Discovery of the First Potent and Selective $\alpha_v\beta_5$ Integrin Inhibitor Based on an Amide-Containing Core

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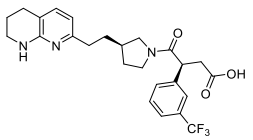
ABSTRACT

Integrins $\alpha_v\beta_5$ and $\alpha_v\beta_3$ are closely related, proangiogenic members of the wider RGD-binding integrin family. Due to their high sequence homology, the development of $\alpha_v\beta_5$-selective compounds has remained elusive to synthetic and medicinal chemists. Herein, we describe a survey of SAR around a series of amide-containing 3-aryl-succinamic acid-based RGD mimetics. This resulted in the discovery of α,α,α-trifluorotolyl **12** which exhibits 800× selectivity for $\alpha_v\beta_5$ *versus* $\alpha_v\beta_3$ with a pyrrolidine amide linker that confers selectivity for $\alpha_v\beta_5$ by positioning a key aryl ring in the SDL of $\alpha_v\beta_5$ with good complementarity; binding in this mode is disfavoured in $\alpha_v\beta_3$ due to clashes with key residues in the β_3-subunit. Compound **12** exhibits selective inhibition by a cell adhesion assay, high passive permeability and solubility which enables potential use of this inhibitor as an $\alpha_v\beta_5$-selective *in vitro* tool compound.



12

MDCK permeability: 295 nm/s
CAD solubility: 141 μg/mL
IVC: heps <0.45 ((mL/min)/g liver) (human)
14.3 ((mL/min)/g liver) (rat)

pIC50 ($\alpha_v\beta_5$): 8.2
pIC50 ($\alpha_v\beta_3$): 5.3
pIC50 ($\alpha_v\beta_1$): 5.6
pIC50 ($\alpha_v\beta_6$): 4.3
pIC50 ($\alpha_v\beta_8$): 4.3

INTRODUCTION

Integrins are a family of heterodimeric transmembrane glycoprotein receptors comprising of non-covalently associated α- and β-subunits. The mammalian genome encodes eighteen known α-subunits and eight β-subunits which combine to give twenty-four unique integrins.[1] Of these twenty-four integrin receptors, at least eight (all five α_v containing integrins: $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$ and $\alpha_5\beta_1$, $\alpha_8\beta_1$ and $\alpha_{IIb}\beta_3$) bind ligands *via* recognition of the arginine-glycine-aspartic acid (RGD) tripeptide sequence.[2]

Integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ play key roles in angiogenesis (operating by independent, distinct mechanisms)[3] and regulation of vascular permeability. Blocking/genetic absence of $\alpha_v\beta_5$ in pulmonary epithelial cells prevents increases in vascular permeability in acute lung injury (ALI) models.[4] Conversely, mice lacking the β_3-subunit exhibit increased mortality due to vascular leakage and endothelial permeability.[5] This is particularly significant in sepsis syndrome where increased vascular leakage is a central pathophysiological feature. Investigations have identified possible links between vascular leakage and $\alpha_v\beta_5$ regulation.[6] It is reported that $\alpha_v\beta_5$ (which is widely expressed, including on endothelial cells) regulates vascular leakage *via* endothelial cytoskeletal reorganisation. Integrin β_5-subunit knockout mice and wild-type mice treated with $\alpha_v\beta_5$ blocking antibodies resulted in decreased mortality, indicating $\alpha_v\beta_5$ as a potential therapeutic target for sepsis treatment.

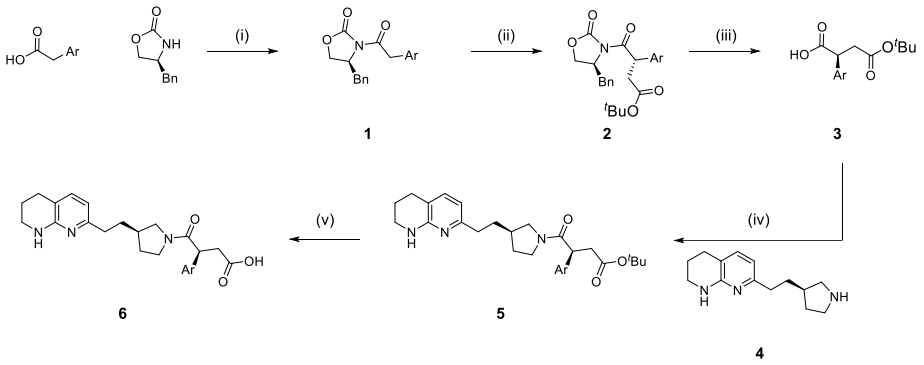
Studies of this type utilise knockout models and antibody blockade. These techniques benefit from high selectivity; however, there are greater financial and time costs associated with antibody-based studies than small molecule alternatives, which are not presently available for $\alpha_v\beta_5$.[7] Existing small molecule $\alpha_v\beta_5$ inhibitors display near-equipotency with the highly homologous $\alpha_v\beta_3$. As the two most homologous β-subunits, β_3 and β_5 share 56% identity between amino acid sequences.[8] Residues key to ligand binding, such as those comprising the α/β interface, the I-like domain and regions assumed to be crucial for specificity such as the specificity determining-loop (SDL) structure are highly conserved between the two integrins;[9, 10] however, slight divergence within the SDL itself presumably infers ligand binding preference.

The ligand binding specificity of $\alpha_v\beta_3$ is generally accepted to be more relaxed than $\alpha_v\beta_5$ as $\alpha_v\beta_3$ is known to bind at least six more endogenous ligands than $\alpha_v\beta_5$.[11, 12] For this reason, the development of $\alpha_v\beta_3$-selective compounds has been more straightforward with selective tool compounds available for purchase.[7] Given the various disease indications associated with overexpression of $\alpha_v\beta_5$ (including ocular, fibrotic and respiratory diseases)[13-16] and gaps in the knowledge of the related structural and functional biology, a highly active, $\alpha_v\beta_5$ selective tool compound would be of great benefit for target/pathway validation and potential therapy design. Inhibition of multiple integrins complicates this picture as other biological pathways are affected with potential toxic outcomes;[7] selectivity over other α_v integrins is essential for such a tool.

Herein, we disclose an $\alpha_v\beta_5$-selective integrin inhibitor based on an amide-containing core which confers considerable binding preference over the closely related $\alpha_v\beta_3$—and the other α_v integrins—and the impact of modifications around this core.

SYNTHESIS

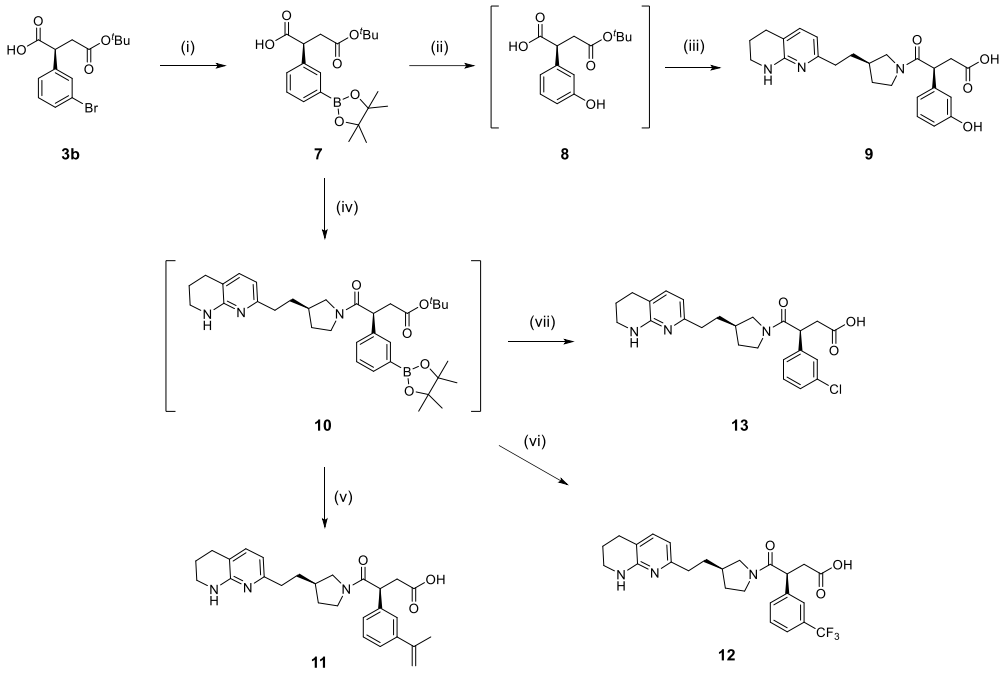
Inhibitors based on amide cores were prepared asymmetrically using Evans type chemistry as previously reported.[17] Commercially available arylacetic acids were converted to chiral oxazolidinones **1** and alkylated using *tert*-butyl bromoacetate to give oxazolidinones **2** in good diastereoselectivity (*d.r.* ≈10:1), with the major diastereoisomers isolated by normal phase flash chromatography. Hydrolysis afforded enantiopure acids **3** and coupling with an appropriate amine, such as pyrrolidine **4**,[18] afforded *tert*-butyl ester **5** which revealed the final acid **6** upon acidic deprotection (Scheme 1).



Scheme 1. General synthetic route towards amide-containing integrin inhibitors. Reagents and conditions: (i) PivCl, DIPEA, *n*-BuLi, THF, 0 → −78 °C, 45–82% yield; (ii) LiHMDS/NaHMDS, *tert*-butyl bromoacetate THF, −78 °C, 30–81% yield; (iii) LiOH, 30% (w/w) H_2O_2 in H_2O, THF, 0 °C, 35–84% yield; (iv) HATU, DIPEA, CH_2Cl_2; (v) TFA or 4 M HCl in 1,4-dioxane, CH_2Cl_2, 32–83% yield over 2 steps

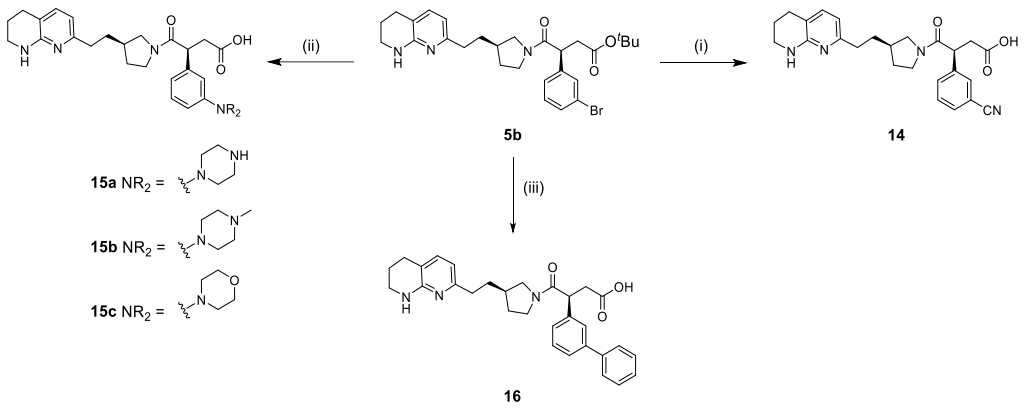
Where bromoarylacetic acids were used, metal-mediated modification of the C–Br bond allowed access to a wide range of analogues (Scheme 2). Miyaura borylation of aryl bromide **3b** gave boronate ester **7** in 87% yield which could be oxidised to the corresponding phenol **8** prior to amide coupling and deprotection to afford compound **9** in 28% yield over three steps. Boronate ester **7** was stable to amide coupling conditions, allowing formation of amide **10** which was used *in situ*; Suzuki–Miyaura cross-coupling of boronate **10** with 2-bromopropene gave compound **11** in

sufficient yield upon deprotection, whilst formation of α,α,α-trifluorotolyl **12** and chloride **13** was achieved using conditions reported by Hartwig *et al*.[19, 20]



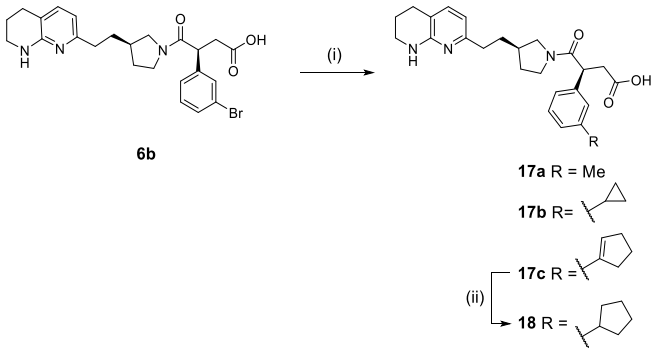
Scheme 2. Synthetic routes to compounds **9**, **11**, **12** and **13**. Reagents and conditions: (i) $Pd(dppf)Cl_2$, B_2Pin_2, KOAc, 1,4-dioxane, 90 °C, 87% yield (ii) 30% (w/w) H_2O_2 in H_2O, 2 M aq. NaOH, THF; (iii) Amine **4**, HATU, CH_2Cl_2 then TFA, CH_2Cl_2, 28% yield over 3 steps; (iv) Amine **4**, HATU, CH_2Cl_2; (v) $Pd(PPh_3)_4$, 2-bromopropene, aq. K_2CO_3, 1,4-dioxane, 80 °C then TFA, CH_2Cl_2, 5% yield over 3 steps; (vi) $(phen)CuCF_3$, KF, DMF, 50 °C then TFA, CH_2Cl_2, 23% yield over 3 steps; (vii) $CuCl_2$, 1:1 MeOH:H_2O, 90 °C, then TFA, CH_2Cl_2, 46% yield over 3 steps.

Aryl nitrile **14** was formed from bromide **5b** using a modified Rosenmund–von Braun reaction developed by Buchwald *et al.*[21] Buchwald–Hartwig aminations allowed for access to various aryl amines **15a–c** (Scheme 3). Suzuki–Miyaura cross-coupling between bromide **5b** and phenylboronic acid pinacol ester, followed by deprotection, afforded biphenyl **16** in 68% yield over two steps.



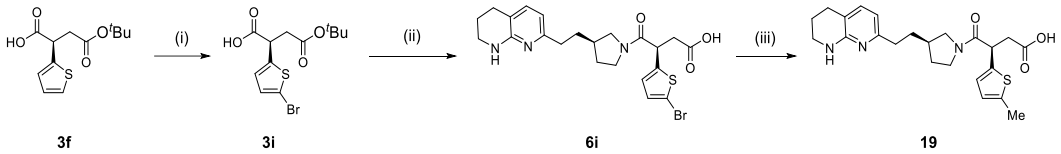
Scheme 3. Synthetic routes to aryl nitrile **14**, aryl amines **15a–c** and biphenyl **16**. Reagents and conditions: (i) CuI, KI, NaCN, DMEDA, toluene then TFA, CH_2Cl_2, 86% yield over 2 steps; (ii) amine, Cs_2CO_3, RuPhos Pd G3, 1,4-dioxane, 90 °C then TFA, CH_2Cl_2, 37–77% yield; (iii); phenylboronic acid pinacol ester, 2′-(dimethylamino)-2-biphenylyl-palladium(II) chloride dinorbornylphosphine complex, 2 M aq. NaOH, MeOH, 120 °C then TFA, CH_2Cl_2, 68% yield over 2 steps.

Suzuki–Miyaura cross-coupling of bromide **6b** with trimethyl boroxine, cyclopropylboronic acid and cyclopentene-1-boronic acid allowed access to compounds **17a–c**. Reduction of cyclopentene **17c** afforded sp^3-richer cyclopentane **18** (Scheme 4).



Scheme 4. Synthetic routes to compounds **17a–c and 18**. Reagents and conditions: (i) boronic acid/anhydride, 2′-(dimethylamino)-2-biphenylyl-palladium(II) chloride dinorbornylphosphine complex, 2 M aq. NaOH, MeOH, 120 °C, 3–39% yield (ii) H_2, Pd/C, MeOH, 6% yield over 2 steps.

Where 2-thiopheneacetic acid was applied in the general asymmetric alkylation process (Scheme 1), thiophene **3f** was regiospecifically brominated using *N*-bromosuccinimide to provide bromide **3i** in 70% yield (Scheme 5). Amide coupling and deprotection gave compound **6i** in 52% yield over two steps, which was cross-coupled with trimethylboroxine to provide methylthiophene **19.**

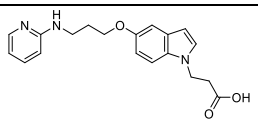
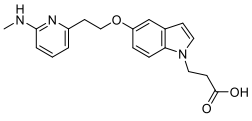


Scheme 5. Synthetic route to compound **19**. Reagents and conditions: (i) NBS, DMF, 70% yield; (ii) Amine **4**, HATU, DIPEA, CH_2Cl_2 then TFA, CH_2Cl_2, 62% yield over 2 steps; (iii) trimethylboroxine, Cs_2CO_3, XPhos Pd G4, 4:1 1,4-dioxane:water, 90 °C, 8% yield.

RESULTS AND DISCUSSION

Marugàn *et al*. previously disclosed indol-1-yl propionic acid **20** (Table 1) which was reported to show 200× selectivity for $\alpha_v\beta_5$ over $\alpha_v\beta_3$. Remarkably, it was also claimed that inversion of the basic aminopyridine moiety to afford compound **21** inverted selectivity towards $\alpha_v\beta_3$ as determined using an ELISA.[22] When resynthesised and tested in our fluorescence polarisation (FP) assays [see Supporting Information (SI)] no significant selectivity (<10×), or indeed inversion of selectivity, was observed. This discrepancy in assay data may be due to non-linearity of detection signals in ELISA which has been previously reported.[23] Although protocols have since been developed to overcome this issue,[24] ELISA equipment for retesting of these compounds was not available in-house.

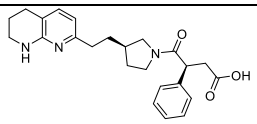
Table 1. ELISA and FP assay data for compounds **20** and **21**[a]

Compound	Structure	ELISA pIC_{50}[22]			FP pIC_{50}		
		$\alpha_v\beta_3$	$\alpha_v\beta_5$	Selectivity ($\alpha_v\beta_5$ vs $\alpha_v\beta_3$)	$\alpha_v\beta_3$	$\alpha_v\beta_5$	Selectivity ($\alpha_v\beta_5$ vs $\alpha_v\beta_3$)
20		6.3	8.6	200×	6.6	7.4	6×
21		7.3	6.7	−4×	7.4	8.0	4×

[a]The pIC_{50} is the negative log of the IC_{50}. Standard deviations and n numbers are detailed in the Supporting Information. FP = fluorescence polarisation

Of ≈4000 compounds from the GlaxoSmithKline library previously assessed against $\alpha_v\beta_5$, designed as part of historic α_v programmes,[18, 25] compound **6j** (Table 2) was selected for further investigation on account of the selectivity for $\alpha_v\beta_5$ over the other α_v integrins. High selectivity is seen over $\alpha_v\beta_1$ and $\alpha_v\beta_3$, with no potency detected for $\alpha_v\beta_6$ and $\alpha_v\beta_8$. Compound **6j** was originally synthesised as part of work for the purposes of stereochemical determination, although was not investigated further at the time.[17] This molecule was one of very few (≈5) in the library containing an amide moiety (usually the carbonyl is not present), which prompted suspicion that this moiety was significant for the selectivity profile seen; where an amine is present instead this profile is not seen. We sought to explore the role of the amide in this selectivity and means by which improved selectivity, potency and pharmacokinetic properties could be obtained by structural changes to this ligand.

Table 2. Integrin affinity profile of compound **6j** showing selectivity for $\alpha_v\beta_5$ as determined by the FP assay.

Compound	Structure	pIC_{50}					Selectivity ($\alpha_v\beta_5$ vs $\alpha_v\beta_3$)
		$\alpha_v\beta_1$	$\alpha_v\beta_3$	$\alpha_v\beta_5$	$\alpha_v\beta_6$	$\alpha_v\beta_8$	
6j		5.4	6.0	**8.4**	<4.1	<4.1	250×

see general footnotes in Table 1

Using the crystal structure of Cilengitide-bound $\alpha_v\beta_3$ (1L5G) as a template,[9] a homology model of $\alpha_v\beta_5$ was developed to try to elucidate the origin of this selectivity [See Supporting Information (SI) for further detail]. Human amino acid sequences for these proteins were aligned in MOE.[26] Due to the peculiar nature of the β_5 SDL region which is two amino acids longer than the β_3 SDL,[11] additional modelling was performed on this key region. The structure of this region was calculated by considering high-resolution chain fragments which superimpose well with the loops. Of the models generated, the solution with optimum contact energy was selected and a conformational analysis of the region was performed using the LowMode MD protocol in a vacuum using the MMFFX94 force field. The top ranked solution was then selected for use in the model which was imported into Schrödinger Maestro.[27] Binding of ligands in the active site of this homology model (or $\alpha_v\beta_3$ crystal structure) was modelled using Schrödinger Maestro and preferred poses were selected based on criteria of favourable ligand–protein interactions, ligand geometry and shape/surface complementarity with the receptor in question.

Two key interactions are known to be critical for the binding to the α_v integrin family: the salt-bridge interaction between the tetrahydronaphthyridine moiety and an Asp residue in the α_v region, and the interaction between the carboxylate and the metal ion-dependent adhesion site (MIDAS) of the β region.[9] Docking of compound **6j** into this homology model suggests that, with these

interactions in place, the combination of amide and linker geometry positions the aromatic ring within the SDL in a region that is less sterically confined in $\alpha_v\beta_5$ than $\alpha_v\beta_3$. The size and structure of this region in $\alpha_v\beta_5$ (cyan, Figure 1) is defined by a Tyr205 residue above the phenyl ring (as shown) and a Leu148 residue adjacent. In $\alpha_v\beta_3$ these are replaced by a Met122 residue and Tyr89 residue, defining a smaller region (orange, Figure 1). Binding of phenyl **6j** within $\alpha_v\beta_3$ requires reorientation of these residues incurring a significant energy cost. Indeed, the docking suggests that, in this pose, the phenyl ring cannot be accommodated in the SDL of $\alpha_v\beta_3$ due to prohibitive steric clashes with residues comprising the active site; an alternative binding pose is predicted for $\alpha_v\beta_3$ instead. Contortion of the central linker places the phenyl ring away from the SDL of $\alpha_v\beta_3$, thus becoming solvent exposed. Therefore, no interactions are made with the SDL region which could otherwise contribute positively to binding. Favourable contacts made in the SDL of $\alpha_v\beta_5$ but not $\alpha_v\beta_3$ likely contributes to selectivity. Based on the docking model, substitution around the phenyl ring is a possible means for eliciting greater selectivity for $\alpha_v\beta_5$ while maintaining activity. In this binding mode, *para* substituents may be expected clash with the active site of $\alpha_v\beta_5$ (as well as $\alpha_v\beta_3$), whereas *meta* substituents may not clash to the same extent.

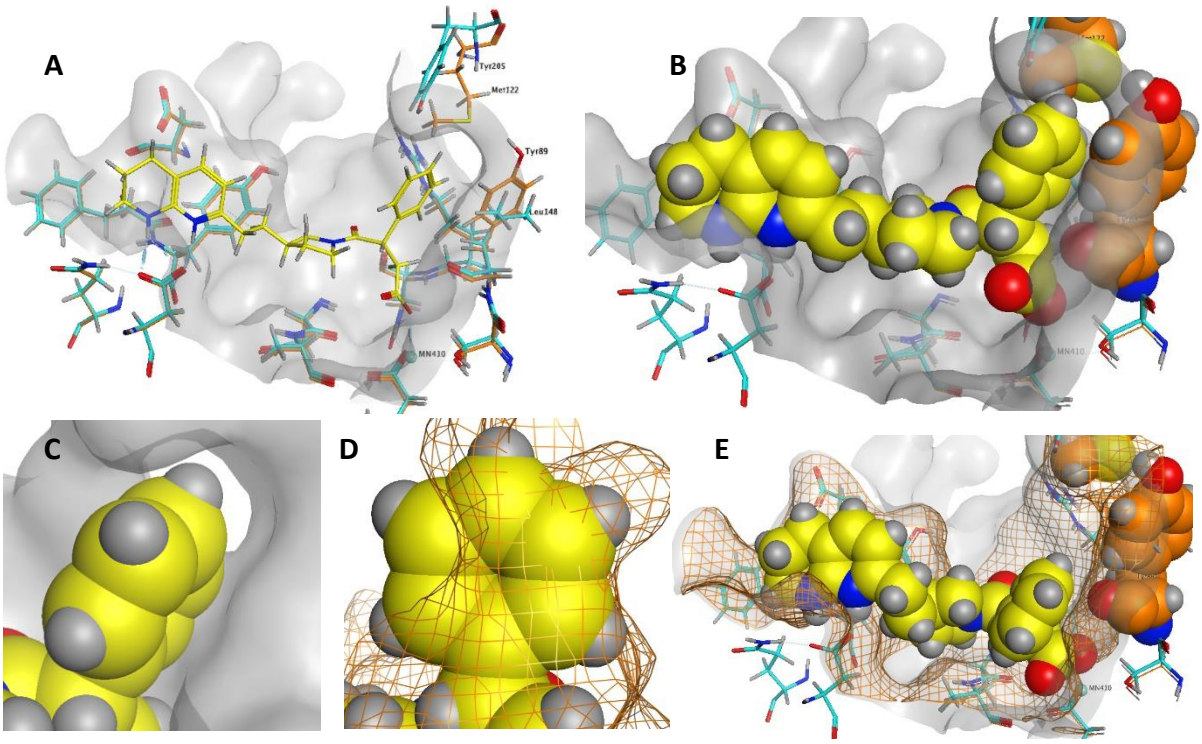


Figure 1. A: Docking of compound **6j** (yellow) in the $\alpha_v\beta_5$ homology model (cyan, grey surface) overlaid with the $\alpha_v\beta_3$ crystal structure (orange, orange surface), suggesting that differences in SDL structures are key for the observed selectivity. A larger region in $\alpha_v\beta_5$ defined by Tyr205 and Leu148 accommodates the phenyl ring; a smaller region in $\alpha_v\beta_3$ defined by Met122 and Tyr89 does not. **B:** A space filling model of binding showing that the phenyl ring occupies a less confined region in $\alpha_v\beta_5$ than $\alpha_v\beta_3$. **C:** Good complementarity between the phenyl ring of the ligand and SDL of $\alpha_v\beta_5$ is predicted. **D:** The phenyl ring clashes considerably with the surface of the $\alpha_v\beta_3$ site, preventing binding in this pose. **E:** Docking in the crystal structure of $\alpha_v\beta_3$ predicts an alternative binding pose whereby the phenyl ring is solvent exposed, removed protein–ligand clashes in the SDL, affording lower affinity.

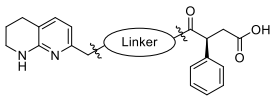
The relatively large size of the β_1-subunit and reasonable structural similarity to the β_3-subunit may enable a small degree of binding, although affinity is low.[7] The lack of a basic nitrogen in the central pyrrolidine linker likely contributes to the absence of potency at $\alpha_v\beta_6$. Docking models predict that, when protonated, a key hydrogen bond interaction is formed between the nitrogen cation and Thr238 upon binding. This may also be applicable to $\alpha_v\beta_8$ as small-molecule binding to this integrin correlates well with $\alpha_v\beta_6$, although selective small molecules and peptides have been

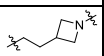
reported.[18, 28, 29] Ligand rigidity and conformation may also play a role although docking in a crystal structure of $\alpha_v\beta_6$ (4UM9;[30] see SI for more detail) reveals no clear reason for the observed low affinity.

Structure–Activity Relationships: Linker Structure.

While tetrahydro-1,8-naphthyridine moieties are generally the preferred replacement for Arg present in endogenous ligands due to the more favourable synthetic and biological properties such as enhanced permeability and absorption, linker structures, spanning the α/β interfacial G region can be more varied.[7] In order to assess the effects of varying the linker structure and distance between basic and acidic termini, alternative amide cores were first investigated (Table 3). Linear and azetidine linkers (**22**–**24**) were chosen as more and less conformationally flexible alternatives to the pyrrolidine core respectively. Piperidine linked **25** was investigated as a larger alternative as well. Modification of the acid is generally not tolerated and was not investigated.[18]

Table 3. Integrin affinity profile for compounds possessing varying linker structures as determined by the FP assay.[a]



Compound	Linker	pIC$_{50}$		Selectivity ($\alpha_v\beta_5$ vs $\alpha_v\beta_3$)
		$\alpha_v\beta_3$	$\alpha_v\beta_5$	
22		5.3	6.7	25×
23		5.5	7.6	125×
24		6.1	8.1	100×
6j		6.0	8.4	250×

25		5.2	6.3	13×

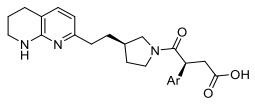
[a] Data for remaining α_v integrins, standard deviations and n numbers are detailed in the Supporting Information.

Linear, azetidine and piperidine cores are all detrimental to potency and selectivity *versus* the pyrrolidine core of the initial hit. Due to the binding constraints on the basic and acidic termini, the increased conformational flexibility of the linear, aliphatic linker (Compound **22**) lowers affinity as binding is less favoured entropically. The data also reveal a loss of potency and selectivity upon moving from the pyrrolidine to ethyl azetidine linker (compound **23**). This is potentially be due to the decreased linker length as key interactions may become sub-optimal upon truncating of the central linker. Homologation of this linker is actually detrimental to selectivity although greater potency is seen at $\alpha_v\beta_5$ (Compound **24**), perhaps suggesting that the longer linker may be more preorganised for binding to $\alpha_v\beta_5$. Upon moving to the larger piperidine linker (racemic at the piperidine) a substantial decrease in potency is seen. This is may be due to clashes with residues on the α/β interface in both $\alpha_v\beta_3$ and $\alpha_v\beta_5$. Historically, the (*S*)-pyrrolidine enantiomer has not been seen to be beneficial towards potency.[18] As such, the (*R*)-pyrrolidine core appears to represent the best combination of amide rigidity and ligand length/conformation for binding in the active site, yielding the greatest selectivity of the cores tested.

Structure–Activity Relationships: Substitution Pattern Around Phenyl Ring.

In order to ascertain if substitution around the phenyl ring is beneficial to potency and selectivity, *ortho*-, *meta*- and *para*-substituted bromide analogues **6a–c** were synthesised using the asymmetric route highlighted (Scheme 1) and profiled (Table 4). These analogues were selected due to the hydrophobic nature of the large bromine atom (allowing for probing of the steric and electronic properties of the SDL) and the possibility of modification of the C–Br bond, providing a synthetic handle for late-stage functionalisation.

Table 4. Integrin affinity profile for *ortho*- **6a,** *meta*- **6b** and *para*-aryl bromides **6c** as determined by the FP assay.



Compound	Ar	pIC_{50}		Selectivity ($\alpha_v\beta_5$ *vs* $\alpha v\beta_3$)
		$\alpha_v\beta_3$	$\alpha_v\beta_5$	
6a		4.9	5.9	10×
6b		6.1	8.4	200×
6c		5.9	8.2	200×

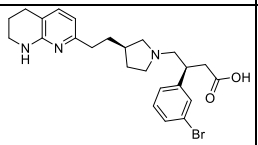
see general footnotes in Table 3

Ortho substitution gave both a lower selectivity and activity than the corresponding *meta*- and *para*-substituted analogues. *Para* and *meta* substitution gave equal selectivity by FP with *meta* bromide **6b** exhibiting slightly higher affinity. Due to this higher affinity, in combination with the docking model and literature reports (which both suggest that *meta* substitution is preferred to *para* substitution for selectivity),[31] *meta* substitution was selected for further investigation. As anticipated from the docking of **6j**, the docking model of **6b** (Figure 2, left) suggests that *meta* substituents clash considerably with Met122 of $\alpha_v\beta_3$, with *para* substituents clashing with Tyr89 of $\alpha_v\beta_3$, providing selectivity. Intriguingly, bromide **6b** and phenyl **6j** are equipotent at $\alpha_v\beta_5$, suggesting that multiple low energy binding conformations may be possible.

When the amide is exchanged for a less rigid amine (**26**, Table 5), a lower selectivity is observed. Docking suggests that the greater flexibility of the amine allows the ligand to adopt a conformation such that clashes with residues within the active site of $\alpha_v\beta_3$ are minimised, with positioning of the

aryl ring in the SDL possible (Figure 2, right). Potency at $\alpha_v\beta_6$ (and $\alpha_v\beta_8$) is also restored, as would be expected, as basicity of the pyrrolidine nitrogen is reintroduced [pIC_{50} = 8.1 ($\alpha_v\beta_6$); 8.0 ($\alpha_v\beta_8$)].

Table 5. Integrin affinity profile for amine **26** showing that conformational flexibility lowers selectivity for $\alpha_v\beta_5$ as determined by the FP assay.

Compound	Structure	pIC_{50}		Selectivity ($\alpha_v\beta_5$ *vs* $\alpha_v\beta_3$)
		$\alpha_v\beta_3$	$\alpha_v\beta_5$	
26[18]		8.0	8.4	2.5×

see general footnotes in Table 3

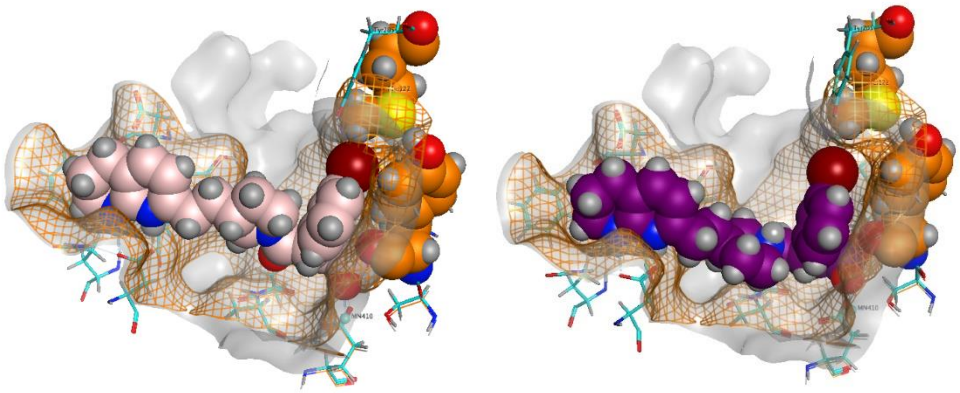


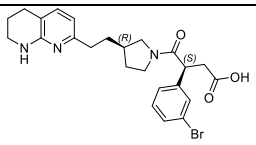
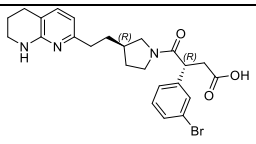
Figure 2. Docking of matched pair amide **6b** (pink, left) and amine **26** (dark magenta, right) in $\alpha_v\beta_5$ homology model (cyan, grey surface) overlaid with $\alpha_v\beta_3$ crystal structure (orange) suggesting that enhancing ligand flexibility allows for minimisation of clashes with residues in the SDL upon binding.

Structure–Activity Relationships: Preferred Stereochemistry.

Previous reports have determined that the (*R*, *S*) configuration is optimal for integrin binding across amine-based pan-α_v and $\alpha_v\beta_6$ targeting series.[17, 32] In order to confirm this to be consistent with this novel amide core, the (*R*, *R*) isomer **6d** was synthesised using the route outlined (Scheme 1), using the (*R*)-oxazolidinone. The presence of the opposite stereochemistry was supported by equal

and opposite specific rotation values for enantiomeric intermediates. As expected, the (*R*) configuration at the benzylic position resulted in a lower potency (Table 6), with 500-fold decrease in affinity observed for the less active isomer. Generally, the (*R*, *R*) epimer was inactive against the other α_v integrins suggesting that these ligands bind to the other integrins in similar conformations.

Table 6. Integrin binding profile for epimers **6b** and **6d**, as determined by the FP assay, showing that (*S*) stereochemistry at the benzylic positions is preferred for binding to $\alpha_v\beta_5$.

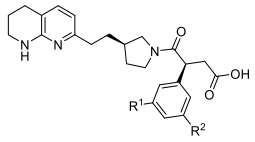
Compound	Structure	pIC_{50}		Selectivity ($\alpha_v\beta_5$ *vs* $\alpha_v\beta_3$)
		$\alpha_v\beta_3$	$\alpha v\beta_5$	
6b		6.1	8.4	200×
6d		5.0	5.7	5×

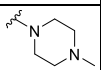
see general footnotes in Table 3

Structure–Activity Relationships: *meta* Substituent Structure.

In order to further probe the hypothesis that optimal space-filling of the aforementioned SDL cavity could allow greater selectivity to be attained, analogues of various sized *meta* substituents were prepared and tested (Table 7). The substituents were selected in order to assess a range of size and polarity, whilst remaining synthetically accessible.

Table 7. Integrin affinity profile for different *meta* substituted analogues as determined by the FP assay.



Compound	R^1	R^2	pIC_{50}		Selectivity ($\alpha_v\beta_5$ *vs* $\alpha_v\beta_3$)
			$\alpha_v\beta_3$	$\alpha_v\beta_5$	
6b			6.1	8.4	200×
6j			6.0	8.4	250×
9			6.8	8.4	40×
11			5.6	8.3	500×
12			5.3	8.2	800×
13			6.0	8.6	400×
14			6.3	8.5	160×
15a			5.8	7.8	100×
15b			5.9	8.0	125×
15c			5.7	7.9	160×
16			5.7	8.2	320×

17a			5.8	8.4	400×
17b			5.2	8.1	800×
17c			5.9	8.1	160×
18			5.6	7.9	200×
6e			5.8	8.3	320×
27			5.4	8.0	400×

see general footnotes in Table 3

Little variation was seen in binding affinities for $\alpha_v\beta_5$ (pIC_{50} 7.8–8.6) with a wide range of groups tolerated. This may suggest multiple low energy binding conformations are possible and that the rigid amide moiety is the overriding factor towards affinity (and selectivity); alternatively the physicochemical properties of the binding pocket may allow the accommodation of different chemical groups. Greater variation was observed in $\alpha_v\beta_3$ affinities (pIC_{50} 5.2–6.8). Smaller substituents such as a proton (phenyl **6j**) or hydroxy (compound **9**) reduce the impact of clashes of with residues within the active site of $\alpha_v\beta_3$, exhibiting greater affinities ($pIC_{50} \geq 6.0$) than larger groups such a cyclopropyl (compound **17b**) and cyclopentyl (compound **18**) moieties ($pIC_{50} \leq 5.6$).

Hydrophobic and hydrophilic groups are both tolerated in the SDL of $\alpha_v\beta_5$ as indicated by the equipotency of phenol **9** and bromide **6b**. Chloride **13** exhibits the greatest affinity for $\alpha_v\beta_5$ of all compounds tested, indicating this as the optimal substituent size for binding to this receptor; however, selectivity was sub-optimal (400×). Hydrophobic groups of intermittent size (larger than a methyl/chloride moiety, smaller than cyclopentyl moiety)[33] exhibit the greatest selectivity for

$\alpha_v\beta_5$. Isopropenyl **11**, trifluoromethyl **12** and cyclopropyl **17b** substituents all yield excellent affinities ($pIC_{50} \geq 8.1$) and selectivities (≥500×). Trifluorotolyl **12** and cyclopropyl **17b** exhibit near 1000x fold selectivity for $\alpha_v\beta_5$, with trifluorotolyl having slightly greater affinity for $\alpha_v\beta_5$. Docking suggests that the $-CF_3$ moiety of compound **12** fits well within the region of the $\alpha_v\beta_5$ SDL defined by Tyr205 and Leu148, while possessing ideal size and 3D characteristics (the larger but flatter biphenyl **16** is more active at $\alpha_v\beta_3$) for clashing considerably with the Met122 and Tyr89 residues of $\alpha_v\beta_3$, preventing binding (Figure 3). Significant distortion of the ligand and repositioning of the carboxylate moiety which may affect interaction with the MIDAS cation is predicted in the docking into $\alpha_v\beta_3$, accounting for the low affinity. It is also possible that the electron deficiency of the trifluorotolyl ring contributes to selectivity.

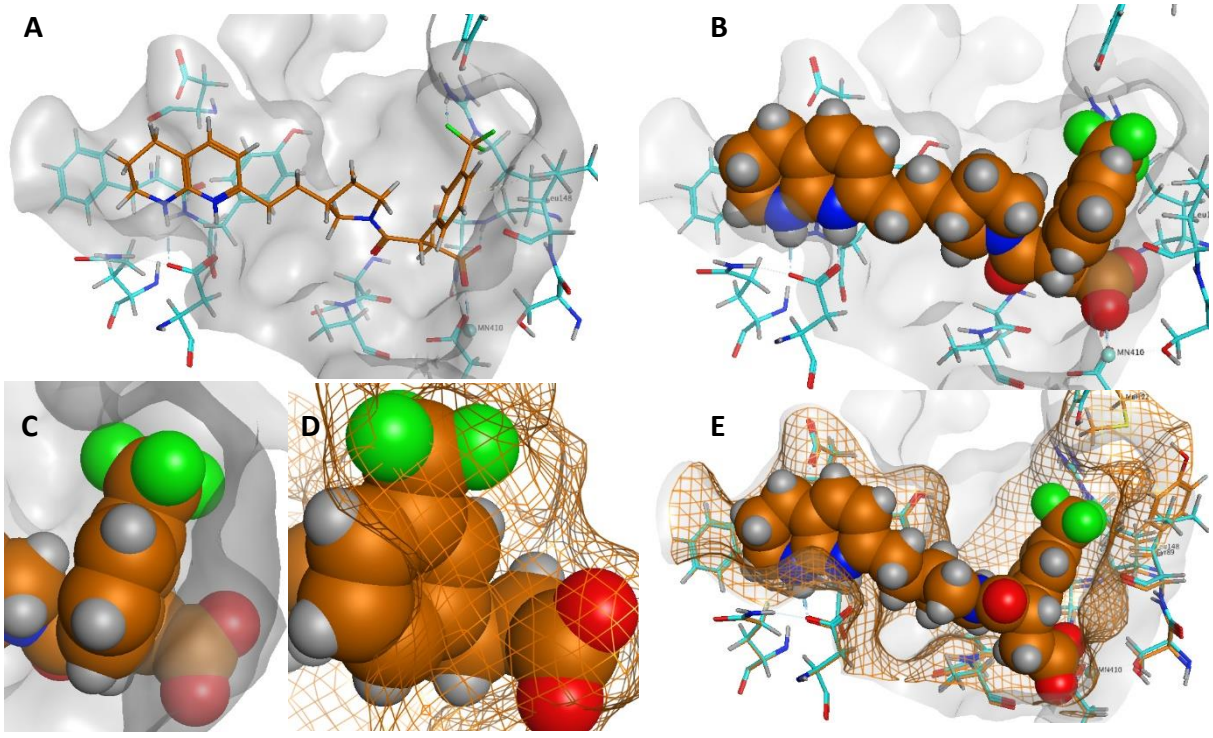


Figure 3. A: Docking of compound **12** (dark orange) in the $\alpha_v\beta_5$ homology model (cyan, grey surface). **B:** The –CF3 moiety is predicted to occupy the SDL of $\alpha_v\beta_5$ with good complementarity. **C:** A close-up view of the α,α,α-trifluorotoluene group in the SDL of $\alpha_v\beta_5$ showing a good size/shape complementarity. **D:** In this pose, the α,α,α-

trifluorotoluene group clashes considerably with the surface of the $\alpha_v\beta_3$ SDL, preventing binding. **E:** Docking in the crystal structure of $\alpha_v\beta_3$ predicts an alternative binding pose whereby the ligand is distorted and the carboxylate moiety is repositioned, accounting for the low affinity.

Although basic moieties are tolerated (**15a** and **15b**, Table 7), the selectivity of these derivatives is moderate (≤125×) and increases slightly as basicity of the non-aniline nitrogen atom is decreased.[34] Selectivity is further raised upon moving from piperazine to morpholine **15c**, although the trend may be due to assay variability. Where *meta* substituents are large, docking suggests that the aryl ring can rotate such that the *meta* proton occupies the SDL with the bulkier *meta* substituent becoming solvent exposed, avoiding ligand–protein clash. This binding pose may explain why the affinity of cyclopentene **17c** for $\alpha_v\beta_5$ (and $\alpha_v\beta_3$) is only slightly below that of phenyl **6j** (see SI for additional docking images).

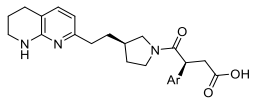
To prevent this potential rotation, 1,3,5-trisubstituted compounds **6e** and **27** were tested as increased substitution would ensure that ligand–protein clash would be unavoidable. Although this approach was successful in lowering $\alpha_v\beta_3$ affinity, (monobromide **6b** *versus* dibromide **6e**: pIC_{50} 6.1 *vs* 5.8; monomethyl **17a** *versus* dimethyl **27**: pIC_{50} 5.8 vs 5.4), $\alpha_v\beta_5$ affinity was also lessened, possibly due to clashes within the active site of $\alpha_v\beta_5$. This was more profound with the introduction of an additional methyl group. Dibromide **6e** was moderately more selective than monobromide **6b** whilst monomethyl **17a** and dimethyl **27** exhibited equal selectivity (400×). These data suggest that a single, hydrophobic *meta* substituent is preferred for $\alpha_v\beta_5$ affinity, with no definitive benefit for selectivity over $\alpha_v\beta_3$ achieved by introducing a second *meta* substituent.

Structure–Activity Relationships: Alternative Pendant Aryl Rings.

Various thiophene (a bioisostere of phenyl rings)[35] containing analogues were prepared and synthesised to explore if greater selectivity could be obtained using a more electron-rich aryl ring

with an alternative binding vector to the phenyl ring of **6j**. Replacement of phenylacetic acid derivatives in Scheme 1 with thiopheneacetic acid derivatives allowed investigation of the effect of replacing the phenyl ring in the SDL with a thiophene moiety (Table 8).

Table 8. Integrin affinity profile for thiophene-based antagonists **6f–i, 21, 28** (phenyl **6j** shown for reference) as determined by the FP assay.



Compound	Ar	pIC_{50}		Selectivity ($\alpha_v\beta_5$ *vs* $\alpha_v\beta_3$)
		$\alpha_v\beta_3$	$\alpha_v\beta_5$	
6j		6.0	8.4	250×
6f		6.1	8.3	160×
6g		6.3	8.4	125×
6h		6.5	8.5	100×
6i		6.7	8.0	20×
19		6.8	8.2	25×
28		6.2	8.5	200×

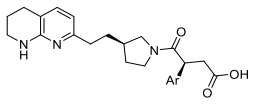
see general footnotes in Table 3

Both regioisomers of unsubstituted thiophene-containing inhibitors displayed moderate selectivity for $\alpha_v\beta_5$ (**6f** and **6g**); however, neither heteroaryl derivative offered a significant benefit over phenyl **6j** in terms of selectivity, suggesting that no additional beneficial interactions are elicited. Substitution around the thiophene generally lowered selectivity (compounds **6h**, **6i** and **19**) due to enhanced potency against $\alpha_v\beta_3$, indicating that the SAR cannot be directly transferred from the phenyl template to this thiophene template. Assay data suggest that the space-filling properties of 2,4-disubstituted thiophenes (**6h** and **28**) best mimic that of the 1,3-disubstitution pattern of the phenyl isostere, although this increased substitution was not particularly advantageous to selectivity. Due to this, and potential toxicity risks of unfused thiophenes, thiophene derivatives were not investigated further.

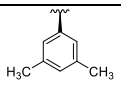
Cell Adhesion Assay Profile

Compounds exhibiting selectivity of ≥400× were further investigated by the lower-throughput cell adhesion assay using the myelogenous leukemia K562 cell line ($\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_8$, $\alpha_v\beta_8$; see SI for more details) or the human lung carcinoma epithelial cell line A549 ($\alpha_v\beta_1$) (Table 9), as previously described.[36-38] The pIC_{50} values generated measure the ability of the ligands to inhibit the binding of the endogenous peptide ligand to the integrin that is recombinantly expressed in the cell line.

Table 9. Integrin affinity profile of selected compounds further investigated using the cell adhesion assay.



Compound	Ar	pIC_{50}	
		$\alpha_v\beta_3$	$\alpha_v\beta_5$

11		<5	6.5
12		<5	6.1
13		5.2[a]	6.9
17a		5.2[b]	7.1
17b		<5	6.5
27		<5	6.3

see general footnotes in Table 3. [a]Tested <5 on two occasions; tested on four occasions; [b]Tested <5 on one occasion; tested on two occasions.

All compounds tested were able to inhibit binding $\alpha_v\beta_5$ to endogenous vitronectin in the cell adhesion assay with minimal-to-no detectable activity at $\alpha_v\beta_3$. Generally, a decrease in affinity was seen upon moving the cell adhesion assay which is not uncommon. A larger than expected decrease in affinity was observed for trifluorotolyl **12** with methyl **17a** exhibiting the greatest affinity and selectivity. Indeed, the $\alpha_v\beta_5$ potency of this compound may be underpredicted by the biochemical FP as the affinity for $\alpha_v\beta_5$ approaches the upper detectable limit of the assay. The reasons for this selectivity are expected to be the same as those discussed in the case of trifluorotolyl **12**. This assay format for $\alpha_v\beta_5$ has been previously reported to show a strong correlation to the true binding affinity (K_i) with an average +1.0 log increase from pIC_{50} to pK_i.[37] A lack of cytotoxicity is inferred by inactivity against the other α_v integrins as no indiscriminate effect on analogous cell lines was observed.

Physicochemical and *in vitro* Pharmacokinetic profile of Lead Compounds

Trifluorotolyl compound **12** exhibits the greatest selectivity by the FP assay of all compounds investigated with <10 nM affinity for $\alpha_v\beta_5$ and near 1000× fold over the closely related $\alpha_v\beta_3$; affinity for $\alpha_v\beta_1$ is similar to that of $\alpha_v\beta_3$ (pIC_{50} 5.6 *versus* 5.3 respectively) whilst affinity for $\alpha_v\beta_6$ and $\alpha_v\beta_8$ are <5 (Figure 4). Selective inhibition of $\alpha_v\beta_5$ was seen in the cell adhesion assay, although inhibition was more moderate than anticipated whereas methyl **17a** showed the greatest potency and selectivity by the cell adhesion assay.

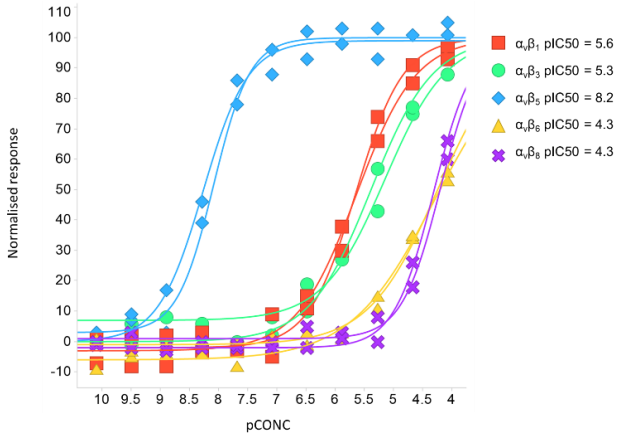


Figure 4. Dose response curves for compound **12** at all five α_v integrins.

A range of physicochemical (lipophilicity, solubility and permeability) and ADME (*in vitro* metabolism) properties of compounds **12** and **17a** were investigated (Table 10). Nitrile **14** was also profiled as a less hydrophobic alternative, thus encompassing a range of lipophilicities to assess the effect of varying this property on the stability of the amide-containing cores.

Table 10. Physicochemical and metabolic properties of $\alpha_v\beta_5$ selective inhibitors **12**, **14** and **17a**

Compound	ChromLogD	CAD solubility (µg/mL)	MDCK P_{exact} (nm/s)	*In Vitro* Clearance (mL/min/g tissue)		Well-Stirred Model CL_h (mL/min/kg)	
				Human	Rat	Human	Rat

				Mics / Heps	Mics / Heps	Mics / Heps	Mics / Heps
12	5.05	141	295	<0.40 / <0.45	<0.46 / 14.3	<6 / <7	<14 / 68
17a	4.16	142	176	<0.40 / <0.45	<0.46 / 3.2	<6 / <7	<14 / 46
14	3.69	192	57	<0.40 / <0.45	<0.46 / 1.4	<6 / <7	<14 / 30

Mic. = microsomes; Hep. = Hepatocytes

Compounds **12** shows high solubility and high MDCK passive permeability. Metabolic stability is observed in microsomes (human/rat) and human hepatocytes; however, high turnover is seen in rat hepatocytes. The hepatocyte *in vitro* clearance for human and rat were both scaled to an *in vivo* hepatic clearance (CL_h) using the non-restrictive well-stirred model.[39] Accordingly, the predicted CL_h for human and rat are <7 mL/min/kg (equivalent to <38% liver blood flow) and 68 mL/min/kg (equivalent to 87% liver blood flow) respectively. Given the high predicted CL_h in rat, compound **12** was not tested *in vivo.* Methyl **17a** similarly shows high solubility and passive permeability with lower rat hepatocyte turnover. Unsurprisingly, lowering of the ChromLogD correlates to greater *in vitro* stability and lower predicted *in vivo* hepatic clearance, as exemplified by nitrile **14** and tolyl **17a**.

CONCLUSION

In conclusion, a new amide-containing core has been identified as selective for $\alpha_v\beta_5$ over all other α_v integrins. SAR around this core has been extensively surveyed to determine ideal substitution patterns around the aromatic ring, configuration of stereogenic centres, linker structure, substituent size and substituent basicity/lipophilicity (Figure 5).

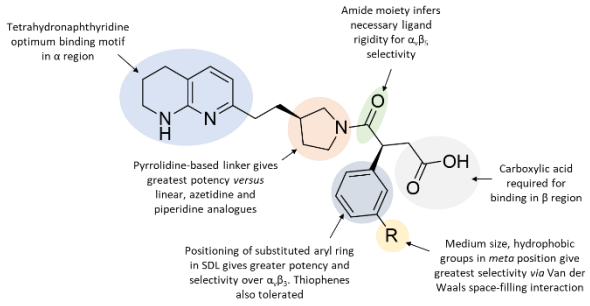


Figure 5. Summary of SAR around an $\alpha_v\beta_5$ selective core.

Trifluorotolyl **12** has been identified as highly selective for $\alpha_v\beta_5$ over the closely related $\alpha_v\beta_3$ (800×) by a biochemical fluorescence polarisation assay. This selectivity has been explained using computational modelling with a newly developed homology model . The steric properties of the –CF_3 moiety is ideal for binding within $\alpha_v\beta_5$ while eliciting considerable steric clashes within the active site of $\alpha_v\beta_3$. As such, docking into a crystal structure $\alpha_v\beta_3$ predicts an alternative pose, with distortion of the ligand and weaker interaction with the MIDAS cation contributing to the low affinity. Weak affinity is seen for $\alpha_v\beta_1$ due to the large size of the β_1-subunit and degree of structural similarity to β_3. The lack of a basic nitrogen in the central linker is proposed to infer selectivity over $\alpha_v\beta_6$ (and $\alpha_v\beta_8$); ligand conformation and rigidity may also play a role. Inhibition of $\alpha_v\beta_5$ has been determined using a cell adhesion assay. Methyl **17a** showed the greatest potency and selectivity by this assay, with potential underprediction of $\alpha_v\beta_5$ potency by the FP assay due to approaching the maximum detectable limit. Compounds **12** and **17a** possess favourable physicochemical and ADME properties for potential use as an *in vitro* $\alpha_v\beta_5$-selective tool compounds such as high solubility and permeability.[40]

EXPERIMENTAL SECTION

General Points

All reagents and solvents were obtained from commercial suppliers and were used without further purification. Reactions were stirred magnetically. Air- and moisture- sensitive reactions were performed using standard Schlenk manifold techniques. 'Room temperature' (rt) indicates temperatures in the range of 20–25 °C. Column chromatography was performed on disposable normal-phase and C18 reversed-phase RediSep Rf columns (12–220 g). Melting points were recorded using a BUCHI Melting Point M-565. Specific rotation measurements were obtained using an Anton Paar MCP 150 Modular Compact Polarimeter. Nuclear magnetic resonance spectra were recorded in the solvent stated, at 303 K unless otherwise stated, on Bruker NMR spectrometers (AVIII 400 MHz and AVIII 700 MHz). Spectra were referenced to the residual solvent peak. Chemical shifts (δ) are quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and NMR spectroscopy and 0.1 ppm for ^{13}C NMR spectroscopy. Coupling constants (*J*) are quoted in Hertz (Hz) to the nearest 0.1 Hz. 2D NMR spectra were obtained to confirm structures where necessary. Multiplicity is quoted as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), m (multiplet), br (broad). Infrared spectra were recorded using a Perkin Elmer FTIR Spectrometer in the range 4000–600 cm^{-1}. Liquid chromatography mass spectra (LC-MS) were recorded as follows: LC conditions: UPLC analysis was conducted on an Acquity UPLC CSH C18 column (50 mm × 2.1 mm i.d. 1.7 μm packing diameter) at 40 °C using the following methods:

1. 2 min HpH: The solvents employed were: A = 10 mM ammonium bicarbonate in water adjusted to pH 10 with ammonia solution, B = Acetonitrile. Gradient: 0.0–1.5 min: 0–97% B; 1.5–1.9 min: 97% B; 1.9–2.0 min: 97–0% B.

2. 2 min For: The solvents employed were: A = 0.1% v/v solution of formic acid in water, B = 0.1% v/v solution of formic acid in acetonitrile. Gradient: 0.0–1.5 min: 3–97% B; 1.5–1.9 min: 97% B; 1.9–2.0 min: 97–2% B.
3. 2 min TFA: The solvents employed were: A = 0.1% v/v solution of trifluoroacetic acid in water, B = 0.1% v/v solution of trifluoroacetic acid in acetonitrile. Gradient: 0.0–1.5 min: 5–95% B; 1.5–1.9 min: 95% B; 1.9–2.0 min: 95–5% B.

The UV detection was a summed signal from wavelength of 210 nm to 350 nm. MS: Waters QDA; ionisation mode: alternate-scan positive and negative electrospray; scan frequency: 5 Hz.

High resolution mass spectra (HRMS) were recorded using an Acquity UPLC CSH C18 column (LC) and Waters XEVO G2-XS QTof (ES+) (MS).

General Procedures

General procedure A for the formation of chiral oxazolidinones: To a stirred solution of arylacetic acid (1.0 eq.) in THF under nitrogen was added DIPEA (1.3 eq.) and the solution was cooled to 0 °C. To the solution was added PivCl (1.0 eq.) and after stirring for 1 h, the resulting suspension was cooled to −78 °C.

Simultaneously in a separate flask, a stirred solution of (*S*)-4-benzyloxazolidin-2-one/(*R*)-4-benzyloxazolidin-2-one (1.5 eq.) in THF under nitrogen was cooled to −78 °C and *n*-BuLi (1.6 eq.) was added dropwise. After stirring for 45 min, the metalated oxazolidinone was transferred to the mixed anhydride *via* cannula.

After full consumption of starting material, the reaction was quenched by addition of sat. NH_4Cl. The phases were separated and the aqueous phase was extracted using ethyl acetate (2x). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by automated flash chromatography to afford the title compound.

General procedure B for asymmetric alkylations: A stirred solution of oxazolidinone **1a–h** (1.0 eq.) in THF under nitrogen was cooled to −78 °C and to this, was added a solution of base (LiHMDS/NaHMDS) (1.1–1.5 eq.) in THF (1 M) dropwise. After stirring for 1 h, *tert*-butyl bromoacetate (3.0 eq.) was added dropwise and the reaction was allowed to warm to rt overnight with stirring. The reaction was quenched with sat. NH_4Cl and the phases were separated. The aqueous phase was extracted using ethyl acetate (2x). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by automated flash chromatography to afford the title compound.

General procedure C for hydroperoxide mediated hydrolysis: A suspension of oxazolidinone **2a–h** (1.0 eq.) in THF at 0 °C was treated with hydrogen peroxide solution (30 wt.% in water) (4.0 eq.) and 1 M aq. LiOH (3.0 eq.) (sequentially or as a pre-prepared solution). After complete consumption of starting material, sat. sodium metabisulfite (sat. sodium thiosulphate was also used interchangeably) was added. After stirring for 15 min, the mixture was acidified with 2 M HCl and extracted using ethyl acetate (3x). The combined organics were washed with brine, passed through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by automated flash chromatography to afford the title compound.

General procedure D for tandem amide coupling and deprotection: To a solution of acid **3a–i** (1.0 eq.) in DCM was added DIPEA (1.5–11.1 eq.) and HATU (1.2–1.5 eq.). After stirring for 15 min, a solution of amine (1.2–1.9 eq.) in DCM was added. After complete consumption of starting material, the reaction mixture was concentrated to ~1–3 mL and to the residue was added acid [TFA or HCl (4 M in 1,4-dioxane)]. After complete consumption of starting material, the reaction was concentrated *in vacuo* and the residue was purified by prep-HPLC to afford the title compound.

General Procedure E for tandem Buchwald–Hartwig amination and deprotection: A flask was charged with *tert*-butyl ester **5b** (1.0 eq.), RuPhos Pd G3 (0.15 eq.), cesium carbonate (4.0 eq.), amine (if solid; 8.0 eq.) and was purged with nitrogen. To this was added 1,4-dioxane (5 mL) and amine (if liquid, 5.3–6.0 eq.) and the reaction was stirred at 90 °C overnight. The reaction was cooled to rt, filtered through celite eluting with ethyl acetate and the filtrate was concentrated *in vacuo*.

The residue was dissolved in DCM (3 mL) and to this, was added TFA (3 mL). After complete consumption of starting material, the reaction was concentrated *in vacuo* and the residue was co-concentrated with DCM ($CHCl_3$ was used interchangeably) (2 x 10 mL). The residue was purified by prep-HPLC to afford the title compound.

General Procedure F for Suzuki–Miyaura cross-couplings using 2'-(dimethylamino)-2-biphenylyl-palladium(II) chloride dinorbornylphosphine complex: A microwave vial was charged with aryl bromide (1.0 eq.), 2'-(dimethylamino)-2-biphenylyl-palladium(II) chloride dinorbornylphosphine complex (0.1 eq.), boronic acid/ester (1–1.5 eq.), 2 M NaOH (0.5–0.6 eq.) and methanol and the reaction was stirred at 120 °C for 0.5–4 h under microwave irradiation. The reaction was filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford the title compound.

General Procedure G for Suzuki–Miyaura cross-couplings using XPhos Pd G4: A flask was charged with aryl bromide (1.0 eq.), XPhos Pd G4 (0.2 eq.), boronic acid (5.0 eq.) and cesium carbonate (3.0 eq.) and was purged with nitrogen. To this, was added 1,4-dioxane (4–8 mL) and water (1–2 mL) and the reaction was stirred at 90 °C for 4–16 h. After this time, the reaction was filtered through celite eluting with ethyl acetate and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford the title compound.

Compound Synthesis and Characterisation

(*S*)-4-Benzyl-3-(2-(2-bromophenyl)acetyl)oxazolidin-2-one 1a: Prepared according to General Procedure A using 2-(2-bromophenyl)acetic acid (1.29 g, 6.00 mmol, 1.0 eq.) in THF (15 mL) and (*S*)-4-benzyloxazolidin-2-one (1.5 eq.) in THF (20 mL). Flash chromatography on silica (0–100% TBME in cyclohexane) afforded the title compound (1.59 g, 4.25 mmol, 71% yield) as a colourless gum. $[\alpha]_D^{20}$ (*c* = 1.05, MeOH): +17; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.38–7.26 (m, 5H), 7.25–7.18 (m, 3H), 4.73 (ddt, *J* = 9.7, 7.4, 3.2 Hz, 1H), 4.57–4.36 (m, 2H), 4.32–4.18 (m, 2H), 3.37 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.82 (dd, *J* = 13.3, 9.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.9, 153.5, 135.2, 134.1, 132.8, 131.8, 129.4, 129.0, 128.9, 127.6, 127.3, 125.3, 66.4, 55.4, 43.1, 37.8; IR (neat): 1776, 1702 cm^{-1}; LC-MS (HpH): 1.27 min (372, 374) ($[M-H]^-$, 97%); HRMS: calculated for $C_{18}H_{17}{}^{79}BrNO_3^+$ ($[M+H]^+$) 374.0386, found 374.0403.

(*S*)-4-Benzyl-3-(2-(3-bromophenyl)acetyl)oxazolidin-2-one 1b: Prepared according to General Procedure A using 2-(3-bromophenyl)acetic acid (1.51 g, 7.02 mmol, 1.0 eq) in THF (15 mL) and (*S*)-4-benzyloxazolidin-2-one (1.5 eq.) in THF (20 mL). Flash chromatography on silica (0–100% TBME in cyclohexane) afforded the title compound (2.12 g, 5.66 mmol, 81% yield) as a white solid. Mp: 105–106 °C; $[\alpha]_D^{20}$ (*c* = 1.21, MeOH): +36; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (t, *J* = 1.7 Hz, 1H), 7.45 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.35–7.27 (m, 4H), 7.26–7.20 (m, 1H), 7.18–7.13 (m, 2H), 4.70 (ddt, *J* = 9.3, 7.2, 3.5 Hz, 1H), 4.37–4.14 (m, 4H), 3.28 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.5, 153.3, 135.7, 135.0, 132.8, 130.4, 130.1, 129.4, 129.0, 128.5, 127.4, 122.6, 66.2, 55.3, 41.1, 37.8; IR (neat): 2921, 1779, 1698 cm^{-1}; LC-MS (HpH): 1.29 min (372, 374) ($[M-H]^-$, 100%); HRMS: calculated for $C_{18}H_{17}{}^{79}BrNO_3^+$ ($[M+H]^+$) 374.0386, found 374.0390.

(*S*)-4-Benzyl-3-(2-(4-bromophenyl)acetyl)oxazolidin-2-one 1c: Prepared according to General Procedure A using 2-(4-bromophenyl)acetic acid (1.29 g, 6.00 mmol, 1.0 eq.) in THF (15 mL) and (*S*)-4-benzyloxazolidin-2-one (1.5 eq.) in THF (20 mL). Flash chromatography on silica (0–100% TBME in cyclohexane) afforded the title compound (1.43 g, 3.82 mmol, 64% yield) as an off-white solid. Mp: 100–102 °C; $[\alpha]_D^{20}$ (*c* = 0.76, MeOH): +11; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51–7.46 (m, 2H), 7.34–7.27 (m, 3H), 7.26–7.21 (m, 2H), 7.17–7.12 (m, 2H), 4.73–4.65 (m, 1H), 4.35–4.16 (m, 4H), 3.27 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.78 (dd, *J* = 13.4, 9.4, Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.6, 153.3, 135.0, 132.5, 131.7, 131.5, 129.4, 129.0, 127.4, 121.4, 66.2, 55.3, 41.0, 37.8; IR (neat): 1775, 1697 cm^{-1}; LC-MS (HpH): 1.30 min (372, 374) ($[M-H]^-$, 90%); HRMS: calculated for $C_{18}H_{17}{}^{79}BrNO_3^+$ ($[M+H]^+$) 374.0386, found 374.0387.

(*R*)-4-Benzyl-3-(2-(3-bromophenyl)acetyl)oxazolidin-2-one 1d: Prepared according to General Procedure A using 2-(3-bromophenyl)acetic acid (430 mg, 2.00 mmol, 1.0 eq.) in THF (5 mL) and (*R*)-4-benzyloxazolidin-2-one (1.5 eq.) in THF (6.5 mL). Flash chromatography on silica (0–40% ethyl acetate in cyclohexane) afforded the title compound (460 mg, 1.23 mmol, 62% yield) as a white solid. $[\alpha]_D^{20}$ (*c* = 1.92, MeOH): −36. Remaining analytical data are consistent with enantiomer.

(*S*)-4-Benzyl-3-(2-(3,5-dibromophenyl)acetyl)oxazolidin-2-one 1e: Prepared according to General Procedure A using 2-(3,5-dibromophenyl)acetic acid (7.99 g, 35.5 mmol, 1.0 eq.) in THF (60 mL) and (*S*)-4-benzyloxazolidin-2-one (1.5 eq.) in THF (60 mL). Flash chromatography on silica (0–40% ethyl acetate in cyclohexane) afforded the title compound (5.50 g, 12.14 mmol, 45% yield) as a yellow oil. $[\alpha]_D^{20}$ (*c* = 1.06, MeOH): +55; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (t, *J* = 1.7 Hz, 1H), 7.45 (d, *J* = 1.7 Hz, 2H), 7.37–7.27 (m, 3H), 7.18–7.13 (m, 2H), 4.70 (ddt, *J* = 9.3, 7.2, 3.5 Hz, 1H), 4.33–4.17 (m, 4H), 3.28 (dd, *J* = 13.2, 3.4 Hz, 1H), 2.80 (dd, *J* = 13.7, 9.3 Hz,

1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.8, 153.3, 137.2, 134.8, 133.0, 131.7, 129.3, 129.0, 127.4, 122.9, 66.3, 55.3, 40.7, 37.8; IR (neat): 1773, 1697 cm^{-1}; LC-MS (For): 1.40 min (450, 452, 454) ($[M-H]^-$, 90%); HRMS: calculated for $C_{18}H_{16}{}^{79}Br_2NO_3^+$ ($[M+H]^+$) 451.9491, found 451.9506.

(*S*)-4-Benzyl-3-(2-(thiophen-2-yl)acetyl)oxazolidin-2-one 1f: Prepared according to General Procedure A using 2-(thiophen-2-yl)acetic acid (853 mg, 6.00 mmol, 1.0 eq.) in THF (25 mL) and (*S*)-4-benzyloxazolidin-2-one (1.5 eq.) in THF (30 mL). Flash chromatography on silica (0–50% ethyl acetate in cyclohexane) afforded the title compound (1.47 g, 4.88 mmol, 81% yield) as a yellow oil. $[\alpha]_D^{20}$ (*c* = 0.53, MeOH): +114; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.25 (m, 4H), 7.20–7.13 (m, 2H), 7.07–6.98 (m, 2H), 4.75–4.67 (m, 1H), 4.64–4.45 (m, 2H), 4.28–4.18 (m, 2H), 3.30 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.80 (dd, *J* = 13.4, 9.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.0, 153.3, 135.0, 134.4, 129.4, 129.0, 127.5, 127.4, 126.8, 125.4, 66.3, 55.3, 37.7, 36.0; IR (neat): 1774, 1698 cm^{-1}; LC-MS (HpH): 1.15 min (302) ($[M+H]^+$, 100%); HRMS: calculated for $C_{16}H_{16}NO_3S^+$ ($[M+H]^+$) 302.0845, found 302.0852.

(*S*)-4-Benzyl-3-(2-(thiophen-3-yl)acetyl)oxazolidin-2-one 1g: Prepared according to General Procedure A using 2-(thiophen-3-yl)acetic acid (853 mg, 6.00 mmol, 1.0 eq.) in THF (25 mL) and (*S*)-4-benzyloxazolidin-2-one (1.5 eq.) in THF (30 mL). Flash chromatography on silica (0–30% ethyl acetate in cyclohexane) afforded the title compound (1.49 g, 4.94 mmol, 82% yield) as a yellow oil. $[\alpha]_D^{20}$ (*c* = 0.53, MeOH): +95; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.25 (m, 5H), 7.17–7.10 (m, 3H), 4.70 (ddt, *J* = 9.3, 7.2, 3.4 Hz, 1H), 4.44–4.16 (m, 4H), 3.27 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.6, 153.3, 135.1, 133.0, 129.4, 129.0, 128.8, 127.4, 125.6, 123.7, 66.1, 55.3, 37.7, 36.4; IR (neat): 1777, 1698 cm^{-1};

LC-MS (For): 1.14 min (302) ([M+H]$^+$, 93%); HRMS: calculated for $C_{16}H_{15}NNaO_3S^+$ ([M+Na]$^+$) 324.0665, found 324.0672.

(*S*)-4-Benzyl-3-(2-(4-bromothiophen-2-yl)acetyl)oxazolidin-2-one 1h:

Prepared according to General Procedure A using 2-(4-bromothiophen-2-yl)acetic acid (3.70 g, 16.7 mmol, 1.0 eq.) in THF (30 mL) and (*S*)-4-benzyloxazolidin-2-one (1.5 eq.) in THF (35 mL). Flash chromatography on silica (0–50% ethyl acetate in cyclohexane) afforded the title compound (3.81 g, 10.0 mmol, 60% yield) as a yellow oil. $[\alpha]_D^{20}$ (*c* = 0.93, MeOH): +95; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.28 (m, 3H), 7.21–7.13 (m, 3H), 6.97 (s, 1H), 4.78–4.64 (m, 1H), 4.58–4.39 (m, 2H), 4.29–4.19 (m, 2H), 3.29 (dd, *J* = 13.2, 3.4 Hz, 1H), 2.81 (dd, *J* = 13.2, 9.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.3, 153.3, 135.9, 134.8, 130.1, 129.4, 129.0, 127.5, 122.8, 109.3, 66.4, 55.3, 37.7, 35.9; IR (neat): 1777, 1699 cm^{-1}; LC-MS (HpH): 1.30 min (378, 380) ([M+H]$^+$, 99%); HRMS: calculated for $C_{16}H_{14}{}^{79}BrNNaO_3S^+$ ([M+Na]$^+$) 401.9770, found 401.9768.

***tert*-Butyl (*S*)-4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(2-bromophenyl)-4-oxobutanoate 2a:**

Prepared according to General Procedure B using **1a** (1.31 g, 3.50 mmol, 1.0 eq.) in THF (15 mL) and LiHMDS (1.2 eq.). Flash chromatography on silica (0–100% TBME in cyclohexane) afforded the title compound (733 mg, 1.50 mmol, 43% yield) as a colourless gum. $[\alpha]_D^{20}$ (*c* = 0.75, MeOH): +53; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.40–7.33 (m, 2H), 7.31–7.26 (m, 3H), 7.25–7.09 (m, 3H), 5.68 (dd, *J* = 11.0, 4.3 Hz, 1H), 4.75–4.66 (m, 1H), 4.18–4.05 (m, 2H), 3.39 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.02 (dd, *J* = 16.9, 11.0 Hz, 1H), 2.85 (dd, *J* = 13.4, 9.8 Hz, 1H), 2.73 (dd, *J* = 16.9, 4.4 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.5 170.6, 152.3, 137.1, 135.5, 133.6, 129.5, 129.0, 128.8, 127.7, 127.6, 127.3, 125.1, 81.0, 65.9, 55.7, 46.3, 38.1, 37.6, 28.1; IR (neat): 1785, 1726, 1699 cm^{-1}; LC-MS (HpH): 1.48 min (486, 488) ([M−H]$^-$, 98%); HRMS: calculated for $C_{24}H_{26}{}^{79}BrNNaO_5^+$ ([M+Na]$^+$) 510.0887, found 510.0904.

***tert*-butyl (*S*)-4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromophenyl)-4-oxobutanoate 2b:** Prepared according to General Procedure B using **1b** (1.89, 5.05 mmol, 1.0 eq.) in THF (40 mL) and NaHMDS (1.5 eq.). Flash chromatography on silica (0–30% ethyl acetate in cyclohexane) afforded the title compound (1.71 g, 3.50 mmol, 69% yield) as a colourless gum. $[\alpha]_D^{20}$ (*c* = 0.40, MeOH): +43; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (t, *J* = 1.8 Hz, 1H), 7.40 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.38–7.33 (m, 3H), 7.31–7.26 (m, 3H), 7.22–7.16 (m, 1H), 5.46 (dd, *J* = 11.1, 4.4 Hz, 1H), 4.67–4.57 (m, 1H), 4.15–4.04 (m, 2H), 3.38 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.27 (dd, *J* = 16.9, 11.1 Hz, 1H), 2.81 (dd, *J* = 13.4, 10.0 Hz, 1H), 2.61 (dd, *J* = 16.9, 4.4 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.7, 170.6, 152.7, 139.3, 135.5, 131.4, 130.9, 130.3, 129.5, 129.0, 127.5, 127.3, 122.7, 81.2, 65.8, 55.8, 44.5, 40.1, 37.5, 28.1; IR (neat): 1782, 1726, 1697 cm^{-1}; LC-MS (For): 1.48 min (510, 512) ([M+Na]$^+$, 100%); HRMS: calculated for $C_{24}H_{26}{}^{79}BrNNaO_5^+$ ([M+Na]$^+$) 510.0887, found 510.0894.

***tert*-Butyl (*S*)-4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(4-bromophenyl)-4-oxobutanoate 2c:** Prepared according to General Procedure B using **1c** (1.40 g, 3.74 mmol, 1.0 eq.) in THF (10 mL) and LiHMDS (1.1 eq.). Flash chromatography on silica (0–100% ethyl acetate in cyclohexane) afforded the title compound (1.46 g, 2.99 mmol, 80% yield) as a colourless gum. $[\alpha]_D^{20}$ (*c* = 1.89, MeOH): +30; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47–7.41 (m, 2H), 7.38–7.32 (m, 2H), 7.31–7.25 (m, 5H), 5.45 (dd, *J* = 11.1, 4.5 Hz, 1H), 4.63–4.56 (m, 1H), 4.14–4.08 (m, 1H), 4.08–4.02 (m, 1H), 3.36 (dd, *J* = 13.4, 3.4 Hz, 1H), 3.26 (dd, *J* = 17.0, 11.1 Hz, 1H), 2.81 (dd, *J* = 13.4, 9.8 Hz, 1H), 2.60 (dd, *J* = 17.0, 4.5 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.9, 170.6, 152.7, 136.1, 135.5, 131.9, 130.3, 129.5, 128.9, 127.3, 121.7, 81.1, 65.8, 55.7, 44.3, 39.9, 37.5, 28.0; IR (neat): 1782, 1726, 1607 cm^{-1}; LC-MS: 1.52 min (486, 488) ([M−H]$^-$, 86%); HRMS: calculated for $C_{24}H_{26}{}^{79}BrNNaO_5^+$ ([M+Na]$^+$) 510.0887, found 510.0895.

***tert*-Butyl (*R*)-4-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromophenyl)-4-oxobutanoate 2d:** Prepared according to General Procedure B using **1d** (990 mg, 2.65 mmol, 1.0 eq.) in THF (10 mL) and LiHMDS (1.2 eq.). Flash chromatography on silica (0–30% ethyl acetate in cyclohexane) afforded the title compound (534 mg, 1.09 mmol, 41% yield) as a colourless gum. $[\alpha]_D^{20}$ (*c* = 2.23, MeOH): −43. Remaining analytical data are consistent with enantiomer.

***tert*-Butyl (*S*)-4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3,5-dibromophenyl)-4-oxobutanoate 2e:** Prepared according to General Procedure B using **1e** (5.30 g, 11.7 mmol, 1.0 eq.) in THF (50 mL) and NaHMDS (1.5 eq.). Flash chromatography on silica (0–30% ethyl acetate in cyclohexane) afforded the title compound (3.84 g, 6.77 mmol, 58% yield) as an orange oil. $[\alpha]_D^{20}$ (*c* = 0.98, MeOH): +102; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.57 (m, 1H), 7.50 (d, *J* = 2.0 Hz, 2H), 7.39–7.27 (m, 5H), 5.42 (dd, *J* = 11.2, 4.5 Hz, 1H), 4.69–4.59 (m, 1H), 4.20–4.06 (m, 2H), 3.37 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.29–3.19 (m, 1H), 2.80 (dd, *J* = 13.2, 9.8 Hz, 1H), 2.60 (dd, *J* = 16.9, 4.6 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 170.3, 152.7, 140.8, 135.4, 133.5, 130.4, 129.5, 129.0, 127.3, 123.2, 81.4, 65.9, 55.7, 44.2, 40.0, 37.5, 28.1; IR (neat): 1781, 1725, 1696 cm^{-1}; LC-MS (HpH): 588, 590, 592 ($[M+Na]^+$, 99%) HRMS: calculated for $C_{24}H_{26}{}^{79}Br_2NO_5^+$ ($[M+H]^+$) 566.0172, found 566.0181.

***tert*-Butyl (R)-4-((S)-4-benzyl-2-oxooxazolidin-3-yl)-4-oxo-3-(thiophen-2-yl)butanoate 2f:** Prepared according to General Procedure B using **1f** (9.54 g, 31.7 mmol, 1.0 eq.) in THF (100 mL) and NaHMDS (1.5 eq.). Flash chromatography on silica (0–25% ethyl acetate in cyclohexane) afforded the title compound (7.65 g, 18.4 mmol, 58% yield) as a yellow gum. $[\alpha]_D^{20}$ (*c* = 0.58, MeOH): +31; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.31 (m, 2H), 7.30–7.25 (m, 3H), 7.24–7.21 (m, 1H), 7.09–7.05 (m, 1H), 6.96–6.92 (m, 1H), 5.86 (dd, *J* = 11.5, 4.2 Hz, 1H), 4.62 (ddt, *J* = 10.1, 7.2, 2.8 Hz, 1H), 4.17–4.07 (m, 2H), 3.43–3.34 (m, 2H), 2.84–2.71 (m, 2H), 1.45 (s, 9H);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.6, 170.5, 152.9, 139.2, 135.6, 129.5, 129.0, 127.3, 126.8, 126.5, 125.3, 81.2, 65.9, 55.8, 40.4, 40.0, 37.6, 28.1; IR (neat): 1782, 1727, 1698 cm^{-1}; LC-MS (For); 1.38 min (438) ($[M+Na]^+$, 97%); HRMS: calculated for $C_{22}H_{25}NNaO_5S^+$ ($[M+Na]^+$) 438.1346, found 438.1357.

***tert*-Butyl (*S*)-4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-oxo-3-(thiophen-3-yl)butanoate 2g:** Prepared according to General Procedure B using **1g** (1.45 g, 4.81 mmol, 1.0 eq.) in THF (25 mL) and NaHMDS (1.5 eq.). Flash chromatography on silica (0–25% ethyl acetate in cyclohexane) afforded the title compound (1.61 g, 3.87 mmol, 81% yield) as a yellow gum. $[\alpha]_D^{20}$ (c = 1.33, MeOH): +95; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.32 (m, 2H), 7.30–7.25 (m, 5H), 7.13–7.10 (m, 1H), 5.66 (dd, J = 11.2, 4.4 Hz, 1H), 4.60 (ddt, J = 10.1, 7.2, 3.1 Hz, 1H), 4.14–4.04 (m, 2H), 3.43–3.27 (m, 2H), 2.80 (dd, J = 13.2, 9.8 Hz, 1H), 2.65 (dd, J = 16.6, 4.4 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.1, 170.8, 152.8, 137.1, 135.6, 129.5, 128.9, 127.2, 125.8 (2C), 123.3, 81.0, 65.8, 55.7, 40.3, 39.4, 37.6, 28.1 (3C); IR (neat): 1778, 1724, 1695 cm^{-1}; LC-MS (For): 1.37 min (438) ($[M+Na]^+$, 99%); HRMS: calculated for $C_{22}H_{25}NNaO_5S^+$ ($[M+Na]^+$) 438.1346, found 438.1352.

***tert*-Butyl (*R*)-4-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(4-bromothiophen-2-yl)-4-oxobutanoate 2h:** Prepared according to General Procedure B using **1h** (3.76 g, 9.89 mmol, 1.0 eq.) in THF (50 mL) and NaHMDS (1.4 eq.). Flash chromatography on silica (0–30% ethyl acetate in cyclohexane) afforded the title compound (1.44 g, 2.91 mmol, 30% yield) as an orange/brown amorphous solid. $[\alpha]_D^{20}$ (c = 0.64, MeOH): +78; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.32 (m, 2H), 7.32–7.27 (m, 3H), 7.13 (d, J = 1.5 Hz, 1H), 6.99 (d, J = 1.5 Hz, 1H), 5.80 (dd, J = 11.2, 4.4 Hz, 1H), 4.63 (ddt, J = 10.0, 6.7, 3.4 Hz, 1H), 4.19–4.10 (m, 2H), 3.42–3.29 (m, 2H), 2.79 (dd, J = 13.4, 10.0 Hz, 1H), 2.73 (dd, J = 16.6, 4.4 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$)

δ = 172.0, 170.2, 152.9, 140.5, 135.5, 129.5, 129.2, 129.0, 127.3, 122.7, 109.4, 81.4, 66.0, 55.8, 40.2, 39.9, 37.5, 28.1; IR (neat): 1781, 1725, 1698 cm^{-1}; LC-MS (HpH): 1.48 min (516, 518) ($[M+Na]^+$, 100%); HRMS: calculated for $C_{22}H_{24}{}^{79}BrNNaO_5S^+$ ($[M+Na]^+$) 516.0451, found 516.0455.

(*S*)-2-(2-Bromophenyl)-4-(*tert*-butoxy)-4-oxobutanoic acid 3a: Prepared according to General Procedure C using **2a** (712 mg, 1.46 mmol, 1.0 eq.) in THF (5 mL) and sequential addition of H_2O_2 (4.0 eq.) and 1 M LiOH (3.0 eq.). Reverse phase flash chromatography on C18 modified silica (30–95% acetonitrile + 0.1% formic acid in water + 0.1% formic acid) afforded the title compound (235 mg, 0.714 mmol, 49% yield) as a straw-coloured gum. $[\alpha]_D^{20}$ (*c* = 0.71, MeOH): +66; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.34–7.28 (m, 2H), 7.15 (ddd, *J* = 8.1, 6.8, 2.2 Hz, 1H), 4.65 (dd, *J* = 9.5, 5.6 Hz, 1H), 3.01 (dd, *J* = 16.6, 9.5 Hz, 1H), 2.67 (dd, *J* = 16.6, 5.6 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.2, 170.1, 136.9, 133.3, 129.2, 128.9, 127.9, 124.6, 81.4, 46.4, 38.0, 28.0; IR (neat): 2980, 1730, 1713; cm^{-1}; LC-MS (For): 1.13 min (327, 329) ($[M-H]^-$, 96%); HRMS: calculated for $C_{14}H_{17}{}^{79}BrNaO_4^+$ ($[M+Na]^+$) 351.0202, found 351.0211.

(*S*)-2-(3-Bromophenyl)-4-(*tert*-butoxy)-4-oxobutanoic acid 3b: Prepared according to General Procedure C using **2b** (1.15 g, 2.36 mmol, 1.0 eq.) in THF (10 mL) and sequential addition of H_2O_2 (4.0 eq.) and 1 M LiOH (3.0 eq.). Reverse phase flash chromatography on C18 modified silica (30–95% acetonitrile + 0.1% formic acid in water + 0.1% formic acid) afforded the title compound (452 mg, 1.373 mmol, 58% yield) as a straw-coloured gum. $[\alpha]_D^{20}$ (*c* = 0.75, MeOH): +69; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 (t, *J* = 1.7 Hz, 1H), 7.43 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.26–7.18 (m, 2H), 4.02 (dd, *J* = 9.7, 5.9 Hz, 1H), 3.07 (dd, *J* = 16.8, 9.7 Hz, 1H), 2.62 (dd, *J* = 16.8, 5.9 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.3, 170.1, 139.2, 131.1, 131.0,

130.3, 126.7, 122.8, 81.5, 46.9, 38.5, 27.9; IR (neat): 2979, 1727, 1709 cm^{-1}; LC-MS (For): 1.16 min (655, 657, 659) ($[2M-H]^-$, 92%); HRMS: calculated for $C_{14}H_{17}{}^{79}BrNaO_4^+$ ($[M+Na]^+$) 351.0202, found 351.0204.

(*S*)-2-(4-Bromophenyl)-4-(*tert*-butoxy)-4-oxobutanoic acid 3c: Prepared according to General Procedure C using **2c** (1.46 g, 2.99 mmol, 1.0 eq.) in THF (5 mL) and sequential addition of H_2O_2 (4.0 eq.) and 1 M LiOH (3.0 eq.). Reverse phase flash chromatography on C18 modified silica (30–95% acetonitrile + 0.1% formic acid in water + 0.1% formic acid) afforded the title compound (445 mg, 1.352 mmol, 45% yield) as a straw-coloured gum.

$[\alpha]_D^{20}$ (*c* = 0.68, MeOH): +74; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.49–7.43 (m, 2H), 7.21–7.16 (m, 2H), 4.01 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.05 (dd, *J* = 16.6, 9.8 Hz, 1H), 2.60 (dd, *J* = 16.6, 5.9, Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.8, 170.1, 136.1, 132.0, 129.7, 121.9, 81.5, 46.7, 38.5, 27.9; IR (neat): 2980, 1729, 1711 cm^{-1}; LC-MS (For): 1.16 min (327, 329) ($[M-H]^-$, 98%), HRMS: calculated for $C_{14}H_{17}{}^{79}BrNaO_4^+$ ($[M+Na]^+$) 351.0202, found 351.0207.

(*R*)-2-(3-Bromophenyl)-4-(*tert*-butoxy)-4-oxobutanoic acid 3d: Prepared according to General Procedure C using **2d** (514 mg, 1.05 mmol, 1.0 eq.) in THF (10 mL) and sequential addition of H_2O_2 (4.0 eq.) and 1 M LiOH (3.0 eq.). Flash chromatography on silica (0–30% TBME in cyclohexane) afforded the title compound (122 mg, 0.371 mmol, 35% yield) as a straw-coloured gum. $[\alpha]_D^{20}$ (*c* = 0.12, MeOH): −69. Remaining analytical data are consistent with enantiomer.

(*S*)-4-(*tert*-Butoxy)-2-(3,5-dibromophenyl)-4-oxobutanoic acid 3e: Prepared according to General Procedure C using **2e** (2.74 g, 4.83 mmol, 1.0 eq.) in THF (25 mL) and a solution of H_2O_2 (4.0 eq.) in 1.5 M LiOH (3.0 eq.). Flash chromatography on silica (0–70% ethyl acetate in cyclohexane) afforded the title compound (1.56 g, 3.82 mmol, 79% yield) as a yellow oil in 77%

a/a purity by LCMS. The mixture was carried forward with no further purification. ^{1}H NMR* (400 MHz, $CDCl_3$) δ = 7.61 (t, *J* = 1.7 Hz, 1H), 7.42 (d, *J* = 1.7 Hz, 2H), 4.01 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.06 (dd, *J* = 16.8, 9.6 Hz, 1H), 2.63 (dd, *J* = 16.7, 5.9 Hz, 1H), 1.42 (s, 9H); LC-MS (HpH): 0.87 min (403, 405, 407) ($[M-H]^-$, 77%). *Major peaks assigned.

(*R*)-4-(*tert*-Butoxy)-4-oxo-2-(thiophen-2-yl)butanoic acid 3f: Prepared according to General Procedure C using **2f** (7.60 g, 18.3 mmol, 1.0 eq.) in THF (70 mL) and a solution of H_2O_2 (4.0 eq.) in 2 M LiOH (3.0 eq.). Flash chromatography on silica (0–40% ethyl acetate in cyclohexane) afforded the title compound (3.26 g, 12.7 mmol, 69% yield) as a colourless gum. $[\alpha]_D^{20}$ (*c* = 1.75, MeOH): +41; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.01–6.97 (m, 1H), 6.97–6.94 (m, 1H), 4.33 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.11 (dd, *J* = 16.6, 9.8 Hz, 1H), 2.75 (dd, *J* = 16.6, 5.4 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.6, 169.9, 138.9, 126.9, 125.9, 125.0, 81.5, 42.5, 39.3, 27.9; IR (neat): 3112, 2973, 1710 cm^{-1}; LC-MS (HpH): 0.63 (279) ($[M+Na]^+$, 100%); HRMS: calculated for $C_{12}H_{16}NaO_4S^+$ ($[M+Na]^+$) 279.0662, found 279.0662.

(*S*)-4-(*tert*-Butoxy)-4-oxo-2-(thiophen-3-yl)butanoic acid 3g: Prepared according to General Procedure C using **2g** (1.56 g, 3.75 mmol, 1.0 eq.) in THF (25 mL) and a solution of H_2O_2 (4.0 eq.) in 1 M LiOH (3.0 eq.). Flash chromatography on silica (0–40% ethyl acetate in cyclohexane) afforded the title compound (809 mg, 3.16 mmol, 84% yield) as a colourless gum. $[\alpha]_D^{20}$ (*c* = 2.04, MeOH): +51; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.17 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.06 (dd, *J* = 5.1, 1.2 Hz, 1H), 4.18 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.06 (dd, *J* = 16.4, 9.8 Hz, 1H), 2.66 (dd, *J* = 16.6, 5.9 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 178.5, 170.3, 136.9, 127.0, 126.1, 122.4, 81.3, 42.8, 38.3, 27.9; IR (neat): 3404–2768, 1707 cm^{-1}; LC-MS (HpH): 0.62 min (255) ($[M-H]^-$, 100%); HRMS: calculated for $C_{12}H_{16}NaO_4S^+$ ($[M+Na]^+$) 279.0662, found 279.0669.

(*R*)-2-(4-Bromothiophen-2-yl)-4-(*tert*-butoxy)-4-oxobutanoic acid 3h: Prepared according to General Procedure C using **2h** (1.25 g, 2.53 mmol, 1.0 eq.) in THF (25 mL) and a solution of H_2O_2 (4 eq.) in 1 M LiOH (3 eq.). Flash chromatography on silica (0–40% ethyl acetate in cyclohexane) afforded the title compound (247 mg, 0.737 mmol, 29% yield) as a yellow oil. $[\alpha]_D^{20}$ (*c* = 1.83, MeOH): +46; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 1.5 Hz, 1H), 6.94–6.92 (m, 1H), 4.27 (dd, *J* = 9.5, 5.6 Hz, 1H), 3.08 (dd, *J* = 16.9, 9.5 Hz, 1H), 2.73 (dd, *J* = 16.9, 5.6 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.8, 169.6, 140.2, 128.8, 122.4, 109.5, 81.8, 42.5, 38.9, 28.0; IR (neat): 3417–2747, 1712 cm^{-1}; LC-MS (HpH): 0.73 min (333, 335) ([M−H]$^-$, 92%); HRMS: calculated for $C_{12}H_{15}{}^{79}BrNaO_4S^+$ ([M+Na]$^+$) 356.9767, found 356.9770.

(*R*)-2-(5-Bromothiophen-2-yl)-4-(*tert*-butoxy)-4-oxobutanoic acid 3i: To a stirred solution of acid **3f** (500 mg, 1.951 mmol) in DMF (10 mL) at 0 °C, was added *N*-bromosuccinimide (347 mg, 1.95 mmol) portionwise over 1 min. The reaction was stirred for 80 min and then was diluted with sat. sodium thiosulfate (15 mL) and was extracted with ethyl acetate (2 x 20 mL). The combined organics were washed with sat. LiCl (2 x 40 mL), passed through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (0–40% ethyl acetate in cyclohexane) to afford the title compound (457 mg, 1.363 mmol, 70% yield) as a pale-yellow oil. $[\alpha]_D^{20}$ (*c* = 0.98, MeOH): +45; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 6.91 (d, *J* = 3.8 Hz, 1H), 6.75 (d, *J* = 3.8 Hz, 1H), 4.24 (dd, *J* = 9.3, 5.5 Hz, 1H), 3.06 (dd, *J* = 16.5, 9.3 Hz, 1H), 2.72 (dd, *J* = 16.5, 5.5 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (176 MHz, $CDCl_3$ δ = 176.2, 169.7, 140.4, 129.6, 126.5, 111.8, 81.8, 42.7, 38.9, 28.0; IR (neat): 3399–2273, 1678, 1632, 1565 cm^{-1}; LC-MS (HpH): 0.74 min (333, 335) ([M−H]$^-$, 100%); HRMS: calculated for $C_{12}H_{15}{}^{79}BrNaO_4S^+$ ([M+Na]$^+$) 356.9767, found 356.9770.

***tert*-Butyl (*S*)-3-(3-bromophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoate 5b:** Prepared according to General Procedure D without addition of acid, using **3b** (1.06 g, 3.22 mmol, 1.0 eq.) in DCM (25 mL), DIPEA (3.0 eq.), HATU (1.5 eq.) and a solution of amine **4** (1.2 eq.) in DCM (25 mL). The reaction was quenched with sat. NH_4Cl and extracted with DCM (2x), passed through a hydrophobic frit and concentrated *in vacuo*. Reverse phase flash chromatography on C18 modified silica (50–100% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (1.29 g, 2.38 mmol, 74% yield) as a colourless gum. Room temperature ^{13}C and ^{1}H NMR spectra in $CDCl_3$ show complex mix of rotamers, complicating interpretation. $[\alpha]_D^{20}$ (c = 0.77, MeOH): +13; ^{1}H NMR (400 MHz, DMSO-d_6, 393 K) δ 7.66–7.22 (m, 4H), 7.18–6.98 (m, 1H), 6.42–6.23 (m, 1H), 5.75 (br s, 1H), 4.30–4.01 (m, 1H), 3.76–3.19 (m, 5H), 3.12–2.77 (m, 4H), 2.77–2.45 (m, 4H), 2.24–1.59 (m, 6H), 1.49–1.34 (m, 9H); ^{13}C NMR (393K, 101 MHz, DMSO-d_6) δ = 169.2, 168.6, 156.0, 155.1–154.9 (m), 141.1, 135.5–135.3 (m), 129.9, 129.8, 129.2, 126.2, 121.1, 109.5, 79.3, 50.9–50.3 (m), 44.8–44.6 (m), 44.6, 34.7–34.5 (m), 31.6, 27.1, 25.3, 20.6; IR (neat): 3309, 2939, 1725, 1642, 1595cm^{-1}; LC-MS (For): 0.87 min (542, 544) ([M+H]$^+$, 94%); HRMS: calculated for $C_{28}H_{37}{}^{79}BrN_3O_3$ ([M+H]$^+$) 542.2013, found 542.2018.

***tert*-Butyl (S)-3-(3,5-dibromophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoate 5e:** Prepared according to General Procedure D without addition of acid, using **3e** (2.02 g, 3.81 mmol, 1.0 eq.) in DCM (20 mL), DIPEA (3.0 eq.), HATU (1.5 eq.) and a solution of amine **4** (1.25 eq.) in DCM (20 mL). The reaction was quenched with sat. NH_4Cl and extracted with DCM (2x), passed through a hydrophobic frit and concentrated *in vacuo*. Reverse phase flash chromatography on C18 modified silica (50–100% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the

title compound (819 mg, 1.32 mmol, 35% yield) as a yellow oil. Room temperature ^{13}C and ^{1}H NMR spectra in $CDCl_3$ show complex mix of rotamers, complicating interpretation. $[\alpha]_D^{20}$ (*c* = 1.05, MeOH): +67; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56–7.52 (m, 1H), 7.44–7.39 (m, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.32–6.27 (m, 1H), 4.82 (br s, 1H), 4.04–3.89 (m, 1H), 3.85–3.49 (m, 2H), 3.44–3.24 (m, 3H), 3.19–2.90 (m, 2H), 2.68 (q, *J* = 6.4 Hz, 2H), 2.60–2.43 (m, 3H), 2.15–1.95 (m, 2H), 1.94–1.83 (m, 2H), 1.81– 1.61 (m, 2H), 1.57–1.42 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.8–170.7 (m), 170.6, 169.1–168.9 (m), 157.4–157.1 (m), 155.7–155.6 (m), 142.7–142.5 (m), 136.6, 133.0–132.9 (m), 129.9–129.7 (m), 123.2–123.1 (m), 113.5–113.3 (m), 111.2–111.0 (m), 80.9–80.7 (m), 51.9, 51.7–51.6 (m), 51.5, 46.3, 46.1, 46.0–45.8 (m), 45.7, 45.5, 41.5, 40.3–40.2 (m), 40.1, 39.1–39.0 (m), 37.1, 36.2–36.1 (m), 33.0–32.9 (m), 32.8–32.7 (m), 31.9–31.8 (m), 30.3–30.1 (m), 28.0, 26.3–26.2 (m), 21.4; IR (neat): 2936, 2866, 1727, 1642, 1599, 1583 cm^{-1}; LC-MS (HpH): 1.53 min (620, 622, 624) ($[M+H]^+$, 98%); HRMS: calculated for $C_{28}H_{36}{}^{79}Br_2N_3O_3$ ($[M+H]^+$) 620.1118, found 620.1121.

(*S*)-3-(2-Bromophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 6a: Prepared according to General Procedure D using **3a** (208 mg, 0.632 mmol, 1.0 eq.) in DCM (10 mL), DIPEA (6.2 eq.), HATU (1.2 eq.) and a solution of amine **4** (1.2 eq.) in DCM (2 mL) followed by addition of HCl (1.58 mL, 10.0 eq.). HPLC using ACCQPrep (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (178 mg, 0.366 mmol, 58% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.84, MeOH): +106; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.65 (br s, 1H), 7.93 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.31–7.26 (m, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.10–7.04 (m, 1H), 6.24 (d, *J* = 7.3 Hz, 1H), 4.98 (dd, *J* = 12.0, 2.7Hz, 1H), 4.83 (d, *J* = 10.3 Hz, 1H), 3.62–3.38 (m, 4H), 3.35–3.24 (m, 2H), 2.87 (td, *J* = 12.9, 2.1 Hz, 1H),

2.69 (t, J = 6.1 Hz, 2H), 2.55 (dd, J = 16.9, 2.7 Hz, 1H), 2.48 (td, J = 12.8, 6.4 Hz, 1H), 2.24–2.13 (m, 1H), 2.06–1.94 (m, 1H), 1.92–1.85 (m, 2H), 1.79–1.60 (m, 2H), 1.48–1.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.3, 173.3, 153.7, 150.2, 139.6, 139.1, 132.3, 130.7, 128.1, 127.7, 124.0, 117.6, 108.9, 50.3, 45.0, 44.0, 42.1, 40.6, 38.5, 33.3, 32.4, 31.0, 25.9, 19.8; IR (neat): 3276, 2935, 2863, 1677, 1625 cm^{-1}; LCMS (For): 0.68 min (486, 488) ([M+H]$^+$, 99%); HRMS: calculated for $C_{24}H_{29}{}^{79}BrN_3O_3^+$ ([M+H]$^+$) 486.1387, found 486.1396.

(*S*)-3-(3-Bromophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 6b: Prepared according to General Procedure D using **3b** (367 mg, 1.12 mmol, 1.0 eq.) in DCM (10 mL), DIPEA (3.5 eq.), HATU (1.2 eq.) and a solution of amine **4** (1.2 eq.) in DCM (2 mL) followed by addition of HCl (2.8 mL, 10.0 eq.). HPLC using ACCQPrep (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (289 mg, 0.594 mmol, 53% yield) as an off-white amorphous solid. $[\alpha]_D^{20}$ (c = 0.52, MeOH): +23; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.67 (br s, 1H), 7.60 (t, J = 2.0 Hz, 1H), 7.48–7.42 (m, 1H), 7.35 (ddd, J = 7.8, 2.0, 1.0 Hz, 1H), 7.20–7.14 (m, 2H), 6.24 (d, J = 7.3 Hz, 1H), 4.79 (d, J = 9.8 Hz, 1H), 4.36 (dd, J = 12.0, 2.7 Hz, 1H), 3.56 (td, J = 12.0, 7.3 Hz, 1H), 3.49–3.25 (m, 5H), 2.81 (td, J = 13.0, 2.0 Hz, 1H), 2.70 (t, J = 6.1 Hz, 2H), 2.55 (dd, J = 16.9, 2.7 Hz, 1H), 2.48 (td, J = 12.7, 6.4 Hz, 1H), 2.25–2.14 (m, 1H), 2.08–1.96 (m, 1H), 1.94–1.85 (m, 2H), 1.77–1.62 (m, 2H), 1.50–1.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.3, 173.5, 153.6, 150.0, 142.9, 139.2, 131.3, 130.0, 129.8, 126.9, 122.3, 117.7, 108.9, 49.7, 46.6, 43.8, 41.8, 40.6, 38.5, 33.4, 32.3, 31.1, 25.9, 19.8; IR (neat): 3253, 2936, 2864, 1680, 1626 cm^{-1}; LC-MS (For): 0.73 min (486, 488) ([M+H]$^+$, 100%); HRMS: calculated for $C_{24}H_{29}{}^{79}BrN_3O_3^+$ ([M+H]$^+$) 486.1387, found 486.1392.

(*S*)-3-(4-Bromophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 6c: Prepared according to General Procedure D using **3c** (430 mg, 1.31 mmol, 1.0 eq.) in DCM (10 mL), DIPEA (3.0 eq.), HATU (1.2 eq.) and a solution of amine **4** (1.2 eq.) in DCM (2 mL) followed by addition of TFA (5 mL, 49.7 eq.). HPLC using ACCQPrep (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (456 mg, 0.937 mmol, 72% yield) as an off-white amorphous solid. $[\alpha]_D^{20}$ (*c* = 1.34, MeOH): +30; 1H NMR (400 MHz, $CDCl_3$) δ = 10.55 (br s, 1H), 7.45–7.29 (m, 4H), 7.17 (d, *J* = 7.1 Hz, 1H), 6.24 (d, *J* = 7.1 Hz, 1H), 4.75 (d, *J* = 9.5 Hz, 1H), 4.35 (dd, *J* = 12.0, 2.7 Hz, 1H), 3.55 (td, *J* = 11.9, 7.5 Hz, 1H), 3.47–3.24 (m, 5H), 2.85–2.75 (m, 1H), 2.69 (t, *J* = 6.2 Hz, 2H), 2.57–2.43 (m, 2H), 2.23–2.13 (m, 1H), 2.06–1.95 (m, 1H), 1.92–1.86 (m, 2H), 1.74–1.62 (m, 2H), 1.49–1.37 (m, 1H); ^{13}C NMR (101MHz, $CDCl_3$) δ = 179.4, 173.7, 153.7, 150.2, 139.6, 139.1, 131.4, 130.0, 120.7, 117.6, 109.0, 49.8, 46.4, 43.9, 41.9, 40.6, 38.5, 33.4, 32.4, 31.1, 25.9, 19.8; IR (neat): 3388, 2937, 2868, 1678, 1623 cm^{-1}; LC-MS (For): 0.74 min (486, 488) ($[M+H]^+$, 100%); HRMS: calculated for $C_{24}H_{29}{}^{79}BrN_3O_3^+$ ($[M+H]^+$) 486.1387, found 486.1393.

(*R*)-3-(3-bromophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 6d: Prepared according to General Procedure D using **3d** (115 mg, 0.349 mmol, 1.0 eq.) in DCM (5 mL), DIPEA (11.1 eq.), HATU (1.2 eq.) and a solution of amine **4** (1.9 eq.) in DCM (2 mL) followed by addition of HCl (3 mL, 34.4 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (92 mg, 0.189 mmol, 54% yield) as an off-white amorphous solid.

$[\alpha]_D^{20}$ (*c* = 1.43, MeOH): −8; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.08 (br s, 1H), 7.59 (t, *J* = 1.7 Hz, 1H), 7.44–7.40 (m, 1H), 7.35 (ddd, *J* = 7.8, 2.0, 1.0 Hz, 1H), 7.20–7.12 (m, 2H), 6.23 (d, *J* = 7.3 Hz, 1H), 4.20–4.03 (m, 3H), 3.50–3.42 (m, 3H), 3.38 (dd, *J* = 16.6, 12.2 Hz, 1H), 3.03 (dd, *J* = 12.0, 4.6 Hz, 1H), 2.70 (t, *J* = 5.9 Hz, 2H), 2.64 (dd, *J* = 13.2, 3.4 Hz, 1H), 2.51 (dd, *J* = 16.6, 3.4 Hz, 1H), 2.43 (td, *J* = 13.2, 5.4 Hz, 1H), 2.23–2.13 (m, 1H), 2.11–1.77 (m, 5H), 1.63–1.51 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.4, 173.9, 153.6, 149.6, 142.0, 139.3, 131.1, 130.1, 129.9, 126.8, 122.5, 118.03, 109.0, 48.6, 45.8, 44.4, 42.7, 40.6, 35.5, 31.6, 31.5, 30.6, 25.9, 19.7; IR (neat): 3265, 2936, 2867, 1678, 1630, 1596 cm^{-1}; LC-MS (TFA): 0.75 min (466, 468) ($[M+H]^+$, 100%); HRMS: calculated for $C_{24}H_{29}{}^{79}BrN_3O_3^+$ ($[M+H]^+$) 486.1387, found 486.1382.

(*S*)-3-(3,5-Dibromophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 6e: To a stirred solution of *tert*-butyl ester **5e** (307 mg, 0.494 mmol, 1.0 eq.) in DCM (5 mL) was added TFA (4 mL, 51.9 mL, 105.0 eq.). After stirring for 1 h, the reaction was concentrated in vacuo and the residue was co-concentrated with DCM (2 x 10 mL). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (250 mg, 0.442 mmol, 90% yield) as a white amorphous solid. Room temperature ^{1}H NMR spectrum in $CDCl_3$ shows 13:7 ratio of rotamers. $[\alpha]_D^{20}$ (*c* = 0.90, MeOH): +4; ^{1}H NMR (400 MHz, DMSO-d_6, 394 K) δ = 8.15 (s, 1H), 7.69–7.50 (m, 3H), 7.11–6.99 (m, 1H), 6.33–6.23 (m, 1H), 4.27–4.13 (m, 1H), 3.61–3.23 (m, 5H), 3.05–2.89 (m, 2H), 2.70–2.59 (m, 2H), 2.57–2.43 (m, 3H), 2.21–2.05 (m, 1H), 2.05–1.91 (m, 1H), 1.86–1.76 (m, 2H), 1.73–1.59 (m, 2H), 1.58–1.42 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 303 K) δ = 178.9, 172.8, 153.6, 149.9, 149.4, 144.5, 143.6, 139.4, 139.2, 132.6, 132.5, 130.2, 130.0, 122.9, 122.7, 118.1, 117.8, 109.0, 108.9, 49.7, 48.6, 46.4, 45.5, 44.4, 43.9, 41.9, 40.6, 40.6, 38.5, 35.5, 33.3, 32.3, 31.6, 31.5, 31.0, 30.5, 25.9, 19.8, 19.6; IR

(neat): 3607–2657, 1680, 1629, 1581, 1553 cm^{-1}; LC-MS (TFA): 0.84 min (564, 566, 568) ($[M+H]^+$, 100%); HRMS: calculated for $C_{24}H_{28}{}^{79}Br_2N_3O_3^+$ ($[M+H]^+$) 564.0492, found 564.0501.

(*R*)-4-Oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(thiophen-2-yl)butanoic acid 6f: Prepared according to General Procedure D using **3f** (142 mg, 0.554 mmol, 1.0 eq.) in DCM (6 mL), DIPEA (3.0 eq.), HATU (1.25 eq.) and a solution of amine **4** (1.4 eq.) in DCM (6 mL) followed by addition of TFA (3 mL, 70.3 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (139 mg, 0.336 mmol, 61% yield) as a white amorphous solid. Room temperature ^{1}H NMR spectrum in $CDCl_3$ shows approximate 9:5 ratio of rotamers. $[\alpha]_D^{20}$ (*c* = 2.74, MeOH): +6; ^{1}H NMR (400 MHz, DMSO-d_6, 393 K) δ = 8.15 (s, 1H), 7.31 (d, *J* = 4.4 Hz, 1H), 7.11–6.88 (m, 3H), 6.37–6.21 (m, 1H), 4.64–4.21 (m, 1H), 3.66–3.23 (m, 5H), 3.10–2.91 (m, 2H), 2.69–2.43 (m, 5H), 2.26–2.08 (m, 1H), 2.06–1.92 (m, 1H), 1.88–1.75 (m, 2H), 1.75–1.62 (m, 2H), 1.58–1.43 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 303 K) δ = 179.0, 178.9, 173.5, 173.1, 153.6, 149.8, 149.5, 143.4, 142.5, 139.2, 139.1, 126.4, 126.2, 124.2, 123.9, 123.8, 117.8, 117.6, 108.9, 108.9, 49.5, 48.6, 44.4, 43.7, 43.2, 42.3, 41.3, 40.5, 40.4, 38.3, 35.5, 33.2, 32.1, 31.4, 31.3, 30.9, 30.6, 25.7, 25.7, 19.6, 19.6; IR (neat): 3254, 2933, 2863, 1678, 1626, 1565 cm^{-1}; LC-MS (TFA): 0.64 min (414) ($[M+H]^+$, 100%); HRMS: calculated for $C_{22}H_{28}N_3O_3S^+$ ($[M+H]^+$) 414.1846, found 414.1854.

(*S*)-4-Oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(thiophen-3-yl)butanoic acid 6g: Prepared according to General Procedure D using **3g** (721 mg, 2.81 mmol, 1.0 eq.) in DCM (12 mL), DIPEA (3.0 eq.), HATU (1.25 eq.) and a solution of amine **4** (1.4 eq.) in DCM (12 mL) followed by addition of TFA (9 mL, 41.5 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water

with 10 mM ammonium bicarbonate modifier) afforded the title compound (970 mg, 2.35 mmol, 83% yield) as a white amorphous solid. Room temperature ^{1}H and ^{13}C NMR spectra in $CDCl_3$ show complex mix of rotamers. $[\alpha]_D^{20}$ (*c* = 1.19, MeOH): +26; ^{1}H NMR (400 MHz, DMSO-d_6, 393 K) δ = 7.40 (dd, *J* = 4.6, 3.2 Hz, 1H), 7.34–7.18 (m, 2H), 7.12–6.98 (m, 1H), 6.43–6.35 (m, 1H), 5.63 (s, 1H), 4.32–4.08 (m, 1H), 3.67–3.41 (m, 2H), 3.38–3.18 (m, 3H), 3.05–2.93 (m, 1H), 2.68 (t, *J* = 6.1 Hz, 2H), 2.62–2.47 (m, 4H), 2.20–2.05 (m, 1H), 2.05–1.92 (m, 1H), 1.87–1.79 (m, 2H), 1.76–1.63 (m, 2H), 1.58–1.43 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 303 K) δ = 179.0, 173.6, 153.5, 149.9, 140.6, 139.3, 127.7, 125.3, 121.2, 117.8, 108.9, 49.8, 44.0, 42.4, 41.6, 40.6, 38.5, 33.3, 32.2, 31.0, 25.8, 19.7; IR (neat): 3258–2491, 1677, 1623, 1562 cm^{-1}; LC-MS (HpH): 0.76 min (414) ($[M+H]^+$, 100%); HRMS: calculated for $C_{22}H_{28}N_3O_3S^+$ ($[M+H]^+$) 414.1846, found 414.1852.

(*R*)-3-(4-Bromothiophen-2-yl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 6h: Prepared according to General Procedure D using **3h** (195 mg, 0.582 mmol, 1.0 eq.) in DCM (5 mL), DIPEA (3.0 eq.), HATU (1.5 eq.) and a solution of amine **4** (1.1 eq.) in DCM (5 mL) followed by addition of TFA (4 mL, 89.0 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (148 mg, 0.301 mmol, 52% yield) as a white gummy solid. Room temperature ^{1}H and ^{13}C NMR spectra show mix of rotamers; major peaks assigned with aid of HMBC. $[\alpha]_D^{20}$ (*c* = 2.44, MeOH): + 22; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.67 (br s, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 1.0 Hz, 1H), 6.91–6.86 (m, 1H), 6.25–6.19 (m, 1H), 4.70 (d, *J* = 9.8 Hz, 1H), 4.58 (dd, *J* = 12.0, 2.7 Hz, 1H), 3.58–3.44 (m, 1H), 3.44–3.21 (m, 5H), 2.76 (td, *J* = 12.7, 2.0 Hz, 1H), 2.67 (t, *J* = 6.1 Hz, 2H), 2.63–2.54 (m, 1H), 2.52–2.36 (m, 1H), 2.23–2.12 (m, 1H), 2.07–1.96 (m, 1H), 1.90–1.76 (m, 2H), 1.71–

1.50 (m, 2H), 1.48–1.34 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 178.6, 172.5, 153.4, 149.6, 144.9, 144.0, 139.2, 127.0, 121.6, 117.8, 108.9, 49.6, 43.8, 43.3, 42.5, 40.5, 38.4, 33.2, 32.1, 30.9, 25.7, 19.6; IR (neat): 3435, 2939, 2869, 1682, 1626, 1564 cm^{-1}; LC-MS (TFA): 0.73 min (492, 494) ($[M+H]^+$, 100%); HRMS: calculated for $C_{22}H_{27}{}^{79}BrN_3O_3S^+$ ($[M+H]^+$) 492.0951, found 492.0958.

(*R*)-3-(5-Bromothiophen-2-yl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 6i: Prepared according to General Procedure D using **3i** (363 mg, 1.08 mmol, 1.0 eq.) in DCM (6 mL), DIPEA (1.5 eq.), HATU (1.2 eq.) and a solution of amine **4** (1.2 eq.) in DCM (6 mL) followed by addition of TFA (3 mL, 36.0 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (331 mg, 0.672 mmol, 62% yield) as a white amorphous solid. Room temperature ^{1}H and ^{13}C NMR spectra in $CDCl_3$ show mix of rotamers. $[\alpha]_D^{20}$ (*c* = 1.10, MeOH): + 4; ^{1}H NMR (400 MHz, DMSO-d_6, 393 K,) δ = 8.15 (s, 1H), 7.33–7.18 (m, 1H), 7.02–6.96 (m, 1H), 6.83–6.77 (m, 1H), 6.46–6.37 (m, 1H), 4.43 (dd, *J* = 8.8, 5.4 Hz, 1H), 3.66–3.44 (m, 2H), 3.41–3.23 (m, 3H), 3.09–2.92 (m, 2H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.64–2.53 (m, 3H), 2.29–2.09 (m, 1H), 2.08–1.96 (m, 1H), 1.84 (quin, *J* = 6.0 Hz, 2H), 1.75–1.65 (m, 2H), 1.62–1.48 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$, 303 K) δ = 178.4, 172.5, 170.0, 153.4, 152.6, 149.5, 149.0, 144.8, 140.3, 139.9, 139.4, 129.5, 129.3, 129.0, 125.9, 125.3, 124.8, 118.5, 118.4, 118.0, 117.3, 115.7, 111.3, 111.0, 110.9, 109.3, 108.9, 51.8, 49.8, 45.8, 45.3, 44.1, 43.1, 42.1, 41.8, 40.8, 40.8, 40.6, 38.6, 38.5, 36.2, 33.2, 32.3, 32.1, 31.4, 31.3, 31.1, 30.9, 30.0, 25.8, 25.8, 25.7, 19.7, 19.5, 19.4; IR (neat): 3399–2273, 1678, 1632, 1565 cm^{-1}; LC-MS (TFA): 0.74 min (492, 494) ($[M+H]^+$, 100%); HRMS: calculated for $C_{22}H_{27}{}^{79}BrN_3O_3S^+$ ($[M+H]^+$) 492.0951, found 492.0958.

(*S*)-4-Oxo-3-phenyl-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 6j: Prepared according to General Procedure D using (*S*)-4-*tert*-butoxy-4-oxo-2-phenylbutanoic acid (Fluorochem) (156 mg, 0.623, 1.0 eq.) in DCM (5 mL), DIPEA (3.0 eq.), HATU (1.5 eq.) and a solution of amine **4** (1.3 eq.) in DCM (5 mL) followed by addition of HCl (3.2 mL, 20.6 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (151 mg, 0.371 mmol, 60% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.72, MeOH): +114; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.61 (br s, 1H), 7.50–7.45 (m, 2H), 7.33–7.27 (m, 2H), 7.25–7.19 (m, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 6.24 (d, *J* = 6.8 Hz, 1H), 4.79 (d, *J* = 9.8 Hz, 1H), 4.41 (dd, *J* = 12.2, 2.9 Hz, 1H), 3.57 (td, *J* = 12.0, 7.3 Hz, 1H), 3.48–3.36 (m, 4H), 3.28 (dd, *J* = 12.2, 9.3 Hz, 1H), 2.83 (td, *J* = 13.0, 2.0 Hz, 1H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.59 (dd, *J* = 16.6, 2.9 Hz, 1H), 2.48 (td, *J* = 12.7, 6.4 Hz, 1H), 2.23–2.13 (m, 1H), 2.06–1.94 (m, 1H), 1.93–1.84 (m, 2H), 1.77–1.60 (m, 2H), 1.48–1.36 (m, 1H); ^{13}C NMR (101MHz, $CDCl_3$) δ = 179.7, 174.2, 153.7, 150.2, 140.6, 139.1, 128.4, 128.2, 126.7, 117.6, 108.9, 49.8, 46.9, 43.8, 41.8, 40.6, 38.5, 33.4, 32.4, 31.1, 25.9, 19.8; IR (neat): 3250, 2866, 1683, 1611 cm^{-1}; LC-MS (For): 0.60 min (408) ($[M+H]^+$, 100%); HRMS: calculated for $C_{24}H_{30}N_3O_3^+$ ($[M+H]^+$) 408.2282, found 408.2287.

***(S)*-4-(*tert*-Butoxy)-4-oxo-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butanoic acid 7:** A solution of acid **3b** (247 mg, 0.750 mmol, 1.0 eq.), potassium acetate (221 mg, 2.251 mmol, 3.0 eq.), $PdCl_2$(dppf) (54.9 mg, 0.075 mmol, 0.1 eq.) and bis(pinacolato)diboron (381 mg, 1.501 mmol, 2.0 eq.) was heated at 90 °C for 90 min. The reaction was cooled to rt and filtered through celite eluting with ethyl acetate. The filtrate was concentrated *in vacuo* and purified by flash chromatography on silica (0–40% ethyl acetate in cyclohexane) to afford the title compound (247 mg, 0.656 mmol, 87% yield) as a colourless oil. $[\alpha]_D^{20}$ (*c* = 1.78, MeOH): +45; ^{1}H NMR (400

MHz, $CDCl_3$) δ = 7.76–7.70 (m, 2H), 7.43–7.38 (m, 1H), 7.36–7.29 (m, 1H), 4.07 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.11 (dd, *J* = 16.6, 10.3 Hz, 1H), 2.61 (dd, *J* = 16.6, 5.4 Hz, 1H), 1.40 (s, 9H), 1.34 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 178.2, 170.4, 136.5, 134.4, 134.2, 130.7, 128.2, 83.9, 81.1, 47.3, 38.8, 27.9, 24.8; IR (neat): 3378–2770, 1728, 1710 cm^{-1}; LC-MS (For): 1.27 min (399) ($[M+Na]^+$, 84%); HRMS: calculated for $C_{20}H_{29}BNaO_6^+$ ($[M+Na]^+$) 399.1949, found 399.1957.

(*S*)-3-(3-Hydroxyphenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 9: To a stirred solution of boronic ester **7** (221 mg, 0.587 mmol, 1.0 eq.) in THF (2 mL) was added 2 M NaOH (0.29 mL, 0.580 mmol, 1.0 eq.) and hydrogen peroxide (30% w/w in water) (0.15 mL, 1.469 mmol, 2.5 eq.). The reaction was stirred for 1 h and then was quenched with water (10 mL). The reaction mixture was acidified to pH 1 using 1 M HCl and was extracted with ethyl acetate (3 x 10 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. To the residue, was added a solution of amine **4** (299 mg, 1.292 mmol, 2.2 eq.) in DCM (10 mL) and HATU (335 mg, 0.881 mmol, 1.5 eq.). After stirring for 1 h, the reaction was concentrated *in vacuo*. The residue was dissolved in DCM (3 mL) and to this was added TFA (2 mL, 26.0 mmol, 44.2 eq.) and the reaction was stirred for 3 h. After this time, the reaction mixture was concentrated *in vacuo* and then co-concentrated with $CHCl_3$ (2 x 10 mL). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (69 mg, 0.163 mmol, 28% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.97, MeOH): +87; ^1H NMR (400 MHz, $CDCl_3$) δ = 10.55 (br s, 1H), 7.42–7.35 (m, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.73–6.68 (m, 1H), 6.23 (d, *J* = 7.3 Hz, 1H), 4.76 (d, *J* = 9.8 Hz, 1H), 4.36 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.63–3.36 (m, 5H), 3.35–3.28 (m, 1H), 2.85–2.76 (m, 1H), 2.71–2.60 (m, 3H), 2.48 (td, *J* = 12.6, 6.6 Hz, 1H), 2.22–2.12 (m, 1H), 2.06–

1.93 (m, 1H), 1.86 (quin, J = 6.0 Hz, 2H), 1.75–1.60 (m, 2H), 1.51–1.38 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.1, 174.6, 157.5, 153.6, 149.8, 141.4, 139.2, 129.0, 119.5, 117.8, 115.5, 114.4, 108.9, 50.0, 46.9, 44.1, 41.9, 40.5, 38.4, 33.3, 32.2, 31.1, 25.8, 19.7; IR (neat): 3188–2739, 1679, 1619, 1562 cm^{-1}; LC-MS (For): 0.55 min (424) ($[M+H]^+$, 100%); HRMS: calculated for $C_{24}H_{30}N_3O_4^+$ ($[M+H]^+$) 424.2231, found 424.2236.

(*S*)-4-Oxo-3-(3-(prop-1-en-2-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 11: To a stirred solution of boronic ester **7** (150 mg, 0.399 mmol, 1.0 eq.) in DCM (4 mL), was added DIPEA (0.21 mL, 1.202 mmol, 3.0 eq.) and HATU (227 mg, 0.598 mmol, 1.5 eq). To this, was added a solution of amine **4** (164 mg, 0.709 mmol, 1.8 eq.) in DCM (4 mL). The reaction was stirred for 45 min and then was quenched with sat. NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with DCM (2 x 10 mL). The combined organics were washed with brine (30 mL), passed through a hydrophobic frit and concentrated *in vacuo*. The residue was charged with tetrakis(triphenylphosphine)palladium(0) (46.1 mg, 0.040 mmol, 0.1 eq.) and to this was added 1,4-dioxane (8 mL) and 2-bromopropene (0.140 mL, 1.595 mmol, 4.0 eq.). To the stirred solution was added a solution of potassium carbonate (165 mg, 1.20 mmol, 3.0 eq.) in water (4 mL) and the reaction was stirred at 80 °C for 2 h. The reaction was cooled to rt and was extracted with DCM (4 x 15 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The residue was dissolved in DCM (2 mL) and to this, was added TFA (2 mL, 26.0 mmol, 65.1 eq.) and the reaction was stirred for 80 min. The reaction was concentrated *in vacuo* and the residue was co-concentrated with $CHCl_3$ (2 x 10 mL). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (9 mg, 0.020 mmol, 5% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (c = 0.29,

MeOH): +35; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.64 (br s, 1H), 7.54 (t, *J* = 1.7 Hz, 1H), 7.43 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.33 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.29–7.23 (m, 1H), 7.17 (d, *J* = 6.8 Hz, 1H), 6.24 (d, *J* = 6.8 Hz, 1H), 5.39–5.35 (m, 1H), 5.09–5.06 (m, 1H), 4.82 (d, *J* = 9.8 Hz, 1H), 4.42 (dd, *J* = 12.0, 2.7 Hz, 1H), 3.64–3.51 (m, 1H), 3.50–3.36 (m, 4H), 3.29 (dd, *J* = 12.2, 9.3 Hz, 1H), 2.83 (td, *J* = 12.8, 2.2 Hz, 1H), 2.70 (t, *J* = 6.1 Hz, 2H), 2.60 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.48 (td, *J* = 12.7, 6.4 Hz, 1H), 2.24–2.14 (m, 4H), 2.00 (tdd, *J* = 12.1, 9.5, 5.9 Hz, 1H), 1.94–1.84 (m, 2H), 1.79–1.63 (m, 2H), 1.49–1.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.7, 174.1, 153.8, 150.3, 143.4, 141.3, 140.5, 139.1, 128.3, 127.4, 125.5, 124.0, 117.6, 112.3, 108.9, 49.8, 47.0, 43.8, 41.9, 40.6, 38.5, 33.5, 32.4, 31.1, 25.9, 21.9, 19.8; IR (neat): 3261, 2939, 2865, 1683, 1626, 1598, 1566 cm^{-1}; LC-MS (TFA): 0.77 min (448) ($[M+H]^+$, 99%); HRMS: calculated for $C_{27}H_{34}N_3O^+$ ($[M+H]^+$) 448.2595, found 448.2598.

(*S*)-4-Oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(3-(trifluoromethyl)phenyl)butanoic acid 12: To a stirred solution of boronic ester **7** (95 mg, 0.252 mmol, 1.0 eq.) in DCM (4 mL), was added DIPEA (0.13 mL, 0.744 mmol, 3.0 eq.) and HATU (144 mg, 0.379 mmol, 1.5 eq.). To this, was added a solution of amine **4** (88 mg, 0.379 mmol, 1.5 eq.) in DCM (4 mL). The reaction was stirred for 45 min and then was quenched with sat. NH_4Cl (10 mL). The phases were separated and the aqueous phase was further extracted with DCM (2 x 10 mL). The combined organics were washed with brine (30 mL), passed through a hydrophobic frit and concentrated *in vacuo*. The residue was charged with (1,10-phenanthroline)(trifluoromethyl)copper(I) (90%) (105 mg, 0.303 mmol, 1.2 eq.) and KF (14.67 mg, 0.252 mmol, 1.0 eq.) and was purged with nitrogen. To this, was added DMF (4 mL) and the reaction was stirred at 50 °C for 14 h. The reaction was cooled to rt and filtered through celite, eluting with ethyl acetate. The filtrate was washed with water (30 mL) and brine (30 mL), passed

through a hydrophobic frit and concentrated *in vacuo*. The residue was dissolved in DCM (4 mL) and to this, was added TFA (2 mL, 26.0 mmol, 103.0 eq.) and the reaction was stirred for 1.5 h. The reaction was concentrated *in vacuo* and the residue was co-concentrated with DCM (2 x 10 mL). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (28 mg, 0.059 mmol, 23% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.99, MeOH): +65; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.67 (br s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.67 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.44–7.38 (m, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 6.24 (d, *J* = 7.3 Hz, 1H), 4.82 (d, *J* = 9.8 Hz, 1H), 4.46 (dd, *J* = 12.2, 2.4 Hz, 1H), 3.55 (td, *J* = 12.0, 7.3 Hz, 1H), 3.48–3.34 (m, 4H), 3.29 (dd, *J* = 12.2, 9.3 Hz, 1H), 2.82 (td, *J* = 13.0, 2.0 Hz, 1H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.56 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.48 (td, *J* = 12.7, 6.4 Hz, 1H), 2.25–2.14 (m, 1H), 2.07–1.95 (m, 1H), 1.94–1.83 (m, 2H), 1.77–1.62 (m, 2H), 1.50–1.36 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.2, 173.4, 153.6, 149.9, 141.6, 139.2, 131.7, 130.5 (q, *J* = 31.5 Hz), 128.8, 125.0 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.2 Hz) 123.6 (q, *J* = 3.7 Hz), 117.7, 108.9, 49.7, 46.8, 43.9, 42.0, 40.6, 38.5, 33.4, 32.3, 31.0, 25.8, 19.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −62.4; IR (neat): 3261, 2980, 2887, 1686, 1629, 1565 cm^{-1}; LC-MS (TFA): 0.76 min (476) ($[M+H]^+$, 99%); HRMS: calculated for $C_{50}H_{57}F_6N_6O_6^+$ ($[2M+H]^+$) 951.4238, found 951.4233.

(*S*)-3-(3-Chlorophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 13: To a stirred solution of boronic ester **7** (85 mg, 0.226 mmol. 1.0 eq.) in DCM (4 mL), was added DIPEA (0.12 mL, 0.687 mmol, 3.0 eq.) and HATU (129 mg, 0.339 mmol, 1.5 eq.). To this, was added a solution of amine **4** (110 mg, 0.475 mmol, 2.1 eq.) in DCM (4 mL). The reaction was stirred for 45 min and then was quenched with sat. NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with DCM (2 x

10 mL). The combined organics were washed with brine (30 mL), passed through a hydrophobic frit and concentrated *in vacuo*. The residue was dissolved in methanol (4 mL) and to this, was added a solution of $CuCl_2$ (91 mg, 0.678 mmol, 3.0 eq.) in water (4 mL) and the reaction was stirred at 90 °C for 20 h. The reaction was cooled to rt was extracted with ethyl acetate (3 x 15 mL). The combined organics were washed with brine (30 mL), passed through a hydrophobic frit and concentrated *in vacuo*. The residue was dissolved in DCM (2 mL) and to this, was added TFA (2 mL, 26.0 mmol, 115.0 eq.) and the reaction was stirred for 80 min. The reaction was concentrated *in vacuo* and the residue was co-concentrated with $CHCl_3$ (2 x 10 mL). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (46 mg, 0.104 mmol, 46% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.68, MeOH): +68; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.69 (br s, 1H), 7.45 (t, *J* = 2.0 Hz, 1H), 7.39 (dt, *J* = 7.0, 1.7 Hz, 1H), 7.26–7.16 (m, 3H), 6.24 (d, *J* = 7.3 Hz, 1H), 4.80 (d, *J* = 9.3 Hz, 1H), 4.37 (dd, *J* = 12.2, 2.4 Hz, 1H), 3.56 (td, *J* = 12.0, 7.3 Hz, 1H), 3.50–3.26 (m, 5H), 2.82 (td, *J* = 13.0, 2.0 Hz, 1H), 2.70 (t, *J* = 6.1 Hz, 2H), 2.56 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.48 (td, *J* = 12.7, 6.4 Hz, 1H), 2.24–2.14 (m, 1H), 2.02 (tdd, *J* = 12.2, 9.4, 6.4 Hz, 1H), 1.94–1.84 (m, 2H), 1.77–1.63 (m, 2H), 1.48–1.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.3, 173.6, 153.7, 150.0, 142.6, 139.2, 134.0, 129.6, 128.4, 126.9, 126.5, 117.7, 108.9, 49.7, 46.7, 43.8, 41.8, 40.6, 38.5, 33.4, 32.3, 31.1, 25.9, 19.8; IR (neat): 3261, 2981, 2887, 1687, 1628, 1568 cm^{-1}; LC-MS (TFA): 0.72 min (442) ($[M+H]^+$, 100%); HRMS: calculated for $C_{24}H_{29}{}^{35}ClN_3O_3^+$ ($[M+H]^+$) 442.1892, found 442.1894.

(*S*)-3-(3-Cyanophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 14: A flask was charged with *tert*-butyl ester **5b** (125 mg, 0.230 mmol, 1.0 eq.), NaCN (14 mg, 0.286 mmol, 1.2 eq.), KI (8 mg, 0.048 mmol, 0.2 eq.) and

CuI (5 mg, 0.026 mmol, 0.1 eq.) and was purged with nitrogen. To this, was added *N*,*N*′-dimethylethylenediamine (0.03 mL, 0.279 mmol, 1.2 eq.) and toluene (2 mL) and the reaction was stirred at 115 °C for 16 h. The reaction was then cooled to rt and filtered through celite eluting with ethyl acetate. The filtrate was washed with water (15 mL), passed through a hydrophobic frit and concentrated *in vacuo*. The residue was dissolved in DCM (3 mL) and to this, was added TFA (3 mL, 38.9 mmol, 169.0 eq.) and the reaction was stirred for 2 h. The reaction was concentrated in vacuo and the residue was dissolved in DCM (2 x 10 mL) and concentrated again. HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (86 mg, 0.199 mmol, 86% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.99, MeOH): +48; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.73 (br s, 1H), 7.79–7.75 (m, 1H), 7.75–7.72 (m, 1H), 7.54–7.49 (m, 1H), 7.45–7.37 (m, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 6.25 (d, *J* = 7.3 Hz, 1H), 4.82 (d, *J* = 9.8 Hz, 1H), 4.42 (dd, *J* = 12.2, 2.4 Hz, 1H), 3.55 (td, *J* = 12.2, 7.3 Hz, 1H), 3.49–3.33 (m, 4H), 3.29 (dd, *J* = 12.2, 9.3 Hz, 1H), 2.82 (td, *J* = 13.0, 2.0 Hz, 1H), 2.70 (t, *J* = 6.1 Hz, 2H), 2.59–2.39 (m, 2H), 2.26–2.17 (m, 1H), 2.10–1.97 (m, 1H), 1.94–1.85 (m, 2H), 1.76–1.53 (m, 2H), 1.51–1.39 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 178.9, 173.1, 153.6, 149.8, 142.1, 139.3, 132.9, 132.0, 130.5, 129.2, 118.9, 117.8, 112.3, 108.9, 49.8, 46.6, 43.9, 41.8, 40.6, 38.5, 33.3, 32.3, 31.0, 25.8, 19.7; IR (neat): 3431, 2935, 2864, 2228, 1684, 1627, 1565 cm^{-1}; LC-MS (TFA): 0.64 min (433) ($[M+H]^+$, 99%); HRMS: calculated for $C_{25}H_{29}N_4O_3^+$ ($[M+H]^+$) 433.2234, found 433.2240.

(*S*)-4-Oxo-3-(3-(piperazin-1-yl)phenyl)-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 15a: Prepared according to General Procedure E using aryl bromide **5b** (125 mg, 0.230 mmol, 1.0 eq.) and piperazine (8.0 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water

with 10 mM ammonium bicarbonate modifier) afforded the title compound (87 mg, 0.177 mmol, 77% yield) as an off-white amorphous solid. $[\alpha]_D^{20}$ (*c* = 1.35, MeOH): +44; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.55 (br s, 1H), 7.22–7.06 (m, 3H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.78 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.23 (d, *J* = 7.3 Hz, 1H), 4.75 (d, *J* = 10.3 Hz, 1H), 4.36 (dd, *J* = 12.2, 2.4 Hz, 1H), 3.55 (td, *J* = 11.9, 7.6 Hz, 1H), 3.48–3.26 (m, 5H), 3.26–3.19 (m, 4H), 3.13–3.05 (m, 4H), 2.81 (t, *J* = 12.0 Hz, 1H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.57 (dd, *J* = 16.6, 2.4 Hz, 1H), 2.47 (td, *J* = 12.6, 6.1 Hz, 1H), 2.25–2.10 (m, 1H), 2.07–1.94 (m, 1H), 1.93–1.83 (m, 2H), 1.78–1.60 (m, 2H), 1.42 (td, *J* = 12.8, 6.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.7, 174.0, 153.8, 151.4, 150.3, 141.5, 139.1, 129.0, 120.3, 117.6, 116.4, 114.6, 108.9, 49.8, 49.5, 47.1, 45.3, 43.8, 42.1, 40.6, 38.5, 33.4, 32.4, 31.1, 25.9, 19.8; IR (neat): 3405, 2939, 2858, 1678, 1623, 1599 cm^{-1}; LC-MS (TFA): 0.49 min (492) ([M+H]+, 100%) ; HRMS: calculated for $C_{28}H_{38}N_5O_3^+$ ($[M+H]^+$) 492.2969, found 492.2974.

(*S*)-3-(3-(4-Methylpiperazin-1-yl)phenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 15b: Prepared according to General Procedure E using aryl bromide **5b** (130 mg, 0.240 mmol, 1.0 eq.) and 1-methylpiperazine (6.0 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (45 mg, 0.089 mmol, 37% yield) as an off-white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.79, MeOH): +44; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.61 (br s, 1H), 7.22–7.09 (m, 3H), 7.02–6.88 (m, 1H), 6.78 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.23 (d, *J* = 7.3 Hz, 1H), 4.77 (d, *J* = 9.8 Hz, 1H), 4.36 (dd, *J* = 12.2, 2.9 Hz, 1H), 3.56 (td, *J* = 12.0, 7.3 Hz, 1H), 3.49–3.21 (m, 9H), 2.82 (td, *J* = 12.8, 1.7 Hz, 1H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.67–2.61 (m, 4H), 2.57 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.47 (td, *J* = 12.7, 5.9 Hz, 1H), 2.39 (s, 3H), 2.25–2.11 (m, 1H), 1.99 (tdd, *J* = 12.0, 9.8, 5.9 Hz, 1H), 1.89 (quin, *J* = 6.0 Hz, 2H),

1.78–1.60 (m, 2H), 1.47–1.36 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.7, 174.0, 153.8, 151.1, 150.3, 141.5, 139.1, 129.0, 120.0, 117.6, 116.3, 114.3, 108.9, 54.9, 49.7, 48.8, 47.1, 45.8, 43.7, 42.1, 40.6, 38.5, 33.4, 32.4, 31.1, 25.9, 19.8; IR (neat): 3408, 2938, 1682, 1627, 1599 cm^{-1}; LC-MS (TFA): 0.49 min (506) ($[M+H]^+$, 100%); HRMS: calculated for $C_{29}H_{40}N_5O_3^+$ ($[M+H]^+$) 506.3126, found 506.3130.

(*S*)-3-(3-Morpholinophenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 15c: Prepared according to General Procedure E using aryl bromide **5b** (175 mg, 0.323 mmol, 1.0 eq.) and morpholine (5.3 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (68 mg, 0.138 mmol, 43% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.67, MeOH): +60; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.62 (br s, 1H), 7.22–7.08 (m, 3H), 6.97 (d, *J* = 7.3 Hz, 1H), 6.82–6.74 (m, 1H), 6.23 (d, *J* = 7.3 Hz, 1H), 4.78 (d, *J* = 9.8 Hz, 1H), 4.37 (dd, *J* = 12.0, 2.7 Hz, 1H), 3.88–3.82 (m, 4H), 3.56 (td, *J* = 12.1, 7.1 Hz, 1H), 3.49–3.33 (m, 4H), 3.28 (dd, *J* = 12.2, 8.8 Hz, 1H), 3.21–3.15 (m, 4H), 2.82 (td, *J* = 13.0, 2.0 Hz, 1H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.58 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.53–2.40 (m, 1H), 2.22–2.12 (m, 1H), 2.06–1.93 (m, 1H), 1.92–1.84 (m, 2H), 1.78–1.61 (m, 2H), 1.48–1.36 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.7, 174.0, 153.8, 151.3, 150.3, 141.6, 139.1, 129.0, 120.2, 117.6, 115.7, 113.9, 108.9, 67.0, 49.7, 49.4, 47.1, 43.7, 42.1, 40.6, 38.5, 33.4, 32.4, 31.1, 25.9, 19.8; IR (neat): 3421, 2936, 2857, 1682, 1627, 1599 cm^{-1}; LC-MS (TFA): 0.59 min (493) ($[M+H]^+$, 100%); HRMS: calculated for $C_{28}H_{37}N_4O_4^+$ ($[M+H]^+$) 493.2809, found 493.2819.

(*S*)-3-([1,1'-Biphenyl]-3-yl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 16: Prepared according to General Procedure F using *tert*-butyl ester **5b** (82 mg, 0.151 mmol, 1.0 eq.), phenylboronic acid pinacol ester (1.5 eq.), 2 M NaOH

(0.6 eq.), and methanol (4 mL), heating at 120 °C for 30 min. The reaction was filtered and concentrated *in vacuo*. The residue was dissolved in DCM (3 mL) and to this, was added TFA (3 mL). After stirring for 2 h, the reaction was concentrated *in vacuo* and the residue co-concentrated with DCM (2 x 10 mL). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (50 mg, 0.103 mmol, 68% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.95, MeOH): +78; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.52 (br s, 1H), 7.67 (t, *J* = 1.7 Hz, 1H), 7.63–7.55 (m, 2H), 7.53–7.28 (m, 6H), 7.18 (d, *J* = 7.3 Hz, 1H), 6.24 (d, *J* = 7.3 Hz, 1H), 4.75 (d, *J* = 9.8 Hz, 1H), 4.47 (dd, *J* = 12.0, 2.7 Hz, 1H), 3.58 (td, *J* = 11.7, 7.3 Hz, 1H), 3.51–3.37 (m, 4H), 3.35–3.25 (m, 1H), 2.83 (td, *J* = 13.0, 2.0 Hz, 1H), 2.75–2.61 (m, 3H), 2.49 (td, *J* = 12.6, 6.1 Hz, 1H), 2.23–2.13 (m, 1H), 2.07–1.95 (m, 1H), 1.94–1.83 (m, 2H), 1.80–1.60 (m, 2H), 1.52–1.38 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.3, 173.9, 153.6, 150.0, 141.3, 141.3, 141.0, 139.2, 128.9, 128.6, 127.3, 127.2, 127.2, 127.1, 125.6, 117.7, 108.9, 49.9, 47.0, 43.9, 41.8, 40.6, 38.5, 33.3, 32.3, 31.0, 25.9, 19.8; IR (neat): 3425, 2938, 2866, 1683, 1629, 1563 cm^{-1}; LC-MS (TFA): 0.83 min (484) ($[M+H]^+$, 97%); HRMS: calculated for $C_{30}H_{34}N_3O_3^+$ ($[M+H]^+$) 484.2595, found 484.2601

(*S*)-4-Oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)-3-(*m*-tolyl)butanoic acid 17a: Prepared according to General Procedure F using aryl bromide **6b** (36 mg, 0.074 mmol, 1.0 eq.), trimethylboroxine (1.0 eq.), 2 M NaOH (0.5 eq.), and methanol (1 mL), heating at 120 °C for 40 min. HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (12 mg, 0.028 mmol, 39% yield) as an off-white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.48, MeOH): +83; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.60 (br s, 1H), 7.32–7.23

(m, 2H), 7.22–7.15 (m, 2H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.23 (d, *J* = 7.3 Hz, 1H), 4.79 (d, *J* = 9.8 Hz, 1H), 4.38 (dd, *J* = 12.2, 2.4 Hz, 1H), 3.56 (td, *J* = 12.0, 7.3 Hz, 1H), 3.47–3.35 (m, 4H), 3.28 (dd, *J* = 12.5, 9.0 Hz, 1H), 2.82 (td, *J* = 13.0, 2.4 Hz, 1H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.57 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.47 (td, *J* = 12.8, 6.1 Hz, 1H), 2.34 (s, 3H), 2.23–2.13 (m, 1H), 2.06–1.94 (m, 1H), 1.93–1.84 (m, 2H), 1.77–1.62 (m, 2H), 1.47–1.36 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.8, 174.3, 153.8, 150.3, 140.5, 139.1, 137.9, 128.9, 128.2, 127.5, 125.4, 117.6, 108.9, 49.8, 46.9, 43.7, 41.7, 40.6, 38.5, 33.4, 32.4, 31.1, 25.9, 21.5, 19.8; IR (neat): 3261, 2937, 2861, 1683, 1623, 1564 cm^{-1}; LC-MS (For): 0.66 min (422) ($[M+H]^+$, 100%); HRMS: calculated for $C_{25}H_{32}N_3O_3^+$ ($[M+H]^+$) 422.2438, found 422.2448.

(*S*)-3-(3-Cyclopropylphenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 17b: Prepared according to General Procedure F using aryl bromide **6b** (150 mg, 0.308 mmol, 1.0 eq.), cyclopropylboronic acid (1.5 eq.), 2 M NaOH (0.6 eq.), and methanol (15 mL), heating at 120 °C for 4 h. HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (4 mg, 8.94 μmol, 3% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 1.10, MeOH): +81; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.59 (br s, 1H), 7.27–7.13 (m, 4H), 6.90–6.84 (m, 1H), 6.22 (d, *J* = 7.3 Hz, 1H), 4.77 (d, *J* = 9.8 Hz, 1H), 4.36 (dd, *J* = 12.2, 2.4 Hz, 1H), 3.54 (td, *J* = 12.0, 7.3 Hz, 1H), 3.45–3.32 (m, 4H), 3.26 (dd, *J* = 12.2, 9.3 Hz, 1H), 2.80 (td, *J* = 13.0, 2.0 Hz, 1H), 2.67 (t, *J* = 6.1 Hz, 2H), 2.55 (dd, *J* = 16.6, 2.9 Hz, 1H), 2.46 (td, *J* = 12.7, 6.4 Hz, 1H), 2.21–2.11 (m, 1H), 2.04–1.81 (m, 4H), 1.75–1.59 (m, 2H), 1.47–1.34 (m, 1H), 0.96–0.87 (m, 2H), 0.75–0.63 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.7, 174.0, 153.7, 150.1, 143.9, 140.4, 139.1, 128.2, 126.0, 125.3, 123.5, 117.5, 108.9, 49.7, 46.8, 43.7, 41.8, 40.5, 38.4, 33.3, 32.3, 31.0, 25.8, 19.7, 15.3, 9.1, 9.1; IR (neat): 3405, 2923, 2862, 1679,

1623, 1564 cm^{-1}; LC-MS (For): 0.73 min (448) ($[M+H]^+$, 100%); HRMS: calculated for $C_{27}H_{34}N_3O_3$ ($[M+H]^+$) 448.2595, found 448.2602.

(*S*)-3-(3-(Cyclopent-1-en-1-yl)phenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 17c: Prepared according to General Procedure F using aryl bromide **6b** (67 mg, 0.140 mmol, 1.0 eq.), cyclopent-1-en-1-ylboronic acid (1.2 eq.), 2 M NaOH (0.6 eq.), and methanol (15 mL), heating at 120 °C for 30 min. HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (24 mg, 0.051 mmol, 37% yield) as an off-white amorphous solid. $[\alpha]_D^{20}$ (c = 0.45, MeOH): +53; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 10.62 (br s, 1H), 7.55–7.46 (m, 1H), 7.39–7.28 (m, 2H), 7.26–7.23 (m, 1H), 7.20–7.15 (m, 1H), 6.26–6.16 (m, 2H), 4.80 (d, J = 9.7 Hz, 1H), 4.40 (dd, J = 12.1, 2.3 Hz, 1H), 3.56 (td, J = 12.0, 7.4 Hz, 1H), 3.47–3.38 (m, 4H), 3.28 (dd, J = 12.1, 9.5 Hz, 1H), 2.86–2.80 (m, 1H), 2.78–2.64 (m, 4H), 2.59 (dd, J = 17.0, 2.5 Hz, 1H), 2.56–2.50 (m, 2H), 2.48 (td, J = 12.9, 6.4 Hz, 1H), 2.21–2.15 (m, 1H), 2.04–1.96 (m, 3H), 1.92–1.86 (m, 2H), 1.75–1.63 (m, 2H), 1.43 (td, J = 13.1, 5.9 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 179.7, 174.1, 153.7, 150.2, 142.5, 140.5, 139.1, 136.9, 128.3, 126.8, 126.1, 125.5, 124.1, 117.6, 108.9, 49.8, 47.0, 43.8, 41.8, 40.6, 38.5, 33.4, 33.3, 33.2, 32.4, 31.1, 25.9, 23.4, 19.8; IR (neat): 3259, 2938, 2865, 1678, 1625, 1564 cm^{-1}; LC-MS (For): 0.85 min (474) ($[M+H]^+$, 100%); HRMS: calculated for $C_{29}H_{36}N_3O_3^+$ ($[M+H]^+$) 474.2751, found 474.2752.

(*S*)-3-(3-Cyclopentylphenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 18: Prepared according to General Procedure F using aryl bromide **6b** (89 mg, 0.183 mmol, 1.0 eq.), cyclopent-1-en-1-ylboronic acid (1.3 eq.), 2 M NaOH (0.7 eq.), and methanol (15 mL), heating at 120 °C for 30 min. The reaction was filtered, washed

with methanol (15 mL) and hydrogenated using an H-cube® Pro (40 °C, 40 bar, 1 mL/min flow rate. 5% Pd/C cartridge) and the reaction mixture was concentrated *in vacuo*. HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (5 mg, 10.5 μmol, 6% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.37, MeOH): +33; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 10.61 (br s, 1H), 7.36–7.28 (m, 2H), 7.25–7.20 (m, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.24 (d, *J* = 7.2 Hz, 1H), 4.80 (d, *J* = 9.7 Hz, 1H), 4.39 (dd, *J* = 12.1, 1.9 Hz, 1H), 3.56 (td, *J* = 12.0, 7.4 Hz, 1H), 3.48–3.36 (m, 3H), 3.32–3.26 (m, 1H), 3.02–2.95 (m, 1H), 2.83 (t, *J* = 12.5 Hz, 1H), 2.70 (t, *J* = 6.1 Hz, 2H), 2.63–2.56 (m, 1H), 2.47 (td, *J* = 12.7, 6.4 Hz, 1H), 2.27–2.14 (m, 2H), 2.11–1.96 (m, 4H), 1.89 (quin, *J* = 5.9 Hz, 2H), 1.85–1.77 (m, 2H), 1.76–1.56 (m, 5H), 1.46–1.39 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 179.9, 174.2, 153.8, 150.3, 146.5, 140.4, 139.1, 128.2, 127.3, 125.7, 125.4, 117.6, 108.9, 49.8, 47.0, 46.0, 43.7, 41.9, 40.6, 38.5, 34.7, 34.6, 33.4, 32.4, 31.1, 25.9, 25.5 (2C), 19.8; IR (neat): 3424, 2939, 2867, 1683, 1626, 1565 cm^{-1}; LC-MS (For): 0.86 min (476) ($[M+H]^+$, 100%); HRMS: calculated for $C_{29}H_{38}N_3O_3^+$ ($[M+H]^+$) 476.2908, found 476.2911.

(*R*)-3-(5-methylthiophen-2-yl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 19: Prepared according to General Procedure G using aryl bromide **6i** (200 mg, 0.406 mmol, 1.0 eq.) and trimethylboroxine (5.0 eq.) in 1,4-dioxane (8 mL)/water (2 mL). After stirring for 4 h at 90 °C, the reaction mixture was filtered through celite and concentrated *in vacuo*. HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (14 mg, 0.033 mmol, 8% yield) as a white amorphous solid. Room temperature ^{1}H and ^{13}C NMR spectra in $CDCl_3$ show complex mix of rotamers. $[\alpha]_D^{20}$ (*c* = 1.13,

MeOH): +25; ^{1}H NMR (400 MHz, DMSO-d_6, 393 K) δ = δ 8.15 (s, 1H), 7.29–7.13 (m, 1H), 6.77–6.69 (m, 1H), 6.63–6.57 (m, 1H), 6.46–6.37 (m, 1H), 4.39–4.15 (m, 1H), 3.68–3.44 (m, 2H), 3.39–3.20 (m, 3H), 3.08–2.92 (m, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.63–2.52 (m, 3H), 2.41–2.37 (m, 3H), 2.20–2.08 (m, 1H), 2.06–1.94 (m, 1H), 1.83 (quin, *J* = 6.0 Hz, 2H), 1.76–1.64 (m, 2H), 1.61–1.45 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 303 K) δ = 179.5, 179.2, 174.0, 173.4, 153.7, 153.7, 150.1, 149.7, 141.1, 140.2, 139.2, 139.1, 138.5, 138.4, 124.5, 124.3, 124.1, 117.9, 117.6, 108.9, 108.8, 49.6, 48.4, 44.3, 43.8, 43.3, 43.1, 42.7, 41.5, 40.6, 40.6, 38.5, 35.5, 33.4, 32.3, 31.6, 31.5, 31.1, 30.5, 25.9, 25.9, 19.8, 19.7, 15.2; IR (neat): 3390–2151, 1679, 1631, 1564 cm^{-1}; LC-MS (TFA): 0.69 min (428) ([M+H]$^+$, 100%); HRMS: calculated for $C_{23}H_{30}N_3O_3S^+$ ([M+H]$^+$) 428.2002, found 428.2002.

Compounds **20** and **21** were prepared as previously reported.[22]

3-(5-(3-(Pyridin-2-ylamino)propoxy)-1*H*-indol-1-yl)propanoic acid 20: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.99–7.94 (m, 1H), 7.38–7.31 (m, 2H), 7.27 (d, *J* = 3.2 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.79 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.51 (t, *J* = 5.4 Hz, 1H), 6.48–6.40 (m, 2H), 6.29 (d, *J* = 3.2 Hz, 1H), 4.34 (t, *J* = 6.8 Hz, 2H), 4.04 (t, *J* = 6.6 Hz, 2H), 3.39 (q, *J* = 6.6 Hz, 2H), 2.70 (t, *J* = 6.8 Hz, 2H), 1.98 (quin, *J* = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 172.5, 158.9, 152.7, 147.5, 136.4, 130.8, 128.9, 128.5, 111.6, 111.3, 110.3, 108.0, 103.4, 100.2, 66.1, 41.7, 37.8, 34.9, 28.9; IR (neat): 3275, 2856, 1683, 1616, 1488 cm^{-1}; LC-MS: (HpH): 0.67 min (340) ([M+H]$^+$, 99%).

3-(5-(2-(6-(Methylamino)pyridin-2-yl)ethoxy)-1*H*-indol-1-yl)propanoic acid 21: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.20 (br s, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.30 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.27 (d, *J* = 3.2 Hz, 1H), 7.06 (d, *J* = 2.2 Hz, 1H), 6.75 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.45 (d, *J* =

7.1 Hz, 1H), 6.35–6.28 (m, 2H), 6.27 (d, *J* = 8.3 Hz, 1H), 4.34 (t, *J* = 6.7 Hz, 2H), 4.28 (t, *J* = 6.9 Hz, 2H), 2.96 (t, *J* = 6.9 Hz, 2H), 2.75 (d, *J* = 4.9 Hz, 3H), 2.71 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 172.4, 159.2, 156.2, 152.6, 136.9, 130.8, 128.9, 128.5, 111.6, 110.5, 110.3, 104.9, 103.4, 100.3, 67.5, 41.6, 37.5, 34.7, 27.9; IR (neat): 3264, 2914, 1689, 1619, 1542, 1239, 1159 cm^{-1}; LC-MS: (HpH): 0.67 min (340) ([M+H]$^+$, 97%).

(*S*)-4-(Methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-4-oxo-3-phenylbutanoic acid 22: Prepared according to General Procedure D using (*S*)-4-*tert*-butoxy-4-oxo-2-phenylbutanoic acid (Fluorochem) (120 mg, 0.479 mmol, 1.0 eq.) in DCM (4 mL), DIPEA (3 eq.), HATU (1.5 eq.) and a solution of *N*-methyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine (prepared as previously described)[41] (1.5 eq.) in DCM (2 mL) followed by addition of HCl (4 mL, 33.4 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (149 mg, 0.377 mmol, 79% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.66, MeOH): +194; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.13 (br s, 1H), 7.42–7.34 (m, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.25–7.19 (m, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 6.20 (d, *J* = 7.3 Hz, 1H), 4.65 (td, *J* = 13.2, 2.9 Hz, 1H), 4.26 (dd, *J* = 12.2, 3.4 Hz, 1H), 3.49–3.41 (m, 2H), 3.33 (dd, *J* = 17.1, 12.2 Hz, 1H), 3.01 (s, 3H), 2.91–2.78 (m, 1H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.59–2.48 (m, 2H), 2.39 (td, *J* = 13.0, 3.9 Hz, 1H), 1.97–1.68 (m, 5H), 1.65–1.51 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.4, 174.5, 153.3, 150.3, 139.6, 139.4, 128.7, 128.0, 126.7, 117.8, 108.8, 46.3, 44.1, 43.3, 40.6, 34.0–33.8 (m, 2C), 26.4, 25.9, 24.9, 19.7; IR (neat): 3265, 2933, 1671, 1633, 1491 cm^{-1}; LC-MS (For): 0.61 min (396) ([M+H]$^+$, 96%); HRMS: calculated for $C_{23}H_{30}N_3O_3^+$ ([M+H]$^+$) 396.2282, found 322.2283.

(*S*)-4-Oxo-3-phenyl-4-(3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)azetidin-1-

yl)butanoic acid 23: Prepared according to General Procedure D using (*S*)-4-*tert*-butoxy-4-oxo-2-phenylbutanoic acid (Fluorochem) (80 mg, 0.320 mmol, 1.0 eq.) in DCM (3 mL), DIPEA (3.0 eq.), HATU (1.5 eq.) and a solution of 7-(3-(azetidin-3-yl)propyl)-1,2,3,4-tetrahydro-1,8-naphthyridine (prepared as previously reported)[42] (1.5 eq.) in DCM (4 mL) followed by addition of HCl (4 mL, 50.1 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (36 mg, 0.091 mmol, 29% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 1.37, MeOH): +137; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.08 (br s, 1H), 7.45–7.38 (m, 2H), 7.31–7.25 (m, 3H), 7.23–7.16 (m, 2H), 6.24 (d, *J* = 7.2 Hz, 1H), 4.98 (d, *J* = 8.1 Hz, 1H), 4.32 (t, *J* = 7.2 Hz, 1H), 4.13 (dd, *J* = 12.2, 2.6 Hz, 1H), 3.98 (dd, *J* = 9.5, 6.4 Hz, 1H), 3.76–3.70 (m, 1H), 3.46 (t, *J* = 5.6 Hz, 2H), 3.37 (dd, *J* = 17.0, 12.1 Hz, 1H), 2.74–2.69 (m, 2H), 2.77–2.69 (m, 1H), 2.57 (dd, *J* = 17.0, 2.7 Hz, 1H), 2.48–2.34 (m, 2H), 2.29–2.17 (m, 1H), 1.96–1.87 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.7, 176.3, 153.9, 149.6, 140.4, 139.2, 128.4, 128.0, 126.7, 118.2, 109.0, 54.7, 54.4, 43.5, 41.3, 40.6, 33.9, 31.4, 30.5, 25.9, 19.7; IR (neat): 3265, 2939, 2871, 1674, 1630, 1600 cm^{-1}; LC-MS (For): 0.57 min (394) ($[M+H]^+$, 96%); HRMS: calculated for $C_{23}H_{28}N_3O_3^+$ ($[M+H]^+$) 394.2125, found 394.2132.

(*S*)-4-Oxo-3-phenyl-4-(3-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl)azetidin-1-yl)butanoic acid 24: Prepared according to General Procedure D using (*S*)-4-*tert*-butoxy-4-oxo-2-phenylbutanoic acid (Fluorochem) (123 mg, 0.491 mmol, 1.0 eq.) in DCM (3 mL), DIPEA (3.0 eq.), HATU (1.5 eq.) and a solution of 7-(2-(azetidin-3-yl)ethyl)-1,2,3,4-tetrahydro-1,8-naphthyridine (prepared as previously reported)[42] (1.2 eq.) in DCM (4 mL) followed by addition of HCl (4 mL, 32.6 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded

the title compound (80 mg, 0.196 mmol, 40% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 1.09, MeOH): +52; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.50 (br s, 1H), 7.41–7.32 (m, 2H), 7.30–7.24 (m, 2H), 7.23–7.14 (m, 2H), 6.20 (d, *J* = 7.3 Hz, 1H), 4.60 (dd, *J* = 8.3, 5.9 Hz, 1H), 4.25 (t, *J* = 8.6 Hz, 1H), 4.00 (dd, *J* = 12.2, 2.9 Hz, 1H), 3.87 (d, *J* = 7.3 Hz, 2H), 3.49–3.40 (m, 2H), 3.34 (dd, *J* = 16.9, 12.5 Hz, 1H), 2.88–2.73 (m, 2H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.63–2.49 (m, 2H), 2.36–2.20 (m, 1H), 1.91–1.78 (m, 3H), 1.69 (tdt, *J* = 13.2, 9.1, 4.5 Hz, 1H), 1.48 (dq, *J* = 14.6, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.8, 175.0, 153.5, 149.8, 139.9, 139.2, 128.4, 127.9, 126.7, 117.9, 108.6, 53.6, 50.7, 43.4, 41.2, 40.5, 35.4, 29.1, 27.5, 26.0, 23.4, 19.6; IR (neat): 3265, 2939, 1683, 1624, 1564 cm^{-1}; LC-MS (TFA): 0.65 min (408) ($[M+H]^+$, 100%); HRMS: calculated for $C_{24}H_{30}N_3O_3^+$ ($[M+H]^+$) 408.2282, found 408.2288.

(3*S*)-4-Oxo-3-phenyl-4-(3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)piperidin-1-yl)butanoic acid 25: Prepared according to General Procedure D using (*S*)-4-*tert*-butoxy-4-oxo-2-phenylbutanoic acid (Fluorochem) (100 mg, 0.400 mmol, 1.0 eq.) in DCM (3 mL), DIPEA (3.0 eq.), HATU (1.5 eq.) and a solution of 7-(2-(piperidin-3-yl)ethyl)-1,2,3,4-tetrahydro-1,8-naphthyridine (prepared as previously reported)[42] (1.3 eq.) in DCM (4 mL) followed by addition of HCl (4 mL, 40.0 eq.). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (78 mg, 0.185 mmol, 46% yield) as a white amorphous solid. $[\alpha]_D^{20}$ (*c* = 0.94, MeOH): +43; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.14 (br s, 1H), 7.41–7.37 (m, 2H), 7.31–7.26 (m, 2H), 7.23–7.14 (m, 2H), 6.19 (d, *J* = 7.3 Hz, 1H), 4.63 (dd, *J* = 11.0, 2.7 Hz, 1H), 4.19–3.83 (m, 2H), 3.54–3.36 (m, 4H), 3.23–3.03 (m, 1H), 2.80 (td, *J* = 12.8, 3.7 Hz, 1H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.55 (dd, *J* = 16.6, 2.9 Hz, 1H), 2.28–2.15 (m, 1H), 2.08–1.93 (m, 1H), 1.92–1.83 (m, 2H), 1.69–1.30 (m, 5H), 1.21 (td, *J* = 13.1, 3.7 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 179.4, 173.8

(br s), 153.6, 151.0, 140.9, 139.1, 128.5, 128.2, 126.6, 117.2, 108.9, 47.8 (br s), 45.0 (br s), 42.9, 41.7 (br s), 40.7, 35.0 (br s), 33.1 (br s), 32.8 (br s), 31.9, 25.9, 21.6 (br s), 19.9; IR (neat): 3276, 2859, 2924, 1672, 1626 cm^{-1}; LC-MS (For): 0.65 min (422) ($[M+H]^+$, 100%); HRMS: calculated for $C_{25}H_{32}N_3O_3^+$ ($[M+H]^+$) 422.2438, found 422.2444.

(*S*)-3-(3,5-Dimethylphenyl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 27: Prepared according to General Procedure G using aryl bromide **5e** (65 mg, 0.105 mmol, 1.0 eq.) and methylboronic acid (5.0 eq.) 1,4-dioxane (4 mL)/water (1 mL). After stirring for 16 h at 90 °C, the reaction mixture was filtered through celite and concentrated *in vacuo*. The residue was dissolved in DCM (3 mL) and to this, was added TFA (3 mL, 372.0 eq.). After stirring for 2 h, the reaction was concentrated *in vacuo* and co-concentrated with DCM (2 x 10 mL). HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (28 mg, 0.064 mmol, 61% yield) as a white amorphous solid. Room temperature ^{1}H NMR spectrum in $CDCl_3$ shows approximate 11:7 ratio of rotamers; ^{1}H NMR spectrum integrated to 2x for ease of assignment. $[\alpha]_D^{20}$ (*c* = 0.84, MeOH): +14; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.95 (br s, 1H), 10.57 (br s, 1H), 7.16 (d, *J* = 7.3 Hz, 2H), 7.12–6.96 (m, 4H), 6.91–6.80 (m, 2H), 6.29–6.15 (m, 2H), 4.76 (d, *J* = 9.8 Hz, 1H), 4.37–4.30 (m, 1H), 4.18–4.04 (m, 2H), 3.65–2.92 (m, 12H), 2.81 (td, *J* = 13.0, 2.0 Hz, 1H), 2.68 (t, *J* = 6.1 Hz, 4H), 2.60–2.38 (m, 4H), 2.29 (s, 12H), 2.21–1.36 (m, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.0, 179.8, 174.6, 174.2, 153.8, 153.7, 150.3, 150.0, 140.4, 139.4, 139.1, 139.0, 137.9, 137.7, 128.5, 128.4, 126.0, 125.9, 117.7, 117.5, 109.0, 108.9, 49.7, 48.5, 46.8, 45.9, 44.4, 43.7, 42.7, 41.9, 40.6, 40.6, 38.5, 35.5, 33.4, 32.4, 31.7, 31.6, 31.1, 30.7, 25.9, 25.9, 21.3, 19.8, 19.7; IR (neat): 3414, 2922,

2864, 1679, 1626, 1603, 1565 cm^{-1}; LC-MS (TFA): 0.76 min (436) ($[M+H]^+$, 100%) HRMS: calculated for $C_{26}H_{36}N_3O_3^+$ ($[M+H]^+$) 438.2595, found 448.2608.

(*R*)-3-(4-Methylthiophen-2-yl)-4-oxo-4-((*R*)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid 28: Prepared according to General Procedure G using aryl bromide **6h** (99 mg, 0.201 mmol, 1.0 eq.) and trimethylboroxine acid (5.0 eq.) in 1,4-dioxane (8 mL)/water (2 mL). After stirring for 4 h at 90 °C, the reaction mixture was filtered through celite and concentrated *in vacuo*. HPLC using Mass Directed Autopurification (Xselect CSH C18 column eluting with 15–55% acetonitrile in water with 10 mM ammonium bicarbonate modifier) afforded the title compound (32 mg, 0.075 mmol, 37% yield) as a white amorphous solid. Room temperature ^1H and ^{13}C NMR spectra show complex mix of rotamers, complicating interpretation. $[\alpha]_D^{20}$ (*c* = 0.54, MeOH): +27; ^1H NMR (400 MHz, $CDCl_3$) δ = 10.67 (br s, 1H), 7.20–7.14 (m, 1H), 6.86–6.79 (m, 1H), 6.74–6.69 (m, 1H), 6.23 (d, *J* = 7.3 Hz, 1H), 4.75–4.53 (m, 1H), 4.38–3.99 (m, 1H), 3.62–3.28 (m, 6H), 3.09–2.75 (m, 1H), 2.72–2.59 (m, 3H), 2.53–2.36 (m, 1H), 2.23–2.14 (m, 4H), 2.09–1.95 (m, 1H), 1.94–1.79 (m, 2H), 1.76–1.52 (m, 2H), 1.51–1.35 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.1, 173.2, 153.7, 150.1, 143.1, 139.3, 139.1, 137.1, 126.9, 126.9, 119.1, 119.0, 118.0, 117.7, 109.0, 108.9, 49.6, 48.5, 44.4, 43.8, 43.1, 42.5, 41.3, 40.6, 38.5, 35.6, 33.4, 32.3, 31.6, 31.5, 31.1, 30.6, 25.9, 19.8, 19.7, 15.7; IR (neat): 3260, 2929, 2865, 1682, 1632, 1564 cm^{-1}; LC-MS (TFA): 0.70 min (428) ($[M+H]^+$, 98%); HRMS: calculated for $C_{23}H_{30}N_3O_3S^+$ ($[M+H]^+$) 428.2002, found 428.2007.

ASSOCIATED CONTENT

General experimental information; full synthetic procedures and characterization data for all new compounds; all assay methodology and full data; computational details and additional docking images.

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Author Contributions

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ABBREVIATIONS

FP, fluorescence polarization; MDCK-MDR1, Madin−Darby canine kidney cells transfected with the human MDR1 gene; MIDAS, metal-ion-dependent adhesion site; RGD, arginine−glycine−aspartic acid; SAR, structure−activity relationship.

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