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Oxadiazole-isopropylamides as Potent and Non-covalent Proteasome Inhibitors.

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ABSTRACT

Screening of the 50,000 ChemBridge compound library led to the identification of the oxadiazole-isopropylamide **1** (**PI-1833**) which inhibited CT-L activity (IC_{50} 0.60 μM) with little effects on the other 2 major proteasome proteolytic activities, T-L and PGPH-L. LC/MS-MS and dialysis show that **1** is a non-covalent and rapidly reversible CT-L inhibitor. Focused library synthesis provided **11ad (PI-1840)** with CT-L activity (IC_{50} 27 nM). Detailed SAR studies indicate that the amide moiety and the 2 phenyl rings are sensitive toward modifications. Hydrophobic residues, such as propyl or butyl, in the *para*-position (not *ortho* or *meta*) of the A-ring and a *meta*-pyridyl group as B-ring significantly improve activity. Compound **11ad** (IC_{50} 0.37 μM) is more potent than **1** (IC_{50} 3.5 μM) at inhibiting CT-L activity in intact MDA-MB-468 human breast cancer cells and inhibiting their survival. The activity of **11ad** warrants further pre-clinical investigation of this class as non-covalent proteasome inhibitors.

INTRODUCTION

The ATP-dependent ubiquitin-proteasome pathway is responsible for the controlled degradation of proteins in eukaryotic cells.[1-6] The 26S proteasome is a multifunctional complex consisting of a 19S regulatory particle (RP) and a 20S core particle (CP).[7] The three main catalytic activities of the proteasome; peptidylglutamyl peptide hydrolyzing-like (PGPH-L), trypsin-like (T-L), and chymotrypsin-like (CT-L) are mediated by three distinct catalytic β-1, β-2, and β-5 subunits, respectively.[8] For each of the catalytic β-subunits, the *N*-terminal Thr-1 serves as the nucleophile that initiate cleavage of the peptide bond.[9,10,11] Development of inhibitors of CT-L activity has been the subject of considerable interest in the treatment of cancer due to its critical role in the degradation of apoptotic and tumor suppressor proteins.[8,10,12] The proteasome inhibitors advanced to clinic or clinical trials are derived from 3 structural classes (Figure 1A): 1. Boronic acid containing compounds such as bortezomib, a dipeptide boronic acid (clinically approved by FDA),[13, 14] MLN9708[15-17] and CEP-18770;[18-21] (Figure 1A). 2. β-lactones such as salinosporamide A (NPI-0052)[22,23] which is a marine microbial natural product (Figure 1A) and 3. Epoxyketone containing tetrapeptide carfilzomib[24] (Figure 1A), clinically approved by FDA which is related to the natural product epoxomicin. Each inhibitor class reacts with the proteasome *N*-terminal threonine (Thr-1 at the active site) by a distinct mechanism. Peptide boronic acids form a covalent and slowly reversible tetrahedral adducts with the OH group of the catalytic Thr-1.[11,25] For the β-lactone salinosporamide A, attack of the lactone ring by catalytic Thr-1[26] forms an ester bond (that undergoes intramolecular rearrangement) which makes this compound an irreversible inhibitor. The epoxyketone[14] moiety of carfilzomib reacts with the OH and the α-amino group of Thr-1 to form 2 covalent bonds, also making the inhibition irreversible.

Covalent proteasome inhibitors are classified as slow reversible or irreversible inhibitors according to their chemical structure and mechanism of inhibition. Covalent irreversible or covalent slow reversible inhibitors as described above possess a chemically reactive group that bind to the proteasome covalently. In contrast, non-covalent inhibitors inhibit the proteasome through a network of interactions (hydrophobic, hydrogen bonds, electrostatic and/or van der Waals). Although some proteasome inhibitors have been

suggested to bind non-covalently[27-34] structural evidence to support this was provided for only three of these. The X-ray structures of TMC-95A,[35-37] hydroxyl urea[38] (Figure 1B) and the peptide[11] from Millenium (Figure 1B) bound to proteasome demonstrate that the binding mode of these compounds are non-covalent.

Since non-covalent inhibitors do not have a reactive electrophilic moiety or 'warhead', which is often associated with metabolic instability, poor specificity, and excessive reactivity, they have the advantage of exerting fewer side effects over the covalent ones. It has been shown that the proteasome activity recovers at the same rate with covalent irreversible inhibitors as with covalent slow reversible inhibitors, presumably *via de novo* proteasome synthesis.[39] The clinical advantages/benefits of non-covalent proteasome inhibitors in cancer treatment are not well understood. Figure 1B shows the structures of small molecules that have been identified as non-covalent proteasome inhibitors.[11,38] We have been actively engaged in the discovery of novel proteasome inhibitors.[40,41] We reported the discovery of the compound **1** as a proteasome inhibitor in a poster at the 2011 American Association for Cancer Research (AACR) meeting.[42] Villoutreix *et al* also have reported oxadiazole-isopropylamide containing compounds as proteasome modulators.[43,44] Although Villoutreix *et al* and our group have independently identified similar scaffolds, each group focused on different modifications of the hits that led to important findings that are complementary but not overlapping. In our study, we have extensively explored SAR (Figure 2) on the oxadiazole-isopropylamide containing compounds as proteasome inhibitors by systematically synthesizing focused libraries around key features of the pharmacophore. We present compound **1** and its most potent analogs as non-peptidic, non-covalent and reversible proteasome inhibitors that have the potential to become clinical candidates.

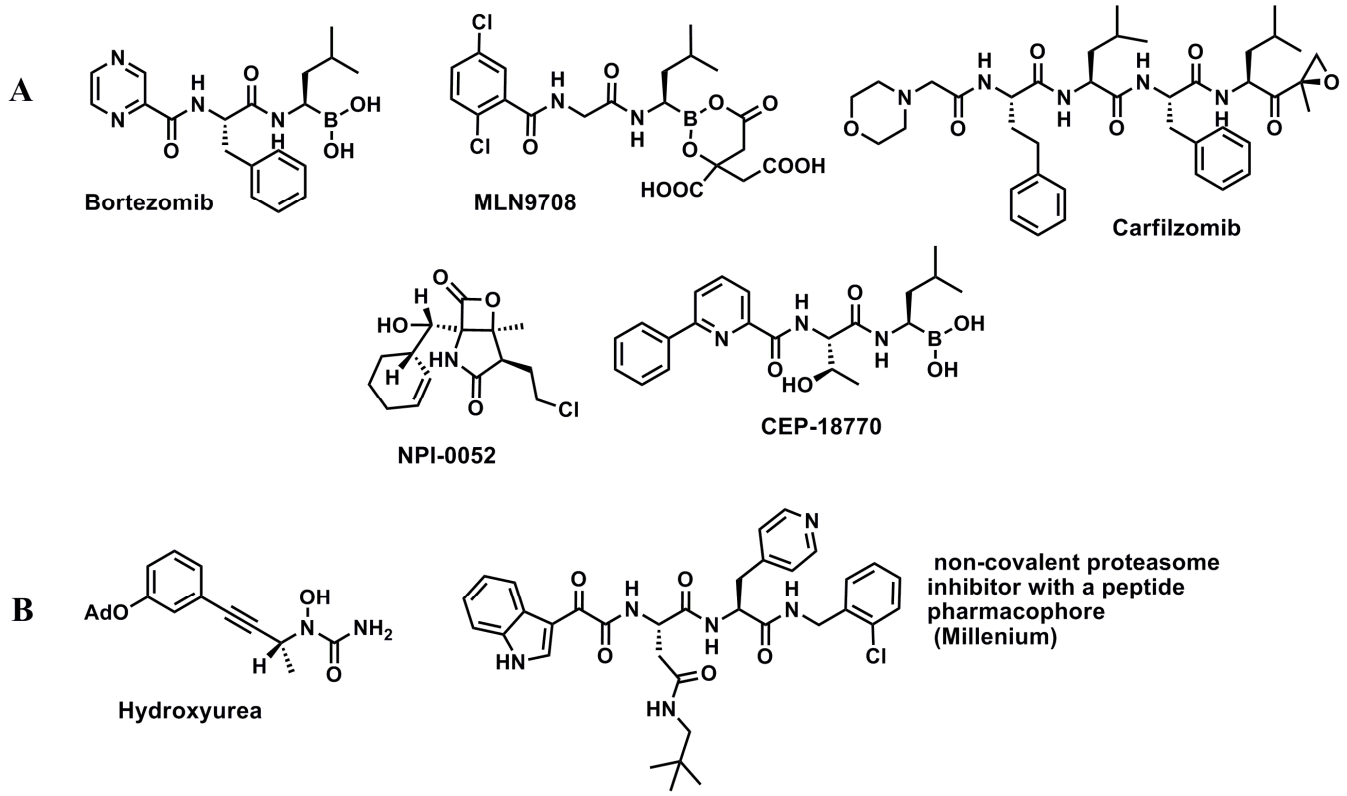


Figure 1: **A**. Structures of clinically advanced covalent proteasome inhibitors **B**. Structures of non-covalent small molecule proteasome inhibitors; hydroxyurea pharmacophore[38] and peptidic pharmacophore from Millennium.[11,45]

CHEMISTRY

The screening hit **1** was identified as a CT-L proteasome inhibitor with an IC_{50} value of 0.60 ± 0.18 μM (*in-vitro*). Validation of the synthetic route to **1** was undertaken to confirm both the structure and the *in vitro* CT-L inhibitory activity. Synthesis of **1** was achieved using the route shown in Scheme 1. The substituted acetyl chloride building block library **5** (Scheme 1) was synthesized from readily available phenol derivatives *via* the ester **3** and acid **4** using reported protocols.[46-50] The oxadiazole portion of the compound **1** was synthesized from readily available nitrile building blocks **6**. The nitrile building blocks were reacted with hydroxylamine hydrochloride and sodium carbonate at 70 ºC in water to yield the hydroxyamidines[51] **7** (Scheme 1, *condition g*). The 5-substituted pyrimidinehydroxyamidine **7h** (*see supporting information*) was synthesized starting from the commercially available methyl pyrimidine-5-carboxylate *via* amide **24** and

nitrile **25**.[52] The intermediate hydroxyamidine library **7** was reacted with chloroacetyl chloride (Scheme 1, *condition h*) to provide the library **8**,[53] which was cyclized in refluxing toluene to provide the oxadiazole portion of the pharmacophore **9**. The library **9** was subsequently reacted with appropriate alkyl amines (isopropyl-, isobutyl-, methyl-. ethyl-, cyclopropyl- and *tert*-butyl amines) to obtain the amine building block library **10**[54] (Scheme 1, *condition j*). For the synthesis of **10n** (R^3 = H), compound **9a** (R^2 = *para*-tolyl, *see supporting information compound **26***) was first reacted with phthalimide in the presence of potassium carbonate in refluxing acetonitrile, followed by reaction with hydrazine to obtain the compound **10n** in high yield.[55] We were able to generate library **10** with a variety of substituted aryl and hetero-aryl R^2 moieties and library **5** with substituted/unsubstituted aromatic R^1 moieties (Scheme 1). Modifications around **1** for library synthesis are shown in Figure 2, and initially we focused our synthetic efforts to modify R^1, R^2 and R^3 moieties. The two key building block libraries **10** and **5** were then reacted in the presence of triethylamine to provide the compound **1**, library **11** and **12** (Scheme 1, Tables 1 and 3) in good yields. The route described in Scheme 1 was efficient and convenient for rapid synthesis and optimization of the substituted phenyl and amide moieties. The final libraries **11**, **12** and compound **1** were characterized using NMR, LC-MS, HRMS and the purity was > 95% as determined by HPLC. The final compound library **11** and **12** (including compound **1**) showed formation of approximately 3:1 atropisomers (hindered rotation about the C-N amide bond) by ^{1}H NMR and ^{13}C NMR spectroscopy (see the experimental section and *supporting information*). Analysis of ^{1}H NMR spectra of compound **1** at variable temperatures (20 °C to 50 °C) showed that the peaks from the minor rotamer coalesced with the major rotamer as the temperature increased.

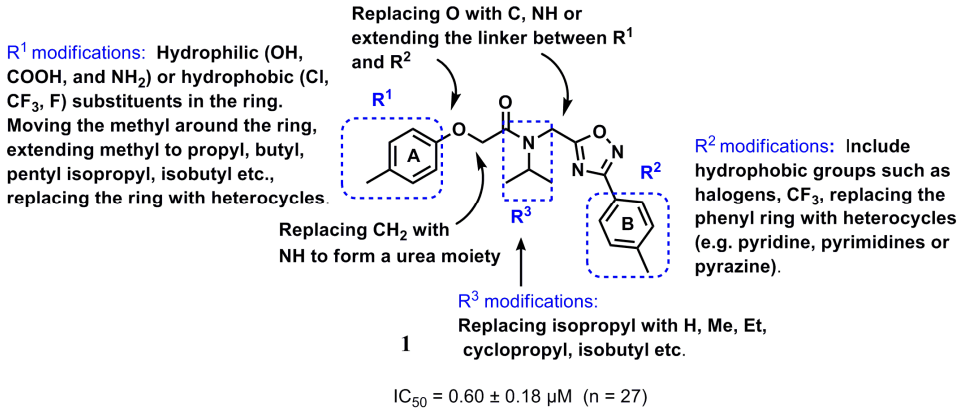
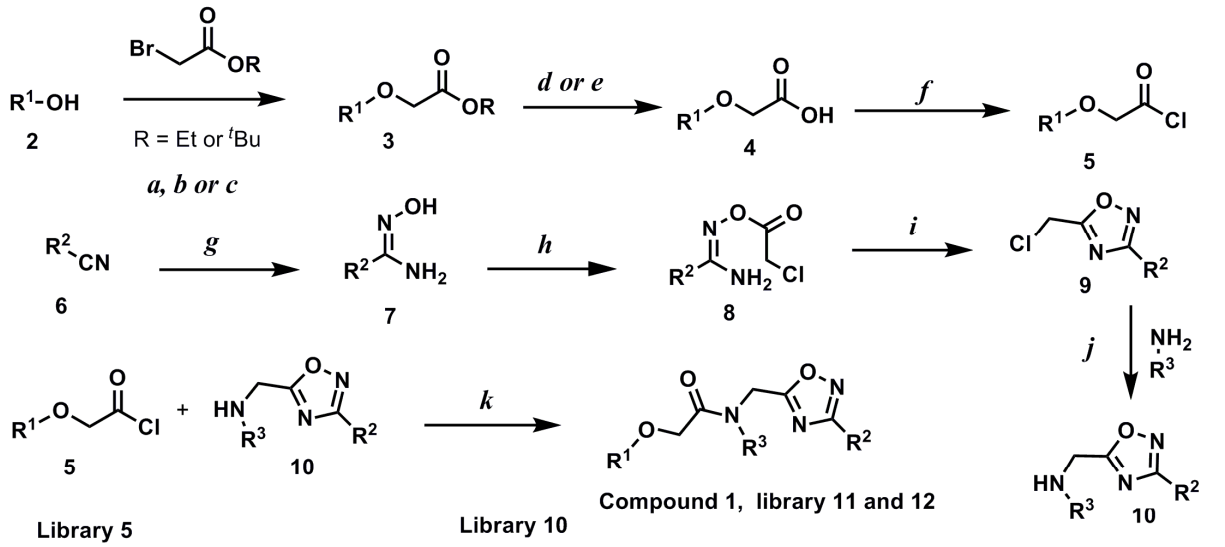


Figure 2: Modifications and library synthesis around **1** for design of new proteasome inhibitors and SAR studies.



Library 5

5a: R^1 = *para*-CH_3-C_6H_4
5b: R^1 = *para*-CF_3-C_6H_4
5c: R^1 = phenyl
5d: R^1= *para*-Cl-C_6H_4
5e: R^1 = *para*-phenyl- C_6H_4
5f: R^1 = *para*-F-C_6H_4
5g: R^1 = 6-bromonaphthalene
5h: R^1 = *meta*-CH_3-C_6H_4
5i: R^1 = *ortho*-CH_3-C_6H_4
5j: R^1 = *para*-ethyl-C_6H_4
5k: R^1 = *para*-propyl-C_6H_4
5l: R^1 = *para*-butyl-C_6H_4
5m: R^1 = *para*-pentyl-C_6H_4
5n: R^1 = *para*-hexyl-C_6H_4
5o: R^1 = *para*-cyclohexyl-C_6H_4
5p: R^1 = *para*-isopropyl-C_6H_4
5q: R^1 = *para*-isobutyl-C_6H_4
5r: R^1 = *para*-^{t}butyl-C_6H_4
5s: R^1 = *para*-OH-C_6H_4

Library 10

10a: R^2 = *para*-CH_3-C_6H_4, R^3 = isopropyl
10b: R^2 = *para*-CF_3-C_6H_4, R^3 = isopropyl
10c: R^2 = *para*-Cl-C_6H_4, R^3 = isopropyl
10d: R^2 = C_6H_5, R^3 = isopropyl
10e: R^2 = *ortho*-pyridyl, R^3 = isopropyl
10f: R^2 = *meta*-pyridyl, R^3 = isopropyl
10g: R^2 = *para*-pyridyl, R^3 = isopropyl
10h: R^2 = 5-substituted pyrimidine, R^3 = isopropyl
10i: R^2 = 2-substituted pyrimidine, R^3 = isopropyl
10j: R^2 = 2-substituted pyrazine , R^3 = isopropyl
10k: R^2 = *para*-CH_3-C_6H_4, R^3 = methyl
10l: R^2 = *para*-CH_3-C_6H_4, R^3 = ethyl
10m: R^2 = *para*-CH_3-C_6H_4,R^3 = isobutyl
10n: R^2 = *para*-CH_3-C_6H_4, R^3 = H
10o: R^2 = *para*-CH_3-C_6H_4, R^3 = ^{t}butyl
10p: R^2 = *para*-CH_3-C_6H_4, R^3 = cyclopropyl

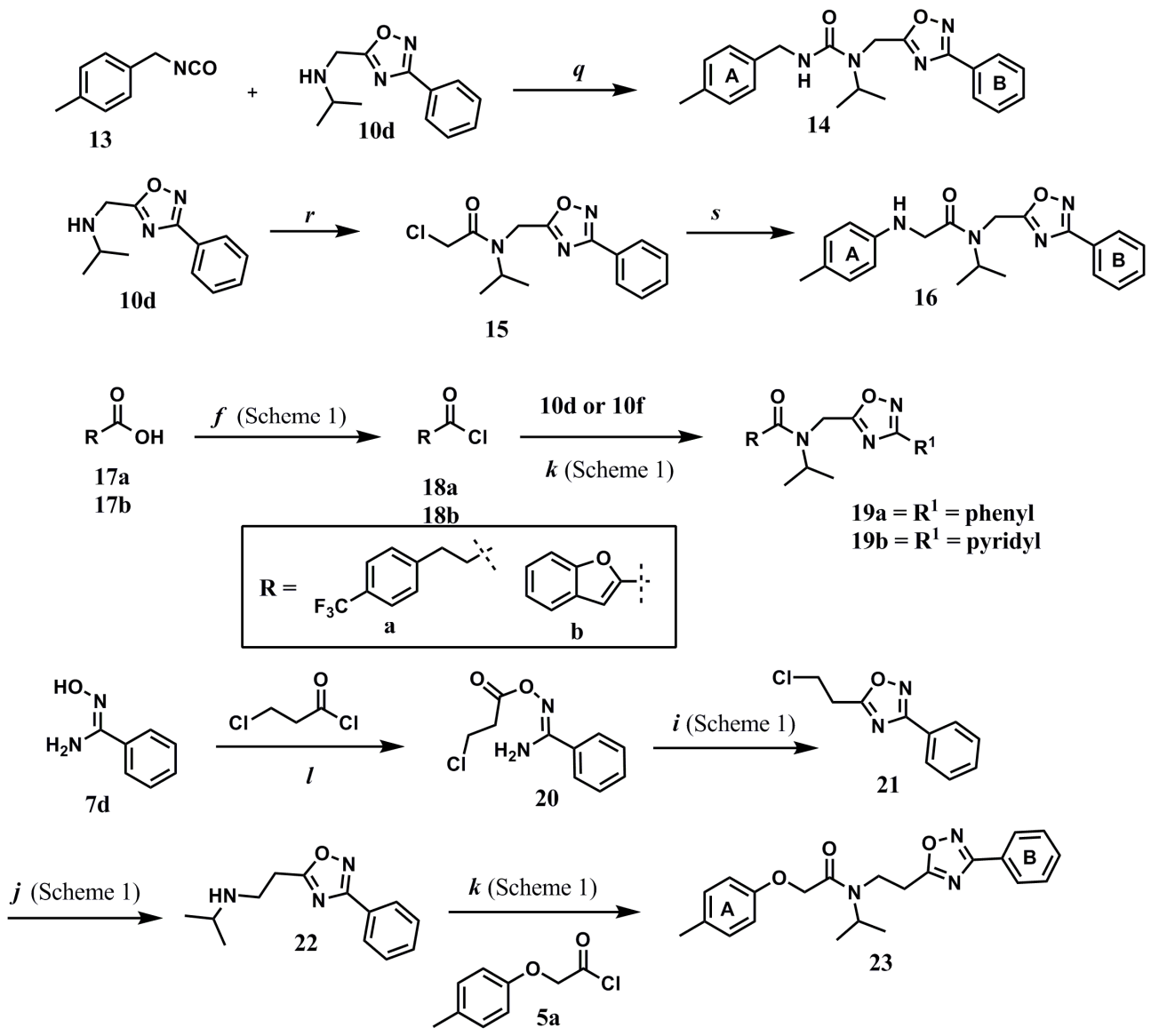
Library 11 and compound 1: See Table 3

Library 12: See Table 1

Scheme 1. Synthetic route to compound **1**, libraries **11** and **12**. *Reagents and conditions:* ***a***. Ethyl bromoacetate, K_2CO_3, Acetone, reflux, 14 h. ***b***. *tert*-Butyl bromoacetate , DMF, 80 ºC, 14 h. ***c***. Ethyl bromoacetate, K_2CO_3, DMF, r.t., 14 h. ***d***. NaOH, THF, reflux, 2 h. (R= Ethyl). ***e***. CF_3COOH, DCM, r.t., 2 h (R = ^{t}Bu). ***f***. $SOCl_2$, benzene, reflux, 3 h. ***g***. $NH_2OH.HCl$, Na_2CO_3, water, 70 ºC, 14 h. ***h***. Chloroacetyl chloride, acetone, r.t., 30 min. ***i***. toluene, reflux, 2 h. ***j***. Alkylamine, K_2CO_3, CH_3CN, reflux, 30 min. ***k***. Et_3N, THF, r.t., 15 min.

Next, we focused our efforts to modify the chemical space between the amide moiety, A and B rings (Figure 2) in compound **1**. First, we introduced a urea moiety to assess the SAR. To install the urea moiety, the intermediate **10d** was reacted with commercially available isocyanate **13** in the presence of triethylamine in refluxing benzene, and under these conditions urea **14** was obtained in good yield (Scheme 2, *condition q*). Further modifications included replacement of the ether moiety (H-bond acceptor) in **1** (Figure 2) with an NH (H-bond acceptor/donor) group. The amine **10d** was first reacted with chloroacetyl chloride in the presence of triethylamine in THF at room temperature to obtain intermediate **15** (Scheme 2) followed by coupling **15** with *para*-methylaniline using sodium acetate in refluxing ethanol to obtain the final compound **16** (Scheme 2, *conditions r* and *s* respectively) also in good yield. The ether moiety in **1** (Figure 2) was also replaced by a methylene unit using 3-(4-(trifluoromethyl)phenyl)propanoic acid building block (**17a**). The acid starting material **17a** (Scheme 2) was converted to the corresponding acid chloride **18a** and coupled with **10d** to provide the oxadiazole **19a** (Scheme 2). The final compound **19b** with bulky R-groups was synthesized following the route in Scheme 2 starting from benzofuran-2-carboxylic acid (**17b**) *via* the formation of acid chloride **18b** and subsequent coupling with **10f**. The intermediate **10d** was chosen for synthesis of compounds **14**, **16**, and **19a** since our early SAR indicated unsubstituted B ring is desirable to retain *in vitro* CT-L potency together with *para*-CH_3 group on the A ring and the isopropyl moiety in the amide group. Extension of the linker between the oxadiazole moiety and amide group in **1** (Figure 2) by one carbon atom was achieved by first reacting the intermediate **7d** with 3-chloropropanoyl chloride to generate intermediate **20** which provided **21** upon refluxing in toluene. The intermediate **21** was next reacted with

isopropylamine to obtain **22**, which was further reacted with intermediate **5a** (see supporting information) to obtain the final compound **23** in good yield. The intermediates and final compounds were characterized by ^{1}H NMR, ^{13}C NMR, HRMS, LC-MS; the purity of final compounds was determined using HPLC.



Scheme 2: Reagents and conditions: ***q***. Et_3N, benzene, reflux, 14 h, 78%. ***r***. Chloroacetyl chloride, Et_3N, THF, r.t., 15 min., 80%. ***s***. *para*-Methylaniline, NaOAc, ethanol, reflux, 15 h, 78%. ***f***. $SOCl_2$, benzene, reflux, 3 h, 94%. ***i***. toluene, reflux, 2 h, 81%. ***j***. Isopropylamine, K_2CO_3, CH_3CN, reflux, 30 min., 86%. ***k***. Et_3N, THF, r.t., 15 min., 88% (**19a**), 82% (**19b**), 87%, (**23**). ***l***. DCM, r.t., 14 h, 76%.

RESULTS AND DISCUSSIONS

Unlike lactacystin, 1 is a non-covalent and reversible CT-L inhibitor

To determine whether our hit compound **1** is a non-covalent CT-L inhibitor, we used two approaches, Liquid Chromatography Tandem Mass Spectrometry (LC/MS-MS) and dialysis. With both approaches we used lactacystin, a known covalent and irreversible CT-L inhibitor as a control.[56,57] For LC/MS-MS, **1** or lactacystin were incubated with the 20S proteasome, digested with trypsin and the resulting peptides purified by HPLC and analyzed by LC/MS-MS as described under Methods. Figure 3A shows that peptides purified from the vehicle-treated samples contained unmodified TTTLAFK peptide (observed as a protonated molecule at m/z 781.4401) corresponding to the *N*-terminal tryptic peptide of rabbit proteasome subunit β type-5. Figure 3B shows that peptides purified from the compound **1** treated samples also contained the unmodified Thr-1 containing TTTLAFK peptide (Figure 3D). Both intact mass spectrum and tandem mass spectrum indicate unmodified Thr-1 containing peptide. Figure 3C shows that lactacystin-treated samples contained a lactacystin-modified Threonine adduct corresponding to the doubly charged modified peptide at m/z 497.7795 (structure shown in Figure 3E). The searches matching experimental data to peptides, from the database of rabbit proteasome subunits produced only one modified peptide, which indicated that Thr-1 on β-5 was modified by lactacystin. No other modifications to β-5 subunit from samples treated with DMSO, compound **1** or lactacystin were observed. In addition, no modifications were detected for other proteasome subunits, such as β-1 and β-2 subunits included in the database (n =21). These results suggest that, unlike lactacystin, **1** does not bind covalently to the proteasome.

To confirm these results, we incubated **1** and lactacystin with the 20S proteasome and determined the reversibility of binding by dialysis as described under Methods. The Figure 4 shows that more than 70% of the CT-L activity in the dialysis compartment from the sample that was treated with **1** was recovered within the first 20 min., and recovered fully by 2 hours of dialysis. In contrast, very little CT-L activity was recovered from the sample that was treated with lactacystin even after 18 hours of dialysis (Figure 4). Taken together these results confirm the well established fact that lactacystin is a covalent and irreversible CT-L

inhibitor and indicate that **1** is a non-covalent and reversible CT-L inhibitor. This is consistent with the chemical structure of **1** that lacks any reactive groups, unlike *clasto*-lactacystin that contains the reactive *beta*-lactone moiety. The β-lactone moiety of the *clasto*-lactacystin covalently modifies the β-subunits of the proteasome and is responsible for inhibiting 20S proteasome in an irreversible mode of action[57].

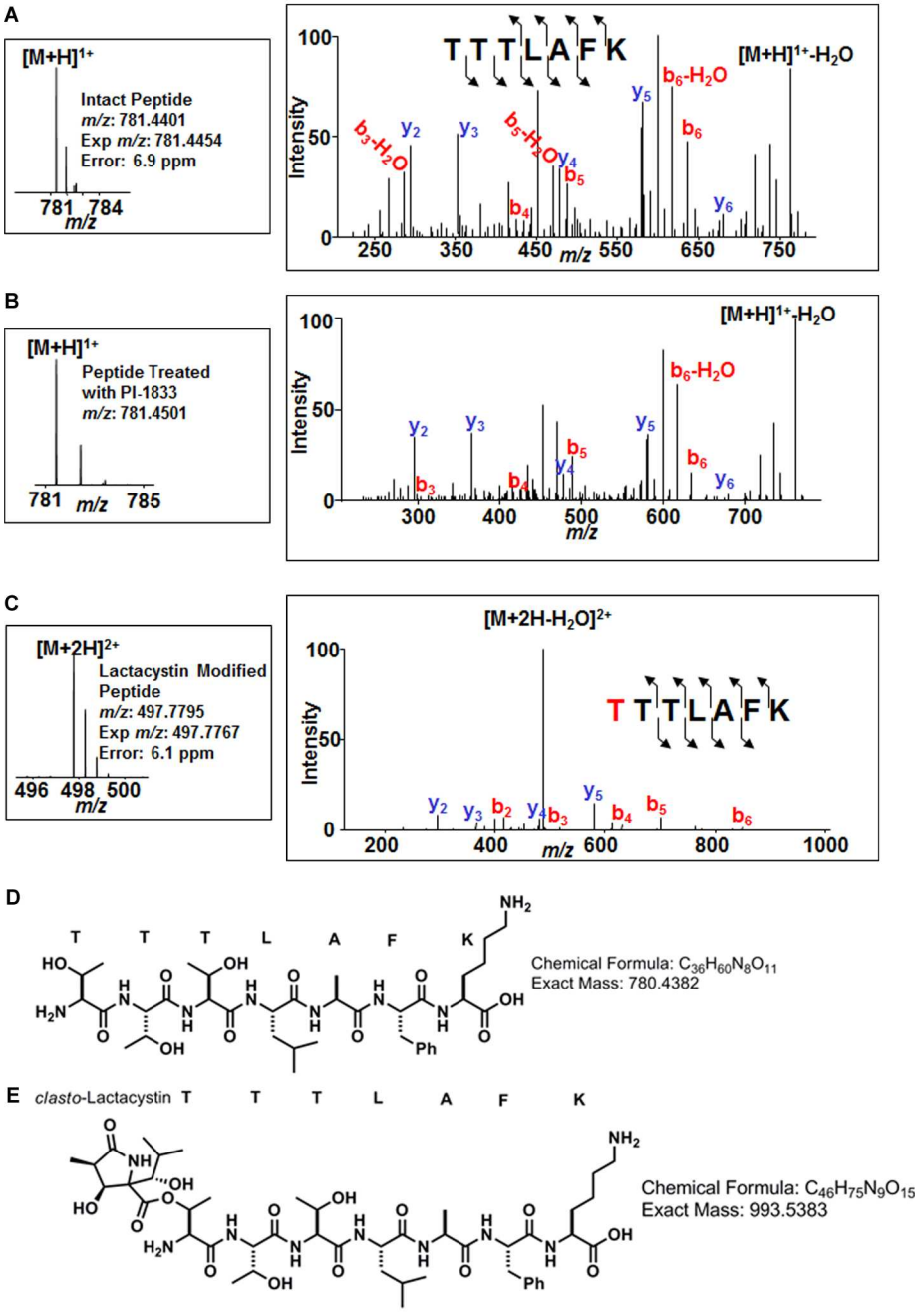


Figure 3: **A**: LC/MS-MS analysis of tryptic digests from proteasome CT-L subunit after incubation with vehicle. LC/MS-MS analysis of Thr-1 containing peptide from the proteasome CT-L subunit β5 after tryptic digestion is shown. Singly charged unmodified peptide was observed at m/z 781.4401, which represents a mass error of 6.9 ppm. The tandem mass spectrum was matched to peptide TTTLAFK. The b ions (labeled in red), contain the *N*-terminus of the peptide; and y ions, (labeled in blue), contain the *C*-terminus of the peptide. The number associated with each ion indicates the number of amino acids in that fragment (for example, y4 contains LAFK from C-terminus of the peptide). **B**: LC/MS-MS analysis of tryptic digests from proteasome CT-L subunit after incubation with compound **1**. The Thr-1 containing peptide didn't show any modification. Both intact mass spectrum and tandem mass spectrum indicate unmodified Thr-1 containing peptide. **C**: LC/MS-MS analysis of tryptic digests from proteasome CT-L subunit after incubation with lactacystin shows *clasto*-lactacystin-modified Thr-1 containing peptide. Doubly charged lactacystin-Thr modified peptide was detected at m/z 497.7795, which represents a mass error 6.1 ppm. The tandem mass spectrum confirms the modification of the peptide by lactacystin. **D**: Structure of the unmodified TTTLAFK tryptic peptide. **E**: Structure of the *clasto*-lactacystin modified peptide.

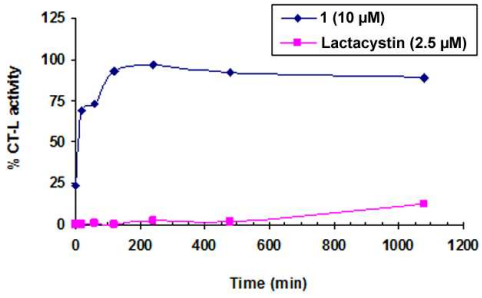


Figure 4: Recovery of CT-L activity upon dialysis of the 20S proteasome-compound complexes after pre-incubation with lead **1** and lactacystin.

Structure Activity Relationship studies and chemistry leading to compound 11ad.

Our screening efforts of the 50,000 in-house ChemBridge compound library led to the discovery of the hit **1**, an inhibitor of the CT-L activity of the proteasome. After confirming the structure and *in vitro* CT-L activity of the in-house synthesized **1** (Scheme 1), we embarked on synthetic modifications to develop

structure and activity relationship (SAR) data to identify novel, potent and selective CT-L proteasome inhibitors that block the action of the proteasome in a non-covalent manner. Proteasome CT-L activity was measured using a fluorogenic assay as previously described.[41] Focused library synthesis was undertaken by independently varying the R^1, R^2 and R^3 groups in compound **1** (Figure 2). Initially, we replaced the isopropyl R^3 group in **1** with H, isobutyl, ethyl, methyl, *tert*-butyl and cyclopropyl moieties (Table 1). The loss of CT-L activities of these analogs indicated that the isopropyl group is essential and optimal for proteasome inhibitory activity (see Table 1). The isobutyl amide **12a** and ethyl amide **12b** (Table 1, Entries 2 and 3) showed 4- to 10-fold loss of activity with IC_{50} values of 2.37 and 6.02 μM respectively compared to **1**. Methyl, H, t*ert*-butyl and cyclopropyl as R^3 groups were detrimental for CT-L activity (**12c**, **12d**, **12e, 12f** in Table 1 showed weak or no proteasome inhibition at 10 μM). The ^1H and ^{13}C NMR spectra of the compound **1** with isopropyl amide group indicated the presence of a mixture of 3:1 atropisomers (isomers that exist due to the hindered rotation about the carbon-nitrogen bond). We observed a similar ratio of atropisomers with **12b** (R^3 = ethyl), and **12c** (R^3 = methyl) by analysis of ^1H and ^{13}C NMR spectra. Compounds **12d** with unsubstituted amide (Entry 5, R^3 = H, Table 1), **12e** with bulky *tert*-butyl group (Entry 6, R^3 = ^{t}Bu, Table 1) and **12f** with cyclopropyl group (Entry 7, R^3 = cyclopropyl) did not show any atropisomers by ^1H or ^{13}C NMR spectra.

In the next generation of synthetic analogs, we retained the isopropyl R^3 group (Figure 2) and modified the phenyl rings in **1** [i.e. library **11**, (Scheme 1 and Table 3)]. Initial SAR studies demonstrated that substitutions on the *para*-position of the R^1 and R^2 with small hydrophobic groups are tolerable. For example, changing the *para*-methyl in R^1 and R^2 to trifluoromethyl or chlorine as in compounds **11a**, **11c**, **11d**, **11e, 11f, 11g, 11i** and **11n** retained the *in vitro* CT-L inhibitory activities (Entries 14, 16-20, 22, 27, Table 3). Next we demonstrated that the R^1 methyl is required whereas the R^2 methyl is dispensable. Indeed, compounds **11b**, **11h** and **11m** (Entries 15, 21 and 26, Table 3) with an unsubstituted phenyl ring as R^2 showed slightly improved IC_{50} values around 0.3 to 0.5 μM indicating *para*-substitution of R^2 phenyl in **1** is not required for inhibitory activity. However, compound **11j** with both unsustituted phenyl rings resulted

in 10 fold loss of CT-L activity (Entry 23, Table 3, IC_{50} = 6.22 μM). Removal of the R^1 *para*-methyl group as in compounds **11k** and **11l** (Entries 24 and 25, Table 3) also led to 14- and 18-fold loss of activity with IC_{50} values of 8.5 and 11 μM, respectively. The loss of *in vitro* potency of compounds **11j**, **11k** and **11l** suggest that *para*-substitution in R^1 phenyl ring is critical to maintain CT-L proteasome activity. Changing the R^1 *para*-methyl to *meta*- or *ortho*-positions as in compounds **11o** and **11p** (Entries 28 and 29, Table 3) was detrimental for *in vitro* potency further suggesting that R^1 *para*-substitution is important for CT-L proteasome activity. Overall our SAR indicated that the *para*-methyl group in R^1 but not in R^2 and the R^3 isopropyl amide are key features that are responsible for retaining the CT-L proteasome activity of compound **1** and loss of activity was consistent with unsubstituted R^1 aromatic rings in this class of compounds.

We next modified the chemical space between the amide moiety and R^1/R^2 in the parent compound **1** (Figure 2) using the synthetic routes and protocols described in Scheme 2 (also see supporting information). First, replacement of the ether-oxygen by methylene showed significant loss of CT-L activity (**19a**, IC_{50} 53.48 μM, Entry 8, Table 2). Furthermore, substituting the amide group by urea as in **14** (Entry 9, IC_{50} > 10 μM, Table 2) also led to loss of activity. Replacement of the ether (H-bond acceptor) with NH (H-bond donor/acceptor) also decreased the *in vitro* CT-L activity (**16**, IC_{50} 5.67 μM, Entry 10, Table 2). These modifications confirmed that the ether moiety, most likely, as H-bond acceptor, is critical for focused library synthesis and improving the CT-L inhibitory activity. Extending the spacer between the amide and the oxadiazole by one carbon as shown in **23** (Entry 11, IC_{50} > 10 μM, Table 2) was detrimental for CT-L inhibitory activity, probably due to the increased flexibility of the molecule. Compound **19b** (IC_{50} 0.37 μM, Entry 12, Table 2), a bulky R^1 substituent with a rigid ether moiety and *meta*-pyridyl as R^2 showed improved inhibitory activity compared to **1** (pyridyl moiety was chosen for the synthesis of **19b**, based on the most potent analogs described in Table 3). Overall, synthetic modifications of the linkers between R^1, R^2 and the amide moiety in **1** were not tolerated.

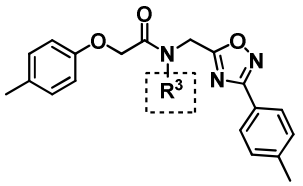
To gain more insight in the interactions between R^1 and the binding region, we modified the R^1 *via* several synthetic modifications. For example, synthesis of **11q** and **11r** that possessed large hydrophobic groups such as phenyl and Br-naphthyl as *para*-R^1 groups respectively further revealed that large hydrophobic groups are not tolerated in the binding region (Entries 30, 31, IC_{50} > 10 μM, Table 3). Replacement of the R^1 methyl group in compound **1** by small hydrophobic fluorine as in **11s** (Entry 32, Table 3) also displayed poor CT-L inhibitory activity. The 16-fold loss of CT-L inhibitory activity in compound **11s** with *para*-fluorine compared to **11b** with *para*-CF_3 (Entry 15, IC_{50} = 0.43 μM) was not unexpected since fluorine is isosteric to hydrogen[58] and as described above we have already observed the detrimental effects of unsubstituted R^1 rings in compounds **11k**, **11l** and **11ac** (Entries 24, 25 and 42, Table 3) toward the CT-L inhibitory activity. The hydrophilic COOH, COO^{t}Bu and OH groups in the *para*-position of the R^1 as in compounds **11t, 11aq** and **11v** respectively also failed to maintain the CT-L inhibitory activity (Entries 33, 56 and 35, Table 3) indicating H-bond acceptor/donor moieties are not desirable. In contrast compound **11u** (Entry 34, Table 3) with *para*-hydroxyphenyl as R^1 and *meta*-pyridyl as R^2 showed an IC_{50} value of 1 μM, and comparison of *in vitro* CT-L activities of **11u** and **11v** (Entries 34 and 35, Table 3) with *para*-hydoxyphenyl as R^1 highlights the significance of the R^2 *meta*-pyridyl group toward CT-L activity in this class of compounds.

We next made 2 major observations that led us to our most potent compounds. First, we demonstrated that increasing the alkyl length from methyl in **1** to a propyl as in **11ap** (IC_{50} = 0.27 μM) increased potency (Entry 55, Table 3). Second, replacing the tolyl R^2 in **1** by a *meta*-pyridyl (as in **11x,** Entry 37, Table 3) or *para*- pyridyl (as in **11y,** Entry 38, Table 3) but not *ortho*-pyridyl (as in **11w,** Entry 36, Table 3) improved potency with the *meta*-pyridyl (IC_{50} 0.22 μM) being slightly better than the *para*-pyridyl (IC_{50} 0.37 μM, Table 3). Substituting both, the R^1 methyl with a propyl and the R^2 tolyl with a *meta*-pyridyl as in **11ad** (combined features of compounds **11ap** and **11x**) resulted in our most potent compound with an IC_{50} value of 27 nM. Furthermore, the length of the alkyl group in *para*-position of the R^1-ring is critical with the propyl or butyl groups being the optimal size. Indeed, decreasing the size from propyl (or butyl) to ethyl, methyl

and hydrogen as in **11ab**, **11x** and **11ac**, resulted in progressive loss of inhibitory activity from 27 nM to 99 nM, 220 nM and 2710 nM, respectively. Increasing the size of the R^1 *para*-hydrophobic moiety also resulted in progressive loss of potency from propyl or butyl to pentyl, hexyl, isobutyl, isopropyl, cyclohexyl and *tert*-butyl as in **11af** (IC_{50} 120 nM), **11ag** (IC_{50} 430 nM), **11ak** (IC_{50} 140 nM), **11ai** (IC_{50} 440 nM), **11ah** (IC_{50} 1356 nM) and **11aj** (IC_{50} 46.49 μM), respectively. Furthermore, substituting the pyridyl in **11ad** with 3,5-pyrazine as in **11al** did not alter the potency (IC_{50} 32 nM) which further supports the importance of a *meta*-positioned nitrogen atom in the ring. In contrast, substituting the pyridyl in **11ad** by 2,5-pyrazine as in **11am** (Entry 52, IC_{50} 105 nM, Table 3) with one *meta*-positioned nitrogen or 2,6-pyrimidine as in **11ao** (Entry 54, IC_{50} 1269 nM) which possess two *ortho*-positioned nitrogen atoms, led to 3-fold and 40-fold loss of CT-L activity respectively (Table 3) further highlighting the importance of the nitrogen in the *meta*-position of the ring. Compounds **11am** and **11an** that show CT-L inhibitory activities with IC_{50} values in the range of 100 nM also demonstrate propyl or butyl in the *para*-position of the R^1 are equally tolerated in the binding region. Interestingly, compound **11ar** and **11as** with hydrophobic, electron withdrawing fluorine and chlorine in the *para*-position of the R^1 and *meta*-pyridyl as R^2 (Entries 57 and 58, Table 3) showed 3-5-fold improvement in inhibitory activities respectively comparing to its related analogs **11s** (Entry 32, Table 3) **11h** and (Entry 21, Table 3). Overall, our detailed SAR studies signify the importance of *meta*-pyridyl, isopropylamide and *para*-propyl/-butyl phenyl groups in the oxadiazole pharmacophore shown in **1** for inhibition of CT-L activity of the proteasome.

The parent compound **1** and **11ad** were further evaluated for T-L and PGPH-L activities of the proteasome as shown in the Table 4. The *in vitro* data (IC_{50}) indicated that this class of compounds shows excellent selectivity for CT-L inhibitory activity over both T-L and PGPH-L activities. This level of CT-L selectivity is impressive for a non-peptidic, small molecule as compared to the covalent proteasome inhibitors reported to date. Only a small number of compound classes have been reported with this level of activity. [11, 38]

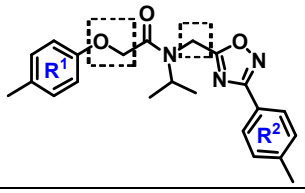
Table 1: Synthetic analogs of Library **12** and SAR.

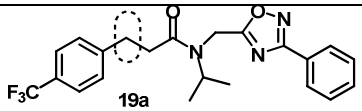
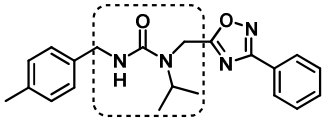
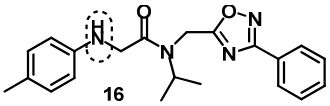
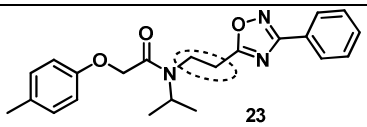
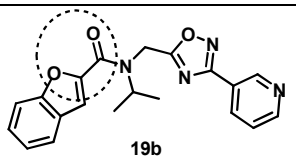


Entry	Compound ID	R^3	IC_{50} (μM) CT-L[a]
1	**1**	isopropyl	0.60 ± 0.18 (n=27)
2	**12a**	isobutyl	2.37 ± 0.40 (n=2)
3	**12b**	ethyl	6.04 ± 1.34 (n=3)
4	**12c**	methyl	29.90 ± 3.9 (n=2)
5	**12d**	H	No inhibition @ 10 μM
6	**12e**	*tert*-butyl	No inhibition @ 10 μM
7	**12f**	cyclopropyl	No inhibition @ 10 μM

[a] IC_{50} values are given as the average of 2 or more determinations; n = number of determinations.

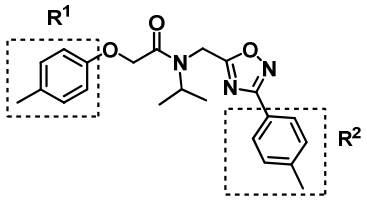
Table 2. Modifications of the spacer between the amide, R^1 and R^2 groups and SAR.

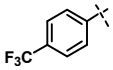
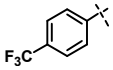
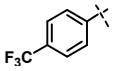
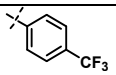
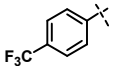
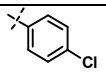
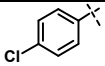
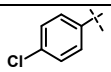
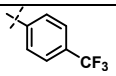
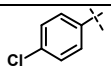
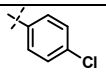
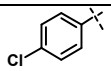


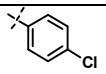
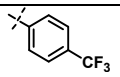
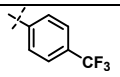
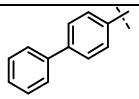
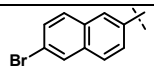
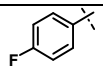
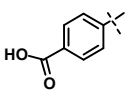
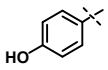
Entry #	Compound Structure and ID	IC_{50} (μM) CT-L[a]
8	 19a	53.48 ± 10.89 (n=3)
9	 14	No inhibition @ 10 μM
10	 16	5.67 ± 0.96 (n=4)
11	 23	No inhibition @ 10 μM
12	 19b	0.379 ± 0.06 (n=3)

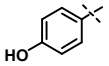
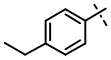
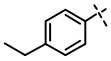
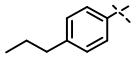
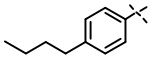
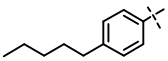
[a] IC_{50} values are given as the average of 2 or more determinations; n = number of determinations.

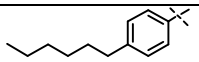
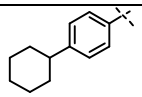
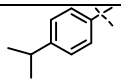
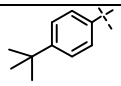
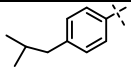
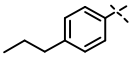
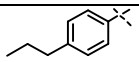
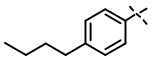
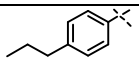
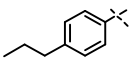
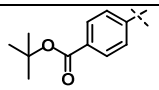
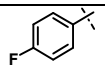
Table 3: Compound **1**, synthetic analogs of library **11** and SAR.

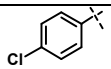


Entry	Compound ID	R^1	R^2	IC_{50} (μM) CT-L [a]
13	**1**			0.60 ± 0.18 (n=27)
14	**11a**			1.08 ± 0.33 (n=4)
15	**11b**			0.43 ± 0.12 (n=4)
16	**11c**			2.53 ± 0.95 (n=5)
17	**11d**			0.94 ± 0.26 (n=8)
18	**11e**			1.12 ± 0.33 (n=5)
19	**11f**			1.41 ± 0.19 (n=2)
20	**11g**			1.07 ± 0.05 (n=4)
21	**11h**			0.51 ± 0.16 (n=6)

22	**11i**			0.45 ± 0.15 (n=4)
23	**11j**			6.20 ± 1.1 (n=2)
24	**11k**			8.50 ± 0.60 (n=2)
25	**11l**			11.20 ± 2.1 (n=3)
26	**11m**			0.31 ± 0.08 (n=4)
27	**11n**			0.97 ± 0.15 (n=2)
28	**11o**			No inhibition @ 10 μM
29	**11p**			No inhibition @ 10 μM
30	**11q**			No inhibition @ 10 μM
31	**11r**			No inhibition @ 10 μM
32	**11s**			10.09 ± 1.63(n=3)
33	**11t**			No inhibition @ 10 μM
34	**11u**			0.98 ± 0.50 (n=3)

35	**11v**			10.12 ± 4.5 (n=3)
36	**11w**			3.75 ± 1.47 (n=6)
37	**11x**			0.22 ± 0.084 (n=6)
38	**11y**			0.37 ± 0.05 (n=4)
39	**11z**			4.0 ± 0.90 (n=3)
40	**11aa**			0.26 ± 0.05 (n=6)
41	**11ab**			0.099 ± 0.032 (n=14)
42	**11ac**			2.71 ± 0.56 (n=5)
43	**11ad**			0.027 ± 0.014 (n=20)
44	**11ae**			0.039 ± 0.01 (n=7)
45	**11af**			0.120 ± 0.04 (n=3)

46	**11ag**			0.43 ± 0.04 (n=3)
47	**11ah**			1.36 ± 0.18 (n=3)
48	**11ai**			0.44 ± 0.07 (n=3)
49	**11aj**			46.49 ± 1.23(n=3)
50	**11ak**			0.140 ± 0.05 (n=3)
51	**11al**			0.032 ± 0.003 (n=3)
52	**11am**			0.105 ± 0.031 (n=3)
53	**11an**			0.107 ± 0.013 (n=3)
54	**11ao**			1.27 ± 0.22 (n=3)
55	**11ap**			0.273 ± 0.10 (n=3)
56	**11aq**			No inhibition @ 10 μM
57	**11ar**			1.93 ± 0.61 (n=4)

58	**11as**			0.14 ± 0.064 (n=4)

[a] IC_{50} values are given as the average of 2 or more determinations; n = number of determinations.

Table 4: IC_{50} values of **1** and **11ad** for CT-L, T-L and PGPH-L activities of the proteasome.

Compound	CT-L (μM)	T-L (μM)[a]	PGPH-L (μM)[a]
1	0.60 ± 0.18 (n= 27)	>100	>100
11ad	0.027 ± 0.014 (n = 20)	>100	>100

[a] The values given are the means of 3 experiments; n = number of determinations.

Lead compound 11ad is more potent than the parent compound 1 at inhibiting CT-L activity and survival/proliferation of intact human breast cancer cells

Our *in vitro* SAR studies demonstrated that substituting the methyl of ring A with a propyl and replacing ring B tolyl with *meta*-pyridine in **1** (IC_{50} 600 nM) led to 22 fold more potent **11ad** (IC_{50} 27 nM). To determine whether these CT-L proteasome inhibitors are cell permeable and inhibit CT-L activity in intact cells, human breast cancer MDA-MB-468 cells were treated with increasing concentrations of **1** or **11ad** for 2 hours and the cells were processed for CT-L activity[41] determination as described under Methods. Figure 5A shows that **1** inhibited CT-L activity in a dose dependent manner with an IC_{50} value of 3.5 μM. Figure 5A also shows that consistent with the *in vitro* results, **11ad** was more potent than the parent compound **1** and inhibited the CT-L activity with an IC_{50} value of 0.37 μM. We next determined whether compounds **1** and **11ad** are capable of inhibiting tumor cell survival/proliferation. To this end, MDA-MB-468 cells were treated with parent compound **1** and **11ad** and processed for MTT assay as described under Methods. Figure 5B shows that treatment with both compounds inhibited survival/proliferation but that **11ad** was more potent than the parent compound **1**.

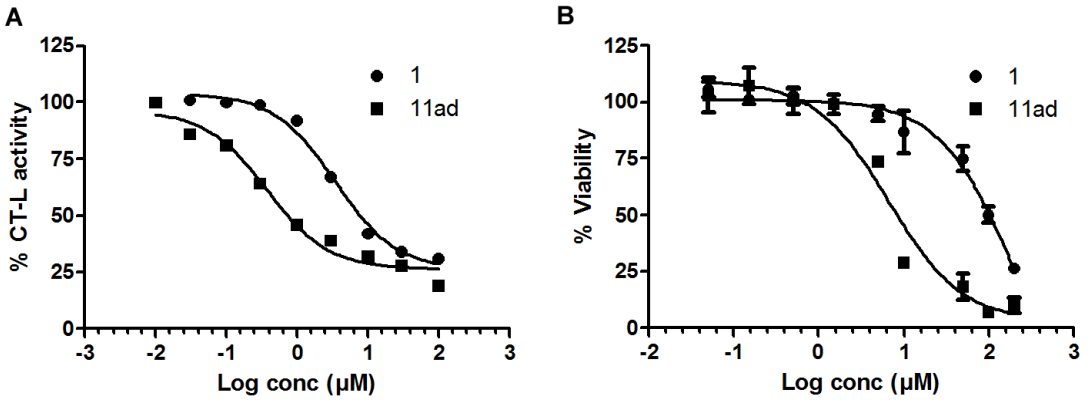


Figure 5. **A**: Lead **11ad** is more potent at inhibiting proteasomal CT-L activity in intact human MDA-MB-468 cancer cells compared to the parent compound **1**. **B**: Lead **11ad** is more potent at inhibiting proliferation/survival of human MDA-MB-468 cells compared to the parent hit **1**.

CONCLUSIONS: In this study we have extensively explored the SAR of oxadiazole-isopropylamide containing analogs as non-covalent CT-L proteasome inhibitors. The structure of the hit, **1** (IC_{50} = 0.60 ± 0.18 μM) served as a starting point for synthetic modifications and design and synthesis of novel, highly potent and non-covalent proteasome inhibitors. The LC/MS-MS and dialysis experiments confirmed that **1** binds to CT-L β-5 subunit of the proteasome in a non-covalent and rapidly reversible binding mode. Compound **11ad** with an IC_{50} value of 27 nM was identified as one of the most potent and cell permeable proteasome inhibitors. Our detailed SAR analysis indicated that extending the R^1-methyl in **1** to an optimal size with propyl or butyl in combination with *meta*-pyridyl as R^2 significantly improves the CT-L proteasome inhibitory activity (**11ad** and **11ae**, IC_{50} 27 and 39 nM respectively). The isopropyl amide and the ether moieties in **1** are critical for inhibitory activity and modification of these moieties substantially reduced the CT-L inhibitory activity. The SAR demonstrated the importance of the length and composition of the linking chain between the amide moiety, R^1 and R^2 groups. The potent lead **11ad** demonstrated efficacy in cellular assays and showed anti-proliferative activity at low micromolar concentrations. Our *in vitro* data also highlighted that this class of compounds shows high level of selectivity for CT-L proteasome inhibition over T-L and PGPH-L activities. Moreover, activities observed for some of the other analogs

presented herein (such as **11al** [IC_{50} 32 nM], **11am** [IC_{50} 105 nM] and **11an** [IC_{50} 107 nM]) could also be optimized in the development of novel non-covalent CT-L proteasome inhibitors.

MATERIALS AND METHODS

CT-L, T-L, PGPH-L proteolytic activity assays. In the high-throughput screen, we used fluorogenic peptides as substrates to assay (at 10 μM) the 50,000 compounds library from ChemBridge for inhibitory activity against the CT-L proteolytic activity of the purified rabbit 20S proteasome, resulting in the identification of hit **1**. To test for selectivity for CT-L over T-L and PGPH-L we used the corresponding fluorogenic peptides. Briefly, 1 nM of purified 20S rabbit proteasome was incubated with 20 μM Suc-Leu-Leu-Val-Tyr-AMC for the CT-L activity, Bz-Val-Gly-Arg-AMC for the T-L activity, and benzyloxycarbonyl Z-Leu-Leu-Glu-AMC for the PGPH-L activity for 1 h at 37 ºC in 100 μl of assay buffer (50 mM Tris-HCl, pH 7.6) with or without compound. After incubation, production of hydrolyzed 7-amido-4-methyl-coumarin (AMC) groups was measured using a WALLAC Victor^2 1420 Multilabel Counter with an excitation filter of 355 nm and an emission filter of 460 nm (Perkin Elmer Life Sciences, Turku, Finland). The amount of AMC released is within the linear range. Bortezomib was used as a positive control for IC_{50} determinations (IC_{50} of Bortezomib was typically around 10-30 nM). We used the following equation to calculate the *in vitro* IC_{50} values, $A=1/1+([I]/IC_{50})^n$, where A is the fraction of activity remaining, [I] is the concentration of inhibitor, and n is the Hill Slope Coefficient. To determine proteasome activity in whole cell, extracts (5 μg) from cultured cell lysate was used instead of 20S rabbit proteasome, and followed the same assay mentioned above except using the following equation; Y = M + (L – M)/ (1+10^ ((X-logIC_{50})) from GraphPad software, where Y = % inhibition, X = inhibitor concentration, M= maximum % inhibition, L = lowest % inhibition.

Cell culture and cell lysate preparation. Human MDA-MB-468 breast cancer cells were cultured in DMEM medium containing 10% fetal bovine serum (FBS) supplemented with 100 units/ml of penicillin and 100 μg/ml of streptomycin. Cells were maintained at 37 ºC in a humidified incubator in an atmosphere of 5% CO_2.

Whole cell lysates were prepared as follows. Cells were harvested, washed with PBS twice, and homogenized in a lysis buffer (50 mM Tris-HCl, pH 8.0, 5 mM EDTA, 150 mM NaCl, 0.5% NP-40) for 30 min at 4 ºC. Cell lysates were centrifuged at 12,000 *g* for 15 min, and the supernatants were collected as whole cell lysates.

Dialysis using purified rabbit 20S proteasome. To measure the effect of dialysis on CT-L activity, compounds **1** (10 μM), lactacystin (2.5 μM) or vehicle (DMSO) were added to rabbit 20S proteasome at a final concentration of 1 nM in proteasome assay buffer (50 mM Tris-HCl, pH 7.6) and incubated at room temperature for 30 min. After 30 min of incubation, proteasome-compound mixtures were added to 3500 MWCO Thermo Scientific Slide-A-Lyzer Mini Dialysis Units (Rockford, IL) and dialyzed against proteasome assay buffer. Immediately (t = 0) and 0.25, 1, 2, 4, and 18 hour of dialysis at 4 ºC, samples were removed from the dialysis cassette and the CT-L activity of 20S proteasome was determined as described above under "CT-L, T-L, and PGPH-L proteolytic activity assays" section. Proteasome activity was normalized against proteasome activity of DMSO control.

MTT (3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide) proliferation/survival assay. Cells were plated in 96-well plates in 100 μl medium and allowed to attach overnight. Cells were then incubated for 120 h with varying concentrations of inhibitors. Media was aspirated and replaced with 100 μl complete media containing 1 mg/ml MTT and incubated for three hours at 37 °C in 5% CO_2 humidified incubator. Media was then aspirated and DMSO was added. Cells were incubated for 10 min at room temperature while shaking, and the absorbance was determined at 540 nm using a μQuant spectrophotometric plate reader (Bio-TEK, Winooski, VT). The IC_{50} values were determined using equation under CT-L, T-L, PGPH-L proteolytic activity assays.

Protein Digestion and Peptide Purification.

Rabbit 20S Proteasome (1 nM), inhibitors and buffer (50 mM Tris-Hcl, pH 7.6) were incubated (450 μl total reaction volume) for 30 min at room temperature. After incubation, 112.5 μl of acetonitrile was added and

trypsin was added to quench the reaction and denature the protein. Trypsin was added with an enzyme-to-substrate ratio of 1:50. The digestion was carried out for 4 hours at 37 ºC. The digest was concentrated by vacuum centrifugation (ISS110, Speedvac, Thermo), and the peptides were extracted with C18 reversed phase pipette tip columns (Ziptip, Millipore). An aliquot (25%) of the total digest was injected into mass spectrometer. To assess LC/MS-MS performance, tryptic peptides from horse apomyoglobin (25 fmol) were spiked in each LC/MS-MS analysis.

LC/MS-MS Analysis:

Liquid chromatography-tandem mass spectrometry (LC/MS-MS) peptide sequencing experiments were performed using a nanoflow liquid chromatograph (U3000, Dionex, Sunnyvale, CA) interfaced with an electrospray ion trap mass spectrometer (LTQ-Orbitrap, Thermo, San Jose, CA) in order to detect and localize modified peptides from the proteasome. The sample was first loaded onto a trap column (5mm x 300 µm ID packed with C18 reversed-phase resin, 5µm particle size, 100Å pore size) and washed for 8 minutes with aqueous 2% acetonitrile and 0.04% trifluoroacetic acid. The trapped peptides were eluted onto the analytical column, (C18 Pepmap 100, 75 µm ID x 15 cm, Dionex, Sunnyvale, CA). The 120-minute gradient was programmed as: 95% solvent A (2% acetonitrile + 0.1% formic acid) for 8 minutes, solvent B (90% acetonitrile + 0.1% formic acid) from 5% to 50% in 90 minutes, then solvent B from 50% to 90% B in 7 minutes and held at 90% for 5 minutes, followed by solvent B from 90% to 5% in 1 minute and re-equilibration for 10 minutes. The flow rate on analytical column was 300 nl/min. Five tandem mass spectra were collected in a data-dependent manner following each survey scan. The MS survey scans were performed in Orbitrap to obtain accurate peptide mass measurement and the MS/MS scans were performed in linear ion trap using 60 second exclusion for previously sampled peptide peaks.

Database Searching and Data Analysis

Sequest[59] searches were performed against a database containing all rabbit proteasome protein sequences (n = 22) extracted from the UniProt (http://www.uniprot.org). Cleavage was set to fully tryptic, allowing up to

two missed cleavages; the precursor mass tolerance was 1.08 Da and MS/MS mass tolerance was 0.8 Da. Dynamic modifications included oxidation (Met + 15.99492), and potential modifications on threonine (Thr +379.18957 for compound **1**, Thr +394.20047 for compound **11ad** and +213.10009 for β-lactone modification by lactacystin[60]). The search results were summarized in Scaffold 3.0. (www.proteomesoftware.com). The integrated peak areas for peptide quantification were calculated from extracted ion chromatograms (EIC) using QuanBrowser from Xcalibur 2.0. These values were restricted by m/z (+/- 0.02) and retention time (120 seconds). The accuracy of the m/z values and the fragmentation patterns of the target peptides were manually inspected to insure proper sequence assignment.

EXPERIMENTAL

General. All reagents were purchased from commercial suppliers and used without further purification. Melting points were determined using a Barnstead international melting point apparatus or Optimelt automated melting point system (Stanford Research Systems) and remain uncorrected. Proton NMR spectra were recorded on an Agilent-Varian Mercury 400 MHz spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent. Carbon (^{13}C) NMR spectra are recorded at 100 MHz. All coupling constants are measured in Hertz (Hz) and the chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) relative to TMS (δ 0), which was used as the internal standard. Formula guided High resolution mass spectroscopy (HRMS) was carried out on an Agilent 6210 LC-MS (ESI-TOF). HPLC analysis was performed using a JASCO HPLC system equipped with a PU-2089 Plus quaternary gradient pump and a UV-2075 Plus UV-VIS detector, using an Alltech Kromasil C-18 column (150 × 4.6 mm, 5 μm) and Agilent Eclipse XDB-C18 (150 × 4.6 mm, 5 μm). Thin layer chromatography was performed using silica gel 60 F254 plates (Fisher), with observation under UV when necessary. Anhydrous solvents (acetonitrile, dimethylformamide, ethanol, isopropanol, methanol and tetrahydrofuran) were used as purchased from Aldrich. Burdick and Jackson HPLC grade solvents (methanol, acetonitrile and water) were purchased from VWR for HPLC and high resolution mass analysis. HPLC grade TFA was purchased from Fisher.

***N*-Isopropyl-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide (1)**: To a solution of **10a** (187 mg, 0.81 mmol) and triethylamine (164 mg, 1.62 mmol) in THF (15 ml) at r.t., was added **5a** (179 mg, 0.97 mmol) in THF (3 mL) dropwise (1-2 min). Upon addition of the acetyl chloride **5a**, a precipitate was formed and the reaction was completed in 15 min (monitored by tlc, R_f = 0.75, TLC, EtOAc/Hexane [1:1]). The THF was evaporated and the residue was dissolved in EtOAc (20 ml), washed with HCl (4M, 2 x15 ml) and water (15 ml). The organic phase was dried ($MgSO_4$), evaporated and the crude product obtained was purified by SiO_2 chromatography (EtOAc/Hexane gradient elution) to obtain **1** (270 mg, 88%) as a white solid. mp 142.1-143.4 °C. HPLC 100% (t_R = 11.8 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2H, [7.93 minor isomer]), 7.30-7.25 (m, 2H), 7.10 (d, *J* = 8.3 Hz, 2H, [7.05 minor isomer]), 6.87 (d, *J* = 8.5 Hz, 2H, [6.82 minor isomer]), 4.78 (s, 2H, [4.84 minor isomer]), 4.70 (s, 2H, [4.83 minor isomer]), 4.45-4.39 (m, 1H), 2.40 (s, 3H, [2.42 minor isomer]), 2.28 (s, 3H, [2.25 minor isomer]), 1.29 (d, *J* = 6.6 Hz, 6H, [1.15 minor isomer]); ^1H NMR (400 MHz, d_6-DMSO) δ 7.84 (d, *J* = 8.2 Hz, 2H, [7.87 minor isomer]), 7.36 (d, *J* = 7.9 Hz, 2H, [7.37 minor]), 7.01 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H, [6.75 minor isomer]), 4.88 (s, 2H, [4.98 minor isomer]), 4.71 (s, 2H, [4.82 minor isomer]), 4.31-4.21 (m, 1H, [4.62-4.52 minor isomer]), 2.37 (s, 3H), 2.18 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 6H, [1.06 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.40 [176.54 minor isomer], 168.51, 168.56, 156.01 [155.81 minor isomer], 141.68, 131.23 [131.25 minor isomer shown], 130.29 [130.24 minor isomer], 129.68 [129.84 minor isomer shown], 127.65, 124.08, 114.68 [114.64 minor isomer], 67.99 [68.74 minor isomer], 48.96 [46.96 minor isomer], 37.20 [38.40 minor isomer], 21.49 [19.97 minor isomer], 20.81, 20.73; Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.51; H, 6.74; N, 11.13; LC-MS (ESI+) *m/z* 380.20 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{26}N_3O_3$ $(M+H)^+$ 380.1969, found 380.1975.

***N*-Isopropyl-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-2-(4-(trifluoromethyl)phenoxy)acetamide (11a)**: This compound was prepared from **5b** (149 mg, 0.62 mmol) and **10a** (120 mg, 0.52 mmol) using triethylamine (105 mg, 1.04 mmol) in a similar manner as described for compound **1**. The crude product was

purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11a** (196 mg, 87%) as a white solid. mp 76.6-78.5 °C. HPLC 99.5% (t_R = 14.8 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.57-7.49 (m, 2H), 7.25 (d, *J* = 7.9 Hz, 2H, [7.29 minor isomer]),7.04 (d, *J* = 8.5 Hz, 2H, [6.99 minor isomer]), 4.88 (s, 2H, [4.94 minor isomer]), 4.71 (s, 2H, [4.76 minor isomer]), 4.38-4.32 (m, 1H), 2.41 (s, 3H, [2.43 minor isomer]), 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100MHz, $CDCl_3$) δ 176.16 [176.23 minor isomer], 168.57 [167.84 minor isomer], 167.80 [167.87 minor isomer], 160.48, 141.86 [142.43 minor isomer], 129.73, 127.58, 127.29 (q, *J* = 3.67 Hz), 124.47 (q, *J* = 270 Hz), 124.11 (q, *J* = 32.5 Hz), 123.88 [123.86 minor isomer], 114.96 [114.82 minor isomer], 67.48 [67.90 minor isomer], 49.00 [47.05 minor isomer], 37.23 [38.35 minor isomer], 21.81, 21.45 [19.96 minor isomer]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.02 [-62.06 minor isomer]; LC-MS (ESI+) *m/z* 434.18 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{23}F_3N_3O_3$ $(M+H)^+$ 434.1686, found 434.1711.

***N*-Isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-2-(4-(trifluoromethyl)phenoxy)acetamide (11b)**: This compound was prepared from **5b** (131 mg, 0.55 mmol) and **10d** (100 mg, 0.46 mmol) using triethylamine (93 mg, 0.92 mmol) in a similar manner as described for compound **1**. The crude product was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11b** (172 mg, 89%) as a white solid. mp 97.9-99.3 °C. HPLC 100% (t_R = 10.4 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.02-7.98 (m, 2H), 7.55-7.43 (m, 5H), 7.04 (d, *J* = 8.8 Hz, 2H, [7.01 minor isomer]), 4.88 (s, 2H, [4.94 minor isomer]), 4.72 (s, 2H, [4.79 minor isomer]), 4.39-4.35 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100MHz, $CDCl_3$) δ 176.36 [176.47 minor isomer], 168.58 [168.54 minor isomer shown], 167.66 [166.71 minor isomer], 160.50 [160.47 minor isomer], 131.47 [131.92 minor isomer], 129.00 [129.20 minor isomer], 127.65, 127.29 (q, *J* = 3.74 Hz), 126.78 [126.17minor isomer], 124.46 (q, *J* = 270 Hz), 124.14 (q, *J* = 32.7 Hz), 114.97 [114.90 minor isomer], 67.56 [68.07 minor isomer], 48.96 [47.07 minor isomer], 37.21 [38.41 minor isomer], 21.48 [19.98 minor isomer]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.03 [-62.07 minor isomer];

LC-MS (ESI+) *m/z* 420.16 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{21}F_3N_3O_3$ $(M+H)^+$ 420.1530, found 420.1547.

***N*-Isopropyl-2-(4-(trifluoromethyl)phenoxy)-*N*-((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11c)**: This compound was prepared from **5b** (100 mg, 0.42 mmol) and **10b** (100 mg, 0.35 mmol) using triethylamine (71 mg, 0.70 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11c** (157 mg, 92%) as a white solid. mp 96.8-98.9 °C. HPLC 95% (t_R = 19.0 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 4:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H, [7.49 minor isomer]), 7.04 (d, *J* = 8.7 Hz, 2H, [6.97 minor isomer]), 4.88 (s, 2H, [4.91 minor isomer]), 4.72 (s, 2H, [4.84 minor isomer]), 4.42-4.38 (m, 1H), 1.34 (d, *J* = 6.6 Hz, 6H, [1.17 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.91, 167.87 [167.90 minor isomer], 167.60, 160.42 [160.02 minor isomer], 133.18 (q, *J* = 33 Hz), 130.16, 128.01 [128.12 minor isomer], 127.32 (q, *J* = 3.59 Hz), 126.03 (q, *J* = 3.81 Hz), 124.41 (q, *J* = 270 Hz), 124.23 (q, *J* = 32.59 Hz), 123.94 (q, *J* = 270 Hz), 114.94 [114.83 minor isomer], 67.51 [64.80 minor isomer], 49.08, 37.30, 29.94, 21.50 [19.97 minor isomer]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.07 [-62.02 minor isomer], -62.13 [-62.14 minor isomer], -62.45 [-62.52 minor isomer]; LC-MS (ESI+) *m/z* 488.14 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{20}F_6N_3O_3$ $(M+H)^+$ 488.1403, found 488.1419.

***N*-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-*N*-isopropyl-2-(4-(trifluoromethyl)phenoxy) acetamide (11d)**: This compound was prepared from **5b** (115 mg, 0.48 mmol) and **10c** (101 mg, 0.40 mmol) using triethylamine (81 mg, 0.80 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11d** (154 mg, 85%) as a white solid. mp 79.0-80.5 °C. HPLC 100% (t_R = 16.5 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H, [7.50 minor isomer]), 7.43 (d, *J* = 8.6 Hz, 2H, [7.46 minor isomer]),

7.04 (d, J = 8.6 Hz, 2H, [6.99 minor isomer]), 4.88 (s, 2H, [4.92 minor isomer]), 4.70 (s, 2H, [4.80 minor isomer]), 4.41-4.35 (m, 1H), 1.32 (d, J = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.60 [176.74 minor isomer], 167.81, 167.70, 160.46 [160.40 minor isomer], 137.61, 129.35 [129.54 minor isomer], 128.96, 127.31 (q, J = 3.7 Hz), 125.28, 124.45 (q, J = 270 Hz), 124.17(q, J = 32 Hz), 114.95 [114.87 minor isomer], 67.54 [68.25 minor isomer], 49.00 [47.16 minor isomer], 37.25 [38.50 minor isomer], 21.50 [19.98 minor isomer]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.03 [-62.08 minor isomer]; LC-MS (ESI+) *m/z* 454.12 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{20}ClF_3N_3O_3$ $(M+H)^+$ 454.1140, found 454.1149.

2-(4-Chlorophenoxy)-*N*-isopropyl-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11e): This compound was prepared from **5d** (106 mg, 0.52 mmol) and **10a** (100 mg, 0.43 mmol) using triethylamine (87 mg, 0.86 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11e** (151 mg, 88%) as a white solid. mp 133.1-136.5 °C. HPLC 99.6% (t_R = 12.5 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^{1}H NMR showed 3:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.3 Hz, 2H, [7.91 minor isomer]), 7.30-7.26 (m, 2H), 7.23 (d, J = 9.0 Hz, 2H, [7.20 minor isomer]), 6.86 (d, J = 9.0 Hz, 2H, [6.87 minor isomer]), 4.81 (s, 2H, [4.86 minor isomer]), 4.70 (s, 2H, [4.79 minor isomer]), 4.42-4.35 (m, 1H), 2.41 (s, 3H, [2.41 minor isomer]), 1.30 (d, J = 6.6 Hz, 6H, [1.15 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.22 [176.34 minor isomer], 168.57, 168.01, 156.75, 141.75 [142.36 minor isomer], 129.90, 129.74 [129.72 minor isomer], 129.67, 127.61 [126.90 minor isomer], 123.98 [123.42 minor isomer], 116.24 [116.17 minor isomer], 67.95 [68.47 minor isomer], 48.93 [46.97 minor isomer], 37.17 [38.37 minor isomer], 21.82, 21.47 [19.98 minor isomer]; LC-MS (ESI+) *m/z* 400.15 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{23}ClN_3O_3$ $(M+H)^+$ 400.1423, found 400.1448.

2-(4-Chlorophenoxy)-*N*-isopropyl-*N*-((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl) acetamide (11f): This compound was prepared from **5d** (86 mg, 0.42 mmol) and **10b** (100 mg, 0.35 mmol) using triethylamine (71 mg, 0.70 mmol) in a similar manner as described for compound **1**. The crude

product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11f** (129 mg, 81%) as a white solid. mp 106.4-108.9 °C. HPLC 99.8% (t_R = 17.1 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 4:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 2H, [8.13 minor isomer]), 7.73 (d, *J* = 8.2 Hz, 2H, [7.76 minor isomer]), 7.23 (d, *J* = 9.0 Hz, 2H, [7.18 minor isomer]), 6.91 (d, *J* = 9.0 Hz, 2H, [6.83 minor isomer]), 4.81 (s, 2H, [4.85 minor isomer]), 4.70 (s, 2H, [4.83 minor isomer]), 4.45-4.39 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.00 [177.20 minor isomer], 168.16, 167.64, 156.68, 133.11 (q, *J* = 32.6 Hz), 130.18, 129.76, 128.04, 126.96, 126.08 (q, *J* = 3.8 Hz), 123.96 (q, *J* = 270 Hz), 116.20 [116.08 minor isomer], 67.91 [68.88 minor isomer], 49.01 [47.09 minor isomer], 37.24 [38.52 minor isomer], 21.50 [19.88 minor isomer]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.40 [-63.46 minor isomer]; LC-MS (ESI+) *m/z* 454.11 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{20}ClF_3N_3O_3$ $(M+H)^+$ 454.1140, found 454.1142.

2-(4-Chlorophenoxy)-*N*-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-*N*-isopropylacetamide (11g): This compound was prepared from **5d** (98 mg, 0.48 mmol) and **10c** (101 mg, 0.40 mmol) using triethylamine (81 mg, 0.80 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11g** (133 mg, 79%) as a white solid. mp 133.4-135.8 °C. HPLC 99.9% (t_R = 15.5 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 4:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.7 Hz, 2H, [7.96 minor isomer]), 7.44 (d, *J* = 8.6 Hz, 2H, [7.48 minor isomer]), 7.23 (d, *J* = 9.0 Hz, 2H, [7.19 minor isomer]), 6.91 (d, *J* = 9.1 Hz, 2H, [6.84 minor isomer]), 4.80 (s, 2H, [4.83 minor isomer]), 4.69 (s, 2H, [4.81 minor isomer]), 4.40-4.37 (m, 1H), 1.30 (d, *J* = 6.6 Hz, 6H, [1.15 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.66 [176.83 minor isomer], 168.10, 167.78, 156.69, 137.56, 129.75, 129.36 [129.54 minor isomer], 128.99, 126.93, 125.29, 116.20 [116.11 minor isomer], 67.90 [68.68 minor isomer], 48.96, 37.20, 21.49 [19.98 minor isomer]; LC-MS (ESI+) *m/z* 420.08 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{20}Cl_2N_3O_3$ $(M+H)^+$ 420.0876, found 420.0891.

2-(4-Chlorophenoxy)-*N*-isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11h): This compound was prepared from **5d** (119 mg, 0.58 mmol) and **10d** (104 mg, 0.48 mmol) using triethylamine (97 mg, 0.96 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11h** (152 mg, 82%) as a white solid. mp 108.3-109.5 °C. HPLC 99.8% (t_R = 9.5 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.03-7.99 (m, 2H), 7.56-7.41 (m, 3H), 7.23 (d, *J* = 9.0 Hz, 2H, [7.19 minor isomer]), 6.91 (d, *J* = 9.0 Hz, 2H, [6.87 minor isomer]), 4.80 (s, 2H, [4.85 minor isomer]), 4.70 (s, 2H), 4.43-4.36 (m, 1H), 1.30 (d, *J* = 6.6 Hz, 6H, [1.15 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.42, 168.56, 168.08, 156.73, 131.44 [131.87 minor isomer], 129.75 [129.68 minor isomer], 129.75 [129.02 minor isomer], 127.69, 126.91, 126.79, 116.23 [116.16 minor isomer], 67.92 [68.52 minor isomer], 48.97 [47.07 minor isomer], 37.19 [38.43 minor isomer], 21.47 [19.98 minor isomer]; LC-MS (ESI+) *m/z* 386.14 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{21}ClN_3O_3$ $(M+H)^+$ 386.1266, found 386.1269.

***N*-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-*N*-isopropyl-2-(p-tolyloxy)acetamide (11i)**: This compound was prepared from **5a** (89 mg, 0.48 mmol) and **10c** (101 mg, 0.40 mmol) using triethylamine (81 mg, 0.80 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11i** (131 mg, 82%) as a white solid. mp 133.5-134.3 °C. HPLC 99.7% (t_R = 21.0 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H, [7.45 minor isomer]), 7.08 (d, *J* = 8.3 Hz, 2H, [7.03 minor isomer]), 6.87 (d, *J* = 8.6 Hz, 2H, [6.79 minor isomer]), 4.78 (s, 2H, [4.86 minor isomer]), 4.69 (s, 2H, [4.81 minor isomer]), 4.46-4.40 (m, 1H), 2.28 (s, 3H, [2.25 minor isomer]), 1.30 (d, *J* = 6.6 Hz, 6H, [1.15 minor isomer]); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.85, [176.00 minor isomer], 168.56, 167.78, 156.26, 137.34, 131.26, 130.28 [130.24 minor], 129.30 [129.45 minor isomer], 129.04, 125.42, 114.67 [114.59 minor isomer], 67.98 [68.95 minor isomer],

48.96 [47.05 minor isomer], 37.22 [38.48 minor isomer], 21.50 [19.99 minor isomer], 20.74; LC-MS (ESI+) *m/z* 400.14 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{23}ClN_3O_3$ $(M+H)^+$ 400.1423, found 400.1423.

***N*-Isopropyl-2-phenoxy-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11j)**: This compound was prepared from **5c** (47 mg, 0.28 mmol) and **10d** checked (50 mg, 0.23 mmol) using triethylamine (47 mg, 0.46 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11j** (61 mg, 76%). as a white solid. mp 77.9-79.0 °C. HPLC 94.4% (t_R = 11.6 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 4:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.1, 1.6 Hz, 2H, partially overlapped, [8.05 minor isomer, overlapped]), 7.53-7.43 (m, 3H), 7.32-7.25 (m, 2H), 7.03-6.85 (m, 3H), 4.83 (s, 2H, [4.88 minor isomer]), 4.72 (s, 2H, [4.86 minor isomer]), 4.46-4.40 (m, 1H), 1.31 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.53 [176.65 minor isomer], 168.72 [168.80 minor isomer], 168.53, 158.01 [157.85 minor isomer], 156.40, 131.44 [131.81 minor isomer], 129.88 [129.82 minor isomer], 129.79, 129.00 [129.17 minor isomer], 127.73 [127.69 minor isomer], 127.04, 126.78, 122.00, 116.21, 114.86 [114.81 minor isomer shown], 67.66 [68.34 minor isomer shown], 49.09 [47.12 minor isomer], 37.28 [38.45 minor isomer], 21.43 [19.95 minor isomer]; LC-MS (ESI+) *m/z* 352.16 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{22}N_3O_3$ $(M+H)^+$ 352.1656, found 352.1662.

***N*-Isopropyl-2-phenoxy-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11k)**: This compound was prepared from **5c** (80 mg, 0.47 mmol) and **10a** (90 mg, 0.39 mmol) using triethylamine (78 mg, 0.77 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11k** (111 mg, 78%) as a white solid. mp 97.8-99.5 °C. HPLC 99.8% (t_R = 8.5 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 2H, [7.93 minor isomer shown]), 7.34-7.22 (m, 4H), 7.02-6.94 (m, 3H), 4.82 (s, 2H [4.87 minor isomer]), 4.71 (s, 2H, [4.83 minor isomer]), 4.45-4.39 (m, 1H), 2.41 (s, 3H [2.42 minor isomer]), 1.30 (d, *J* = 6.6 Hz, 6H, [1.15 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.49 [176.50 minor isomer], 168.34, 168.55, 158.08, 141.68 [142.23 minor

isomer],129.86 [129.81 minor isomer],129.68, 127.65, 124.01, 121.95, 114.86 [114.83 minor isomer], 67.81 [68.49 minor isomer], 48.96 [46.89 minor isomer], 37.21 [38.37 minor isomer], 21.82, 21.48 [19.98 minor isomer]; LC-MS (ESI+) *m/z* 366.19 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{24}N_3O_3$ $(M+H)^+$ 366.1812, found 366.1816.

***N*-Isopropyl-2-phenoxy-*N*-((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11l)**: This compound was prepared from **5c** (57 mg, 0.34 mmol) and **10b** (80 mg, 0.28 mmol) using triethylamine (57 mg, 0.56 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11l** (95 mg, 81%) as a white solid. mp 122.8-123.8 °C. HPLC 100% (t_R = 11.6 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.1 Hz, 2H, [8.15 minor isomer]), 7.72 (d, *J* = 8.2 Hz, 2H, [7.75 minor isomer]), 7.35-7.26 (m, 2H), 7.03-6.94 (m, 3H, [6.90 minor isomer]), 4.83 (s, 2H, [4.89 minor isomer]), 4.72 (s, 2H, [4.86 minor isomer]), 4.48-4.43 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.15 [177.39 minor isomer], 168.45, 167.58, 158.04, 133.07 (q, *J* = 32.6 Hz), 130.29 [130.27 minor isomer shown], 129.87 [129.83 minor isomer],128.09, 125.97 (q, *J* = 3.7 Hz), 123.99 (q, *J* = 271 Hz), 121.99 [122.07 minor isomer], 114.83 [114.75 minor isomer], 67.75 [68.75 minor isomer], 49.01 [47.05 minor isomer], 37.27 [38.58 minor isomer], 21.50 [19.98 minor isomer]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.37, [-63.43 minor isomer]; LC-MS (ESI+) *m/z* 420.15 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{21}F_3N_3O_3$ $(M+H)^+$ 420.1530, found 420.1530.

***N*-Isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide (11m)**: This compound was prepared from **5a** (102 mg, 0.55 mmol) and **10d** (100 mg, 0.46 mmol) using triethylamine (93 mg, 0.92 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11m** (153 mg, 91%). as a white solid. mp 134.7-136.5 °C. HPLC 96.3% (t_R = 8.5 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.6 Hz, 2H overlapped, [8.04 minor isomer overlapped]), 7.55- 7.41 (m, 3H), 7.08 (d, *J* = 8.3 Hz, 2H, [7.04 minor isomer]), 6.87 (d,

J = 8.6 Hz, 2H, [6.81 minor isomer]), 4.78 (s, 2H, [4.85 minor isomer]), 4.71 (s, 2H, [4.83 minor isomer]), 4.45-4.40 (m, 1H), 2.28 (s, 3H, [2.25 minor isomer]), 1.30 (d, J = 6.6 Hz, 6H, [1.15 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.62, 168.55, 168.53, 156.00 [155.80 minor isomer], 131.37 [131.74 minor isomer], 131.22 [131.25 minor isomer], 130.28 [130.24 minor isomer], 128.97 [129.13 minor isomer], 127.73, 126.89, 114.68 [114.62 minor isomer], 67.97 [68.75 minor isomer], 48.93 [46.94 minor isomer], 37.20 [38.44 minor isomer], 21.48, [19.98 minor isomer], 20.74; LC-MS (ESI+) *m/z* 366.18 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{24}N_3O_3$ $(M+H)^+$ 366.1812, found 366.1828.

***N*-Isopropyl-2-(*p*-tolyloxy)-*N*-((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11n)**: This compound was prepared from **5a** (78 mg, 0.42 mmol) and **10b** (100 mg, 0.35 mmol) using triethylamine (71 mg, 0.70 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11n** (127 mg, 84%) as a white solid. mp 146.9-148.6 °C. HPLC 99% (t_R = 16.1 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^{1}H NMR showed 4:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H, overlapped, [7.75 minor isomer, overlapped]), 7.08 (d, J = 8.3 Hz, 2H, [7.02 minor isomer]), 6.87 (d, J = 8.6 Hz, 2H, [6.77 minor isomer]), 4.79 (s, 2H, [4.89 minor isomer]), 4.70 (s, 2H, [4.81 minor isomer]), 4.48-4.42 (m, 1H), 2.28 (s, 3H, [2.23 minor isomer]), 1.31 (d, J = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.20 [177.43 minor isomer], 168.63, 167.57, 155.98 [155.73 minor isomer], 133.05 (q, J = 32.5 Hz), 131.27 [131.37 minor isomer], 130.29 [130.24 minor isomer], 128.09, 125.97 (q, J = 3.8 Hz), 124.0 (q, J = 270.6 Hz), 114.65 [114.54 minor isomer], 67.94 [68.85 minor isomer], 48.97 [47.08 minor isomer], 37.26 [38.63 minor isomer], 21.50 [19.62 minor isomer], 20.74; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.39 [-63.45 minor isomer]; LC-MS (ESI+) *m/z* 434.18 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{23}F_3N_3O_3$ $(M+H)^+$ 434.1686, found 434.1693.

***N*-Isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*m*-tolyloxy)acetamide (11o)**: This compound was prepared from **5h** (66 mg, 0.36 mmol) and **10d** (65 mg, 0.30 mmol) using triethylamine (61 mg, 0.60 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using

SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11o** (83 mg, 76%) as a colorless viscous compound; HPLC 98.8% (t_R = 8.6 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.0, 1.5 Hz, 2H, [8.08 minor isomer]), 7.52-7.42 (m, 4H), 7.17 (t, *J* = 7.6 Hz, 1H, overlapped, [7.15, minor isomer])), 6.82-6.69 (m, 2H), 4.79 (s, 2H, [4.85 minor isomer]), 4.71 (s, 2H, [4.84 minor isomer]), 4.46-4.40 (m, 1H), 2.31 (s, 3H, [2.25 minor isomer]), 1.31 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer shown]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.58, 168.56, 168.43, 158.09, 139.99, 131.36 [131.74 minor isomer], 129.58 [129.53 minor isomer], 128.96 [129.13 minor isomer], 127.72, 126.90, 122.80 [122.84 minor isomer], 115.64 [115.74 minor isomer], 111.70 [111.46 minor isomer], 67.79 [68.59 minor isomer], 48.97 [46.97 minor isomer shown], 37.22 [38.52 minor isomer], 21.76, 21.49 [19.98 minor isomer shown]; LC-MS (ESI+) *m/z* 366.19 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{24}N_3O_3$ $(M+H)^+$ 366.1812, found 366.1817.

***N*-Isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*o*-tolyloxy)acetamide (11p)**: This compound was prepared from **5i** (51 mg, 0.28 mmol) and **10d** (50 mg, 0.23 mmol) using triethylamine (57 mg, 0.56 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11p** (71 mg, 85%) as a white solid. mp 97.3-98.0 °C. HPLC 98.0% (t_R = 9.5 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (broad dd, *J* = 7.9, 1.6 Hz, 2H), 7.51-7.43 (m, 3H), 7.17-7.09 (m, 2H), 6.92-6.87 (m, 2H), 4.82 (s, 2H, [4.81 minor isomer]), 4.71 (s, 2H), 4.48-4.38 (m, 1H), 2.28 (s, 3H, [2.20 minor isomer]), 1.29 (d, *J* = 6.6 Hz, 6H, [1.14 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.57 [176.68 minor isomer], 168.57, 168.50, 156.23, 131.38 [131.77 minor isomer], 131.18, 128.98 [129.15 minor isomer], 127.73, 127.25, 126.87, 126.84, 121.61 [121.69 minor isomer], 111.28 [111.63 minor isomer], 68.01 [68.86 minor isomer], 48.94 [48.90 minor isomer], 37.22 [38.26 minor isomer], 21.51 [20.07 minor isomer], 16.62; LC-MS (ESI+) *m/z* 366.18 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{24}N_3O_3$ $(M+H)^+$ 366.1812, found 366.1821.

2-(Biphenyl-4-yloxy)-*N*-isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11q): This compound was prepared from **5e** (116 mg, 0.47 mmol) and **10d** (85 mg, 0.39 mmol) using triethylamine (79 mg, 0.78 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11q** (145 mg, 87%) as a white solid. mp 147.8-148.7 °C. HPLC 99.6% (t_R = 14.6 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.55-7.36 (m, 9H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H, [7.00 minor isomer]), 4.87 (s, 2H, [4.91 minor isomer]), 4.73 (s, 2H), 4.48-4.42 (m, 1H), 1.33 (d, *J* = 6.6 Hz, 6H, [1.17 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.55 [176.69 minor isomer], 168.58, 168.30 [168.38 minor isomer], 157.63 [157.49 minor isomer], 140.78, 135.04 [135.07 minor isomer], 131.36 [131.77 minor isomer], 128.98 [129.16 minor isomer], 128.94, 128.53, 127.71, 127.04, 127.01, 126.88, 115.17 [115.10 minor isomer], 67.86 [68.62 minor isomer], 48.98 [47.02 minor isomer], 37.22 [38.50 minor isomer], 21.51 [20.00 minor isomer shown]; LC-MS (ESI+) *m/z* 428.19 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{26}H_{26}N_3O_3$ $(M+H)^+$ 428.1969, found 428.1968.

2-(6-Bromonaphthalen-2-yloxy)-*N*-isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11r): This compound was prepared from **5g** (140 mg, 0.47 mmol) and **10d** (85 mg, 0.39 mmol) using triethylamine (79 mg, 0.78 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11r** (141 mg, 75%) as a white solid. mp 97.7-98.4 °C. HPLC 98.1% (t_R = 19.6 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.99-7.86 (m, 3H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.53-7.36 (m, 4H), 7.24 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 4.93 (s, 2H, [4.98 minor isomer]), 4.72 (s, 2H, [4.86 minor isomer]), 4.52-4.46 (m, 1H), 1.33 (d, *J* = 6.6 Hz, 6H, [1.18 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.47, 168.59, 168.14, 156.26, 133.02, 131.80, 131.36 [131.40 minor isomer], 130.63, 130.00 [129.94 minor isomer], 129.82, 129.03 [129.14 minor isomer], 128.94, 127.63 [127.68 minor isomer], 126.75, 119.65 [119.49 minor isomer], 117.90, 107.72, 67.89 [68.50 minor isomer], 49.03 [47.10 minor isomer], 37.23 [38.65 minor isomer], 21.53

[19.99 minor isomer]; LC-MS (ESI+) *m/z* 480.09 and 482.09 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{24}H_{23}BrN_3O_3$ $(M+H)^+$ 480.0917, found 480.0914.

2-(4-Fluorophenoxy)-*N*-isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11s): This compound was prepared from **5f** (95 mg, 0.50 mmol) and **10d** (91 mg, 0.42 mmol) using triethylamine (85 mg, 0.84 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11s** (127 mg, 82%) as a white solid. mp 87.9-89.9 °C. HPLC 99.5 % (t_R = 16.00 min, 50% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.1, 1.6 Hz, 2H, [8.04 minor isomer]), 7.54-7.44 (m, 3H), 7.02-6.88 (m, 4H), 4.80 (s, 2H, [4.85 minor isomer]), 4.72 (s, 2H, [4.83 minor isomer]), 4.44-4.38 (m, 1H), 1.31 (d, *J* = 6.7 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.49 [177.63 minor isomer], 168.82 [168.56 minor isomer], 168.24, 157.98 (d, *J* = 238 Hz), 154.24 (d, *J* = 2.07 Hz), 131.44 [131.86 minor], 129.00 [129.19 minor isomer], 127.69, 126.82, 116.34 (d, *J* = 23 Hz), 116.03 (d, *J* = 8.11 Hz), 68.30 [68.92 minor isomer], 48.91 [46.94 minor isomer], 37.18 [38.39 minor isomer], 21.46 [19.97 minor isomer]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -123.13; LC-MS (ESI+) *m/z* 370.15 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{21}FN_3O_3$ $(M+H)^+$ 370.1562, found 370.1567.

***N*-Isopropyl-(3-phenyl-1,2,4-oxadiazol-5-yl)methylamino-2-oxoethoxy)benzoic acid (11t)**: A solution of **11aq** (50 mg, 0.11 mmol) in trifluoroacetic acid (3 ml) and dichloromethane (5 ml) were stirred at room temperature for 2 h. Acetone (5 ml) was added to the reaction mixture and the solvents were evaporated under vacuum to give the pure compound **11t** (41 mg, 95%) as a white compound. mp 211.3-213.8 °C. HPLC 100 % (t_R = 14.8 min, 40% MeOH in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, DMSO) δ 12.58 (brs, 1H), 7.97-7.90 (m, 2H, [8.03 -7.98 minor isomer]), 7.82 (d, *J* = 8.8 Hz, 2H), 7.58-7.53 (m, 3H), 6.96 (d, *J* = 8.8 Hz, 2H, [6.99 minor isomer]), 5.09 (s, 2H, [5.02 minor isomer]), 4.75 (s, 2H, [5.00 minor isomer]), 4.32-4.20 (m, 1H, [4.66-4.60 minor isomer]), 1.28 (d, *J* = 6.5 Hz, 6H, [1.07 minor isomer]). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.32, 171.41, 168.58, 167.80, 162.38, 132.70 [132.63 minor isomer], 131.48 [131.94 minor isomer], 129.22, 129.01 [129.22 minor isomer], 127.68

[126.71 minor isomer], 122.97 [122.90 minor isomer], 114.71 [114.68 minor isomer], 67.46 [67.96 minor isomer], 49.07 [47.24 minor isomer], 37.24 [38.43 minor isomer], 21.46 [19.96 minor isomer]; LC-MS (ESI+) *m/z* 396.15 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{22}N_3O_5$ $(M+H)^+$ 396.1554, found 396.1566.

2-(4-Hydroxyphenoxy)-*N*-isopropyl-*N*-((pyridin-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11u): To a solution of **10f** (59 mg, 0.27 mmol) and triethylamine (55 mg, 0.54 mmol) in THF (10 ml) at r.t., was added 2-(4-hydroxyphenoxy)acetyl chloride (**5s**) (60 mg, 0.32 mmol) in THF (1 ml, dropwise 3-4 min). Upon addition of acetyl chloride, a precipitate was formed and the reaction was completed in 15 min. (monitored by tlc, R_f = 0.50, EtOAc/Hexane [2:1]). The THF was evaporated and the crude product obtained was purified by SiO_2 chromatography (EtOAc/Hexane gradient elution) to obtain pure **11u** (83 mg, 83%) as a white solid. mp 140.0-142.4 °C. HPLC 95.5% (t_R = 5.47 min, 45% MeOH in 0.1% TFA water 20 min); The ^{1}H NMR showed 5:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H, [9.23 minor isomer]), 8.70 (dd, *J* = 4.8, 1.4 Hz, 1H, [8.74 minor isomer]), 8.30 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.43 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.88 (d, *J* = 9.1 Hz, 2H), 6.80 (d, *J* = 9.1 Hz, 2H), 4.78 (s, 2H, [4.88 minor isomer]), 4.69 (s, 2H), 4.60-4.52 (m, 1H), 1.29 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.39, 169.00, 166.13, 152.05, 151.05, 148.10, 135.85, 124.36, 117.00 [116.45 minor isomer] 115.97, 68.37, 48.88, 37.08, 21.49 [19.99 minor isomer]; LC-MS (ESI+) *m/z* 369.15 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{19}H_{21}N_4O_4$ $(M+H)^+$ 369.1557, found 369.1571.

2-(4-Hydroxyphenoxy)-*N*-isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11v): This compound was prepared from **5s** (52 mg, 0.28 mmol) and **10d** (50 mg, 0.23 mmol) using triethylamine (47 mg, 0.46 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11v** (68 mg, 80%) as a white solid. mp 155.5-158.5 °C. HPLC 100% (t_R = 13.1 min, 40% CH_3CN in 0.1% TFA water 20 min); The ^{1}H NMR showed 3:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.8, 1.7 Hz, 2H, [8.04 minor isomer]), 7.51-7.43 (m, 3H), 6.85 (d, *J* = 9.0 Hz, 2H, [6.80 minor isomer]), 6.73 (d, *J* = 9.0 Hz, 2H,

[6.70 minor isomer]), 4.75 (s, 2H, [4.85 minor isomer]), 4.71 (s, 2H, [4.80 minor isomer]), 4.48-4.41 (m, 1H), 1.30 (d, J = 6.6 Hz, 6H, [1.15 minor isomer]); ^{13}C NMR (100 MHz, DMSO) δ 178.76 [178.92 minor isomer], 168.57 [168.67 minor isomer], 168.12 [168.25 minor isomer], 152.16 [152.02 minor isomer], 151.45, 150.38, 132.27 [132.45 minor isomer], 129.97 [130.02 minor isomer], 127.61 [127.69 minor isomer], 126.78 [126.55 minor isomer], 116.21 [116.30minor isomer], 116.16 [116.13 minor isomer], 67.33 [67.42 minor isomer], 48.31, 37.77, 21.34 [19.94 minor isomer]. LC-MS (ESI+) *m/z* 368.16 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{22}N_3O_4$ $(M+H)^+$ 368.1605, found 368.1615.

***N*-Isopropyl-*N*-((3-(pyridin-2-yl)-1,2,4-oxadizaol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide (11w)**: This compound was prepared from **5a** (43 mg, 0.23 mmol) and **10e** (42 mg, 0.19 mmol) using triethylamine (39 mg, 0.38 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11w** (52 mg, 75%) as a white solid. mp 125.7-126.9 °C; HPLC 96.2% (t_R = 15.7 min, 40% CH_3CN in 0.1% TFA water 30 min); The ^{1}H NMR showed 3:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 4.7 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.82 (td, J = 7.8, 1.7 Hz, 1H), 7.42 (appdd, J = 6.7, 4.9 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H, [7.03 minor isomer]), 6.87 (d, J = 8.5 Hz, 2H, [6.80 minor isomer]), 4.79 (s, 2H, [4.93 minor isomer]), 4.77 (s, 2H, [4.81 minor isomer]), 4.46-4.38 (m, 1H), 2.29 (s, 3H, [2.24 minor isomer]), 1.29 (d, J = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.38, 168.57, 168.37, 155.96, 150.60 [150.73 minor isomer], 146.46, 137.19, 131.25, 130.30, 125.72, 123.51, 114.66, 67.98 [68.99 minor isomer], 49.01, 37.24, 21.44 [19.95 minor isomer], 20.72; LC-MS (ESI+) *m/z* 367.17 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{23}N_4O_3$ $(M+H)^+$ 367.1765, found 367.1774.

***N*-Isopropyl-*N*-((3-(pyridin-3-yl)-1,2,4-oxadizaol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide 11x**: This compound was prepared from **5a** (51 mg, 0.28 mmol) and **10f** (50 mg, 0.23 mmol) using triethylamine (47 mg, 0.46 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11x** (69 mg, 82%) as a white solid. mp 126.5-128.3 °C. HPLC 98.3% (t_R = 10.6 min, 35% CH_3CN in 0.1% TFA water 30 min);

The ^{1}H NMR showed 4:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.72 (appdd, *J* = 4.8, 1.2 Hz, 1H, [8.75 minor isomer]), 8.27 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.0, 4.9 Hz, 1H, [7.43 minor isomer]), 7.08 (d, *J* = 8.6 Hz, 2H, [7.02 minor isomer]), 6.86 (d, *J* = 8.5 Hz, 2H, [6.77 minor isomer]), 4.78 (s, 2H, [4.88 minor isomer]), 4.70 (s, 2H, [4.78 minor isomer]), 4.49-4.39 (m, 1H), 2.27 (s, 3H, [2.22 minor isomer]), 1.31 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.23, 168.60, 166.65, 155.94 [155.72 minor isomer], 152.24 [152.52 minor isomer], 148.92 [148.87 minor isomer], 134.97, 131.30, 130.28, 123.79 [123.86 minor isomer], 123.20, 114.64 [114.53 minor isomer], 67.91 [69.02 minor isomer], 48.99 [48.96 minor isomer], 37.27 [38.66 minor isomer], 21.52 [19.99 minor isomer], 20.72; LC-MS (ESI+) *m/z* 367.17 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{23}N_4O_3$ $(M+H)^+$ 367.1765, found 367.1774.

***N*-Isopropyl-*N*-((3-(pyridin-4-yl)-1,2,4-oxadizaol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide (11y)**: This compound was prepared from **5a** (21 mg, 0.12 mmol) and **10g** (22 mg, 0.10 mmol) using triethylamine (19 mg, 0.19 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11y** (29 mg, 78%) as a white solid. mp 150.6-151.7 °C. HPLC 96.6% (t_R = 14.7 min, 30% CH_3CN in 0.1% TFA water 30 min); The ^{1}H NMR showed 3:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.8 Hz, 2H), 7.87 (d, *J* = 4.6 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H, [7.02 minor isomer]), 6.87 (d, *J* = 8.5 Hz, 2H, [6.76 minor isomer]), 4.80 (s, 2H, [4.90 minor isomer]), 4.70 (s, 2H, [4.79 minor isomer]), 4.51-4.40 (m, 1H), 2.29 (s, 3H, [2.23 minor isomer]), 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.57, 168.65, 167.05, 155.94, 150.79 [150.91 minor isomer], 134.35, 131.30, 130.29, 121.57, 114.64 [114.50 minor isomer], 67.91 [69.08 minor isomer], 49.01[48.97 minor isomer], 37.27 [38.61 minor isomer], 21.52 [19.98 minor isomer], 20.72; LC-MS (ESI+) *m/z* 367.18 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{23}N_4O_3$ $(M+H)^+$ 367.1765, found 367.1780.

***N*-Isopropyl-2-(6-methylpyridin-3-yloxy)-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11z)**: A solution of 6-methyl-3-hydroxypyridin (80 mg, 0.73 mmol), *N*-isopropyl-2-chloro-*N*-((3-phenyl-1,2,4-

oxodiazol-5-yl)methyl)acetamide (**15**) (214 mg, 0.73 mmol) and potassium carbonate (510 mg, 3.67 mmol) in acetonitrile (25 ml) were refluxed for 14 h. The solvent was evaporated; and the residue was dissolved in ethyl acetate (20 ml), washed with water (2 x 20 ml). The organic phase was dried ($MgSO_4$), evaporated and the crude compound obtained was purified by SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford **11z** as (193 mg, 72%) a white solid. mp 130.3-132.2 °C. HPLC 97.26% (t_R = 8.3 min, 30% CH_3CN in 0.1% TFA water 30 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 2.9 Hz, 1H, [8.26 minor isomer]), 8.00 (dd, *J* = 7.9, 1.6 Hz, 1H, [8.04 minor isomer]), 7.52-7.44 (m, 4H), 7.20 (d, *J* = 8.5 Hz, 1H), 4.93 (s, 2H, [5.01 minor isomer]), 4.89-4.80 (m, 1H), 4.72 (s, 2H, [4.78 minor isomer]), 4.30-4.23 (m, 1H, [4.89-4.80 minor isomer]), 2.63 (s, 3H), 1.35 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.25, 168.58, 166.98, 153.61, 149.71, 131.50 [131.94 minor isomer], 129.26, 129.04, 127.69, 126.73, 125.54, 67.68, 48.90 [47.05 minor isomer], 37.21, 21.61, 21.51 [19.99 minor isomer]; LC-MS (ESI+) *m/z* 367.18 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{23}N_4O_3(M+H)^+$ 367.1765, found 367.1759.

2-(4-Ethylphenoxy)-*N*-isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11aa): This compound was prepared from **5j** (93 mg, 0.47 mmol) and **10d** (85 mg, 0.39 mmol) using triethylamine (79 mg, 0.78 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11aa** (123 mg, 83%) as a white solid. mp 106.7-109.2 °C. HPLC 95.5% (t_R = 11.5 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^{1}H NMR showed 2:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.55-7.38 (m, 3H), 7.11 (d, *J* = 8.4 Hz, 2H, [7.07 minor isomer]), 6.90 (d, *J* = 8.5 Hz, 2H, [6.84 minor isomer]), 4.79 (s, 2H, [4.86 minor isomer]), 4.71 (s, 2H, [4.83 minor isomer]), 4.46-4.40 (m, 1H), 2.59 (q, *J* = 7.5 Hz, 2H, [2.55 minor isomer]), 1.31 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer partially overlapped]), 1.20 (t, *J* = 7.6 Hz, 3H, partially overlapped with the doublet at 1.16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.62 [176.77 minor isomer], 168.56 [168.66 minor isomer], 168.55 [168.65 minor isomer], 156.14 [155.94 minor isomer], 137.73, 131.38 [δ 131.75 minor isomer], 129.11, 128.98, 127.73, 126.90, 114.72 [114.65 minor isomer], 67.97 [68.74 minor isomer], 48.98, 37.23 [38.44 minor isomer], 28.21, 21.48 [19.99 minor isomer], 16.01:

LC-MS (ESI+) *m/z* 380.21 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{26}N_3O_3$ $(M+H)^+$ 380.1969, found 380.1964.

2-(4-Ethylphenoxy)-*N*-isopropyl-*N*-((3-pyridin-3-yl)-1,2,4-oxadiazol-5-yl)methylacetamide (11ab): This compound was prepared from **5j** (50 mg, 0.25 mmol) and **10f** (46 mg, 0.21 mmol) using triethylamine (43 mg, 0.42 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ab** (65 mg, 81%) as a white solid. mp 104.4-106.3 °C. HPLC 95.7% (t_R = 5.3 min, 50% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 4:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.67 (brs, 1H), 8.23 (d, *J* = 7.7 Hz, 1H), 7.42-7.29 (broad m, 1H), 7.04 (d, *J* = 8.5 Hz, 2H, [6.98 minor isomer]), 6.82 (d, *J* = 8.5 Hz, 2H, [6.73 minor isomer]), 4.72 (s, 2H, [4.82 minor isomer]), 4.64 (s, 2H, [4.74 minor isomer]), 4.40-4.32 (m, 1H), 2.51 (q, *J* = 7.6 Hz, 2H partially overlapped, [2.47 minor isomer]), 1.25 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]), 1.11 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.26, [177.46 minor isomer], 168.59, [168.65 minor isomer], 166.65, [166.87 minor isomer], 156.09, 152.11, 148.82, 137.79, 135.02, 129.10, 114.68 [114.57 minor isomer], 67.97 [69.01 minor isomer], 49.00 [46.98 minor isomer], 37.29 [38.61 minor isomer], 28.19 [29.93 minor isomer], 21.49 [19.99 minor isomer], 16.00; LC-MS (ESI+) *m/z* 381.19 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{25}N_4O_3(M+H)^+$ 381.1921, found 381.1912.

***N*-Isopropyl-2-phenoxy-*N*-((3-(pyridine-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11ac)**: This compound was prepared from **5c** (55 mg, 0.32 mmol) and **10f** (59 mg, 0.27 mmol) using triethylamine (55 mg, 0.54 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ac** (81 mg, 85%) as a white solid. mp 83.0-85.5 °C. HPLC 97.5 % (t_R = 11.4 min, 30% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 4:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.79 (brs, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.45 (m, 1H), 7.33-7.22 (m, 2H), 7.02-6.87 (m, 3H), 4.82 (s, 2H, [4.89 minor isomer]), 4.71 (s, 2H, [4.84 minor isomer]), 4.51-4.37 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.21 [177.41 minor isomer]), 168.43, 166.62, [166.87 minor isomer], 158.01

[157.83 minor isomer], 152.20 [152.53 minor isomer], 148.85, 134.99, 129.85, 123.83, 123.19, 121.98, 114.81 [114.71 minor isomer], 67.65 [68.66 minor isomer], 48.97 [47.08 minor isomer], 37.28 [38.61 minor isomer], 21.49 [19.97 minor isomer]; LC-MS (ESI+) *m/z* 353.16 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{19}H_{21}N_4O_3(M+H)^+$ 353.1608, found 353.1614.

***N*-Isopropyl-2-(4-propylphenoxy)-*N*-((3-pyridin-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11ad)**: This compound was prepared from **5k** (84 mg, 0.40 mmol) and **10f** (72 mg, 0.33 mmol) using triethylamine (67 mg, 0.66 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ad** (109 mg, 84%) as a white solid. mp 103.2-105.5 °C. HPLC 100% (t_R = 7.58 min, 50% CH_3CN in 0.1% TFA water 20 min); The ^1H NMR showed 4:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.78-8.70 (m, 1H), 8.29 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.42 (appdd, *J* = 8.0, 4.9 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H, [7.03 minor isomer]), 6.87 (d, *J* = 8.6 Hz, 2H, [6.79 minor isomer]), 4.78 (s, 1H), 4.79 (s, 2H, [4.89 minor isomer]), 4.70 (s, 2H, [4.81 minor isomer shown]), 4.48-4.38 (m, 1H), 2.51 (t, *J* = 7.7 Hz, 2H, [2.47 minor isomer]), 1.63-1.52 (m, 2H), 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]), 0.91 (t, *J* = 7.3 Hz, 3H, [0.89 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.06 [177.24 minor isomer], 168.34 [168.40 minor isomer], 166.33 [166.57 minor isomer], 155.86 [155.62 minor isomer], 151.74 [152.16 minor isomer], 148.44 [148.50 minor isomer]), 135.98 [136.05 minor isomer], 134.93[134.83 minor isomer], 129.45 [129.41 minor isomer], 123.66 [123.09 minor isomer], 114.34 [114.24 minor isomer], 67.62 [68.73 minor isomer], 48.74 [46.81 minor isomer], 37.11 [38.41 minor isomer], 37.06, 24.69 [23.47 minor isomer], 21.26 [19.74 minor isomer], 13.78; LC-MS (ESI+) *m/z* 395.21 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{27}N_4O_3$ $(M+H)^+$ 395.2078, found 395.2080.

2-(4-Butylphenoxy)-*N*-isopropyl-*N*-((3-(pyridine-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11ae): This compound was prepared from **5l** (76 mg, 0.34 mmol) and **10f** (61 mg, 0.28 mmol) using triethylamine (57 mg, 0.56 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ae** (94 mg, 82%) as a

white solid. mp 94.5-95.2 °C. HPLC 98.13% (t_R = 10.2 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 4:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H, [9.26 minor isomer overlapped]), 8.80-8.73 (m, 1H), 8.46 (d, *J* = 7.7 Hz, 1H, [8.33 minor isomer]), 7.56-7.52 (m, 1H [7.50 minor isomer]), 7.09 (d, *J* = 8.6 Hz, 2H, [7.02 minor isomer]), 6.87 (d, *J* = 8.6 Hz, 2H, [6.78 minor isomer]), 4.78 (s, 2H, [4.90 minor isomer]), 4.70 (s, 2H, [4.80 minor isomer]), 4.47-4.40 (m, 1H), 2.54 (t, *J* = 7.3 Hz, 2H, [2.48 minor isomer]), 1.59-1.46 (m, 2H), 1.36-1.29 [m, 8H and around 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.23, 168.58, 166.66, 156.07, 152.24 [152.54 minor isomer]), 148.93, 136.46, 134.97, 129.64, 123.80, 123.21, 114.59 [114.50 minor isomer]), 67.91, 48.97, 37.29, 34.95, 34.03, 22.53, 21.50 [19.99 minor isomer], 14.20; LC-MS (ESI+) *m/z* 409.23 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{23}H_{29}N_4O_3(M+H)^+$ 409.2234, found 409.2238.

***N*-Isopropyl-2-(4-pentylphenoxy)-*N*-((3-pyridin-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11af)**: This compound was prepared from **5m** (78 mg, 0.32 mmol) and **10f** (59 mg, 0.27 mmol) using triethylamine (55 mg, 0.54 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11af** (95 mg, 83%) as a white solid. mp 93.0-95.9 °C. HPLC 96.5 % (t_R = 17.1 min, 70% MeOH in 0.1% TFA water 20 min); ^1H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H, [9.24 minor isomer]), 8.67 (appdd, *J* = 4.9, 1.6 Hz, 1H), 8.24-8.22 (m, 1H, [8.30 minor isomer]), 7.37-7.28 32 (m, 1H), 7.02 (d, *J* = 8.4 Hz, 2H, [6.95 minor isomer]), 6.81 (d, *J* = 8.4 Hz, 2H, [6.72 minor isomer]), 4.72 (s, 2H, [4.83 minor isomer]), 4.64 (s, 2H, [4.74 minor isomer]), 4.40-4.33 (m, 1H), 2.46 (t, *J* = 7.8 Hz, 2H, partially overlapped [2.41 minor isomer partially overlapped]), 1.52-1.41 (m, 2H), 1.36-1.13 [broad m, 10H, and around 1.25 (d, *J* = 6.8 Hz, 6H)]), 0.81 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.29 [177.50 minor isomer], 168.62, [168.67 minor isomer], 166.56 [166.79 minor isomer], 156.07 [155.82 minor isomer], 152.19, 151.88 [152.19 minor isomer], 148.60, 136.51 [136.33 minor isomer], 135.25, 129.63 [129.59 minor isomer], 123.97, 114.60 [114.50 minor isomer], 67.90 [69.04 minor isomer], 49.00 [47.08 minor isomer], 37.30 [38.65 minor isomer], 35.24, 31.69, 31.57 [29.93

minor], 22.77, 21.51 [19.99 minor isomer], 14.29; LC-MS (ESI+) *m/z* 423.24 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{24}H_{31}N_4O_3(M+H)^+$ 423.2391, found 423.2393.

2-(4-Hexylphenoxy)-*N*-isopropyl-*N*-((3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11ag): This compound was prepared from **5n** (98 mg, 0.38 mmol) and **10f** (70 mg, 0.32 mmol) using triethylamine (65 mg, 0.64 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ag** (122 mg, 87%) as a white solid. mp 94.4-96.1 °C. HPLC 93.8 % (t_R = 7.7 min, 80% MeOH in 0.1% TFA water 20 min); The ^{1}H NMR showed 4:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.75 (brs, 1H), 8.33 (appd, *J* = 7.9 Hz, 1H, [8.29 minor isomer]), 7.50-7.43 (m, 1H), 7.09 (d, *J* = 8.6 Hz, 2H, [7.03 minor isomer]), 7.87 (d, *J* = 8.7 Hz, 2H, [6.79 minor isomer]), 4.79 (s, 2H, [4.90 minor isomer]), 4.71 (s, 2H, [4.81 minor isomer]), 4.49-4.36 (m, 1H), 2.53 (t, *J* = 7.8 Hz, 2H partially overlapped, [2.48 minor isomer partially overlapped]), 1.59-1.51 (m, 2H), 1.33-1.27 (m, 12H and around 1.32 [d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]), 0.91-0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.32 [177.51 minor isomer], 168.58, [168.64 minor isomer], 166.54, 156.07 [155.82 minor isomer], 151.91 [152.38 minor isomer], 148.59 [148.68 minor isomer], 136.48 [136.54 minor isomer], 135.25 [135.13 minor isomer], 129.62 [129.58 minor isomer], 123.99 [123.40 minor isomer], 114.59 [114.50 minor isomer], 67.86 [68.96 minor isomer], 48.97 [47.05 minor isomer], 37.30 [38.64 minor isomer], 35.27 [35.22 minor isomer], 31.96, 31.85, 29.17, 22.84, 21.49 [19.97 minor isomer], 14.35; LC-MS (ESI+) *m/z* 437.25 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{25}H_{33}N_4O_3(M+H)^+$ 437.2547, found 437.2548.

***N*-Isopropyl-2-(4-cyclohexylphenoxy)-*N*-((3-pyridin-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11ah)**: This compound was prepared from **5o** (79 mg, 0.31 mmol) and **10f** (57 mg, 0.26 mmol) using triethylamine (53 mg, 0.52 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ah** (88 mg, 78%) as a sticky solid. HPLC 97.00 % (t_R = 17.0 min, 70% MeOH in 0.1% TFA water 30 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.78-8.72 (m, 1H), 8.30 (appdt, *J* = 8.0, 2.0 Hz, 1H), 7.42-7.39 (m,

1H), 7.12 (d, *J* = 8.7 Hz, 2H, [7.06 minor isomer]), 6.88 (d, *J* = 8.7 Hz, 2H, [6.80 minor isomer]), 4.78 (s, 2H, [4.89 minor isomer]), 4.71 (s, 2H, [4.81 minor isomer]), 4.46-4.39 (m, 1H), 2.48-2.38 (m, 2H), 1.83-1.71 (m, 4H), 1.38-1.24 (brm, 11H, and around 1.32 [d, *J* = 6.6 Hz, 6H, [1.17 (minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.26 [177.47 minor isomer], 168.57, 166.66 [166.88 minor isomer], 156.11 [155.86 minor isomer], 152.20 [152.49 minor isomer], 148.91 [148.86 minor isomer],141.82, 141.75, 134.96, 128.03, 123.86, 114.60 [114.50 minor isomer], 67.88 [69.03 minor isomer], 48.98 [47.07 minor isomer], 43.88, 37.30 [38.66 minor isomer], 34.85, 27.13 [29.93 minor isomer], 26.36, 21.51 [19.99 minor isomer]; LC-MS (ESI+) *m/z* 435.24 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{25}H_{31}N_4O_3(M+H)^+$ 435.2391, found 435.2395.

***N*-Isopropyl-2-(4-isopropylphenoxy)-*N*-((3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11ai)**: This compound was prepared from **5p** (61mg, 0.29 mmol) and **10f** (52 mg, 0.24 mmol) using triethylamine (49 mg, 0.48 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ai** (77 mg, 81%) as a sticky white solid. HPLC 99.1% (t_R = 6.7 min, 50% CH_3CN in 0.1% TFA water 20 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.77-8.70 (m, 1H), 8.30 (dt, *J* = 8.0,1.8 Hz, 1H), 8.40 (appdd, *J* = 7.7, 5.0 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H, [7.08 minor isomer]), 6.89 (d, *J* = 8.6 Hz, 2H, [6.81 minor isomer]), 4.79 (s, 2H, [4.89 minor isomer]), 4.71 (s, 2H, [4.81 minor isomer]), 4.45-4.39 (m, 1H), 2.88-2.78 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 6H, [1.17 minor isomer]), 1.20 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.26 [177.47 minor isomer], 168.56, 166.65 [166.88 minor isomer], 156.11 [155.88 minor isomer], 152.22 [152.52 minor isomer], 148.91, 142.44, 134.96, 127.66, 123.81 [123.91 minor isomer], 123.25, 114.64 [114.53 minor isomer], 67.89 [69.01 minor isomer], 48.98 [47.06 minor isomer], 37.30 [38.65 minor isomer], 33.49, 24.37, 21.50 [19.99 minor isomer]; LC-MS (ESI+) *m/z* 395.20 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{27}N_4O_3(M+H)^+$ 395.2078, found 395.2074.

***N*-Isopropyl-2-(4-*tert*-butylphenoxy)-*N*-((3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11aj)**: This compound was prepared from **5r** (63 mg, 0.28 mmol) and **10f** (50 mg, 0.23 mmol) using triethylamine

(47 mg, 0.46 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11aj** (78 mg, 83%) as a sticky colorless solid. HPLC 97.96% (t_R = 9.1 min, 50% CH_3CN in 0.1% TFA water 20 min); ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.73 (brs, 1H), 8.20 (appd, *J* = 8.0 Hz, 1H), 7.40 (appdd, *J* = 7.7, 4.9 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H, [7.24 minor isomer shown]), 6.89 (d, *J* = 8.7 Hz, 2H, [6.81 minor isomer]), 4.78 (s, 2H, [4.89 minor isomer]), 4.71 (s, 2H, [4.83 minor isomer]), 4.43-4.37 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.27 [177.48 minor isomer], 168.62, [168.53 minor isomer], 166.64 [166.86 minor isomer], 155.76 [155.53 minor isomer], 152.23 [152.52 minor isomer], 148.89, 144.69, 134.97, 126.64 [126.60 minor isomer], 123.87, 123.26, 114.26 [114.15 minor isomer], 67.75 [68.86 minor isomer], 48.98 [47.00 minor isomer], 37.32 [38.62 minor isomer], 34.35, 31.70 [31.67 minor isomer], 21.52 [20.01 minor isomer]; LC-MS (ESI+) *m/z* 409.22 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{23}H_{29}N_4O_3(M+H)^+$ 409.2234, found 409.2233.

***N*-Isopropyl-2-(4-isobutylphenoxy)-*N*-((3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11ak)**: This compound was prepared from **5q** (74 mg, 0.32 mmol) and **10f** (59 mg, 0.27 mmol mmol) using triethylamine (55 mg, 0.54 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ak** (97 mg, 88%) as a white solid. mp 121.5-123.7 °C. HPLC 98.3% (t_R = 10.8 min, 50% CH_3CN in 0.1% TFA water 20 min); ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.74 (brs, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.41(brm, 1H), 7.05 (d, *J* = 8.6 Hz, 2H, [7.00 minor isomer]), 6.87 (d, *J* = 8.6 Hz, 2H, [6.79 minor isomer]), 4.79 (s, 2H, [4.90 minor isomer]), 4.71 (s, 2H, [4.81 minor isomer]), 4.47-4.40 (m, 1H), 2.40 (d, *J* = 7.2 Hz, 2H, partially overlapped, [2.36 minor isomer partially overlapped]), 1.85-1.73 (m, 1H), 1.31 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]), 0.87 (d, *J* = 6.6 Hz, 6H, [0.85 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.24, 168.59, 166.72, 156.15 [155.92 minor isomer], 152.14, 148.89, 135.26 [135.34 minor isomer], 134.93, 130.35, 114.46 [114.37 minor isomer], 67.93 [69.06 minor isomer], 48.98 [47.06 minor isomer], 44.73, 37.30 [38.65 minor isomer], 30.53 [30.49 minor isomer], 22.52, 21.51 [19.98 minor isomer]; LC-MS

(ESI+) *m/z* 409.23 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{23}H_{29}N_4O_3(M+H)^+$ 409.2234, found 409.2231.

***N*-Isopropyl-2-(4-propylphenoxy)-*N*-((3-(pyrimidin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11al)**: This compound was prepared from **5k** (46 mg, 0.22 mmol) and **10h** (40 mg, 0.18 mmol) using triethylamine (36 mg, 0.36 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11al** (58 mg, 81%) as a white solid. mp 92.7-94.0 °C. HPLC 97.2 % (t_R = 12.1 min, 50% CH_3CN in 0.1% TFA water 20 min); ^1H NMR (400 MHz, $CDCl_3$) δ 9.39-9.28 (m, 3H), 7.09 (d, *J* = 8.5 Hz, 2H, [7.01 minor isomer]), 6.87 (d, *J* = 8.6 Hz, 2H, [6.75 minor isomer]), 4.78 (s, 2H, [4.92 minor isomer]), 4.70 (s, 2H), 4.49-4.41 (m, 1H), 2.52 (t, *J* = 7.6 Hz, 2H, [2.45 minor isomer]), 1.64-1.47 (m, 2H), 1.32 (d, *J* = 6.8 Hz, 6H, [1.17 minor isomer]), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.87, 168.67, 164.52, 160.62 [160.82 minor isomer], 155.72 [156.04 minor isomer], 136.33, 129.71, 121.78, 114.54 [114.40 minor isomer], 67.83, 49.03 [49.00 minor isomer], 37.34 [38.87 minor isomer], 24.92, 21.53 [20.05 minor isomer],14.02; LC-MS (ESI+) *m/z* 396.20 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{26}N_5O_3(M+H)^+$ 396.2030, found 396.2031.

***N*-Isopropyl-2-(4-propylphenoxy)-*N*-((3-(pyrazin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11am)**: This compound was prepared from **5k** (77 mg, 0.36 mmol) and **10j** (66 mg, 0.30 mmol) using triethylamine (61 mg, 0.60 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11am** (101 mg, 85%) as a colorless sticky solid. HPLC 97.3 % (t_R = 11.1 min, 50% MeOH in 0.1% TFA water 30 min); ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (appd, *J* = 1.4 Hz, 1H, [9.26 minor isomer]), 8.73-8.70 (m, 2H), 7.08 (d, *J* = 8.6 Hz, 2H, [7.01 minor isomer]), 6.86 (d, *J* = 8.6 Hz, 2H, [6.77 minor isomer]), 4.78 (s, 2H, [4.94 minor isomer]), 4.76 (s, 2H, [4.79 minor isomer]), 4.46-4.36 (m, 1H), 2.50 (t, *J* = 7.8 Hz, 2H, [2.45 minor isomer]), 1.63-1.51 (m, 2H), 1.30 (d, *J* = 6.6 Hz, 6H, [1.15 minor isomer]), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.00, 168.64, 166.65 [166.86 minor isomer], 156.08 [155.82 minor isomer], 146.96, [146.67 minor isomer], 145.02 [145.09 minor isomer], 144.62, 142.47, 136.29, 129.72 [129.67 minor

isomer], 114.58 [114.50 minor isomer], 67.92 [69.16 minor isomer], 49.02 [47.08 minor isomer], 37.35 [38.85 minor isomer], 24.92, 21.49 [19.96 minor isomer], 14.02; LC-MS (ESI+) *m/z* 396.19 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{26}N_5O_3(M+H)^+$ 396.2030, found 396.2028.

2(-4-Butylphenoxy)-*N*-isopropyl-*N*-((3-(pyrazin-2-yl)-1,2,4-oxadiazol-5-yl)methylecetamide (11an): This compound was prepared from **5l** (54 mg, 0.24 mmol) and **10j** (44 mg, 0.20 mmol) using triethylamine (41 mg, 0.40 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11an** (64 mg, 78%) as a yellow/green sticky solid. HPLC 97.97 % (t_R = 9.7 min, 70% MeOH in 0.1% TFA water 30 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 1.4 Hz, 1H), 9.27 (brs, 1H), 8.74-8.71 (m, 1H), 7.09 (d, *J* = 8.6 Hz, 2H, [7.02 minor isomer]), 6.87 (d, *J* = 8.6 Hz, 2H, [6.78 minor isomer]), 4.80 (s, 2H, [4.95 minor isomer]), 4.76 (s, 2H, [4.80 minor isomer]), 4.48-4.39 (m, 1H), 2.53 (t, *J* = 7.7 Hz, 2H, [2.47 minor isomer])), 1.63-1.48 (m, 3H), 1.37-1.14 [m, 10H and around 1.30 (d, *J* = 6.7 Hz, 6H)] 1.16 minor isomer]), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.00, 168.64, 166.64, 156.05 [155.78 minor isomer], 146.65 [146.94 minor isomer], 145.00 [145.08 minor isomer], 144.61, 142.47 [142.08 minor isomer], 136.49 [136.57 minor isomer], 129.65 [129.80 minor isomer], 114.60 [114.53 minor isomer], 67.93 [69.17 minor isomer], 49.01 [47.13 minor isomer], 37.34 [38.85 minor isomer], 34.94, 34.00, 22.52 [21.11 minor isomer], 21.47 [19.95 minor isomer shown], 14.17; LC-MS (ESI+) *m/z* 410.222 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{28}N_5O_3(M+H)^+$ 410.2187, found 410.2185.

***N*-Isopropyl-2-(4-propylphenoxy)-*N*-((3-(pyrimidin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acetamide (11ao)**: This compound was prepared from **5k** (46 mg, 0.22 mmol) and **10i** (40 mg, 0.18 mmol) using triethylamine (36 mg, 0.36 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ao** (63 mg, 88%) as a colorless sticky solid; HPLC 97.9 % (t_R = 7.1 min, 50% CH_3CN in 0.1% TFA water 20 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 4.9 Hz, 2H), 7.45 (t, *J* = 4.9 Hz, 1H, [7.48 minor isomer]), 7.10 (d, *J* = 8.6 Hz, 2H, [7.04 minor isomer]), 6.88 (d, *J* = 8.6 Hz, 2H, [6.81 minor isomer]), 4.83 (s, 2H, [4.99 minor isomer]),

4.80 (s, 2H, [4.81 minor isomer]), 4.44-4.34 (m, 1H), 2.52 (t, J = 7.7 Hz, 2H, partially overlapped [2.48 minor isomer, partially overlapped]), 1.66-1.51 (m, 2H, [1.46-1.38 minor isomer]), 1.28 (d, J = 6.6 Hz, 2H, [1.14 minor isomer]), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.04, 168.62 [167.47 minor isomer], 167.85, 158.19 [158.27 minor isomer], 156.27, 156.09, 136.24, 129.73, 122.37, 114.59, 67.97 [69.02 minor isomer], 49.02 [47.00 minor isomer], 37.36 [38.85 minor isomer], 37.34, 24.93, 21.42 [19.90 minor isomer], 14.02; LC-MS (ESI+) *m/z* 396.19 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{26}N_5O_3(M+H)^+$ 396.2030, found 396.2025.

***N*-Isopropyl-2-(4-propylphenoxy)-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)acetamide (11ap):** This compound was prepared from **5k** (140 mg, 0.66 mmol) and **10a** (127 mg, 0.55 mmol) using triethylamine (111 mg, 1.10 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ap** (195 mg, 87%) as a white solid. mp 121.7-122.3 °C. HPLC 99.3 % (t_R = 11.1 min, 45% MeOH in 0.1% TFA water 30 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 2H), 7.29-7.20 (m, 2H), 7.07 (d, J = 8.6 Hz, 2H, [7.03 minor isomer]), 6.87 (d, J = 8.6 Hz, 2H, [6.82 minor isomer]), 4.77 (s, 2H, [4.83 minor isomer]), 4.69 (s, 2H, [4.82 minor isomer]), 4.45-4.34 (m, 1H), 2.54-2.46 (m, 2H), 2.39 (s, 3H, [2.40 minor isomer]), 1.60-1.50 (m, 2H), 1.29 (d, J = 6.6 Hz, 6H, [1.13 minor isomer]), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.43 [δ 176.57 minor isomer]), 168.56 [168.80 minor isomer]), 168.50, 156.18 [155.99 minor isomer]), 141.66 [142.14 minor isomer]), 136.16, 129.69 [129.83 minor isomer]), 127.65, 124.09 [123.58 minor isomer]), 114.64 [114.59 minor isomer]), 67.99 [68.74 minor isomer]), 48.94 [46.89 minor isomer]), 37.37 [38.41 minor isomer]), 37.22, 24.92, 21.82, 21.47 [19.98 minor isomer]), 14.03; LC-MS (ESI+) *m/z* 408.22 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{24}H_{30}N_3O_3(M+H)^+$ 408.2282, found 408.2279.

***tert*-Butyl-4-(2-(isopropyl((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)amino)-2-oxoethoxy)benzoate (11aq)**: A solution of *tert*-Butyl-4-hydroxybenzoate (**27**, *see supporting information for* **27**) (27 mg, 0.14 mmol), **15** (41 mg, 0.14 mmol) and potassium carbonate (97 mg, 0.70 mmol) in acetonitrile (20 ml) was heated under reflux overnight. Acetonitile was evaporated and the residue was dissolved in ethyl acetate (20 ml) and

washed with water (20 ml x 2). The organic phase was dried ($MgSO_4$) and the product obtained was purified by SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11aq** (51 mg, 80% as a white solid). mp 143.0-144.4 °C. HPLC 99.7% (t_R = 14.1 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.8 Hz, 2H, [8.01 minor isomer]), 7.94 (d, *J* = 8.8 Hz, 2H, [7.88 minor isomer]), 7.50-7.38 (m, 3H), 6.96 (d, *J* = 8.9 Hz, 2H, overlapped, [6.93 minor isomer, overlapped]), 4.86 (s, 2H, [4.91 minor isomer]), 4.69 (s, 2H, [4.78 minor isomer]), 4.41-4.31 (m, 1H), 1.55 (s, 9H), 1.29 (d, *J* = 6.6 Hz, 6H, [1.14 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) 176.14 [176.24 minor isomer], 168.32, 167.60 [167.68 minor isomer], 165.40 [165.65 minor isomer],161.11 [161.06 minor isomer], 159.73, 131.60 [131.64 minor isomer], 131.51 [131.45 minor isomer],128.77 [128.96 minor isomer], 127.45 [126.50 minor isomer], 125.51 [125.46 minor isomer], 124.25, 114.96, 114.11 [114.06 minor isomer], 80.74 [80.51 minor isomer], 67.30 [67.84 minor isomer], 48.78 (46.83 minor isomer), 36.98 [38.22 minor isomer], 28.24 [29.70 minor isomer], 21.24 [19.75 minor isomer]; LC-MS (ESI+) *m/z* 469.26 $(M+NH_4)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{25}H_{30}N_3O_5$ $(M+H)^+$ 452.2180, found 452.2191.

2-(4-Fluorophenoxy)-*N*-isopropyl-*N*-((3-(pyridin-3-yl)1,2,4-oxadiazol-5-yl)methyl)acetamide (11ar): This compound was prepared from **5f** (93 mg, 0.49 mmol) and **10f** (90 mg, 0.41 mmol) using triethylamine (83 mg, 0.82 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11ar** (132 mg, 87%) as a white solid. mp 83.8-84.6 °C. HPLC 100% (t_R = 10.8 min, 30% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 4.5:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.73 (d, *J* = 4.1 Hz, 1H, [8.76 minor isomer]), 8.25 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.40 (dd, *J* = 7.9, 4.9 Hz, 1H, partially overlapped, [7.43 minor isomer]), 7.05-6.83 (m, 4H, [6.88-6.78 minor isomer]), 4.79 (s, 2H, [4.81 minor isomer]), 4.71 (s, 2H, [4.86 minor isomer]), 4.47-4.35 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 6H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) 176.97 [177.10 minor isomer], 168.06, 166.25 [166.62 minor isomer], 157. 72 (d, *J* = 239 Hz), 153.93 (d, *J* = 2.06 Hz), 151.39 [152.19 minor isomer], 148.07 [148.41 minor isomer],

135.18 [134.86 minor isomer], 123.80, 123.16, 116.03 (d, J = 23 Hz), 115.75 (d, J = 8 Hz), 67.91 [68.67 minor isomer], 48.72 [46.89 minor isomer], 37.03 [38.34 minor isomer], 21.26 [19.75 minor isomer]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.60 [-122.53 minor isomer]; LC-MS (ESI+) *m/z* 371.15 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{19}H_{20}FN_4O_3$ $(M+H)^+$ 371.1514, found 371.1517.

2-(4-Chlorophenoxy)-*N*-isopropyl-*N*-((3-(pyridin-3-yl)1,2,4-oxadiazol-5-yl)methyl)acetamide (11as): This compound was prepared from **5d** (66 mg, 0.32 mmol) and **10f** (59 mg, 0.27 mmol) using triethylamine (55 mg, 0.54 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **11as** (91 mg, 87%) as a white solid. mp 118.1-119.9 °C. HPLC 99.0% (t_R = 10.4 min, 35% CH_3CN in 0.1% TFA water 30 min); The ^{1}H NMR showed 4:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.73 (dd, J = 4.8, 1.4 Hz, 1H, overlapped [8.76 minor isomer, overlapped]), 8.24 (dt, J = 7.9, 1.9 Hz, 1H), 7.41 (dd, J = 8.0, 4.9 Hz, 1H), 7.22 (d, J = 9.0 Hz, 2H, [7.18 minor isomer]), 6.90 (d, J = 9.0 Hz, 2H, [6.83 minor isomer]), 4.80 (s, 2H, [4.85minor isomer]), 4.70 (s, 2H, [4.83 minor isomer]), 4.48-4.31 (m, 1H), 1.32 (d, J = 6.6 Hz, 6H, [1.17 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) 176.74, 167.82, 166.35, 156.39, 152.39 [152.03 minor isomer], 148.59 [148.55 minor isomer], 134.59, 129.51 [129.47 minor isomer], 126.68, 123.63 [122.89 minor isomer], 115.89 [115.83 minor isomer], 67.59 [68.57 minor isomer], 48.75 [46.93 minor isomer], 37.03 [38.38 minor isomer], 21.24 [18.67 minor isomer]; LC-MS (ESI+) *m/z* 387.03 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{19}H_{20}ClN_4O_3$ $(M+H)^+$ 387.1218, found 387.1212.

***N*-Isobutyl-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide (12a)**: This compound was prepared from **5a** (95 mg, 0.52 mmol) and **10m** (106 mg, 0.43 mmol) using triethylamine (87 mg, 0.86 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **12a** (147 mg, 87%) as a white solid. mp 78.4-79.8 °C. HPLC 99.1 % (t_R = 11.8 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^{1}H NMR showed approximately 2:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 2H), 7.30-7.25 (m, 2H), 7.08 (d, J = 8.3 Hz, 2H, [7.04 minor isomer]), 6.86 (d, J = 8.6 Hz, 2H, [6.81 minor

isomer]), 4.85 (s, 2H, [4.93 minor isomer]), 4.79 (s, 2H, [4.86 minor isomer]), 3.36-3.34 (m, 2H), 2.41 (s, 3H, [2.42 minor isomer]), 2.27 (s, 3H, [2.24 minor isomer]), 2.06-1.94 (m, 1H), 1.01 (d, J = 6.6 Hz, 6H, [0.86 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.43 [175.48 minor isomer], 169.22 [169.08 minor isomer], 168.61 [168.79 minor isomer], 156.04 [155.63 minor isomer], 141.82 [142.15 minor isomer], 131.21 [131.33 minor isomer], 130.24, 129.74 [129.84 minor isomer], 127.66 [127.67 minor isomer], 123.92 [123.53 minor isomer], 114.82 [114.54 minor isomer], 67.23 [68.55 minor isomer], 55.50 [54.51 minor isomer], 42.10 [43.59 minor isomer], 27.73 [26.86 minor isomer], 21.85, 20.75 [20.70 minor isomer], 20.28 [20.15 minor isomer]; LC-MS (ESI+) *m/z* 394.20 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{23}H_{28}N_3O_3$ $(M+H)^+$ 394.2125, found 394.2127.

***N*-Ethyl-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide (12b)**: This compound was prepared from **5a** (51 mg, 0.28 mmol) and **10l** (50 mg, 0.23 mmol) using triethylamine (47 mg, 0.46 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **12b** (69 mg, 82%) as a white solid. mp 97.4-100.1 °C. HPLC 99.6% (t_R = 9.0 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^{1}H NMR showed 2:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 2H, partially overlapped, [7.89 minor isomer]), 7.31-7.27 (m, 2H), 7.09 (d, J = 8.2 Hz, 2H, [7.03 minor isomer]), 6.87 (d, J = 8.6 Hz, 2H, [6.79 minor isomer]), 4.84 (s, 2H, [4.91 minor isomer]), 4.78 (s, 2H, [4.82 minor isomer]), 3.63 (q, J = 7.1 Hz, 2H, partially overlapped, [3.59 minor isomer overlapped]), 2.41 (s, 3H, [2.42 minor isomer]), 2.29 (s, 3H, [2.24 minor isomer]), 1.29 (t, J = 7.1 Hz, 3H, [1.16 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.56 [175.49 minor isomer], 168.86 [168.80 minor isomer], 168.66 [168.48 minor isomer], 156.00 [155.65 minor isomer], 141.85 [142.12 minor isomer], 131.27 [131.32 minor isomer], 130.30 [130.27 minor isomer], 129.75 [129.82 minor isomer], 127.66, 123.89 [123.56 minor isomer], 114.72 [114.52 minor isomer], 67.61 [68.52 minor isomer], 43.31 [42.97 minor isomer], 41.30 [42.72 minor isomer], 21.83, 20.74 [20.68 minor isomer], 14.14 [12.56 minor isomer]; LC-MS (ESI+) *m/z* 366.19 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{24}N_3O_3$ $(M+H)^+$ 366.1812, found 366.1810.

***N*-Methyl-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide (12c)**: This compound was prepared from **5a** (67 mg, 0.36 mmol) and **10k** (61 mg, 0.30 mmol) using triethylamine (61 mg, 0.60 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **12c** (100 mg, 95%) as a white solid. mp 99.1-100.9 °C. HPLC 96.7% (t_R = 7.4 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 2:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3 Hz, 2H, overlapped, [7.90 minor isomer, overlapped]), 7.30-7.26 (m, 2H), 7.08 (d, *J* = 8.1 Hz, 2H, [7.03 minor isomer]), 6.87 (d, *J* = 8.8 Hz, 2H, [6.78 minor isomer]), 4.87 (s, 2H [4.94 minor isomer]), 4.78 (s, 2H, [4.82 minor isomer]), 3.28 (s, 3H, [3.12 minor isomer]), 2.41 (s, 3H, [2.42 minor isomer)], 2.28 (s, 3H, [2.23 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.13 [175.03 minor isomer], 169.08 [168.92 minor isomer shown], 168.80 [168.68 minor isomer shown], 155.58 [155.89 minor isomer], 141.91 [142.12 minor isomer], 131.32 [131.38 minor isomer], 130.29, 129.77 [129.82 minor isomer], 127.65, 123.82 [123.54 minor isomer], 114.76, [114.44 minor isomer], 67.53 [67.49 minor isomer], 43.98 [45.45 minor isomer], 35.77 [35.22 minor isomer], 21.85 [21.83 minor isomer], 20.75 [20.74 minor isomer]; LC-MS (ESI+) *m/z* 352.17 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{22}N_3O_3$ $(M+H)^+$ 352.1657, found 352.1658.

***N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide (12d)**: This compound was prepared from **5a** (58 mg, 0.31 mmol) and **10n** (49 mg, 0.26 mmol) using triethylamine (54 mg, 0.53 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **12d** (69 mg, 79%) as a white solid. mp 113.7-115.5 °C. HPLC 99.9% (t_R = 6.5 min, 60% CH_3CN in 0.1% TFA water 30 min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.84 (d, *J* = 5.9 Hz, 2H), 4.59 (s, 2H), 2.42 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.46, 169.14, 168.66, 155.20, 142.02, 131.98, 130.49, 129.82, 127.64, 123.67, 114.82, 67.70, 35.46, 21.85, 20.77; LC-MS (ESI+) *m/z* 360.14 $(M+Na)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{19}H_{20}N_3O_3$ $(M+H)^+$ 338.1499, found 338.1505.

***N-tert*-Butyl-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl-2-(*p*-tolyloxy)acetamide (12e)**: This compound was prepared from **5a** (40 mg, 0.22 mmol) and **10o** (44 mg, 0.18 mmol) using triethylamine (36 mg, 0.36 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **12e** (53 mg, 75%) as a white solid. mp 129.1-130.0 °C. HPLC 96.2% (t_R = 18.3 min, 60% CH_3CN in 0.1% TFA water 30 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.27 (m, 2H), 7.02 (m, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.95 (s, 2H), 4.76 (s, 2H), 2.42 (s, 3H), 2.24 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.97, 169.45, 168.78, 155.88, 142.11, 131.07, 130.17, 129.81, 127.66, 123.62, 114.55, 69.81, 59.15, 40.71, 28.47, 21.86, 20.72; LC-MS (ESI+) *m/z* 394.22 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{23}H_{28}N_3O_3$ $(M+H)^+$ 394.2125, found 394.2114.

***N*-Cyclopropyl-*N*-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*p*-tolyloxy)acetamide (12f)**: This compound was prepared from **5a** (74 mg, 0.40 mmol) and **10p** (76 mg, 0.33 mmol) using triethylamine (67 mg, 0.66 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **12f** (98 mg, 79%) as a white solid. mp 113.8-115.2 °C. HPLC 94.8% (t_R = 6.2 min, 70% MeOH in 0.1% TFA water 20 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.31-7.23 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 4.97 (s, 2H), 4.88 (s, 2H), 3.10-3.02 (m, 1H), 2.42 (s, 3H), 2.26 (s, 3H), 1.05-0.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.92, 171.51, 168.61, 156.24, 141.86, 131.02, 130.19, 129.75, 127.65, 123.91, 114.81, 67.14, 43.44, 29.96, 21.82, 20.72, 9.29; LC-MS (ESI+) *m/z* 378.18 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{24}N_4O_3(M+H)^+$ 378.1812, found 378.1811.

1-Isopropyl-3-(4-methylbenzyl)-1-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)urea (14): A solution of **10d** (70 mg, 0.32 mmol), 4-methylbenzyl isocyanate **13** (47 mg, 0.32 mmol) and triethylamine (40 mg, 0.39 mmol) were heated under reflux in benzene overnight (14-15h). The organics were evaporated and the residue was dissolved in ethyl acetate (20 ml) and washed with HCl (4M, 3x10 mL) and water (2x20 mL). The organic phase was dried ($MgSO_4$), evaporated, and the crude product obtained was purified by SiO_2

chromatography (EtOAc/Hexane gradient elution) to obtain pure **14** (91 mg, 78%) as a white solid. mp 87.6-89.1 °C. HPLC 96.26% (t_R = 14.98 min, 50% CH_3CN in 0.1% TFA water 30 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.44-7.49 (m, 1H), 7.49-7.44 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 5.52 (apparent t, 1H), 4.63 (s, 2H), 4.43 (d, *J* = 4.7 Hz, 2H), 4.40-4.34 (m, 1H), 2.33 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.63, 168.47, 158.01, 137.13, 136.32, 131.58, 129.52, 129.03, 128.03, 127.71, 126.53, 47.12, 45.27, 37.62, 21.36, 20.96; LC-MS (ESI+) *m/z* 365.20 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{25}N_4O_2$ $(M+H)^+$ 365.1972, found 365.1988.

***N*-Isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-2-(*p*-tolylamino)acetamide (16)**: A solution of *p*-toluidine (19 mg, 0.18 mmol), **15** (65 mg, 0.22 mmol) and sodium acetate (18 mg, 0.22 mmol) in ethanol (20 ml) were refluxed for 15 h. Ethanol was evaporated and the product was purified by SiO_2 chromatography (EtOAc/Hexane gradient elution) to obtain **16** as a yellow-brown sticky solid (51 mg, 78%); HPLC 96.59% (t_R = 12.2 min, 45% CH_3CN in 0.1% TFA water 30 min); The ^{1}H NMR showed 4:1 ratio of atropisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.04 (m, 2H), 7.54-7.44 (m, 3H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.59 (d, *J* = 8.3 Hz, 2H), 4.76 (s, 2H, [4.71 minor isomer]), 4.29-4.16 (m, 1H, [4.98-4.90 minor isomer]), 4.05 (s, 2H), 2.25 (s, 3H, [2.23 minor isomer]), 1.34 (d, *J* = 6.6 Hz, 6H, [1.18 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.66 [176.22 minor isomer], 169.91 [169.69 minor isomer], 168.65 [168.92 minor isomer], 145.14, 131.43 [131.83 minor isomer], 130.01 [130.14 minor isomer], 129.00 [129.18 minor isomer], 127.74 [127.70 minor isomer], 127.33, 126.82, 113.51 [113.65 minor isomer], 47.98 [49.59 minor isomer], 46.18 [46.74 minor isomer], 37.25 [37.44 minor isomer], 21.32 [19.96 minor isomer], 20.65 [20.14 minor isomer]; LC-MS (ESI+) *m/z* 365.19 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{21}H_{25}N_4O_2(M+H)^+$ 365.1972, found 365.1978.

***N*-Isopropyl-*N*-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-3-(4-(trifluoromethyl)phenyl)propanamide (19a)**: This compound was prepared from **18a** (131 mg, 0.55 mmol) and **10d** (100 mg, 0.46 mmol) using triethylamine (93 mg, 0.92 mmol) in a similar manner as described for compound **1**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **19a** (169

mg, 88%) as a white solid. mp 96.1-97.7 °C. HPLC 98.5% (t_R = 5.27 min, 60% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.9, 1.7 Hz, 2H, overlapped [8.03 minor isomer overlapped]), 7.56-7.42 (m, 5H), 7.37 (d, *J* = 8.1 Hz, 2H, [7.33 minor isomer]), 4.70 (s, 2H, [4.61 minor isomer]), 4.25-4.18 (m, 1H, [4.97 minor isomer]), 3.08 (t, *J* = 7.6 Hz, 2H, [3.02 minor isomer]), 2.79 (t, *J* = 7.6 Hz, 2H, [2.71minor isomer]), 1.24 (d, *J* = 6.7 Hz, 6H, [1.12 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.07 [176.66 minor isomer], 171.92 [172.02 minor isomer], 168.58, 145.48, 131.40 [131.84 minor isomer], 129.19, 129.07, 129.00 [128.88 minor isomer], 127.70 [127.67 minor isomer], 126.94, 125.64 (q, *J* = 3.76 Hz), 124.50 (q, *J* = 271 Hz), 48.78 [45.82 minor isomer], 37.16 [38.72 minor isomer], 34.81 [35.30 minor isomer], 31.09 [31.17 minor isomer], 21.33 [20.20 minor isomer]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75,[-62.78 minor isomer]; LC-MS (ESI+) *m/z* 418.18 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{23}F_3N_3O_2$ $(M+H)^+$ 418.1737, found 418.1745.

Benzofuran-2-carboxylic acid isopropyl-(3-pyridin-3-yl-[1,2,4]oxadiazol-5-yl)methyl)-amide (19b): This compound was prepared from **18b** (63 mg, 0.35 mmol) and **10f** (63 mg, 0.29 mmol using triethylamine (59 mg, 0.58 mmol) in a similar manner as described for compound **11u**. The crude product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **19b** (86 mg, 82%) as a sticky colorless solid. HPLC 96.1% (t_R = 4.1 min, 70% MeOH in 0.1% TFA water 20 min); ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.71 (appd, *J* = 4.0 Hz, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.46-7.38 (m, 3H, [7.57-7.46 minor isomer]), 7.31-7.25 (m, 2H), 5.03-4.93 (m, 1H), 4.89 (brs, 2H), 1.37 (d, *J* = 3.1 Hz, 6H, [7.50 minor isomer]). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.69, 161.31, 154.93, 152.05, 148.69, 135.19, 127.05 [126.98 minor isomer], 123.98 [123.95 minor isomer], 122.63 [123.26 minor isomer] 113.13, 112.13, 49.89, 38.21, 22.78, 21.66: LC-MS (ESI+) *m/z* 363.16 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{20}H_{19}N_4O_3(M+H)^+$ 363.1452, found 363.1455.

***N*-Isopropyl-*N*-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)-2-(*p*-tolyloxy)acetamide (23)**: This compound was prepared from **5a** (56 mg, 0.55 mmol) and **22** (106 mg, 0.46 mmol, *see supporting information for the synthesis of* **22**) using triethylamine (93 mg, 0.92 mmol) in a similar manner as described for compound 1. The crude

product obtained was purified using SiO_2 chromatography (EtOAc/Hexane gradient elution) to afford pure **23** (152 mg, 87%) as a sticky colorless solid. HPLC 97.51% (t_R = 22.7 min, 50% CH_3CN in 0.1% TFA water 30 min); The ^1H NMR showed 3:1 ratio of atropisomers: ^1H NMR (400 MHz, $CDCl_3$) δ 8.07-8.02 (m, 2H), 7.52-7.44 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.69 (s, 2H), 4.29-4.20 (m, 2H, [4.55-4.44 minor isomer]), 3.72 (t, *J* = 7.4 Hz, 2H, [3.89 minor isomer]), 3.28 (t, *J* = 7.4 Hz, 2H), 2.28, (s, 3H, [2.26 minor isomer]), 1.28 (d, *J* = 6.7 Hz, 6H, [1.20 minor isomer]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.76, 168.50, 168.40, 155.99, 131.37 [131.18 minor isomer], 130.29, 129.05, 127.66 [126.99 minor isomer], 114.59 [114.67 minor isomer], 68.31 [68.99 minor isomer], 48.80 [47.87 minor isomer shown], 38.56 [41.31 minor isomer], 26.18 [28.64 minor isomer], 21.36 [20.45 minor isomer]; 20.72. LC-MS (ESI+) *m/z* 380.20 $(M+H)^+$; HRMS (ESI+ve) *m/z* calculated for $C_{22}H_{26}N_3O_3(M+H)^+$ 380.1969, found 380.1965.

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ABBREVIATIONS USED

CT-L, chymotrypsin like; T-L, trypsin like; SAR, structure activity relationship; PGPH-L, postglutamylpeptidase hydrolysis-like; DCM, dichloromethane; THF, tetrahydrofuran; DMF, dimethylformamide; DMSO, dimethylsulfoxide; TFA, trifluoroacetic acid; LC/MS-MS, Liquid chromatography-tandem mass spectrometry; LC-MS, Liquid chromatography mass spectrometry; HRMS, High resolution mass spectroscopy; ESI, Electrospray ionization; HPLC, High performance liquid chromatography, AMC: 7-amino-4-methyl-coumarin.

Supporting information available: (i) Synthetic protocols and characterization for libraries **5** and **10**, and compounds **15**, **18a-b**, **20-27** (except 23) (ii) Scanned NMR spectra, HPLC, HRMS and LC-MS reports for **1**, **11x**, **11aa**, **11ab**, **11ac**, **11ad**, **11ae**, **11af**, **11ah**, **11al**, **11am**, **11an**, **11ao**, **11ap**, **12d**, **12e**. This material is available free of charge *via* the Internet at http:// pubs.acs.org.

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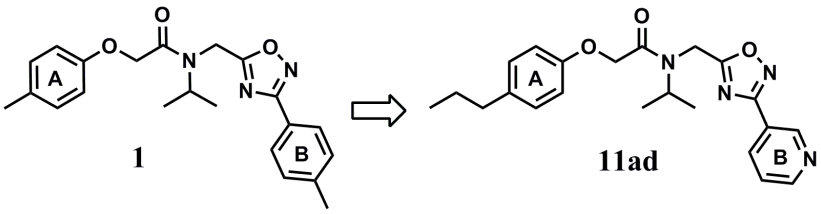
Table of Contents Graphic



IC_{50} = 0.60 ± 0.18 μM, (n = 27) **Hit compound**

IC_{50} = 27 ± 14 nM, (n = 20) **Lead compound**

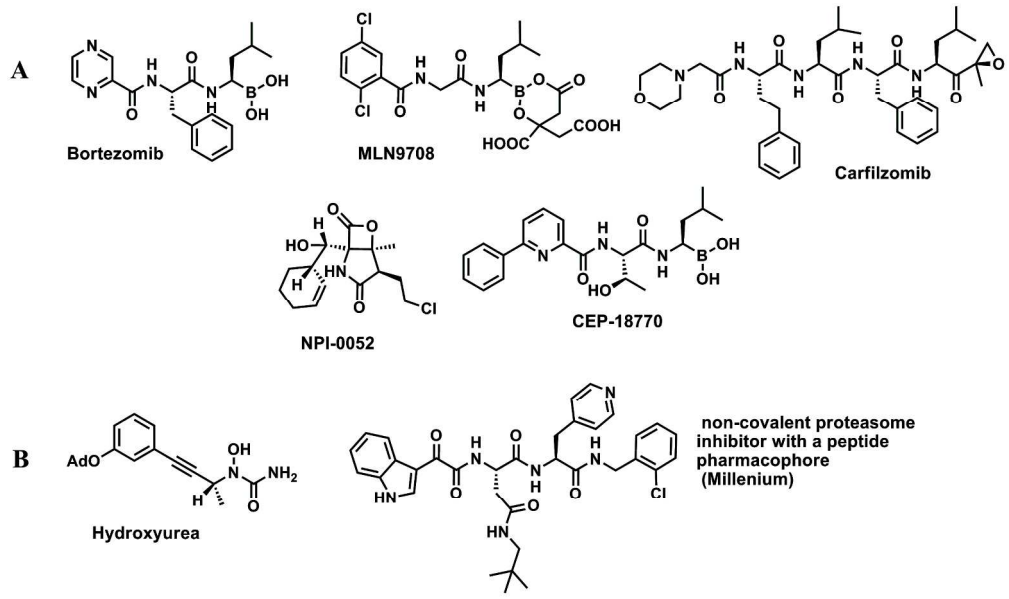


Figure 1: A. Structures of clinically advanced covalent proteasome inhibitors B. Structures of non-covalent small molecule proteasome inhibitors; hydroxyurea pharmacophore38 and peptidic pharmacophore from Millennium.
220x130mm (300 x 300 DPI)

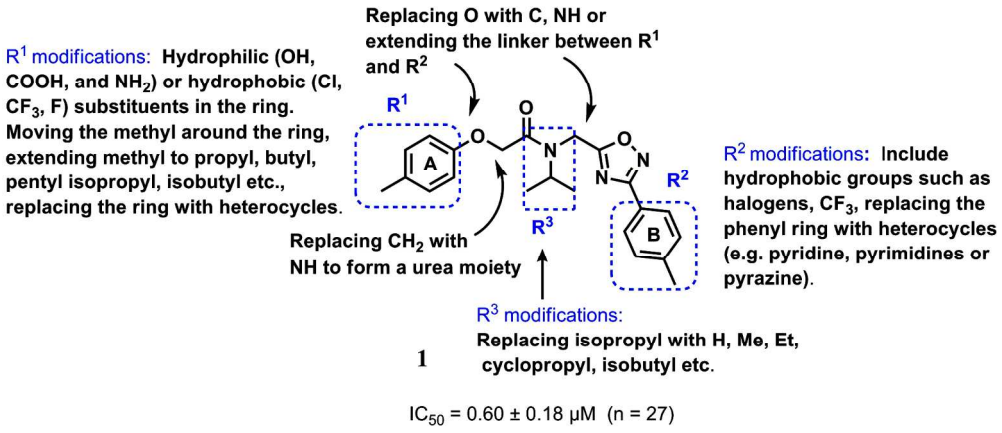


Figure 2: Modifications and library synthesis around 1 for design of new proteasome inhibitors and SAR studies.
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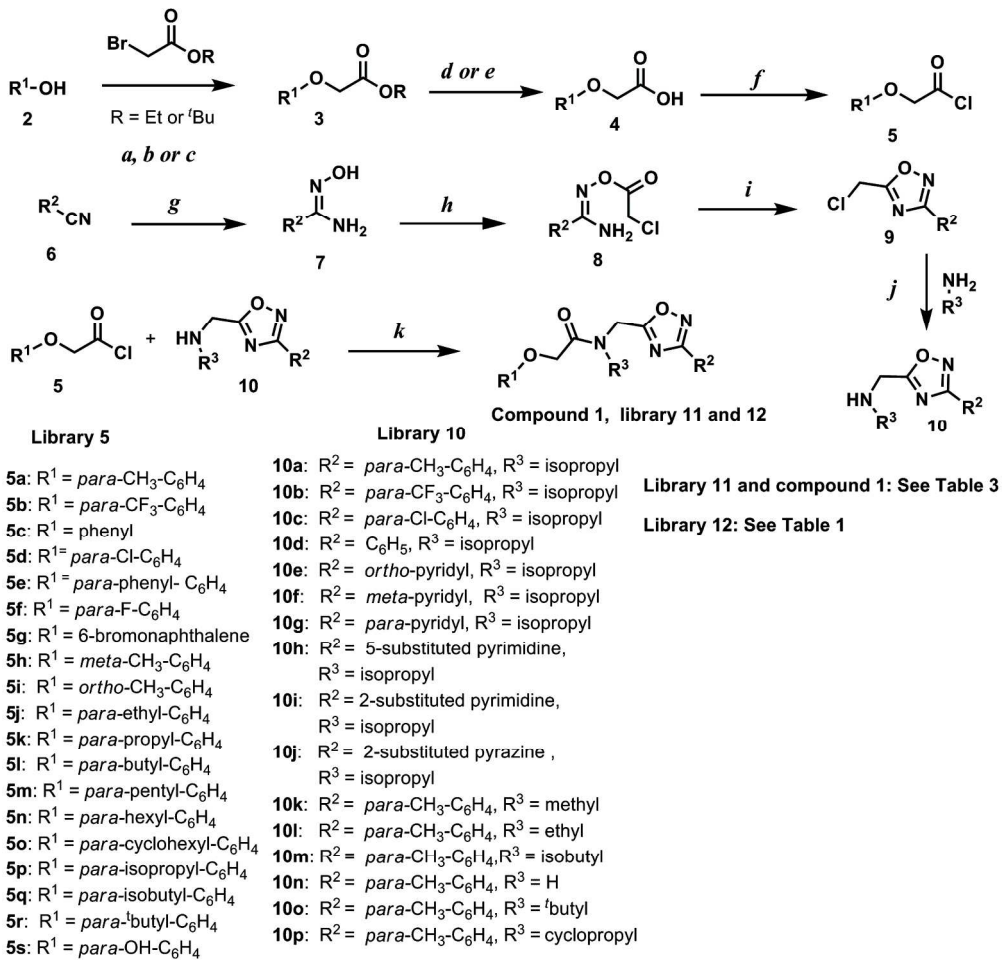
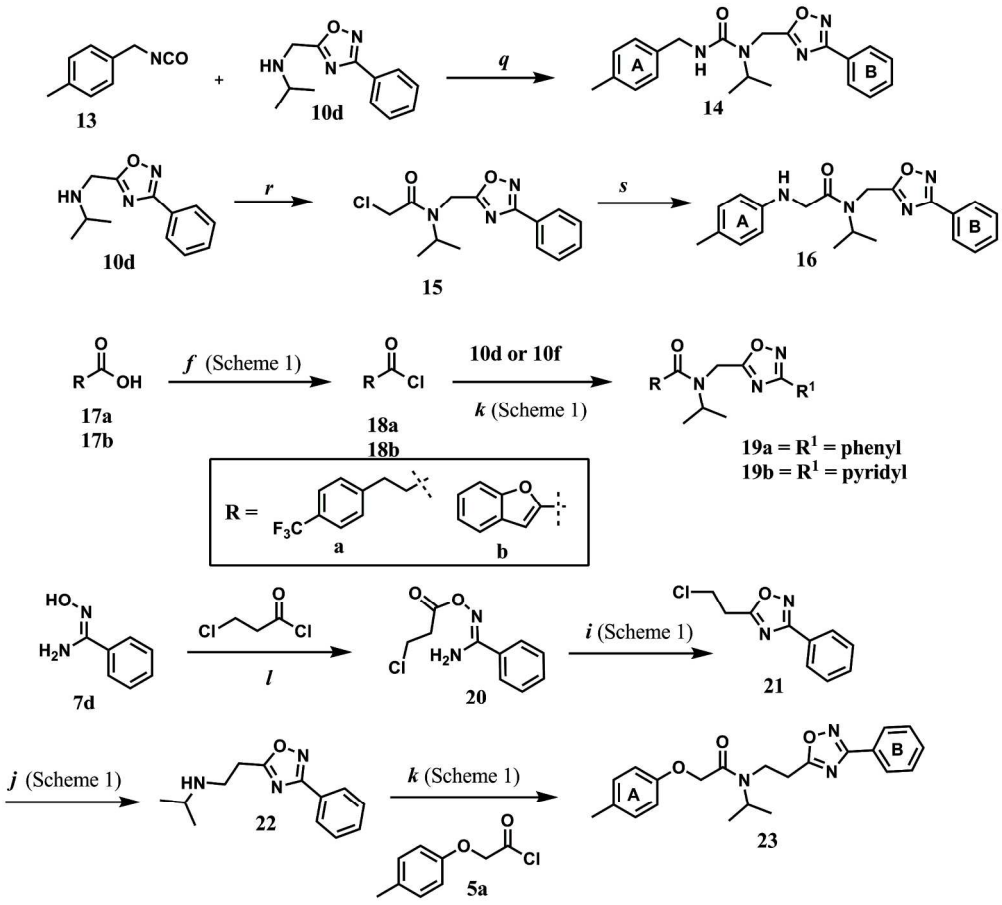


Scheme 1. Synthetic route to compound 1, libraries 11 and 12. Reagents and conditions: a. Ethyl bromoacetate, K2CO3, Acetone, reflux, 14 h. b. tert-Butyl bromoacetate , DMF, 80 ºC, 14 h. c. Ethyl bromoacetate, K2CO3, DMF, r.t., 14 h. d. NaOH, THF, reflux, 2 h. (R= Ethyl). e. CF3COOH, DCM, r.t., 2 h (R = tBu). f. SOCl2, benzene, reflux, 3 h. g. NH2OH.HCl, Na2CO3, water, 70 ºC, 14 h. h. Chloroacetyl chloride, acetone, r.t., 30 min. i. toluene, reflux, 2 h. j. Alkylamine, K2CO3, CH3CN, reflux, 30 min. k. Et3N, THF, r.t., 15 min.
189x181mm (300 x 300 DPI)



Scheme 2: Reagents and conditions: q. Et3N, benzene, reflux, 14 h, 78%. r. Chloroacetyl chloride, Et3N, THF, r.t., 15 min., 80%. s. para-Methylaniline, NaOAc, ethanol, reflux, 15 h, 78%. f. SOCl2, benzene, reflux, 3 h, 94%. i. toluene, reflux, 2 h, 81%. j. Isopropylamine, K2CO3, CH3CN, reflux, 30 min., 86%. k. Et3N, THF, r.t., 15 min., 88% (19a), 82% (19b), 87%, (23). l. DCM, r.t., 14 h, 76%.
201x180mm (300 x 300 DPI)

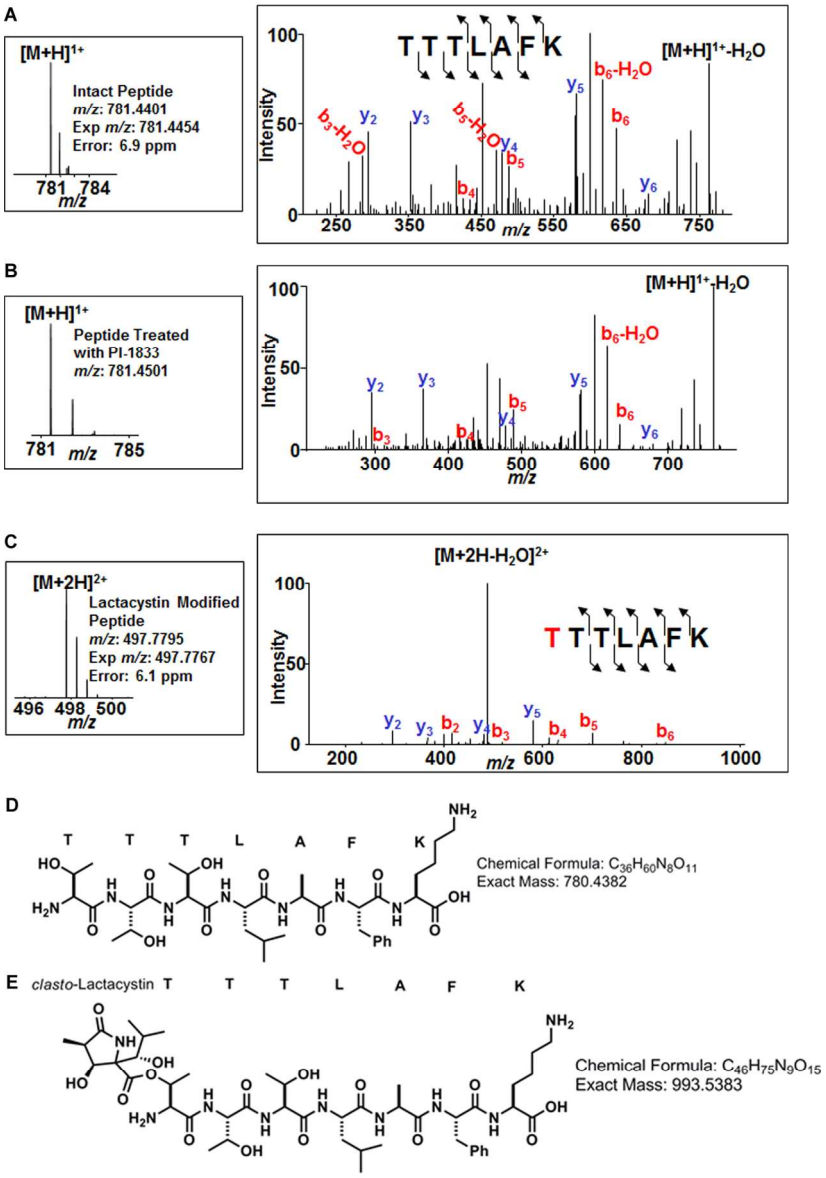


Figure 3: A: LC/MS-MS analysis of tryptic digests from proteasome CT-L subunit after incubation with vehicle. LC/MS-MS analysis of Thr-1 containing peptide from the proteasome CT-L subunit β5 after tryptic digestion is shown. Singly charged unmodified peptide was observed at m/z 781.4401, which represents a mass error of 6.9 ppm. The tandem mass spectrum was matched to peptide TTTLAFK. The b ions (labeled in red), contain the N-terminus of the peptide; and y ions, (labeled in blue), contain the C-terminus of the peptide. The number associated with each ion indicates the number of amino acids in that fragment (for example, y4 contains LAFK from C-terminus of the peptide). B: LC/MS-MS analysis of tryptic digests from proteasome CT-L subunit after incubation with compound 1. The Thr-1 containing peptide didn't show any modification. Both intact mass spectrum and tandem mass spectrum indicate unmodified Thr-1 containing peptide. C: LC/MS-MS analysis of tryptic digests from proteasome CT-L subunit after incubation with lactacystin shows clasto-lactacystin-modified Thr-1 containing peptide. Doubly charged lactacystin-Thr modified peptide was detected at m/z 497.7795, which represents a mass error 6.1 ppm. The tandem mass spectrum confirms the modification of the peptide by lactacystin. D: Structure of the unmodified TTTLAFK

tryptic peptide. E: Structure of the clasto-lactacystin modified peptide.
127x177mm (300 x 300 DPI)

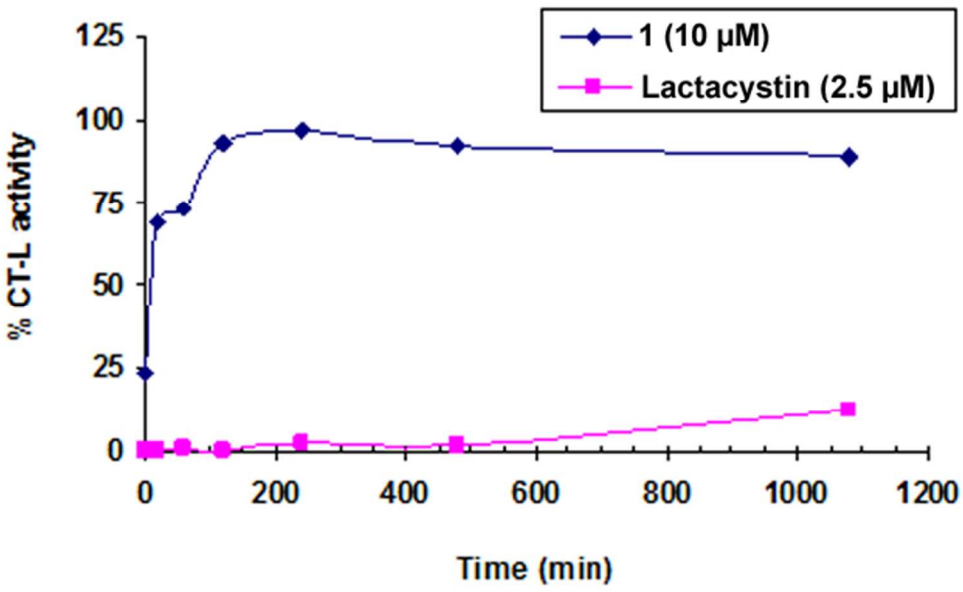


Figure 4: Recovery of CT-L activity upon dialysis of the 20S proteasome-compound complexes after pre-incubation with lead 1 and lactacystin.
54x33mm (300 x 300 DPI)

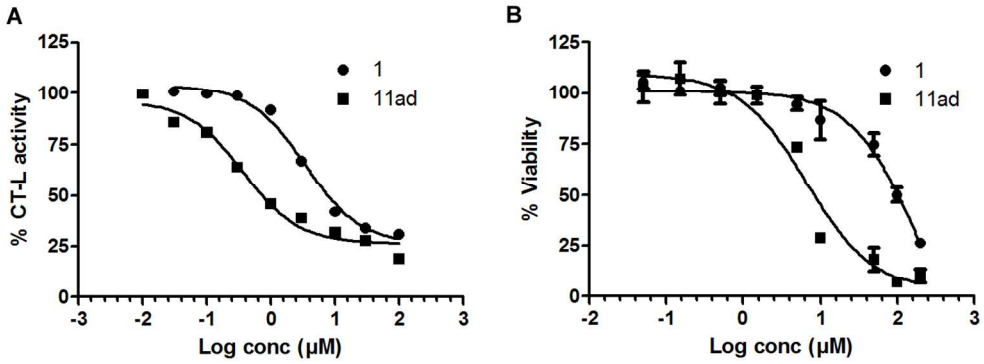


Figure 5. A: Lead 11ad is more potent at inhibiting proteasomal CT-L activity in intact human MDA-MB-468 cancer cells compared to the parent compound 1. B: Lead 11ad is more potent at inhibiting proliferation/survival of human MDA-MB-468 cells compared to the parent hit 1.
121x45mm (300 x 300 DPI)