 ± 6.2	1.20
10g	4-(Trifluoromethyl)piperidyl	158 ± 10	1.55
10h	1-Methylpiperazinyl	42.4 ± 1.8	-0.02
10j	Piperazinyl	27.0 ± 1.9	-0.40

[a] SEM values of $K_i^{(app)}$ are obtained from three individual experiments

Most heteroaromatic analogues **6j**–**n** displayed a decreased level of potency against APN, except 4-pyridyl analogue **6m** which showed an increased inhibitory activity of $K_i^{(app)}$ = 2.41 nM. The potent activity of compound **6m** compared to phenyl analogue **6e** could be due to the pyridine moiety that is capable of participating in hydrogen bonding interactions. Five-membered heteroaromatic furan analogue **6j** and thiophene analogue **6k** displayed potency of $K_i^{(app)}$ = 34.6 nM and 10.2 nM, respectively. In addition, pyrimidyl analogue **6n** exhibited a reduced inhibition activity ($K_i^{(app)}$ = 49.0 nM) compared to 3-pyridyl analogue **6l** and 4-pyridyl analogue **6m** by 5- and 10-fold. The preference towards pyridyl compounds over pyrimidyl could be explained by the differences in electronic characteristics and basicity. Due to the electron-withdrawing and inductive effect, protonation at the second nitrogen atom is unlikely, making pyrimidine less basic than pyridine. Therefore, it can be suggested that more basic group is favoured at the S1 subsite of APN.

According to our molecular modelling in the previous studies, the biphenyl scaffold engaged in multiple hydrophobic interactions with a flexible loop located in domain IV, and it was proposed that these interactions might play an imperative role in locking inhibitors within the active site of APN effectively.[26] Therefore, it was hypothesised that analogues containing alkyl groups as replacement of 3,4,5-trifluorophenyl (i.e. compounds **6o**–**s**, **10a**–**h**, and **10j**) would display reduced potency. Indeed, a decreased level of potency was observed from the majority of alkyl analogues, except the cyclopropyl analogue **6o** and cyclohexyl analogue **6s** which displayed tight-bindings to APN. Despite the small size and less degree of planarity, the cyclopropyl analogue **6o** retained good activity ($K_i^{(app)}$ = 9.74 nM). Interestingly, a trend of decreasing activities was observed from cycloalkenyl analogues compared to its saturated cycloalkyl pairs. Cyclopentyl **6r** showed a $K_i^{(app)}$ value of 11.4 nM, but the cyclopentenyl analogue **6p** showed a decreased potency ($K_i^{(app)}$ of 90.6 nM). Similarly, the cyclohexyl **6s** ($K_i^{(app)}$ = 4.87 nM) which was equipotent to the parent compound **3**, was nearly 70-fold more active than the cyclohexenyl **6q** ($K_i^{(app)}$ = 343 nM). However, there was an exceptional case as well, where the phenyl analogue **6e** was equally potent to the cyclohexyl **6s**.

The amine analogues **10a**–**h** and **10j** were not well tolerated and showed significantly diminished inhibitory activities. *N,N*-Diethyl analogue **10a** showed a potency of $K_i^{(app)}$ = 54.8 nM and the activity deteriorated even more when cyclised amino groups were incorporated (**10b**–**g**). Additional fluorine(s) of 4-fluoropiperidyl **10e** ($K_i^{(app)}$ = 54.8 nM) and 4,4-difluoropiperidyl **6f** were able to enhance the potency ($K_i^{(app)}$ = 63.5 nM) compared to the unsubstituted piperidyl analogue **10b** ($K_i^{(app)}$ = 151 nM) or the 4-methylpiperidyl analogue **10d** ($K_i^{(app)}$ = 212 nM). Piperazinyl analogues were determined to be more potent than its corresponding piperidyl compounds. For example, the piperazinyl analogue **10j** ($K_i^{(app)}$ = 27.0 nM) was nearly 6-fold more active than the piperidyl analogue **10b** ($K_i^{(app)}$ = 151 nM). A similar relationship was observed between the 4-methylpiperidyl analogue **10d** and the 1-methylpiperazinyl **10h** ($K_i^{(app)}$ = 42.4 nM). Two aspects potentially contributed to the enhanced potency of piperazinyl compounds compared to piperidyl compounds are suggested. Firstly, piperazine derivatives possess an additional basic aliphatic nitrogen atom that can be readily ionised in physiological pH condition. However, the nitrogen atom present in piperidine derivatives would have similar properties as arylamines, which are significantly less basic than aliphatic amines. With the greater capacity of ionisation, the piperazinyl analogues may form strong ionic interactions with nearby residues. Secondly, the aliphatic amine of piperazinyl is also able to engage in hydrogen bonding interactions, acting as a hydrogen bond donor. These results were also in line with the relationships between the pyridyl (**6l** and **6m**) and the pyrimidyl analogue (**6n**) where the compound bearing more basic moiety was favoured.

Conclusion

Interests in the discovery of novel therapeutic agents targeting metastasis and angiogenesis for the treatment of cancer are ever-increasing. APN has been shown to involved in a number of complex biological processes such as ECM degradation, angiogenesis, cell adhesion, and cell motility which can all accelerate metastasis. Therefore, APN has been extensively studied as a therapeutic target for cancer. In this study, we have performed further modifications of a previously discovered potent APN inhibitor **3** by replacing the 3,4,5-trifluorophenyl moiety. A small library of hydroxamic acid containing analogues was designed to probe the binding interactions around the S1 pocket of APN. A diverse range of substituents was introduced to enhance the solubility of the lead compound. Comprehensive SAR were established, and an extremely potent APN inhibitor **6f** ($K_i^{(app)}$ = 0.66 nM) was identified, which displayed 7-fold improved inhibitory activity compared to the parent compound **3** with a reduced cLogP value of 1.81. Further pharmacological evaluations on compound **6f** will be required to measure the cellular activity, toxicity, and selectivity prior to pursuing as a potential anti-cancer drug candidate.

Experimental Section

Biology

Protein Expression and Purification: A soluble form of human APN ectodomain was expressed and purified as reported previously.[26] Human APN was expressed in a transfected HEK293S GnT1^{-} cell line, which was a kind gift from Professor James Rini from the University of Toronto, Canada. The cell growth, cell passaging, and collection of the culture supernatant were conducted by Monash Protein Production Unit. Cells were grown in DMEM/F-12 supplemented with 3% FBS Invitrogen, 1 × penicillin-streptomycin (Invitrogen), 1 mg/liter of doxycycline (Sigma), and 1 mg/liter of aprotinin (Bioshop Canada). The APN–protein A fusion protein was purified by IgG-Sepharose (GE Healthcare) affinity chromatography. The protein A tag was removed by on-column tobacco etch virus protease digestion, and the liberated APN was further purified by size exclusion chromatography on a Superdex S200 10/300 column in 50 mM HEPES pH 8.0, 300 mM NaCl, 5% glycerol buffer. Biochemical parameters K_m (31 ± 5 μM) and k_{cat} (456 ± 14 FU/sec^{-1}) were determined in the presence of L-Leucine-7-amido-4-methylcoumarin hydrochloride (H-Leu-NHMec) (Sigma L2145).

APN Enzymatic Analysis: Aminopeptidase assays were based on the previously published Lee *et al*.[26] The activity of APN was determined by measuring the release of the fluorogenic leaving group, NH_2Mec, from the fluorogenic peptide H-Leu-NHMec (Sigma L2145). The reactions were carried out in 384-well microtitre plates, 50 μL total volume at 37 ºC using a spectrofluorimeter (BMG FLUOstar) with excitation at 355 nm and emission at 460 nm. APN was pre-incubated in 100 mM Tris pH 8.0 at 37 ºC with the inhibitors for 10 min prior to the addition of substrate (25 μM). Inhibitor concentrations were diluted 1:4 to assess an overall 1000-fold concentration series. The fluorescence signal was monitored for 1 hour at 37 ºC. The only linear range of velocity was considered in data analysis. $K_i^{(app)}$ values were then calculated by using the Morrison equation for competitive and tight-binding inhibitors.[37] Analysis and graphical output were performed in GraphPad Prism® 7.

Chemistry: Chemicals and solvents were purchased from standard suppliers and used without further purification unless otherwise indicated. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker Avance Nanobay III 400 MHz Ultrashield Plus spectrometer at 400.13, 376.46 and 100.61 MHz, respectively. Data acquisition and processing were managed using Topspin software package version 3. Chemical shifts (δ) are recorded in parts per million with reference to the chemical shift of the deuterated solvent. Coupling constants (*J*) and carbon-fluorine coupling constants (J_{CF}) are recorded in hertz and multiplicities are described as singlet (s), doublet (d), triplet (t), multiplet (m), doublet of doublets (dd), doublet of triplets (dt), doublet of doublets of doublets (ddd), and broad (br). Overlapped non-equivalent ^{13}C peaks were identified by HSQC and HMBC NMR.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F^{254} aluminium-backed plates were visualised by fluorescence quenching under a UV lamp at 254 nm or by $Fe(III)Cl_3$ staining for hydroxamic acid compounds. Flash chromatography was performed with silica gel 60 (particle size 0.040–0.063 μm).

Analytical HPLC was performed using an Agilent 1260 Infinity Analytical HPLC with a Zorbax Eclipse Plus C18 Rapid Resolution 4.6 × 100 m, 3.5 m column. Buffer A: 0.1% TFA in H_2O and buffer B: 0.1 % TFA in MeCN were used. Samples were run at a gradient of 5% buffer B/ buffer A (0–9 min) to 100% buffer B (9–10 min) at a flow rate of 1 mL/min. Unless otherwise indicated, all compounds were > 95% by HPLC (254 nm and 214 nm) prior to biological evaluation.

Preparative HPLC was performed using an Agilent 1260 Infinity instrument coupled with a binary preparative pump and an Agilent 1260 FC-PS fraction collector using Agilent OpenLAB CDS software (revision C.01.04) and an Altima C8 22 × 250 mm, 5 μM column and a 1260 Infinity diode array detector VL. The following buffers were used: buffer A: 0.1% TFA in H_2O and buffer B: 0.1% TFA in MeCN. The sample was run at a gradient of 30% to 100% buffer B over 10 min at a flow rate of 20 mL/min.

LC-MS was performed using Agilent 6120 series Single Quadrupole instrument coupled to an Agilent 1260 series HPLC instrument fitted with a Poroshell 120 EC-C18 50 × 3.0 mm, 2.7 μm column. The following buffers were used: buffer A, 0.1% formic acid in H_2O; buffer B, 0.1% formic acid in MeCN. Samples were run at a flow rate of 0.5 mL/min for 5 min: 5% buffer B/ buffer A (0–1 min), 100% buffer B (1–2.5 min) and held at this composition until 3.8 min, 5% buffer B/ buffer A (3.8–4 min) and held until 5 min at this composition. Mass spectra were obtained in positive and negative ion modes with a scan range of 100-1000 *m/z*. UV detection was carried out at 214 and 254 nm.

HRMS was carried out using an Agilent 6224 TOF LC-MS mass spectrometer coupled to an Agilent 1290 Infinity. All data were acquired and referenced via dual-spray electrospray ionization (ESI) source. Acquisition was performed using Agilent Mass Hunter Data Acquisition software version B.05.00 Build 5.0.5042.2 and analysis was conducted using Mass Hunter Qualitative Analysis version B.05.00 Build 5.0.519.13.

Instant JChem was used for data management and calculation of cLogP values; Instant JChem 16.9.12.0, ChemAxon (http://www.chemaxon.com).

General Procedure A: Acid catalysed the esterification of substituted 2-amino-2-phenylacetic acids. To a round bottom flask was added appropriate 2-amino-2-phenylacetic acid (1.0 eq.), MeOH (13 mLmmol^{-1}) and conc. H_2SO_4 (4.0 eq.) dropwise. The mixture was heated at reflux for overnight. Upon completion, the mixture was concentrated *in vacuo* and neutralised by sat. $NaHCO_3$ to pH 7–8 and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and

concentrated *in vacuo*. The crude product obtained was used for subsequent reactions without further purifications.

General Procedure B: Amide coupling using EDCI and DMAP. Methyl 2-amino-2-phenylacetate (1.0 eq.), carboxylic acid (1.2 eq.), EDCI (1.2 eq.) and DMAP (1.3 eq.) were dissolved in DCM/DMF (1:1) mixture (10 mLmmol^{-1}) and stirred at room temperature for overnight. DCM was removed *in vacuo*, and the resulting mixture was diluted with a 1 M HCl (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer were washed with water (2 × 20 mL) and brine (20 mL), which was then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude was taken up into a minimum amount of DMF and added to ice-water dropwise. The solid was filtered with minimal MeOH wash and dried under vacuum overnight.

General Procedure C: Suzuki-coupling reaction between aryl bromide 5d and arylboronic acids. To a N_2 flushed 0.5–2 mL microwave vial was added the aryl bromide **5d** (1.0 eq.), boronic acid (1.2 eq.), K_3PO_4 (2.4 eq.) and anhydrous DMF (2 mL), which was stirred and degassed for 5 min before adding $Pd(PPh_3)_2Cl_2$ (0.05 eq.). The mixture was heated at 100 °C for 1–20 h in a microwave reactor until completion. The reaction mixture was diluted with a 1 M HCl (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were further washed with water (2 × 20 mL) and brine (20 mL), which was then dried over anhydrous Na_2SO_4 followed by concentration *in vacuo*. The crude was taken up into a minimal amount of DMF and added to ice-water dropwise. The solid was filtered with minimal MeOH or Et_2O wash and dried under vacuum overnight.

General Procedure D: Suzuki-coupling reaction between aryl bromide 5d and alkenylboronic acids. A dry round bottom flask was charged with compound **5d** (1.0 eq.), cycloalkenylboronic acid (1.6 eq.), K_2CO_3 (4.5 eq.), and anhydrous THF (10 mLmmol^{-1}). The mixture was bubbled through N_2 for 10 min prior to the addition of $Pd(dppf)Cl_2$ (0.15 eq). The mixture was refluxed for overnight. Upon completion, THF was removed *in vacuo*, the residue was acidified with a 1 M HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was triturated with appropriate organic solvents or was purified by column chromatography.

General Procedure E: Buchwald-Hartwig amination between aryl bromide 7 and alkylamines. A mixture of aryl bromide **7** (1.0 eq.), $Pd_2(dba)_3$ (0.03 eq.), XPhos (0.1 eq.), Cs_2CO_3 (2.5–5.0 eq.), and amine (2.5 eq.) in a degassed anhydrous toluene (10 mL) was heated at reflux for overnight. After cooling, the mixture was diluted with water (6 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude was purified by column chromatography.

General Procedure F: Synthesis of aryl sulfonamide compounds 5t-ab from Boc-protected intermediates 8a–i. A round bottom flask was charged with Boc-protected intermediate (1.0 eq.) and 20% TFA in DCM (10 mLmmol^{-1}). The mixture was stirred at room temperature for 3 h. Upon completion, excess TFA was removed *in vacuo*, and the residue was dried under vacuum overnight. The residue was dissolved in DCM (5 mLmmol^{-1}) and DIPEA (3.0 eq.), which was stirred for 30 min (mixture 1). To a separate dried round bottom flask was added 4-(methylsulfonamido)benzoic acid (1.1 eq.), HCTU (1.2 eq.), DIPEA (2.0 eq.), and DMF (5 mLmmol^{-1}) and the mixture was stirred for 30 min (mixture 2). Mixture 1 and 2 were combined and stirred at room temperature for overnight. Upon completion, the mixture was concentrated *in vacuo*, diluted with a half sat. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were further washed with water (3 × 20 mL) and brine (20 mL) followed by drying over anhydrous Na_2SO_4 and concentration *in vacuo*. The crude was purified by column chromatography.

General Procedure G: Direct aminolysis of methyl ester to the hydroxamic acid. To a solution of methyl ester (1.0 eq.) in anhydrous MeOH (3 mLmmol^{-1}) was added $NH_2OH{\cdot}HCl$ (8.0 eq.), followed by 5 M KOH in anhydrous MeOH (10 eq.). The reaction was stirred at room temperature for overnight. Upon completion, the suspension was concentrated *in vacuo* followed by addition of a 10% citric acid (10 mL) and extraction with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentration *in vacuo*. The crude product was purified by column chromatography or preparative HPLC.

Methyl 2-amino-2-phenylacetate (4a). Compound **4a** was synthesised from 2-amino-2-phenylacetic (200 mg, 1.32 mmol) according to General Procedure A. The crude product (164 mg, 75%) was obtained as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.42–7.29 (m, 5H), 4.65 (s, 1H), 3.70 (s, 3H), 2.49 (br. s, 2H); ^{13}C NMR ($CDCl_3$) δ 170.6, 129.0, 128.3, 128.2, 127.0, 58.9, 52.6;

Methyl 2-amino-2-(4-fluorophenyl)acetate (4b). Compound **4b** was synthesised from 2-amino-2-(4-fluorophenyl)acetic acid (200 mg, 1.18 mmol) according to General Procedure A. The crude product (188 mg, 87%) was obtained as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.41–7.29 (m, 2H), 7.11–6.96 (m, 2H), 4.63 (s, 1H), 3.70 (s, 3H), 2.27 (br. s, 2H); ^{19}F NMR ($CDCl_3$) δ -114.1; ^{13}C NMR ($CDCl_3$) δ 174.2, 162.6 (d, J_{CF} = 246.7 Hz), 135.8 (d, J_{CF} = 3.3 Hz), 128.7 (d, J_{CF} = 8.2 Hz), 115.8 (d, J_{CF} = 21.6 Hz), 58.1, 52.7.

Methyl 2-amino-2-(4-chlorophenyl)acetate (4c). Compound **4c** was synthesised from 2-amino-2-(4-chlorophenyl)acetic acid (200 mg, 1.08 mmol) according to General Procedure A. The crude product (181 mg, 84%) was obtained as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.33 (app. s, 4H), 4.61 (s, 1H), 3.70 (s, 3H), 2.13 (br. s, 2H); ^{13}C NMR ($CDCl_3$) δ 174.0, 138.5, 134.11, 129.1, 128.4, 58.6, 52.7.

Methyl 2-amino-2-(4-bromophenyl)acetate (4d). Compound **4d** was synthesised from 2-amino-2-(4-bromophenyl)acetic acid (2.00 g, 8.69 mmol) according to General Procedure A. The crude product (1.90 g, 90%) was obtained as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.48 (d, *J* = 7.4 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 4.70 (s, 1H), 3.70 (s, 3H), 3.42 (br. s, 2H).

Methyl 2-(4-(methylsulfonamido)benzamido)-2-phenylacetate (5a). Compound **4a** (164 mg, 0.993 mmol) was coupled to (methylsulfonamido)benzoic acid (228 mg, 1.19 mmol) according to General Procedure B. The desired product was obtained as a white solid (220 mg, 61%). ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H), 9.06 (d, *J* = 7.1 Hz, 1H), 8.01–7.79 (m, 2H), 7.47 (m, 2H), 7.44–7.33 (m, 3H), 7.30–7.09 (m, 2H), 5.65 (d, *J* = 7.1 Hz, 1H), 3.65 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.1, 165.8, 141.5, 136.2, 129.2, 128.5, 128.2, 128.2, 128.1, 117.8, 56.9, 52.2, 39.5; *m/z* MS $C_{17}H_{19}N_2O_5S$ $[MH]^+$ 362.8.

Methyl 2-(4-fluorophenyl)-2-(4-(methylsulfonamido)benzamido) acetate (5b). Compound **4b** (188 mg, 1.03 mmol) was coupled to (methylsulfonamido)benzoic acid (236 mg, 1.23 mmol) according to General Procedure B. The desired product was obtained as a white solid (300 mg, 77%). ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H), 9.07 (d, *J* = 7.1 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.59–7.45 (m, 2H), 7.27–7.21 (m, 4H), 5.67 (d, *J* = 7.0 Hz, 1H), 3.65 (s, 3H), 3.06 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -114.1; ^{13}C NMR (DMSO-d_6) δ 171.0, 165.8, 161.9 (d, J_{CF} = 244.4 Hz), 141.5, 132.5, 130.4 (d, J_{CF} = 8.4 Hz), 129.2, 128.1, 117.8, 115.3 (d, J_{CF} = 21.5 Hz), 56.1, 52.3, 39.6; *m/z* MS $C_{17}H_{18}FN_2O_5S$ $[MH]^+$ 380.8.

Methyl 2-(4-chlorophenyl)-2-(4-(methylsulfonamido)benzamido) acetate (5c). Compound **4c** (181 mg, 0.907 mmol) was coupled to (methylsulfonamido)benzoic acid (209 mg, 1.09 mmol) according to General Procedure B. The reaction produced the desired product (332 mg, 92%), which was used for the next reaction without further purification. ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 9.10 (d, *J* = 7.1 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.53–7.44 (m, 4H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.69 (d, *J* = 7.1 Hz,

1H), 3.66 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.3, 166.3, 142.1, 135.9, 133.4, 130.7, 129.7, 129.0, 128.5, 118.3, 56.6, 52.8, 40.2; *m/z* MS $C_{17}H_{18}ClN_2O_5S$ $[MH]^+$ 396.8.

Methyl 2-(4-bromophenyl)-2-(4-(methylsulfonamido)benzamido) acetate (**5d**)**.** 4-(Methylsulfonamido)benzoic acid (2.06 g, 9.59 mmol) was coupled to compound **4d** (1.95 g, 7.99 mmol) according to General Procedure B. The desired product was obtained as a light yellow solid (2.32 g, 66%). ^{1}H NMR (DMSO-d_6) δ 10.15 (s, 1H), 9.11 (d, *J* = 7.1 Hz, 1H), 7.97–7.81 (m, 2H), 7.64–7.56 (m, 2H), 7.48–7.39 (m, 2H), 7.31–7.20 (m, 2H), 5.67 (d, *J* = 7.1 Hz, 1H), 3.66 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 170.7, 165.8, 141.6, 135.8, 131.4, 130.5, 129.2, 128.0, 121.5, 117.8, 56.2, 52.4, 39.6; *m/z* MS $C_{17}H_{18}BrN_2O_5S$ $[MH]^+$ 441.3.

Methyl 2-([1,1'-biphenyl]-4-yl)-2-(4-(methylsulfonamido)benzamido) acetate (**5e**)**.** Phenylboronic acid (49.7 mg, 0.408 mmol) was coupled to compound **5d** (150 mg, 0.340 mmol) according to General Procedure C. The reaction mixture was heated at 120 °C for 4 h to complete. The desired product was obtained as a white solid (58.5 mg, 39%). ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H), 9.11 (d, *J* = 7.0 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.73–7.62 (m, 4H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.52–7.43 (m, 2H), 7.42–7.34 (m, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 5.71 (d, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.1, 165.8, 141.5, 140.1, 139.7, 135.4, 129.2, 129.0, 128.9, 128.1, 127.6, 126.9, 126.7, 117.8, 56.6, 52.3, 39.6; *m/z* MS $C_{23}H_{23}N_2O_5S$ $[MH]^+$ 438.8.

Methyl 2-(3'-fluoro-[1,1'-biphenyl]-4-yl)-2-(4-(methylsulfonamido) benzamido)acetate (**5f**)**.** (3-Fluorophenyl)boronic acid (57.1 mg, 0.406 mmol) was coupled to compound **5d** (150 mg, 0.340 mmol) according to General Procedure C. The reaction mixture was heated at 100 °C for 1.5 h to complete. The desired product was obtained as a light pink solid (114 mg, 74%). ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 9.13 (d, *J* = 7.1 Hz, 1H), 8.00–7.84 (m, 2H), 7.78–7.70 (m, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.56–7.48 (m, 3H), 7.29–7.24 (m, 2H), 7.23–7.18 (m, 1H), 5.73 (d, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 3.07 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -112.7; ^{13}C NMR (DMSO-d_6) δ 171.0, 165.8, 162.7 (d, J_{CF} = 243.3 Hz), 142.1 (d, J_{CF} = 7.8 Hz), 141.6, 138.6 (d, J_{CF} = 2.2 Hz), 136.1, 130.9 (d, J_{CF} = 8.6 Hz), 129.2, 128.9, 128.1, 127.0, 122.8, 117.8, 114.3 (d, J_{CF} = 21.0 Hz), 113.4 (d, J_{CF} = 22.1 Hz), 56.5, 52.3, 39.6; *m/z* MS $C_{23}H_{22}FN_2O_5S$ $[MH]^+$ 456.7.

Methyl 2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-2-(4-(methylsulfonamido) benzamido)acetate (**5g**)**.** A nitrogen flushed 5 mL microwave vial was charged with compound **5d** (150 mg, 0.340 mmol), (4-fluorophenyl)boronic acid (57.1 mg, 0.408 mmol), 1 M Na_2CO_3 (1 mL) and degassed DMF (3 mL). The mixture was bubble through N_2 while stirring for 5 min before adding $Pd(PPh_3)_2Cl_2$ (11.9 mg, 0.017 mmol). The mixture was heated at 100 °C for 15 min. After cooling, the mixture was diluted with a 1 M HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water (2 × 20 mL) and brine (20 mL) and then dried over anhydrous Na_2SO_4 before concentration *in vacuo*. The crude product was purified by column chromatography using DCM/MeOH (95:5 to 90:10) to afford the desired product (118 mg, 77%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 9.12 (d, *J* = 7.1 Hz, 1H), 8.00–7.87 (m, 2H), 7.75–7.69 (m, 2H), 7.68–7.64 (m, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.36–7.21 (m, 4H), 5.72 (d, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 3.07 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -115.2; ^{13}C NMR (DMSO-d_6) δ 171.1, 165.9, 162.0 (d, J_{CF} = 244.5 Hz), 141.6, 139.1, 136.2 (d, J_{CF} = 3.0 Hz), 135.4, 129.2, 128.9, 128.7 (d, J_{CF} = 8.2 Hz), 128.2, 126.8, 117.8, 115.8 (d, J_{CF} = 21.4 Hz), 56.6, 52.3, 39.6; *m/z* MS $C_{23}H_{22}FN_2O_5S$ $[MH]^+$ 456.8.

Methyl 2-(3',4'-difluoro-[1,1'-biphenyl]-4-yl)-2-(4-(methylsulfonamido) benzamido)acetate (**5h**)**.** (3,4-Difluorophenyl)boronic acid (51.5 mg, 0.326 mmol) was coupled to compound **5d** (120 mg, 0.271 mmol) according to General Procedure C. The reaction mixture was heated at 100 °C for 1.5 h to complete. The crude was dissolved in minimum amount of DMF and added into ice-water mixture dropwise. The desired product was obtained as a light beige solid (95.0 mg, 74%). ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 9.13 (d, *J* = 7.1 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.84–7.75 (m, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.61–7.50 (m, 4H), 7.26 (d, *J* = 8.8 Hz, 2H), 5.73 (d, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 3.07 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -138.1 (d, *J* = 22.5 Hz), -140.6 (d, *J* = 22.5 Hz); ^{13}C NMR (DMSO-d_6) δ 171.0, 165.8, 149.8 (dd, J_{CF} = 245.3/12.6 Hz), 149.2 (dd, J_{CF} = 246.4/12.7 Hz), 141.6, 137.8, 137.3 (dd, J_{CF} = 6.1/3.9 Hz), 136.1, 129.2, 128.9, 128.1, 126.9, 123.5 (dd, J_{CF} = 6.6/3.3 Hz), 118.0 (d, J_{CF} = 17.0 Hz), 117.8, 115.8 (d, J_{CF} = 17.8 Hz), 56.5, 52.3, 39.64; *m/z* MS $C_{23}H_{21}F_2N_2O_5S$ $[MH]^+$ 474.8.

Methyl 2-(3',5'-difluoro-[1,1'-biphenyl]-4-yl)-2-(4-(methylsulfonamido) benzamido)acetate (**5i**)**.** (3,5-Difluorophenyl)boronic acid (51.5 mg, 0.326 mmol) was coupled to compound **5d** (120 mg, 0.271 mmol) according to General Procedure C. The reaction mixture was heated at 100 °C for 1.5 h to complete. The desired product was obtained as a yellow solid (69.0 mg, 53%). ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 9.14 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.47 (dd, *J* = 9.0/2.2 Hz, 2H), 7.32–7.18 (m, 3H), 5.74 (d, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 3.07 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -109.4; ^{13}C NMR (DMSO-d_6) δ 171.0, 165.8, 162.9 (dd, J_{CF} = 245.6/13.7 Hz), 143.3 (dd, J_{CF} = 9.8/9.8 Hz), 141.6, 137.4 (dd, J_{CF} = 2.4/2.4 Hz), 136.9, 129.2, 128.9, 128.1, 127.1, 117.8, 111.2–109.1 (m), 102.9 (dd, J_{CF} = 26.0/26.0 Hz), 56.5, 52.4, 39.6; *m/z* MS $C_{23}H_{21}F_2N_2O_5S$ $[MH]^+$ 474.8.

Methyl 2-(4-(furan-3-yl)phenyl)-2-(4-(methylsulfonamido)benzamido) acetate (**5j**)**.** Furan-3-ylboronic acid (36.5 mg, 0.326 mmol) was coupled to compound **5d** (120 mg, 0.271 mmol) according to General Procedure C. The reaction mixture was heated at 100 °C for 1 h to complete. The desired product was obtained as a pale yellow solid (96 mg, 82%). ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H), 9.06 (d, *J* = 7.0 Hz, 1H), 8.26–8.08 (m, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.78–7.68 (m, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.30–7.20 (m, 2H), 6.97 (dd, *J* = 1.9/0.8 Hz, 1H), 5.65 (d, *J* = 7.0 Hz, 1H), 3.66 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 170.9, 165.5, 141.5, 134.8, 131.9, 129.2, 128.7, 128.1, 125.6, 125.4, 117.8, 108.6, 52.3, 39.6 *CH signals of furan around 144.0 and 139.0 ppm were very small to be detected but these signals were easily found in the corresponding hydroxamic acid analogue **6j**.; *m/z* MS $C_{21}H_{21}N_2O_6S$ $[MH]^+$ 428.8.

Methyl 2-(4-(methylsulfonamido)benzamido)-2-(4-(thiophen-3-yl) phenyl)acetate (**5k**)**.** Thiophen-3-ylboronic acid (41.8 mg, 0.326 mmol) was coupled to compound **5d** (120 mg, 0.271 mmol) according to General Procedure C. The reaction mixture was heated at 100 °C for 1 h to complete. The crude obtained (116 mg, 95%) was used for the subsequent reaction without further purification. ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H), 9.08 (d, *J* = 7.1 Hz, 1H), 7.94–7.90 (m, 2H), 7.90–7.85 (m, 1H), 7.76–7.71 (m, 2H), 7.67–7.64 (m, 1H), 7.57–7.54 (m, 2H), 7.52–7.49 (m, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.67 (d, *J* = 7.0 Hz, 1H), 3.67 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.5, 158.2, 141.5, 140.9, 135.1, 134.9, 129.2, 128.9, 128.8, 128.7, 126.2, 126.1, 121.3, 117.8, 56.6, 52.3, 39.6; *m/z* MS $C_{21}H_{19}N_2O_5S_2$ $[M\text{-}H]^-$ 442.8.

Methyl 2-(4-(methylsulfonamido)benzamido)-2-(4-(pyridin-3-yl) phenyl)acetate (**5l**)**.** Pyridin-3-ylboronic acid (40.4 mg, 0.326 mmol) was coupled to compound **5d** (120 mg, 0.272 mmol) according to General Procedure C. Only 70% of conversion to the desired product was observed based on LC-MS after heating at 100 °C for 20 h. After cooling, the solvent was removed by concentrating *in vacuo*. 1 M HCl was added dropwise to the residue to adjust pH to 8–9 and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (20 mL) and then dried over anhydrous Na_2SO_4 before concentration *in vacuo*. The crude was dissolved in a minimum amount of DMF and added into ice-water mixture dropwise. The precipitate was filtered and washed with minimal MeOH to afford the desired product (40.0 mg, 33%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 9.13 (d, *J* = 7.1 Hz, 1H), 8.96–8.86 (m, 1H), 8.64–8.53 (m, 1H), 8.14–8.04 (m, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.79–7.73 (m, 2H), 7.64–7.58 (m, 3H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.74 (d, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (DMSO-d_6) δ

171.0, 165.8, 148.7, 147.7, 141.6, 137.0, 136.3, 135.1, 134.2, 129.3, 129.1, 128.1, 127.1, 124.0, 117.8, 56.5, 52.3, 39.6; *m/z* MS $C_{22}H_{22}N_3O_5S$ $[MH]^+$ 439.8.

Methyl 2-(4-(methylsulfonamido)benzamido)-2-(4-(pyridin-4-yl) phenyl)acetate (**5m**)**.** Pyridin-4-ylboronic acid (40.1 mg, 0.326 mmol) was coupled to compound **5d** (120 mg, 0.271 mmol) according to General Procedure C. The reaction mixture was heated at 100 °C for 1.5 h to complete. The desired product was obtained as a yellow solid (67.4 mg, 56%). ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 9.15 (d, *J* = 7.1 Hz, 1H), 8.65 (d, *J* = 6.1 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.86–7.81 (m, 2H), 7.75–7.69 (m, 2H), 7.65–7.59 (m, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.75 (d, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 170.9, 165.8, 150.3, 147.2, 141.4, 137.4, 137.0, 129.2, 129.1, 128.2, 127.0, 121.2, 117.8, 56.5, 52.4, 39.6; *m/z* MS $C_{22}H_{22}N_3O_5S$ $[MH]^+$ 439.8.

Methyl 2-(4-(methylsulfonamido)benzamido)-2-(4-(pyrimidin-5-yl) phenyl)acetate (**5n**)**.** Pyrimidin-5-ylboronic acid (40.4 mg, 0.326 mmol) was coupled to compound **5d** (120 mg, 0.272 mmol) according to General Procedure C. The reaction mixture was heated at 100 °C for 6 h to complete. After cooling, the solvent was removed by concentrating *in vacuo*. 1 M HCl was added dropwise to the concentrated residue and sonicated for 2 min. The precipitate formed was filtered and washed with minimal Et_2O to afford the desired product (70 mg, 58%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H), 9.20 (s, 1H), 9.18–9.14 (m, 3H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.76 (d, *J* = 7.2 Hz, 1H), 3.68 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 170.9, 165.8, 154.8, 141.6, 137.2, 133.6, 132.8, , 129.2, 128.1, 127.1, 126.9, 117.8, 56.4, 52.4, 39.6; *m/z* MS $C_{21}H_{21}N_4O_5S$ $[MH]^+$ 440.8.

Methyl 2-(4-cyclopropylphenyl)-2-(4-(methylsulfonamido) benzamido)acetate (**5o**)**.** Cyclopropylboronic acid (21.4 mg, 0.245 mmol) was coupled to compound **5d** (100 mg, 0.227 mmol) according to General Procedure D. The crude obtained (85.9 mg, 94%) was used for the subsequent reaction without further purification. ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H), 8.98 (d, *J* = 7.0 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 5.57 (d, *J* = 6.9 Hz, 1H), 3.64 (s, 3H), 3.06 (s, 3H), 1.95–1.79 (m, 1H), 1.06–0.83 (m, 2H), 0.77–0.53 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 171.2, 165.8, 143.9, 141.5, 133.0, 129.2, 128.2, 125.5, 117.8, 56.6, 52.2, 39.6, 14.8, 9.5, 9.4 *one quaternary carbon around 128.0 was extremely small to be detected. However, this signal was easily observed in the corresponding hydroxamic acid compound **6o**; *m/z* MS $C_{20}H_{23}N_2O_5S$ $[MH]^+$ 402.8.

Methyl 2-(4-(cyclopent-1-en-1-yl)phenyl)-2-(4-(methylsulfonamido) benzamido)acetate (**5p**)**.** 1-Cyclopentenylboronic acid (162 mg, 1.45 mmol) was coupled to compound **5d** (400 mg, 906 µmol) according to General Procedure D. The crude product was triturated with Et_2O and the filtered solid was washed with minimum amount of 1:2 MeOH/Et_2O to obtain the desired product (337 mg, 87%) as a dark brown solid. ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H), 9.04 (d, *J* = 7.1 Hz, 1H), 7.93–7.85 (m, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.29–7.17 (m, 2H), 6.35–6.18 (m, 1H), 5.63 (d, *J* = 7.0 Hz, 1H), 3.65 (s, 3H), 3.06 (s, 3H), 2.73–2.58 (m, 2H), 2.49–2.44 (m, 2H), 2.04–1.84 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 171.1, 165.8, 141.5 (2C), 136.1, 134.7, 129.2, 128.3, 128.2, 126.6, 125.6, 117.8, 56.6, 52.2, 39.6, 32.9, 32.7, 22.7; *m/z* MS $C_{22}H_{25}N_2O_5S$ $[MH]^+$ 429.0.

Methyl 2-(4-(methylsulfonamido)benzamido)-2-(2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)acetate (**5q**)**.** 1-Cyclohexenylboronic acid (185 mg, 1.46 mmol) was coupled to compound **5d** (404 mg, 915 µmol) according to General Procedure D. The crude product was purified by column chromatography using PE/EtOAc (70:30 to 0:100) to afford the desired product (315 mg, 78%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H), 9.03 (d, *J* = 7.0 Hz, 1H), 8.03–7.79 (m, 2H), 7.40 (app. s, 4H), 7.29–7.19 (m, 2H), 6.23–6.09 (m, 1H), 5.62 (d, *J* = 7.0 Hz, 1H), 3.65 (s, 3H), 3.06 (s, 3H), 2.41–2.27 (m, 2H), 2.26–2.05 (m, 2H), 1.82–1.68 (m, 2H), 1.67–1.47 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 171.1, 165.8, 141.8, 141.5, 135.6, 134.4, 129.2, 128.2, 128.2, 124.8, 124.7, 117.8, 56.6, 52.2, 39.6, 26.7, 25.3, 22.5, 21.6; *m/z* MS $C_{23}H_{27}N_2O_5S$ $[MH]^+$ 443.0.

Methyl 2-(4-cyclopentylphenyl)-2-(4-(methylsulfonamido)benzamido) acetate (**5r**)**.** A 50 mL round bottom flask was charged with compound **5p** (174 mg, 406 µmol), ammonium formate (256 mg, 4.06 mmol) and EtOH (10 mL). The mixture was stirred and purged with N_2 thoroughly before adding 10% Pd/C (20 mg), which was refluxed for 2 h. Upon completion, the reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated *in vacuo* and extracted with EtOAc (3 × 10 mL) from water (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude was obtained (144 mg, 83%) as a white solid and was used for subsequent reaction without further purification. ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H), 8.99 (d, *J* = 6.9 Hz, 1H), 7.94–7.87 (m, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.31–7.20 (m, 4H), 5.58 (d, *J* = 6.9 Hz, 1H), 3.64 (s, 3H), 3.06 (s, 3H), 3.00–2.90 (m, 1H), 2.06–1.89 (m, 2H), 1.82–1.71 (m, 2H), 1.71–1.59 (m, 2H), 1.59–1.45 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 171.2, 165.8, 146.0, 141.5, 133.5, 129.2, 128.2, 128.1, 127.2, 117.8, 56.7, 52.2, 45.1, 39.6, 34.2, 25.0; *m/z* MS $C_{22}H_{27}N_2O_5S$ $[MH]^+$ 431.0.

Methyl 2-(4-cyclohexylphenyl)-2-(4-(methylsulfonamido)benzamido) acetate (**5s**)**.** A 50 mL round bottom flask was charged with compound **5q** (263 mg, 594 µmol), ammonium formate (375 mg, 5.94 mmol) and MeOH (10 mL). The mixture was stirred and purged with N_2 thoroughly before adding 10% Pd/C (20 mg), which was refluxed for overnight. Upon completion, the reaction mixture turned turbid and DMF was added until the mixture becomes a homogeneous black solution to dissolve the solid formed. Pd was filtered through Celite and the filtrate was concentrated *in vacuo* and extracted with EtOAc (3 × 20 mL) from water (30 mL). The combined organic layers were further washed with water (3 × 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the desired product (210 mg, 80%) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 10.10 (s, 1H), 9.00 (d, *J* = 6.9 Hz, 1H), 7.97–7.76 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.28–7.21 (m, 4H), 5.58 (d, *J* = 6.9 Hz, 1H), 3.64 (s, 3H), 3.06 (s, 3H), 1.87–1.49 (m, 6H), 1.49–1.09 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 171.2, 165.8, 147.6, 141.5, 133.5, 129.2, 128.2, 128.1, 126.9, 117.8, 56.7, 52.2, 43.5, 39.6, 33.9, 33.8, 26.3, 25.6; *m/z* MS $C_{23}H_{29}N_2O_5S$ $[MH]^+$ 445.0.

***N*-(2-(Hydroxyamino)-2-oxo-1-phenylethyl)-4-(methylsulfonamido) benzamide** (**6a**)**.** Compound **5a** (120 mg, 0.331 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (27 mg, 23%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 10.12 (s, 1H), 9.02 (s, 1H), 8.75 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.55–7.46 (m, 2H), 7.41–7.32 (m, 2H), 7.32–7.27 (m, 1H), 7.27–7.20 (m, 2H), 5.60 (d, *J* = 8.1 Hz, 1H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.7, 165.5, 141.4, 138.5, 129.2, 128.5, 128.3, 127.6, 127.4, 117.8, 54.6, 39.6; *m/z* HRMS (TOF ES$^+$) $C_{16}H_{18}N_3O_5S$ $[MH]^+$ calcd 364.0962, found 364.0950; HPLC 98%.

***N*-(1-(4-Fluorophenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide** (**6b**)**.** Compound **5b** (100 mg, 0.263 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (78 mg, 78%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.03 (s, 1H), 10.12 (s, 1H), 9.04 (s, 1H), 8.79 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.58–7.50 (m, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.23–7.15 (m, 2H), 5.60 (d, *J* = 8.1 Hz, 1H), 3.06 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -114.9; ^{13}C NMR (DMSO-d_6) δ 166.7, 165.6, 161.7 (d, J_{CF} = 243.7 Hz), 141.4, 134.8 (d, J_{CF} = 3.0 Hz), 129.5 (d, J_{CF} = 8.3 Hz), 129.3, 128.5, 117.8, 115.1 (d, J_{CF} = 21.4 Hz), 53.9, 39.5; *m/z* HRMS (TOF ES$^+$) $C_{16}H_{17}FN_3O_5S$ $[MH]^+$ calcd 382.0867, found 382.0861; HPLC 98%.

***N*-(1-(4-Chlorophenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide** (**6c**)**.** Compound **5c** (152 mg, 0.383 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (80 mg, 53%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.13 (s, 1H), 9.06 (s, 1H), 8.82 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.46–7.38 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 5.60 (d, *J* = 8.1 Hz, 1H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.4, 165.6, 141.5, 137.5, 132.3, 129.3, 129.2, 128.4, 128.3, 117.8, 54.0, 40.0; *m/z* HRMS (TOF ES$^+$) $C_{16}H_{17}ClN_3O_5S$ [MH]$^+$ calcd 398.0572, found 398.0569; HPLC 98%.

***N*-(1-(4-Bromophenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide** (**6d**)**.** Compound **5d** (600 mg, 1.36 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (109 mg, 18%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.04 (app. d, *J* = 1.0 Hz, 1H), 10.12 (s, 1H), 9.05 (app. d, *J* = 1.3 Hz, 1H), 8.81 (d, *J* = 8.1 Hz, 1H), 8.01–7.85 (m, 2H), 7.62–7.54 (m, 2H), 7.50–7.42 (m, 2H), 7.26–7.19 (m, 2H), 5.57 (d, *J* = 8.1 Hz, 1H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.3, 165.6, 141.4, 137.9, 131.2, 129.6, 129.2, 128.4, 120.8, 117.7, 54.0, 39.6; *m/z* HRMS (TOF ES$^+$) $C_{16}H_{17}BrN_3O_5S$ [MH]$^+$ calcd 442.0067, found 442.0073; HPLC 95%.

***N*-(1-([1,1'-Biphenyl]-4-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide** (**6e**)**.** Compound **5e** (126 mg, 0.287 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified preparative HPLC to afford the desired product (31 mg, 14%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H), 10.12 (s, 1H), 9.03 (s, 1H), 8.79 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.71–7.63 (m, 4H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.54–7.42 (m, 2H), 7.39–7.33 (m, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 5.64 (d, *J* = 8.1 Hz, 1H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.6, 165.5, 141.4, 139.8, 139.6, 137.7, 129.2, 128.9, 128.5, 128.0, 127.5, 126.7, 126.6, 117.8, 54.3, 39.6; *m/z* HRMS (TOF ES$^+$) $C_{22}H_{22}N_3O_5S$ [MH]$^+$ calcd 440.1275, found 440.1276; HPLC 95%.

***N*-(1-(3'-Fluoro-[1,1'-biphenyl]-4-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide** (**6f**)**.** Compound **5f** (114 mg, 0.250 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH/AcOH (99:0:1 to 84:15:1) and preparative HPLC to afford the desired product (4.2 mg, 4%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 8.81 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.56–7.42 (m, 3H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.23–7.10 (m, 1H), 5.64 (d, *J* = 8.1 Hz, 1H), 3.06 (s, 3H) *exchangeable protons of hydroxamic acid and sulfonamide were not observed; ^{19}F NMR (DMSO-d_6) δ -112.8; *m/z* HRMS (TOF ES$^+$) $C_{22}H_{21}FN_3O_5S$ [MH]$^+$ calcd 458.1180, found 458.1180; HPLC 95%.

***N*-(1-(4'-Fluoro-[1,1'-biphenyl]-4-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide** (**6g**)**.** Compound **5g** was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH/AcOH (99:0:1 to 89:9:1) to afford the desired product (60 mg, 52%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.15 (s, 1H), 9.06 (s, 1H), 8.81 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.75–7.67 (m, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.33–7.20 (m, 4H), 5.65 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -115.4; ^{13}C NMR (DMSO-d_6) δ 166.7, 165.6, 161.9 (d, J_{CF} = 244.3 Hz), 141.5, 138.6, 137.7, 136.3 (d, J_{CF} = 3.1 Hz), 129.2, 128.7 (d, J_{CF} = 8.2 Hz), 128.5, 128.0, 126.6, 117.8, 115.8 (d, J_{CF} = 21.3 Hz), 54.3, 39.7; *m/z* HRMS (TOF ES$^+$) $C_{22}H_{21}FN_3O_5S$ [MH]$^+$ calcd 458.1180, found 458.1185; HPLC 98%.

***N*-(1-(3',4'-Difluoro-[1,1'-biphenyl]-4-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide** (**6h**)**.** Compound **5h** (85.0 mg, 0.179 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (38 mg, 45%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.12 (s, 1H), 9.05 (s, 1H), 8.82 (d, *J* = 8.1 Hz, 1H), 7.96–7.87 (m, 2H), 7.82–7.73 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.55–7.45 (m, 2H), 7.31–7.19 (m, 2H), 5.65 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -138.2 (d, *J* = 22.5 Hz), -140.8 (d, *J* = 22.5 Hz); ^{13}C NMR (DMSO-d_6) δ 166.6, 165.7, 149.8 (dd, J_{CF} = 245.2/12.8 Hz), 149.2 (dd, J_{CF} = 246.2/12.6 Hz), 141.5, 138.4, 137.5 (dd, J_{CF} = 6.1/3.8 Hz), 137.4, 129.3, 128.5, 128.1, 126.8, 123.5 (dd, J_{CF} = 6.4/3.3 Hz), 118.0 (d, J_{CF} = 17.0 Hz), 117.8, 115.8 (d, J_{CF} = 17.7 Hz), 54.3, 39.7; *m/z* HRMS (TOF ES$^+$) $C_{22}H_{20}F_2N_3O_5S$ [MH]$^+$ calcd 476.1086, found 476.1078; HPLC 95%.

***N*-(1-(3',5'-Difluoro-[1,1'-biphenyl]-4-yl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide** (**6i**)**.** Compound **5i** (59.0 mg, 0.124 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH/AcOH (100:0:1 to 89:9:1) and preparative HPLC to afford the desired product (13.3 mg, 23%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.13 (s, 1H), 9.05 (s, 1H), 8.83 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.45 (dd, *J* = 8.9/2.0 Hz, 2H), 7.34–7.03 (m, 3H), 5.65 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -109.4; ^{13}C NMR (DMSO-d_6) δ 166.5, 165.6, 162.9 (dd, J_{CF} = 245.5/13.7 Hz), 143.4 (d, J_{CF} = 9.8 Hz), 141.4, 139.1, 136.9, 129.2, 128.4, 128.0, 126.8, 117.8, 110.1–109.6 (m), 102.6 (d, J_{CF} = 26.2 Hz), 54.23, 39.6; *m/z* HRMS (TOF ES$^+$) $C_{22}H_{20}F_2N_3O_5S$ [MH]$^+$ calcd 476.1086, found 476.1085; HPLC 98%

***N*-(1-(4-(Furan-3-yl)phenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide** (**6j**)**.** Compound **5j** (96.0 mg, 0.224 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (59.5 mg, 62%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.03 (s, 1H), 10.13 (s, 1H), 8.77 (d, *J* = 8.1 Hz, 1H), 8.26–8.13 (m, 1H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.77–7.70 (m, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.96 (dd, *J* = 1.8/0.7 Hz, 1H), 5.60 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H) *one exchangeable proton of hydroxamic acid was not observed; ^{13}C NMR (DMSO-d_6) δ 166.7, 165.6, 144.3, 141.4, 139.4, 137.1, 131.4, 129.2, 128.6, 127.9, 125.5, 125.4, 117.8, 108.8, 54.4, 39.7; *m/z* HRMS (TOF ES$^+$) $C_{20}H_{20}N_3O_6S$ [MH]$^+$ calcd 430.1067, found 430.1072; HPLC 98 %.

***N*-(2-(Hydroxyamino)-2-oxo-1-(4-(thiophen-3-yl)phenyl)ethyl)-4-(methylsulfonamido)benzamide** (**6k**)**.** Compound **5k** (116.0 mg, 0.260 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (64.0 mg, 55%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.13 (s, 1H), 9.05 (s, 1H), 8.79 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 2H), 7.89–7.85 (m, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.66–7.61 (m, 1H), 7.60–7.49 (m, 3H), 7.26 (d, *J* = 8.7 Hz, 2H), 5.62 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.7, 165.6, 141.4, 141.1, 137.3, 134.6, 129.2, 128.5, 127.9, 127.1, 126.2, 126.0, 121.0, 117.8, 54.4, 39.7; *m/z* HRMS (TOF ES$^+$) $C_{20}H_{20}N_3O_5S_2$ [MH]$^+$ calcd 446.0839, found 446.0837; HPLC 95%

***N*-(2-(Hydroxyamino)-2-oxo-1-(4-(pyridin-3-yl)phenyl)ethyl)-4-(methylsulfonamido)benzamide TFA salt** (**6l**)**.** Compound **5l** (40.0 mg, 0.910 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by preparative HPLC to afford the desired product (12.5 mg, 31%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.09 (s, 1H), 10.14 (s, 1H), 9.05 (br. s, 1H), 8.86 (d, *J* = 8.1 Hz, 1H), 8.72 (br. s, 1H), 8.40 (br. d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.82–7.72 (m, 3H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.67 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -74.5; ^{13}C NMR (DMSO-d_6) δ 166.3, 165.5, 145.3, 144.6, 141.3, 139.2, 137.6, 136.4, 135.0, 129.1, 128.3, 128.1, 126.9, 125.1, 117.7, 54.2, 39.5 *one

exchangeable proton was not observed. Due to the extensive proton exchange between the pyridinium and water present in DMSO the protons of pyridinium were broadened. The carbon signals of pyridinium were substantially small compared to the other aromatic CH signals; *m/z* HRMS (TOF ES$^+$) $C_{21}H_{21}N_4O_5S$ [MH]$^+$ calcd 441.1227, found 441.1233; HPLC 95%

***N*-(2-(Hydroxyamino)-2-oxo-1-(4-(pyridin-4-yl)phenyl)ethyl)-4-(methylsulfonamido)benzamide TFA salt (6m).** Compound **5m** (62.0 mg, 0.141 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by preparative HPLC to afford the desired product (22.4 mg, 36%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.11 (s, 1H), 10.14 (s, 1H), 8.90 (d, *J* = 8.1 Hz, 1H), 8.83 (d, *J* = 6.3 Hz, 2H), 8.12 (d, *J* = 6.5 Hz, 2H), 8.04–7.86 (m, 4H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.70 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H) *one exchangeable proton was not observed. Due to extensive proton exchange between the pyridinium and water present in DMSO, the salt signal was observed as an extremely broadened signal at 4.64 ppm; ^{19}F NMR (DMSO-d_6) δ -74.3; ^{13}C NMR (DMSO-d_6) δ 166.4, 165.6, 149.8, 147.1, 141.4, 139.8, 136.4, 129.2, 128.4, 128.2, 126.8, 121.4, 117.8, 54.3, 39.6; *m/z* HRMS (TOF ES$^+$) $C_{21}H_{21}N_4O_5S$ [MH]$^+$ calcd 441.1227, found 441.1223; HPLC 95 %

***N*-(2-(Hydroxyamino)-2-oxo-1-(4-(pyrimidin-5-yl)phenyl)ethyl)-4-(methylsulfonamido)benzamide TFA salt (6n).** Compound **5n** (87.0 mg, 0.198 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by preparative HPLC to afford the desired product (12 mg, 14%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10.13 (s, 1H), 9.19 (s, 1H), 9.14 (s, 2H), 8.85 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 5.66 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H) *one exchangeable proton of hydroxamic acid was not observed. Due to extensive proton exchange between the pyridinium and water present in DMSO, the salt signal was observed as an extremely broadened signal at 5.20 ppm; ^{19}F NMR (DMSO-d_6) δ -74.5; ^{13}C NMR (DMSO-d_6) δ 166.5, 165.6, 157.3, 154.7, 141.4, 139.4, 133.1, 133.0, 129.2, 128.5, 128.3, 126.9, 117.8, 54.4, 39.6; *m/z* HRMS (TOF ES$^+$) $C_{20}H_{20}N_5O_5S$ [MH]$^+$ calcd 442.1180, found 442.1166; HPLC 95%

***N*-(1-(4-Cyclopropylphenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide (6o).** Compound **5o** (86.0 mg, 0.214 mmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) and preparative HPLC to afford the desired product (31.8 mg, 37%) as a sticky solid. ^{1}H NMR (DMSO-d_6) δ 10.94 (s, 1H), 10.10 (s, 1H), 8.97 (s, 1H), 8.66 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 5.53 (d, *J* = 8.1 Hz, 1H), 3.06 (s, 3H), 2.03–1.69 (m, 1H), 1.10–0.86 (m, 2H), 0.76–0.57 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.9, 165.4, 143.2, 141.5, 135.4, 129.2, 128.4, 127.3, 125.2, 117.8, 54.3, 39.7, 14.8, 9.4, 9.3; *m/z* HRMS (TOF ES$^+$) $C_{19}H_{22}N_3O_5S$ [MH]$^+$ calcd 404.1275, found 404.1275; HPLC 95%

***N*-(1-(4-(Cyclopent-1-en-1-yl)phenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide (6p).** Compound **5p** (150 mg, 350 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by a preparative HPLC to afford the desired product (30 mg, 20%) as a light apricot solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.11 (s, 1H), 9.01 (s, 1H), 8.73 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.44 (app. s, 4H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.32–6.21 (m, 1H), 5.57 (d, *J* = 8.1 Hz, 1H), 3.06 (s, 3H), 2.71–2.59 (m, 2H), 2.50–2.43 (m, 2H), 2.03–1.87 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 165.5, 141.6, 141.4, 137.1, 135.5, 129.2, 128.5, 127.4, 126.1, 125.4, 117.8, 54.4, 39.6, 32.9, 32.7, 22.7; *m/z* HRMS (TOF ES$^+$) $C_{21}H_{24}N_3O_5S$ [MH]$^+$ calcd 430.1431, found 430.1436; HPLC 98%.

***N*-(2-(Hydroxyamino)-2-oxo-1-(2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)ethyl)-4-(methylsulfonamido)benzamide (6q).** Compound **5q** (120 mg, 271 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by preparative HPLC to afford the desired product (58 mg, 48%) as an apricot solid. ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 10.11 (s, 1H), 9.01 (s, 1H), 8.71 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.13 (m, 1H), 5.57 (d, *J* = 8.1 Hz, 1H), 3.06 (s, 3H), 2.40–2.23 (m, 2H), 2.26–2.04 (m, 2H), 1.79–1.66 (m, 2H), 1.66–1.48 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.8, 165.5, 141.4, 141.3, 136.8, 135.7, 129.2, 128.5, 127.3, 124.6, 124.4, 117.8, 54.3, 39.6, 26.7, 25.3, 22.6, 21.7; *m/z* HRMS (TOF ES$^+$) $C_{22}H_{26}N_3O_5S$ [MH]$^+$ calcd 444.1588, found 444.1600; 95%.

***N*-(1-(4-Cyclopentylphenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide (6r).** Compound **5r** (134 mg, 311 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by preparative HPLC to afford the desired product (53 mg, 40%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.96 (s, 1H), 10.11 (s, 1H), 8.97 (s, 1H), 8.67 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.38–7.07 (m, 4H), 5.53 (d, *J* = 8.0 Hz, 1H), 3.06 (s, 3H), 2.99–2.86 (m, 1H), 2.07–1.92 (m, 2H), 1.83–1.70 (m, 2H), 1.69–1.57 (m, 2H), 1.58–1.42 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.9, 165.5, 145.4, 141.4, 135.9, 129.2, 128.6, 127.3, 126.8, 117.8, 54.4, 45.0, 39.7, 34.3, 25.0; *m/z* HRMS (TOF ES$^+$) $C_{21}H_{26}N_3O_5S$ [MH]$^+$ calcd 432.1588, found 432.1588; HPLC 98%.

***N*-(1-(4-Cyclohexylphenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide (6s).** Compound **5s** (200 mg, 450 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude product was purified by preparative HPLC to afford the desired product (73 mg, 36%) as a light pink solid. ^{1}H NMR (DMSO-d_6) δ 10.96 (s, 1H), 10.11 (s, 1H), 8.98 (s, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.28–7.14 (m, 4H), 5.54 (d, *J* = 8.0 Hz, 1H), 3.06 (s, 3H), 2.49–2.41 (m, 1H), 1.84–1.62 (m, 5H), 1.51–1.13 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 166.9, 165.5, 147.0, 141.4, 135.9, 129.2, 128.5, 127.4, 126.5, 117.8, 54.4, 43.5, 39.6, 33.9, 26.4, 25.6; *m/z* HRMS (TOF ES$^+$) $C_{22}H_{28}N_3O_5S$ [MH]$^+$ calcd 446.1744, found 446.1744; HPLC 97%.

Methyl 2-(4-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)acetate (7). In a round bottom flask was added compound **4d** (3.10 g, 12.7 mmol), sat. $NaHCO_3$ (30 mL) and water (30 mL). The mixture was stirred at room temperature for 30 min after adding Boc_2O (2.77 g, 12.7 mmol). Additional Boc_2O (1.39 g, 6.35 mmol) and THF (90 mL) were added. The reaction mixture was stirred at room temperature for overnight. Upon completion, THF was removed under reduced pressure. 1 M HCl was added to the residue until pH 3 and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography using PE/EtOAc (100:0 to 40:60) to afford the desired product (3.28 g, 75%) as a pale-yellow foam. ^{1}H NMR (DMSO-d_6) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.43–7.12 (m, 2H), 5.23 (d, *J* = 8.1 Hz, 1H), 3.61 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 171.0, 155.1, 136.1, 131.4, 130.1, 121.3, 78.7, 56.9, 52.3, 28.1.

Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-(diethylamino)phenyl) acetate (8a). To a dried 20 mL microwave vessel was added **7** (250 mg, 726 µmol), $Pd_2(dba)_3$ (20.0 mg, 21.8 µmol), XPhos (34.6 mg, 72.6 µmol), Cs_2CO_3 (592 mg, 1.82 mmol), diethylamine (376 µL, 3.63 mmol), and a degassed anhydrous toluene (10 mL). The mixture was heated at reflux for overnight. Upon completion, the mixture was diluted with water (6 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography using PE/EtOAc (100:0 to 70:30) to afford the desired product (204 mg, 83%) as a dark brown solid. ^{1}H NMR (DMSO-d_6) δ 7.51 (d, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 5.00 (d, *J* = 7.8 Hz, 1H),

3.58 (s, 3H), 3.34–3.12 (m, 4H), 1.38 (s, 9H), 1.06 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 172.1, 155.2, 147.1, 128.8, 122.3, 111.1, 78.3, 57.1, 51.9, 43.6, 28.2, 12.4.

Methyl 2-(4-(diethylamino)phenyl)-2-(4-(methylsulfonamido) benzamido)acetate (**9a**)**.** Compound **8a** (292 mg, 868 µmol) was converted to the desired compound according to General Procedure F. The crude was purified by column chromatography PE/EtOAc (100:0 to 40:60) to afford the desired product (264 mg, 70%) as an apricot solid. ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H), 8.82 (d, *J* = 6.6 Hz, 1H), 7.97–7.82 (m, 2H), 7.30–7.13 (m, 4H), 6.64 (d, *J* = 8.9 Hz, 2H), 5.41 (d, *J* = 6.6 Hz, 1H), 3.62 (s, 3H), 3.33 (q, *J* = 7.1 Hz, 4H), 3.06 (s, 3H), 1.08 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 171.7, 165.8, 147.3, 141.4, 129.3, 129.2, 128.3, 121.7, 117.7, 111.2, 56.6, 51.9, 43.6, 39.6, 12.4; *m/z* MS $C_{21}H_{28}N_3O_5S$ $[MH]^+$ 434.0.

Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-(piperidin-1-yl)phenyl) acetate (**8b**)**.** Compound **7** (363 mg, 1.05 mmol) was coupled to piperidine (260 µL, 2.64 mmol) according to General Procedure E. The crude was purified by column chromatography using PE/EtOAc (100:0 to 70:30) to afford the desired product (186 mg, 50%) as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.18 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.46 (d, *J* = 6.8 Hz, 1H), 5.19 (d, *J* = 7.3 Hz, 1H), 3.67 (s, 3H), 3.17–3.04 (m, 4H), 1.83–1.59 (m, 4H), 1.61–1.48 (m, 2H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.0, 154.9, 151.7, 128.0, 127.0, 116.5, 79.9, 57.1, 52.5, 50.4, 28.3, 25.6, 24.2; *m/z* MS $C_{19}H_{29}N_2O_4$ $[MH]^+$ 349.1.

Methyl 2-(4-(methylsulfonamido)benzamido)-2-(4-(piperidin-1-yl) phenyl)acetate (**9b**)**.** Compound **8b** (186 mg, 534 µmol) was converted to the titled product according to General Procedure F. The crude was purified by column chromatography using PE/EtOAc (70:30 to 10:90) to afford the desired product (149 mg, 58%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H), 8.90 (d, *J* = 6.7 Hz, 1H), 8.06–7.78 (m, 2H), 7.44–7.14 (m, 4H), 6.92 (br. d, *J* = 6.8 Hz, 2H), 5.48 (d, *J* = 6.7 Hz, 1H), 3.63 (s, 3H), 3.22–3.10 (m, 4H), 3.06 (s, 3H), 1.67–1.43 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 171.5, 165.8, 151.4, 141.4, 129.2, 129.0, 128.3 (2C), 117.8, 115.8 (br.), 56.5, 52.0, 49.3, 39.6, 25.1, 23.9; *m/z* MS $C_{22}H_{28}N_3O_5S$ $[MH]^+$ 446.0.

Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-morpholinophenyl) acetate (**8c**)**.** Compound **7** (250 mg, 726 µmol) was coupled to morpholine (158 mg, 1.82 mmol) according to General Procedure E. The crude was purified by column chromatography using PE/EtOAc (100:0 to 50:50) to afford the desired product (233 mg, 91%) as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.07 (d, *J* = 7.9 Hz, 1H), 3.80–3.64 (m, 4H), 3.59 (s, 3H), 3.19–2.97 (m, 4H), 1.38 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 171.8, 155.2, 150.8, 128.5, 126.7, 114.8, 78.4, 66.1, 57.0, 52.0, 48.2, 28.2; *m/z* MS $C_{18}H_{27}N_2O_5$ $[MH]^+$ 351.0.

Methyl 2-(4-(methylsulfonamido)benzamido)-2-(4-morpholinophenyl) acetate (**9c**)**.** Compound **8c** (218 mg, 622 µmol) was converted to the titled compound according to General Procedure F. The crude was triturated with MeOH (10 mL) and filtered to afford the desired product (114 mg, 41%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H), 8.91 (d, *J* = 6.8 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.50 (d, *J* = 6.8 Hz, 1H), 3.78–3.69 (m, 4H), 3.63 (s, 3H), 3.16–3.08 (m, 4H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.5, 165.8, 151.0, 141.4, 129.2., 129.0, 128.2, 126.3, 117.8, 114.9, 66.0, 56.5, 52.1, 48.3, 39.6; *m/z* MS $C_{21}H_{26}N_3O_6S$ $[MH]^+$ 447.9.

Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-(4-methylpiperidin-1-yl) phenyl)acetate (**8d**)**.** Compound **7** (200 mg, 582 µmol) was coupled to 4-methylpiperidine (172 µL, 1.45 mmol) according to General Procedure E. The crude was purified by column chromatography using PE/EtOAc (100:0 to 70:30) to afford the desired product (137 mg, 65%) as an orange crystalline solid. ^{1}H NMR (DMSO-d_6) δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.04 (d, *J* = 7.9 Hz, 1H), 3.74–3.62 (m, 2H), 3.59 (s, 3H), 2.63 (td, *J* = 12.3/2.3 Hz, 2H), 1.75–1.58 (m, 2H), 1.57–1.44 (m, 1H), 1.38 (s, 9H), 1.25–1.15 (m, 2H), 0.92 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.9, 155.2, 150.9, 128.5, 125.7, 115.3, 78.4, 57.0, 52.0, 48.5, 33.4, 30.2, 28.2, 21.8; *m/z* MS $C_{20}H_{31}N_2O_4$ $[MH]^+$ 363.1.

Methyl 2-(4-(4-methylpiperidin-1-yl)phenyl)-2-(4-(methylsulfonamido) benzamido)acetate (**9d**)**.** Compound **8d** (137 mg, 378 µmol) was converted to the titled compound according to General Procedure F. The crude was purified by column chromatography using PE/EtOAc (70:30 to 20:80) to afford the desired product (99 mg, 62%) as a beige solid. ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 6.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.64 (d, *J* = 6.8 Hz, 1H), 3.73 (s, 3H), 3.66–3.51 (m, 2H), 2.97 (s, 3H), 2.76–2.64 (m, 2H), 1.71 (app. d, *J* = 11.4 Hz, 2H), 1.60–1.45 (m, 1H), 1.44–1.28 (m, 2H), 0.95 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.0, 166.2, 150.7, 140.9, 129.4, 129.0, 128.5, 119.1, 117.0 (br.), 60.6, 56.6, 53.0, 50.3, 39.7, 33.6, 30.5, 21.8; *m/z* MS $C_{23}H_{30}N_3O_5S$ $[MH]^+$ 460.0.

Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-(4-fluoropiperidin-1-yl) phenyl)acetate (**8e**)**.** Compound **7** (250 mg, 726 µmol) was coupled to 4-fluoropiperidine hydrochloride (253 mg, 1.82 mmol) according to General Procedure E. The crude was purified by column chromatography using PE/EtOAc (100:0 to 60:40) to afford the desired product (264 mg, 99%) as a sticky yellow solid. ^{1}H NMR (DMSO-d_6) δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.98–6.82 (m, 2H), 5.06 (d, *J* = 7.9 Hz, 1H), 4.95–4.65 (m, 1H), 3.59 (s, 3H), 3.45–3.31 (m, 2H), 3.21–3.05 (m, 2H), 2.07–1.87 (m, 2H), 1.82–1.68 (m, 2H), 1.38 (s, 9H); ^{19}F NMR (DMSO-d_6) δ -177.2; ^{13}C NMR (DMSO-d_6) δ 171.8, 155.2, 150.2, 128.6, 126.2, 115.5, 88.5 (d, J_{CF} = 169.4 Hz), 78.4, 57.0, 52.0, 44.8 (d, J_{CF} = 6.8 Hz), 30.5 (d, *J* = 19.0 Hz), 28.2; *m/z* MS $C_{19}H_{28}FN_2O_4$ $[MH]^+$ 367.0.

Methyl 2-(4-(4-fluoropiperidin-1-yl)phenyl)-2-(4-(methylsulfonamido) benzamido)acetate (**9e**)**.** Compound **8e** (226 mg, 617 µmol) was converted to the titled compound according to General Procedure F. The crude was taken up into 5 mL of MeOH and filtered to afford the desired product (132 mg, 46%) as a light beige solid. ^{1}H NMR (DMSO-d_6) δ 10.06 (s, 1H), 8.91 (d, *J* = 6.8 Hz, 1H), 8.01–7.78 (m, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.26–7.18 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.49 (d, *J* = 6.8 Hz, 1H), 5.01–4.65 (m, 1H), 3.63 (s, 3H), 3.44–3.33 (m, 2H), 3.21–3.09 (m, 2H), 3.06 (s, 3H), 2.04–1.86 (m, 2H), 1.86–1.69 (m, 2H); ^{19}F NMR (DMSO-d_6) δ -177.2; ^{13}C NMR (DMSO-d_6) δ 171.5, 165.8, 150.4, 141.5, 129.2, 129.0, 128.2, 125.7, 117.7, 115.6, 88.5 (d, J_{CF} = 169.4 Hz), 56.5, 52.1, 44.8 (d, J_{CF} = 6.9 Hz), 39.6, 30.5 (d, J_{CF} = 19.0 Hz); *m/z* MS $C_{22}H_{27}FN_3O_5S$ $[MH]^+$ 464.0.

Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-(4,4-difluoropiperidin-1-yl)phenyl)acetate (**8f**)**.** Compound **7** (270 mg, 784 µmol) was coupled to 4,4-difluoropiperidine hydrochloride (309 mg, 1.96 mmol) according to General Procedure E. The crude was purified by column chromatography using PE/EtOAc (100:0 to 70:30) to afford the desired product (245 mg, 81%) as an orange oil. ^{1}H NMR (DMSO-d_6) δ 7.63 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.08 (d, *J* = 7.9 Hz, 1H), 3.59 (s, 3H), 3.39–3.28 (m, 4H), 2.02 (ddd, *J* = 19.8/14.1/6.0 Hz, 4H), 1.38 (s, 9H); ^{19}F NMR (DMSO-d_6) δ -95.2; ^{13}C NMR (DMSO-d_6) δ 171.8, 155.2, 149.3, 128.7, 126.8, 122.8 (t, J_{CF} = 240.7/240.7 Hz), 115.8, 78.4, 57.0, 52.0, 45.5 (t, J_{CF} = 5.0/5.0 Hz), 32.8 (t, J_{CF} = 22.4/22.4 Hz), 28.2; *m/z* MS $C_{19}H_{27}F_2N_2O_4$ $[MH]^+$ 385.0.

Methyl 2-(4-(4,4-difluoropiperidin-1-yl)phenyl)-2-(4-(methylsulfonamido)benzamido)acetate (**9f**)**.** Compound **8f** (225 mg, 585 µmol) was converted to the titled compound according to General Procedure F. The crude was purified by triturating with MeOH (10 mL) to afford the desired product (123 mg, 44%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H), 8.92 (d, *J* = 6.9 Hz, 1H), 8.06–7.77 (m, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.26–7.19 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.51 (d, *J* = 6.8 Hz, 1H), 3.63 (s, 3H), 3.40–3.33 (m, 4H), 3.06 (s, 3H), 2.03 (ddd,

J = 19.8/14.0/5.6 Hz, 4H); ^{19}F NMR (DMSO-d_6) δ -95.2; ^{13}C NMR (DMSO-d_6) δ 171.5, 165.8, 149.5, 141.5, 129.2, 129.1, 128.2, 126.3, 122.8 (t, J_{CF} = 240.7/240.7 Hz), 117.8, 115.9, 56.4, 52.1, 45.5 (t, J_{CF} = 5.2/5.2 Hz), 39.6, 32.8 (t, J_{CF} = 22.4/22.4 Hz); *m/z* MS $C_{22}H_{26}F_2N_3O_5S$ $[MH]^+$ 482.0.

Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-(4-(trifluoromethyl) piperidin-1-yl)phenyl)acetate (**8g**)**.** Compound **7** (250 mg, 726 µmol) was coupled to 4-(trifluoromethyl)piperidine hydrochloride (344 mg, 1.82 mmol) according to General Procedure E. The crude was purified by column chromatography using PE/EtOAc (100:0 to 70:30) to afford the desired product (278 mg, 92%) as orange flakes. ^{1}H NMR (DMSO-d_6) δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.25–7.14 (m, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.06 (d, *J* = 7.9 Hz, 1H), 3.91–3.72 (m, 2H), 3.59 (s, 3H), 2.79–2.62 (m, 2H), 2.49–2.42 (m, 1H), 1.98–1.77 (m, 2H), 1.66–1.42 (m, 2H), 1.38 (s, 9H); ^{19}F NMR (DMSO-d_6) δ -72.5; ^{13}C NMR (DMSO-d_6) δ 171.8, 155.2, 150.3, 129.2, 128.6, 126.4, 115.6, 78.4, 57.0, 52.0, 47.2 (d, J_{CF} = 3.4 Hz), 38.9 (d, J_{CF} = 26.5 Hz), 28.7, 23.7 *J coupling of CF_3 signal was difficult to observe; *m/z* MS $C_{20}H_{28}F_3N_2O_4$ $[MH]^+$ 417.0.

Methyl 2-(4-(methylsulfonamido)benzamido)-2-(4-(4-(trifluoromethyl) piperidin-1-yl)phenyl)acetate (**9g**)**.** Compound **8g** (258 mg, 620 µmol) was converted to the titled compound according to General Procedure F. The crude was triturated with MeOH to afford the desired product (134 mg, 56%) as a light beige solid. ^{1}H NMR (DMSO-d_6) δ 8.91 (d, *J* = 6.8 Hz, 1H), 7.95–7.79 (m, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.26–7.18 (m, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 5.50 (d, *J* = 6.8 Hz, 1H), 3.92–3.72 (m, 2H), 3.63 (s, 3H), 3.06 (s, 3H), 2.81–2.62 (m, 3H), 1.92–1.79 (m, 2H), 1.68–1.40 (m, 2H) * NH of sulfonamide was not observed; ^{19}F NMR (DMSO-d_6) δ -72.5; ^{13}C NMR (DMSO-d_6) δ 171.5, 165.8, 150.5, 141.5, 129.2, 129.1, 128.2, 125.9, 117.8, 115.7, 56.5, 52.1, 47.2, 47.1, 39.6, 38.9–38.1 (m), 23.6; *m/z* MS $C_{23}H_{27}F_3N_3O_5S$ $[MH]^+$ 513.9.

Methyl 2-((*tert*-butoxycarbonyl)amino)-2-(4-(4-methylpiperazin-1-yl) phenyl)acetate (**8h**)**.** Compound **7** (250 mg, 726 µmol) was coupled to 1-methylpiperazine (201 µL, 1.82 mmol) according to General Procedure E. Upon completion, the mixture was cooled to room temperature and concentrated *in vacuo*. The residue was extracted with 2 M HCl (3 × 20 mL) from Et_2O (15 mL). The aqueous layer was basified with sat. $NaHCO_3$ to pH 8 and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the desired product (195 mg, 73%) as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.06 (d, *J* = 7.8 Hz, 1H), 3.59 (s, 3H), 3.16–3.02 (m, 4H), 2.46–2.35 (m, 4H), 2.21 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 171.8, 155.2, 150.7, 128.5, 126.3, 115.0, 78.4, 57.0, 54.5, 52.0, 47.8, 45.7, 28.2; *m/z* MS $C_{19}H_{30}N_3O_4$ $[MH]^+$ 364.1.

Methyl 2-(4-(4-methylpiperazin-1-yl)phenyl)-2-(4-(methylsulfonamido)benzamido)acetate (**9h**)**.** Compound **8h** (195 mg, 537 µmol) was converted to the titled compound according to General Procedure F. The crude was obtained (131 mg, 83%) as a brown oil and was used for subsequent reaction without further purification. ^{1}H NMR (DMSO-d_6) δ 10.20 (s, 1H), 8.90 (d, *J* = 6.8 Hz, 1H), 7.97–7.79 (m, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.26–7.20 (m, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.49 (d, *J* = 6.8 Hz, 1H), 3.63 (s, 3H), 3.21–3.08 (m, 4H), 3.06 (s, 3H), 2.47–2.33 (m, 4H), 2.22 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.5, 165.8, 150.9, 141.5, 129.1, 129.0, 128.2, 125.8, 117.8, 115.1, 56.5, 54.5, 52.1, 47.9, 45.7, 39.6; *m/z* MS $C_{22}H_{29}N_4O_5S$ $[MH]^+$ 461.0.

Benzyl 4-(4-(1-((*tert*-butoxycarbonyl)amino)-2-methoxy-2-oxoethyl) phenyl)piperazine-1-carboxylate (**8i**)**.** Compound **7** (350 mg, 1.02 mmol) was coupled to benzyl piperazine-1-carboxylate (560 mg, 2.54 mmol) according to General Procedure E. The crude was purified by column chromatography using PE/EtOAc (100:0 to 50:50) to afford the desired product (463 mg, 94%) as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.41–7.29 (m, 5H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.01–6.84 (m, 2H), 5.10 (s, 2H), 5.07 (d, *J* = 7.8 Hz, 1H), 3.59 (s, 3H), 3.53 (br. s, 4H), 3.15–3.09 (m, 4H), 1.38 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 171.6, 154.4, 150.5, 136.8, 128.6, 128.4, 127.9, 127.6, 127.0, 115.6, 78.4, 66.3, 57.0, 52.0, 48.1, 43.2, 28.2 *one quaternary carbon at ~155.0 was difficult to observe. However, this signal was easily detected from the corresponding aryl sulfonamide analogue **5ab**; *m/z* MS $C_{26}H_{34}N_3O_6$ $[MH]^+$ 484.1.

Benzyl 4-(4-(2-methoxy-1-(4-(methylsulfonamido)benzamido)-2-oxoethyl)phenyl)piperazine-1-carboxylate (**9i**)**.** Compound **8i** (493 mg, 937 µmol) was converted to the titled compound according to General Procedure F. The crude product was triturated with Et_2O to afford the desired product (271 mg, 50%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H), 8.92 (d, *J* = 6.8 Hz, 1H), 8.02–7.72 (m, 2H), 7.43–7.28 (m, 7H), 7.28–7.18 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.51 (d, *J* = 6.8 Hz, 1H), 5.11 (s, 2H), 3.63 (s, 3H), 3.54 (br. s, 4H), 3.21–3.08 (m, 4H), 3.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.4, 165.8, 154.4, 150.7, 141.4, 136.8, 129.2, 129.0, 128.4, 128.2, 127.9, 127.6, 126.6, 117.8, 115.8, 66.3, 56.4, 52.1, 48.1, 43.2, 39.6; *m/z* MS $C_{29}H_{33}N_4O_7S$ $[MH]^+$ 581.0.

Methyl 2-(4-(methylsulfonamido)benzamido)-2-(4-(piperazine-1-yl) phenyl)acetate (**9j**)**.** A 50 mL round bottom flask was charged with **9i** (261 mg, 450 µmol), ammonium formate (283 mg, 4.49 mmol) and MeOH (10 mL). The mixture was stirred and purged with N_2 thoroughly before adding 10 % Pd/C (20 mg), which was refluxed for 4 h. Upon completion, the reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated *in vacuo* and extracted with EtOAc (3 × 10 mL) from water (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 14 mg of a clear oil. LC-MS of the aqueous layer indicated the presence of the product which was recovered by lyophilisation to afford the desired product (118 mg, 59%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.91 (d, *J* = 6.9 Hz, 1H), 8.32 (s, 1H), 8.03–7.74 (m, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.26–7.16 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.50 (d, *J* = 6.8 Hz, 1H), 3.63 (s, 3H), 3.28–3.14 (m, 4H), 3.05 (s, 3H), 3.02–2.90 (m, 4H) *NH of sulfonamide was not observed; ^{13}C NMR (DMSO-d_6) δ 171.5, 165.8, 150.9, 141.7, 129.2, 129.0, 128.1, 126.4, 117.8, 115.4, 56.4, 52.1, 47.6, 44.1, 39.6; *m/z* MS $C_{21}H_{27}N_4O_5S$ $[MH]^+$ 447.0.

***N*-(1-(4-(Diethylamino)phenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide TFA salt** (**10a**)**.** Compound **9a** (150 mg, 346 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) followed by preparative HPLC to afford the desired product (88 mg, 59%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.13 (s, 1H), 8.72 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.51 (br. d, *J* = 6.2 Hz, 2H), 7.31–6.71 (m, 4H), 5.56 (d, *J* = 7.9 Hz, 1H), 3.48 (br. d, *J* = 6.9 Hz, 4H), 3.06 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 6H) *one exchangeable proton of hydroxamic acid was not observed. Due to extensive proton exchange between the ammonium and water present in DMSO, the CH_2 signals were observed as a broadened peak, and the salt signal was observed as a broadened singlet around 3.80 ppm; ^{19}F NMR (DMSO-d_6) δ -74.5; ^{13}C NMR (DMSO-d_6) δ 166.7, 165.5, 141.4, 129.2, 128.9, 128.5, 117.8 (2C), 54.1, 39.6, 11.2 *Quaternary carbon atoms of the arylamine group and ethylene carbon atom were difficult to observe; *m/z* HRMS (TOF ES$^+$) $C_{20}H_{27}N_4O_5S$ $[M]^+$ calcd 435.1697, found 435.1704; HPLC 95%

***N*-(2-(Hydroxyamino)-2-oxo-1-(4-(piperidin-1-yl)phenyl)ethyl)-4-(methylsulfonamido)benzamide** (**10b**)**.** Compound **9b** (122 mg, 274 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (58 mg, 48%) as a light pink solid. ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1H), 10.10 (s, 1H), 8.95 (s, 1H), 8.58 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.47 (d, *J* = 8.0 Hz, 1H), 3.16–3.08 (m, 4H), 3.06 (s, 3H), 1.68–1.46 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 167.3, 165.4, 151.2, 141.3, 129.2, 128.7, 128.1, 128.0, 117.8, 115.5, 54.1, 49.6, 39.6, 25.1, 24.0; *m/z* HRMS (TOF ES$^+$) $C_{21}H_{27}N_4O_5S$ $[MH]^+$ calcd 447.1697, found 447.1706; HPLC 95%

***N*-(2-(Hydroxyamino)-1-(4-morpholinophenyl)-2-oxoethyl)-4-(methylsulfonamido)benzamide (10c).** Compound **9c** (104 mg, 232 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (36 mg, 35%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.92 (s, 1H), 10.17 (s, 1H), 8.96 (s, 1H), 8.60 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.29–7.12 (m, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.48 (d, *J* = 8.0 Hz, 1H), 3.87–3.51 (m, 4H), 3.10–2.91 (m, 7H); ^{13}C NMR (DMSO-d_6) δ 167.2, 165.4, 150.7, 141.4, 129.2, 129.0, 128.7, 128.2, 117.8, 114.9, 66.1, 54.1, 48.6, 39.6; *m/z* HRMS (TOF ES$^+$) $C_{20}H_{25}N_4O_6S$ [MH]$^+$ calcd 449.1489, found 449.1466; HPLC 99%

***N*-(2-(Hydroxyamino)-1-(4-(4-methylpiperidin-1-yl)phenyl)-2-oxoethyl)-4-(methylsulfonamido)benzamide (10d).** Compound **9d** (96 mg, 209 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (60 mg, 63%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1H), 10.11 (s, 1H), 8.95 (s, 1H), 8.58 (d, *J* = 8.1 Hz, 1H), 8.01–7.80 (m, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.29–7.15 (m, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.47 (d, *J* = 8.0 Hz, 1H), 3.79–3.53 (m, 2H), 3.06 (s, 3H), 2.62 (td, *J* = 12.3/2.4 Hz, 2H), 1.84–1.58 (m, 2H), 1.48 (ddd, *J* = 11.1/9.0/5.4 Hz, 1H), 1.19 (m, 2H), 0.92 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 167.3, 165.4, 150.8, 141.3, 129.2, 128.7, 128.2, 128.0, 117.8, 115.3, 54.1, 48.9, 39.6, 33.4, 30.3, 21.8; *m/z* HRMS (TOF ES$^+$) $C_{22}H_{29}N_4O_5S$ [MH]$^+$ calcd 461.1853, found 461.1864; HPLC 95%.

***N*-(1-(4-(4-Fluoropiperidin-1-yl)phenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide (10e).** Compound **9e** (122 mg, 263 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (88 mg, 72%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.92 (s, 1H), 10.12 (s, 1H), 8.96 (s, 1H), 8.60 (d, *J* = 8.1 Hz, 1H), 8.13–7.77 (m, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.29–7.13 (m, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.48 (d, *J* = 8.0 Hz, 1H), 5.10–4.60 (m, 1H), 3.49–3.26 (m, 2H), 3.17–3.08 (m, 2H), 3.06 (s, 3H), 2.13–1.81 (m, 2H), 1.86–1.60 (m, 2H); ^{19}F NMR (DMSO-d_6) δ -177.1; ^{13}C NMR (DMSO-d_6) δ 167.2, 165.4, 150.1, 141.4, 129.2, 128.7, 128.5, 128.3, 117.8, 115.5, 88.6 (d, J_{CF} = 169.3 Hz), 54.1, 45.1 (d, J_{CF} = 6.8 Hz), 39.6, 30.5 (d, J_{CF} = 18.9 Hz); *m/z* HRMS (TOF ES$^+$) $C_{21}H_{26}FN_4O_5S$ [MH]$^+$ calcd 465.1602, found 465.1592; HPLC 99%

***N*-(1-(4-(4,4-Difluoropiperidin-1-yl)phenyl)-2-(hydroxyamino)-2-oxoethyl)-4-(methylsulfonamido)benzamide (10f).** Compound **9f** (108 mg, 224 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) to afford the desired product (76.5 mg, 71%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.93 (s, 1H), 10.08 (s, 1H), 8.98 (s, 1H), 8.63 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.50 (d, *J* = 8.1 Hz, 1H), 3.36–3.28 (m, 4H), 3.06 (s, 3H), 2.02 (ddd, *J* = 19.8/14.0/5.5 Hz, 4H); ^{19}F NMR (DMSO-d_6) δ -95.1; ^{13}C NMR (DMSO-d_6) δ 167.2, 165.4, 149.2, 141.4, 129.2, 129.0, 128.7, 128.3, 122.8 (t, J_{CF} = 240.7/240.7 Hz), 117.8, 115.8, 54.1, 45.8 (t, J_{CF} = 5.1/5.1 Hz), 39.6, 32.8 (t, J_{CF} = 22.4/22.4 Hz); *m/z* HRMS (TOF ES$^+$) $C_{21}H_{25}F_2N_4O_5S$ [MH]$^+$ calcd 483.1508, found 483.1517; HPLC 98%

***N*-(2-(Hydroxyamino)-2-oxo-1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)ethyl)-4-(methylsulfonamido)benzamide (10g).** Compound **9g** (114 mg, 222 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. The crude was purified by column chromatography using DCM/MeOH (100:0 to 90:10) and triturated with Et_2O to afford the desired product (55 mg, 48%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1H), 10.10 (s, 1H), 8.94 (s, 1H), 8.60 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.47 (d, *J* = 8.1 Hz, 1H), 3.78 (app. d, *J* = 12.6 Hz, 2H), 3.05 (s, 3H), 2.70 (dd, *J* = 12.4/10.5 Hz, 2H), 1.97–1.64 (m, 2H), 1.63–1.43 (m, 2H) *CH of trifluoromethylpiperidine was hidden under DMSO solvent peak; ^{19}F NMR (DMSO-d_6) δ -72.5; ^{13}C NMR (DMSO-d_6) δ 167.2, 165.4, 150.2, 141.3, 129.1, 128.7, 128.6, 128.2, 126.4, 117.8, 115.7, 54.0, 47.5, 39.6, 38.8–38.1 (m), 23.6; *m/z* HRMS (TOF ES$^+$) $C_{22}H_{26}F_3N_4O_5S$ [MH]$^+$ calcd 515.1571, found 515.1558; HPLC 95%.

***N*-(2-(Hydroxyamino)-1-(4-(4-methylpiperazin-1-yl)phenyl)-2-oxoethyl)-4-(methylsulfonamido)benzamide TFA salt (10h).** Compound **9h** (169 mg, 367 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. Upon completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (63 mg, 37%) as a yellow fluffy solid. ^{1}H NMR (DMSO-d_6) δ 10.95 (s, 1H), 10.13 (s, 1H), 9.88 (s, 1H), 8.98 (s, 1H), 8.64 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.50 (d, *J* = 8.1 Hz, 1H), 3.83 (br. s, 2H), 3.51 (br. s, 2H), 3.15 (br. s, 2H), 3.06 (s, 3H), 2.94 (br. s, 2H), 2.85 (s, 3H); ^{19}F NMR (DMSO-d_6) δ -73.6; ^{13}C NMR (DMSO-d_6) δ 166.9, 165.3, 148.9, 141.3, 129.9, 129.0, 128.5, 128.2, 117.7, 115.6, 53.8, 52.1, 45.6, 42.0, 39.5; *m/z* HRMS (TOF ES$^+$) $C_{21}H_{28}N_5O_5S$ [M]$^+$ calcd 462.1806, found 462.1815; HPLC 95%.

***N*-(2-(Hydroxyamino)-2-oxo-1-(4-(piperazin-1-yl)phenyl)ethyl)-4-(methylsulfonamido)benzamide TFA salt (10j).** Compound **9j** (108 mg, 242 µmol) was converted to the corresponding hydroxamic acid according to General Procedure G. Upon completion, the reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to afford the desired product (67 mg, 62%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.96 (s, 1H), 10.13 (s, 1H), 8.93 (s, 2H), 8.64 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 5.50 (d, *J* = 8.0 Hz, 1H), 3.33 (br. s, 4H), 3.23 (br. s, 4H), 3.06 (s, 3H) *one exchangeable proton of hydroxamic acid was not observed; ^{19}F NMR (DMSO-d_6) δ -73.9; ^{13}C NMR (DMSO-d_6) δ 167.0, 165.4, 149.6, 141.4, 123.0, 129.2, 128.6, 128.3, 117.8, 115.8, 54.0, 45.7, 42.6, 39.6; *m/z* HRMS (TOF ES$^+$) $C_{20}H_{26}N_5O_5S$ [M]$^+$ calcd 448.1649, found 448.1657; HPLC 95%.

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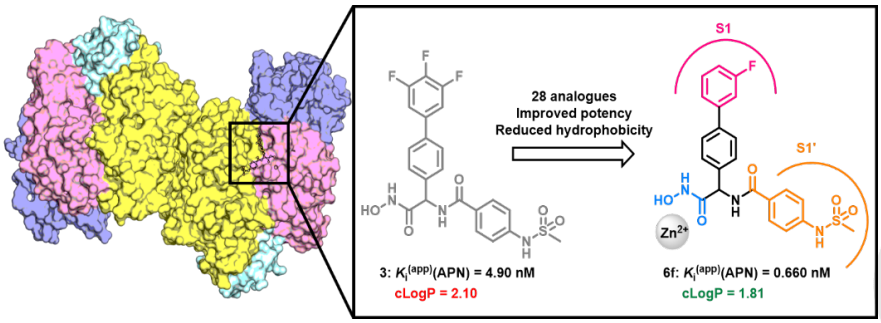
Entry for the Table of Contents



Hydroxamic acid bearing small molecules were synthesised as potent inhibitors of Aminopeptidase N (APN) for the treatment of cancer. The 3,4,5-trifluorophenyl group of the lead compound **3** was replaced with various substituents to improve both potency and solubility. The SAR results indicated that 3-fluorophenyl analogue **6f** was the most potent APN inhibitor that showed inhibitory activity in the sub-nanomolar range.