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Original article

Synthesis and biological evaluation of isoxazole, oxazole, and oxadiazole containing heteroaryl analogs of biaryl ureas as DGAT1 inhibitors

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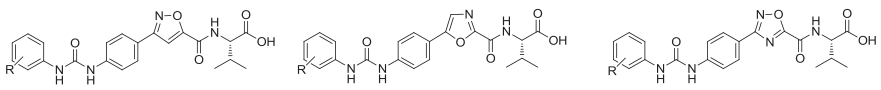
HIGHLIGHTS

- Identification of a 3-phenylisoxazole scaffold as potent inhibitor of hDGAT1.
- DGAT1 activity of 3-phenylisoxazoles translates to *in vivo* triglyceride reduction.
- 3-Phenylisoxazole analogs with improved cLogP result in improved solubility.
- Compound **40a** may serve as a new lead for developing newer anti-obesity agents.

GRAPHICAL ABSTRACT



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ABSTRACT

Diacylglycerol acyltransferase, DGAT1, is a promising target enzyme for obesity due to its involvement in the committed step of triglyceride biosynthesis. Amino biphenyl carboxylic acids, exemplified by compound **4**, are known potent inhibitors of hDGAT1. However the high cLogP and poor solubility of these biphenyl analogs might tend to limit their development. We have synthesized and evaluated compounds containing 3-phenylisoxazole, 5-phenyloxazole, and 3-phenyl-1,2,4-oxadiazole biaryl units for their hDGAT1 inhibition. Our aim in synthesizing such heterocyclic analogs was to improve the cLogP and solubility of these molecules while retaining hDGAT1 potency. Several compounds within the 3-phenylisoxazole series exhibited potent hDGAT1 inhibition when evaluated using an *in vitro* enzymatic assay. Certain promising compounds were studied for their potential to reduce triglyceride levels using an *in vivo* fat tolerance test in mice and were also evaluated for any possible improvement to their solubility. Compound **40a** (IC_{50} = 64 nM) with an *in vivo* plasma triglyceride reduction of 90 percent, and a solubility of 0.43 mg/ml at pH 7.4 may serve as a new lead for developing newer anti-obesity agents.

1. Introduction

Obesity is a chronic condition characterized by abnormal or excessive fat accumulation. Body mass index (BMI), serves as an estimate of body fat in humans and is measured using the weight and height of an individual. Individuals with a BMI equal to or

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greater than 30 kg m^{-2} are considered clinically obese [1]. One WHO statistic highlights that a billion adults worldwide are overweight, of whom 300 million are clinically obese [2]. The high peripheral lipid stores responsible for obesity have been implicated in an array of additional health problems, including increased risk of insulin resistance, type 2 diabetes, fatty liver disease, atherosclerosis, hypertension, and cardiovascular disease [3]. Orlistat, the only marketed anti-obesity drug prevents the absorption of fat from human diet [4]. However severe adverse effects such as steatorrhea, fecal incontinence, and urgent bowel movements are frequently observed following the use of this drug thereby necessitating the need for newer anti-obesity agents exhibiting fewer side-effects [5]. The peripheral lipid levels are essentially controlled by triglyceride biosynthetic pathways. Hence inhibition of triglyceride biosynthesis may act as an effective strategy to either reverse or prevent obesity and its related medical consequences. Enzymes catalyzing various steps of triglyceride biosynthesis have thus become attractive targets for developing anti-obesity agents [6]. Acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) is one such enzyme known to catalyze the final rate-determining step of triglyceride biosynthesis [7]. Of late efforts directed towards exploiting this target for the development of anti-obesity agents have led to the identification of several potent hDGAT1 inhibitors. A few of these inhibitors have been studied clinically (Fig. 1) [8–10].

Bayer Pharmaceuticals have patented a potent series of amino biphenyl carboxylic acids as hDGAT1 inhibitors [10,11]. Compounds within this series, exemplified by structure **4**, position the carboxylic acid through an amide to the biaryl core. The IC_{50} of compound **4** is not reported in literature. We synthesized compound **4** [11] and in our hands it exhibited an *in vitro* hDGAT1 IC_{50} of 35 nM. Despite its potency, compound **4** possesses a high cLogP of 6.31 log units that could possibly limit its development due to low solubility. A compound with low aqueous solubility often exhibits low oral bioavailability thereby requiring a higher dose to achieve therapeutically relevant plasma concentration. Low aqueous solubility can also present several challenges for formulation development during later stages of drug development. Thus attempts to address this issue early during design and synthesis of molecules could prove beneficial.

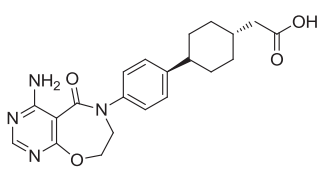
In this study we have attempted to incorporate certain structural features to compound **4** that would result in cLogP reduction and subsequently improve its aqueous solubility while retaining hDGAT1 activity. We hypothesized that cLogP reduction could be achieved by introducing five membered heterocycles in place of the phenyl B-ring within the biphenyl core of compound **4**. To this effect compound **5** (cLogP = 5.40), a 3-phenylisoxazole analog possessing an isoxazole in place of the phenyl B-ring, was synthesized. It exhibited a marginal loss in hDGAT1 potency (IC_{50} = 120 nM) coupled with a 1 log unit lowering of its cLogP over compound **4**. We envisaged that a further cLogP reduction of compound **5** can be achieved following the replacement of its amino fluorobenzothiazole subunit with a phenyl urea. Successful implementation of this strategy towards cLogP reduction coupled with an improvement in hDGAT1 potency on diverse biaryl scaffolds has been reported [11–13]. We hence explored the feasibility of this phenyl urea modification in combination with the 3-phenylisoxazole, 5-phenyloxazole and 3-phenyl-1,2,4-oxadiazole scaffolds (Fig. 2). Following the B-ring optimization with five membered aromatic heterocycles, we explored the scope of seven different linkers in place of urea. This included an evaluation of amide, thiourea, sulfonylurea, sulfonamide, 2-hydroxyacetamide, oxalamide, and ether linkers in place of the urea linker (Fig. 2). The efforts thus undertaken were focused on developing and optimizing a heteroaryl scaffold that exhibits improved solubility while retaining hDGAT1 activity.

2. Chemistry

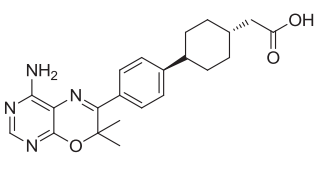
To synthesize compound **5** (Scheme 1) 4-nitro benzaldehyde (**7**) was converted to its corresponding oxime (**8**) using hydroxylamine hydrochloride [14] that on treatment with *N*-chlorosuccinimide was converted to its chloro oxime (**9**) [15]. Compound **9** was cyclized using ethyl propiolate to obtain ethyl 3-(4-nitrophenyl) isoxazole-5-carboxylate (**10**) [11]. Iron-ammonium chloride mediated reduction of compound **10** afforded ethyl 3-(4-aminophenyl) isoxazole-5-carboxylate (**11**) [16] that was subsequently coupled with 2-chloro-6-fluoro benzothiazole under acidic conditions to yield ethyl 3-(4-((6-fluorobenzo[*d*]thiazol-2-yl)amino)phenyl)isoxazole-5-carboxylate (**12**). Subsequent hydrolysis of compound **12** using 1.0 M sodium hydroxide at 55–60 °C yielded its acid (**13**). Coupling of compound **13** with L-valine methyl ester hydrochloride using standard peptide coupling reagents such as dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBT) in DMF yielded the corresponding methyl ester (**14**) [10] that on hydrolysis using 1.0 M lithium hydroxide in water yielded compound **5**.

The synthesis of 3-phenylisoxazole analogs (Scheme 2) involved a hydrolysis of ethyl 3-(4-nitrophenyl)isoxazole-5-carboxylate (**10**) to yield its corresponding acid (**15**). Coupling of **15** with L-valine methyl ester hydrochloride using isobutyl chloroformate and *N*-methyl morpholine yielded compound **16** [12,17] that on iron-ammonium chloride mediated reduction afforded the corresponding amine (**17**). Subsequently 3-phenylisoxazole urea analogs (**30a**–**56a**) were synthesized by coupling compound **17** with substituted phenyl isocyanates followed by a basic hydrolysis using 1.0 M lithium hydroxide in water [18].

The synthesis of 5-phenyloxazole derivatives (Scheme 3) involved bromination of 4-nitrophenyl acetophenone to 2-bromo-1-(4-nitrophenyl)ethanone (**19**). Conversion of compound **19** to its hydrochloride salt (**20**) followed by a reflux with ethyl chlorooxalate and pyridine in chloroform yielded methyl 2-(2-(4-nitrophenyl)-2-oxoethylamino)-2-oxoacetate (**21**). This was cyclized to methyl 5-(4-nitrophenyl)oxazole-2-carboxylate (**22**) using phosphorus oxychloride [19]. Coupling of compound **22** with L-valine methyl ester hydrochloride yielded compound **23** that on reduction using iron-ammonium chloride yielded its corresponding amine, (*S*)-methyl 2-(5-(4-aminophenyl)oxazole-2-carboxamido)-3-methylbutanoate



1, PF-4620110
(Pfizer Ltd., WO 2009016462)



2, JTT-553
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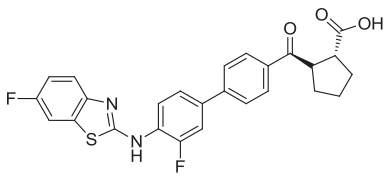


3, BAY-744113
(Bayer Pharmaceuticals, US Patent 7091228)

Fig. 1. Clinically studied hDGAT1 inhibitors.

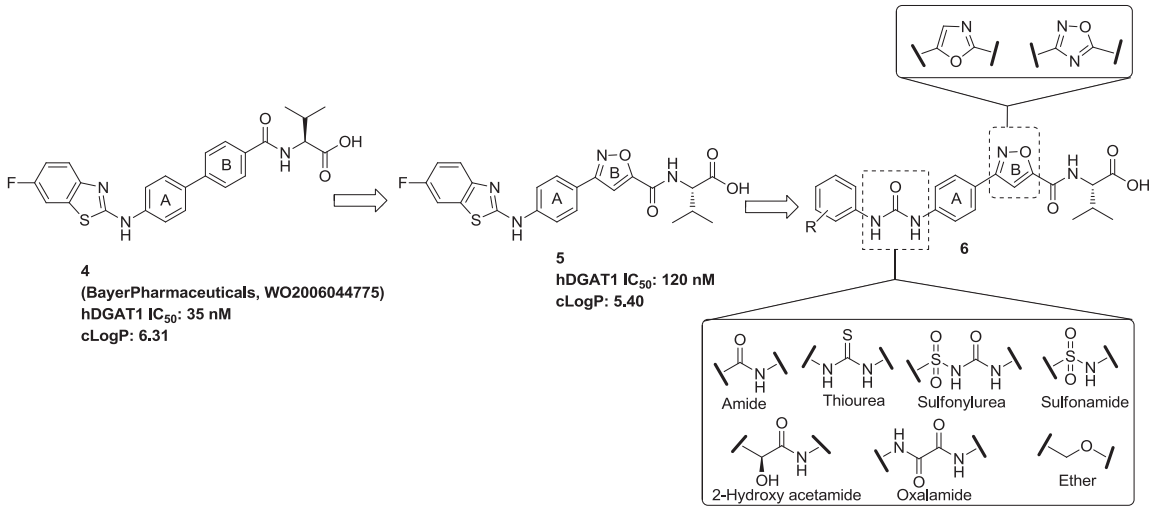
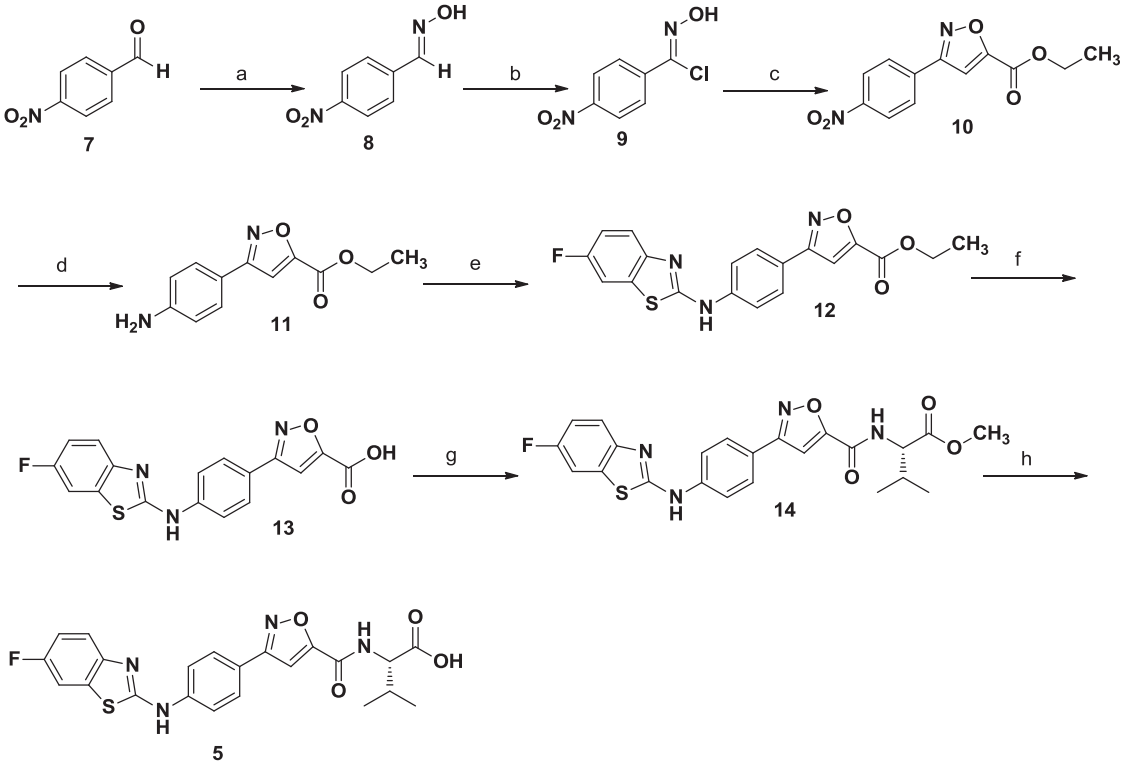


Fig. 2. Stepwise development of the isoxazole containing heteroaryl scaffold.

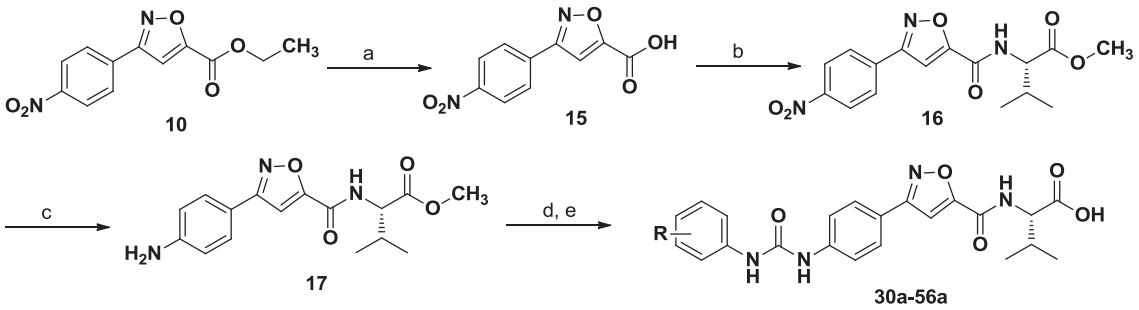
(**24**). Treatment of compound **24** with substituted phenyl isocyanates followed by alkaline hydrolysis afforded the desired 5-phenyloxazole acids (**30b**–**36b**) [18].

Synthesis of 3-phenyl-1,2,4-oxadiazole analogs (Scheme 4) involved a conversion of 4-nitro benzonitrile (**25**) to *N*′-hydroxy-4-nitrobenzamidine (**26**) using hydroxylamine hydrochloride [20]. Compound **26** when refluxed with ethyl chlorooxalate in pyridine gave ethyl 3-(4-nitrophenyl)-1,2,4-oxadiazole-5-carboxylate (**27**) [21,22] that on subsequent coupling with L-valine methyl ester hydrochloride yielded (*S*)-methyl 3-methyl-2-(3-(4-nitrophenyl)-1,2,4-oxadiazole-5-carboxamido)butanoate (**28**). Sequential reduction of the nitro group to its amine followed by coupling with substituted phenyl isocyanates afforded the corresponding ureas that on subsequent deprotection of the methyl ester using alkaline hydrolysis yielded the desired 3-phenyl-1,2,4-oxadiazole acids (**30c**–**33c** and **37c**–**39c**) [18].

After the 3-phenylisoxazole scaffold was found to be optimal for hDGAT1 inhibition, efforts to optimize the linker portion of 3-phenylisoxazole were undertaken. Seven diverse linkers, in addition to the urea linker evaluated earlier, were synthesized in this study (Fig. 2). These included thiourea, 2-hydroxyacetamide, sulfonylurea, oxalamide, amide, sulfonamide, and ether linkers. These various linker analogs (**57**–**62**) were synthesized (Scheme 5 and Table 2) by incorporating



Scheme 1. Reagents and conditions: (a) Hydroxylamine hydrochloride, MeOH, 65 °C, 2 h; (b) *N*-chlorosuccinimide, DMF, rt, 5 h; (c) Ethyl propiolate, TEA, toluene, 80 °C, 2.5 h; (d) Fe/NH_4Cl, EtOH/water/THF, 80 °C, 3 h; (e) 6-Fluoro-2-chlorobenzothiazole, 4.0 M HCl in dioxane, EtOH, 80 °C, 20 h; (f) 1.0 M NaOH, isopropanol, 55–60 °C, 0.5 h; (g) L-valine methyl ester hydrochloride/Et_3N/DCC/HOBT, DMF, rt, 18 h; (h) 1.0 M LiOH in water, THF/water, 40–45 °C, 16 h.



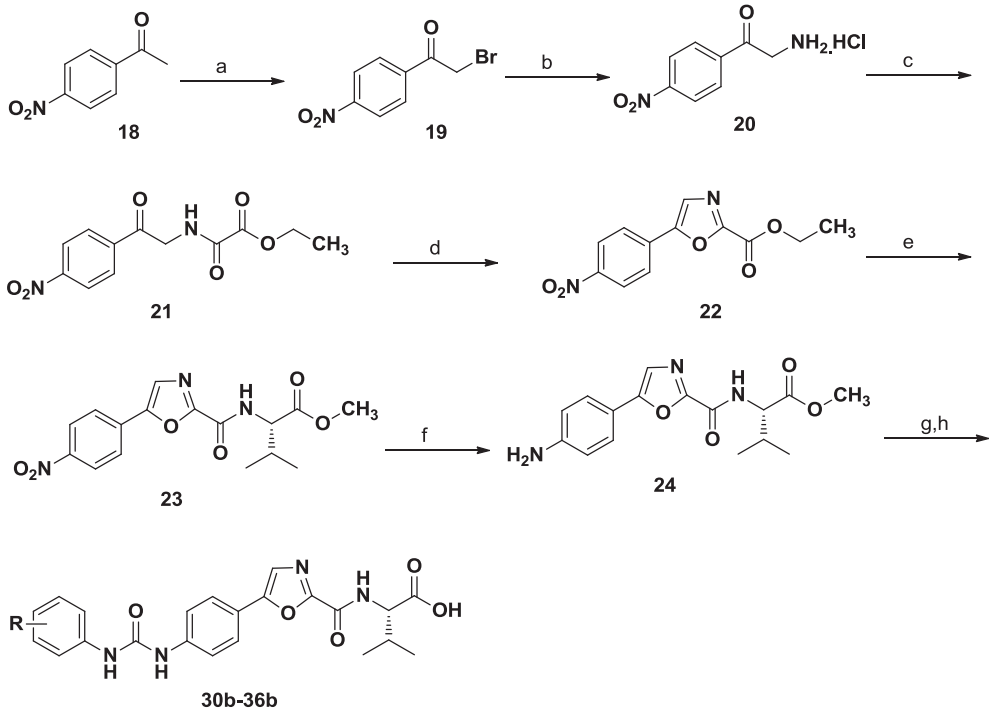
Scheme 2. Reagents and conditions: (a) 1.0 M NaOH, THF, rt, 30 min; (b) L-valine methyl ester hydrochloride, isobutyl chloroformate, *N*-methyl morpholine, TEA, THF, −20 °C–rt, 1 h; (c) Fe/NH_4Cl, EtOH/water/THF, 80 °C, 3 h; (d) Substituted phenyl isocyanates, THF, rt, 16 h; (e) 1.0 M LiOH, THF, water, rt, 16 h.

modifications at the penultimate step wherein (*S*)-methyl 2-(3-(4-aminophenyl)isoxazole-5-carboxamido)-3-methylbutanoate (**17**) was coupled using 2-fluoro phenylisothiocyanate for a thiourea linker [23], (*R*)-2-hydroxy-2-phenylacetic acid for a 2-hydroxyacetamide linker, 2-methylbenzenesulfonyl isocyanate for a sulfonylurea linker, 3-trifluoromethyl aniline and oxalyl chloride for a oxalamide linker, 4-fluoro benzoyl chloride for a amide linker, and 2,6-difluoro benzenesulfonyl chloride for a sulfonamide linker [24]. This coupling was followed by an alkaline hydrolysis to yield the respective acids **57**–**62**. Compound **72** possessing an ether linker, was synthesized as outlined in Scheme 6. This synthetic scheme involved introducing a benzyl protection on 4-hydroxy benzaldehyde (**63**) followed by the sequential synthesis of 3-(4-(benzyloxy)phenyl)isoxazole-5-carboxylic acid (**68**) and subsequent coupling with L-valine methyl ester hydrochloride to give compound **69**. The benzyl group was deprotected using hydrogenation to yield **70** followed by its reaction with 4-fluoro benzyl bromide in the penultimate step to give **71**. Compound **71** on alkaline hydrolysis afforded compound **72**. All of these synthesized analogs were consequently studied for their hDGAT1 inhibition.

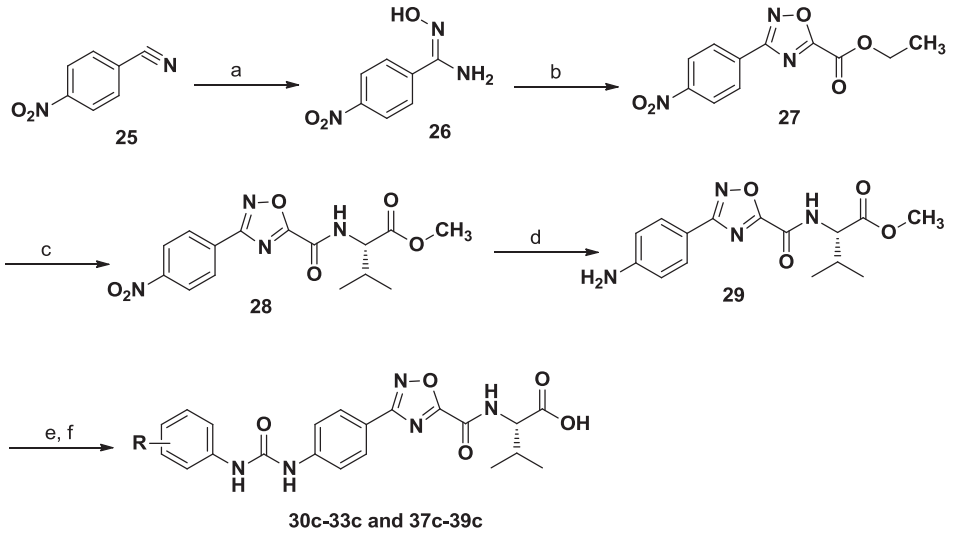
3. Pharmacology

3.1. In vitro evaluation

The synthesized heterocyclic analogs were studied *in vitro* for their hDGAT1 inhibition using an enzymatic assay [25] that measured a triolein output from diolein and radiolabeled oleoyl-CoA. These hDGAT1 assays were performed using 2.5 μg of the protein from a post nuclear supernatant preincubated with 100 μl of the assay buffer [100 mM Tris–HCl (pH 7.5), 250 mM sucrose, and 1.25 mg/ml fatty acid free BSA] containing a known concentration of the inhibitor and supplemented with 2047.5 μM of 1,2-dioleoylglycerol. The hDGAT1 reaction was initiated following an addition of 16.8 nCi of [^{14}C]-oleoyl-CoA. The reaction was terminated after 10 min of incubation at 37 °C using 300 μl alkaline ethanol stop solution mix (AESSM) [12.5% of 100% non-denatured ethanol, 10% deionized water, 2.5% NaOH, and 75% stop solution (78.4% isopropanol, 19.6% *n*-heptane, 2% deionized water)]. The ^{14}C triglyceride formed in this reaction was extracted using 600 μl of



Scheme 3. Reagents and conditions: (a) Bromine/$AlCl_3$, diethyl ether, rt, 30 min; (b) Hexamine, DCM, rt, 1 h; (c) Ethylchlorooxoacetate, EtOH, 80 °C, 2 h; (d) $POCl_3$, 80 °C, 6 h; (e) L-valine methyl ester hydrochloride/Et_3N, EtOH, 110 °C, 2 d; (f) Fe/NH_4Cl, EtOH/THF/water, 80 °C, 3 h; (g) Substituted phenyl isocyanates, THF, rt, 16 h; (h) 1.0 M LiOH, THF, rt, 16 h.



Scheme 4. Reagents and conditions: (a) Hydroxylamine hydrochloride/K_2CO_3, EtOH, 80 °C, 5 h; (b) Ethyl chlorooxalate/pyridine, $CHCl_3$, 60 °C, 14 h; (c) L-valine methyl ester hydrochloride, TEA, EtOH, 80 °C, 16 h; (d) Fe/NH_4Cl, EtOH/THF/water, 80 °C, 4 h; (e) Substituted phenyl isocyanate, THF, rt, 16 h; (f) 1.0 M LiOH, THF, rt, 16 h.

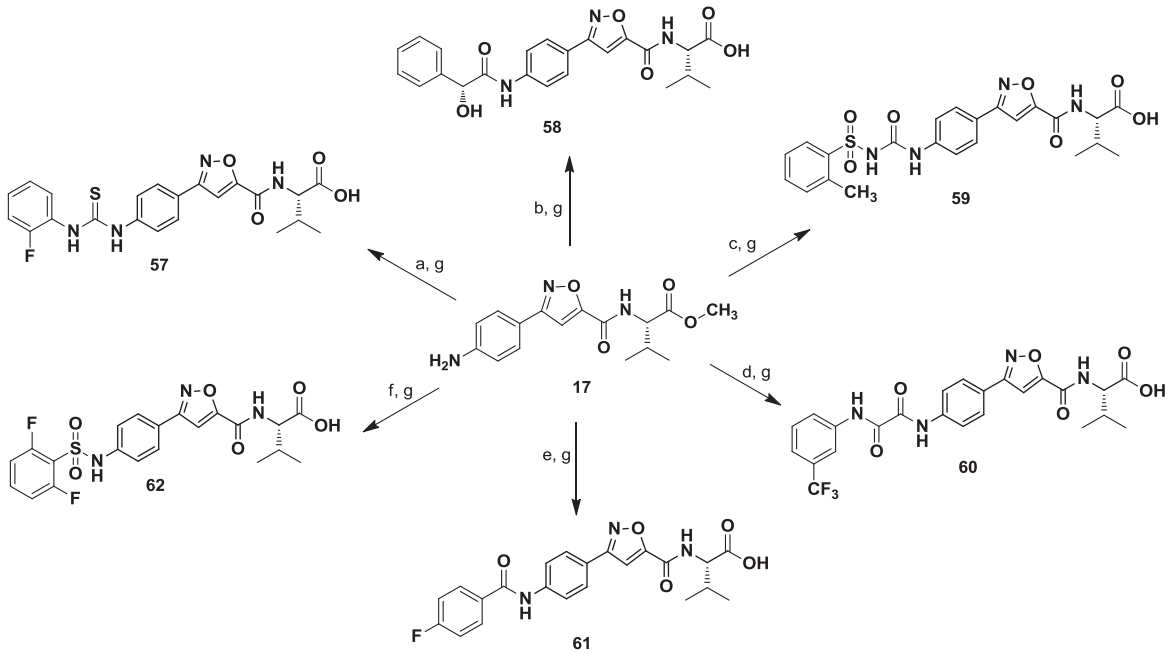
heptane. 250 μl of this extracted heptane was added to scintillation fluid and subjected to radioactivity measurement. The primary screening of hDGAT1 inhibitors was carried out at 1.0 μM concentration. IC_{50} values were evaluated for compounds that exhibited inhibition greater that 75% during the primary screening, by generating a concentration–response curve at nine varying concentrations ranging from 0.1 nM to 1.0 μM.

3.2. In vivo evaluation

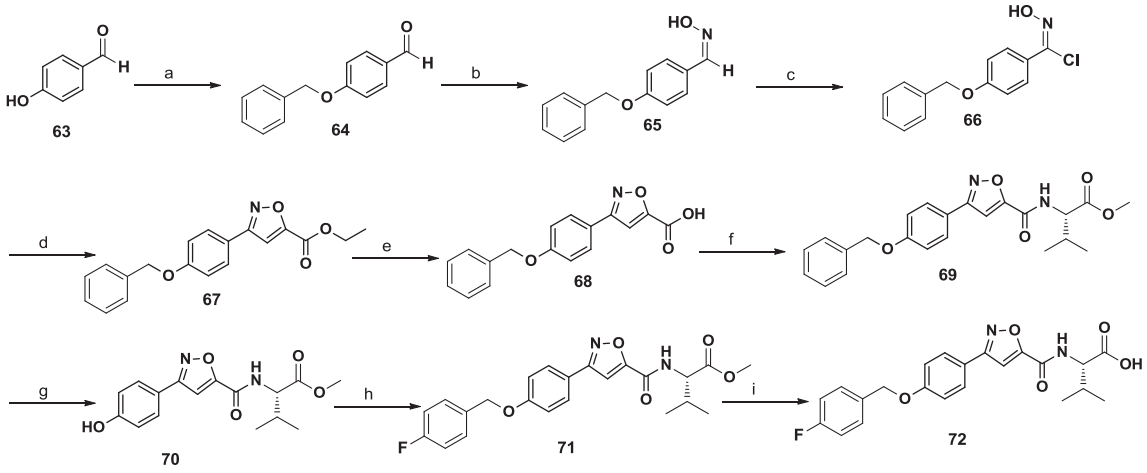
The *in vitro* results were confirmed following an acute *in vivo* fat tolerance test (FTT). In an FTT fasted swiss mice, belonging to the age range of 4–5 weeks and body weight range of 25–30 g, were administered with either a vehicle (0.5% CMC) or the test compound [3 mg/kg] by oral gavage. The test compounds were formulated as a suspension in 0.5% CMC containing Tween 80 (25 μl). An hour later, a bolus dose of olive oil (10 ml/kg) was given to the animals. Blood samples were subsequently collected at 1,2,3, and 4 h, the plasma was separated, and triglyceride levels were monitored using a commercially available kit (Diasys, Germany). Percent reduction in triglyceride levels was calculated by dividing area under curve (AUC_{0-4h}) in presence of the test compound by that of the vehicle group, which was considered to be equal to 100 percent.

4. Results and discussion

Initially a set of ten compounds belonging to the 3-phenylisoxazole scaffold (Type A, **30a**–**39a**), seven compounds belonging to the 5-phenyloxazole scaffold (Type B, **30b**–**36b**) and



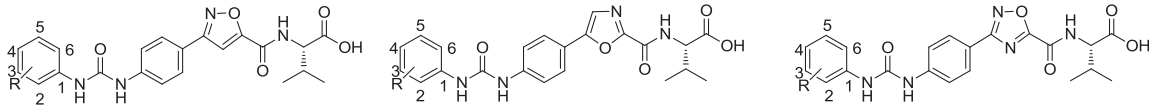
Scheme 5. Reagents and conditions: (a) 1-Fluoro-2-isothiocyanatobenzene, THF, rt, 16 h; (b) Mandelic acid/DCC/HOBT, DMF, rt, 16 h; (c) *ortho*-tolylsulfonyl isocyanate, THF, rt, 16 h; (d) 3-Trifluoromethyl aniline, oxalyl chloride, EtOAc, rt, 3 h; (e) 4-Fluorobenzoyl chloride/Et_3N, rt, 3 h; (f) 2,6-Difluorobenzene sulfonyl chloride/pyridine, DCM, rt, 3 h; (g) 1.0 M LiOH, THF, rt, 16 h.



Scheme 6. Reagents and conditions: (a) Benzyl bromide, K_2CO_3, acetone, 65 °C, 3 h; (b) Hydroxylamine hydrochloride, MeOH, 65 °C, 3 h; (c) *N*-chlorosuccinimide, DMF, rt, 3 h; (d) Ethyl propiolate, Et_3N, toluene, 80 °C, 2 h; (e) 1.0 M NaOH, THF, rt, 20 min; (f) L-valine methyl ester hydrochloride/isobutyl chloroformate/*N*-methyl morpholine/Et_3N, THF, −20 °C–rt, 1 h; (g) 10% Pd/C, 50 psi, THF, rt, 3 h; (h) 1-(Bromomethyl)-4-fluorobenzene/K_2CO_3, acetone, 65 °C, 2 h; (i) 1.0 M LiOH, THF, rt, 16 h.

seven compounds belonging to the 3-phenyl-1,2,4-oxadiazole scaffold (Type C, **30c**–**33c**, **37c**–**39c**) were synthesized and evaluated for their hDGAT1 inhibition (Table 1). Compounds belonging to these three heterocyclic scaffolds exhibited cLogP values ranging from 2.61 to 4.72 log units. This study aimed at identifying a preferred five membered aromatic heterocycle in place of the phenyl B-ring. All ten compounds (**30a**–**39a**) belonging to the 3-phenylisoxazole scaffold, three compounds (**30b**, **33b**, **35b**) belonging to the 5-phenyloxazole scaffold, and only one compound (**37c**) belonging to the 3-phenyl-1,2,4-oxadiazole scaffold exhibited inhibition greater than 75% in our primary screening and subsequently IC_{50} values were determined for each of these compounds. Within the 3-phenylisoxazole scaffold, the ten compounds (**30a**–**39a**) exhibited IC_{50} values ranging between 24 and 124 nM. On the contrary, each of the three compounds (**30b**, **33b**, **35b**) belonging to the 5-phenyloxazole scaffold and one compound (**37c**) belonging to the 3-phenyl-1,2,4-oxadiazole scaffold exhibited IC_{50} values greater than 200 nM. The results thereby highlight a preference for the 3-phenylisoxazole scaffold over the 5-phenyloxazole and 3-phenyl-1,2,4-oxadiazole scaffolds as hDGAT1 inhibitors.

Table 1
In vitro evaluation of isoxazole, oxazole, and 1,2,4-oxadiazole analogs.



Scaffold Type A | Scaffold Type B | Scaffold Type C

Compound number	Scaffold type	R	hDGAT1 inhibitory activity		cLogP[b]
			% Inhibition[a] [1 μM]	IC_{50}[a] (nM)	
30a	A	2-Chloro	90 ± 1	44 ± 9	3.18
30b	B		80 ± 1	282 ± 13	2.61
30c	C		62 ± 2	ND	3.80
31a	A	3-Chloro	84 ± 1	45 ± 3	3.18
31b	B		72 ± 2	ND	2.61
31c	C		71 ± 1	ND	3.80
32a	A	4-Chloro	84 ± 1	124 ± 7	3.18
32b	B		59 ± 5	ND	2.61
32c	C		40 ± 2	ND	3.80
33a	A	3-Trifluoromethyl	85 ± 1	66 ± 3	3.55
33b	B		75 ± 1	458 ± 6	2.97
33c	C		48 ± 2	ND	4.16
34a	A	3,4-Dimethyl	83 ± 1	44 ± 4	3.60
34b	B		69 ± 1	ND	3.03
35a	A	2-Phenoxy, 4-chloro	91 ± 1	86 ± 2	4.72
35b	B		91 ± 1	230 ± 5	4.15
36a	A	2-Fluoro, 4-chloro	90 ± 1	24 ± 3	3.34
36b	B		70 ± 1	ND	2.77
37a	A	2,4-Difluoro	85 ± 1	62 ± 3	2.94
37c	C		75 ± 1	259 ± 5	3.56
38a	A	4-Fluoro	78 ± 3	60 ± 5	2.78
38c	C		61 ± 2	ND	3.40
39a	A	4-Methyl	80 ± 1	61 ± 5	3.11
39c	C		61 ± 1	ND	3.73

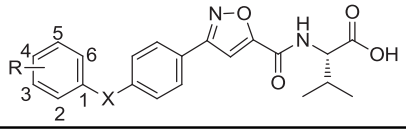
ND – not determined.
[a] Results are shown as mean ± SEM ($n = 2$).
[b] cLogP values were calculated using ChemDraw version 12.0.

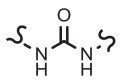
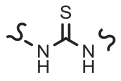
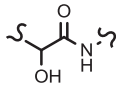
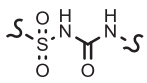
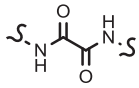
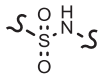
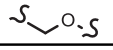
Following identification of the 3-phenylisoxazole scaffold for hDGAT1 activity, efforts were focused on optimization of the linker subunit in this scaffold. Apart from the urea linker studied earlier, we synthesized seven additional 3-phenylisoxazole analogs with different linkers (**57**–**62**, **72**). These included thiourea (**57**), 2-hydroxyacetamide (**58**), sulfonylurea (**59**), oxalamide (**60**), amide (**61**), sulfonamide (**62**), and ether (**72**) linkers (Table 2). Compounds synthesized with these varied linkers exhibited cLogPs in the range of 2.24–3.93 log units. Three unit long linkers such as urea (Compound **38a**, Inhibition = 78%), thiourea (Compound **57**, Inhibition = 72%), and 2-hydroxyacetamide (Compound **58**, Inhibition = 59%) are tolerated at the hDGAT1 enzyme with the urea linker exhibiting maximum hDGAT1 inhibition. Expanding the chain length to four units as seen with sulfonylurea (Compound **59**, Inhibition = 26%) and oxalamide (Compound **60**, Inhibition = 16%) linkers or shortening the linker chain length to two units as exemplified by amide (Compound **61**, Inhibition = 44%), sulfonamide (Compound **62**, Inhibition = 23%), and methylether (Compound **72**, Inhibition = 18%) linkers led to substantial loss of hDGAT1 inhibition. The study thereby hints towards a three unit urea linker as being tolerated for hDGAT1 inhibition.

Following this study, seventeen other 3-phenylisoxazole analogs (**40a**–**56a**) possessing various electron donating and electron withdrawing substituents on the phenyl urea were synthesized and evaluated for their hDGAT1 inhibition (Table 3) in addition to the ten 3-phenylisoxazole analogs (**30a**–**39a**) synthesized and evaluated earlier. Within this total set of twenty-seven 3-phenylisoxazole analogs (Tables 1 and 3, **30a**–**56a**) a 6-fold difference in potency was observed between the most potent analog **36a** (IC_{50} = 24 nM) and the least potent analog **50a** (IC_{50} = 185 nM). Four systematic series of *ortho*-, *meta*-, and *para*-substituted phenyl compounds have been synthesized of which two series possess electron withdrawing chloro and fluoro groups and the other two possess electron donating methyl and trifluoromethyl groups. However no specific trend in activity was observed with respect to the substitution pattern on the phenyl ring indicating that the structure–activity relationship at the phenyl urea portion of the molecule is driven primarily by steric considerations and to a lesser extent by electrostatic interactions. Both mono- and di-substituions on the phenyl ring appear well tolerated at the hDGAT1 enzyme. This study has identified several *in vitro* potent hDGAT1 inhibitors belonging to the novel 3-phenylisoxazole scaffold possessing cLogP much lower than that of compound **4**.

For FTT, compounds possessing the novel 3-phenylisoxazole urea scaffold that exhibit potent yet similar *in vitro* activity and a cLogP separation of about 1 log unit were sought. Three compounds, **35a** (IC_{50} = 86 nM, cLogP = 4.72), **39a** (IC_{50} = 61 nM, cLogP = 3.11), and **40a** (IC_{50} = 64 nM, cLogP = 2.50) were thus selected and studied *in vivo* for triglyceride reduction (Table 4) and compared along with compounds **4** (IC_{50} = 35 nM, cLogP = 6.31) and **5** (IC_{50} = 120 nM, cLogP = 5.40). Compound **4**, the fluorobenzothiazole biphenyl acid, exhibited an 84% triglyceride

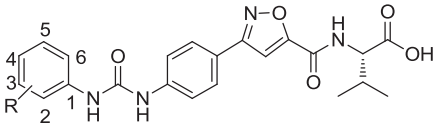
Table 2
In vitro evaluation of isoxazole analogs possessing different linkers.



Compound number	X	R	hDGAT1% Inhibition[a] [1 μM]	cLogP[b]
38a		4-Fluoro	78 ± 3	2.78
57		2-Fluoro	72 ± 2	3.93
58		–	59 ± 1	2.24
59		2-Methyl	26 ± 4	2.66
60		3-Trifluoromethyl	16 ± 8	3.41
61		4-Fluoro	44 ± 2	3.68
62		2,6-Difluoro	23 ± 4	3.92
72		4-Fluoro	18 ± 4	3.91

[a] Results are shown as mean ± SEM (n = 2).
[b] cLogP values were calculated using ChemDraw version 12.0.

Table 3
In vitro evaluation of isoxazole analogs.



Compound number	R	hDGAT1 inhibition IC_{50}[a] (nM)	cLogP[b]
40a	4-Methoxy	64 ± 3	2.50
41a	2-Fluoro	141 ± 16	2.78
42a	3-Fluoro	94 ± 5	2.78
43a	2-Methyl	84 ± 6	3.11
44a	3-Methyl	54 ± 4	3.11
45a	2-Trifluoromethyl	54 ± 4	3.55
46a	4-Trifluoromethyl	80 ± 3	3.55
47a	3,4-Difluoro	75 ± 9	2.94
48a	3,5-Difluoro	75 ± 3	2.94
49a	2,5-Difluoro	141 ± 7	2.94
50a	2,6-Difluoro	185 ± 13	2.94
51a	2,4-Dimethyl	85 ± 8	3.60
52a	3,5-Dimethyl	114 ± 10	3.60
53a	2-Fluoro, 5-methyl	54 ± 4	3.27
54a	3-Fluoro, 4-methyl	178 ± 8	3.27
55a	2-Methyl, 4-fluoro	90 ± 4	3.27
56a	2-Methyl, 5-fluoro	69 ± 5	3.27

[a] Results are shown as mean ± SEM (n = 2).
[b] cLogP values were calculated using ChemDraw version 12.0.

Table 4
Plasma triglyceride reduction following an *in vivo* fat tolerance test and solubility data.

Compound number	hDGAT1 inhibition IC50[a] (nM)	FTT[b] (% TG reduction at 3 mpk)	Solubility[c] (mg/ml)
4	35 ± 6	84 ± 8	0.01
5	120 ± 7	29 ± 17	0.06
35a	86 ± 2	35 ± 15	0.14
39a	61 ± 5	79 ± 4	0.38
40a	64 ± 3	90 ± 4	0.43

[a] Results are shown as mean ± SEM (n = 2).
[b] Results are shown as mean ± SEM (n = 8).
[c] Solubility determined at pH 7.4.

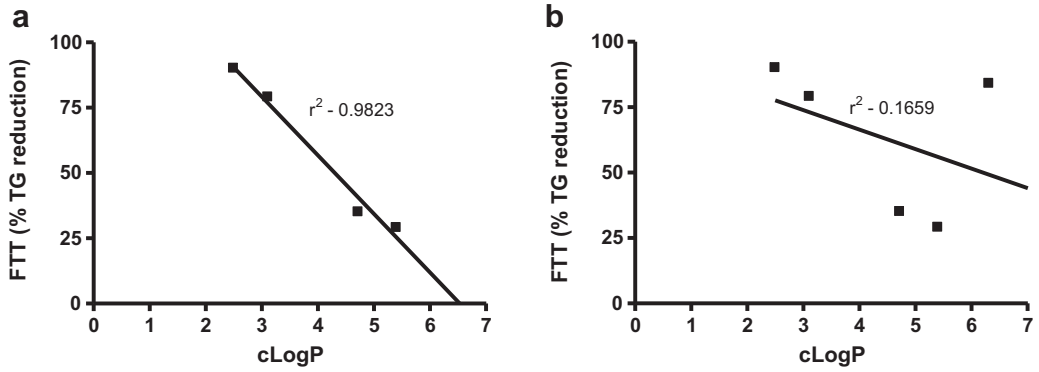


Fig. 3. Scatter plots of FTT vs cLogP. Plot (a) includes four compounds (**5**, **35a**, **39a**, and **40a**) belonging to the 3-phenylisoxazole series and they show a high correlation ($r^2 = 0.9823$) in their ability to reduce triglycerides *in vivo* and corresponding cLogP values. Plot (b) includes the biphenyl analog, compound **4**, in addition to the four 3-phenylisoxazole compounds. Inclusion of compound **4** ($r^2 = 0.1659$) highlights a very low correlation in between the ability of compound **4** to reduce triglycerides *in vivo* and its cLogP.

reduction *in vivo* whereas its corresponding 3-phenylisoxazole analog, compound **5**, exhibited a mere 29% triglyceride reduction. Compound **35a** also exhibited a low 35% triglyceride reduction *in vivo*. However compound **39a**, a 4-methyl phenylurea analog, and compound **40a**, a 4-methoxy phenylurea analog, exhibited 79% and 90% triglyceride reduction respectively at a dose of 3 mg/kg. Compounds **39a** and **40a** thus appear equi-efficacious to compound **4** when studied *in vivo*. The lower triglyceride reduction of compound **5** and compound **35a** can be attributed to their relatively higher cLogP values that might result in reduced oral bioavailability. However compounds **39a** and **40a** with low cLogPs exhibit potent triglyceride reduction *in vivo*. The physicochemical property, cLogP, thus appears to play an important role for the *in vivo* activity of 3-phenylisoxazole urea scaffold. The equilibrium solubilities of these compounds were also evaluated in an attempt to rationalize their cLogP values.

The equilibrium solubility was evaluated in a buffer of pH 7.4 prepared using USP specifications. The solubility was determined on a shaker water bath operating at 100 rpm for 24 h at 37 °C. Compound **4** (cLogP = 6.31) exhibited an extremely low solubility of 0.01 mg/ml. The amino fluorobenzothiazole analog, compound **5** (cLogP = 5.40), possessing the 3-phenylisoxazole scaffold also exhibited a low solubility of 0.06 mg/ml. The 3-phenylisoxazole analog, compound **35a** (cLogP = 4.72), exhibited a modest improvement in solubility to 0.14 mg/ml. However a further lowering of cLogP within the 3-phenylisoxazole scaffold as seen in compound **39a** (cLogP = 3.11) and compound **40a** (cLogP = 2.50) resulted in a vastly improved solubility of 0.38 mg/ml and 0.43 mg/ml respectively. The assessment of this physicochemical property thus highlights a substantial improvement in the solubility of these molecules following a cLogP reduction as compared to compound **4** (solubility = 0.01 mg/ml) and compound **5** (solubility = 0.06 mg/ml). These solubility results thereby rationalize the low *in vivo* potency observed in case of compound **35a** and effective potency of compounds **39a** and **40a**. However a similar justification for compound **4**, possessing the biphenyl scaffold, cannot be offered and further studies are warranted to rationalize the *in vivo* potency of compound **4** despite its high cLogP and low solubility. However for the 3-phenylisoxazole scaffold, there appears to be a definite correlation in between the *in vivo* triglyceride reduction and the aqueous solubility of the molecules that in turn can be predicted using cLogP (Fig. 3).

5. Conclusions

In this study, we have developed a 3-phenylisoxazole scaffold possessing improved cLogP and resulting in enhanced solubility. A preliminary comparison between 3-phenylisoxazole, 5-phenyloxazole, and 3-phenyl 1,2,4-oxadiazole scaffolds highlighted a preference for the 3-phenylisoxazole scaffold at the hDGAT1 enzyme. A subsequent study highlighted the urea linker to be optimum for hDGAT1 activity over seven other linker units. Several analogs possessing the 3-phenylisoxazole scaffold in combination with the urea linker were evaluated and found to substantially inhibit the hDGAT1 enzyme. Of these molecules compound **40a** exhibited a 90% triglyceride reduction when studied *in vivo* at a dose of 3 mg/kg and was found to be equi-efficacious to compound **4**. Compound **40a** (cLogP = 2.50) and the other compounds in this series were designed with an intention of lowering the high cLogP of compound **4** (cLogP = 6.31) while retaining hDGAT1 activity. This improvement in cLogP of compound **40a** translated to its much improved solubility of 0.43 mg/ml over that of compound **4** (solubility = 0.01 mg/ml). Thus with compound **40a** we were able to markedly improve the aqueous solubility while retaining its *in vitro* hDGAT1 inhibitory activity and *in vivo* ability to reduce triglycerides. These attributes earmark compound **40a** as a potential new lead for developing therapeutically applicable hDGAT1 inhibitors. The study also highlights a correlation between the *in vivo* triglyceride reduction and the aqueous solubility of the molecules for the 3-phenylisoxazole scaffold.

6. Experimental

6.1. Chemistry

Unless mentioned otherwise all reactions were performed under atmosphere. Unless otherwise specified all reagents were obtained from Aldrich and solvents were obtained from Thomas Baker and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C respectively using either $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts, δ, are reported in parts per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 (^{1}H NMR), and 77.3 (^{13}C NMR); DMSO-d_6, δ 2.50 (^{1}H NMR), and 40.2 (^{13}C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants, *J*, are reported in Hertz. Mass spectral (MS) data were obtained on a Bruker Daltonics spectrometer using an electrospray ionization-quadrapole-time of flight (ESI-QTOF) analyzer. All melting points have been determined on a manually operated Veego (VMP-1) melting point apparatus and are reported uncorrected. HPLC purities have been determined using a Waters Alliances 2695 system implementing either Method A, Method B or Method C for chromatographic separation.

HPLC solvents: A1: Acetonitrile. B1: 0.01 M NH_4OAc + 0.5% TEA, pH 5.0 with AcOH. B2: 0.1% Trifluoroacetic acid.

HPLC Columns: Column 1: Ascentis TM Express (50 × 4.6 mm I.D.), 2.7 μm operated at 1 ml/min, detection at 288 nm. Column 2: Kromasil 250 × 4.6 mm, 3.5 μm, C18 operated at 1 ml/min, detection at 276 nm.

HPLC Methods: *Method A*: Elution with 20–80% linear gradient of A1 in 6 min followed by 20–80% linear gradient of B1 in 1 min that is continued using an isocratic elution with 80% B1 for 3 min using Column 1. *Method B*: Elution with 10–90% linear gradient of A1 in 20 min followed by 10–90% linear gradient of B2 in 2 min that is continued using an isocratic elution with 90% B2 for 8 min using Column 2. *Method C*: Elution with 10–90% linear gradient of A1 in 20 min followed by 10–90% linear gradient of B1 in 2 min that is continued using an isocratic elution with 90% B1 for 8 min using Column 2.

6.1.1. 4-Nitrobenzaldehyde oxime (**8**)

A mixture of 4-nitrobenzaldehyde (10.0 g, 66 mmol, 1.0 equiv) and hydroxylamine hydrochloride (6.9 g, 99 mmol, 1.5 equiv) in methanol (100 ml) was heated at 65 °C for 2 h. Following reaction completion methanol was evaporated under reduced pressure. The obtained material was dissolved in ethyl acetate, washed with water, brine, dried over sodium sulfate, and the solvent was removed under reduced pressure. The solid thus obtained was then recrystallized from ethyl acetate and petroleum ether to afford the title compound (10.4 g, 95%) as an off white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.69–8.66 (d, J = 9.0 Hz, 2H), 8.62 (s, 1H), 8.19–8.16 (d, J = 9.0 Hz, 2H); MS (ESI−) m/z 165 $[M - H]^-$.

6.1.2. N-Hydroxy-4-nitrobenzimidoyl chloride (**9**)

To a solution of compound **8** (20.0 g, 120 mmol, 1.0 equiv) in DMF (100 ml) was added *N*-chlorosuccinimide (20.9 g, 156 mmol, 1.3 equiv) and stirred at rt for 5 h. Following reaction completion DMF was removed under reduced pressure and the obtained material was dissolved in ethyl acetate, washed with water, brine, dried over sodium sulfate, and the solvent was removed under reduced pressure to obtain a crude solid that was used without further purification for the following step.

6.1.3. 3-(4-Nitro-phenyl)-isoxazol-5-carboxylic acid ethyl ester (**10**)

To a solution of compound **9** (2.0 g, 10 mmol, 1.0 equiv) and ethyl propiolate (2.02 ml, 20 mmol, 2.0 equiv) in toluene (25 ml) was added Et_3N (1.46 ml, 10.5 mmol, 1.05 equiv) over 10 min. The resulting reaction mixture was heated at 80 °C for 2.5 h and then further diluted with EtOAc (50 ml). The organic layer was washed with 0.1 M HCl, water, and brine. The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated, and the residue was crystallized from chloroform and petroleum ether to afford the title compound (1.35 g, 51.7%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.37–8.34 (d, J = 9.0 Hz, 2H), 8.05–8.02 (d, J = 9.0 Hz, 2H), 7.32 (s, 1H), 4.52–4.45 (q, J = 7.2 Hz, 2H), 1.47–1.43 (t, J = 7.2 Hz, 2H); MS (ESI+) m/z 263 $[M + H]^+$.

6.1.4. 3-(4-Amino-phenyl)-isoxazole-5-carboxylic acid ethyl ester (**11**)

To a solution of compound **10** (7.5 g, 28.6 mmol, 1.0 equiv) in ethanol (120 ml), THF (60 ml) and water (30 ml) were added ammonium chloride (4.59 g, 85.8 mmol, 3.0 equiv) and iron powder (3.76 g, 67.3 mmol, 2.3 equiv) and the reaction mixture was refluxed at 80 °C for 3 h. The crude product was purified by flash column chromatography (1:9 EtOAc/$CHCl_3$) to afford the title compound (4.2 g, 63%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66 (s, 1H), 7.61 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 8.4 Hz, 2H), 5.64 (s, 2H), 4.39 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); MS (ESI+) m/z 233 $[M + H]^+$.

6.1.5. 3-[4-(6-Fluoro-benzothiazol-2-ylamino)-phenyl]-isoxazole-5-carboxylic acid ethyl ester (**12**)

Compound **11** (3.0 g, 12.9 mmol, 1.0 equiv) and 2-chloro-6-fluoro benzothiazole (2.67 g, 14.2 mmol, 1.1 equiv) were refluxed in ethanol (60 ml) at 80 °C to obtain a clear solution. To this hot solution 4.0 M HCl in dioxane (1.6 ml, 6.45 mmol, 0.5 equiv) was added and the resulting reaction mixture was refluxed for 20 h. The reaction mixture was cooled to rt and the solid was filtered, washed with ethanol, and dried under vacuum to obtain the title compound (2.83 g, 57%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (bs, 1H), 7.99 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 9.0 Hz, 2H), 7.87 (s, 1H), 7.81 (dd, J = 2.7, 8.7 Hz, 1H), 7.69 (m, 1H), 7.24 (m, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 6.9 Hz, 3H); MS (ESI−) m/z 382 $[M - H]^-$.

6.1.6. 3-[4-(6-Fluoro-benzothiazol-2-ylamino)-phenyl]-isoxazole-5-carboxylic acid (**13**)

Compound **12** (8 g, 20.87 mmol, 1.0 equiv) was dissolved in isopropyl alcohol (500 ml) by heating at 55–60 °C. The solution was cooled and to this solution 1.0 M NaOH in water (6.4 g, 160 mmol, 7.6 equiv) was added and the reaction was stirred overnight at rt. Following reaction completion, the reaction mixture was acidified with 2.0 M HCl to pH 2 and extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine, dried over anhydrous sodium sulfate and the solvent evaporated to obtain the title compound (6.4 g, 86%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.86 (bs, 1H), 7.96–7.89 (m, 4H), 7.78 (dd, J = 2.7, 8.7 Hz, 1H), 7.73 (s, 1H), 7.67 (m, 1H), 7.21 (m, 1H); MS (ESI+) m/z 356 $[M + H]^+$.

6.1.7. 2-({3-[4-(6-Fluoro-benzothiazol-2-ylamino)-phenyl]-isoxazole-5-carbonyl}-amino)-3-methyl-butyric acid methyl ester (**14**)

To a chilled solution of compound **13** (3.0 g, 8.45 mmol, 1.0 equiv) and (*S*)-Valine methyl ester hydrochloride (1.67 g, 10.14 mmol, 1.2 equiv) in DMF (75 ml) were sequentially added Et_3N (1.41 ml, 10.14 mmol, 1.2 equiv) and DCC (2.09 g, 10.14 mmol, 1.2 equiv). After 5 min HOBT (1.42 g, 8.45 mmol, 1.0 equiv) was added and the reaction mixture was stirred at 0 °C for 1 h and then at rt for 18 h. The precipitated DCU was filtered off and the filtrate was evaporated to obtain a brown residue that was purified by flash column chromatography (3:7 EtOAc/Pet. Ether). The obtained solid was triturated in DCM and filtered to afford the title compound (2.9 g, 73.4%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 1H), 9.24 (d, J = 8.1 Hz, 1H), 7.93 (s, 4H), 7.78 (dd, J = 2.7, 8.7 Hz, 1H), 7.70 (s, 1H), 7.69 (m, 1H), 7.20 (m, 1H), 4.35 (t, J = 8.1 Hz, 1H), 3.68 (s, 3H), 2.23 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); MS (ESI+) m/z 467 $[M + H]^+$.

6.1.8. 2-({3-[4-(6-Fluoro-benzothiazol-2-ylamino)-phenyl]-isoxazole-5-carbonyl}-amino)-3-methyl-butyric acid (**5**)

To a solution of compound **14** (500 mg, 1.0 mmol, 1.0 equiv) in THF (3 ml) was added a 1.0 M solution of LiOH in water (5.3 ml, 5.0 mmol, 5.0 equiv) and the resulting mixture was stirred for 16 h at 40–45 °C. The solvent was removed and the residue diluted with water and acidified to pH 2 using 2.0 M HCl. The semi solid material thus obtained was extracted with ethyl acetate, washed with water, and dried over anhydrous sodium sulfate. The residue was purified by flash column chromatography (1:9 MeOH/$CHCl_3$). The material thus obtained was triturated with acetone and petroleum ether,

filtered, and dried under vacuum to yield the title compound (410 mg, 85%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.90 (bs, 1H), 10.78 (s, 1H), 8.98 (d, J = 8.4 Hz, 1H), 7.91 (s, 4H), 7.79 (dd, J = 3.2, 8.7 Hz, 1H), 7.69 (s, 1H), 7.67 (m, 1H), 7.22 (m, 1H), 4.29 (t, J = 6.9 Hz, 1H), 2.24 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7, 163.8, 162.5, 161.5, 156.9, 156.5, 149.0, 142.8, 132.5, 128.1 (2C), 121.6, 120.7, 118.3 (2C), 114.3, 109.1, 105.1, 58.5, 29.9, 19.6, 19.1; MS (ESI+) m/z 454 [M + H]$^+$; mp 262–265 °C; HPLC Retention time – 12.218 min, Purity – 99.21% (Method C).

*6.1.9. 3-(4-Nitrophenyl)isoxazole-5-carboxylic acid (**15**)*

Compound **10** (11.0 g, 42 mmol, 1.0 equiv) was dissolved in THF (220 ml) followed by the addition of 1.0 M aqueous solution of NaOH in water (210 ml, 210 mmol, 5.0 equiv) and stirred at rt for 30 min. The reaction mass was acidified with 1.0 M HCl in water. The organic layer was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain an off white solid that was crystallized in acetone and petroleum ether to afford the title compound (8.0 g, 81%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (d, J = 7.8 Hz, 2H), 8.27 (d, J = 7.8 Hz, 2H), 7.97 (s, 1H); MS (ESI+) m/z 235 [M + H]$^+$.

*6.1.10. Methyl 3-methyl-2-(3-(4-nitrophenyl)isoxazole-5-carboxamido) butanoate (**16**)*

To a solution of compound **15** (2.0 g, 8.54 mmol, 1.0 equiv) in THF (80 ml) was added *N*-methyl morpholine (0.94 ml, 8.54 mmol, 1.0 equiv) and the mixture was stirred at rt for 10 min. The reaction mixture was then cooled to −20 °C and isobutyl chloroformate (1.1 ml, 8.54 mmol, 1.0 equiv) was added to it and the reaction mixture was further stirred for an additional 15–20 min at −20 °C. To this stirred mixture was added L-valine methyl ester hydrochloride (2.0 g, 11.96 mmol, 1.4 equiv) that has been pre-dissolved in THF (20 ml) and neutralized using Et_3N (1.66 ml, 11.96 mmol, 1.4 equiv). The reaction mixture was stirred at −20 °C for 5 min and then gradually warmed to rt over a period of 1 h. The solvent was removed under pressure and the crude material was separated using flash column chromatography (1.5:8.5 EtOAc/$CHCl_3$) to obtain an off white solid that when crystallized in dichloromethane–petroleum ether afforded the title compound (2.2 g, 74%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.31 (d, J = 7.8 Hz, 1H), 8.39 (d, J = 8.7 Hz, 2H), 8.21 (d, J = 8.7 Hz, 2H), 7.89 (s, 1H), 4.34 (t, J = 7.8 Hz, 1H), 3.66 (s, 3H), 2.23 (m, 1H), 0.98 (t, J = 6.9 Hz, 3H); 0.94 (t, J = 6.6 Hz, 3H); MS (ESI−) m/z 346 [M − H]$^-$.

*6.1.11. Methyl 2-(3-(4-aminophenyl)isoxazole-5-carboxamido)-3-methylbutanoate (**17**)*

Compound **16** (2.0 g, 5.76 mmol, 1.0 equiv) was dissolved in ethanol (20 ml), tetrahydrofuran (8 ml), and water (8 ml). To this solution ammonium chloride (0.92 g, 17.29 mmol, 3.0 equiv) and iron (0.75 g, 13.54 mmol, 2.3 equiv) were added and the reaction mixture was refluxed at 80 °C for 3 h. Following this reaction the mixture was cooled, filtered through celite, and the solvent removed under reduced pressure to obtain a dark brown residue that was taken up in water and extracted using ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated to obtain a dark brown residue that was purified by flash column chromatography (1:1 ethyl acetate/petroleum ether) to afford a yellow solid that was crystallized in DCM–petroleum ether to yield the title compound (1.2 g, 65%) as a pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.11 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.51 (s, 1H), 6.64 (d, J = 8.4 Hz, 2H), 5.63 (bs, 2H), 4.29 (t, J = 7.5 Hz, 1H), 3.65 (s, 3H), 2.24 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H); 0.92 (d, J = 6.9 Hz, 3H); MS (ESI+) m/z 318 [M + H]$^+$.

6.1.12. General procedure for the synthesis of isoxazole analogs possessing a urea linker

To a solution of compound **17** (0.5 mmol, 1 equiv) in THF (3 ml) was added the appropriately substituted phenyl isocyanate (1.1 equiv) and the mixture was stirred for 16 h at rt. The reaction mixture was then concentrated and purified using flash column chromatography (2:8 EtOAc/petroleum ether) to afford the desired methyl ester. To a solution of the methyl ester (1 equiv) in THF was added 1.0 M solution of LiOH in water (5 equiv) and stirred for 16 h at rt. The solvent was removed and the obtained residue was diluted with water and acidified to pH 2 using 2.0 M HCl. The material thus obtained was extracted with ethyl acetate, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain a solid that was crystallized in ethyl acetate to yield the desired acid.

*6.1.12.1. 2-(3-(4-(3-(2-Chlorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**30a**).* Prepared as described above in the general procedure using 2-chlorophenyl isocyanate (84.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (157.5 mg, 69.1%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.85 (bs, 1H), 9.70 (s, 1H), 8.98 (d, J = 8.1 Hz, 1H), 8.41 (s, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.71 (s, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 4.31 (t, J = 7.2 Hz, 1H), 2.27 (m, 1H), 0.99 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 163.4, 162.2, 156.4, 152.7, 140.6, 134.7, 131.6, 130.8, 128.6, 127.9 (2C), 125.3, 123.9, 121.3, 118.6 (2C), 105.2, 58.7, 30.0, 19.6, 19.2; MS (ESI−) m/z 455 [M − H]$^-$, (ESI+) m/z 457 [M + H]$^+$; mp 226–228 °C; HPLC retention time – 3.034 min, purity – 95.80% (Method A).

*6.1.12.2. 2-(3-(4-(3-(3-Chlorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**31a**).* Prepared as described above in the general procedure using 3-chlorophenyl isocyanate (84.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (176.5 mg, 77.4%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.96 (s, 1H), 9.48 (s, 1H), 9.42 (s, 1H), 8.89 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.75–7.59 (m, 4H), 7.33 (m, 2H), 7.05 (m, 1H), 4.30 (t, J = 7.8 Hz, 1H), 2.28 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 163.8, 162.6, 156.5, 152.8, 142.4, 141.7, 133.6, 130.8, 127.9 (2C), 121.9, 121.5, 118.9 (2C), 118.1, 117.2, 105.1, 58.6, 30.0, 19.7, 19.1; MS (ESI+) m/z 465 (M + H)$^+$; mp 216–218 °C; HPLC retention time – 3.342 min, purity – 98.33% (Method A).

*6.1.12.3. 2-(3-(4-(3-(4-Chlorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**32a**).* Prepared as described above in the general procedure using 4-chlorophenyl isocyanate (84.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (182.6 mg, 80.1%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 12.91 (s, 1H), 9.09 (s, 1H), 8.99 (s, 1H), 8.96 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.7 Hz, 2H), 7.69 (s, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 4.31 (t, J = 7.8 Hz, 1H), 2.27 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.6, 156.5, 152.7, 142.3, 138.9, 129.1 (2C), 127.9 (2C), 126.0, 121.6, 120.3 (2C), 118.8 (2C), 105.1, 58.5, 29.9, 19.7, 19.1; MS (ESI+) m/z 457 (M + H)$^+$; mp 236–238 °C; HPLC retention time – 3.517 min, purity – 96.80% (Method A).

*6.1.12.4. 3-Methyl-2-(3-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl) isoxazole-5-carboxamido)butanoic acid (**33a**).* Prepared as described above in the general procedure using 3-(trifluoromethyl) phenyl isocyanate (103 mg, 0.55 mmol, 1.1 equiv) as the substituted

isocyanate to afford the title compound (65.8 mg, 26.8%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.88 (bs, 1H), 9.15 (s, 1H), 9.11 (s, 1H), 8.95 (d, J = 8.1 Hz, 1H), 8.02 (bs, 1H), 7.85 (d, J = 8.7 Hz, 2H), 7.59 (s, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.59 (m, 2H), 7.33 (d, J = 7.2 Hz, 1H), 4.29 (t, J = 7.8 Hz, 1H), 2.25 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.9, 162.7, 156.7, 152.9, 142.2, 140.9, 130.3, 129.9, 128.1 (2C), 126.5, 123.0, 122.4, 121.9, 121.4, 119.1 (2C), 105.2, 58.6, 30.0, 19.8, 19.2; MS (ESI+) m/z 491 (M + H)$^+$; mp 232–235 °C; HPLC retention time – 3.783 min, purity – 99.80% (Method A).

*6.1.12.5. 2-(3-(4-(3-(3,4-Dimethylphenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methyl butanoic acid (**34a**).* Prepared as described above in the general procedure using 3,4-dimethylphenyl isocyanate (81 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (145.8 mg, 64.8%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.79 (s, 1H), 8.95 (d, J = 7.2 Hz, 1H), 8.62 (s, 1H), 7.85 (d, J = 8.7 Hz, 2H), 7.69 (s, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.25 (s, 1H), 7.22–7.12 (m, 2H), 7.05 (s, 1H), 4.31 (t, J = 7.8 Hz, 1H), 2.25 (m, 7H), 0.99 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.6, 156.5, 152.8, 142.6, 137.6, 136.8, 130.1, 129.7, 127.9, 121.1, 120.1, 119.9, 118.6, 116.4, 116.1, 105.1, 58.5, 59.9, 20.1, 19.6, 19.1, 18.9; MS (ESI−) m/z 449 (M − H)$^-$, (ESI+) m/z 451 (M + H)$^+$; mp 190–192 °C; HPLC retention time – 3.550 min, purity – 95.31% (Method A).

*6.1.12.6. 2-(3-(4-(3-(4-Chloro-2-phenoxyphenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**35a**).* Prepared as described above in the general procedure using 4-chloro-2-phenoxyphenyl isocyanate (135 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (177.4 mg, 64.7%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.87 (s, 1H), 8.39 (d, J = 1.8 Hz, 1H), 8.20 (m, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.67 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 6.9 Hz, 1H), 7.10 (d, J = 8.1 Hz, 2H), 7.02 (dd, J = 2.1, 6.3 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 4.09 (t, J = 7.8 Hz, 1H), 2.28 (m, 1H), 0.92–0.84 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.1, 164.4, 162.7, 156.8, 155.6, 152.7, 144.7, 142.1, 132.8, 130.6 (2C), 128.0 (2C), 127.7, 124.4, 122.2, 121.7, 119.9, 119.5, 119.1 (2C), 118.7 (2C), 104.7, 59.4, 30.9, 20.0, 18.8; MS (ESI−) m/z 547 [M − H]$^-$, (ESI+) m/z 549 (M + H)$^+$; mp 250–252 °C; HPLC retention time – 4.623 min, purity – 99.66% (Method A).

*6.1.12.7. 2-(3-(4-(3-(4-Chloro-2-fluorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**36a**).* Prepared as described above in the general procedure using 4-chloro-2-fluorophenyl isocyanate (94.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (158.6 mg, 66.9%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.85 (s, 1H), 9.38 (s, 1H), 8.97 (d, J = 9.9 Hz, 1H), 8.75 (s, 1H), 8.21 (t, J = 8.7, 9.0 Hz, 1H), 7.87 (d, J = 8.7 Hz, 2H), 7.70 (s, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.50 (dd, J = 1.8, 8.7 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 4.31 (t, J = 7.2 Hz, 1H), 2.27 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.5, 156.5, 152.3, 150.7, 141.9, 128.0 (2C), 127.0, 125.9, 125.1, 121.9, 118.7 (2C), 116.3, 115.9, 105.1, 58.5, 29.9, 19.6, 19.1; MS (ESI−) m/z 473 (M − H)$^-$, (ESI+) m/z 475 (M + H)$^+$; mp 245–247 °C; HPLC retention time – 3.750 min, purity – 95.42% (Method A).

*6.1.12.8. 2-(3-(4-(3-(2,4-Difluorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**37a**).* Prepared as described above in the general procedure using 2,4-difluorophenyl isocyanate (85.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (62.4 mg, 27.2%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.81 (bs, 1H), 9.28 (s, 1H), 8.94 (d, J = 8.1 Hz, 1H), 8.58 (s, 1H), 8.09 (m, 1H), 7.84 (d, J = 8.7 Hz, 2H), 7.67 (s, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.34 (m, 1H), 7.04 (m, 1H), 4.28 (t, J = 6.9 Hz, 1H), 2.19 (t, J = 6.9 Hz, 1H), 0.96 (d, J = 6.6 Hz, 6H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.2, 164.3, 163.0, 161.7, 161.2, 157.0, 153.1, 142.6, 128.5 (2C), 124.8, 123.2, 119.2 (2C), 112.2, 111.9, 105.6, 104.8, 58.9, 30.4, 20.1, 19.6; MS (ESI+) m/z 459 [M + H]$^+$; mp 252–254 °C; HPLC retention time – 3.086 min, purity – 95.64% (Method A).

*6.1.12.9. 2-(3-(4-(3-(4-Fluorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**38a**).* Prepared as described above in the general procedure using 4-fluorophenyl isocyanate (75.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (77.6 mg, 35.2%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (bs, 1H), 8.96 (s, 1H), 8.95 (d, J = 8.4 Hz, 1H), 8.79 (s, 1H), 7.84 (d, J = 8.7 Hz, 2H), 7.68 (s, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.49 (m, 2H), 7.15 (t, J = 9.0 Hz, 2H), 4.29 (t, J = 7.5 Hz, 1H), 2.21 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.6, 156.8, 156.6, 152.9, 142.4, 136.2, 127.9 (2C), 121.4, 120.7, 120.6, 118.8 (2C), 115.9, 115.7, 105.1, 58.5, 29.8, 19.6, 19.1; MS (ESI+) m/z 458 (M + H)$^+$; mp 248–251 °C; HPLC retention time – 3.092 min, purity – 98.15% (Method A).

*6.1.12.10. 3-Methyl-2-(3-(4-(3-p-tolylureido)phenyl)isoxazole-5-carboxamido)butanoic acid (**39a**).* Prepared as described above in the general procedure using 4-methylphenyl isocyanate (73 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (93.4 mg, 42.8%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.81 (bs, 1H), 8.95 (d, J = 8.4 Hz, 1H), 8.91 (s, 1H), 8.64 (s, 1H), 7.83 (d, J = 8.7 Hz, 2H), 7.68 (s, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 4.29 (q, J = 7.2 Hz, 1H), 2.23 (s, 3H), 2.19 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 163.9, 162.7, 156.7, 152.9, 142.6, 137.4, 131.5, 129.8 (2C), 128.0 (2C), 121.4, 119.0 (2C), 118.8 (2C), 105.2, 58.6, 29.9, 20.9, 19.8, 19.2; MS (ESI+) m/z 437 (M + H)$^+$; mp 224–226 °C; HPLC retention time – 3.203 min, purity – 95.84% (Method A).

*6.1.12.11. 2-(3-(4-(3-(4-Methoxyphenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**40a**).* Prepared as described above in the general procedure using 4-methoxyphenyl isocyanate (82 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (70.7 mg, 31.2%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.61 (bs, 1H), 9.01 (s, 1H), 8.93 (d, J = 8.1 Hz, 1H), 8.69 (s, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.68 (s, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.29 (t, J = 7.2 Hz, 1H), 3.70 (s, 3H), 2.23 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 163.9, 162.7, 156.6, 155.2, 153.1, 142.8, 133.1, 128.0 (2C), 121.3, 120.7 (2C), 118.7 (2C), 114.6 (2C), 105.2, 58.7, 55.7, 30.6, 19.8, 19.2; MS (ESI+) m/z 453 [M + H]$^+$; mp 220–222 °C; HPLC retention time – 2.750 min, purity – 95.57% (Method A).

*6.1.12.12. 2-(3-(4-(3-(2-Fluorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**41a**).* Prepared as described above in the general procedure using 2-fluorophenyl isocyanate (75.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (116.8 mg, 53.1%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (bs, 1H), 9.34 (s, 1H), 8.96 (d, J = 8.1 Hz, 1H), 8.64 (s, 1H), 8.133 (t, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.69 (s, 1H), 7.62 (d, J = 8.7 Hz, 2H), 7.24 (m, 1H), 7.14 (m, 1H), 7.03

(m, 1H), 4.29 (t, $J = 7.2$ Hz, 1H), 2.21 (m, 1H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 163.4, 162.1, 156.1, 152.0, 150.5, 141.6, 127.6 (2C), 127.4, 127.3, 124.6, 124.5, 120.7, 118.2 (2C), 115.2, 104.6, 58.0, 29.4, 19.2, 18.6; MS (ESI+) m/z 441 $[M + H]^+$; mp 237–239 °C; HPLC retention time – 3.166 min, purity – 98.06% (Method A).

*6.1.12.13. 2-(3-(4-(3-(3-Fluorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**42a**).* Prepared as described above in the general procedure using 3-fluorophenyl isocyanate (75.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (66.1 mg, 30.1%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.87 (bs, 1H), 9.12 (s, 1H), 9.08 (s, 1H), 8.93 (d, $J = 8.1$ Hz, 1H), 7.85 (d, $J = 8.7$ Hz, 2H), 7.73 (s, 1H), 7.63 (d, $J = 8.7$ Hz, 2H), 7.51 (m, 1H), 7.34 (m, 1H), 7.15 (d, $J = 8.7$ Hz, 1H), 6.82 (m, 1H), 4.31 (t, $J = 7.8$ Hz, 1H), 2.25 (m, 1H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 164.6, 163.9, 162.7, 156.6, 152.8, 142.3, 142.1, 130.8, 128.1 (2C), 121.8, 119.0 (2C), 114.7, 109.1, 108.7, 105.2, 58.7, 30.0, 19.8, 19.2; MS (ESI+) m/z 441 $[M + H]^+$; mp 224–226 °C; HPLC retention time – 3.949 min, purity – 99.12% (Method A).

*6.1.12.14. 3-Methyl-2-(3-(4-(3-o-tolylureido)phenyl)isoxazole-5-carboxamido) butanoic acid (**43a**).* Prepared as described above in the general procedure using 2-methylphenyl isocyanate (73 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (102.9 mg, 47.2%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (bs, 1H), 9.33 (s, 1H), 8.94 (d, $J = 8.1$ Hz, 1H), 8.04 (s, 1H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.79 (s, 1H), 7.68 (s, 1H), 7.63 (d, $J = 8.7$ Hz, 2H), 7.18 (m, 2H), 6.98 (t, $J = 7.5$ Hz, 1H), 4.29 (t, $J = 7.5$ Hz, 1H), 2.24 (s, 3H), 2.19 (m, 1H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 163.9, 162.7, 156.7, 153.1, 142.7, 137.7, 130.8, 128.5, 128.1 (2C), 126.8, 123.6, 121.9, 121.4, 118.7 (2C), 105.2, 58.6, 30.0, 19.8, 19.2, 18.5; MS (ESI+) m/z 437 $[M + H]^+$; mp 232–234 °C; HPLC retention time – 3.056 min, purity – 98.93% (Method A).

*6.1.12.15. 3-Methyl-2-(3-(4-(3-m-tolylureido)phenyl)isoxazole-5-carboxamido) butanoic acid (**44a**).* Prepared as described above in the general procedure using 3-methylphenyl isocyanate (73 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (112.4 mg, 51.6%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.83 (bs, 1H), 8.95 (s, 1H), 8.92 (s, 1H), 8.68 (d, 1H), 7.84 (d, 2H), 7.68 (s, 1H), 7.62 (s, 2H), 7.30 (s, 1H), 7.24 (m, 2H), 6.80 (d, 1H), 4.29 (m, 1H), 2.48 (s, 3H), 2.19 (m, 1H), 0.97 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 172.8, 163.8, 162.6, 156.5, 152.8, 142.5, 139.9, 138.4, 129.1, 127.9 (2C), 123.2, 121.3, 119.3, 118.7 (2C), 115.9, 105.1, 58.5, 29.9, 21.7, 19.6, 19.1; MS (ESI+) m/z 437 $[M + H]^+$; mp 130–133 °C; HPLC retention time – 3.431 min, purity – 97.28% (Method A).

*6.1.12.16. 3-Methyl-2-(3-(4-(3-(2-(trifluoromethyl)phenyl)ureido) phenyl) isoxazole-5-carboxamido)butanoic acid (**45a**).* Prepared as described above in the general procedure using 2-(trifluoromethyl) phenyl isocyanate (103 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (165.3 mg, 67.5%) as an off white solid.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.89 (s, 1H), 9.69 (s, 1H), 8.95 (d, $J = 8.1$ Hz, 1H), 8.23 (s, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 8.7$ Hz, 2H), 7.71 (t, $J = 4.5$ Hz, 2H), 7.65 (d, $J = 8.7$ Hz, 3H), 7.34 (t, $J = 7.5$ Hz, 1H), 4.31 (t, $J = 6.9$ Hz, 1H), 2.25 (m, 1H), 0.99 (d, $J = 6.9$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.6, 156.5, 152.9, 142.2, 136.5, 133.4, 128.0 (2C), 126.5 (2C), 124.5, 121.7, 120.8, 120.6, 118.8 (2C), 105.1, 58.5, 29.9, 19.6, 19.1; MS (ESI–) m/z 489 $(M - H)^-$, (ESI+) m/z 491 $[M + H]^+$; mp 160–162 °C; HPLC retention time – 3.492 min, purity – 99.82% (Method A).

*6.1.12.17. 3-Methyl-2-(3-(4-(3-(4-(trifluoromethyl)phenyl)ureido) phenyl)isoxazole-5-carboxamido)butanoic acid (**46a**).* Prepared as described above in the general procedure using 4-(trifluoromethyl) phenyl isocyanate (103 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (87.5 mg, 35.7%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.89 (bs, 1H), 9.22 (s, 1H), 9.13 (s, 1H), 8.94 (d, $J = 8.1$ Hz, 1H), 7.86 (d, $J = 8.7$ Hz, 2H), 7.69 (d, $J = 9.0$ Hz, 2H), 7.66 (m, 5H), 4.29 (t, $J = 7.2$ Hz, 1H), 2.25 (m, 1H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 8.4$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 163.9, 162.7, 156.7, 152.7, 143.8, 142.2, 131.8, 128.1 (2C), 126.7 (2C), 123.3, 121.9, 119.1 (2C), 118.6 (2C), 105.2, 58.6, 30.0, 19.8, 19.2; MS (ESI+) m/z 491 $[M + H]^+$; mp 248–251 °C; HPLC retention time – 5.817 min, purity – 99.57% (Method A).

*6.1.12.18. 2-(3-(4-(3-(3,4-Difluorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**47a**).* Prepared as described above in the general procedure using 3,4-difluorophenyl isocyanate (85.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (57.4 mg, 25.1%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.78 (s, 1H); 9.08 (s, 1H); 9.02 (s, 1H); 8.97 (d, $J = 8.1$ Hz, 1H); 7.87 (d, $J = 8.7$ Hz, 2H); 7.73–7.67 (m, 2H); 7.64 (d, $J = 8.7$ Hz, 2H); 7.39 (m, 1H); 7.17 (m, 1H); 4.31 (t, $J = 7.2$ Hz, 1H); 2.26 (m, 1H); 0.99 (d, $J = 6.9$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.6, 156.5, 152.7, 142.1, 137.1, 127.9 (2C), 121.7, 118.9 (2C), 117.9, 117.8, 115.0, 107.9, 107.7, 105.1, 58.5, 29.9, 19.6, 19.1; MS (ESI–) m/z 457 $[M - H]^-$, (ESI+) m/z 459 $[M + H]^+$; mp 228–230 °C; HPLC retention time – 3.342 min, purity – 98.37% (Method A).

*6.1.12.19. 2-(3-(4-(3-(3,5-Difluorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**48a**).* Prepared as described above in the general procedure using 3,5-difluorophenyl isocyanate (85.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (90.5 mg, 39.5%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (bs, 1H), 9.20 (s, 1H), 9.17 (s, 1H), 8.96 (d, $J = 8.1$ Hz, 1H), 7.87 (d, $J = 8.7$ Hz, 2H), 7.70 (s, 1H), 7.64 (d, $J = 8.7$ Hz, 2H), 7.25 (m, 2H), 6.86 (m, 1H), 4.31 (t, $J = 6.9$ Hz, 1H), 2.27 (m, 1H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 164.6, 163.9, 162.6, 161.4, 156.5, 152.6, 142.8, 141.9, 127.9 (2C), 121.8, 119.1 (2C), 105.1, 101.7, 101.3, 97.4, 58.5, 29.9, 19.7, 19.1; MS (ESI–) m/z 457 $[M - H]^-$, (ESI+) m/z 459 $[M + 1]^+$; mp 150–152 °C; HPLC retention time – 3.533 min, purity – 99.01% (Method A).

*6.1.12.20. 2-(3-(4-(3-(2, 5-Difluorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**49a**).* Prepared as described above in the general procedure using 2,5-difluorophenyl isocyanate (85.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (186.2 mg, 81.3%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.12 (s, 1H), 9.48 (s, 1H), 8.97 (d, $J = 8.4$ Hz, 1H), 8.89 (s, 1H), 8.08 (m, 1H), 7.88 (d, $J = 8.7$ Hz, 2H), 7.71 (s, 1H), 7.64 (d, $J = 8.7$ Hz 2H), 7.35 (m, 1H), 6.89 (m, 1H), 4.31 (t, $J = 7.2$ Hz, 1H), 2.25 (m, 1H), 0.99 (d, $J = 6.3$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.5, 156.6, 152.3, 150.1, 146.9, 141.7, 128.1 (2C), 121.9, 18.9 (2C), 116.5, 108.8, 107.4, 107.0, 105.1, 58.6, 29.8, 19.6, 19.1; MS (ESI–) m/z 457 $[M - H]^-$, (ESI+) m/z 459 $[M + H]^+$; mp 236–238 °C; HPLC retention time – 3.248 min, purity – 96.73% (Method A).

*6.1.12.21. 2-(3-(4-(3-(2,6-Difluorophenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**50a**).* Prepared as described above in the general procedure using 2,6-difluorophenyl isocyanate (85.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (150.2 mg, 65.6%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.83 (bs, 1H), 9.25 (s, 1H), 8.94 (d, J = 8.1 Hz, 1H), 8.22 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.68 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.36 (m, 1H), 7.18 (m, 2H), 4.29 (t, J = 7.5 Hz, 1H), 2.25 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 163.4, 162.1, 159.7, 156.4, 156.1, 152.4, 141.9, 127.5 (2C), 127.3, 121.2, 118.3 (2C), 115.1, 111.9, 111.6, 104.7, 58.0, 29.4, 19.2, 18.6; MS (ESI+) m/z 459 [M + H]$^+$; mp 219–221 °C; HPLC retention time – 2.766 min, purity – 96.39% (Method A).

*6.1.12.22. 2-(3-(4-(3-(2,4-Dimethylphenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methyl butanoic acid (**51a**).* Prepared as described above in the general procedure using 2,4-dimethylphenyl isocyanate (81 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (119.7 mg, 53.2%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.91 (s, 1H), 9.24 (s, 1H), 8.96 (d, J = 8.1 Hz, 1H), 7.96 (s, 1H), 7.85 (d, J = 8.7 Hz, 2H), 7.69 (s, 1H), 7.66 (t, J = 7.5 Hz, 3H), 7.00–6.95 (m, 2H), 4.31 (t, J = 7.5 Hz, 1H), 2.23 (m, 7H), 0.99 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7, 163.8, 162.6, 156.6, 153.1, 142.7, 134.9, 132.4, 131.2, 128.6 (2C), 127.9, 127.1, 122.2, 121.2, 118.5 (2C), 105.1, 58.5, 29.9, 20.8, 19.6, 19.1, 18.3; MS (ESI–) m/z 449 [M – H]$^-$, (ESI+) m/z 451 [M + H]$^+$; mp 212–214 °C; HPLC retention time – 3.433 min, purity – 95.49% (Method A).

*6.1.12.23. 2-(3-(4-(3-(3,5-Dimethylphenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methyl butanoic acid (**52a**).* Prepared as described above in the general procedure using 3,5-dimethylphenyl isocyanate (81 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (176.1 mg, 78.2%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.95 (d, J = 4.8 Hz, 1H), 8.94 (s, 1H), 8.61 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.70 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.09 (s, 2H), 6.64 (s, 1H), 4.31 (t, J = 7.2 Hz, 1H), 2.24 (s, 6H), 2.19 (m, 1H), 0.99 (d, J = 6.0 Hz, 3H), 0.96 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 163.1, 162.2, 156.7, 153.0, 142.5, 134.9, 134.4, 131.2, 128.4 (2C), 127.6, 127.2, 122.2, 122.0, 118.6 (2C), 105.3, 58.4, 29.8, 20.7, 19.5, 19.1, 18.4; MS (ESI–) 449 m/z [M – H]$^-$, (ESI+) m/z 451 [M + H]; mp 228–230 °C; HPLC retention time – 3.481 min, purity – 95.96% (Method A).

*6.1.12.24. 2-(3-(4-(3-(2-Fluoro-5-methylphenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**53a**).* Prepared as described above in the general procedure using 2-fluoro-5-methylphenyl isocyanate (83 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (97.4 mg, 42.9%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (bs, 1H), 9.36 (s, 1H), 8.96 (d, J = 8.1 Hz, 1H), 8.59 (s, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 8.7 Hz, 2H), 7.71 (s, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.15 (m, 1H), 6.84 (m, 1H), 4.31 (t, J = 7.5 Hz, 1H), 2.28 (s, 3H), 2.25 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.6, 156.5, 152.5, 149.3, 142.2, 133.9, 128.0 (2C), 127.3, 123.4, 121.6, 118.6 (2C), 115.1, 114.9, 105.1, 58.5, 29.9, 21.2, 19.6, 19.0; MS (ESI+) m/z 455 [M + H]$^+$; mp 241–243 °C; HPLC retention time – 3.517 min, purity – 98.01% (Method A).

*6.1.12.25. 2-(3-(4-(3-(3-Fluoro-4-methylphenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**54a**).* Prepared as described above in the general procedure using 3-fluoro-4-methylphenyl isocyanate (83 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (132.3 mg, 58.3%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.87 (bs, 1H), 9.04 (s, 1H), 8.95 (s, 1H), 8.92 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.69 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.47 (m, 1H), 7.21 (t, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 4.31 (t, J = 7.5 Hz, 1H), 2.27 (m, 1H), 2.17 (s, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.6, 159.4, 156.5, 152.7, 142.3, 139.5, 131.9, 127.9, 121.5, 118.8, 117.6, 117.4, 114.4, 105.7, 105.3, 105.1, 58.5, 29.9, 19.6, 19.1, 14.0; MS (ESI+) m/z 455.2 [M + H]$^+$; mp 236–238 °C; HPLC retention time – 3.533 min, purity – 98.78% (Method A).

*6.1.12.26. 2-(3-(4-(3-(4-Fluoro-2-methylphenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**55a**).* Prepared as described above in the general procedure using 4-fluoro-2-methylphenyl isocyanate (83 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate afford the title compound (92.9 mg, 40.9%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.81 (bs, 1H), 9.26 (s, 1H), 8.92 (d, J = 8.1 Hz, 1H), 8.04 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.74 (m, 1H), 7.67 (s, 1H), 7.62 (d, J = 8.7 Hz, 2H), 7.08 (m, 1H), 7.00 (m, 1H), 4.29 (t, J = 7.2 Hz, 1H), 2.24 (s, 3H), 2.21 (m, 1H), 0.97 (d, J = 6.3 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 163.3, 162.1, 156.5, 156.1, 152.7, 142.1, 133.4, 131.4, 127.5 (2C), 123.7, 118.1 (2C), 116.4, 112.6, 112.3, 104.6, 58.0, 29.4, 19.2, 18.6, 17.8; MS (ESI–) m/z 453 [M – H]$^-$, (ESI+) m/z 455 [M + H]$^+$; mp 226–228 °C; HPLC retention time – 3.242 min, purity – 98.39% (Method A).

*6.1.12.27. 2-(3-(4-(3-(5-Fluoro-2-methylphenyl)ureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**56a**).* Prepared as described above in the general procedure using 5-Fluoro-2-methylphenyl isocyanate (83 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (130.7 mg, 57.6%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.90 (bs, 1H), 9.47 (s, 1H), 8.96 (d, J = 7.8 Hz, 1H), 8.15 (s, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.83 (m, 1H), 7.70 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 7.8 Hz, 1H), 6.79 (m, 1H), 4.31 (t, J = 7.2 Hz, 1H), 2.23 (bs, 4H), 0.99 (d, J = 6.0 Hz, 3H), 0.98 (d, J = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.8, 162.6, 162.1, 156.6, 152.7, 142.2, 139.1, 131.5, 128.0 (2C), 122.8, 121.6, 118.7 (2C), 108.9, 107.3, 105.1, 58.5, 29.9, 19.6, 19.1, 17.6; MS (ESI–) m/z 453 [M – H]$^-$; mp 230–233 °C; HPLC retention time – 3.458 min, purity – 98.35% (Method A).

*6.1.12.28. 2-Bromo-1-(4-nitrophenyl)ethanone (**19**).* A solution of 4-nitroacetophenone (25 g, 151 mmol, 1.0 equiv) in ether (250 ml) was treated with catalytic amount of aluminum chloride followed by bromine (7.77 ml, 151 mmol, 1.0 equiv) over 10 min and the reaction was stirred for an additional 30 min. The reaction was then quenched with aqueous sodium bicarbonate, the ether layer separated, dried over sodium sulfate, and evaporated under reduced pressure. The residue was crystallized using ethyl acetate and petroleum ether to afford the title compound (25.5 g, 69%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.39–8.36 (d, J = 8.7 Hz, 2H), 8.19–8.16 (d, J = 8.7 Hz, 2H), 4.48 (s, 2H); MS (ESI–) m/z 243 [M – H]$^-$, MS (ESI+) m/z 245 [M + H]$^+$.

*6.1.12.29. 2-Amino-1-(4-nitrophenyl)ethanone hydrochloride (**20**).* To a solution of compound **19** (25 g, 102 mmol, 1.0 equiv) in DCM (250 ml) was added hexamethylenetetramine (20.1 g, 143 mmol, 1.4 equiv) and the mixture was stirred for 1 h. The reaction mixture was then filtered to yield an off white solid. The solid was taken in EtOH (162 ml) and concentrated HCl (40 ml) was added and stirred

for 3 h. The resulting mixture was then left standing for two days. The reaction mixture was filtered, the residue washed with water, and dried to yield the title compound (11.8 g, 72%) as an off white solid.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.57 (bs, 2H), 8.41–8.38 (d, J = 9.0 Hz, 2H), 8.28–8.25 (d, J = 9.0 Hz, 2H), 4.68 (s, 2H); MS (ESI+) m/z 181.1 $[M + H]^+$.

*6.1.12.30. Ethyl 2-(2-(4-nitrophenyl)-2-oxoethylamino)-2-oxoacetate (**21**).* To a solution of compound **20** (11.5 g, 31 mmol, 1.0 equiv) in EtOAc (115 ml) was added Et_3N (6.45 g, 62 mmol, 2.0 equiv). To this mixture a solution of ethylchlorooxoacetate (8.69 g, 62 mmol, 2.0 equiv) in EtOAc (35 ml) was added dropwise and the reaction was refluxed for 2 h. The reaction mixture was cooled and quenched with water. The organic layer was separated, dried over sodium sulfate, and evaporated under reduced pressure to obtain a dark brown oil that was purified using flash column chromatography (3:7 ethyl acetate/petroleum ether) to afford the desired product (8.9 g, 59%) as a yellow solid.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.21 (t, 1H), 8.38–8.35 (d, J = 8.7 Hz, 2H), 8.25–8.22 (d, J = 8.7 Hz, 2H), 4.78–4.76 (d, J = 5.7 Hz, 2H), 4.32–4.25 (q, J = 7.2 Hz, 2H), 1.32–1.27 (t, J = 7.2 Hz, 3H); MS (ESI−) m/z 279 $[M - H]^-$, (ESI+) m/z 281 $(M + H)^+$.

*6.1.12.31. Ethyl 5-(4-nitrophenyl)oxazole-2-carboxylate (**22**).* A solution of compound **21** (8.5 g, 30 mmol, 1.0 equiv) in $POCl_3$ (55 ml, 220 mmol, 7.3 equiv) was refluxed for 6 h. Following its completion the reaction mixture was cooled, cautiously quenched in ice, and neutralized using sodium carbonate. The compound was subsequently extracted with DCM, the organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain a dark brown residue. The residue was separated using flash column chromatography (2:8 ethyl acetate/petroleum ether) to get a pale brown colored solid that when crystallized in chloroform–petroleum ether afforded the title compound (4.82 g, 60%) as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 8.7 Hz, 2H), 7.73 (s, 1H), 4.58 (q, J = 7.2 Hz, 2H), 1.52–1.47 (t, J = 7.2 Hz, 3H); MS (ESI−) m/z 261 $[M - H]^-$, (ESI+) m/z 263 $[M + H]^+$.

*6.1.12.32. Methyl 3-methyl-2-(5-(4-nitrophenyl)oxazole-2-carboxamido) butanoate (**23**).* Compound **22** (3.4 g, 13 mmol, 1.0 equiv) and L-valine methyl ester hydrochloride (5.43 g, 32 mmol, 2.4 equiv) were dissolved in ethanol (34 ml) and taken in a sealed tube. Triethylamine (4.52 ml, 32 mmol, 2.4 equiv) was added and the resulting mixture was heated at 110 °C for two days. Following reaction completion, ethanol was removed under reduced pressure and the crude material was separated using flash column chromatography (1:99 ethyl acetate/petroleum ether) to obtain a solid that was crystallized in an ethyl acetate–petroleum ether mixture to afford the title compound (700 mg, 31%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (d, J = 7.8 Hz, 1H), 8.40 (d, J = 8.7 Hz, 2H), 8.24 (s, 1H), 8.15 (d, J = 8.7 Hz, 2H), 4.35 (m, 1H), 3.68 (s, 3H), 2.29 (m, 1H), 0.99 (d, J = 6.9 Hz, 6H), 0.96 (d, J = 7.2 Hz, 6H); MS (ESI−) m/z 346 $[M - H]^-$, (ESI+) m/z 348 $[M + H]^+$.

*6.1.12.33. Methyl 2-(5-(4-aminophenyl)oxazole-2-carboxamido)-3-methyl butanoate (**24**).* Compound **23** (700 mg, 2.01 mmol, 1.0 equiv) was dissolved in ethanol (7 ml), THF (2.8 ml), and water (2.8 ml). To this mixture were added ammonium chloride (323 mg, 6.09 mmol, 3.0 equiv) and iron (264 mg, 4.7 mmol, 3.0 equiv) and the resulting solution was refluxed at 80 °C for 3 h. Following completion of this reaction, the reaction mixture was cooled, filtered through celite, and solvent evaporated under reduced pressure to obtain a dark brown residue that was taken in water and extracted using ethyl acetate. The dark brown residue was purified by flash column chromatography (2.5:7.5 ethyl acetate/chloroform) to obtain a solid that was crystallized in DCM–petroleum ether to afford the desired compound (550 mg, 86%) as a yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.83 (d, J = 8.1 Hz, 1H), 7.55 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 5.64 (s, 2H), 4.31 (m, 1H), 3.67 (s, 3H), 2.29 (m, 1H), 0.96–0.91 (t, J = 7.2 Hz, 6H); MS (ESI−) m/z 316 $[M - H]^-$, (ESI+) m/z 318 $[M + H]^+$.

6.1.13. General procedure for the synthesis of oxazole analogs possessing a urea linker

To a solution of compound **24** (0.5 mmol, 1 equiv) in THF (3 ml) was added the appropriately substituted phenyl isocyanate (1.1 equiv) and the mixture stirred for 16 h at rt. The reaction mixture was then concentrated and purified using flash column chromatography (3:7 EtOAc/$CHCl_3$) to yield the desired methyl ester. To a solution of the methyl ester (1 equiv) THF was added 1.0 M solution of LiOH in water (5 equiv) and stirred for 16 h at rt. The solvent was removed and the obtained residue was diluted with water and acidified to pH 2 using 2.0 M HCl. The material thus obtained was extracted with ethyl acetate, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain a solid that was crystallized in ethyl acetate to yield the desired acid.

*6.1.13.1. 3-Methyl-2-(5-(4-(3-(2-chlorophenyl)ureido)phenyl)oxazole-2-carboxamido)butanoic acid (**30b**).* Prepared as described above in the general procedure using 2-chlorophenyl isocyanate (84.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (145.8 mg, 63.9%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.94 (s, 1H), 9.68 (s, 1H), 8.64 (d, J = 8.1 Hz, 1H), 8.39 (s, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.4 Hz, 3H), 7.64 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 4.31 (t, J = 8.1 Hz, 1H), 2.41 (m, 1H), 0.98–0.95 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 155.3, 153.7, 153.3, 152.4, 141.2, 136.2, 129.7, 128.1, 126.2 (2C), 124.0, 122.8, 122.6, 121.9, 120.8, 118.8 (2C), 58.4, 30.1, 19.7, 18.9; MS (ESI−) m/z 455 $[M - H]^-$, (ESI+) m/z 457 $[M + H]^+$; mp 122–124 °C; HPLC retention time – 3.169 min, purity – 99.98% (Method A).

*6.1.13.2. 2-(5-(4-(3-(3-Chlorophenyl)ureido)phenyl)oxazole-2-carboxamido)-3-methylbutanoic acid (**31b**).* Prepared as described above in the general procedure using 3-chlorophenyl isocyanate (84.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (201.2 mg, 88.2%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.93 (s, 1H), 9.06 (s, 1H), 8.99 (s, 1H), 8.67 (d, 1H), 7.81 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.73 (m, 1H), 7.63 (d, J = 9.0 Hz, 2H), 7.35–7.27 (m, 2H), 7.05 (m, 1H), 4.31–4.26 (d, J = 6.9 Hz, 1H), 2.279 (m, 1H), 0.97–0.95 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 155.3, 153.7, 153.3, 152.7, 141.5, 141.2, 133.7, 130.9, 126.1 (2C), 122.8, 122.1, 120.7, 118.9 (2C), 118.1, 117.2, 58.4, 30.1, 19.7, 18.9; MS (ESI−) m/z 455 $[M - H]^-$, (ESI+) m/z 457 $[M + H]^+$; mp 188–190 °C; HPLC: retention time – 3.284 min, purity – 95.87% (Method A).

*6.1.13.3. 2-(5-(4-(3-(4-Chlorophenyl)ureido)phenyl)oxazole-2-carboxamido)-3-methylbutanoic acid (**32b**).* Prepared as described above in the general procedure using 4-chlorophenyl isocyanate (84.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (188.7 mg, 82.7%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.94 (s, 1H), 9.06 (s, 1H), 8.96 (s, 1H), 8.66 (d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 4.30–4.25 (d, J = 6.6 Hz, 1H), 2.28 (m, 1H), 0.97–0.95 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 155.3, 153.7, 153.4, 152.7, 141.3, 138.9, 133.1, 129.1 (2C), 126.1 (2C), 122.7, 120.6, 120.3 (2C), 118.9 (2C), 58.4, 30.1, 19.6, 18.9; MS (ESI−) m/z 455 [M − H]$^-$, (ESI+) m/z 457 [M + H]$^+$; 210–212 °C; HPLC retention time − 3.266 min, purity − 96.56% (Method A).

*6.1.13.4. 3-Methyl-2-(5-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl) oxazole-2-carboxamido)butanoic acid (**33b**).* Prepared as described above in the general procedure using 3-(trifluoromethyl)phenyl isocyanate (103 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (185.4 mg, 75.6%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.95 (s, 1H), 9.09 (d, J = 8.4 Hz, 2H), 8.64 (d, J = 8.1 Hz, 1H), 8.03 (s, 1H), 7.80 (s, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.58–7.50 (m, 2H), 7.35 (d, J = 7.2 Hz, 1H), 4.31 (t, J = 8.1 Hz, 1H), 2.38 (m, 1H), 0.98–0.90 (d, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 155.3, 153.7, 153.3, 152.8, 141.1, 140.8, 130.4, 129.8, 129.3, 126.1 (2C), 122.8, 122.4, 120.8, 119.1 (2C), 118.7, 114.7, 58.4, 30.0, 19.6, 18.9; MS (ESI−) m/z 498 [M − H]$^-$, (ESI+) m/z 491 [M + H]$^+$; mp 222–224 °C; HPLC retention time − 3.540 min, purity − 99.94% (Method A).

*6.1.13.5. 2-(5-(4-(3-(3,4-Dimethylphenyl)ureido)phenyl)oxazole-2-carboxamido)-3-methylbutanoic acid (**34b**).* Prepared as described above in the general procedure using 3,4-dimethylphenyl isocyanate (81 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (145.7 mg, 64.7%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.90 (s, 1H), 8.63 (d, J = 8.4 Hz, 1H), 8.57 (s, 1H), 7.83 (s, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.25 (bs, 1H), 7.19–7.16 (d, 8.1 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 4.31–4.26 (m, 1H), 2.32 (m, 1H), 0.97–0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 155.3, 153.6, 153.4, 152.8, 141.7, 137.6, 136.8, 130.1 (2C), 126.0 (2C), 122.6, 120.3, 120.1, 118.6 (2C), 116.3, 58.5, 30.1, 20.1, 19.7, 19.1, 18.9; MS (ESI−) m/z 449 [M − H]$^-$, (ESI+) m/z 451 [M + H]$^+$; mp 194–196 °C; HPLC retention time − 3.273 min, purity − 99.41% (Method A).

*6.1.13.6. 2-(5-(4-(3-(4-Chloro-2-phenoxyphenyl)ureido)phenyl)oxazole-2-carboxamido)-3-methylbutanoic acid (**35b**).* Prepared as described above in the general procedure using 4-chloro-2-phenoxyphenyl isocyanate (135 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (175.3 mg, 63.9%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.96 (s, 1H), 9.62 (s, 1H), 8.74 (s, 1H), 8.64 (d, J = 7.8 Hz, 1H), 8.39 (s, 1H), 7.81 (d, J = 9.9 Hz, 3H), 7.61 (d, J = 8.1 Hz, 2H), 7.47 (t, J = 6.3 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.11 (d, J = 7.5 Hz, 2H), 7.03 (d, J = 7.8 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 4.30 (t, J = 6.9 Hz, 1H), 2.27 (m, 1H), 0.97–0.95 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7, 155.3, 156.5, 153.9, 153.4, 152.2, 145.1, 138.4, 133.7, 128.7 (2C), 125.6 (2C), 123.4, 122.8, 122.6, 121.9, 121.2, 120.8, 119.7, 119.5, 118.9 (2C), 116.3, 58.8, 30.2, 19.7, 18.9; MS (ESI−) m/z 547 [M − H]$^-$, (ESI+) m/z 549 [M + H]$^+$; mp > 275 °C; HPLC retention time − 3.723 min, purity − 95.98% (Method A).

*6.1.13.7. 2-(5-(4-(3-(4-Chloro-2-fluorophenyl)ureido)phenyl)oxazole-2-carboxamido)-3-methylbutanoic acid (**36b**).* Prepared as described above in the general procedure using 4-chloro-2-fluorophenyl isocyanate (94.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (207.6 mg, 87.4%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.93 (s, 1H), 9.41 (s, 1H), 8.76 (s, 1H), 8.67 (d, J = 8.4 Hz, 1H), 8.21 (t, J = 9.0 Hz, 1H), 7.82 (s, 1H), 7.81 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.51–7.47 (d, 11.5 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 4.31 (m, 1H), 2.28 (m, 1H), 0.97–0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7, 155.3, 153.7, 153.3, 152.3, 150.7, 140.9, 127.0, 126.1 (2C), 125.1, 122.8, 121.9, 120.9, 118.8 (2C), 116.3, 115.9, 58.4, 30.0, 19.6, 18.9; MS (ESI−) m/z 473 [M − H]$^-$, (ESI+) m/z 475 [M + H]$^+$; mp > 244–242 °C; HPLC retention time − 3.456 min, purity − 97.70% (Method A).

*6.1.13.8. N′-Hydroxy-4-nitrobenzimidamide (**26**).* To a solution of 4-nitrobenzonitrile (50 g, 485 mmol, 1.0 equiv) in ethanol (100 ml) were added potassium carbonate (100 g, 728 mmol, 1.5 equiv) and hydroxylamine hydrochloride (50 g, 728 mmol, 1.5 equiv) and the reaction was refluxed at 80 °C for 5 h. Following reaction completion the solvent was removed under reduced pressure and the crude obtained was dissolved in ethyl acetate, washed with water, brine, dried using anhydrous sodium sulfate, and concentrated to obtain a solid. This solid was purified by flash column chromatography (3:7 EtOAc/$CHCl_3$) and further crystallized from ethyl acetate–petroleum ether to obtain the desired title compound (28.0 g, 42%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.25 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 6.07 (s, 2H); MS (ESI+) m/z 180 [M − H]$^-$, (ESI+) m/z 182 [M + H]$^+$.

*6.1.13.9. Ethyl 3-(4-nitrophenyl)-1,2,4-oxadiazole-5-carboxylate (**27**).* A solution of ethyl oxalyl chloride (20.41 g, 149 mmol, 1.2 equiv) in anhydrous chloroform (100 ml) was slowly added at 0 °C over a period of 45 min to a stirred solution of compound **26** (22 g, 121 mmol, 1.0 equiv) and pyridine (9.77 ml, 121 mmol, 1.0 equiv) in chloroform (350 ml). The mixture was stirred at rt for 1 h followed by reflux at 60 °C for 14 h. Following reaction completion chloroform was added to the reaction and the resulting product was successively washed with 2.0 M HCl, water and bicarbonate solution. The organic layer was then dried over anhydrous sodium sulfate and evaporated to obtain a pale green colored solid. This solid was crystallized from chloroform–petroleum ether to afford the title product (18 g, 56%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 4H), 4.63 (q, J = 7.2 Hz, 2H), 1.53 (t, J = 7.2 Hz, 3H); MS (ESI−) m/z 262 [M − H]$^-$, (ESI+) m/z 264 [M + H]$^+$.

*6.1.13.10. Methyl 2-(3-(4-nitrophenyl)-1,2,4-oxadiazole-5-carboxamido)-3-methyl butanoate (**28**).* Compound **27** (15 g, 57 mmol, 1.0 equiv) was taken in ethanol (150 ml) and refluxed to make a clear solution. To this a solution of L-valine methyl ester hydrochloride (28.68 g, 171 mmol, 3.0 equiv) neutralized with triethylamine (24.67 ml, 171 mmol, 3.0 equiv) in ethanol (100 ml) was added and the reaction mixture was refluxed overnight. Following completion the reaction mass was concentrated to dryness and the crude product obtained was dissolved in ethyl acetate, washed with water, brine, dried over anhydrous sodium sulfate, and concentrated to give a crude solid. The solid was purified by flash column chromatography (3:7 EtOAc/$CHCl_3$) and further crystallized from chloroform–petroleum ether to afford the title compound (15.5 g, 78.60%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (d, J = 9.0 Hz, 2H), 8.36 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 8.7 Hz, 1H), 4.79–4.75 (dd, J = 4.5, 8.7 Hz, 1H), 3.83 (s, 3H), 2.39 (m, 1H), 1.06 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.3 Hz, 3H); MS (ESI+) m/z 349 [M + H]$^+$.

*6.1.13.11. Methyl 2-(3-(4-aminophenyl)-1,2,4-oxadiazole-5-carboxamido)-3 methylbutanoate (**29**).* To a solution of compound **28** (15 g, 43 mmol, 1.0 equiv) in ethanol (150 ml), THF (75 ml) and

water (35 ml) were added iron powder (5.68 g, 101 mmol, 2.3 equiv) and ammonium chloride (10.02 g, 187 mmol, 4.3 equiv) and the reaction mixture was refluxed at 80 °C for 4 h. Following completion the reaction mass was filtered through celite and the filtrate was concentrated to obtain a crude material that was dissolved in ethyl acetate, washed with water, brine solution, dried over anhydrous sodium sulfate, and then concentrated to give a solid .This solid was then purified by flash column chromatography (3:7 EtOAc/$CHCl_3$). Finally, the compound was crystallized from chloroform–petroleum ether to afford the title compound (12 g, 79%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.61 (d, J = 4.5 Hz, 1H), 7.74 (d, J = 5.1 Hz, 2H), 6.69 (d, J = 4.5 Hz, 2H), 5.87 (s, 2H), 4.34 (t, J = 4.5 Hz, 1H), 3.69 (s, 3H), 2.25 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); MS (ESI+) m/z 319 $[M + H]^+$.

6.1.14. General procedure for the synthesis of oxadiazole analogs possessing a urea linker

To a solution of compound **29** (0.5 mmol, 1.0 equiv) in THF (3 ml) was added the appropriately substituted phenyl isocyanate (1.1 equiv) and the mixture was stirred for 16 h at rt. The reaction mixture was then concentrated and purified using flash column chromatography (2:8 EtOAc/petroleum ether) to yield the desired methyl ester. To a solution of the methyl ester (1 equiv) in THF was added 1.0 M solution of LiOH in water (5 equiv) and stirred for 16 h at rt. The solvent was removed and the obtained residue was diluted with water and acidified to pH 2 using 2.0 M HCl. The material thus obtained was extracted with ethyl acetate, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain a solid that was crystallized in ethyl acetate to yield the desired acid.

*6.1.14.1. 2-(3-(4-(3-(2-Chlorophenyl)ureido)phenyl)-1,2,4-oxadiazole-5-carboxamido)-3-methylbutanoic acid (**30c**).* Prepared as described above in the general procedure using 2-chlorophenyl isocyanate (84.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (96.1 mg, 42.1%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.03 (s, 1H), 9.83 (s, 1H), 9.42 (d, J = 8.4 Hz, 1H), 8.54 (s, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 4.32 (m, 1H), 2.27 (m, 1H), 0.99 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 169.3, 168.2, 154.3, 152.4, 143.4, 136.1, 129.7, 128.8 (2C), 128.1, 124.2, 122.7, 122.0, 119.1, 118.7 (2C), 58.8, 29.9, 19.6, 18.9; MS (ESI−) m/z 456 $[M - H]^-$; mp 206–208 °C; HPLC retention time – 3.469 min, purity – 96.16% (Method A).

*6.1.14.2. 2-(3-(4-(3-(3-Chlorophenyl)ureido)phenyl)-1,2,4-oxadiazole-5-carboxamido)-3-methylbutanoic acid (**31c**).* Prepared as described above in the general procedure using 3-chlorophenyl isocyanate (84.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (123.1 mg, 54.0%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.69 (s, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H), 7.86 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 4.23 (m, 1H), 2.35 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.9, 169.5, 168.2, 153.5, 152.7, 144.8, 142.7, 133.5, 130.7, 128.3 (2C), 121.5, 118.6 (2C), 118.4, 118.0, 117.1, 59.8, 31.5, 19.8, 18.9; MS (ESI+) m/z 458 $[M + H]^+$; mp 214–216 °C; HPLC retention time – 3.599 min, purity – 95.76% (Method A).

*6.1.14.3. 2-(3-(4-(3-(4-Chlorophenyl)ureido)phenyl)-1,2,4-oxadiazole-5-carboxamido)-3-methylbutanoic acid (**32c**).* Prepared as described above in the general procedure using 4-chlorophenyl isocyanate (84.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (147.2 mg, 64.6%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.69 (s, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H), 7.86 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 4.23 (m, 1H), 2.35 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 169.3, 168.2, 154.3, 152.6, 143.5, 138.9, 129.1 (2C), 128.7 (2C), 126.2, 120.4 (2C), 118.9, 118.7 (2C), 58.8, 29.9, 19.6, 18.9; MS (ESI+) m/z 458 $[M + H]^+$; mp 230–232 °C; HPLC retention time – 5.948 min, purity – 98.17% (Method A).

*6.1.14.4. 3-Methyl-2-(3-(4-(3-(3-(trifluoromethyl)phenyl)ureido) phenyl)-1,2,4-oxadiazole-5-carboxamido)butanoic acid (**33c**).* Prepared as described above in the general procedure using 3-(trifluoromethyl)phenyl isocyanate (103 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (189.1 mg, 77.1%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.05 (s, 1H), 9.31 (s, 1H), 8.07 (s, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 4.32 (m, 1H), 2.29 (m, 1H), 0.99 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.5, 169.4, 168.2, 153.8, 152.9, 143.6, 140.9, 130.4, 129.3, 128.6 (2C), 124. 3, 123.6, 122.4, 121.7, 118.9 (2C), 114.8, 59.0, 30.2, 19.6, 18.9; MS (ESI+) m/z 492 $[M + H]^+$; mp 220–222 °C; HPLC retention time – 3.808 min, purity – 98.84% (Method A).

*6.1.14.5. 2-(3-(4-(3-(2,4-Difluorophenyl)ureido)phenyl)-1,2,4-oxadiazole-5-carboxamido)-3-methylbutanoic acid (**37c**).* Prepared as described above in the general procedure using 2,4-difluorophenyl isocyanate (85.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (184.0 mg, 80.3%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) 13.025 (s, 1H), 9.393 (s, 1H), 9.372 (s, 1H), 8.610 (s, 1H), 8.102–8.051 (m, 1H), 8.011 (d, J = 8.4 Hz, 2H), 7.675 (d, J = 8.7 Hz, 2H), 7.350 (m, 1H), 7.077 (t, J = 8.7 Hz, 1H), 4.317 (t, J = 7.2 Hz, 1H), 2.292 (m, 1H), 0.969–0.947 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 169.3, 168.2, 154.3, 152.5, 143.3, 128.8 (2C), 124.1, 122.7, 119.1, 118.6 (2C), 111.7, 111.4, 104.6, 104.3, 58.8, 29.9, 19.6, 18.9; MS (ESI−) m/z 458 $[M - H]^-$, (ESI+) m/z 460 $[M + H]^+$; mp 221–223 °C; HPLC retention time – 3.285 min, purity – 99.66% (Method A).

*6.1.14.6. 2-(3-(4-(3-(4-Fluorophenyl)ureido)phenyl)-1,2,4-oxadiazole-5-carboxamido)-3-methylbutanoic acid (**38c**).* Prepared as described above in the general procedure using 4-fluorophenyl isocyanate (75.5 mg, 0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (86.7 mg, 39.4%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.02 (s, 1H), 9.40 (d, J = 7.5 Hz, 1H), 9.23 (s, 1H), 9.12 (s, 1H), 8.01 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.50–7.48 (m, 2H), 7.16 (t, J = 8.5 Hz, 2H), 4.33 (t, J = 7.0 Hz, 1H), 2.28 (m, 1H), 0.97–0.92 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 169.3, 168.2, 158.9, 154.3, 152.8, 143.7, 136.2, 128.7 (2C), 120.7, 120.6 (2C), 118.8, 118.7, 115.9, 115.7, 58.8, 29.9, 19.6, 18.9; MS (ESI−) m/z 440 $[M - H]^-$, (ESI+) 442 $[M + H]^+$; mp > 242–244 °C; HPLC retention time – 3.153 min, purity – 97.12% (Method A).

*6.1.14.7. 3-Methyl-2-(3-(4-(3-p-tolylureido)phenyl)-1,2,4-oxadiazole-5-carboxamido)butanoic acid (**39c**).* Prepared as described above in the general procedure using 4-methyl phenyl isocyanate (73 mg,

0.55 mmol, 1.1 equiv) as the substituted isocyanate to afford the title compound (138.3 mg, 63.4%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.04 (s, 1H), 9.39 (d, J = 8.1 Hz, 1H), 9.03 (s, 1H), 8.68 (s, 1H), 7.99 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 4.32–4.27 (d, 6.6 Hz, 1H), 2.27–2.20 (m, 1H), 2.23 (s, 3H), 0.97–0.95 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 169.4, 168.3, 154.4, 152.9, 143.9, 137.3, 131.6, 129.8 (2C), 128.8 (2C), 119.1 (2C), 118.8, 118.7 (2C), 58.9, 30.0, 20.9, 19.7, 19.0; MS (ESI−) m/z 436 [M − H]$^-$, (ESI+) m/z 438 [M + H]$^+$; mp 236–238 °C; HPLC retention time − 3.348 min, purity − 96.02% (Method A).

*6.1.14.8. 2-(3-(4-(3-(2-Fluorophenyl)thioureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**57**).* To a solution of compound **17** (800 mg, 2.5 mmol, 1.0 equiv) in THF (10 ml) was added 1-fluoro-2-isothiocyanatobenzene (0.47 ml, 3.8 mmol, 1.5 equiv) and the mixture was stirred for 16 h at rt. Following reaction completion the solvent was reduced by evaporation and the solid thus obtained was filtered and washed with THF to provide the methyl ester, methyl 2-(3-(4-(3-(2-fluorophenyl)thioureido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoate, as a white solid. The methyl ester was subsequently deprotected using general procedure II at the second step to obtain the title compound (757 mg, 66%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (s, 1H), 10.19 (s, 1H), 9.65 (s, 1H), 8.98 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.72–7.69 (d, J = 8.7 Hz, 2H), 7.71 (s, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.28–7.14 (m, 3H), 4.29 (t, J = 7.2 Hz, 1H), 2.26 (m, 1H), 0.97–0.95 (dd, J = 3.9, 2.7 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7, 166.3, 165.2, 163.9, 163.0, 162.5, 156.5, 141.7, 131.6, 130.9, 127.7 (2C), 123.3, 120.9 (2C), 116.0, 115.7, 105.2, 58.6, 29.9, 19.7, 19.1; MS (ESI−) m/z 455 [M − H]$^-$, (ESI+) m/z 457 [M + H]$^+$; mp 180–182 °C; HPLC retention time − 2.917 min, purity − 97.22% (Method A).

*6.1.14.9. 2-(3-(4-(2-Hydroxy-2-phenylacetamido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**58**).* To a solution of mandelic acid (200 mg, 1.3 mmol, 1.0 equiv) and compound **17** (417 mg, 1.3 mmol, 1.0 equiv) in DMF (5 ml) were added DCC (406 mg, 1.9 mmol, 1.5 equiv) and HOBT (177 mg, 1.3 mmol, 1.0 equiv) and the reaction was stirred at rt for 16 h. Following completion, the reaction mixture was filtered and concentrated to obtain a brown oil that was purified by flash column chromatography (2:8 EtOAc/$CHCl_3$) to obtain a pale brown solid that was crystallized in DCM–petroleum ether to obtain the methyl ester, methyl 2-(3-(4-((*R*)-2-hydroxy-2-phenylacetamido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoate, as an off white solid. The methyl ester was subsequently deprotected using general procedure II at the second step to obtain the title compound (228 mg, 40%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.86 (bs, 1H), 10.20 (d, J = 8.7 Hz, 1H), 8.97 (d, J = 8.1 Hz, 1H), 7.91 (q, J = 8.7 Hz, 4H), 7.70 (s, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.39–7.29 (m, 3H), 6.52 (d, J = 3.9 Hz, 1H); 5.14 (d, J = 3.0 Hz, 1H); 4.29 (t, J = 7.8 Hz, 1H), 2.22 (m, 1H); 0.98 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 181.1, 172.9, 164.1, 162.6, 156.6, 155.4, 142.1, 134.3, 129.2 (2C), 128.1, 128.0, 127.6 (2C), 127.4, 124.8, 123.9 (2C), 105.4, 58.6, 29.9, 19.8, 19.2; MS (ESI+) m/z 438 [M + H]$^+$; mp 218–220 °C; HPLC retention time − 2.633 min, purity − 99.75% (Method A).

*6.1.14.10. 3-Methyl-2-(3-(4-(3-(o-tolylsulfonyl)ureido)phenyl)isoxazole-5-carboxamido)butanoic acid (**59**).* To a solution of compound **17** (500 mg, 1.5 mmol, 1.0 equiv) in THF (10 ml) was added *o*-tolylsulfonyl isocyanate (466 mg, 2.3 mmol, 1.5 equiv) and the mixture was stirred for 16 h at rt. Following reaction completion the solvent was reduced by evaporation and the solid thus obtained was filtered and washed with THF to provide the methyl ester, methyl-3-methyl-2-(3-(4-(3-(*o*-tolylsulfonyl)ureido)phenyl) isoxazole-5-carboxamido) butanoate, as a white solid. The methyl ester was subsequently deprotected using general procedure II at the second step to obtain the title compound (420 mg, 53.30%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.87 (bs, 1H), 11.02 (bs, 1H), 8.95 (s, 1H), 8.91 (s, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.67 (s, 1H), 7.59–7.34 (m, 5H), 4.28 (t, J = 7.8 Hz, 1H), 2.61 (s, 3H); 2.24 (m, 1H), 0.96 (d, 3H), 0.95 (d, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.9, 162.5, 156.6, 149.8, 140.9, 138.5, 137.3, 133.9, 132.9, 130.7, 128.1 (2C), 126.9, 122.8, 119.6 (2C), 105.2, 58.6, 29.9, 20.5, 19.7, 19.2; MS (ESI+) m/z 501 [M + H]$^+$; mp 80–82 °C; HPLC retention time − 2.042 min, purity − 95.90% (Method A).

*6.1.14.11. 3-Methyl-2-(3-(4-(2-oxo-2-((3(trifluoromethyl)phenyl)amino) acetamido) phenyl)isoxazole-5-carboxamido)butanoic acid (**60**).* To a solution of 3-trifluoromethyl aniline (0.12 ml, 0.9 mmol, 1.0 equiv) and compound **17** (300 mg, 0.9 mmol, 1.0 equiv) in EtOAc (3 ml) was added oxalyl chloride (0.08 ml, 1.0 mmol, 1.1 equiv) in EtOAc (3 ml) and the reaction was stirred at rt for 3 h. Following completion, water was added to the reaction followed by extraction with ethyl acetate. The separated organic layer was dried over sodium sulfate and concentrated to obtain a solid that was subjected to flash column chromatography (1:9 EtOAc/$CHCl_3$) to obtain a methyl ester, methyl 3-methyl-2-(3-(4-(2-oxo-2-((3-(trifluoromethyl)phenyl)amino)acetamido)phenyl)isoxazole-5-carboxamido) butanoate, as an off white solid. The methyl ester was subsequently deprotected using general procedure II at the second step to obtain the title compound (146 mg, 30%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.24 (s, 1H); 11.14 (s, 1H); 9.01 (d, J = 7.2 Hz, 1H), 8.35 (bs, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 8.7 Hz, 2H), 8.97 (d, J = 8.7 Hz, 2H), 7.73 (s, 1H), 7.67 (t, J = 7.8 Hz, 1H); 7.54 (d, J = 7.8 Hz, 1H), 4.31 (t, J = 7.8 Hz, 1H); 2.27 (m, 1H); 0.99 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 164.1, 163.8, 162.4, 156.8, 152.7, 142.1, 140.8, 130.3, 129.7, 128.2 (2C), 126.4, 123.1, 122.2, 122.0, 121.3, 119.1 (2C), 105.7, 58.4, 30.1, 19.7, 19.1; MS (ESI+) m/z 519 [M + H]$^+$; mp 272–274 °C; HPLC retention time − 3.949 min, purity − 99.12% (Method A).

*6.1.14.12. 2-(3-(4-(4-Fluorobenzamido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**61**).* Compound **17** (125 mg, 0.394 mmol, 1.0 equiv) and 4-fluorobenzoyl chloride (0.055 ml, 0.473 mmol, 1.2 equiv) were dissolved in DCM (5 ml). To this mixture was added TEA (0.170 ml, 1.182 mmol, 3.0 equiv) and stirred at rt for 3 h. Following completion the reaction mass was diluted with DCM, washed with water, followed by brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude solid so obtained was purified by flash column chromatography (2:8 ethyl acetate/petroleum ether) to provide the methyl ester, methyl 2-(3-(4-(4-fluorobenzamido) phenyl)isoxazole-5-carboxamido)-3-methylbutanoate, as a white solid. The methyl ester was subsequently deprotected using general procedure II at the second step to obtain the title compound (108 mg, 72.2%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (s, 1H), 10.52 (s, 1H), 8.97 (d, J = 8.1 Hz, 1H), 8.09–8.05 (dd, J = 2.7, 6.0 Hz, 2H), 7.98 (d, J = 8.7 Hz, 2H), 7.94 (d, J = 8.7 Hz, 2H), 7.74 (s, 1H), 7.43 (t, J = 9.0 Hz, 2H), 4.30 (t, J = 7.5 Hz, 1H), 2.28 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7, 172.1, 163.9, 162.5, 156.5, 141.1, 128.6 (2C), 128.1, 127.7 (2C), 127.0 (2C), 123.2, 120.4 (2C), 105.2, 74.5, 58.5, 29.9, 19.6, 19.1; MS (ESI−) m/z 424 [M − H]$^-$, (ESI+) m/z 426 [M + H]$^+$; mp 242–244 °C; HPLC retention time − 2.836 min, purity − 95.86% (Method A).

*6.1.14.13. 2-(3-(4-(2,6-Difluorophenylsulfonamido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**62**).* To a solution of compound **17** (500 mg, 1.6 mmol, 1.0 equiv) and pyridine (0.15 ml, 1.9 mmol, 1.2 equiv) in DCM (6 ml) was added 2,6-difluorobenzene sulfonyl chloride (401 mg, 1.8 mmol, 1.2 equiv) and the mixture was stirred for 3 h at rt. Following completion, water was added to the reaction followed by extraction with ethyl acetate. The organic layer was washed with 1.0 N HCl to remove the pyridine and the organic layer was concentrated to get a solid compound that was purified by flash column chromatography (1:9 EtOAc/$CHCl_3$) provide the methyl ester, methyl 2-(3-(4-(2,6-difluorophenylsulfonamido)phenyl)isoxazole-5-carboxamido)-3-methylbutanoate, as a white solid. The methyl ester was subsequently deprotected using general procedure II at the second step to obtain the title compound (369 mg, 49%) as an off white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.86 (bs, 1H), 11.30 (s, 1H), 8.99 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 8.7 Hz, 2H), 7.77–7.67 (m, 1H), 7.65 (s, 1H), 7.33–7.28 (m, 4H), 4.29 (t, J = 7.5 Hz, 1H), 2.27 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7, 164.1, 162.5, 159.3, 158.9, 156.5, 140.1, 138.9, 130.5, 127.8 (2C), 124.6, 124.3, 121.3 (2C), 117.2, 105.4, 58.5, 29.9, 19.6, 19.1; MS (ESI−) m/z 478 $[M - H]^-$, (ESI+) m/z 480 $[M + H]^+$; mp 190–192 °C; HPLC retention time − 2.652 min, purity − 95.02% (Method A).

*6.1.14.14. 4-(Benzyloxy)benzaldehyde (**64**).* To a solution of 4-hydroxy benzaldehyde (10 g, 82.0 mmol, 1.0 equiv) in acetone (200 ml) was added potassium carbonate (16.96 g, 123 mmol, 1.5 equiv) and the reaction mixture was stirred for 30 min. To this benzyl bromide (12.67 ml, 106.5 mmol, 1.3 equiv) was added and the resulting mixture was refluxed for 3 h and then cooled. Following completion the solid was filtered and the filtrate was concentrated to yield a pale brown colored oil that solidified at rt. This product was crystallized in DCM–petroleum ether to afford the title compound (13.0 g, 74%) as a pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.88 (d, J = 9.0 Hz, 2H), 7.47–7.34 (m, 5H), 7.12 (d, J = 8.7 Hz, 2H), 5.18 (s, 2H); MS (ESI+) m/z 212.9 $[M + H]^+$.

*6.1.14.15. (Z)-4-(Benzyloxy)benzaldehyde oxime (**65**).* To a solution of compound **64** (12.9 g, 60.8 mmol, 1.0 equiv) in methanol (129 ml) was added hydroxylamine hydrochloride (6.34 g, 91.2 mmol, 1.5 equiv) and the reaction mixture was refluxed for 3 h. Following completion the reaction mixture was cooled and concentrated to obtain a pale brown residue. Water was added to this residue and the product was extracted using ethyl acetate. The organic layers were collected, dried over anhydrous sodium sulfate, and concentrated to obtain an off white solid that was crystallized in DCM–petroleum ether to afford the title compound (11.5 g, 83%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.06 (s, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.46–7.33 (m, 5H), 7.05 (d, J = 8.7 Hz, 2H), 5.13 (s, 2H); MS (ESI+) m/z 227.8 $[M + H]^+$.

*6.1.14.16. 4-(Benzyloxy)-N-hydroxybenzimidoyl chloride (**66**).* To a solution of compound **65** (11.3 g, 49.7 mmol, 1.0 equiv) in DMF (57 ml), was added *N*-chlorosuccinimide (7.98 g, 59.7 mmol, 1.2 equiv) and the reaction mixture was stirred at rt for 3 h following which the solvent was evaporated to give a dark brown residue. To this residue water was added and the organic layer was extracted using ethyl acetate. The organic layers were pooled together, dried over anhydrous sodium sulfate, and the solvent was removed to yield a pale brown solid. The solid was further crystallized in DCM–petroleum ether to afford the title compound (7.9 g, 60%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.17 (s, 1H), 7.74 (d, J = 8.7 Hz, 2H), 7.47–7.34 (m, 5H), 7.12 (d, J = 9.0 Hz, 2H), 5.16 (s, 2H).

*6.1.14.17. Ethyl 3-(4-(benzyloxy)phenyl)isoxazole-5-carboxylate (**67**).* To a solution of compound **66** (7.8 g, 29.8 mmol, 1.0 equiv) in toluene (78 ml) was added ethyl propiolate (7.25 ml, 71.5 mmol, 2.4 equiv) and the reaction mixture was stirred for 30 min. To this mixture Et_3N (4.58 ml, 32.8 mmol, 1.1 equiv) was carefully added drop wise following which the reaction mixture was heated to 80 °C for 2 h and then cooled. The reaction mixture was diluted with ethyl acetate and washed successively with 0.1 M aqueous HCl, water, and brine. The organic layers were collected and concentrated to obtain a dark brown residue that was purified by flash column chromatography using DCM to obtain a pale brown solid that on crystallization in DCM–petroleum ether afforded the title compound (2.83 g, 29%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81 (d, J = 9.0 Hz, 2H), 7.48–7.36 (m, 5H), 7.28 (s, 1H), 7.10 (d, J = 8.7 Hz, 2H) 5.15 (s, 2H), 4.51 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H); MS (ESI+) m/z 324 $[M + H]^+$.

*6.1.14.18. 3-(4-(Benzyloxy)phenyl)isoxazole-5-carboxylic acid (**68**).* To a solution of compound **67** (900 mg, 2.8 mmol, 1.0 equiv) in THF (18 ml), a 1.0 M solution of sodium hydroxide in water (13.9 ml, 13.9 mmol, 5.0 equiv) was added and the reaction mixture was stirred for 20 min. Following completion, the reaction mixture was acidified with 1.0 M HCl and the product extracted using ethyl acetate. The organic layers were collected, dried over anhydrous sodium sulfate, and concentrated to obtain a pale yellow solid that was crystallized using ethyl acetate–petroleum ether to afford the title compound (765 mg, 93%) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 8.7 Hz, 2H), 7.73 (s, 1H), 7.49–7.34 (m, 5H), 7.17 (d, J = 8.7 Hz, 2H), 5.19 (s, 2H); MS (ESI+) m/z 296 $[M + H]^+$.

*6.1.14.19. Methyl 2-(3-(4-(benzyloxy)phenyl)isoxazole-5-carboxamido)-3-methylbutanoate (**69**).* To a solution of compound **68** (300 mg, 1.0 mmol, 1.0 equiv) in THF (10 ml), *N*-methyl morpholine (0.11 ml, 1.0 mmol, 1.0 equiv) was added and the reaction mixture was stirred for 10 min at rt. The reaction mixture was cooled to −20 °C followed by the addition of isobutyl chloroformate (0.13 ml, 1.0 mmol, 1.0 equiv) and the mixture was stirred for 20 min at −20. L-Valine methyl ester hydrochloride (238 mg, 1.4 mmol, 1.4 equiv) neutralized with triethylamine (0.198 ml, 1.4 mmol, 1.4 equiv) in THF (5 ml) was added to the above mixture and the stirring was continued at −20 for an additional 5 min. The resulting reaction mixture was gradually warmed to rt over a period of 1 h. The organic solvent was evaporated to obtain a pale brown solid that was purified by flash column chromatography (3:7 ethyl acetate/chloroform) to give an off white solid that on subsequent crystallization using ethyl acetate–petroleum ether afforded the title compound (232 mg, 55%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.19 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.68 (s, 1H), 7.49–7.32 (m, 5H), 7.19 (d, J = 8.7 Hz, 2H), 5.19 (s, J = 8.7 Hz, 2H), 4.33 (t, J = 7.5 Hz, 1H), 3.68 (s, 3H), 2.25 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H); MS (ESI+) m/z 409 $[M + H]^+$.

*6.1.14.20. Methyl 2-(3-(4-hydroxyphenyl)isoxazole-5-carboxamido)-3-methylbutanoate (**70**).* To a solution of compound **69** (6 g, 14.7 mmol, 1 equiv) in THF (120 ml), was added 10% Pd/C (600 mg, 10% w/w) and the mixture subjected to hydrogenation at 50 psi for 3 h. The reaction mixture was filtered through celite and the filtrate was concentrated to give a yellow residue that was purified by flash column chromatography (3:7ethyl acetate/chloroform) to obtain a yellow solid. This solid on crystallization using DCM–petroleum ether afforded the title compound (2.25 g, 48%) as a pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01 (bs, 1H), 9.16 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 8.7 Hz, 2H), 7.62 (s, 1H), 6.91 (d, J = 8.7 Hz, 2H), 4.33 (t, J = 7.5 Hz, 1H), 3.68 (s, 3H), 2.24 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); MS (ESI+) m/z 319 $[M + H]^+$.

*6.1.14.21. Methyl 2-(3-(4-(4-fluorobenzyloxy)phenyl)isoxazole-5-carboxamido)-3-methylbutanoate (**71**).* To a solution of compound **70** (150 mg, 0.4 mmol, 1.0 equiv) in acetone (3 ml), was added potassium carbonate (78 mg, 0.5 mmol, 1.2 equiv) and the mixture was stirred for 30 min. To this, 1-(bromomethyl)-4-fluorobenzene (0.07 ml, 0.5 mmol, 1.2 equiv) was added and the reaction mixture was refluxed for 2 h and then cooled. The reaction mixture was filtered and the filtrate was concentrated to obtain a pale brown residue. Water was added to this residue and the resulting mixture was extracted using ethyl acetate. The organic layers were collected and dried over anhydrous sodium sulfate and concentrated to obtain an off white solid that was crystallized using DCM–petroleum ether to afford the title compound (170 mg, 84%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.19 (d, J = 3.9 Hz, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.69 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.27 (m, 2H), 7.19 (d, J = 9.0 Hz, 2H), 5.18 (s, 2H), 4.31 (m, 1H), 3.68 (s, 3H), 2.25 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H). 0.95 (d, J = 6.9 Hz, 3H); MS (ESI+) m/z 427 $[M + H]^+$.

*6.1.14.22. 2-(3-(4-(4-Fluorobenzyloxy)phenyl)isoxazole-5-carboxamido)-3-methylbutanoic acid (**72**).* Compound **71** (120 mg, 0.3 mmol, 1.0 equiv) was deprotected by following general procedure II to obtain the title compound (65 mg, 56%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.95 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.69 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.27 (t, J = 9.0 Hz, 2H), 7.19 (d, J = 9.0 Hz, 2H), 5.17 (s, 2H), 4.30 (t, J = 7.8 Hz, 1H); 2.28 (m, 1H); 0.99 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 163.9, 162.5, 160.7, 160.5, 156.4, 133.4, 130.6, 130.5, 128.7 (2C), 120.9, 115.9 (3C), 115.6, 105.1, 69.1, 58.6, 30.0, 19.7, 19.0; MS (ESI+) m/z 413 $[M + H]^+$; mp 178–180 °C; HPLC retention time – 3.933 min, purity – 99.07% (Method A).

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