Bioorganic & Medicinal Chemistry 28 (2020) 115659

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and activity of isoleucine sulfonamide derivatives as novel botulinum neurotoxin serotype A light chain inhibitors

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ARTICLE INFO

Keywords:
Botulinum neurotoxin
Amino acids
Protease inhibitors
Sulfonamide
Biphenyl
Hydroxamic acid

ABSTRACT

The botulinum neurotoxin (BoNT) is the most lethal protein known to man causing the deadly disease botulinum. The neurotoxin, composed of a heavy (HC) and light (LC) chain, work in concert to cause muscle paralysis. A therapeutic strategy to treat individuals infected with the neurotoxin is inhibiting the catalytic activity of the BoNT LC. We report the synthesis, inhibition study and computational docking analysis of novel small molecule BoNT/A LC inhibitors. A structure activity relationship study resulted in the discovery of D-isoleucine functionalized with a hydroxamic acid on the C-terminal and a biphenyl with chlorine at C- 2 connected by a sulfonamide linker at the *N*-terminus. This compound has a measured IC_{50} of 0.587 μM for the BoNT/A LC. Computational docking analysis indicates the sulfonamide linker adopts a geometry that is advantageous for binding to the BoNT LC active site. In addition, Arg363 is predicted to be involved in key binding interactions with the scaffold in this study.

1. Introduction

The botulinum neurotoxin (BoNT), produced by the bacteria *Clostridium botulinum*, is the most lethal toxin known to man with an LD_{50} of 1–1.3 ng per kg of body weight for the A sereotype.[1–3] BoNT intoxication causes muscle paralysis resulting in botulism, a life-threatening illness, which can affect major organs such as the heart and lungs leading to death.[1,4] The most common cause of botulism is the ingestion of food contaminated with the bacteria and/or the BoNT.[5] There are seven different serotypes of the neurotoxin (A-G) with serotype A being the most lethal.[3] Due to the potency, ease of production, lethality, and stability in the environment, BoNT is classified as a category A agent by the USA Centers for Disease Control and Prevention, which represents the most dangerous biological agents that could be used as a weapon for bioterrorism.[1,2] Currently, there are no readily available treatments for botulism, only prophylactic measures exist that can treat a limited number of individuals and is ineffective once the toxin enters the cell.[1] Such minimal treatments are expensive, ineffective after a BoNT attack and are not ideal for a large population infected with the BoNT. Hence, there is a need for therapeutics, such as small molecules, that can inhibit the toxin inside and/or outside the cell.

The BoNT is a 150 KDa polyprotein composed of a heavy (HC) and light chain (LC) linked via a disulfide bond.[1,6] The HC (~100 kDa) binds to the membrane of neurons and inserts the LC (~50 kDa) into the cytosol.[5] The LC is a zinc metalloprotease that cleaves soluble *N*-ethylmaleimide-sensitive factor attachment receptor (SNARE) proteins.[7,8] The SNARE proteins, consisting of synaptobrevin, SNAP-25, and syntaxin are required for the synaptic vesicle to dock with the membrane. Once the synaptic vesicle has fused to the membrane, it releases acetylcholine in the synaptic cleft resulting in the nervous system triggering muscle contraction.[9] Disruption of the SNARE complex via BoNT intoxication prohibits the release of acetylcholine into the synaptic cleft halting neurotransmission leading to muscle paralysis.[5,6] Each BoNT serotype cleaves a specific peptide bond on a SNARE protein. Serotypes B, D, F and G cleave synaptobrevin, serotypes A, C and E cleave SNAP-25 and syntaxin is cleaved by serotype C.[1,5,6] Cleavage of a SNARE protein by BoNT is irreversible and results in flaccid paralysis, which can lead to a variety of symptoms, the most lethal being respiratory failure.[1,2]

The lack of viable treatment options for a large population contracting botulism creates a need for new therapeutics countermeasures. Since there are only two FDA approved vaccines, Botulism Immune Globulin Intravenous (BIG-IV) used to treat infant botulism and Heptavalent equine antitoxin (HBAT) for the treatment of botulism in adults, therapeutics for BoNT exposure are limited and expensive.[1,2]

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https://doi.org/10.1016/j.bmc.2020.115659
Received 12 June 2020; Received in revised form 7 July 2020; Accepted 10 July 2020
Available online 23 July 2020

Furthermore, vaccines are a prophylactic method and do not protect once the BoNT has been internalized into the cell.[1,2] Even though vaccines already exist, an ideal therapeutic would be small molecule inhibitors that have a low cost per treatment, widely available in case of a bioterrorism attack and can be designed to target BoNT inside or outside the cell.[10,11] Thus, making this therapeutic method attractive for further development.

There are reported compounds that inhibit the BoNT/A LC[11–13]; however, none have been therapeutically optimized for clinical trials. Thus, our laboratory is focused on developing novel inhibitors that target the BoNT/A LC with the overall goal of producing new treatment options for BoNT intoxication. In our previous studies, we designed molecules that successfully inhibited the BoNT/A LC.[14] These molecules were functionalized amino acids that contained a biphenyl ring attached at the *N*-terminus via a sulfonamide linker and the *C*-terminus was armed with a hydroxamic acid to act via a competitive mode of inhibition. The original structure activity relationship (SAR) study of the lead compound resulted in the discovery of **1** as a competitive inhibitor with an IC_{50} of 0.95 μM for the BoNT/A LC.[14]

2. Results and discussion

2.1. The design of BoNT/A LC inhibitors

The BoNT/A LC active site is a deep hydrophobic pocket that is extremely flexible in nature.[15,16] These characteristics have led to the discovery of structurally diverse BoNT/A LC inhibitors, resulting in the active site adopting various induced fit enzyme-inhibitor complexes.[13,14,17–21] The scaffold in this study is inspired by matrix metalloproteinase (MMP) inhibitors.[22] MMPs are similar to the BoNT/A LC as they are both zinc-dependent endopeptidase. Many MMP inhibitors are reported to contain a hydroxamic acid as the warhead to coordinate with zinc in the active site.[23,24] Our inhibitors also employed hydroxamic acids as a zinc chelator to improve active site binding, as this group is found on many BoNT/A LC competitive inhibitors.[10–12] In addition, a biphenyl was incorporated into the scaffold to compliment the large hydrophobic active site. In the present study, we investigated the structural elements of **1** vital for BoNT/A LC competitive inhibition, specifically focused on the biphenyl, amino acid side chain (**2a–p**) and the sulfonamide linkage (**3a–g**) to produce a library of novel compounds that were evaluated for BoNT/A LC inhibition (Fig. 1).

2.2. Chemistry

Compounds **2a–p** were synthesized as described in Scheme 1. Briefly, amino acids were coupled to 3-bromobenzenesulfonyl chloride under basic conditions to give the sulfonamide intermediates **4a–d**. A palladium catalyzed Suzuki coupling with various boronic acids was accomplished to construct the biaryl intermediates **5a–p**.[25] The final step involved an aminolysis of the methyl esters to afford the hydroxamic acids **2a–p**.[26]

The amide series was synthesized as outlined in Scheme 2. Construction of the biaryl moiety was carried out by a palladium catalyzed Suzuki coupling between methyl 3-bromobenzoate and various boronic acids to give the corresponding methyl esters **6a–e**. The methyl esters were hydrolyzed to the carboxylic acids (**7a–e**), followed by coupling with amino acid methyl esters to afford intermediates **8a–g**. Finally, the methyl esters underwent aminolysis to yield the hydroxamic acids **3a–g**.

2.3. BoNT/A LC inhibition studies

Compounds **2a–p** and **3a–g** were evaluated as BoNT/A LC inhibitors via an established fluorescence resonance energy transfer (FRET) enzymatic assay.[27] The compounds were screened in a high throughput format at a concentration of 30 μM and reported as percent inhibition of the BoNT/A LC compared to the control (no inhibitor present) in duplicate. The IC_{50} values were determined for several compounds that displayed greater than 90% inhibition in the initial enzyme inhibition assay screen.

The biaryl was conserved throughout this study due to the large size and hydrophobic nature of the BoNT/A LC active site. In previous studies, chlorine was proposed to engage in polar contacts with residues in the active site, specifically Arg363.[16,26,28,29] In the present study, interactions between chlorine and the active site were probed to identify the optimal position for this key binding interaction. A series of compounds were synthesized that included chlorine(s) attached at different positions on the biphenyl and their inhibition reported in Table 1. The best inhibitor from this series was **2f**, which contained chlorines at C-‘2 and ‘6 of the biphenyl. The chlorine at C-‘2 is participating in an important contact with residue(s) in the active site. This conclusion is supported by the results of Table 1, as analogs with the highest inhibition include a chlorine at C-‘2. An exception to this trend was **2e**, as inhibition decreased with chlorines at C-‘2 and ‘5. The lower inhibition could be a result of a steric clash between C-‘5 chlorine and the active site. Interestingly, **2b** has comparable inhibition to **2a**, suggesting that there is an additional interaction available in proximity to C-‘3 or the highly flexible BoNT/A LC active site engages in an induced fit that orientates residue(s) to form an interaction with chlorine at C-‘3. In addition, a substituent at C-‘2 would increase the non-coplanarity about the biphenyl. The non-coplanar biphenyl is believed to enhance the hydrophobic interactions with the BoNT/A LC active site. The non-coplanar geometry of the biphenyl would be greatest for **2f**, which was also experimentally measured to have the highest inhibition in the series. The polar contact between chlorine and the active site and non-coplanar geometry synergistically contributes to binding and inhibition. Furthermore, a nitro substituent was incorporated at C-‘3 (**2g**) and C-‘4 (**2h**) of the biphenyl to probe both functional group size and increased electron-withdrawing ability compared to chlorine. The nitro group at either position did not improve inhibition compared to **2b**. This is not a surprising result as the nitro group is significantly larger than the chlorine and is mostly likely resulting in a steric clash within the active site. The high electronegativity of the nitro group also does not appear to enhance binding and inhibition. This initial SAR study indicates a key contact between chlorine at C-‘2 and residue(s) in the active site. In addition, the non-coplanar geometry of the biphenyl is believed to be

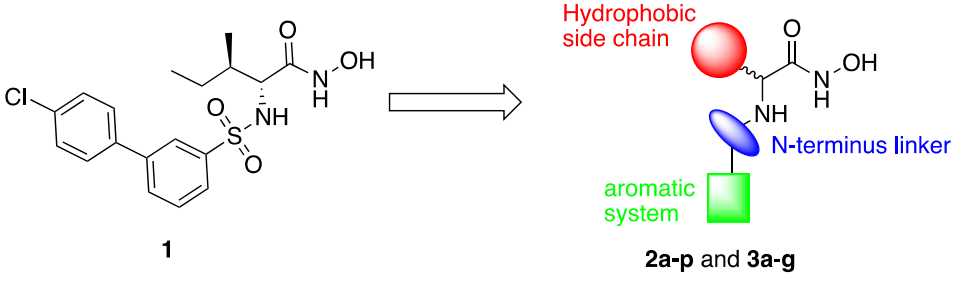
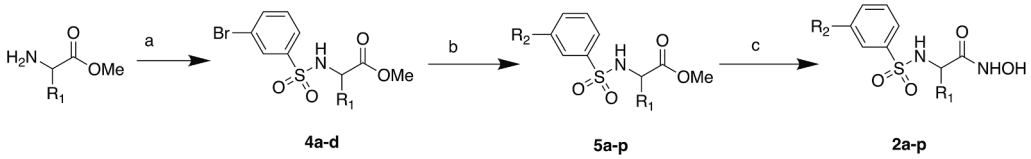


Fig. 1. SAR study of **1**, focusing on the amino acid side chain, stereochemistry, *N*-terminus linker and aromatic system for BoNT/A LC inhibition.



Scheme 1. Synthesis of **2a–p**. Reagents and conditions: (a) 3-bromobenzene sulfonyl chloride, DIPEA, DCM, 3 hr, RT (40–100%); (b) $R_2B(OH)_2$, Pd $(PPh_3)_4$, Na_2CO_3, DME/H_2O/EtOH, 24 h, 80 °C (45–92%); (c) method A: 50% aq. NH_2OH, KCN, THF/MeOH, 24 hr, RT (3–11%) or method B: NH_2OH• HCl, NaOEt, EtOH (15–23%).

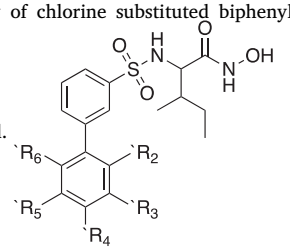
the preferred geometry for binding to the BoNT/A LC active site.

To further investigate the biphenyl and associated intermolecular interactions, analogs were synthesized that replaced the biphenyl with phenyl-furan and phenyl-benzofuran (Table 2). Of the three compounds, **2i** displayed the highest inhibition followed by **2j**. The phenyl-benzofuran is structurally similar to the biphenyl leading to comparable hydrophobic interactions and inhibition. In addition, the oxygen of benzofuran is positioned in an equivalent region as the chlorine of **2a** to take advantage of the intermolecular polar interactions observed with **2a** and **2f**.

The position of the oxygen was explored by comparing the BoNT/A LC inhibition of **2j** and **2k**. Compound **2j** displayed higher inhibition than **2k**, however lower inhibition than **2i**. The lower inhibition of **2j** relative to **2i** was expected, as this analog lacks a benzene ring resulting in less hydrophobic interactions with the BoNT/A LC active site. When comparing **2j** and **2k** there is a significant difference in inhibition due to the orientation of the furan oxygen. The furan of **2j** is connected at C-‘2 allowing the oxygen to occupy the same area as **2i**, which maintains a crucial interaction. Compound **2k** contains furan connected at C-‘3 that causes the oxygen to be orientated away from the proposed polar contact, resulting in the lower inhibition relative to **2j**. The results indicate that two connected aromatic rings maximize binding in the active site and there is an essential polar interaction in proximity to the C-‘2 position of the biphenyl.

Sulfonamides are present in many therapeutic agents, due to their water solubility, hydrogen bonding properties and molecular geometry.[22,30] It is hypothesized that the sulfonamide is essential for the inhibitor scaffold in this study. This concept was examined by synthesizing analogs with an amide linker and evaluating inhibitor activity (Table 3). Replacing the sulfonamide with an amide resulted in similar or improved inhibition. The amide linker with the highest inhibition contained benzofuran (**3e**). The sulfonamide is an isostere of an amide, so it is not unexpected that the amide would result in similar or increased inhibition. However, there is a large difference in the molecular geometries of sulfonamide and amide. The sulfonamide adopts a tetrahedral geometry about the sulfur resulting in a gauche conformation, while the amide maintains a planar geometry. The amide will extend the overall length of the analogs, thereby expanding hydrophobic interactions within the active site. In addition, the amide linker would cause the analogs to adopt a “peptide-like” conformation to increase favorable interactions with the peptide backbone of the active site. Comparing the amide analogs containing chlorine(s) at various positions on the biphenyl reveals similar sensitivity to inhibition as the sulfonamide analogs. The C-‘2,‘3-dichloro amide analog exhibited the best inhibition for the chlorine analogs, which does not match the

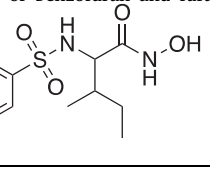
Table 1
SAR study of chlorine substituted biphenyl L-isoleucine sulfonamide hydroxamic acid.

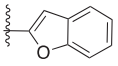


Compound	‘R_2	‘R_3	‘R_4	‘R_5	‘R_6	Percent Inhibition at 30 μM[a]
2a	Cl	H	H	H	H	50
2b	H	Cl	H	H	H	44
2c	H	Cl	Cl	H	H	26
2d	Cl	H	Cl	H	H	48
2e	Cl	H	H	Cl	H	29
2f	Cl	H	H	H	Cl	66
2g	H	NO_2	H	H	H	34
2h	H	H	NO_2	H	H	41

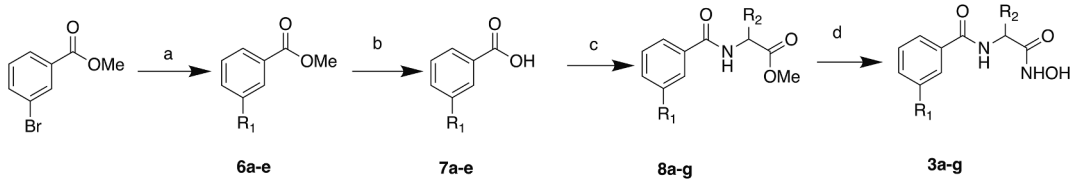
[a] Enzymatic assays were run in duplicate and normalized to the control.

Table 2
SAR study of benzofuran and furan of L-isoleucine sulfonamide hydroxamic acid.



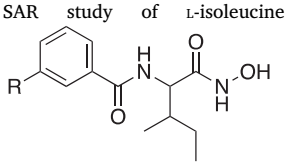
Compound	R	Percent Inhibition at 30 μM[a]
2i		61
2j		40
2k		14

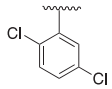
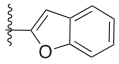
[a] Enzymatic assays were run in duplicate and normalized to the control.



Scheme 2. Synthesis of **3a–g**. Reagents and conditions: (a) $R_1B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O/EtOH, 24 hr, 80 °C (45–92%); (b): LiOH, H_2O/MeOH/THF, 24 hr, RT, (60–92%), (c): amino acid, DCM, DMAP, DCC, 6 hr, 25–35 °C, (55–96%), (d) method A: 50% aq. NH_2OH, KCN, THF/MeOH, 24 h, RT (3–11%) or method B: NH_2OH• HCl, NaOEt, EtOH (10%).

Table 3
SAR study of L-isoleucine amide biphenyl hydroxamic acids.



Compound	R	Percent Inhibition at 30 μM[a]
3a		50
3b		64
3c		68
3d		58
3e		80

[a] Enzymatic assays were run in duplicate and normalized to the control.

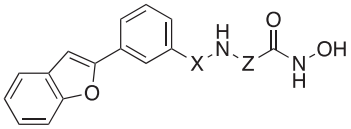
sulfonamide results. These observations suggest that the amide analogs participate in an alternative binding mode than the sulfonamide analogs.

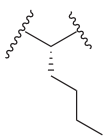
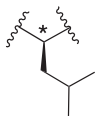
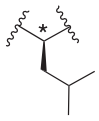
We had previously studied several natural amino acids and determined isoleucine, specifically the D-isomer was the preferred amino acid for the scaffold. In this study, amino acids with branched alkyl side chains and non-natural amino acids with both the sulfonamide and amide linker were evaluated for inhibitor activity (Table 4). A butyl side chain with a sulfonamide linker (**2l**) resulted in lower inhibition relative to the native *sec*-butyl side chain of isoleucine. This would indicate that the side chain of the scaffold is positioned into a shallow pocket of the BoNT/A LC active site. Cyclopropyl (**2m**) was also investigated as a side chain with the sulfonamide linker and displayed no inhibition. This is likely due to the significant change in the overall molecular shape caused by the cyclopropyl leading to poor inhibition.

The stereochemistry of the amino acid was also investigated to determine how this would affect inhibition (Table 4). In our previous study, incorporation of D-isoleucine into the scaffold increased inhibition.[14] This is consistent with other reported studies that found stereochemistry to be an essential aspect to binding and inhibition.[28] D-leucine (**2n**) and D-isoleucine (**2o**) were observed to increase inhibition compared to the L-isoleucine sulfonamide analogs. Interestingly, when the sulfonamide was replaced with the amide linker, as in **3f** and **3g** the inhibition drastically decreased for both D-leucine and D-isoleucine, respectively. If the amide analogs are interacting with the peptide backbone of the active site, a D-amino acid would not form strong interactions with the native peptide backbone of the active site resulting in a lower inhibition, which is observed. The inhibition data reinforces two distinct binding modes for the sulfonamide and amide analogs. Overall, **2o** displayed the highest BoNT/A LC inhibition in the SAR study and revealed D-isoleucine, sulfonamide linker and a biaryl are essential for BoNT/A LC inhibition.

The SAR study provided a clear description of elements required for binding and inhibition. Based on the results, a molecule was synthesized that incorporated essential groups for binding and was evaluated for BoNT/A LC inhibition. Compound **2p** was comprised of D-isoleucine with a hydroxamic acid at the *C*-terminus and '2-chloro-3-biphenyl via a sulfonamide linker at the *N*-terminus (Fig. 2). The IC_{50} value of **2p**

Table 4
SAR study of amino acids and sulfonamide/amide benzofuran-phenyl hydroxamic acid.



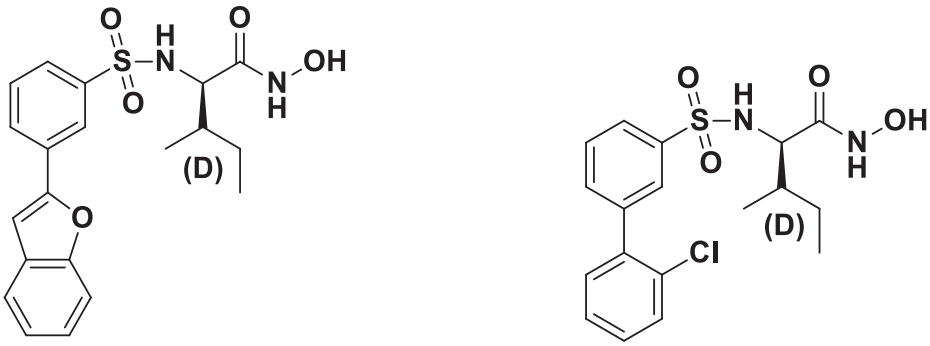
Compound	X	Z	Percent Inhibition at 30 μM[a]
2l			44
2m			No Inhibition
2n			86
2o			94
3f			58
3g			16

[a] Enzymatic assays were run in duplicate and normalized to the control. *D-amino acid.

was determined to be 0.586 μM for the BoNT/A LC, which is an approximate 2-fold increase in inhibition compared to **1**. This establishes a key polar interaction between chlorine at C-'2 and residue(s) in the active site. In addition, the chlorine is sterically forcing the biphenyl ring to adopt a non-coplanar geometry that is proposed to increase binding and inhibition. For comparison, the IC_{50} value of **2o**, the highest inhibitor discovered from the SAR study was determined to be 14 μM. Compound **2o** contains a larger hydrophobic aromatic system that would be advantageous for interacting with the hydrophobic active site. However, **2p** is 30-fold more active than **2o**, indicating the chlorine is involved in critical interactions that are not available for **2o**.

2.4. Molecular docking calculations

AutoDock Vina[31] was used to computationally dock **2o**, **2p** and **3e** into the BoNT/A LC active site (PDB # 2ISH)[32] to investigate intermolecular interactions. The compounds were docked and their lowest energy docking complexes were analyzed and compared. All inhibitors in this study contain a hydroxamate, which has been shown in previous inhibitor studies[15,26,29] and crystal structures[16,20] to chelate zinc found in the BoNT/A LC active site and inhibit through a competitive mechanism. The molecules in this study are also believed to chelate zinc in the active site as competitive inhibitors, which is reinforced by the docking studies that displays typical hydroxamate chelation to the catalytic zinc ion. All three molecules occupied similar space within the active site, with the only difference being the orientations of the amino acid side chains. Additionally, the lowest energy docking complexes



2o: IC_{50} = 14 μM

2p: IC_{50} = 0.587 μM

Fig. 2. Structures and IC_{50} values for highest inhibitor discovered via the SAR study (**2o**) and 2nd generation inhibitor derived from SAR results (**2p**).

have torsional angles (C-1, 2,'1,'2) of 57°, −70° and 111° for **2p**, **2o** and **3e** respectively, indicating all biaryls are non-coplanar.

The docking simulations revealed the sulfonamide of both **2o** and **2p** to be positioned in proximity to Arg363 and the diaryl is in contact with the hydrophobic wall (Fig. 3). Arg363 has been identify as a key interaction for several other small molecule BoNT/A LC inhibitors.[16] Furthermore, the sulfonamide causes the inhibitors to adopt a tetrahedral geometry that orientates the diaryl to maximize hydrophobic interactions within the active site. The diaryl of **2o** and **2p** occupied the same area within the active site, interacting specifically with hydrophobic residues Phe369, Val70, Phe194 and Val258 along the wall of the active site. The C-'2 chlorine on the biphenyl points towards Arg363, indicating a polar contact is possible, while the benzofuran's oxygen of **2o** is in close proximity to the hydroxyl of Tyr366 suggesting a potential hydrogen bond.

Docking of **3e** to the BoNT/A LC (Fig 4) revealed an alternative molecular shape than **2o** and **2p**. The side chain of **3e** is directed inside the active site, while the side chains of both **2o** and **2p** are jutting out of the active site as a result of the opposite stereochemistry. Furthermore, Arg363 is not observed to be involved in binding with any structural elements of **3e**, due to the amide geometry. There is a potential for the benzofuran oxygen of **3e** to engage in a hydrogen bond with the hydroxyl of Tyr366. Moreover, the positioning of the side chain into the active site as observed in the docking model of **3e** appears to have a detrimental effect on binding. The docking poses of **2o** and **2p** indicate the sulfonamide's tetrahedral geometry and the stereochemistry of the D-amino acid reinforces the diaryl's participation in intermolecular interactions with the active site's hydrophobic wall. The computational docking reveals that the diaryl is responsible for the majority of interactions within the BoNT/A LC active site. The docking results are consistent with the experimental observations, demonstrating that D-isoleucine, sulfonamide and biphenyl containing chlorine are essential for binding and inhibition of the BoNT/A LC.

3. Conclusion

Through chemical synthesis, enzyme inhibitor assays and computational docking, novel insights into small molecule BoNT/A LC inhibition were discovered. This study revealed that D-isoleucine containing a hydroxamic acid at the *C*-terminus and a diaryl attached via a sulfonamide linkage at the *N*-terminus, were vital structural elements for BoNT/A LC competitive inhibition. Exploring substituents on the biphenyl indicated that chlorine at C-'2 contributes to an important polar contact with residue(s) in the active site. Computational molecular docking simulations suggest that the sulfonamide is significant for inhibition due to the induced molecular geometry of the scaffold and increased potential for intermolecular interactions. Based on the initial SAR study, **2p** was synthesized and inhibited the BoNT/A LC with an IC_{50} of 0.587 μM, a ~ 2-fold increase in activity from **1**. Future studies will explore substituents at the C-'2 position of the biphenyl and investigate interactions between Arg363 and analogs.

4. Experimental section

4.1. Chemistry

All chemicals and reagents were obtained from Fisher Scientific and used without further purification. All reactions were followed by TLC silica gel 60 F_{254} with detection by UV light. Silica gel was used for columns with a variety of mobile phases. All hydroxamic acids were purified by a Shimadzu preparatory HPLC with a C18 reverse phase column (VYDAC cat # 218TP10152), Total Flow was 10 mL/min; monitored at 254 and 214 nm wavelengths. A two solvent system was used with nanopure water (0.01% TFA) (A) and acetonitrile (B). The

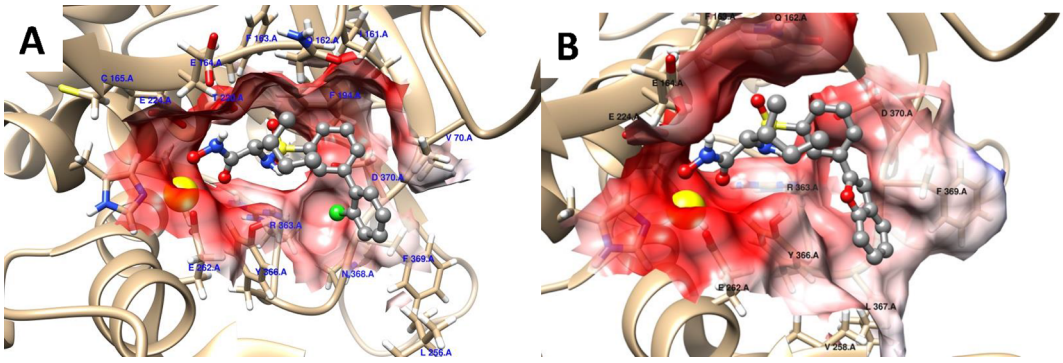


Fig. 3. Molecular docking of inhibitors (ball and stick model) to the BoNT/A LC active site (PDB #2ISH) A: **2p** and B: **2o**.

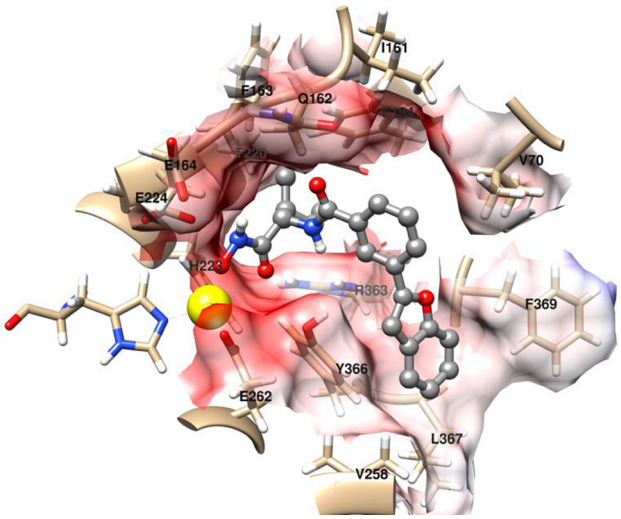


Fig. 4. Molecular docking of **3e** (Ball and Stick) to the BoNT/A LC active site (PDB #2ISH).

gradient was as follows: Solvent B 10% (0.00–5.00 min), 10–80% (5.00–38.00 min), 80–90% (38.00–42.00 min), and hold 90% (42.00–50.00 min). Fractions were collected and lyophilized to obtain solid material. NMR spectra was recorded utilizing a Bruker 400 MHz NMR operating at 400 MHz for proton (^{1}H) NMR and 100 MHz for carbon (^{13}C) NMR in either $CDCl_3$ or d_6-DMSO solvent as indicated. High resolution mass spectra (HRMS) data was collected by a Q Exactive Focus mass spectrometer.

4.1.1. General procedures for the synthesis of sulfonamide amino acid methyl esters ***(4a–e)***

In a 50 mL round bottom flask equipped with a stir bar was added bromobenzene sulfonyl chloride (3.30 mmol) and the appropriate amino acid methyl ester (3.30 mmol) in DCM (12 mL) at 0 °C. N,*N*-Diisopropylethylamine (1.2 mL, 9.90 mmol) was then added to the solution. The mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with water and extracted with DCM. The extracts were washed with 1 M HCl and dried over anhydrous magnesium sulfate. The mixture was concentrated in *vacuo* to give the crude product. The product was purified by column chromatography with DCM to yield the pure product. The product was characterized by ^{1}H and ^{13}C NMR.

4.1.2. (2S,3S)-methyl 2-(3-bromophenylsulfonamido)-3-methylpentanoate ***(4a)***

3-Bromobenzene sulfonyl chloride (3.30 mmol) and L-isoleucine methyl ester (3.30 mmol) were reacted similar to 4.1.1 to yield: 1.2044 g (100%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (t, J = 1.9 Hz, 1H), 7.77 (ddd, J = 7.9, 1.8, 1.0 Hz, 1H), 7.70 (ddd, J = 8.1, 2.0, 1.0 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 5.26–5.17 (m, 1H), 3.82 (dd, J = 10.1, 5.5 Hz, 1H), 3.49 (s, 3H), 1.79 (dddd, J = 9.5, 6.8, 4.0, 2.8 Hz, 1H), 1.48–1.38 (m, 1H), 1.22–1.10 (m, 1H), 0.94–0.84 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.52, 141.61, 135.76, 130.57, 130.15, 125.78, 122.85, 60.41, 52.27, 38.32, 24.64, 15.36, 11.19.

4.1.3. (S)-methyl 2-(3-bromophenylsulfonamido)-hexanoate ***(4b)***

Bromobenzene sulfonyl chloride (1.38 mmol) and L-Norleucine methyl ester (1.38 mmol) were reacted similar to 4.1.1 to yield 339 mg (68%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (t, J = 1.9 Hz, 1H), 7.78 (ddd, J = 7.8, 1.8, 1.0 Hz, 1H), 7.70 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 5.29 (d, J = 9.4 Hz, 1H), 3.95 (ddd, J = 9.4, 7.7, 5.3 Hz, 1H), 3.54 (s, 3H), 1.67–1.57 (m, 2H), 1.35–1.23 (m, 4H), 0.91–0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.19, 141.85, 135.91, 130.71, 130.24, 125.83, 123.03, 77.48, 77.16, 76.84, 55.94, 52.64, 33.10, 31.04, 27.11, 22.12, 13.87.

4.1.4. (S)-methyl 2-(3-bromophenylsulfonamido)-cyclopropionate ***(4c)***

Bromobenzenesulfonyl chloride (3.29 mmol) and cyclopropionate methyl ester (3.29 mmol) were reacted similar to 4.1.1 to yield 1.06 g (97%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (t, J = 1.8 Hz, 1H), 7.81 (ddd, J = 7.8, 1.7, 1.0 Hz, 1H), 7.71 (ddd, J = 8.0, 1.9, 1.0 Hz, 1H), 7.40 (td, J = 7.9, 0.4 Hz, 1H), 3.39 (s, 3H), 1.55–1.40 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.80, 141.91, 135.80, 130.47, 130.43, 126.11, 122.79, 64.46, 52.51, 35.99, 25.35, 17.02.

4.1.5. (R)-methyl 2-(3-bromophenylsulfonamido)-4-methylpentanoate ***(4d)***

Bromobenzene sulfonyl chloride (3.30 mmol) and D-leucine methyl ester (3.30 mmol) were reacted similar to 4.1.1 to yield 542.2 mg (45%). ^{1}H NMR (400 MHz, Chloroform-d) 7.98 (t, J = 1.8 Hz, 1H), 7.78 (ddd, J = 7.8, 1.8, 1.0 Hz, 1H), 7.70 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 5.23 (d, J = 9.2 Hz, 1H), 4.04–3.91 (m, 1H), 3.50 (s, 3H), 1.78 (dt, J = 13.7, 6.7 Hz, 1H), 1.51 (dd, J = 7.8, 6.5 Hz, 2H), 0.91 (t, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.46, 141.60, 135.80, 130.58, 130.15, 125.77, 122.88, 54.51, 52.46, 42.24, 24.32, 22.71, 21.37.

4.1.6. General procedure for the synthesis of biaryl sulfonamide amino acid methyl esters ***(5a–p)***

A solution of sodium carbonate (0.55 mmol) in water (1.75 mL) and EtOH (1.25 mL) was prepared and degassed. In a 10 mL vial Tetrakis (triphenylphosphine) palladium (0.055 mmol) was added to a solution of 4a-e (0.275 mmol) in DME (5 mL) in a 10 mL vial. Argon was bubbled into the DME solution with stirring for 10 min. The boronic acid (1.650 mmol) was added to the vial followed by the addition of the sodium carbonate mixture. The vial was sealed under argon and heated to 80 °C while stiring for 12 h. The mixture was diluted in water and extracted with ethyl acetate. The extracts were washed with brine and dried over magnesium sulfate. The mixture was concentrated in *vacuo* to give the product as an oil. The product was purified in by column chromatography and characterized by ^{1}H and ^{13}C NMR.

4.1.7. (2S,3S)-methyl 2-(2′-chloro-[1,1′-biphenyl]-3-ylsulfonamido)-3-methylpentanoate ***(5a)***

4a (0.275 mmol) and 2-chlorophenyl boronic acid (1.650 mmol) were reacted following general procedure 4.1.6 to yield 100 mg (92%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (t, J = 1.8 Hz, 1H), 7.85 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.67 (dt, J = 7.8, 1.4 Hz, 1H), 7.61–7.52 (m, 2H), 7.50 (ddd, J = 6.3, 3.5, 2.0 Hz, 1H), 7.40–7.33 (m, 3H), 7.33–7.20 (m, 2H), 5.19 (d, J = 10.0 Hz, 1H), 3.84 (dd, J = 10.0, 5.4 Hz, 1H), 3.44 (s, 3H), 1.79 (dddd, J = 9.5, 6.9, 5.4, 4.3 Hz, 1H), 1.48–1.37 (m, 1H), 1.28–1.10 (m, 2H), 0.94–0.83 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 171.59, 140.31, 139.63, 138.53, 133.85, 132.26, 131.21, 130.12, 129.44, 128.70, 128.19, 127.20, 126.40, 60.34, 52.17, 38.36, 24.65, 15.36, 11.21.

4.1.8. (2S,3S)-methyl 2-(3′-chloro-[1,1′-biphenyl]-3-ylsulfonamido)-3-methylpentanoate ***(5b)***

4a (0.275 mmol) and 3-chlorophenyl boronic acid (1.650 mmol) were reacted following general procedure 4.1.6 to yield 80 mg (74%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90–7.81 (m, 2H), 7.63–7.46 (m, 4H), 7.40 (d, J = 7.2 Hz, 1H), 5.32 (br, 1H), 3.85–3.78 (m, 1H), 3.49–3.37 (m, 1H), 1.83–1.74 (m, 1H), 1.45 (dt, J = 6.2, 3.2 Hz, 1H), 1.22–1.14 (m, 1H), 0.98–0.83 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.75, 140.48, 139.68, 138.66, 134.01, 132.43, 131.32, 130.27, 129.57, 128.82, 128.35, 127.31, 126.54, 60.44, 52.33, 38.54, 24.76, 15.48, 11.35.

*4.1.9. (2S,3S)-methyl 2-(3′,4′-dichloro-[1,1′-biphenyl]-3-ylsulfonamido)-3-methylpentanoate **(5c)***

4a (0.275 mmol) and 3,4-chlorophenyl boronic acid (1.650 mmol) were reacted following general procedure 4.1.6 to yield 90 mg (76%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03–7.98 (m, 1H), 7.86 (ddd, J = 7.8, 1.8, 1.1 Hz, 1H), 7.79–7.69 (m, 2H), 7.65–7.53 (m, 3H), 7.46 (dd, J = 8.3, 2.2 Hz, 1H), 5.20 (br, 1H), 3.87 (d, J = 5.5 Hz, 1H), 3.41 (s, 3H), 1.53–1.41 (m, 1H), 1.30–1.14 (m, 2H), 0.98–0.86 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.68, 140.62, 139.81, 139.12, 133.36, 132.72, 131.08, 131.04, 129.79, 128.98, 126.72, 126.33, 125.68, 60.41, 52.17, 38.43, 24.65, 15.38, 11.22.

*4.1.10. (2S,3S)-methyl 2-(2′,4′-dichloro-[1,1′-biphenyl]-3-ylsulfonamido)-3-methylpentanoate **(5d)***

4a (0.275 mmol) and 2-chlorophenyl boronic acid (1.650 mmol) were reacted following general procedure 4.1.6 to yield 100 mg (85%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94–7.85 (m, 2H), 7.72–7.57 (m, 2H), 7.57–7.51 (m, 1H), 7.45–7.36 (m, 1H), 7.36–7.26 (m, 2H), 5.24 (t, J = 7.8 Hz, 1H), 3.91–3.81 (m, 1H), 3.53–3.42 (m, 3H), 1.86–1.77 (m, 1H), 1.49–1.39 (m, 1H), 1.25–1.14 (m, 1H), 0.91 (ddt, J = 14.8, 11.0, 4.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.65, 171.62, 139.82, 139.29, 137.10, 134.78, 133.76, 133.10, 131.95, 129.97, 128.86, 128.16, 127.57, 126.73, 60.35, 52.22, 38.44, 29.71, 24.66, 15.38, 11.24.

*4.1.11. (2S,3S)-methyl 2-(2′,5′-dichloro-[1,1′-biphenyl]-3-ylsulfonamido)-3-methylpentanoate **(5e)***

4a (0.275 mmol) and 2,5-chlorophenyl boronic acid (1.650 mmol) were reacted following general procedure 4.1.6 to yield 80 mg (68%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01–7.93 (m, 2H), 7.90–7.81 (m, 5H), 7.71–7.67 (m, 1H), 7.67–7.51 (m, 8H), 7.51–7.39 (m, 6H), 7.39–7.27 (m, 7H), 5.61–5.46 (m, 3H), 3.96–3.86 (m, 2H), 3.86–3.79 (m, 2H), 3.51–3.36 (m, 10*H*), 1.99–1.91 (m, 1H), 1.87–1.74 (m, 4H), 1.50–1.39 (m, 4H), 1.29–1.18 (m, 4H), 1.18–1.11 (m, 3H), 1.10–0.99 (m, 3H), 0.90 (tt, J = 14.6, 9.3 Hz, 24H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.65, 171.59, 139.96, 139.06, 133.64, 132.97, 131.27, 130.98, 130.67, 129.40, 128.96, 128.92, 128.04, 127.27, 126.91, 60.37, 60.30, 52.23, 52.20, 52.08, 38.35, 38.33, 24.66, 24.65, 15.38, 15.33, 11.22, 11.18.

*4.1.12. (2S,3S)-methyl 2-(2′,6′-dichloro-[1,1′-biphenyl]-3-ylsulfonamido)-3-methylpentanoate **(5f)***

4a (0.275 mmol) and 2,6-chlorophenyl boronic acid (1.650 mmol) were reacted following general procedure 4.1.6 to yield 73 mg (62%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94–7.82 (m, 1H), 7.81–7.76 (m, 1H), 7.66–7.54 (m, 1H), 7.54–7.49 (m, 1H), 7.49–7.40 (m, 2H), 7.33–7.25 (m, 1H), 5.33 (d, J = 9.5 Hz, 1H), 3.51 (d, J = 1.2 Hz, 2H), 1.86–1.71 (m, 1H), 1.46–1.34 (m, 1H), 1.22–1.11 (m, 1H), 0.90 (ddt, J = 17.3, 8.5, 5.4 Hz, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.60, 139.76, 137.85, 137.57, 134.73, 134.67, 134.21, 129.86, 129.01, 128.99, 128.75, 128.31, 128.26, 127.30, 126.96, 60.24, 52.30, 38.48, 24.63, 15.41, 11.33.

*4.1.13. (2S,3S)-methyl 2-(3′-nitro-[1,1′-biphenyl]-3-ylsulfonamido)-3-methylpentanoate **(5g)***

4a (0.549 mmol) and 3-nitrophenyl boronic acid (1.098 mmol) were reacted following general procedure 4.1.6 to yield 172.2 mg (77%). ^{1}H NMR (400 MHz, Chloroform-d) 8.49–8.43 (m, 1H), 8.28 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 8.08 (td, J = 1.9, 0.5 Hz, 1H), 7.99–7.79 (m, 3H), 7.66 (dtd, J = 14.5, 8.0, 0.5 Hz, 2H), 5.28 (d, J = 10.1 Hz, 1H), 3.88 (dd, J = 10.1, 5.5 Hz, 1H), 3.42 (s, 3H), 1.88–1.74 (m, 1H), 1.45 (dqd, J = 13.6, 7.5, 4.3 Hz, 1H), 1.19 (ddq, J = 13.5, 9.1, 7.3 Hz, 1H), 0.98–0.81 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) 171.78, 148.99, 141.01, 140.98, 139.86, 133.20, 131.42, 130.32, 130.08, 127.25, 126.06, 123.16, 122.11, 60.55, 52.33, 38.54, 24.78, 15.52, 11.35

*4.1.14. (2S,3S)-methyl 2-(4-nitro-[1,1′-biphenyl]-3-ylsulfonamido)-3-methylpentanoate **(5h)***

4a (0.301 mmol) and 3-nitrophenyl boronic acid (0.602 mmol) were reacted following general procedure 4.1.6 to yield 116 mg (95%). ^{1}H NMR (400 MHz, Chloroform-d) 8.34 (m, 2H), 8.08 (dt, J = 1.9, 0.9 Hz, 1H), 7.91 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.73 (m, 3H), 7.64 (td, J = 7.8, 0.5 Hz, 1H), 5.24 (d, J = 10.2 Hz, 1H), 2.15 (m, 0H), 3.87 (dd, J = 10.1, 5.5 Hz, 1H), 3.40 (s, 3H), 1.81 (m, 1H), 1.44 (dqd, J = 13.4, 7.5, 4.3 Hz, 1H),1.09 (m, 1H), 0.81 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) 171.78, 147.87, 145.56, 140.96, 139.95, 131.57, 130.06, 128.15, 127.54, 126.30, 124.52, 60.56, 52.31, 38.54, 24.78, 15.53, 11.35.

*4.1.15. (2S,3S)-methyl 2-(3-(benzofuran-2-yl)phenylsulfonamido)-3-methylpentanoate **(5i)***

4a (0.275 mmol) and benzo[*b*]furan-2-boronic acid (1.650 mmol) were reacted following general procedure 4.1.6 to yield 110 mg (91%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (dp, J = 3.2, 1.6 Hz, 1H), 8.06–7.98 (m, 1H), 7.87–7.78 (m, 1H), 7.65–7.50 (m, 3H), 7.38–7.34 (m, 1H), 7.34–7.24 (m, 2H), 7.18–7.11 (m, 1H), 5.47 (td, J = 7.8, 3.9 Hz, 1H), 3.92 (ddd, J = 9.8, 5.0, 2.2 Hz, 1H), 3.42 (dt, J = 4.0, 2.2 Hz, 3H), 1.87–1.79 (m, 1H), 1.53–1.43 (m, 1H), 1.26–1.17 (m, 1H), 0.99–0.85 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.66, 155.05, 153.67, 140.60, 131.54, 129.60, 128.80, 128.62, 126.72, 125.15, 123.46, 123.33, 121.36, 111.36, 103.19, 60.47, 52.18, 38.39, 24.69, 15.40, 11.23.

*4.1.16. (2S,3S)-methyl 2-(3-(furan-2-yl)phenylsulfonamido)-3-methylpentanoate **(5j)***

4a (0.549 mmol) and 2-furanyl boronic acid (3.33 mmol) were reacted following general procedure 4.1.6 to yield 140 mg (73%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, J = 6.8 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.72 (dd, J = 11.2, 6.6 Hz, 1H), 7.52 (tt, J = 10.4, 6.1 Hz, 2H), 6.83–6.75 (m, 1H), 6.55–6.48 (m, 1H), 5.31 (d, J = 9.7 Hz, 1H), 3.91–3.83 (m, 1H), 3.49–3.41 (m, 2H), 3.40 (d, J = 3.1 Hz, 2H), 1.84–1.76 (m, 1H), 1.50–1.41 (m, 1H), 1.24–1.15 (m, 1H), 0.97 (d, J = 6.4 Hz, 1H), 0.95–0.84 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.65, 151.99, 143.05, 140.33, 131.82, 129.47, 127.56, 125.54, 122.35, 112.02, 106.87, 60.39, 52.12, 38.38, 24.67, 15.35, 11.21.

*4.1.17. (2S,3S)-methyl 2-(3-(furan-3-yl)phenylsulfonamido)-3-methylpentanoate **(5k)***

4a (0.549 mmol) and 3-furanyl boronic acid (1.098 mmol) were reacted following general procedure 4.1.6 to yield 131.6 mg (68%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (t, J = 1.8 Hz, 1H), 7.81 (t, J = 1.2 Hz, 1H), 7.75–7.63 (m, 2H), 7.54–7.46 (m, 2H), 6.73 (dd, J = 1.9, 1.0 Hz, 1H), 5.14 (d, J = 10.2 Hz, 1H), 3.84 (dd, J = 10.1, 5.6 Hz, 1H), 3.39 (s, 3H), 1.80–1.75 (m, 1H), 1.50–1.39 (m, 1H), 1.28–1.11 (m, 2H), 0.94–0.84 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) 171.82, 144.35, 140.37, 139.45, 133.80, 129.97, 129.66, 125.61, 125.13, 124.47, 108.67, 60.50, 52.27, 38.55, 24.79, 15.47, 11.33.

*4.1.18. (2S,3S)-methyl 2-(3-(benzofuran-2-yl)phenylsulfonamido)-hexanoate **(5l)***

4b (0.686 mmol) and benzo[*b*]furan-2-boronic acid (1.37 mmol) were reacted following general procedure 4.1.6 to yield 71.3 mg (26%). ^{1}H NMR (400 MHz, Chloroform-d) 8.29 (t, J = 1.8 Hz, 1H), 8.02 (ddd, J = 7.9, 1.8, 1.1 Hz, 1H), 7.78 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.33 (ddd, J = 8.3, 7.2, 1.4 Hz, 1H), 7.27 (m, 1H), 7.14 (d, J = 0.9 Hz, 1H), 5.22 (d, J = 10.2 Hz, 1H), 3.83 (dd, J = 10.2, 5.5 Hz, 1H), 3.39 (s, 3H),1.51 (m, 4H), 0.94 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$)f 171.74, 155.18, 153.79, 140.65, 131.66, 129.72, 128.90, 128.74, 126.83, 125.28, 123.59, 123.45, 121.47, 111.49, 103.28, 61.00, 52.32, 41.19, 29.44, 28.14, 25.95, 25.92, 25.89.

*4.1.19. Methyl 2-(3-(benzofuran-2-yl)phenylsulfonamido)-cyclopropionate **(5m)***

4c (0.600 mmol) and benzo[*b*]furan-2-boronic acid (1.20 mmol) were reacted following general procedure 4.1.6 to yield 204 mg (91%). ^{1}H NMR (400 MHz, Chloroform-d) δ8.36 (td, J = 1.8, 0.5 Hz, 1H), 8.05 (ddd, J = 7.8, 1.8, 1.1 Hz, 1H), 7.83 (ddd, J = 7.8, 1.8, 1.1 Hz, 1H), 7.67–7.50 (m, 3H), 7.38–7.22 (m, 2H), 7.15 (d, J = 0.9 Hz, 1H), 5.63 (s, 1H), 5.30 (s, 1H), 3.31 (d, J = 0.4 Hz, 3H), 1.63–1.42 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.97, 155.20, 153.81, 140.95, 131.67, 129.61, 128.91, 128.84, 127.18, 125.30, 123.94, 123.47, 121.48, 111.51, 103.27, 53.57, 52.57, 36.20, 17.12.

*4.1.20. (R)-methyl 2-(3-(benzofuran-2-yl)phenylsulfonamido)-4-methylpentanoate **(5n)***

4d (0.549 mmol) and benzo[*b*]furan-2-boronic acid (3.3 mmol) were reacted following general procedure 4.1.6 to yield 168.9 mg (74%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (q, J = 1.7 Hz, 1H), 8.08–8.01 (m, 1H), 7.83 (dd, J = 8.0, 1.7 Hz, 1H), 7.68–7.53 (m, 3H), 7.41–7.31 (m, 1H), 7.28 (dd, J = 8.1, 6.8 Hz, 1H), 7.17 (d, J = 3.0 Hz, 1H), 5.32 (td, J = 7.2, 6.7, 4.4 Hz, 1H), 4.12–4.03 (m, 1H), 3.50–3.40 (m, 3H), 1.83 (dt, J = 13.6, 6.7 Hz, 1H), 1.55 (tdd, J = 8.1, 5.2, 3.3 Hz, 2H), 1.02–0.90 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.61, 155.08, 153.67, 140.63, 131.58, 129.63, 128.80, 128.67, 126.71, 125.17, 123.46, 123.34, 121.37, 111.38, 103.20, 54.57, 52.35, 42.31, 24.36, 22.74, 21.44.

*4.1.21. (2R,3R)-2-(3-(benzofuran-2-yl)phenylsulfonamido)-3-methylpentanoic acid **(5o)***

4e (0.286 mmol) and benzo[*b*]furan-2-boronic acid (1.713 mmol) were reacted following general procedure 4.1.6 to yield 68.5 mg (62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ12.62 (s, 1H), 8.32–8.09 (m, 2H), 7.83–7.56 (m, 4H), 7.42–7.26 (m, 4H), 3.63 (t, J = 7.2 Hz, 1H), 1.82–1.64 (m, 1H), 1.43–1.26 (m, 1H), 1.22–1.04 (m, 1H), 0.86–0.72 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ175.71, 155.18, 153.75, 140.60, 131.72, 129.72, 128.90, 126.79, 125.32, 123.55, 123.49, 121.49, 111.50, 103.31, 60.23, 38.30, 24.57, 21.19, 15.52,11.44.

*4.1.22. (2R,3R)-methyl 2-(2′-chloro-[1,1′-biphenyl]-3-ylsulfonamido)-3-methylpentanoate **(5p)***

4e (0.549 mmol) and 2-chlorophenyl boronic acid (1.098 mmol) were reacted following general procedure 4.1.6, with the exception, the reaction was conducted in a CEM microwave reactor (180 °C for 30 min) to yield 184.2 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.80 (m, 2H), 7.67 (ddd, J = 7.7, 1.7, 1.2 Hz, 1H), 7.56 (td, J = 7.8, 0.6 Hz, 1H), 7.53–7.42 (m, 1H), 7.42–7.28 (m, 3H), 5.18 (d, J = 10.0 Hz, 1H), 3.89–3.78 (m, 1H), 3.44 (s, 3H), 1.79 (dddd, J = 9.4, 6.8, 5.4, 4.4 Hz, 1H), 1.61 (s, 1H), 1.49–1.35 (m, 1H), 1.30–1.08 (m, 1H), 1.00–0.79 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.79, 140.51, 139.69, 138.68, 134.04, 132.45, 131.34, 130.29, 129.59, 128.84, 128.38, 127.32, 126.56, 60.45, 52.36, 38.57, 24.78, 15.50, 11.38.

*4.1.23. General procedure for hydrolysis of methyl ester to hydroxamic acid **(2a–p)***

Method A: 50% aq. Hydroxylamine (0.36 mL) and KCN (0.017 mmol) were added to a mixture of methyl ester (0.253 mmol) in THF (1.5 mL) and MeOH (0.5 mL). The reaction was stirred at room temperature for 18 h. The reaction mixture was acidified with 1 M HCl and extracted with ethyl acetate. The extracts were washed with water and brine and dried over magnesium sulfate. The mixture was concentrated by evaporation and purified by a preparatory HPLC (C18 reverse phase VYDAC HPLC column). Fractions were collected and lyophilized to obtain solid material.

Method B: Methyl ester was added into a microwave tube with a stir bar and EtOH (4 mL/mmol). The solution cooled to 0 °C and bubbled under argon. Hydroxylamine hydrochloride (10 equiv.) and sodium ethoxide (20 equiv.) were added into a round bottom with a stir bar and a minimal amount of EtOH was added while the solution was stirred for 5 min. This mixture was then added into the microwave tube and sealed. The reaction was allowed to stirred between 2 and 24 h. Afterwards, the reaction was quenched with 6 N HCl and the pH was adjusted to 8 with 1 M NaOH. The EtOH was removed under vacuum and the remaining aqueous solution was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed. The final compound was purified via purified by a preparatory HPLC (C18 reverse phase VYDAC HPLC column). Fractions were collected and lyophilized to obtain solid material. The hydroxamic acid was fully characterized by ^{1}H, ^{13}C NMR and HRMS.

*4.1.24. (2S,3S)-2-(2′-chloro-[1,1′-biphenyl]-3-ylsulfonamido)-N-hydroxy-3-methylpentanamide **(2a)***

5a (0.253 mmol) was reacted following method A described in 4.1.23 to yield 4.7 mg (5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.77 (d, J = 1.7 Hz, 1H), 8.08–7.98 (m, 2H), 7.88 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.82–7.69 (m, 3H), 7.62 (t, J = 7.8 Hz, 1H), 7.30–7.21 (m, 2H), 3.48–3.36 (m, 4H), 3.39–3.33 (m, 1H), 1.57 (d, J = 8.6 Hz, 1H), 1.08–0.90 (m, 1H), 0.76–0.64 (m, 6H). ^{13}C NMR (400 MHz, DMSO-d_6) δ172.10, 141.14, 139.18, 138.37, 133.03, 131.42, 131.21, 129.95, 129.89, 128.96, 127.71, 127.17, 125.80, 60.07, 36.90, 24.36, 15.35, 10.89. HRMS $C_{18}H_{21}ClN_2O_4S$ $[M + H]^+$: calculated 397.0983, observed 397.0981.

*4.1.25. (2S,3S)-2-(3′-chloro-[1,1′-biphenyl]-3-ylsulfonamido)-N-hydroxy-3-methylpentanamide **(2b)***

5b (0.253 mmol) was reacted following method A described in 4.1.23 to yield: 4.7 mg (5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.76 (s, 1H), 8.11–8.01 (m, 2H), 7.92 (dt, J = 7.8, 1.4 Hz, 1H), 7.83–7.74 (m, 2H), 7.70 (dt, J = 7.6, 1.5 Hz, 1H), 7.67–7.63 (m, 1H), 7.63–7.57 (m, 1H), 7.57–7.46 (m, 2H), 3.41 (d, J = 8.8 Hz, 2H), 2.55 (s, 1H), 1.62–1.54 (m, 1H), 1.46 (ddd, J = 13.5, 7.5, 3.5 Hz, 1H), 0.99 (dt, J = 13.2, 7.6 Hz, 1H), 0.79–0.67 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.87, 142.73, 141.52, 139.72, 134.32, 131.36, 130.99, 130.13, 128.44, 127.17, 126.20, 126.17, 125.17, 58.63, 37.14, 24.77, 15.42, 10.82. HRMS $C_{18}H_{21}ClN_2O_4S$ $[M+H]^+$: Calculated 397.0983, observed 397.0981.

*4.1.26. (2S,3S)-2-(3′,4′-dichloro-[1,1′-biphenyl]-3-ylsulfonamido)-N-hydroxy-3-methylpentanamide **(2c)***

5c (0.253 mmol) was reacted following method A described in 4.1.23 to yield: 8.9 mg (9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.75 (s, 1H), 8.08 (s, 1H), 7.94 (ddd, J = 7.7, 1.9, 1.1 Hz, 2H), 7.82–7.76 (m, 2H), 7.73 (dd, J = 8.4, 2.1 Hz, 2H), 7.64 (t, J = 7.8 Hz, 1H), 3.39 (d, J = 8.6 Hz, 1H), 1.58 (dq, J = 11.7, 4.1, 3.1 Hz, 2H), 1.47 (ddd, J = 13.5, 7.5, 3.4 Hz, 1H), 1.00 (dt, J = 13.0, 7.5 Hz, 1H), 0.82–0.68 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 166.36, 142.31, 139.53, 138.19, 131.86, 131.13, 130.94, 130.53, 129.74, 128.81, 127.21, 125.97, 124.64, 58.17, 36.65, 30.69, 24.31, 14.96, 10.34. HRMS $C_{18}H_{20}Cl_2N_2O_4S$ $[M-H]^-$: Calculated 429.0448, observed 429.0416.

*4.1.27. (2S,3S)-2-(2′,4′-dichloro-[1,1′-biphenyl]-3-ylsulfonamido)-N-hydroxy-3-methylpentanamide **(2d)***

5d (0.253 mmol) was reacted following method A described in 4.1.23 to yield: 13 mg (13%). ^{1}H NMR (400 MHz, Chloroform-d) 7.82 (m, 2H), 7.63–7.47 (m, 3H), 7.33 (dd, J = 8.2, 2.1 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 5.25 (d, J = 9.8 Hz, 1H), 3.88 (dd, J = 9.8, 4.9 Hz, 1H), 1.83 (m, 1H), 1.37 (dtt, J = 14.6, 7.3, 3.2 Hz, 1H), 1.14 (ddq, J = 14.1, 9.1, 7.3 Hz, 1H), 0.81 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 144.0, 139.0, 138.5, 134.0, 133.0, 132.5, 130.5, 130.0, 127.5, 126.0, 125.5, 58.0, 36.0, 24.0, 14.5, 11.0. HRMS $C_{18}H_{20}Cl_2N_2O_4S$ $[M-H]^-$: Calculated 429.0448, observed 429.0416.

*4.1.28. (2S,3S)-2-(2′,5′-dichloro-[1,1′-biphenyl]-3-ylsulfonamido)-N-hydroxy-3-methylpentanamide **(2e)***

5e (0.253 mmol) was reacted following method A described in 4.1.23 to yield: 4 mg (4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 9.0 Hz, 1H), 7.86–7.77 (m, 2H), 7.71–7.60 (m, 3H), 7.57 (d, J = 2.6 Hz, 1H), 7.51 (dd, J = 8.6, 2.6 Hz, 1H), 3.33 (t, J = 8.8 Hz, 1H), 1.60–1.52 (m, 1H), 1.41 (dq, J = 10.9, 3.7 Hz, 1H), 0.94 (ddd, J = 13.6, 8.5, 7.2 Hz, 1H), 0.70 (q, J = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 166.72, 141.62, 140.41, 138.14, 133.23, 132.33, 131.70, 131.22, 130.33, 129.81, 129.25, 127.26, 126.43, 58.41, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 36.74, 24.51, 15.12, 10.52. HRMS $C_{18}H_{20}Cl_2N_2O_4S$ $[M-H]^-$: Calculated 429.0448, observed 429.0417.

*4.1.29. (2S,3S)-2-(2′,6′-dichloro-[1,1′-biphenyl]-3-ylsulfonamido)-N-hydroxy-3-methylpentanamide **(2f)***

5f (0.253 mmol) was reacted following method A described in 4.1.23 to yield: 12.9 mg (11%). ^{1}H NMR (400 MHz, DMSO) δ 10.52 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.49–7.38 (m, 2H), 3.27 (t, J = 8.4 Hz, 1H), 2.44 (s, 1H), 1.45 (q, J = 8.5, 7.4 Hz, 1H), 1.21 (ddt, J = 15.6, 11.8, 5.8 Hz, 1H), 0.72 (dd, J = 14.2, 7.1 Hz, 1H), 0.70–0.55 (m, 4H), 0.54 (d, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 166.95, 141.92, 137.54, 137.04, 133.89, 133.36, 130.87, 129.42, 128.59, 127.31, 126.31, 58.41, 36.57, 24.36, 14.97, 10.70. HRMS $C_{18}H_{20}Cl_2N_2O_4S$ $[M-H]^-$: Calculated 429.0448, Observed 429.0417.

*4.1.30. (2S,3S)-2-(3′-nitro-[1,1′-biphenyl]-3-ylsulfonamido)-N-hydroxy-3-methylpentanamide **(2g)***

5g (0.246 mmol) was reacted following method A described in 4.1.23 to yield: 8.29 mg (8%) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.49–8.43 (m, 1H), 8.28 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 8.08 (td, J = 1.9, 0.5 Hz, 1H), 7.99–7.79 (m, 3H), 7.66 (dtd, J = 14.5, 8.0, 0.5 Hz, 2H), 5.28 (d, J = 10.1 Hz, 1H), 3.88 (dd, J = 10.1, 5.5 Hz, 1H), 3.42 (s, 3H), 1.88–1.74 (m, 1H), 1.45 (dqd, J = 13.6, 7.5, 4.3 Hz, 1H), 1.19 (ddq, J = 13.5, 9.1, 7.3 Hz, 1H), 0.98–0.81 (m, 6H). ^{13}C NMR (101 MHz, CDCl3) δ171.78, 148.99, 141.01, 140.98, 139.86, 133.20, 131.42, 130.32, 130.08, 127.25, 126.06, 123.16, 122.11, 60.55, 52.33, 38.54, 24.78, 15.52, 11.35. HRMS $C_{18}H_{21}N_3O_6S$ $[M+H]^+$: Calculated 408.1224, Observed 408.1221.

*4.1.31. (2S,3S)-2-(4′-nitro-[1,1′-biphenyl]-3-ylsulfonamido)-N-hydroxy-3-methylpentanamide **(2h)***

5h (0.194 mmol) was reacted following method A described in 4.1.23 to yield: 5.23 mg (7%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.77 (d, J = 1.7 Hz, 1H), 8.08–7.98 (m, 2H), 7.88 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.82–7.69 (m, 3H), 7.62 (t, J = 7.8 Hz, 1H), 7.30–7.21 (m, 2H), 3.93–3.33 (m, 1H), 1.63–1.40 (m, 1H) 1.57 (d, J = 8.6 Hz, 1H), 1.08–0.90 (m, 1H), 0.76–0.64 (m, 6H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.54, 142.28, 139.82, 139.43, 135.68, 130.08, 129.66, 128.50, 125.10, 124.25, 119.81, 58.17, 36.70, 24.31, 14.97, 10.38. HRMS $C_{18}H_{21}N_3O_6S$ $[M+H]^+$: Calculated 408.1224, Observed 408.1222.

*4.1.32. (2S,3S)-2-(3-(benzofuran-2-yl)phenylsulfonamido)-N-hydroxy-3-methylpentanamide **(2i)***

5i (0.253 mmol) was reacted following method A described in 4.1.23 to yield: 4.5 mg (5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.76 (d, J = 1.6 Hz, 1H), 8.17–8.10 (m, 2H), 7.77 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.73–7.62 (m, 3H), 7.37 (ddd, J = 8.2, 7.2, 1.4 Hz, 1H), 7.30 (td, J = 7.4, 1.1 Hz, 1H), 3.46–3.37 (m, 2H), 1.59 (d, J = 5.7 Hz, 1H), 1.45 (ddd, J = 13.4, 7.5, 3.4 Hz, 1H), 0.99 (dt, J = 13.2, 7.6 Hz, 1H), 0.82–0.66 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ167.50, 154.50, 154.00, 143.50, 130.50, 130.00, 129.00, 128.50, 127.00, 126.00, 124.00, 123.00, 122.50, 112.50, 103.50, 58.50, 37.00, 24.00, 15.43, 10.84. HRMS $C_{20}H_{22}N_2O_5S$: $[M-H]^-$ Calculated 401.1177, observed 401.1148.

*4.1.33. (2S,3S)-2-(3-(furan-2-yl)phenylsulfonamido)-N-hydroxy-3-methylpentanamide **(2j)***

5j (0.253 mmol) was reacted following method A described in 4.1.23 to yield: 14 mg (14%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (d, J = 1.8 Hz, 1H), 8.81 (d, J = 1.8 Hz, 1H), 8.32–8.24 (m, 1H), 8.00 (d, J = 8.9 Hz, 1H), 7.94 (t, J = 1.8 Hz, 1H), 7.86–7.77 (m, 2H), 7.64 (ddd, J = 7.9, 1.9, 1.2 Hz, 1H), 7.56 (q, J = 8.0 Hz, 1H), 7.03–6.98 (m, 1H), 3.42 (d, J = 8.7 Hz, 2H), 2.54 (s, 1H), 1.44 (ddd, J = 13.5, 7.5, 3.5 Hz, 1H), 0.97 (ddd, J = 13.3, 8.4, 7.0 Hz, 1H), 0.79–0.66 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 167.06, 145.11, 142.82, 140.60, 133.17, 129.92, 129.56, 125.32, 125.01, 123.49, 109.14, 58.68, 40.89, 40.66, 40.61, 40.40, 40.19, 39.98, 39.77, 39.57, 39.36, 37.21, 24.74, 15.44, 10.88. HRMS $C_{16}H_{20}N_2O_5S$ $[M+H]^+$: Calculated 353.1166, observed 353.1163.

*4.1.34. (2S,3S)-2-(3-(furan-3-yl)phenylsulfonamido)-N-hydroxy-3-methylpentanamide **(2k)***

5 k (0.285 mmol) was reacted following method A described in 4.1.23 to yield: 13.6 mg (14%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (d, J = 1.8 Hz, 1H), 8.80 (d, J = 1.8 Hz, 1H), 8.31–8.24 (m, 1H), 7.99 (d, J = 8.9 Hz, 1H), 7.94 (t, J = 1.8 Hz, 1H), 7.86–7.77 (m, 1H), 7.63 (ddd, J = 7.9, 1.9, 1.2 Hz, 1H), 7.55 (q, J = 8.0 Hz, 1H), 7.03–6.97 (m, 1H), 3.41 (d, J = 8.7 Hz, 1H), 1.61–1.51 (m, 1H), 1.44 (ddd, J = 13.5, 7.5, 3.5 Hz, 1H), 0.97 (ddd, J = 13.3, 8.4, 7.0 Hz, 2H), 0.81–0.66 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 167.06, 145.11, 142.82, 140.60, 133.17, 130.01, 129.92, 129.56, 125.32, 125.25, 125.01, 124.34, 123.49, 122.82, 109.14, 108.99, 72.33, 58.68, 40.61, 40.40, 40.19, 37.21, 24.74, 15.44, 10.88. $C_{16}H_{20}N_2O_5S$ $[M+H]^+$: Calculated 353.1166, observed 353.1161.

*4.1.35. (2S,3S)-2-(3-(benzofuran-2-yl)phenylsulfonamido)-N-hydroxylhexanamide **(2l)***

5 l (0.249 mmol) was reacted following method A described in 4.1.23 to yield: 46.7 mg (46%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.69 (q, J = 7.4, 6.3 Hz, 3H), 7.58 (s, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 3.56 (t, J = 7.2 Hz, 1H), 1.40 (ddq, J = 30.0, 13.3, 5.2, 3.0 Hz, 2H), 1.14–0.97 (m, 4H), 0.67 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.21, 154.40, 153.71, 130.41, 129.89, 128.60, 128.23, 126.36, 125.25, 123.51, 122.14, 121.55, 111.29, 103.52, 53.85, 32.34, 27.09, 21.46, 13.67. $C_{20}H_{22}N_2O_5S$ $[M+H]^+$: Calculated 403.1322, observed 403.1320.

*4.1.36. 2-(3-(benzofuran-2-yl)phenylsulfonamido)-N-hydroxycyclopropanamide **(2m)***

5m (0.510 mmol) was reacted following method A described in 4.1.23 to yield: 54.7 mg (29%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (bs, 1H), 8.26 (t, J = 1.8 Hz, 1H), 8.18 (dt, J = 7.6, 1.5 Hz, 1H), 7.80–7.66 (m, 2H), 7.60 (d, J = 0.9 Hz, 1H), 7.38 (ddd, J = 8.3, 7.2, 1.4 Hz, 2H), 7.30 (td, J = 7.4, 1.0 Hz, 2H), 1.12–1.00 (m, 2H), 0.83–0.71 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 168.13, 154.40, 153.46, 143.31, 130.58, 130.14, 128.56, 128.52, 126.25, 125.30, 123.52, 121.89, 121.58, 111.31, 103.74, 34.93, 30.69, 13.69. $C_{18}H_{16}N_2O_5S$ $[M+H]^+$: Calculated 373.0853, observed 373.0850.

*4.1.37. (R)-2-(3-(benzofuran-2-yl)phenylsulfonamido)-N-hydroxy-4-methylpentanamide **(2n)***

5n (0.253 mmol) was reacted following method A described in 4.1.23 to yield 43.1 mg (43%). ^{1}H NMR (400 MHz, DMSO-d_6) 10.70 (s, 1H), 8.29 (t, J = 1.7 Hz, 1H), 8.17 (dd, J = 9.8, 7.9 Hz, 2H), 7.88–7.62 (m, 3H), 7.58 (s, 1H), 7.43–7.26 (m, 2H), 3.64 (q, J = 7.9 Hz, 1H), 1.50–1.19 (m, 3H), 0.75 (d, J = 6.5 Hz, 3H), 0.65 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) 167.27, 154.38, 153.68, 142.34, 130.36,

129.89, 128.59, 128.25, 126.37, 125.24, 123.50, 122.17, 121.54, 111.27, 103.51, 99.53, 52.35, 41.69, 23.80, 22.42, 21.70. HRMS $C_{20}H_{22}N_2O_5S$ $[M-H]^-$: Calculated 401.1177, observed 401.1144.

*4.1.38. (2R,3R)-2-(3-(benzofuran-2-yl)phenylsulfonamido)-N-hydroxy-3-methylpentanamide **(2o)***

5o (0.321 mmol) was reacted following method B described in 4.1.23 to yield: 29 mg (23%). ^{1}H NMR (400 MHz, DMSO) δ 10.58 (s, 1H), 8.80–8.75 (m, 1H), 8.28 (t, J = 1.8 Hz, 1H), 8.20–8.10 (m, 2H), 7.78 (dt, J = 8.0, 1.4 Hz, 1H), 7.75–7.61 (m, 3H), 7.58 (d, J = 0.9 Hz, 1H), 7.38 (ddd, J = 8.3, 7.2, 1.4 Hz, 1H), 7.31 (td, J = 7.5, 1.1 Hz, 1H), 3.42 (t, J = 8.7 Hz, 1H), 1.59 (qt, J = 10.2, 4.8 Hz, 1H), 1.45 (ddt, J = 14.8, 7.4, 3.7 Hz, 1H), 1.00 (dt, J = 13.2, 7.6 Hz, 1H), 0.89–0.67 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 166.48, 154.40, 153.77, 142.50, 130.31, 129.81, 128.63, 128.18, 126.37, 125.23, 123.51, 122.17, 121.55, 111.30, 103.49, 58.21, 36.71, 24.29, 14.99, 10.38. HRMS $C_{20}H_{22}N_2O_5S$ $[M+H]^+$: Calculated 403.1322 observed 403.1318.

*4.1.39. (2R,3R)-2-(2′-chloro-[1,1′-biphenyl]-3-ylsulfonamido)-N-hydroxy-3-methylpentanamide **(2p)***

5p (0.475 mmol), was reacted following method B described in 4.1.23 to yield 29.7 mg (16%). ^{1}H NMR (400 MHz, DMSO) δ 10.59 (s, 1H), 8.05 (d, J = 8.9 Hz, 1H), 7.82 (dd, J = 6.2, 2.1 Hz, 2H), 7.74–7.57 (m, 3H), 7.53–7.42 (m, 3H), 3.36 (t, J = 8.7 Hz, 1H), 1.56 (dp, J = 12.0, 3.4 Hz, 1H), 1.39 (dqd, J = 15.0, 7.5, 3.4 Hz, 1H), 0.99–0.86 (m, 1H), 0.78–0.63 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 166.82, 141.60, 139.42, 138.65, 133.21, 131.75, 131.41, 130.05, 129.13, 127.85, 127.22, 125.87, 58.35, 36.71, 24.41, 15.07, 10.51. HRMS $C_{18}H_{21}ClN_2O_4S$ $[M+H]^+$: Calculated 397.0983, observed 397.0981.

General procedure for the synthesis of diaryl methyl esters **(6a-e)**

*4.1.40. Methyl (2′-chloro-[1,1′-biphenyl])-3-carboxylate **(6a)***

Methyl-3-bromobenzoate (1.394 mmol) and 2-chlorophenylboronic acid (2.788 mmol) were reacted following general procedure 4.1.6 to yield: 160 mg (93%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21–8.16 (m, 1H), 8.11 (dt, J = 7.8, 1.4 Hz, 1H), 7.68 (ddd, J = 7.7, 1.9, 1.2 Hz, 1H), 7.57–7.48 (m, 2H), 7.40–7.33 (m, 3H), 7.32 (dd, J = 3.9, 2.5 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.90, 139.68, 139.50, 134.02, 132.49, 131.33, 130.63, 130.19, 130.05, 129.04, 128.83, 128.19, 127.02, 52.22.

*4.1.41. Methyl (3′-chloro-[1,1′-biphenyl])-3-carboxylate **(6b)***

Methyl-3-bromobenzoate (1.394 mmol) and 3-chlorophenyl boronic acid (2.788 mmol) were reacted following general procedure 4.1.6 to yield**:** 290 mg (89%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (dd, J = 8.1, 2.8 Hz, 2H), 7.65–7.58 (m, 1H), 7.56 (d, J = 6.9 Hz, 1H), 7.53–7.35 (m, 3H), 5.35–5.27 (m, 1H), 3.84 (ddt, J = 20.8, 9.7, 4.4 Hz, 1H), 3.49–3.36 (m, 3H), 1.82–1.73 (m, 1H), 1.45 (tdt, J = 14.2, 11.5, 7.4, 3.9 Hz, 1H), 1.29–1.10 (m, 2H), 0.99–0.82 (m, 6H); ^{13}C NMR (101 MHz, Chloroform-d) δ 166.82, 141.92, 140.04, 134.83, 131.42, 130.84, 130.18, 128.97, 128.42, 127.77, 127.29, 126.61, 125.31, 52.26.

*4.1.42. Methyl (2′,5′-dichloro-[1,1′-biphenyl])-3-carboxylate **(6c)***

Methyl-3-bromobenzoate (1.394 mmol) and 2,5-chlorophenylboronic acid (2.788 mmol) were reacted following general procedure 4.1.6 to yield: 180.8 mg (92%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15–8.06 (m, 4H), 7.66–7.59 (m, 2H), 7.52 (t, J = 7.8 Hz, 3H), 7.44–7.32 (m, 6H), 7.28 (dd, J = 8.5, 2.7 Hz, 3H), 3.95 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.66, 140.89, 138.40, 133.76, 132.77, 131.13, 131.08, 130.84, 130.42, 130.35, 129.28, 128.95, 128.34, 52.26.

*4.1.43. Methyl 3-(furan-2-yl)benzoate **(6d)***

Methyl-3-bromobenzoate (1.394 mmol) and 2-furanylboronic acid (2.788 mmol) were reacted following general procedure 4.1.6 to yield 132 mg (70%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (d, J = 13.4 Hz, 1H), 7.92 (t, J = 8.5 Hz, 1H), 7.84 (t, J = 7.9 Hz, 1H), 7.48 (td, J = 20.4, 19.2, 10.1 Hz, 2H), 6.75 (dt, J = 14.8, 3.7 Hz, 1H), 6.56–6.46 (m, 1H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.84, 152.93, 142.52, 131.18, 130.66, 128.79, 128.20, 127.90, 124.85, 111.81, 105.91, 52.19.

*4.1.44. Methyl 3-(benzofuran-2-yl)benzoate **(6e)***

Methyl-3-bromobenzoate (1.394 mmol) and benzo[*b*]furan-2-boronic acid (2.788 mmol) were reacted following general procedure 4.1.6 to yield This material was prepared as above on a 250 mg scale, replacing 3-chlorophenylboronic acid with benzo[*b*]furan-2-boronic acid. Yield: 222 mg (95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.52 (t, J = 1.8 Hz, 1H), 8.03 (ddt, J = 13.0, 7.8, 1.4 Hz, 2H), 7.60 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.57–7.48 (m, 2H), 7.31 (ddd, J = 8.2, 7.2, 1.4 Hz, 1H), 7.24 (td, J = 7.5, 1.1 Hz, 2H), 7.11 (d, J = 1.0 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.75, 155.00, 154.79, 130.88, 130.85, 129.41, 129.03, 129.01, 128.96, 126.04, 124.69, 123.12, 121.13, 111.29, 102.25, 52.32.

*4.1.45. General procedure for hydrolysis of methyl ester to carboxylic acid **(7a–e)***

Methyl ester (0.793 mmol) was dissolved in MeOH (5 mL) and THF (4 mL). LiOH (3.964 mmol) was dissolved in water (2.75 mL) separately and was added to the solution. The mixture was stirred for 24 h at room temperature. The mixture was concentrated in *vacuo* and acidified with 1 M HCl. The solution was filtered to give the acid as a white solid. The product was characterized by ^{1}H and ^{13}C NMR.

*4.1.46. 2′-chloro-[1,1′-biphenyl]-3-carboxylic acid **(7a)***

6a was reacted following general procedure 4.1.46 to yield: 174.1 mg (80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (dt, J = 9.2, 1.6 Hz, 2H), 7.69 (dt, J = 7.7, 1.5 Hz, 1H), 7.65–7.56 (m, 2H), 7.49–7.39 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.51, 139.39, 139.33, 134.09, 131.95, 131.70, 131.31, 130.40, 130.38, 130.08, 129.15, 129.09, 128.15, 40.62, 40.41, 40.20, 39.99, 39.78, 39.57, 39.36.

*4.1.47. 3′-chloro-[1,1′-biphenyl]-3-carboxylic acid **(7b)***

6b was reacted following general procedure 4.1.46 to yield 146.5 mg (91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (br, 1H), 8.23–8.17 (m, 1H), 8.10–8.00 (m, 2H), 7.96 (d, J = 9.2 Hz, 1H), 7.78 (d, J = 12.8 Hz, 3H), 7.59 (ddq, J = 54.2, 17.1, 8.1, 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.56, 141.91, 139.45, 134.32, 132.13, 131.73, 131.37, 129.89, 129.32, 128.20, 127.94, 127.03, 126.04.

*4.1.48. 2′,5′-dichloro-[1,1′-biphenyl]-3-carboxylic acid **(7c)***

6c was reacted following general procedure 4.1.46 to yield: 225.7 mg (91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05–7.93 (m, 8H), 7.73–7.66 (m, 4H), 7.62 (dt, J = 7.8, 3.5 Hz, 8H), 7.58–7.48 (m, 8H), 7.48 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.41, 141.05, 138.10, 134.01, 132.57, 131.96, 131.44, 131.35, 130.57, 130.39, 129.82, 129.54, 129.23.

*4.1.49. 3-(furan-2-yl)benzoic acid **(7d)***

6d was reacted following general procedure 4.1.46 to yield: 112.2 mg (80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.24 (td, J = 1.8, 0.5 Hz, 1H), 7.96 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.86 (ddd, J = 7.7, 1.7, 1.1 Hz, 1H), 7.81 (dd, J = 1.8, 0.7 Hz, 1H), 7.57 (td, J = 7.8, 0.6 Hz, 1H), 7.08 (dd, J = 3.4, 0.8 Hz, 1H), 6.64 (dd, J = 3.4, 1.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.50, 152.51, 143.91, 131.98, 131.10, 129.78, 128.55, 128.04, 124.33, 112.71, 107.24

*4.1.50. 3-(benzofuran-2-yl)benzoic acid **(7e)***

6e was reacted following general procedure 4.1.46 to yield: 190 mg (100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 2.1 Hz, 1H), 8.18

(d, J = 7.8 Hz, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.72–7.61 (m, 3H), 7.58 (d, J = 4.7 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 167.37, 154.82, 154.61, 132.16, 130.59, 129.98, 129.90, 129.34, 129.17, 125.52, 125.44, 123.85, 121.86, 111.72, 103.42

4.1.51. General procedure for coupling of amino acid to carboxylic acid ***(8a–g)***

Carboxylic acid (**7a-e**) (0.420 mmol), DMAP (0.63 mmol) and EDC and the appropriate methyl ester amino acid (0.420 mmol) were dissolved in DCM (4.2 mL). The solution was allowed to stir at room temperature for 16 h. The reaction was acidified with 2 M HCl and separated with ethyl acetate. The extracts were washed with brine, dried over magnesium sulfate, and concentrated in *vacuo* to give the crude product. The amide was purified by column chromatography to give the pure product. The product was characterized by ^{1}H and ^{13}C NMR.

4.1.52. (2S, 3S)-methyl 2-((2′-chloro-[1,1′-biphenyl]-3-yl)formamido)-3-methylpentanoate ***(8a)***

7a and L-isoleucine methyl ester•HCl were reacted following general procedure 4.1.52 to Yield 310 mg (87%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92–7.84 (m, 2H), 7.82 (dt, J = 7.7, 1.7 Hz, 1H), 7.65–7.57 (m, 2H), 7.50 (dtd, J = 13.1, 6.9, 6.5, 4.0 Hz, 4H), 7.33 (tq, J = 10.2, 3.0 Hz, 6H), 6.76 (d, J = 8.7 Hz, 1H), 4.84 (dd, J = 8.5, 4.9 Hz, 1H), 3.85–3.73 (m, 5H), 2.04 (ddt, J = 7.5, 4.6, 2.5 Hz, 2H), 1.59–1.49 (m, 2H), 1.33–1.16 (m, 4H), 1.10–1.05 (m, 1H), 0.99 (pd, J = 10.9, 9.5, 2.8 Hz, 10*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.63, 166.90, 139.85, 139.49, 134.17, 132.81, 132.46, 131.32, 130.04, 129.03, 128.36, 128.09, 127.01, 126.30, 56.86, 52.20, 38.25, 25.40, 15.52, 11.61.

4.1.53. (2S, 3S)-methyl 2-((3′-chloro-[1,1′-biphenyl]-3-yl)formamido)-3-methylpentanoate ***(8b)***

7b and L-isoleucine methyl ester•HCl were reacted following general procedure 4.1.52 to Yield: 300 mg (92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, J = 7.8 Hz, 1H), 8.18 (t, J = 1.8 Hz, 1H), 7.93 (dt, J = 7.8, 1.4 Hz, 1H), 7.88–7.78 (m, 2H), 7.70 (dt, J = 7.8, 1.4 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.44 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 4.46 (t, J = 7.7 Hz, 1H), 3.41 (s, 3H), 2.07 (s, 1H), 2.04–1.97 (m, 1H), 1.54 (ddd, J = 13.6, 7.4, 4.2 Hz, 1H), 1.29 (ddd, J = 13.7, 8.6, 7.3 Hz, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.74, 167.04, 142.20, 139.06, 134.99, 134.29, 131.20, 130.28, 129.49, 128.04, 127.06, 126.63, 126.30, 126.07, 57.78, 52.05, 36.24, 25.03, 15.97, 11.27.

4.1.54. (2S, 3S)-methyl 2-((2′,5′-dichloro-[1,1′-biphenyl]-3-yl) formamido)-3-methylpentanoate ***(8c)***

7c and L-isoleucine methyl ester•HCl were reacted following general procedure 4.1.52 to Yield: 165.8 mg (55%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87–7.79 (m, 2H), 7.58 (dt, J = 7.7, 1.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 2.6 Hz, 1H), 7.32–7.25 (m, 1H), 6.78 (dd, J = 8.6, 3.3 Hz, 1H), 4.83 (dd, J = 8.5, 5.0 Hz, 1H), 3.77 (s, 3H), 2.07–1.97 (m, 1H), 1.54 (ddd, J = 13.6, 7.4, 4.7 Hz, 1H), 1.35–1.22 (m, 2H), 1.02–0.88 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.61, 166.70, 140.89, 138.66, 134.32, 132.78, 132.60, 131.13, 131.09, 130.82, 128.98, 128.52, 128.02, 126.67, 56.90, 52.23, 38.23, 25.41, 15.52, 11.60.

4.1.55. (2S,3S)-methyl 2-(3-(furan-2-yl)benzamido)-3-methylpentanoate ***(8d)***

7d and L-isoleucine methyl ester•HCl were reacted following general procedure 4.1.52 to Yield: 132.2 mg (52%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (t, J = 1.8 Hz, 1H), 7.77 (ddd, J = 7.8, 1.8, 1.1 Hz, 1H), 7.65 (ddd, J = 7.8, 1.7, 1.1 Hz, 1H), 7.47 (dd, J = 1.8, 0.7 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.71 (dd, J = 3.3, 0.8 Hz, 1H), 6.47 (dd, J = 3.4, 1.8 Hz, 1H), 4.83 (dd, J = 8.5, 5.2 Hz, 1H), 3.76 (s, 3H), 2.03 (ddd, J = 9.2, 4.6, 2.1 Hz, 1H), 1.55 (ddd, J = 13.6, 7.5, 4.7 Hz, 1H), 1.34–1.22 (m, 1H), 1.01–0.92 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.66, 166.95, 152.91, 142.52, 134.64, 131.31, 128.92, 126.72, 125.60, 122.53, 111.82, 106.01, 56.89, 52.16, 38.16, 25.41, 15.50, 11.57.

4.1.56. (2S,3S)-methyl 2-(3-(benzofuran-2-yl)benzamido)-3-methylpentanoate ***(8e)***

7e and L-isoleucine methyl ester•HCl were reacted following general procedure 4.1.52 to Yield: 170.2 mg (74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ8.82 (d, J = 9.0 Hz, 1H), 8.38 (d, J = 19.3 Hz, 1H), 8.13–8.02 (m, 1H), 7.94–7.84 (m, 1H), 7.66 (ddd, J = 25.4, 13.5, 7.4 Hz, 2H), 7.54 (d, J = 3.4 Hz, 1H), 7.42–7.25 (m, 3H), 4.41 (q, J = 14.0, 10.8 Hz, 1H), 3.71–3.60 (m, 3H), 2.12–1.95 (m, 1H) 1.57–1.46 (m, 1H), 1.30 (dd, J = 15.2, 8.2 Hz, 1H), 0.97–0.82 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ172.22, 166.40, 154.50, 154.31, 134.63, 129.76, 129.08, 128.70, 128.00, 127.44, 124.88, 123.67, 121.34, 111.19, 102.82, 57.39, 51.64, 38.89, 30.67, 25.23, 15.52, 10.85.

4.1.57. (2R)-methyl 2-(3-(benzofuran-2-yl)benzamido)-4-methylpentanoate ***(8f)***

7e and L-leucine methyl ester•HCl were reacted following general procedure 4.1.52 to Yield: 129.2 mg (84%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (td, J = 1.8, 0.5 Hz, 1H), 8.05 (ddd, J = 7.8, 1.7, 1.1 Hz, 1H), 7.80 (ddd, J = 7.9, 1.9, 1.1 Hz, 1H), 7.66–7.52 (m, 3H), 7.39–7.19 (m, 11*H*), 7.16 (d, J = 1.0 Hz, 1H), 5.06 (d, J = 10.1 Hz, 1H), 4.09–3.99 (m, 1H), 3.40 (s, 3H), 1.82 (dt, J = 13.7, 6.7 Hz, 1H), 1.56–1.47 (m, 7H), 0.92 (dd, J = 6.7, 3.0 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-d) δ 172.57, 155.08, 153.66, 140.55, 131.60, 129.62, 128.78, 128.68, 126.71, 125.18, 123.47, 123.34, 121.35, 111.38, 103.17, 54.55, 52.36, 42.39, 24.35, 22.74, 21.44.

4.1.58. (2R,3R)-methyl 2-(3-(benzofuran-2-yl)benzamido)-3-methylpentanoate ***(8g)***

7e (0.548 mmol), EDC (0.548 mmol), DMAP (0.457 mmol) and and D-isoleucine methyl ester•HCl (0.548 mmol) was reacted under microwave conditions (120° C for 20 min) to yield: 157.4 mg (94%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (t, J = 1.8 Hz, 1H), 7.92 (dt, J = 7.9, 1.4 Hz, 1H), 7.83–7.70 (m, 1H), 7.70–7.61 (m, 1H), 7.60–7.33 (m, 3H), 7.24 (dtd, J = 25.8, 7.3, 1.2 Hz, 1H), 7.10–6.98 (m, 1H), 4.83 (ddd, J = 14.8, 8.5, 5.3 Hz, 1H), 3.74 (d, J = 11.4 Hz, 2H), 2.11–1.96 (m, 1H), 1.54 (ddtd, J = 16.5, 14.9, 7.4, 4.6 Hz, 1H), 1.38–1.18 (m, 1H), 1.01–0.92 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.67, 166.83, 154.88, 154.68, 128.95, 128.50, 127.73, 127.05, 126.73, 124.61, 123.73, 123.04, 121.08, 111.18, 102.28, 56.98, 52.12, 38.04, 25.44, 15.49, 11.51.

Synthesis of hydroxamic acids (**3a–3g**)

4.1.59. (2S, 3S)-2-((2′-chloro-[1,1′-biphenyl]-3-yl)formamido)-N-hydroxy-3-methylpentanamide ***(3a)***

8a (0.278 mmol) was reacted following method A described in 4.1.23 to yield 28 mg (28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 8.89 (s, 1H), 8.55 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 9.1 Hz, 2H), 7.63–7.49 (m, 5H), 7.49–7.42 (m, 3H), 4.20 (d, J = 9.1 Hz, 1H), 1.93 (s, 1H), 1.73 (d, J = 12.6 Hz, 1H), 1.61 (s, 1H), 1.53–1.47 (m, 2H), 1.26–1.10 (m, 3H), 1.05 (d, J = 11.4 Hz, 1H), 0.87 (d, J = 7.5 Hz, 3H), 0.86–0.75 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.22, 166.30, 139.75, 139.05, 134.70, 132.46, 132.06, 131.77, 130.28, 129.93, 128.70, 128.55, 128.01, 127.50, 55.83, 33.81, 25.31, 15.79, 10.94. HRMS $C_{19}H_{21}ClN_2O_3$ $[M+H]^+$: Calculated 361.1313, observed 361.1312.

*4.1.60. (2S, 3S)-2-((3′-chloro-[1,1′-biphenyl]-3-yl)formamido)-N-hydroxy-3-methylpentanamide **(3b)***

8b (0.278 mmol), was reacted following method A described in 4.1.23 to yield 16 mg (16%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (d, J = 2.2 Hz, 1H), 8.93–8.88 (m, 1H), 8.66 (d, J = 9.4 Hz, 1H), 8.20–8.15 (m, 1H), 7.93–7.82 (m, 2H), 7.78–7.71 (m, 1H), 7.61–7.57 (m, 1H), 7.57–7.44 (m, 2H), 4.25 (d, J = 10.0 Hz, 1H), 2.14–2.06 (m, 2H), 1.99 (s, 1H), 0.92–0.80 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 168.0, 166.5, 142.5, 139.0, 135.5, 134.5, 131.5, 130.0, 129.5, 128.0, 127.0, 126.5, 55.5, 36.0, 25.33, 15.82, 10.93. HRMS $C_{19}H_{21}ClN_2O_3$ $[M+H]^+$: Calculated 361.1313, observed 361.1312.

*4.1.61. (2S, 3S)-2-((2′,5′-dichloro-[1,1′-biphenyl]-3-yl)formamido)-N-hydroxy-3-methylpentanamide **(3c)***

8c (0.254 mmol) was reacted following method A described in 4.1.23 to yield 10 mg (10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.56 (d, J = 8.7 Hz, 1H), 7.94 (dp, J = 3.6, 1.7 Hz, 2H), 7.67–7.59 (m, 3H), 7.59–7.49 (m, 2H), 4.20 (t, J = 9.2 Hz, 1H), 1.97–1.89 (m, 1H), 1.51 (ddd, J = 13.6, 7.5, 3.3 Hz, 1H), 1.16 (dt, J = 13.4, 7.6 Hz, 3H), 0.95–0.79 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.18, 166.18, 141.47, 137.72, 134.79, 132.46, 131.95, 131.43, 130.66, 129.72, 128.67, 128.59, 128.05, 55.80, 35.86, 25.31, 15.79, 10.93. HRMS $C_{19}H_{21}ClN_2O_3$ $[M+H]^+$: Calculated 395.0924, observed 395.0923.

*4.1.62. (2S, 3S)-2-(3-(furan-2-yl)benzamido)-N-hydroxy-3-methylpentanamide **(3d)***

8d (0.317 mmol) was reacted following method A described in 4.1.23 to yield: 15.7 mg (16%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.89 (s, 13H), 8.57 (d, J = 8.7 Hz, 1H), 8.19 (t, J = 1.8 Hz, 1H), 7.84 (dt, J = 7.9, 1.5 Hz, 1H), 7.82–7.75 (m, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.04 (dd, J = 3.4, 0.8 Hz, 1H), 6.63 (dd, J = 3.4, 1.8 Hz, 1H), 4.20 (t, J = 9.2 Hz, 1H), 1.96 (q, J = 6.9 Hz, 1H), 1.52 (ddd, J = 13.5, 7.5, 3.3 Hz, 1H), 1.16 (dt, J = 14.4, 7.6 Hz, 2H), 0.90–0.80 (m, 6H); ^{13}C NMR (101 MHz, DMSO) δ 167.74, 165.80, 152.47, 143.25, 134.82, 130.25, 128.84, 126.56, 125.98, 122.39, 112.16, 106.58, 55.34, 40.15, 35.32, 24.85, 15.32, 10.46, 0.10. HRMS $C_{17}H_{20}N_2O_4$ $[M-H]^-$:Calculated 315.1350, observed 315.1327.

*4.1.63. (2S, 3S)-2-(3-(1-benzofuran-2-yl)benzamido)-N-hydroxy-3-methylpentanamide **(3e)***

8e (0.274 mmol) was reacted following method A described in 4.1.23 to yield 22.7 mg (23%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.66 (d, J = 8.9 Hz, 1H), 8.44–8.40 (m, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.73–7.62 (m, 2H), 7.62–7.50 (m, 2H), 7.37–7.29 (m, 2H), 7.29–7.25 (m, 1H), 4.22 (m, 1H), 1.53 (m, 2H), 1.20–1.15 (m, 2H), 0.92–0.82 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.21, 166.12, 155.09, 154.78, 135.40, 130.17, 129.51, 129.19, 128.43, 127.70, 125.32, 124.06, 123.81, 121.79, 111.65, 103.24, 55.86, 35.85, 25.33, 15.80, 10.95. HRMS $C_{21}H_{22}N_2O_4$ $[M+H]^+$: Calculated 367.1652, observed 367.1651.

*4.1.64. (2R)-2-(3-(1-benzofuran-2-yl)benzamido)-N-hydroxy-4-methylpentanamide **(3f)***

8f (0.274 mmol) was reacted following method A described in 4.1.23 to yield 60.8 mg (61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (d, J = 1.7 Hz, 1H), 8.85 (d, J = 1.7 Hz, 1H), 8.67 (d, J = 8.2 Hz, 1H), 8.44 (t, J = 1.8 Hz, 1H), 8.07 (dt, J = 7.9, 1.4 Hz, 1H), 7.92 (dt, J = 7.8, 1.4 Hz, 1H), 7.73–7.64 (m, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.53 (s, 1H), 7.35 (td, J = 8.1, 7.7, 1.4 Hz, 1H), 7.29 (td, J = 7.5, 1.1 Hz, 1H), 4.55–4.45 (m, 1H), 1.80–1.60 (m, 2H), 1.60–1.50 (m, 1H), 0.91 (dd, J = 16.4, 6.4 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.19, 166.13, 155.11, 154.78, 135.36, 130.15, 129.48, 129.19, 128.45, 127.71, 125.33, 124.11, 123.82, 121.79, 111.66, 103.21, 50.09, 24.85, 23.34, 22.17. HRMS $C_{21}H_{22}N_2O_4$ $[M+H]^+$: Calculated 367.1652, observed 367.1650.

*4.1.65. (2R, 3R)-2-(3-(1-benzofuran-2-yl)benzamido)-N-hydroxy-3-methylpentanamide **(3g)***

8g (0.431 mmol) was reacted following method B described in 4.1.23 to yield 15.7 mg (10%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.92 (d, J = 2.0 Hz, 1H), 8.65 (d, J = 8.8 Hz, 1H), 8.45–8.39 (m, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.73–7.50 (m, 2H), 7.40–7.24 (m, 1H), 4.24 (t, J = 9.4 Hz, 1H), 3.36–3.23 (m, 3H), 1.97 (s, 1H), 1.53 (s, 1H), 0.94–0.80 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 167.74, 165.65, 154.61, 154.30, 134.93, 129.70, 129.04, 128.71, 127.96, 127.23, 124.85, 123.59, 123.33, 121.32, 111.18, 102.76, 99.51, 55.38, 35.38, 24.86, 15.33, 10.48. HRMS $C_{21}H_{22}N_2O_4$ $[M+H]^+$: Calculated 367.1652 observed 367.1649.

4.2. Enzymatic assay

In a 96-well plate, 30 nM of BoNT/A light chain (List laboratories, product #610A) was incubated for 2 min at 37 °C with a small molecule at 30 μM in 50 mM HEPES buffer at pH 7.4. The reactions were initiated by adding 10 μM of SNAPtide substrate (List laboratories, product #523) to give a final volume of 100 μL. The reactions were monitored by a Spectramax M2 plate reader (Molecular Devices, Sunnyvale, CA, USA) using an excitation of 490 nm and emission of 523 nm for 15 min. The initial rates (0–5 mins) for each enzyme reaction was compared to a control (no inhibitor present) to determine the percent inhibition. The enzyme reactions were performed in duplicate.

4.3. IC_{50} calculations

The enzymatic assay was performed as described in 4.2 for each compound at various inhibitor concentrations in triplicate. The rate at each inhibitor concentration was normalized to the rate of the control. The log (inhibitor) vs. normalized response – variable rate model was used to calculate the IC_{50} using Prism 6.0 (Graftpad, San diego, CA).

4.4. Molecular docking

Molecular Docking was performed using AutoDock Vina (The Scripps Research Institute, La Jolla, CA) on a Dell Precision T1650 desktop running Windows 8 with an Intel core i7-3770 CPU. The solved X-ray crystal structure of the BoNT/A LC (pdb# 2ISH) was used as a static receptor for docking. The crystal structure was prepared for docking by removing all crystallographic waters and merging all non-polar hydrogens into the structure and leaving polar hydrogens. A docking grid box (22.5 × 23.25 × 15.0 Angstrom) was generated and centered around the zinc in active site and used as the search space for docking.

The small molecule ligands were drawn using ChemDraw (Perkin Elmer) and minimized with Chem3D (Perkin Elmer). The docking was set at an exhaustiveness of 20 and twelve binding conformation were produced. The best binding energies (kcal/mol) for **3e**, **2o** and **2p** in the active site are shown in Fig 3 and 4.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are grateful to Allergan Foundation, California State University program in Education and Research in Biotechnology (CSUPERB) and California State University, Fullerton for financial support of this research. Instrumentation support was provided by the Department of Defense (68816-RT-REP) and the National Science Foundation MRI

(CHE1726903) for the acquisition of an UPLC-HRMS. Molecular graphics and analyses were performed with the UCSF Chimera package (supported by NIGMS P41-GM103311).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2020.115659.

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