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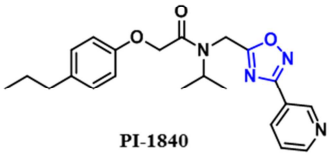
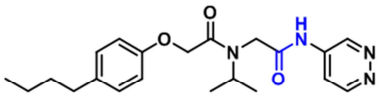


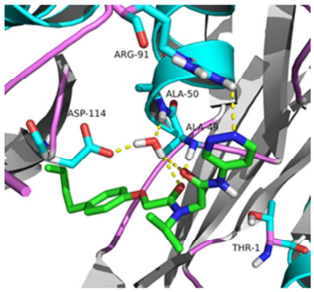
PI-1840

CT-L : IC_{50} = 92 nM
Human liver microsome stability :
43% remaining at 0.5 h



18x

CT-L : IC_{50} = 49 nM
HepG2 : IC_{50}= 3.91 µM
HGC27 : IC_{50}= 4.62 µM
Human liver microsome stability :
80% remaining at 0.5 h



Design, synthesis, and biological evaluation of novel phenol ether derivatives as non-covalent proteasome inhibitors

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[1]*Equal contribution*

Abstract

A series of novel phenol ether derivatives were designed, synthesized, and evaluated as non-covalent proteasome inhibitors. Most compounds exhibited moderate to excellent proteasome inhibitory activity. In particular, compound **18x** proved to be the most potent compound (chymotrypsin-like: IC_{50} = 49 nM), exhibiting a 2-fold higher potency compared to the reported PI-1840. Besides, compound **18x** exhibited excellent metabolic stability and selective anti-proliferative activity against solid cancer cell lines including HepG2 and HGC27, providing incentive for the further development as a potential anticancer agent against solid cancers.

Key words: proteasome inhibitor, non-covalent, non-peptide, phenol ether, solid cancers

Introduction

The ubiquitin-proteasome system (UPS) [1] represents the major pathway for regulating the degradation of intracellular proteins [2] and is generally involved in numerous physiologically important cellular processes, such as cell cycle progression [3, 4], signal transduction [5], and immune response [6]. The 20S proteasome is a key player in the pathway, consisting of four stacked heptameric rings: two outer α-rings and two inner β-rings. Each β-ring contains the three proteolytic subunits β1c, β2c, and β5c, which are responsible for caspase-like (C-L), trypsin-like (T-L), and chymotrypsin-like (ChT-L) activity [7], respectively. These subunits can be replaced by their interferon γ-inducible counterparts LMP2 (β1i), MECL-1 (β2i), and LMP7 (β5i), respectively, resulting in alternatively assembled immunoproteasomes. Because of the crucial role of proteasome in a wide variety of cellular processes, the regulation of its protease activity by inhibitors is of therapeutic interest [8].

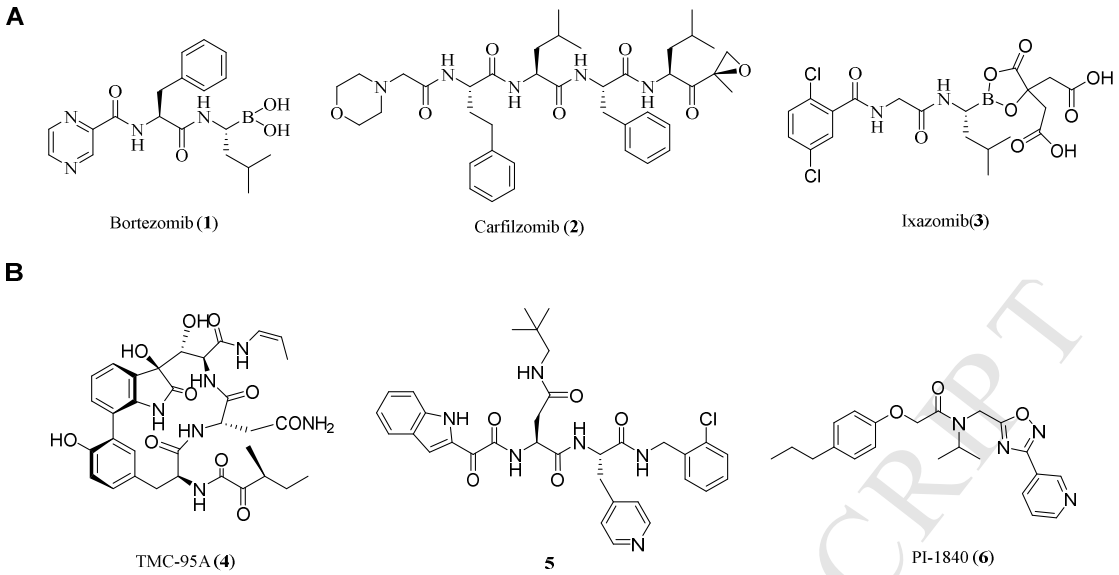


Figure 1. Proteasome inhibitors. (A) FDA-approved covalent proteasome inhibitor Bortezomib, Carfilzomib, and Ixazomib. (B) Non-covalent proteasome inhibitors including the peptidic inhibitor TMC-95A, compound **5**, and non-peptidic inhibitor PI-1840.

FDA approval of the proteasome inhibitors Bortezomib, Carfilzomib, and Ixazomib (**1**-**3**, Fig. 1A) has validated the proteasome as a promising target for cancer therapy. All of the approved inhibitors carry an electrophilic warhead at the C-terminal end of a peptidic backbone and are covalently bound to the catalytic Thr1 residues of the β subunits [9]. However, the peptidic backbone and the electrophilic warhead of these agents are believed to be the major cause of side effects, acquired drug resistance, and unsatisfactory pharmacokinetic profiles [10-12]. Therefore, non-covalent inhibitors have attracted significant attention in recent years. These inhibitors are devoid of any electrophilic warhead and interact with the proteasome active site through a network of interactions (hydrophobic, H-bonds, electrostatic, and van der Waals forces). However, most of the non-covalent inhibitors are still equipped with a peptidic backbone [13-18](e.g. compounds **4** and **5**, Fig. 1B), are generally believed to be unstable and less selective, with several potent non-peptide non-covalent inhibitors having been published [19-21]. PI-1840 (**6**, Fig. 1B) represents one of the most potent non-peptide non-covalent inhibitors with an IC_{50} value of 27 nM against CT-L [22]. Further studies indicated that PI-1840 suppresses the growth of human breast tumor

xenografts in nude mice [23]. Nevertheless, according to a study reported by Boström, J. *et al*. [24], 1,2,4-oxadiazole derivatives are more frequently recognized by cytochrome P450 enzymes, leading to a higher metabolic turnover in human liver microsomes (HLMs). To further verify this notion, we evaluated the metabolic stability of PI-1840 in HLMs. The results indicated that PI-1840 displayed a high metabolic susceptibility in HLMs, metabolized more than 50% within 30 min after treatment with HLMs (Fig. 3). Considering this finding, our modification of PI-1840 prioritized replacing its 1, 2, 4-oxadiazole moiety with different isosteres containing urea or amide to improve the metabolic stability of the compounds. After confirming the optimal replacement of the 1,2,4-oxadiazole moiety, we designed and synthesized a series of phenol ether derivatives to explore the SARs of ring A and the R group residing on the phenyl ring (Fig. 2). The anti-proliferative activity against various cancer cells of selected compounds were also evaluated in this manuscript.

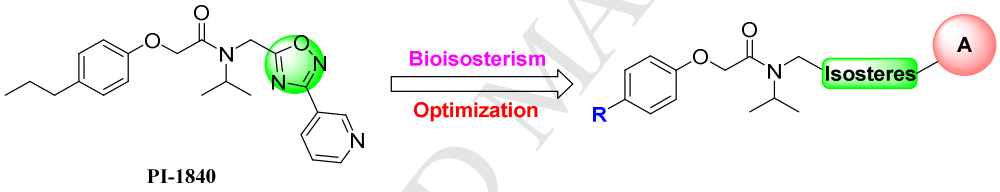


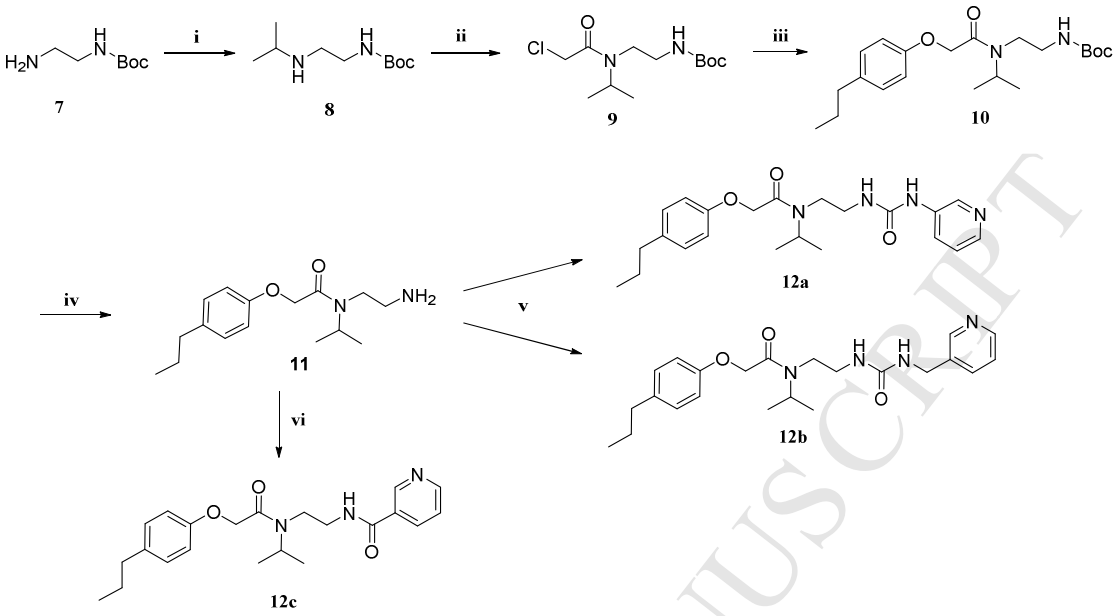
Figure 2. Design of new non-covalent proteasome inhibitors based on PI-1840.

2. Results and discussion

2.1. Chemistry

The synthetic routes for the corresponding phenol ether derivatives are outlined in Schemes 1 and 2. Substitution of tert-butyl (2-aminoethyl)carbamate **7** with 2-bromopropane in MeCN, afforded tert-butyl (2-(isopropylamino)ethyl)carbamate **8**, which was subsequently converted to compound **9** via condensation with chloroacetyl chloride. Treatment of precursor **9** with 4-propylphenol in the presence of potassium carbonate in refluxing acetonitrile, followed by removal of the Boc group yielded the primary amine **11**. Afterwards, the primary amine **11** reacted with pyridin-3-amine or pyridin-3-ylmethanamine in the presence of triphosgene to produce urea **12a** or **12b**.

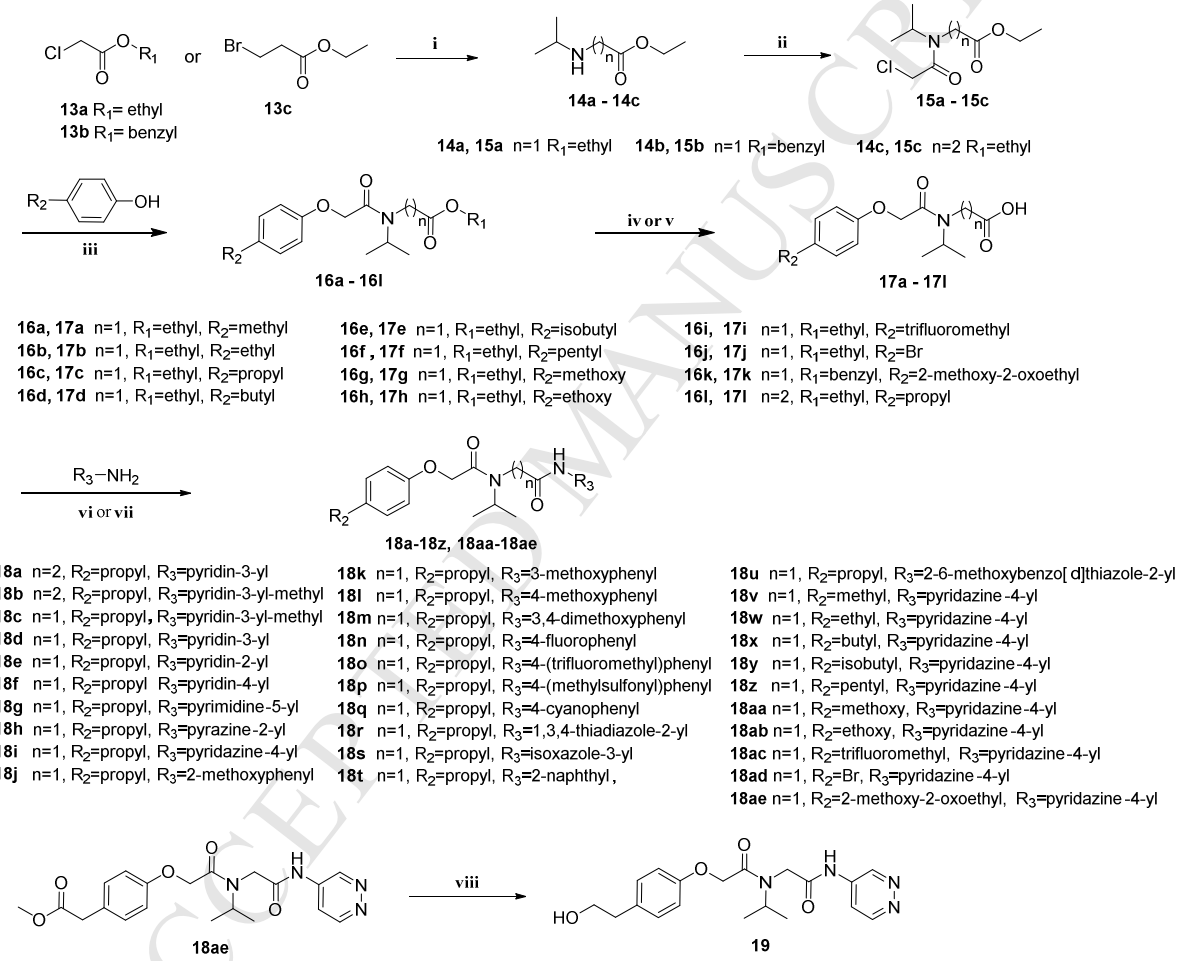
In addition, the primary amine **11** was condensed with nicotinic acid using HOBt and EDCI as condensation agents to provide amide **12c** (Scheme 1).



Scheme 1. Synthetic route for target compounds **12a-12c**. Reagents and conditions: (i) 2-bromopropane, TEA, MeCN, r.t., overnight; (ii) chloroacetyl chloride, TEA, THF, 0 °C - r.t., 30 min; (iii) 4-propylphenol, K_2CO_3, MeCN, reflux, 2 h; (iv) HCl-saturated ethyl acetate, 0 °C - r.t., 2 h, then $NaHCO_3$ (aq.), 0 °C, 10min; (v) pyridin-3-amine or pyridin-3-ylmethanamine, triphosgene, TEA, anhydrous DCM, 0 °C - r.t., 1 h; (vi) nicotinic acid, EDCI, HOBt, DIPEA, DCM, 0 °C - r.t., 5 h.

The phenol ether derivatives **18a-18z**, **18aa-18ae**, and **19** were prepared as shown in Scheme 2. Ethyl 2-chloroacetate **13a**, benzyl 2-chloroacetate **13b**, or ethyl 3-bromopropanoate **13c** was first allowed to react with propan-2-amine in the presence of triethylamine in MeCN at room temperature to produce intermediate **14a-14c**, followed by condensation with chloroacetyl chloride to obtain compounds **15a-15c**. Reaction of **15a-15c** with various phenols furnished intermediates **16a-16l**, which were hydrolyzed or debenzylated to afford the corresponding carboxylic acids **17a-17l**. Finally, the carboxylic acids **17a-17l** were condensed with the corresponding amines to produce the target compounds **18a-18z** and **18aa-18ae**. In this step, we adopted two different condensation methods (vi and vii, Scheme 2), due to the

different nucleophilicities of the amines. Compound **19** was synthesized from compound **18ae** via reduction with sodium borohydride in the presence of $CaCl_2$. Most of final compounds were obtained in isomer mixture, we have carried out variable temperature ^1H NMR experiments to confirm the existence of atropisomers. As the temperature was raised for **18x**, the two sets of peaks observed in the ^1H NMR spectrum at 20 °C coalesced at 100 °C. The ^1H NMR spectra of **18x** at different temperature were provided in supplemental material.



Scheme 2. Synthetic routes for the target compounds **18a-18z**, **18aa-18ae**, and **19**. Reagents and conditions: (i) propan-2-amine, TEA, MeCN, r.t., overnight; (ii) chloroacetyl chloride, TEA, THF, 0 °C - r.t., 30 min; (iii) K_2CO_3, MeCN, reflux, 2 h; (iv) 1N NaOH (aq), 0 °C - r.t., 2 h, then 1N HCl (aq.), 0 °C, PH =2~3; (v) H_2, 10% Pd/C, MeOH, r.t., 2 h; (vi) HOBt, EDCI, DIPEA, DCM, 0 °C - r.t., 5 h; (vii) isobutyl chloroformate, 4-methylmorpholine, anhydrous THF, –10 °C - r.t., 6 h; (viii) $NaBH_4$, $CaCl_2$, MeOH, 0 °C - r.t., 30 min.

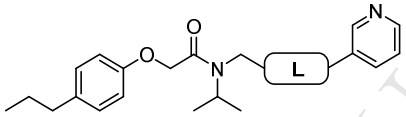
2.2. Biological evaluation

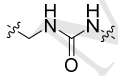
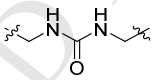
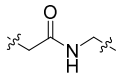
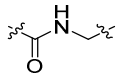
2.2.1. Proteasome inhibitory activity and metabolic stability in liver microsomes

All synthesized target compounds were evaluated for their 20S proteasome chymotrypsin-like inhibitory activity *in vitro*. In this study, PI-1840 was employed as positive control. The results are summarized in Tables 1-3. Most compounds exhibited moderate to excellent proteasome inhibitory activity.

Table 1.

20S proteasome chymotrypsin-like inhibitory activity of target compounds (**12a-12c** and **18a-18d**).



Compd.	L	Inhibitory rate at 10 μM (%)[a]
12a		13.80 ± 6.64
12b		38.68 ± 1.76
12c		30.79 ± 7.57
18a		15.50 ± 3.20
18b		12.66 ± 5.11
18c		1.16 ± 6.53
18d		58.18 ± 0.02
PI-1840	-	80.20 ± 2.10

[a] The inhibitory rate is shwon as an average of three independent determinations.

First, the modification of PI-1840 prioritized replacing its 1, 2, 4-oxadiazole moiety with different isosteres containing urea or amide to afford compounds **12a-12c** and **18a-18d**. As illustrated in Table 1, only compound **18d** showed 58.18% inhibition at

10 μM, all other compounds demonstrated disappointing results (<50% inhibition at 10 μM). For **18d**, replacing the 1,2,4-oxadiazole moiety of PI-1840 with an amide led to a decrease in inhibitory potency to some extent, but the following stability test of compound **18d** and PI-1840 in HLMs indicated that compound **18d** was more stable than PI-1840 in HLMs (Fig. 3). Encouraged by this finding, we identified compound **18d** as a lead compound for further modification.

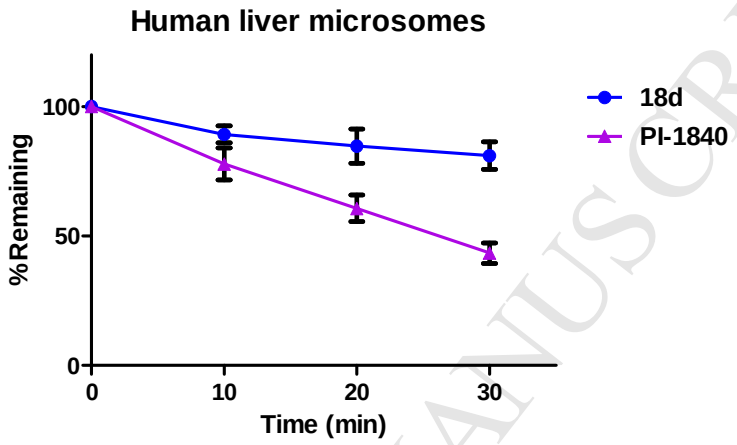
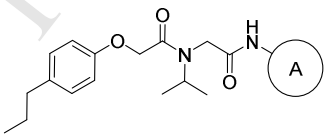


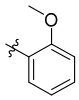
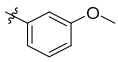
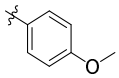
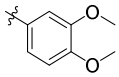
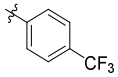
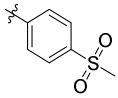
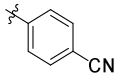
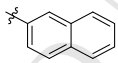
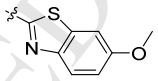
Figure 3. Metabolic stability of compound **18d** and PI-1840 in human liver microsomes.

Table 2.

20S proteasome chymotrypsin-like inhibitory activity of target compounds (**18d-18u**).



Compd.	A	IC_{50} (nM)[a]
18d		1682 ± 42
18e		836 ± 137
18f		100 ± 10
18g		280 ± 18
18h		395 ± 30
18i		89 ± 25

18j		>10000
18k		2000 ± 340
18l		952 ± 180
18m		4726 ± 1251
18n		1197 ± 231
18o		922 ± 386
18p		230 ± 72
18q		361 ± 23
18r		3863 ± 1131
18s		2011 ± 323
18t		5907 ± 1648
18u		1111 ± 257
PI-1840	-	92 ± 5

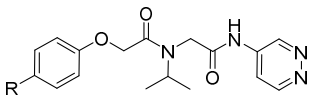
[a] The IC_{50} values are shown as an average of three independent determinations.

In order to determine the SARs around ring A present in **18d**, we replaced ring A with various heteroaryl rings (compounds **18e-18i** and compounds **18r** and **18s**), substituted aryl rings (compounds **18j**-**18q**), and fused rings (compounds **18t** and **18u**). Firstly, compared with **18d**, **18e**, and **18f**, we found that the position of the nitrogen atom in the pyridine ring was critical to potency. Replacing the *m*-pyridyl moiety in **18d** with an *o*-pyridyl (as in **18e**) and a *p*-pyridyl (as in **18f**) moiety increased the potency 2-fold and 16-fold, respectively. Furthermore, replacing the *m*-pyridyl moiety in **18d** with pyrimidine (as in **18g**), pyrazine (as in **18h**), or pyridazine (as in **18i**) also led to potency increase, and the compound **18i** containing 4-substituted pyridazine

exhibited a comparable potency to PI-1840. Meanwhile, in order to explore the most potent compound, various substituted aryl rings were also introduced to ring A. Similarly to the pyridine ring, the most suitable position of the methoxy substituent in the phenyl ring was determined to be in para-position (**18l**), but the CT-L inhibitory activity was found to be lost when the methoxy substituent was moved into ortho-position (**18j**, IC_{50} > 10 μM) or meta-position (**18k**, IC_{50} = 2 μM). Moreover, substituting the 4-methoxyphenyl in **18l** by 3,4-dimethoxyphenyl (as in **18m)** led to a 5-fold loss of potency. Therefore, we introduced different substituents in the para-position on the phenyl ring to afford the compounds **18n**, **18o**, **18p**, and **18q** with IC_{50} values of 1197, 922, 230, and 361 nM, respectively. However, all compounds in which the pyridazine rings were replaced by substituted aryl rings exhibited a loss of CT-L inhibitory activity compared to **18i**. In addition, replacing ring A with five-membered heteroaryl rings (compounds **18r**, **18s**) and fused rings (compounds **18t**, **18u**) was also found to be of no benefit to CT-L inhibitory potency. According to above-mentioned modification of the ring A, we identified the 4-substituted pyridazine ring as optimal group.

Table 3.

20S proteasome chymotrypsin-like inhibitory activity of target compounds (**18v-18z, 18aa-18ae,** and **19**).



Compd.	R	IC_{50} (nM)[a]
18v		481 ± 131
18w		243 ± 57
18i		89 ± 25
18x		49 ± 12
18y		118 ± 38
18z		64 ± 13

18aa		579 ± 242
18ab		259 ± 34
18ac		952 ± 180
18ad		405 ± 100
18ae		1561 ± 13
19		968 ± 179
PI-1840	-	92 ± 5

[a] The IC_{50} values are shown as an average of three independent determinations.

In the next modification, the influence of the R group in para-position of the phenyl ring was assessed, with a series of compounds (**18v-18z**, **18aa-18ae** and **19**) being synthesized. The length of the alkyl group in the para position of the phenyl ring was shown to be important, increasing the length of the R group from methyl (**18v**) to ethyl (**18w**), propyl (**18i**), and butyl (**18x**) resulted in progressive improvement of inhibitory activity from 481 to 243, 89, and 49 nM, respectively. However, an excessive length of the R group such as pentyl (as in **18z**) was demonstrated to be detrimental to the inhibitory activity. Meanwhile, compared with compounds **18x** and **18y**, we could find that a linear alkyl substituent was better to potency than a branched alkyl substituent of the phenyl ring. Indeed, an isobutyl substituent present in compound **18y** resulted in a 2-fold loss of CT-L inhibitory activity compared to a butyl substituent present in **18x**. Moreover, that the R group prefers hydrophobic group to hydrophilic group with a propyl substituent (as in **18i**) being 10-fold more potent than a hydroxyethyl substituent (as in **19**). However, replacing the alkyl substituent with an alkoxy substituent was shown to be detrimental to the CT-L inhibitory activity (**18w** *vs* **18aa**, **18i** *vs* **18ab**). Furthermore, we also attempted to introduce various other groups to the phenyl ring such as trifluoromethyl (**18ac**), bromide (**18ad**), and 2-methoxy-2-oxoethyl (**18ae**), but all of these compounds demonstrated unsatisfactory CT-L inhibitory activity.

Overall, we identified compound **18x** as the most potent compound exhibiting an

almost 2-fold higher potency than PI-1840. Furthermore, subsequent assays of the metabolic stability of **18x** and PI-1840 in human liver microsomes showed that compound **18x** was more stable than PI-1840 (Fig. 4)**.**

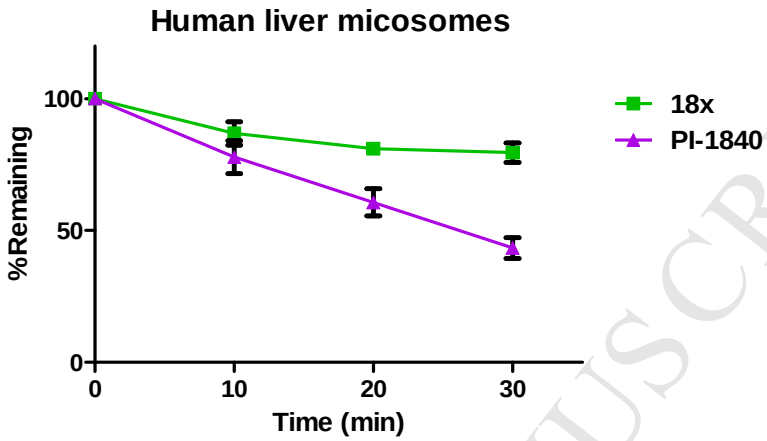


Figure 4. Metabolic stability of **18x** and PI-1840 in human liver microsomes.

Table 4.

Inhibition for β1c, β2c, β5c and β5i of 18p, 18x, PI-1840 and carfilzomib

Compd.	**IC_{50}(nM)**			
	C-L (β1c)	**T-L(β2c)**	**CT-L(β5c)**	**LMP7(β5i)**
18p	>10000	>10000	230 ± 72	>10000
18x	>10000	>10000	49 ± 12	>10000
PI-1840	>10000	>10000	92 ± 5	>10000
Carfilzomib	1452 ± 400	825 ± 305	5 ± 0	27 ± 7

[a] The IC_{50} values are shown as an average of three independent determinations.

We have also assessed the subunits selective inhibitory activity of **18p** and **18x**. The experimental results demonstrated that **18p** and **18x** exhibited the same selective inhibitory activity as PI-1840 with only targeting β5c (Table 4), but carfilzomib can inhibit several subunits. These results indicated that our compounds was β5c selective proteasome inhibitors which were different from approved carfilzomib.

2.2.2. Anti-proliferation activity against cancer cell lines

Table 5.

Anti-proliferation activity of compound **18p** and **18x** against different cancer cell lines

Compd.	Anti-proliferative activity (IC_{50}, μM)[a]				
	HepG2	**HGC27**	**RPMI 8226**	**MM1S**	**MV-4-11**
18p	2.87 ± 0.51	2.47 ± 0.12	>20	>20	>20
18x	3.91 ± 0.95	4.62 ± 1.44	>20	>20	>20
PI-1840	2.95 ± 0.77	3.35 ± 1.09	>20	>20	>20

[a] The IC_{50} values are shown as an average of three independent determinations.

We selected the two potent compounds **18p** and **18x** to further assess their anti-proliferative activity in vitro against various cancer cell lines including HepG2, HGC27, RPMI 8226, MM1S, and MV-4-11. Interestingly, we found that the two selected compounds exhibited more potent anti-proliferation activity against solid cancer cell lines compared to blood cancer cell lines. Compounds **18p** and **18x** inhibited the viability of the two tested solid cancer cell lines HepG2, HGC27, with IC_{50} values ranging from 2 μM to 5 μM. However, both compounds were shown to only weakly inhibit the viability of the three blood cancer cell lines RPMI 8226, MM1S, and MV-4-11, with IC_{50} values of more than 20 μM. Several studies[25, 26] have shown that higher immunoproteasome expression over constitutive proteasome in B-cell malignancies, suggesting the importance of the immunoproteasome in hematologic malignancies[27, 28]. As described in table 4, **18p** and **18x** shown selectivity for β5c inhibitory activity with no β5i inhibition, this may be the reason for a lack of efficacy in blood cancer cells versus solid cancer cells. Therefore, other than approved inhibitors that may only be applied to blood cancers, these compounds could be applied to solid cancers.

2.3. Binding mode analysis

To elucidate the binding modes of this class of compounds within the β5 site of

proteasome, molecular docking calculations were performed. First, the ligand in the crystal structure of 3MG6 (PDB ID) was extracted and re-docked into the binding pocket [29-31]. The root mean square deviation (RMSD) between the docked pose and the original conformation of the ligand was calculated, and a RMSD = 0.3 Å suggests that the Glide docking with the SP scoring can successfully recognize the near-native conformations. Then, the binding mode of compound **18x** within the proteasome was predicted by the Glide docking. As depicted in Fig. 5, the 4-butylphenyl moiety of compound **18x** appears to provide a well fit for the important hydrophobic S3 pocket (Fig. 5B), while four critical hydrogen bonds were also observed (Fig. 5A and Fig. 5C). As discussed in SARs, the para-position of A ring was important to inhibitory activity, we found that *p*-nitrogen atom of pyridazine ring formed a hydrogen bond with Arg91. Particularly, two other hydrogen bonds were formed between the ligand and Ala50N and Asp114O^{γ} via a bridge water molecule. Besides, carbonyl group (near to phenyl ring) was predicted to form the last hydrogen bond with Ala49N. The docking studies may allow the rational design of more potent proteasome inhibitors. While a hydrogen bond acceptor group or atom was needed in the para-position of A ring in this class and the R group prefer to be hydrophobic group to bind to S3 pocket.

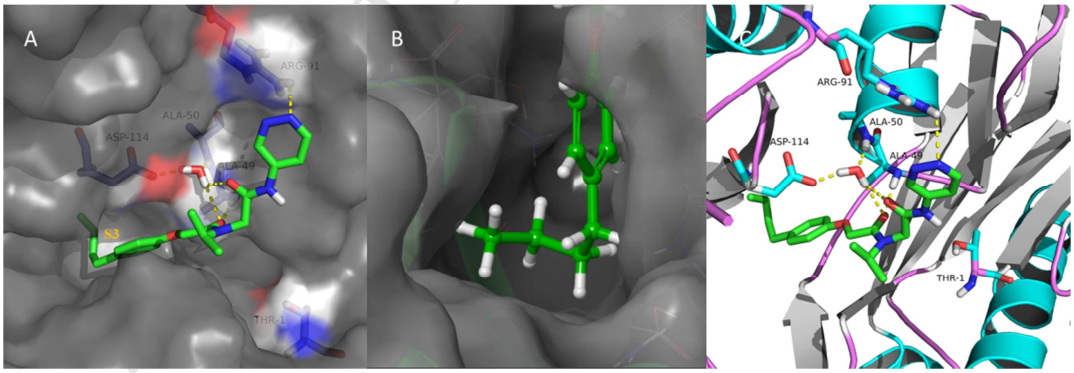


Figure 5. Binding modes of compound **18x** within the β5 site of proteasome. A: Binding modes of compound **18x** within the β5 site of proteasome displayed as Connolly surface. B: Close-up view of the S3 pocket to illustrate occupancy by the 4-butylphenyl moiety of compound **18x** in the β5 active site. C: Binding modes of compound **18x** within the β5 site of proteasome represented as a ribbon model. H-bonds are shown as dashed yellow lines

3. Conclusions

In this study, we found that the reported PI-1840 displayed a high metabolic susceptibility in HLMs due to the presence of a 1, 2, 4-oxadiazole moiety. In order to explore novel proteasome inhibitors with higher metabolic stability, we rationally designed and synthesized a series of phenol ether derivatives based on the structural features of PI-1840. Most of these compounds exhibited moderate to excellent proteasome inhibitory activity. Compound **18x** in particular was found to be the most potent compound with being 2-fold more potent than PI-1840. In addition, compound **18x** was also found to be more stable than PI-1840 in HLMs. Moreover, further test results confirmed that compounds **18p** and **18x** exhibited selective anti-proliferative activity against solid cancer cell lines, including HepG2 and HGC27. Docking studies were also carried out to predict the binding modes of this class of compounds within proteasome. Taken in concert, we identified a new class of non-covalent proteasome inhibitors with higher metabolic stability and potent activity, providing incentive for the further development of such compounds as potential anticancer agents in the treatment of solid cancers.

4. Experimental section

^{1}H and ^{13}C NMR spectra were recorded on Brüker 400/500 MHz spectrometer (Brüker Bioscience, Billerica, MA, USA) with $CDCl_3$ or DMSO-d_6 as solvent (Instead of **18x**, all NMR experiments performed at 20 °C). Chemical shifts (d) were reported in parts per million (ppm) relative to internal TMS, and coupling constants (*J*) were reported in Hertz (Hz). Splitting patterns were designated as singlet (s), broad singlet (brs), doublet (d), double doublet (dd), triplet (t), quartet (q) and multiplet (m). Melting points were determined using a Buchi B-540 capillary melting point apparatus and are uncorrected. Electrospray ionization mass spectroscopy (ESI-MS) spectra were obtained with a Shimadzu LCMS-2020 mass spectrometer with mobile phases as methanol and water containing 0.1% formic

acid. High resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF LC/MS spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points were determined using a Buchi B-540 capillary melting point apparatus and are uncorrected. HPLC analysis was performed using an Agilent 1100 Series system with a COSMOSIL 5C18-MS-II (4.6 mm I.D. × 250 mm) column and detected at 254 nm wavelength. The details of the HPLC methods can be found in supplementary data. Reagents and solvents were purchased from common commercial suppliers and were used without further purification unless stated otherwise. Column chromatography was performed using silica gel (200-300 mesh). All yields are unoptimized and generally represent.

4.1. Chemistry

4.1.1. tert-Butyl (2-(isopropylamino)ethyl)carbamate **8**

To a solution of tert-butyl (2-aminoethyl) carbamate **7** (123 mg, 1.0 mmol) and TEA (202 mg, 2.0 mol) in 5 mL MeCN was added 2-bromopropane (160 mg, 1.0 mmol) at 0 °C. Then the reaction mixture was warmed to room temperature and stirred overnight. The MeCN was evaporated, and the residue was dissolved in EtOAc (15 mL), washed with water (10 mL × 3) and brine (10 mL × 3). The organic layer was dried over Na_2SO_4, concentrated under vacuum and purified by SiO_2 chromatography (ethyl acetate: petroleum ether=1:1) to afford the compound **8** as a colourless liquid (144 mg, 70%).^{1}H NMR (500 MHz, DMSO-d_6) δ 6.88 – 6.55 (m, 1H), 3.44 – 3.13 (m, 1H), 3.02 – 2.88 (m, 2H), 2.72 – 2.63 (m, 1H), 2.53 – 2.48 (m, 2H), 1.38 (s, 9H), 0.95 (d, J = 6.5 Hz, 6H). ESI-MS: m/z = 203.1 $[M+H]^+$.

4.1.2. tert-Butyl (2-(2-chloro-N-isopropylacetamido)ethyl)carbamate **9**

To a solution of **8** (130 mg, 0.64 mmol) and triethylamine (129 mg, 1.28 mmol) in anhydrous THF (5 mL) under a nitrogen atmosphere at 0 °C was added chloroacetyl chloride (108 mg, 0.96 mmol) dropwise. After stirring at room temperature for 30 min, 10 mL H_2O was added to the reaction mixture at 0 °C. The

THF was evaporated concentrated and the crude residue was extracted with ethyl acetate (10 mL × 3). The organic layer was washed with saturated aqueous Na_2CO_3 (10 mL × 3) and brine (10 mL × 3), dried over anhydrous Na_2SO_4, evaporated and purified by SiO_2 chromatography to afford the compound **9** as a colourless liquid (158 mg, 89%). The ^{1}H NMR showed 3:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (s, 1H), 4.06 (s, 2H [4.14 minor isomer]), 4.02 – 3.94 (m, 1H [4.46 minor isomer]), 3.40 – 3.12 (m,4H), 1.51 – 1.29 (m, 9H), 1.21 (d, J = 6.5 Hz, 6H [1.15 minor isomer]). ESI-MS: m/z = 279.1 $[M+H]^+$.

4.1.3. tert-Butyl (2-(N-isopropyl-2-(4-propylphenoxy)acetamido)ethyl)carbamate **10**

To a solution of **9** (158 mg, 0.57 mmol) in anhydrous 5 mL MeCN was added K_2CO_3 (236 mg, 1.71 mmol) at 0°C, followed by 4-propylphenol (86 mg, 0.70 mmol). The reaction mixture was heated at reflux under nitrogen atmosphere for 2h. After cooling to room temperature, the reaction mixture was concentrated and dissolved with ethyl acetate (10 mL), washed with water (10 mL × 3) and brine (10 mL × 3). The organic layer was dried over Na_2SO_4, concentrated under vacuum and purified by SiO_2 chromatography (ethyl acetate: petroleum ether=1:5) to afford the compound **10** as a colourless liquid (198 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.15 – 7.13 (m, 2H), 6.67 (s, 1H), 4.49 (s, 2H), 3.40 – 3.38 (m, 2H), 3.15 – 3.02 (m, 1H), 2.89 (t, J = 6.0 Hz, 2H), 2.50 (t, J = 6.5 Hz, 2H), 1.60 – 1.50 (m, 2H), 1.44 (s, 9H), 1.15 (d, J = 6.5 Hz, 6H), 0.92 (t, J = 7.5 Hz, 3H). ESI-MS: m/z = 379.2 $[M+H]^+$.

4.1.4. N-(2-Aminoethyl)-N-isopropyl-2-(4-propylphenoxy)acetamide **11**

To a solution of **10** (378 mg, 1.00 mmol) in 2 mL ethyl acetate was added saturated hydrogen chloride in ethyl acetate (4 mL) at 0°C. After stirring at room temperature for 2 h, the reaction mixture was concentrated and dissolved with ethyl acetate (15 mL), with 15 mL saturated aqueous Na_2CO_3 was added at 0°C. The mixture was kept at 0°C and stirred for 10min. Then the organic layer was washed

with brine (10 mL × 3), dried over Na_2SO_4, concentrated under vacuum and purified by SiO_2 chromatography to afford the compound **11** as pale yellow oil (256 mg, 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (t, J = 5.6 Hz, 2H), 7.14 – 7.05 (m, 2H), 6.93 – 6.86 (m, 2H), 4.46 (s, 2H), 3.43 – 3.36 (m, 2H), 3.14 – 3.01 (m, 1H), 2.85 (t, J = 6.0 Hz, 2H), 2.48 (t, J = 6.5 Hz, 2H), 1.59 – 1.49 (m, 2H), 1.14 (d, J = 6.5 Hz, 6H), 0.87 (t, J = 7.5 Hz, 3H). ESI-MS: m/z = 279.2 $[M+H]^+$.

4.1.5. N-Isopropyl-2-(4-propylphenoxy)-N-(2-(3-(pyridin-3-yl)ureido)ethyl) acetamide **12a**

Pyridin-3-amine (94 mg, 1.00 mmol) and triethylamine (303 mg, 3.00 mmol) dissolved in 3 mL anhydrous DCM , and the mixture was added to a solution of triphosgene (95 mg, 0.32 mmol) in anhydrous DCM (5 mL) under a nitrogen atmosphere at 0 °C. After stirring at room temperature for 1 h, compound **11** (278 mg, 1.00 mol) dissolving in 1 mL anhydrous DCM was added to the reaction mixture at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Then the reaction mixture was concentrated and dissolved with ethyl acetate (10 mL), washed with water (10 mL × 3) and brine (10 mL × 3), dried over anhydrous Na_2SO_4, and then evaporated. The residues purified by SiO_2 chromatography (DCM: MeOH=12:1) to afford the compound **12a** as a pale yellow solid (230 mg, 58%). Mp: 113.1-114.3 °C. HPLC purity = 99.99%, HPLC t_R = 14.84 min (Method A). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, J = 2.5 Hz, 1H), 8.78 (s, 1H), 8.24 (d, J = 4.5 Hz, 1H), 8.20 – 8.11 (m, 1H), 7.32 – 7.23 (m, 1H), 7.21 (dd, J = 8.5, 4.5 Hz, 1H), 7.15-7.08 (m, 2H), 6.88-6.77 (m, 2H), 4.75 – 4.59 (m, 1H), 4.55 (s, 2H), 3.53 – 3.42 (m, 2H), 3.39 – 3.30 (m, 2H), 2.54 (t, J = 7.5 Hz, 2H), 1.66 – 1.56 (m, 2H), 1.15 (d, J = 6.5 Hz, 6H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.87, 155.29, 155.12, 143.28, 141.57, 137.32, 136.68, 129.71, 126.78, 123.29, 114.39, 67.23, 45.34, 40.52, 39.43, 37.09, 24.65, 20.86, 13.72. HRMS (ESI) m/z: calcd for $C_{22}H_{31}N_4O_3$ $[M + H]^+$, 399.2391; found 399.2421.

4.1.6. N-Isopropyl-2-(4-propylphenoxy)-N-(2-(3-(pyridin-3-ylmethyl)ureido)ethyl) acetamide **12b**

This compound was prepared from pyridin-3-ylmethanamine (108mg, 1.00 mmol), triethylamine (303 mg, 3.00 mmol) and triphosgene (95 mg, 0.32 mmol) in a similar manner as described for compound **12a**. The product was obtained as pale yellow oil (260 mg, 63%). HPLC purity = 96.32%, HPLC t_R = 12.96 min (Method A). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 1.5 Hz, 1H), 8.43 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.38 (s, 1H), 7.19 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.81 – 6.75 (m, 3H), 4.51 – 4.38 (m, 5H), 3.41 – 3.31 (m, 2H), 3.27 – 3.18 (m, 2H), 2.51 (t, *J* = 7.5, 2H), 1.63 – 1.51 (m, 2H), 1.08 (d, *J* = 6.5 Hz, 6H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 170.30, 157.96, 155.20, 149.11, 148.10, 136.53, 135.94, 135.62, 129.65, 123.42, 114.40, 67.24, 45.58, 42.29, 40.36, 39.62, 37.09, 24.66, 20.92, 13.72. HRMS (ESI) m/z: calcd for $C_{23}H_{33}N_4O_3$ $[M + H]^+$, 413.2547; found 413.2540.

4.1.7. N-(2-(N-Isopropyl-2-(4-propylphenoxy)acetamido)ethyl)nicotinamide **12c**

To a solution of nicotinic acid (128 mg, 1.00 mmol) in DCM (5 mL) were added HOBt (162 mg, 1.20 mmol) and EDCI (228 mg, 1.50 mmol) at 0 °C. The reaction mixture was stirred for 30 min. Then compound **11** (278 mg, 1.00 mmol) and diisopropylethylamine (0.5 mL, 3.00 mmol) were added. After stirring at room temperature for another 5 h, the resulting mixture was washed with aqueous $NaHCO_3$ solution (10 mL × 3), brine (10 mL × 3) and dried over Na_2SO_4. The organic layer was evaporated in vacuo and the crude product was purified by SiO_2 chromatography (ethyl acetate: petroleum ether: TEA=1:1:3%) to afford the compound **12c** as a white solid (341 mg, 89%). Mp: 54.5-56.8 °C. HPLC purity = 99.10%, HPLC t_R = 11.30 min (Method A). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.67 – 8.62 (m, 1H), 8.59 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.44 (s, 1H), 7.37 – 7.27 (m, 1H), 7.11 – 7.04 (m, 2H), 6.82 (d, *J* = 7.5 Hz, 2H), 4.45 (s, 2H), 3.98 – 3.85 (m, 1H), 3.69 – 3.50 (m, 4H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.64 – 1.51 (m, 2H), 1.31 – 1.05 (m, 6H), 0.93 – 0.85 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 169.96, 169.11,

155.37, 150.54, 147.05, 136.31, 134.12, 132.71, 129.58, 123.51, 114.47, 67.43, 50.84, 39.76, 39.00, 37.10, 24.66, 21.17, 13.73. HRMS (ESI) m/z: calcd for $C_{22}H_{30}N_3O_3$ $[M + H]^+$, 384.2282; found 384.2291.

4.1.8. Ethyl isopropylglycinate **14a**

To a solution of propan-2-amine (4.72 g, 80.00 mmol) and TEA (2.00 g, 20.00 mol) in 50 mL MeCN was added ethyl 2-chloroacetate (2.44 g, 20.00 mmol) at 0 °C. Then the reaction mixture was warmed to room temperature and stirred overnight. The MeCN was evaporated, and the residue was dissolved in EtOAc (50 mL), washed with water (50 mL × 3) and brine (50 mL × 3). The organic layer was dried over Na_2SO_4, concentrated under vacuum and the crude product was purified SiO_2 chromatography (ethyl acetate: petroleum ether =1:4) to afford the compound **14a** as a colourless liquid (2.10 g, 72%).^{1}H NMR (400 MHz, DMSO-d_6) δ 4.12 – 4.02 (m, 2H), 3.42 – 3.19 (m, 3H), 2.78 – 2.65 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H), 0.94 (d, J = 6.4 Hz, 6H). ESI-MS: m/z = 146.1 $[M+H]^+$.

4.1.9. Benzyl isopropylglycinate **14b**

This compound was prepared from propan-2-amine (4.72 g, 80.00 mmol), triethylamine (2.00 g, 20.00 mmol) and benzyl 2-chloroacetate 13b (4.16 g, 20.00 mmol) in a similar manner as described for compound **14a**. The product was obtained as a colourless liquid (3.22 g, 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 – 7.28 (m, 5H), 5.12 (s, 2H), 3.37 (s, 2H), 2.72 (hept, J = 6.2 Hz, 1H), 1.85 (s, 1H), 0.94 (d, J = 6.2 Hz, 6H). ESI-MS: m/z = 208.1 $[M+H]^+$.

4.1.10. Ethyl 3-(isopropylamino)propanoate **14c**

This compound was prepared from propan-2-amine (4.72 g, 80.00 mmol), triethylamine (2.00 g, 20.00 mmol) and ethyl 3-bromopropanoate **7c** (3.60 g, 20.00 mmol) in a similar manner as described for compound **14a**. The product was obtained as a colourless liquid (2.20, 69%).^{1}H NMR (400 MHz, DMSO-d_6) δ 4.04 (q, J = 7.2 Hz, 2H), 3.17 (brs, 1H), 2.77 – 2.58 (m, 3H), 2.38 (t, J = 6.8 Hz, 2H),

1.17 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 6H). ESI-MS: m/z = 160.1 $[M+H]^+$.

4.1.11. Ethyl N-(2-chloroacetyl)-N-isopropylglycinate **15a**

This compound was prepared from **14a** (0.93 g, 6.40 mmol), triethylamine (1.29 g, 12.80 mmol) and chloroacetyl chloride (1.08 g, 9.60 mmol) in a similar manner as described for compound **9**. The product was obtained as a colourless liquid (1.2 g, 90%). The ^{1}H NMR showed 5:2 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 – 4.15 (m, 3H, [4.84-4.76 minor isomer]), 4.14 (s, 2H, [4.02 minor isomer]), 3.90 (s, 2H, [3.97 minor isomer]), 1.31 – 1.24 (m, 3H), 1.23 (d, *J* = 6.5 Hz, 6H, [1.09-1.08 minor isomer]). ESI-MS: m/z = 222.1 $[M+H]^+$.

4.1.12. Benzyl N-(2-chloroacetyl)-N-isopropylglycinate **15b**

This compound was prepared from **14b** (1.32 g, 6.40 mmol), triethylamine (1.29 g, 12.80 mmol) and chloroacetyl chloride (1.08 g, 9.60 mmol) in a similar manner as described for compound **9**. The product was obtained as a colourless liquid (1.68 g, 93%). The ^{1}H NMR showed 3:1 ratio of atropisomers.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H), 5.17 (s, 2H [5.20 minor isomer]), 4.20 – 4.11 (m, 3H [4.80 minor isomer], [4.07 minor isomer]), 3.99 – 3.94 (m, 2H), 1.22 (d, *J* = 6.5 Hz, 6H [1.06 minor isomer]). ESI-MS: m/z = 284.1 $[M+H]^+$.

4.1.13. Ethyl 3-(2-chloro-N-isopropylacetamido)propanoate **15c**

This compound was prepared from **14c** (1.02 g, 6.40 mmol), triethylamine (1.29 g, 12.80 mmol) and chloroacetyl chloride (1.08 g, 9.60 mmol) in a similar manner as described for compound **9**. The product was obtained as a colourless liquid (1.43 g, 95%). The ^{1}H NMR showed 3:1 ratio of atropisomers.^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 – 4.07 (m, 3H), 4.05 (s, 2H), 3.46 (t, *J* =7.5 Hz, 2H), 2.60 (t, *J* =7.5 Hz, 2H), 1.30 – 1.12 (m, 9H). ESI-MS: m/z = 236.1 $[M+H]^+$.

4.1.14. Ethyl N-isopropyl-N-(2-(p-tolyloxy)acetyl)glycinate **16a**

This compound was prepared from **15a** (180 mg, 0.81 mmol), p-cresol (105 mg,

0.98 mmol) and K_2CO_3 (449 mg, 3.26 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (187 mg, 79%). The ^{1}H NMR showed 2:1 ratio of atropisomers.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 – 7.02 (m, 2H), 6.90 – 6.75 (m, 2H), 4.73 (s, 2H, [5.62 minor isomer]), 4.34 – 4.22 (m, 1H, [4.82 minor isomer]), 4.21 – 4.13 (m, 2H), 3.92 (s, 2H, [4.07 minor isomer]), 2.28 (s, 3H), 1.29 – 1.22 (m, 3H), 1.20 (d, J = 6.6 Hz, 6H, [1.09 minor isomer]). ESI-MS: m/z = 294.1 $[M+H]^+$.

4.1.15. Ethyl N-(2-(4-ethylphenoxy)acetyl)-N-isopropylglycinate **16b**

This compound was prepared from **15a** (180 mg, 0.81 mmol), 4-ethylphenol (119 mg, 0.98 mmol) and K_2CO_3 (449 mg, 3.26 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (225 mg, 90%). The ^{1}H NMR showed 2:1 ratio of atropisomers.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.04 (m, 2H), 6.92 – 6.80 (m, 2H), 4.73 (s, 2H, [4.62 minor isomer]), 4.33 – 4.22 (m, 1H, [4.81 minor isomer]), 4.20 – 4.12 (m, 2H), 3.92 (s, 2H, [4.07 minor isomer]), 2.58 (q, J = 7.6 Hz, 2H), 1.33 – 1.15 (m, 12H, [1.09 minor isomer]). ESI-MS: m/z = 308.2 $[M+H]^+$.

4.1.16. Ethyl N-isopropyl-N-(2-(4-propylphenoxy)acetyl)glycinate **16c**

This compound was prepared from **15a** (180 mg, 0.81 mmol), 4-propylphenol (133 mg, 0.98 mmol) and K_2CO_3 (449 mg, 3.26 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (228 mg, 87%). The ^{1}H NMR showed 2:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 2H), 6.91 – 6.88 (m, 2H, [6.87-6.85 minor isomer]), 4.76 (s, 2H, [4.65 minor isomer]), 4.36 – 4.26 (m, 1H, [4.89-4.80 minor isomer]), 4.20 (m, 2H), 3.95 (s, 2H, [4.10 minor isomer]), 2.69 – 2.43 (m, 2H), 1.69 – 1.57 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 1.23 (d, J = 6.5 Hz, 6H, [1.12 minor isomer]), 0.96-0.93 (m, 3H). ESI-MS: m/z = 322.2 $[M+H]^+$.

4.1.17. Ethyl N-(2-(4-butylphenoxy)acetyl)-N-isopropylglycinate **16d**

This compound was prepared from **15a** (150 mg, 0.68 mmol), 4-butylphenol (122 mg, 0.82 mmol) and K_2CO_3 (375 mg, 2.72 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (160 mg, 71%). The ^{1}H NMR showed 2:1 ratio of atropisomers.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 – 7.05 (m, 2H), 6.89 – 6.85 (m, 2H, [6.84 minor isomer]), 4.73 (s, 2H, [4.62 minor isomer]), 4.32 – 4.24 (m, 1H, [4.82 minor isomer]), 4.17 – 4.13 (m, 2H), 3.92 (s, 2H, [3.91 minor isomer]), 2.58 – 2.49 (m, 2H), 1.61 – 1.49 (m, 2H), 1.37 – 1.24 (m, 5H), 1.21 (d, J = 6.5 Hz, 6H, [1.1 minor isomer]), 0.94 – 0.88 (m, 3H). ESI-MS: m/z = 336.2 $[M+H]^+$.

4.1.18. Ethyl N-isopropyl-N-(2-(4-isobutylphenoxy)acetyl)glycinate **16e**

This compound was prepared from **15a** (150 mg, 0.68 mmol), 4-isobutylphenol (122 mg, 0.82 mmol) and K_2CO_3 (375 mg, 2.72 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (157 mg, 69%). The ^{1}H NMR showed 2:1 ratio of atropisomers.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.02 (m, 2H), 6.89 – 6.85 (m, 2H, [1.10 minor isomer]), 4.74 (s, 2H, [4.63 minor isomer]), 4.33 – 4.25 (m, 1H, [4.82 minor isomer]), 4.18 – 4.15 (m, 2H), 3.93 (s, 2H, [4.01 minor isomer]), 2.43 – 2.37 (m, 2H), 1.86 – 1.76 (m, 1H), 1.29 – 1.25 (m, 3H), 1.21 (d, J = 6.5 Hz, 6H, [1.10 minor isomer]), 0.90 – 0.85 (m, 6H). ESI-MS: m/z = 336.2 $[M+H]^+$.

4.1.19. Ethyl N-isopropyl-N-(2-(4-pentylphenoxy)acetyl)glycinate **16f**

This compound was prepared from **15a** (150 mg, 0.68 mmol), 4-pentylphenol (134 mg, 0.82 mmol) and K_2CO_3 (375 mg, 2.72 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (167 mg, 70%). The ^{1}H NMR showed 2:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 – 7.06 (m, 2H), 6.89 – 6.85 (m, 2H, [6.84 minor isomer]), 4.73 (s, 2H, [4.62 minor isomer]), 4.32 – 4.24 (m, 1H, [4.82 minor isomer]), 4.19 – 4.13 (m, 2H), 3.93 (s, 2H, [4.08 minor isomer]), 2.57 – 2.48 (m, 2H), 1.61 – 1.52 (m, 2H), 1.33 – 1.26 (m, 7H), 1.21 (d, J = 6.5 Hz, 6H, [1.12 minor isomer]), 0.92 – 0.86 (m, 3H).

ESI-MS: m/z = 350.2 $[M+H]^+$.

4.1.20. Ethyl N-isopropyl-N-(2-(4-methoxyphenoxy)acetyl)glycinate **16g**

This compound was prepared from **15a** (180 mg, 0.81 mmol), 4-methoxyphenol (121 mg, 0.98 mmol) and K_2CO_3 (449 mg, 3.26 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (205 mg, 82%). The ^{1}H NMR showed 2:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 – 6.85 (m, 2H), 6.85 – 6.81 (m, 2H), 4.71 (s, 2H, [4.60 minor isomer]), 4.34 – 4.23 (m, 1H, [4.83 minor isomer]), 4.21 – 4.15 (m, 2H), 3.92 (s, 2H, [4.07 minor isomer]), 3.77 – 3.75 (m, 3H), 1.28 – 1.22 (m, 3H), 1.21 (d, J = 6.5 Hz, 6H, [1.10 minor isomer]). ESI-MS: m/z = 310.2 $[M+H]^+$.

4.1.21. Ethyl N-(2-(4-ethoxyphenoxy)acetyl)-N-isopropylglycinate **16h**

This compound was prepared from **15a** (180 mg, 0.81 mmol), 4-ethoxyphenol (135 mg, 0.98 mmol) and K_2CO_3 (449 mg, 3.26 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (190 mg, 73%). The ^{1}H NMR showed 2:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 – 6.84 (m, 2H), 6.84 – 6.78 (m, 2H), 4.70 (s, 2H, [4.59 minor isomer]), 4.33 – 4.23 (m, 1H, [4.82 minor isomer]), 4.20 – 4.14 (m, 2H), 4.00 – 3.94 (m, 2H), 3.92 (s, 2H, [4.07 minor isomer]), 1.41 – 1.35 (m, 3H), 1.28 – 1.22 (m, 3H), 1.20 (d, J = 6.5 Hz, 6H, [1.09 minor isomer]).ESI-MS: m/z = 324.2 $[M+H]^+$.

4.1.22. Ethyl N-isopropyl-N-(2-(4-(trifluoromethyl)phenoxy)acetyl)glycinate **16i**

This compound was prepared from **15a** (180 mg, 0.81 mmol), 4-(trifluoromethyl)phenol (158 mg, 0.98 mmol) and K_2CO_3 (449 mg, 3.26 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (260 mg, 93%). The ^{1}H NMR showed 2:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.05 – 6.99 (m, 2H), 4.87 – 4.79 (m, 2H, [4.71 minor isomer]), 4.26 – 4.14 (m, 3H), 3.94 (s, 2H, [4.02 minor isomer]), 1.31 – 1.18 (m, 9H, [1.11 minor isomer]). ESI-MS: m/z = 348.1 $[M+H]^+$.

4.1.23. Ethyl N-(2-(4-bromophenoxy)acetyl)-N-isopropylglycinate **16j**

This compound was prepared from **15a** (180 mg, 0.81 mmol), 4-bromophenol (158 mg, 0.98 mmol) and K_2CO_3 (449 mg, 3.26 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (262 mg, 91%). The ^{1}H NMR showed 2:1 ratio of atropisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.33 (m, 2H), 6.88 – 6.79 (m, 2H), 4.74 (s, 2H, [4.63 minor isomer]), 4.27 – 4.12 (m, 3H, [4.81 minor isomer]), 3.92 (s, 2H, [4.02 minor isomer]), 1.31 – 1.23 (m, 3H), 1.21 (d, J = 6.7 Hz, 6H, [1.09 minor isomer]). ESI-MS: m/z = 358.0 $[M+H]^+$.

4.1.24. Benzyl N - isopropyl- N - (2 - (4- (2 – methoxy - 2- oxoethyl) phenoxy) acetyl)glycinate **16k**

This compound was prepared from **15b** (1.00 g, 3.50 mmol), methyl 2-(4-hydroxyphenyl)acetate (0.71 g, 4.20 mmol) and K_2CO_3 (2.42 g, 17.5 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil (0.98 g, 68%). The ^{1}H NMR showed 2:1 ratio of atropisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 7.22 – 7.13 (m, 2H), 6.93 – 6.88 (m, 2H, [6.83 minor isomer]), 5.15 (s, 2H, [5.16 minor isomer]), 4.74 (s, 2H, [4.60 minor isomer]), 4.29 – 4.19 (m, 1H), 3.98 (s, 2H, [4.24 minor isomer]), 3.67 (s, 3H), 3.55 (s, 2H), 1.19 (d, J = 6.6 Hz, 6H, [1.07 minor isomer]). ESI-MS: m/z = 414.2 $[M+H]^+$.

4.1.25. Ethyl 3-(N-isopropyl-2-(4-propylphenoxy)acetamido)propanoate **16l**

This compound was prepared from **15c** (588 mg, 2.50 mmol), 4-propylphenol (374 mg, 2.75 mmol) and K_2CO_3 (1.04 g, 7.5 mmol) in a similar manner as described for compound **10**. The product was obtained as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.64 (s, 2H), 4.25 – 4.04 (m, 3H), 3.49 (t, J = 8.0 Hz, 2H), 2.67 – 2.57 (m, 2H), 2.53 (t, J = 8.0 Hz, 2H), 1.60 – 1.45 (m, 2H), 1.26 – 1.13 (m, 9H), 0.90 (t, J = 7.2 Hz, 3H).

ESI-MS: m/z = 336.2 $[M+H]^+$.

4.1.26. General procedure for the synthesis of carboxylic acids **17a-17j** and **17l**

To a solution of compounds **16l-16j** and **16l** (3.00 mmol) in 6 mL EtOH/THF (V_{EtOH}:V_{THF}=1:1) at 0 °C was added 6 mL 1N NaOH (aq). The mixture was stirred at room temperature for 1 h and EtOH and THF were evaporated in vacuo. The residue was acidified to pH=2~3 with 1 N HCl and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **17a-17j** and **17l** were put into next step without further purification.

4.1.27. N-Isopropyl-N-(2-(4-(2-methoxy-2-oxoethyl)phenoxy)acetyl)glycine **17k**

Compound **16k** (413 mg, 1.00 mmol) was dissolved in methanol (5 mL) in the presence of 10% palladium on carbon (10 mol%), and the reaction mixturewas stirred under an atmosphere of H_2 for 2 h. The Pd/C was removed via filtration through celite, and the solvent was evaporated to obtain compound **17k** in quantitative yield. The crude product was used directly in the next step.

4.1.28.

3-(N-Isopropyl-2-(4-propylphenoxy)acetamido)-N-(pyridin-3-yl)propanamide **18a**

This compound was prepared from **17l** (921 mg, 3.00 mmol), pyridin-3-amine (282 mg, 3.00 mmol), HOBt (486 mg, 3.60 mmol), EDCI (864 mg, 4.50 mmol) and DIPEA (1.5 mL, 9.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as pale yellow oil (402mg, 43%). HPLC purity = 97.73%, HPLC t_R = 12.17 min (Method A). The ^{1}H NMR showed 7:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.68 (s, 1H), 8.29 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.24 – 7.15 (m, 1H), 7.03 (d, J = 8.5 Hz, 2H, [6.98 minor isomer]), 6.77 (d, J = 8.5 Hz, 2H), 4.69 (s, 2H), 4.21 – 3.98 (m, 1H), 3.60 (t, J = 7.0 Hz, 2H, [3.66 minor isomer]), 2.66 (t, J = 7.0 Hz, 2H), 2.48 (t, J = 7.5 Hz, 2H), 1.63 – 1.51 (m, 2H), 1.25 (d, J = 6.5 Hz, 6H, [1.17 minor isomer]), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.31, 168.48, 155.86, 144.69, 141.40, 136.07[135.48

minor isomer], 129.49, 126.88, 123.52, 114.25, 67.46, 48.71, 38.01, 37.59, 37.10, 24.67, 21.15[20.16 minor isomer], 13.77. HRMS (ESI) m/z: calcd for $C_{22}H_{30}N_3O_3$ $[M + H]^+$, 384.2282; found 384.2289.

4.1.29.

3-(N-Isopropyl-2-(4-propylphenoxy)acetamido)-N-(pyridin-3-ylmethyl)propanamide **18b**

This compound was prepared from **17l** (307 mg, 1.00 mmol), pyridin-3-ylmethanamine (108 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as pale yellow oil (325mg, 82%) . HPLC purity = 98.03%, HPLC t_R = 10.86 min (Method A). The ^{1}H NMR showed 7:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.44 (s, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 5.5 Hz, 1H), 7.20 (t, *J* = 4.5 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 2H,[7.01 minor isomer]), 6.78 (d, *J* = 8.0 Hz, 2H), 4.59 (s, 2H, [4.63 minor isomer]), 4.34 (d, *J* = 6.0 Hz, 2H), 4.11 – 4.03 (m, 1H), 3.49 (t, *J* = 7.5 Hz, 2H,[3.58 minor isomer]), 2.55 – 2.41 (m, 4H), 1.62 – 1.49 (m, 2H), 1.19 (d, *J* = 6.5 Hz, 6H, [1.14 minor isomer]), 0.89 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ 171.41[170.40 minor isomer], 168.09, 155.95, 149.10, 148.47, 135.97, 135.62, 134.35, 129.46, 123.54, 114.33[114.48 minor isomer], 67.66, 48.58[47.51 minor isomer], 40.85[39.91 minor isomer], 38.17, 37.09[37.49 minor isomer], 36.41, 24.68, 21.10[20.13 minor isomer], 13.76. HRMS (ESI) m/z: calcd for $C_{23}H_{31}N_3O_3$ $[M + H]^+$, 398.2438; found 398.2440.

4.1.30.

N-Isopropyl-N-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-2-(4-propylphenoxy)acetamide **18c**

This compound was prepared from **17c** (293 mg, 1.00 mmol), pyridin-3-ylmethanamine (108 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as

described for compound **12c**. The product was obtained as pale yellow oil (302mg, 79%). HPLC purity = 99.99%, HPLC t_R = 11.22 min (Method A). The ^{1}H NMR showed 7:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dd, J = 5.0, 1.0 Hz, 1H), 8.40 (s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.09 – 6.98 (m, 3H), 6.81 (d, J = 8.5 Hz, 2H, [6.71 minor isomer]), 4.71 (s, 2H, [4.56 minor isomer]), 4.29 (d, J = 6.1 Hz, 2H, [4.34 minor isomer]), 4.27 – 4.18 (m, 1H), 3.94 (s, 2H, [3.96 minor isomer]), 2.47 (t, J = 7.5 Hz, 2H), 1.60 – 1.49 (m, 2H), 1.19 (d, J = 7.0 Hz, 6H, [1.04 minor isomer]), 0.88 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.88, 169.29 [168.98 minor isomer], 155.67, 148.86 [149.30 minor isomer], 148.59, 136.18 [136.07 minor isomer], 135.27 [135.83 minor isomer], 133.97 [133.73 minor isomer], 129.57, 123.51, 114.27 [114.36 minor isomer], 67.44 [68.18 minor isomer], 49.09 [46.50 minor isomer], 45.28 [45.90 minor isomer], 40.71 [41.04 minor isomer], 37.07, 24.65, 20.94 [19.50 minor isomer], 13.76. HRMS (ESI) m/z: calcd for $C_{22}H_{30}N_3O_3$ $[M + H]^+$, 384.2282; found 384.2299.

4.1.31. N-Isopropyl-N-(2-oxo-2-(pyridin-3-ylamino)ethyl)-2-(4-propylphenoxy) acetamide **18d**

This compound was prepared from **17c** (293 mg, 1.00 mmol), pyridin-3-amine (94 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as pale yellow oil (147mg, 40%). HPLC purity = 99.55%, HPLC t_R = 12.10 min (Method A). The ^{1}H NMR showed 10:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.51 (d, J = 2.5 Hz, 1H, [8.48 minor isomer]), 8.30 (d, J = 4.0 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H, [8.03 minor isomer]), 7.20 (dd, J = 8.5, 4.5 Hz, 1H), 7.08 (d, J = 9.0 Hz, 2H, [7.01 minor isomer]), 6.87 (d, J = 8.5 Hz, 2H, [6.77 minor isomer]), 4.80 (s, 2H, [4.69 minor isomer]), 4.37 – 4.26 (m, 1H), 4.08 (s, 2H, [4.15 minor isomer]), 2.50 (t, J = 7.5 Hz, 2H), 1.62 – 1.51 (m, 2H), 1.30 (d, J = 6.5 Hz, 6H, [1.17 minor isomer]), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.65[169.23 minor isomer], 168.31, 155.74,

144.96, 141.35[141.15 minor isomer], 136.25, 134.85, 129.59, 126.98[127.12 minor isomer], 123.48[123.67 minor isomer], 114.31, 67.37, 49.31, 46.32[46.56 minor isomer], 37.08[34.50 minor isomer], 24.64[29.70 minor isomer], 21.01[19.53 minor isomer], 13.77[14.81 minor isomer]. HRMS (ESI) m/z: calcd for $C_{21}H_{28}N_3O_3$ $[M + H]^+$, 370.2125; found 370.2131.

4.1.32. N-Isopropyl-N-(2-oxo-2-(pyridin-2-ylamino)ethyl)-2-(4-propylphenoxy) acetamide **18e**

This compound was prepared from **17c** (293 mg, 1.00 mmol), pyridin-2-amine (94 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as pale yellow oil (138mg, 37%). HPLC purity = 95.89%, HPLC t_R = 14.99 min (Method B). The ^{1}H NMR showed 4:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H, [8.32 minor isomer]), 8.26 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H, [8.16 minor isomer]), 7.65 (t, J = 8.0 Hz, 1H, [7.70 minor isomer]), 7.11 – 6.95 (m, 3H), 6.87 (d, J = 8.5 Hz, 2H, [6.80 minor isomer]), 4.79 (s, 2H, [4.67 minor isomer]), 4.37 – 4.26 (m, 1H), 4.09 (s, 2H, [4.12 minor isomer]), 2.50 (t, J = 7.5 Hz, 2H, [2.46 minor isomer]), 1.63 – 1.51 (m, 2H), 1.27 (d, J = 7.0 Hz, 6H, [1.15 minor isomer]), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.45, 167.13, 154.81, 150.19, 146.91, 137.13 [137.40 minor isomer], 134.97, 128.50, 118.77 [119.11 minor isomer], 113.29, 113.05, 66.83 [67.50 minor isomer], 48.25 [45.86 minor isomer], 45.42 [45.69 minor isomer], 36.08, 23.63, 20.02 [18.52 minor isomer], 12.73. HRMS (ESI) m/z: calcd for $C_{21}H_{28}N_3O_3$ $[M + H]^+$, 370.2125; found 370.2129.

4.1.33. N-Isopropyl-N-(2-oxo-2-(pyridin-4-ylamino)ethyl)-2-(4-propylphenoxy) acetamide **18f**

This compound was prepared from **17c** (293 mg, 1.00 mmol), pyridin-4-amine (94 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**.

The product was obtained as a white solid (170mg, 46%). Mp: 172.1-175.5 °C. HPLC purity = 99.34%, HPLC t_R = 10.75 min (Method B). The ^{1}H NMR showed 11:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.41 (d, J = 6.0 Hz, 2H), 7.31 (d, J = 6.2 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H, [7.03 minor isomer]), 6.86 (d, J = 8.5 Hz, 2H, [6.74 minor isomer]), 4.80 (s, 2H, [4.69 minor isomer]), 4.36 – 4.26 (m, 1H), 4.07 (s, 2H, [4.15 minor isomer]), 2.52 (t, J = 7.5 Hz, 2H), 1.65 – 1.54 (m, 2H), 1.29 (d, J = 6.5 Hz, 6H, [1.18 minor isomer]), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.04, 167.67, 154.66, 149.44, 143.78, 135.33, 128.62, 113.24, 112.71, 66.40, 48.57, 45.99, 36.07, 23.63, 19.96, 12.72. HRMS (ESI) m/z: calcd for $C_{21}H_{28}N_3O_3$ $[M + H]^+$, 370.2125; found 370.2140.

4.1.34. N-Isopropyl-N-(2-oxo-2-(pyrimidin-5-ylamino)ethyl)-2-(4-propylphenoxy) acetamide **18g**

To a solution of **17c** (100 mg, 0.34 mmol) in 5 mL anhydrous THF was added 4-methylmorpholine (35 mg, 0.34 mmol) and isobutyl carbonochloridate (49 mg, 0.36 mmol) under nitrogen atmosphere at -10°C. The reaction mixture was stirred for 30 min at -10°C, then pyrimidin-5-amine (32mg, 0.34 mmol) was added. After reacting for another 30 min at -10°C, the reaction mixture was warmed to room temperature and stirred for 6 h. The solvent was evaporated and the residues was dissolved in ethyl acetate (10 mL), washed with water (10 mL × 3) and brine (10 mL × 3). The organic layer was dried over Na_2SO_4, concentrated under vacuum and purified on silica gel to afford the compound **18g** as a white solid (56 mg, 43%). Mp: 150.0-153.0 °C. HPLC purity = 99.33%, HPLC t_R = 15.10 min (Method B). The ^{1}H NMR showed 12:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.89 (s, 1H), 8.81 (s, 2H), 7.07 (d, J = 8.5 Hz, 2H, [6.97 minor isomer]), 6.83 (d, J = 8.5 Hz, 2H, [6.70 minor isomer]), 4.78 (s, 2H, [4.67 minor isomer]), 4.30 – 4.21 (m, 1H), 4.02 (s, 2H, [4.16 minor isomer]), 2.49 (t, J = 7.5 Hz,2H), 1.62 – 1.51 (m, 2H), 1.27 (d, J = 6.5 Hz, 6H, [1.16 minor isomer]), 0.89 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.86, 167.39, 154.63, 152.97, 146.63, 135.37, 132.46, 128.59, 113.26, 66.17, 48.37, 45.19, 36.05, 23.59, 19.95,

12.73. HRMS (ESI) m/z: calcd for $C_{20}H_{27}N_4O_3$ [M + H] $^+$, 371.2078; found 371.2088.

4.1.35. N-Isopropyl-N-(2-oxo-2-(pyrazin-2-ylamino)ethyl)-2-(4-propylphenoxy) acetamide **18h**

This compound was prepared from **17c** (100 mg, 0.34 mmol), pyrazin-2-amine (94 mg, 1.00 mmol), 4-methylmorpholine (35 mg, 0.34 mmol) and isobutyl carbonochloridate (49 mg, 0.36 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (189mg, 51%). Mp: 129.7-134.1 °C. HPLC purity = 98.97%, HPLC t_R = 15.53 min (Method B). The ^{1}H NMR showed 8:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 1H, [9.48 minor isomer]), 9.30 (s, 1H), 8.31 (s, 1H, [8.34 minor isomer]), 8.23 (s, 1H, [8.20 minor isomer]), 7.07 (d, *J* = 8.5 Hz, 2H, [6.98 minor isomer]), 6.86 (d, *J* = 8.5 Hz, 2H, [6.77 minor isomer]), 4.79 (s, 2H, [4.68 minor isomer]), 4.38 – 4.27 (m, 1H), 4.12 (s, 2H, [4.12 minor isomer]), 2.50 (t, *J* = 7.5 Hz, 2H, [2.46 minor isomer]), 1.63 – 1.52 (m, 2H), 1.28 (d, *J* = 6.5 Hz, 6H, [1.18 minor isomer]), 0.90 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.85, 168.23, 155.74, 148.02, 142.20, 140.27, 137.01, 136.16, 129.58, 114.29, 67.78, 49.50, 46.53, 37.12, 24.68, 21.06, 13.77. HRMS (ESI) m/z: calcd for $C_{20}H_{27}N_4O_3$ [M + H] $^+$, 371.2078; found 371.2099.

4.1.36. N-Isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl)-2-(4-propylphenoxy)acetamide **18i**

This compound was prepared from **17c** (100 mg, 0.34 mmol), pyridazin-4-amine (94 mg, 1.00 mmol), 4-methylmorpholine (35 mg, 0.34 mmol) and isobutyl carbonochloridate (49 mg, 0.36 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (263 mg, 71%) . Mp: 211.8-213.2 °C. HPLC purity = 99.79%, HPLC t_R = 12.40 min (Method B). The ^{1}H NMR showed 13:7 ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.69

(s, 1H, [10.91 minor isomer]), 9.31 – 9.26 (m, 1H), 9.03 (d, *J* = 6.0 Hz, 1H, [9.06 minor isomer]), 7.91 (dd, *J* = 6.0, 2.7 Hz, 1H, [7.96 minor isomer]), 7.11 – 7.02 (m, 2H), 6.86 – 6.79 (m, 2H), 4.85 (s, 2H, [4.70 minor isomer]), 4.20 – 4.12 (m, 1H, [4.64 minor isomer]), 4.04 (s, 2H, [4.25 minor isomer]), 2.49 – 2.43 (m, 2H), 1.61 – 1.46 (m, 2H), 1.19 (d, *J* = 6.5 Hz, 6H, [1.04 minor isomer]), 0.90 – 0.81 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.98 [170.88 minor isomer], 167.68 [168.26 minor isomer], 156.61 [156.71 minor isomer], 151.84 [151.99 minor isomer], 143.59 [143.78 minor isomer], 138.51 [138.14 minor isomer], 134.90 [134.67 minor isomer], 129.54 [129.48 minor isomer], 114.85 [114.68 minor isomer], 113.85 [114.29 minor isomer], 66.52, 47.64 [45.23 minor isomer], 44.79 [45.13 minor isomer], 36.84, 24.81, 21.19, 14.08. HRMS (ESI) m/z: calcd for $C_{20}H_{27}N_4O_3$ $[M + H]^+$, 371.2078; found 371.2097.

4.1.37.

N-Isopropyl-N-(2-((2-methoxyphenyl)amino)-2-oxoethyl)-2-(4-propylphenoxy)acetamide **18j**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 2-methoxyaniline (123 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (283 mg, 71%). Mp: 118.4-119.2 °C. HPLC purity = 99.77%, HPLC t_R = 18.66 min (Method B). The ^{1}H NMR showed 4:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H, [8.32 minor isomer]), 7.15 – 6.72 (m, 7H), 4.78 (s, 2H, [4.67 minor isomer]), 4.38 – 4.25 (m, 1H, [4.72 minor isomer]), 4.18 – 4.06 (m, 2H), 3.79 (s, 3H), 2.56 – 2.42 (m, 2H), 1.64 – 1.50 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 6H, [1.22 minor isomer]), 0.91 (t, *J* = 7.3 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.15, 167.72, 156.02, 148.37, 136.04, 129.51[129.37 minor isomer], 127.55, 123.91[124.38 minor isomer], 120.91[120.05 minor isomer], 120.12[119.85 minor isomer], 114.37, 110.08, 67.93[68.48 minor isomer], 55.82[55.65 minor isomer], 49.27[47.81 minor

isomer], 46.56[47.38 minor isomer], 37.13, 24.69[29.71 minor isomer], 21.05, 13.79. HRMS (ESI) m/z: calcd for $C_{23}H_{31}N_2O_4$ [M + H] $^+$, 399.2278; found 399.2287.

4.1.38.

N-Isopropyl-N-(2-((3-methoxyphenyl)amino)-2-oxoethyl)-2-(4-propylphenoxy)acetamide **18k**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 3-methoxyaniline (123 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (318 mg, 80%). Mp: 92.7-95.9 °C. HPLC purity = 99.43%, HPLC t_R = 18.42 min (Method B). The ^{1}H NMR showed 6:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 1H, [8.11 minor isomer]), 7.24 – 7.11 (m, 2H), 7.08 (d, J = 8.5 Hz, 2H, [7.02 minor isomer]), 6.94 – 6.83 (m, 3H, [6.79 minor isomer]), 6.62 (dd, J = 8.0, 2.0 Hz, 1H), 4.78 (s, 2H, [4.66 minor isomer]), 4.34 – 4.21 (m, 1H), 4.06 (s, 2H), 3.76 (s, 3H), 2.51 (t, J = 7.5 Hz, 2H), 1.65 – 1.52 (m, 2H), 1.29 (d, J = 6.5 Hz, 6H, [1.16 minor isomer]), 0.91 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.76, 168.01, 160.06, 155.78, 139.00, 136.22, 129.62, 129.53, 114.29, 112.18, 110.18, 105.54, 67.56, 55.30, 49.47, 46.92, 37.11, 24.64, 20.99, 13.79. HRMS (ESI) m/z: calcd for $C_{23}H_{31}N_2O_4$ [M + H] $^+$, 399.2278; found 399.2283.

4.1.39.

N-Isopropyl-N-(2-((4-methoxyphenyl)amino)-2-oxoethyl)-2-(4-propylphenoxy)acetamide **18l**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 4-methoxyaniline (123 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**.

The product was obtained as a white solid (330 mg, 83%). Mp: 141.2-142.7 °C. HPLC purity = 96.99%, HPLC t_R = 17.96 min (Method B). The ^{1}H NMR showed 7:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H, [7.92 minor isomer]), 7.28 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H, [7.03 minor isomer]), 6.87 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 4.79 (s, 2H, [4.67 minor isomer]), 4.37 – 4.26 (m, 1H), 4.06 (s, 2H), 3.77 (s, 3H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.64 – 1.51 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 6H, [1.18 minor isomer]), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.68, 167.79, 156.35, 155.76, 136.21, 130.89, 129.63, 121.70, 114.29, 114.01, 67.59, 55.47, 49.46, 46.67, 37.11, 24.65, 20.98, 13.78. HRMS (ESI) m/z: calcd for $C_{23}H_{31}N_2O_4$ $[M + H]^+$, 399.2278; found 399.2291.

4.1.40.

N-(2-((3,4-Dimethoxyphenyl)amino)-2-oxoethyl)-N-isopropyl-2-(4-propylphenoxy)acetamide **18m**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 3,4-dimethoxyaniline (153 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (368 mg, 86%) . Mp: 136.5-139.7 °C. HPLC purity = 99.57%, HPLC t_R = 16.84 min (Method B). The ^{1}H NMR showed 7:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H, [7.86 minor isomer]), 7.18 (s, 1H, [7.22 minor isomer]), 7.07 (d, *J* = 8.0 Hz, 2H, [7.03 minor isomer]), 6.90 – 6.71 (m, 4H), 4.79 (s, 2H, [4.68 minor isomer]), 4.36 – 4.20 (m, 1H), 4.06 (s, 2H), 3.84 (s, 6H), 2.50 (t, *J* = 7.5 Hz, 2H), 1.65 – 1.50 (m, 2H), 1.30 (d, *J* = 6.5 Hz, 6H, [1.20 minor isomer]), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CDCl3) δ 169.73, 167.78, 155.79, 148.97, 145.76, 136.22, 131.47, 129.61, 114.30, 111.91, 111.26, 104.72, 67.57, 56.12, 55.95, 49.47, 46.92, 37.10, 24.65, 21.02, 13.77. HRMS (ESI) m/z: calcd for $C_{24}H_{33}N_2O_5$ $[M + H]^+$, 429.2384; found 429.2390.

4.1.41.

N-(2-((4-Fluorophenyl)amino)-2-oxoethyl)-N-isopropyl-2-(4-propylphenoxy)aceta mide **18n**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 4-fluoroaniline (111 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (278 mg, 72%). Mp: 177.2-179.1 °C. HPLC purity = 97.16%, HPLC t_R = 18.56 min (Method B). The ^{1}H NMR showed 9:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H, [7.94 minor isomer]), 7.37 – 7.29 (m, 2H), 7.08 (d, J = 8.5 Hz, 2H, [7.20 minor isomer]), 6.93 (t, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H, [6.77 minor isomer]), 4.79 (s, 2H, [4.68 minor isomer]), 4.38 – 4.24 (m, 1H), 4.06 (s, 2H, [4.10 minor isomer]), 2.51 (t, J = 7.5 Hz, 2H), 1.63 – 1.53 (m, 2H), 1.29 (d, J = 6.5 Hz, 6H, [1.19 minor isomer]), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.76, 167.88, 159.27 (d, $^1J_{C\text{-}F}$ = 241.7 Hz), 155.75, 136.25, 133.82 (d, $^4J_{C\text{-}F}$ = 2.6 Hz), 129.63, 121.61 (d, $^3J_{C\text{-}F}$ = 7.8 Hz), 115.40 (d, $^2J_{C\text{-}F}$= 22.4 Hz), 114.28, 67.50, 49.46, 46.69, 37.10, 24.66, 20.99, 13.76. HRMS (ESI) m/z: calcd for $C_{22}H_{28}FN_2O_3$ $[M + H]^+$, 387.2078; found 387.2092.

4.1.42.

N-Isopropyl-N-(2-oxo-2-((4-(trifluoromethyl)phenyl)amino)ethyl)-2-(4-propylphen oxy)acetamide **18o**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 4-(trifluoromethyl)aniline (161 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (170 mg, 39%). Mp: 176.9-180.9 °C. HPLC purity = 98.71%, HPLC t_R = 20.82 min (Method B). The ^{1}H NMR showed 12:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.46 (s, 4H), 7.08 (d, J = 8.5 Hz, 2H, [7.02 minor isomer]), 6.87 (d, J = 8.5 Hz, 2H, [6.76 minor isomer]), 4.81 (s, 2H, [4.70 minor isomer]), 4.36 – 4.27 (m, 1H), 4.08 (s, 2H), 2.51 (t, J = 7.5 Hz, 2H), 1.62 – 1.53 (m, 2H), 1.31 (d, J = 7.0

Hz, 6H, [7.81 minor isomer]), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.94, 168.20, 155.71, 140.88, 136.31, 129.63, 126.02 (q, *J* = 3.7 Hz) , 119.39, 114.27, 67.42, 49.55, 46.93, 37.09, 24.66, 21.02, 13.75. HRMS (ESI) m/z: calcd for $C_{23}H_{28}F_3N_2O_3$ $[M + H]^+$, 437.2047; found 437.2067.

4.1.43.

N-Isopropyl-N-(2-((4-(methylsulfonyl)phenyl)amino)-2-oxoethyl)-2-(4-propylphenoxy)acetamide **18p**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 4-(methylsulfonyl)aniline (171 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (201 mg, 45%). Mp: 195.2-196.2 °C. HPLC purity = 98.29%, HPLC t_R = 15.47 min (Method B). The ^{1}H NMR showed 14:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.71 (d, *J* = 8.5 Hz, 2H, [7.81 minor isomer]), 7.51 (d, *J* = 8.5 Hz, 2H, [7.62 minor isomer]), 7.09 (d, *J* = 8.5 Hz, 2H, [7.01 minor isomer]), 6.86 (d, *J* = 8.5 Hz, 2H, [6.74 minor isomer]), 4.82 (s, 2H, [4.67 minor isomer]), 4.33 – 4.22 (m, 1H), 4.05 (s, 2H), 3.00 (s, 3H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.64 – 1.51 (m, 2H), 1.30 (d, *J* = 6.5 Hz, 6H, [1.15 minor isomer]), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.79, 168.19, 155.74, 142.83, 136.30, 134.92, 129.62, 128.37, 119.55, 114.30, 67.23, 49.40, 46.70, 44.66, 37.09, 24.68, 21.07, 13.77. HRMS (ESI) m/z: calcd for $C_{23}H_{31}N_2O_5S$ $[M + H]^+$, 447.1948; found 447.1962.

4.1.44.

N-(2-((4-Cyanophenyl)amino)-2-oxoethyl)-N-isopropyl-2-(4-propylphenoxy)acetamide **18q**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 4-aminobenzonitrile (118 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (149 mg, 38%). Mp:

184.5-187.3 °C. HPLC purity = 99.39%, HPLC t_R = 17.79 min (Method B). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.49 (q, *J* = 9.0 Hz, 4H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.80 (s, 2H), 4.35 – 4.25 (m, 1H), 4.07 (s, 2H), 2.51 (t, *J* = 9.0 Hz, 2H), 1.64-1.54 (m, 2H), 1.30 (d, *J* = 6.5 Hz, 6H), 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.05, 168.31, 155.69, 141.89, 136.34, 133.05, 129.64, 119.66, 118.89, 114.27, 106.93, 67.35, 49.59, 47.00, 37.10, 24.69, 21.01, 13.77. HRMS (ESI) m/z: calcd for $C_{23}H_{28}N_3O_3$ $[M + H]^+$, 394.2125; found 394.2150.

4.1.45.

N-(2-((1,3,4-Thiadiazol-2-yl)amino)-2-oxoethyl)-N-isopropyl-2-(4-propylphenoxy) acetamide **18r**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 1,3,4-thiadiazol-2-amine (101 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (214 mg, 57%). Mp: 70.5-74.5 °C. HPLC purity = 99.75%, HPLC t_R = 15.20 min (Method B). The ^{1}H NMR showed 7:2 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H, [8.82 minor isomer]), 7.08 (d, *J* = 8.5 Hz, 2H, [7.00 minor isomer]), 6.85 (d, *J* = 8.5 Hz, 2H, [6.78 minor isomer]), 4.78 (s, 2H, [4.71 minor isomer]), 4.35 (s, 2H, [4.59 minor isomer]), 4.34 – 4.28 (m, 1H, [4.86 minor isomer]), 2.51 (t, *J* = 8.0 Hz, 2H, [2.46 minor isomer]), 1.65 – 1.51 (m, 3H), 1.28 (d, *J* = 7.0 Hz, 6H, [1.15 minor isomer]), 0.95 – 0.85 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.88[167.88 minor isomer], 166.78[167.53 minor isomer], 158.84 [159.26 minor isomer], 154.92 [154.85 minor isomer], 146.57[146.65 minor isomer], 134.93 [134.69 minor isomer], 128.45 [128.26 minor isomer], 113.37, 66.57[67.34 minor isomer], 47.81[45.31 minor isomer], 43.60[44.18 minor isomer], 36.10, 23.66, 20.11[18.67 minor isomer], 12.75. HRMS (ESI) m/z: calcd for $C_{18}H_{25}N_4O_3S$ $[M + H]^+$, 377.1642; found 377.1649.

4.1.46. N-Isopropyl-N-(2-(isoxazol-3-ylamino)-2-oxoethyl)-2-(4-propylphenoxy) acetamide **18s**

This compound was prepared from **17c** (293 mg, 1.00 mmol), isoxazol-3-amine (84 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as colourless oil (133 mg, 38%). HPLC purity = 95.56%, HPLC t_R = 12.61 min (Method B). The ^{1}H NMR showed 17:3 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H, [9.78 minor isomer]), 8.24 (s, 1H, [8.29 minor isomer]), 7.14 – 6.94 (m, 3H), 6.91 – 6.82 (m, 2H), 4.77 (s, 2H, [4.65 minor isomer]), 4.35 – 4.25 (m, 1H), 4.09 (s, 2H, [4.18 minor isomer]), 2.51 (t, *J* = 7.5 Hz, 2H), 1.64 – 1.51 (m, 2H), 1.26 (d, *J* = 7.0 Hz, 6H, [1.13 minor isomer]), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.66, 166.90, 157.73, 156.08, 154.75, 135.11, 128.54, 113.29, 98.30, 66.68, 48.29, 44.91, 36.09, 23.63, 19.97, 12.74. HRMS (ESI) m/z: calcd for $C_{19}H_{26}N_3O_4$ $[M + H]^+$, 360.1918; found 360.1926.

4.1.47. N-Isopropyl-N-(2-(naphthalen-2-ylamino)-2-oxoethyl)-2-(4-propylphenoxy) acetamide **18t**

This compound was prepared from **17c** (293 mg, 1.00 mmol), naphthalen-2-amine (143 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (334 mg, 80%). Mp: 98.3-102.5 °C. HPLC purity = 99.27%, HPLC t_R = 21.25 min (Method B). The ^{1}H NMR showed 7:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H, [8.30 minor isomer]), 8.10 (s, 1H), 7.85 – 7.60 (m, 3H), 7.50 – 7.29 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H, [7.00 minor isomer]), 6.89 (d, *J* = 8.0 Hz, 2H, [6.80 minor isomer]), 4.82 (s, 2H, [4.70 minor isomer]), 4.40 – 4.24 (m, 1H), 4.22 – 4.08 (m, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 1.66-1.48 (m, 2H), 1.32 (d, *J* = 6.5 Hz, 6H, [1.19 minor isomer]), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.84, 168.17, 155.80, 136.23, 135.30, 133.79, 130.62, 129.64, 128.56, 127.64, 127.50,

126.37, 124.90, 120.04, 116.57, 114.32, 67.58, 49.52, 46.97, 37.10, 24.63, 21.03, 13.78. HRMS (ESI) m/z: calcd for $C_{26}H_{30}N_2O_3$ $[M + H]^+$, 419.2329; found 419.2335.

4.1.48. N-Isopropyl-N-(2-((6-methoxybenzo[d]thiazol-2-yl)amino)-2-oxoethyl)-2-(4-propylphenoxy)acetamide **18u**

This compound was prepared from **17c** (293 mg, 1.00 mmol), 6-methoxybenzo[d]thiazol-2-amine (180 mg, 1.00 mmol), HOBt (162 mg, 1.20 mmol), EDCI (188 mg, 1.50 mmol) and DIPEA (0.5 mL, 3.00 mmol) in a similar manner as described for compound **12c**. The product was obtained as a white solid (334 mg, 75%). Mp: 167.2-168.0 °C. HPLC purity = 99.84%, HPLC t_R = 20.11 min (Method B). The ^{1}H NMR showed 7:1 ratio of atropisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.79 (brs, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.25 (d, J = 2.5 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 7.00 (dd, J = 8.5, 2.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 2H, [6.79 minor isomer]), 4.78 (s, 2H, [4.67 minor isomer]), 4.36 – 4.26 (m, 1H), 4.16 (s, 2H, [4.29 minor isomer]), 3.85 (s, 3H), 2.50 (t, J = 7.0 Hz, 2H, [2.43 minor isomer]), 1.61 – 1.48 (m, 2H), 1.26 (d, J = 6.5 Hz, 6H, [1.12 minor isomer]), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.83, 168.01, 156.82, 155.77, 155.68, 142.66, 136.13, 133.43, 129.57, 121.69, 115.17, 114.33, 104.20, 67.69, 55.84, 49.37, 45.57, 37.12, 24.66, 21.08, 13.78. HRMS (ESI) m/z: calcd for $C_{24}H_{30}N_3O_4S$ $[M + H]^+$, 456.1952; found 456.1970.

4.1.49. N-Isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl)-2-(p-tolyloxy) acetamide **18v**

This compound was prepared from **17a** (80 mg, 0.30 mmol), pyridazin-4-amine (32 mg, 0.33 mmol), 4-methylmorpholine (34 mg, 0.34 mmol) and isobutyl carbonochloridate (45 mg, 0.33 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (66 mg, 64%). Mp: 182.4-184.5 °C. HPLC purity = 98.99%, HPLC t_R = 9.19 min (Method B). The ^{1}H NMR showed 13:7

ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.64 (s, 1H, [10.85 minor isomer]), 9.31-9.25 (m, 1H), 9.02 (d, J = 6.0 Hz, 1H, [9.06 minor isomer]), 7.89 (dd, J = 6.0, 3.0 Hz, 1H, [7.95 minor isomer]), 7.11 – 6.99 (m, 2H), 6.87 – 6.69 (m, 2H), 4.84 (s, 2H, [4.69 minor isomer]), 4.21 – 4.12 (m, 1H, [4.63 minor isomer]), 4.03 (s, 2H, [4.25 minor isomer]) 2.23 (s, 3H, [2.21 minor isomer]), 1.19 (d, J = 6.5 Hz, 6H, [1.04 minor isomer]). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.94 [170.84 minor isomer], 167.68 [168.25 minor isomer], 156.43 [156.53 minor isomer], 151.94 [152.05 minor isomer], 143.58 [143.77 minor isomer], 138.32 [138.03 minor isomer], 130.14 [130.07 minor isomer], 130.00 [129.77 minor isomer], 114.91 [114.76 minor isomer], 114.25 [113.79 minor isomer], 66.56 [66.50 minor isomer], 47.64 [45.28 minor isomer], 45.16 [44.78 minor isomer], 21.19 [20.53 minor isomer], 19.84 [20.51 minor isomer]. HRMS (ESI) m/z: calcd for $C_{18}H_{23}N_4O_3$ $[M + H]^+$, 343.1765; found 343.1777.

4.1.50. 2-(4-Ethylphenoxy)-N-isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl) acetamide **18w**

This compound was prepared from **17b** (58 mg, 0.21 mmol), pyridazin-4-amine (22 mg, 0.23 mmol), 4-methylmorpholine (23 mg, 0.23 mmol) and isobutyl carbonochloridate (31 mg, 0.23 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (46 mg, 61%). Mp: 199.3-201.5 °C. HPLC purity = 96.08%, HPLC t_R = 10.33 min (Method B). The ^{1}H NMR showed 13:7 ratio of atropisomers.^{1}H NMR (500 MHz, DMSO-d_6) δ 10.65 (s, 1H, [10.88 minor isomer]), 9.28 (dd, J = 3.0, 1.0 Hz, 1H, [9.29 minor isomer]), 9.02 (dd, J = 6.0, 1.0 Hz, 1H, [9.06 minor isomer]), 7.89 (dd, J = 6.0, 3.0 Hz, 1H), 7.13 – 7.06 (m, 2H), 6.87 – 6.79 (m, 2H), 4.85 (s, 2H, [4.69 minor isomer]), 4.22 – 4.11 (m, 1H, [4.64 minor isomer]), 4.04 (s, 2H, [4.25 minor isomer]), 2.57 – 2.50 (m, 2H), 1.19 (d, J = 6.5 Hz, 6H, [1.04 minor isomer]), 1.17 – 1.07 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.95 [170.85 minor isomer], 167.68 [168.26 minor isomer], 156.60 [156.70 minor isomer], 151.93 [152.04 minor isomer], 143.59 [143.78 minor isomer], 138.32 [138.03 minor isomer], 136.56 [136.34 minor isomer],

128.97 [128.90 minor isomer], 114.94 [114.77 minor isomer], 113.79 [114.25 minor isomer], 66.55 [66.47 minor isomer], 47.65 [45.26 minor isomer], 44.78 [45.14 minor isomer], 27.75, 21.19 [19.84, minor isomer], 16.41. HRMS (ESI) m/z: calcd for $C_{19}H_{25}N_4O_3$ $[M + H]^+$, 357.1921; found 357.1940.

4.1.51. 2-(4-Butylphenoxy)-N-isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl) acetamide **18x**

This compound was prepared from **17d** (104 mg, 0.34 mmol), pyridazin-4-amine (35 mg, 0.37 mmol), 4-methylmorpholine (38 mg, 0.37 mmol) and isobutyl carbonochloridate (51 mg, 0.37 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (85 mg, 61%). Mp: 196.1-198.4 °C. HPLC purity = 99.79%, HPLC t_R = 15.11 min (Method B). The ^{1}H NMR showed 13:7 ratio of atropisomers at 20 °C : ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.64 (s, 1H, [10.84 minor isomer]), 9.30 – 9.23 (m, 1H), 9.01 (d, J = 6.0, 0.5 Hz, 1H, [9.05 minor isomer]), 7.89 (dd, J = 6.0, 2.5 Hz, 1H, [7.94 minor isomer]), 7.10 – 7.03 (m, 2H), 6.84 – 6.79 (m, 2H), 4.84 (s, 2H, [4.69 minor isomer]), 4.20 – 4.10 (m, 1H, [4.64 minor isomer]), 4.03 (s, 2H, [4.24 minor isomer]), 2.49 – 2.46 (m, 2H), 1.54 – 1.44 (m, 2H), 1.33 – 1.23 (m, 2H), 1.19 (d, J = 6.5 Hz, 6H, [1.03 minor isomer]), 0.88 (t, J = 7.5 Hz, 3H). **100 °C**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.30 (d, J = 2.0 Hz, 1H), 9.00 (d, J = 5.6 Hz, 1H), 7.83 (dd, J = 5.6, 2.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.75 (s, 2H), 4.50 – 4.25 (m, 1H), 4.13 (s, 2H), 2.60 – 2.50 (m, 2H), 1.62 – 1.49 (m, 2H), 1.40 – 1.26 (m, 2H), 1.18 (d, J = 3.6 Hz, 6H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.84, 169.94 [170.85 minor isomer], 168.26, 167.68 [170.85 minor isomer], 156.68, 156.58 [170.85 minor isomer], 152.04, 151.93 [170.85 minor isomer], 143.77, 143.58 [170.85 minor isomer], 138.32 [170.85 minor isomer], 138.02, 135.09 [170.85 minor isomer], 134.87, 129.49 [170.85 minor isomer], 129.42, 114.88 [170.85 minor isomer], 114.71, 114.25, 113.78 [170.85 minor isomer], 66.54 [66.48 minor isomer], 45.26, 44.78 [45.14 minor isomer], 34.37, 33.86, 22.14, 21.19 [19.84 minor isomer], 14.24. HRMS (ESI) m/z:

calcd for $C_{21}H_{29}N_4O_3$ $[M + H]^+$, 385.2234; found 385.2252.

4.1.52.

2-(4-Isobutylphenoxy)-N-isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl) acetamide **18y**

This compound was prepared from **17e** (97 mg, 0.32 mmol), pyridazin-4-amine (33 mg, 0.35 mmol), 4-methylmorpholine (35 mg, 0.35 mmol) and isobutyl carbonochloridate (47 mg, 0.35 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (69 mg, 56%). Mp: 231.5-232.9 °C. HPLC purity = 97.39%, HPLC t_R = 15.41 min (Method B). The ^{1}H NMR showed 13:7 ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.68 (s, 1H, [10.88 minor isomer]), 9.28 (dd, J = 3.0, 0.5 Hz, 1H, [9.29 minor isomer]), 9.02 (dd, J = 6.0, 0.5 Hz, 1H, [9.06 minor isomer]), 7.91 (dd, J = 6.0, 3.0 Hz, 1H, [7.95 minor isomer]), 7.07 – 7.01 (m, 2H), 6.86 – 6.79 (m, 2H), 4.85 (s, 2H, [4.70 minor isomer]), 4.21 – 4.11 (m, 1H, [4.64 minor isomer]), 4.04 (s, 2H, [4.25 minor isomer]), 2.40 – 2.34 (m, 2H), 1.82 – 1.70 (m, 1H), 1.19 (d, J = 6.5 Hz, 6H, [1.04 minor isomer]), 0.86 – 0.81 (m, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.97 [170.86 minor isomer], 167.69 [168.27 minor isomer], 156.64 [156.73 minor isomer],151.83 [151.99 minor isomer], 143.59 [143.78 minor isomer], 138.50 [138.13 minor isomer], 133.89 [133.68 minor isomer], 130.15 [130.09 minor isomer], 114.75 [114.58 minor isomer], 113.86 [114.30 minor isomer], 66.54 [66.50 minor isomer], 47.64 [45.26 minor isomer], 44.79 [45.15 minor isomer], 44.19, 30.21, 22.57, 21.20 [19.84 minor isomer]. HRMS (ESI) m/z: calcd for $C_{21}H_{29}N_4O_3$ $[M + H]^+$, 385.2234; found 385.2250.

4.1.53. N-Isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl)-2-(4-pentylphenoxy) acetamide **18z**

This compound was prepared from **17f** (125 mg, 0.39 mmol), pyridazin-4-amine (41 mg, 0.43 mmol), 4-methylmorpholine (43 mg, 0.43 mmol) and isobutyl carbonochloridate (58 mg, 0.43 mmol) in a similar manner as described for

compound **18g**. The product was obtained as a white solid (104 mg, 67%). Mp: 184.7-185.4 °C. HPLC purity = 99.28%, HPLC t_R = 17.23 min (Method B). The ^{1}H NMR showed 13:7 ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.64 (s, 1H, [10.84 minor isomer]), 9.30 – 9.24 (m, 1H), 9.01 (dd, *J* = 6.0, 1.0 Hz, 1H, [9.06 minor isomer]), 7.89 (dd, *J* = 6.0, 2.5 Hz, 1H, [7.94 minor isomer]), 7.10 – 7.02 (m, 2H), 6.86 – 6.78 (m, 2H), 4.85 (s, 2H, [4.70 minor isomer]), 4.20 – 4.11 (m, 1H, [4.63 minor isomer]), 4.03 (s, 2H, [4.24 minor isomer]), 2.50 – 2.44 (m, 2H), 1.58 – 1.46 (m, 2H), 1.34 – 1.22 (m, 4H), 1.19 (d, *J* = 6.5 Hz, 6H, [1.04 minor isomer]), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.94 [170.84 minor isomer], 167.69 [168.27 minor isomer], 156.58 [156.67 minor isomer], 151.93 [152.04 minor isomer], 143.58 [143.77 minor isomer], 138.32 [138.02 minor isomer], 135.12 [134.90 minor isomer], 129.48 [129.42 minor isomer], 114.87 [114.70 minor isomer], 113.78 [114.25 minor isomer], 66.54 [66.47 minor isomer], 47.64 [45.25 minor isomer], 44.78 [45.14 minor isomer], 34.67, 31.37, 31.30, 22.42, 21.19 [19.84 minor isomer], 14.39. HRMS (ESI) m/z: calcd for $C_{22}H_{31}N_4O_3$ $[M + H]^+$, 399.2391; found 399.2407.

4.1.54.

N-Isopropyl-2-(4-methoxyphenoxy)-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl) acetamide **18aa**

This compound was prepared from **17g** (169 mg, 0.60 mmol), pyridazin-4-amine (60 mg, 0.63 mmol), 4-methylmorpholine (63 mg, 0.63 mmol) and isobutyl carbonochloridate (86 mg, 0.63 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (162 mg, 75%). Mp: 197.5-198.5 °C. HPLC purity = 99.51%, HPLC t_R = 6.77 min (Method B). The ^{1}H NMR showed 13:7 ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.64 (s, 1H, [10.85 minor isomer]), 9.31 – 9.22 (m, 1H), 9.01 (d, *J* = 6.0 Hz, 1H, [9.06 minor isomer]), 7.89 (dd, *J* = 6.0, 2.5 Hz, 1H, [7.94 minor isomer]), 6.92 – 6.75 (m, 4H), 4.81 (s, 2H, [4.67 minor isomer]), 4.20 – 4.12 (m, 1H, [4.63 minor isomer]), 4.03 (s, 2H, [4.24 minor isomer]), 3.70 (s, 3H, [3.69 minor isomer]), 1.19 (d, *J* = 6.5 Hz, 6H, [4.64 minor

isomer]). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.54 [170.43 minor isomer], 167.37 [167.94 minor isomer], 153.68 [153.53 minor isomer], 152.16 [152.23 minor isomer], 151.52 [151.63 minor isomer], 143.18 [143.36 minor isomer], 137.92 [137.61 minor isomer], 115.60 [115.37 minor isomer], 114.54 [114.48 minor isomer], 113.38 [113.84 minor isomer], 66.73 [66.63 minor isomer], 55.44, 47.24 [44.86 minor isomer], 44.75 [44.37 minor isomer], 20.78 [19.43 minor isomer]. HRMS (ESI) m/z: calcd for $C_{18}H_{23}N_4O_4$ $[M + H]^+$, 359.1714; found 359.1720.

4.1.55. 2-(4-Ethoxyphenoxy)-N-isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl) acetamide **18ab**

This compound was prepared from **17h** (152 mg, 0.52 mmol), pyridazin-4-amine (52 mg, 0.54 mmol), 4-methylmorpholine (55 mg, 0.54 mmol) and isobutyl carbonochloridate (74 mg, 0.54 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (132 mg, 68%). Mp: 194.2-194.7 °C. HPLC purity = 99.77%, HPLC t_R = 9.00 min (Method B). The ^{1}H NMR showed 13:7 ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.65 (s, 1H, [10.85 minor isomer]), 9.31 – 9.26 (m, 1H), 9.02 (dd, J = 6.0, 0.5 Hz, 1H, [9.05 minor isomer]), 7.90 (dd, J = 6.0, 2.5 Hz, 1H, [7.94 minor isomer]), 6.91 – 6.78 (m, 4H), 4.82 (s, 2H, [4.67 minor isomer]), 4.20 – 4.13 (m, 1H, [4.63 minor isomer]), 4.04 (s, 2H, [4.25 minor isomer]), 3.98 – 3.90 (m, 2H), 1.32 – 1.26 (m, 3H), 1.19 (d, J = 6.5 Hz, 6H, [1.04 minor isomer]). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.94 [170.83 minor isomer], 167.80 [168.38 minor isomer], 153.31 [153.17 minor isomer], 152.48 [152.56 minor isomer], 151.93 [152.04 minor isomer], 143.59 [143.77 minor isomer], 138.33 [138.02 minor isomer], 115.98 [115.77 minor isomer], 115.54 [115.50 minor isomer], 113.79 [114.25 minor isomer], 67.12 [67.02 minor isomer], 63.80, 47.66 [45.26 minor isomer], 44.78 [45.14 minor isomer], 21.18 [19.83 minor isomer], 15.20. HRMS (ESI) m/z: calcd for $C_{19}H_{25}N_4O_4$ $[M + H]^+$, 373.1870; found 373.1876.

4.1.56. N-Isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl)-2-(4-(trifluoromethyl)

phenoxy)acetamide **18ac**

This compound was prepared from **17i** (170 mg, 0.53 mmol), pyridazin-4-amine (53 mg, 0.56 mmol), 4-methylmorpholine (56 mg, 0.56 mmol) and isobutyl carbonochloridate (76 mg, 0.56 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (124 mg, 59%). Mp: 200.9-203.7 °C. HPLC purity = 96.84%, HPLC t_R = 10.08 min (Method B). The ^{1}H NMR showed 3:2 ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.63 (s, 1H, [10.90 minor isomer]), 9.27 (dd, J = 2.5, 0.5 Hz, 1H, [9.31 minor isomer]), 9.03 – 8.99 (m, 1H, [9.07 minor isomer]), 7.88 (dd, J = 6.0, 2.5 Hz, 1H, [7.96 minor isomer]), 7.64 (d, J = 8.5 Hz, 2H), 7.14 – 7.08 (m, 2H), 5.07 (s, 2H, [4.88 minor isomer]), 4.18 – 4.11 (m, 1H, [4.63 minor isomer]), 4.04 (s, 2H, [4.25 minor isomer]), 1.21 (d, J = 6.5 Hz, 6H, [1.07 minor isomer]). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.45 [170.40 minor isomer], 166.61 [167.19 minor isomer], 161.05 [161.24 minor isomer], 151.53 [151.65 minor isomer], 143.17 [143.39 minor isomer], 137.59 [137.88 minor isomer], 126.80 (q, J = 3.6 Hz), 115.26 [115.09 minor isomer], 113.91 [113.39 minor isomer], 65.86 [65.96 minor isomer], 47.12 [44.91 minor isomer], 44.36 [44.64 minor isomer], 20.76 [19.42 minor isomer]. HRMS (ESI) m/z: calcd for $C_{18}H_{20}F_3N_4O_3$ $[M + H]^+$, 397.1482; found 397.1484.

4.1.57. 2-(4-Bromophenoxy)-N-isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl) acetamide **18ad**

This compound was prepared from **17j** (180 mg, 0.55 mmol), pyridazin-4-amine (57 mg, 0.60 mmol), 4-methylmorpholine (61 mg, 0.60 mmol) and isobutyl carbonochloridate (82 mg, 0.60 mmol) in a similar manner as described for compound **18g**. The product was obtained as a yellow solid (178 mg, 80%). Mp: 182.5-184.6 °C. HPLC purity = 98.75%, HPLC t_R = 9.85 min (Method B). The ^{1}H NMR showed 3:2 ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.63 (s, 1H, [10.87 minor isomer]), 9.26 (dd, J = 2.5, 1.0 Hz, 1H, [9.29 minor isomer]), 9.01 (dd, J = 6.0, 1.0 Hz, 1H, [9.06 minor isomer]), 7.89 (dd, J = 6.0, 2.5 Hz, 1H, [7.94 minor isomer]), 7.46 – 7.40 (m, 2H), 6.92 – 6.86 (m, 2H), 4.94 (s, 2H, [4.76 minor isomer]), 4.18 – 4.06 (m,

1H, [4.63 minor isomer]), 4.03 (s, 2H, [4.23 minor isomer]), 1.19 (d, *J* = 6.5 Hz, 6H, [1.03 minor isomer]). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.79 [170.72 minor isomer], 167.25 [167.84 minor isomer], 157.89 [158.05 minor isomer], 151.93 [152.05 minor isomer], 143.51 [143.71 minor isomer], 138.18 [137.88 minor isomer], 132.40 [132.37 minor isomer], 117.45 [117.28 minor isomer], 113.73 [114.22 minor isomer], 112.69 [112.51 minor isomer], 66.44, 47.55 [45.30 minor isomer], 44.73 [45.04 minor isomer], 21.17 [19.83 minor isomer]. HRMS (ESI) m/z: calcd for $C_{17}H_{20}BrN_4O_3$ $[M + H]^+$, 407.0713; found 407.0730.

4.1.58. Methyl 2-(4-(2-(isopropyl(2-oxo-2-(pyridazin-4-ylamino)ethyl)amino)-2-oxoethoxy)phenyl)acetate **18ae**

This compound was prepared from **17k** (590 mg, 1.83 mmol), pyridazin-4-amine (182 mg, 1.92 mmol), 4-methylmorpholine (194 mg, 1.92 mmol) and isobutyl carbonochloridate (261 mg, 1.92 mmol) in a similar manner as described for compound **18g**. The product was obtained as a white solid (390 mg, 55%). Mp: 178.6-179.9 °C. HPLC purity = 98.51%, HPLC t_R = 7.08 min (Method B). The ^{1}H NMR showed 13:7 ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.63 (s, 1H, [10.84 minor isomer]), 9.27 (dd, *J* = 2.5, 1.0 Hz, 1H, [9.28 minor isomer]), 9.01 (d, *J* = 6.0 Hz, 1H, [9.06 minor isomer]), 7.89 (dd, *J* = 6.0, 2.5 Hz, 1H, [7.95 minor isomer]), 7.19 – 7.12 (m, 2H), 6.89 – 6.84 (m, 2H), 4.89 (s, 2H, [4.73 minor isomer]), 4.20 – 4.10 (m, 1H, [4.63 minor isomer]), 4.03 (s, 2H, [4.24 minor isomer]), 3.65 – 3.52 (m, 5H), 1.19 (d, *J* = 6.5 Hz, 6H, [1.04 minor isomer]). ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.91, 169.51 [170.43 minor isomer], 167.14 [167.71 minor isomer], 157.05 [157.18 minor isomer], 151.51 [151.64 minor isomer], 143.17 [143.37 minor isomer], 137.90 [137.59 minor isomer], 130.28 [130.22 minor isomer], 126.71 [126.49 minor isomer], 114.58 [114.41 minor isomer], 113.38 [113.86 minor isomer], 66.00 [65.96 minor isomer], 54.96, 51.66, 47.21 [44.87 minor isomer], 44.37 [44.72 minor isomer], 20.78 [19.43 minor isomer]. HRMS (ESI) m/z: calcd for $C_{20}H_{25}N_4O_5$ $[M + H]^+$, 401.1819; found 401.1833.

4.1.59.

2-(4-(2-Hydroxyethyl)phenoxy)-N-isopropyl-N-(2-oxo-2-(pyridazin-4-ylamino)ethyl)acetamide **19**

To a solution of **18ea** (90 mg, 0.23 mmol) and $CaCl_2$ (125 mg, 1.13 mmol) in 4 mL MeOH was added $NaBH_4$ (43 mg, 1.13 mmol) at 0°C. The reaction mixture was warmed to room temperature and stirred for 30 min. The solvent was evaporated under vacuum and the residues purified by SiO2 chromatography (DCM: MeOH=25:1) to afford the compound **19** as colourless oil (43 mg, 50%). HPLC purity = 99.30%, HPLC t_R = 4.58 min (Method B). The ^{1}H NMR showed 13:7 ratio of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.63 (s, 1H, [10.84 minor isomer]), 9.29 – 9.21 (m, 1H), 9.02 (d, J = 6.0 Hz, 1H, [9.02 minor isomer]), 7.89 (dd, J = 6.0, 2.5 Hz, 1H, [7.94 minor isomer]), 7.16 – 7.05 (m, 2H), 6.87 – 6.78 (m, 2H), 4.85 (s, 2H, [4.70 minor isomer]), 4.61 – 4.57 (m, 1H), 4.20 – 4.12 (m, 1H, [4.64 minor isomer]), 4.03 (s, 2H, [4.24 minor isomer]), 3.61 – 3.50 (m, 2H), 2.69 – 2.58 (m, 2H), 1.19 (d, J = 6.5 Hz, 6H, [7.94 minor isomer]). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.54 [170.43 minor isomer], 167.28 [167.84 minor isomer], 156.42 [156.52 minor isomer], 151.53 [151.64 minor isomer], 143.19 [143.37 minor isomer], 137.92 [137.61 minor isomer], 131.90 [131.66 minor isomer], 129.72 [129.65 minor isomer], 114.41 [114.25 minor isomer], 113.40 [113.87 minor isomer], 66.13 [66.05 minor isomer], 62.48, 47.26 [44.87 minor isomer], 44.39 [44.75 minor isomer], 38.21, 20.79 [19.44 minor isomer]. HRMS (ESI) m/z: calcd for $C_{19}H_{25}N_4O_4$ $[M + H]^+$, 373.1870; found 373.1891.

4.2. Biological evaluation

4.2.1. 20S proteasome chymotrypsin-like inhibition assay

The human constitutive proteasome was given by Dr. Jiang-ping Wu (Notre-Dame Hospital, Montreal, QC, Canada), the immunoproteasome proteasome purchased by Boston Biochem. The inhibition of enzyme activity was determined by monitoring the decrease in hydrolysis of the fluorogenic substrate

Suc-LLVY-AMC for CT-L, Z-VLR-AMC for T-L, Z-LLE-AMC for PGPH-L and Ac-ANW-AMC for LMP7. The reaction under the following buffer conditions: 20 mM Tris,pH 7.5. Inhibitors at a different concentration were incubated with constitutive proteasome or immunoproteasome proteasome for 15 min prior to substrate addition with a final concentration of 50 μM. Reaction was monitored using an excitation wavelength of 355 nm and an emission wavelength of 460 nm using Envision microplate reader (PerkinElmer). The dose response of inhibition test was carried out in duplicate. And the IC50 data was calculated using the software GraphPad Prism 5, and chosen the equation "sigmoidal dose-response (variable slope)" for curve fitting.

4.2.2. Cancer cell anti-proliferation assay

4.2.2.1. Cell culture

The RPMI 8226, MM.1S, and MV-4-11 cell lines were obtained from the American Type Culture Collection (ATCC) (Manassas, VA, USA). The HepG2 and HGC27 cell lines were obtained from Shanghai Institute of Cell Biology (Shanghai, China). All cancer cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. The PRMI 8226, MM.1S, and HGC27 cell lines were cultured in RPMI-1640 media supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin, and 100 μg/mL streptomycin from Invitrogen (Grand Island, NY, USA). The MV-4-11 and HepG2 cell lines were cultured in Iscove's modified Dulbecco's medium supplemented with 10% FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin.

4.2.2.2. Cell proliferation assay

A 90 μL aliquot of RPMI 8226 (5×10^3 cells per well), MM-1S (3×10^4 cells per well), or MV-4-11 cells (8×10^3 cells per well) was seeded into 96-well plates and then treated with 10 μL of 0.2% DMSO or varying concentrations of tested compounds for 72 h. Cell viability was measured using the CellTiter 96® AQ_{ueous} Non-Radioactive Cell Proliferation Assay (MTS; Promega, Madison, WI). First, 20

μL of the combined MTS/PMS solution was pipetted into each well of the 96-well plates and then incubated for 2-4 h at 37 °C in a humidified, 5% CO_2 atmosphere. The optical density was determined at 490 nm (background subtraction at 690 nm) using a SpectraMax 340 microplate reader (Molecular Devices, Sunnyvale, CA, USA).

A 90 μL aliquot of HGC27 (1×10^5 cells per well) or HepG2 (1×10^5 cells per well) was seeded into 96-well plates and then treated with 10 μL of 0.2% DMSO or varying concentrations of tested compounds for 72 h. First, 30 μL of tetrazolium dye (MTT) solution (5 mg/mL) was added to each well and then incubated for 4 h at 37 °C in a humidified, 5% CO_2 atmosphere. The resulting MTT-formazan crystals were dissolved in 150 μL DMSO, and absorbance was measured spectrophotometrically at 570 nm using an ELISA plate reader.

The growth inhibitory ratio was calculated as follows: Growth inhibitory ratio = $(A_{control} - A_{sample})/A_{control}$. IC_{50} values were derived from a nonlinear regression model (curvefit) based on a sigmoidal dose response curve (variable slope) and computed using GraphPad Prism version 5.02, GraphPad Software.

4.2.3. Human liver microsomal stability assay.

The metabolic stability profiles of **18d**, **18x**, and PI-1840 were assessed by monitoring the disappearance of the test compounds in the presence of human liver microsomes (pooled human liver microsomes (Mongolian)) which was obtained from Research Institute for Liver Diseases Co. Ltd. (RILD Inc, Shanghai, P.R. China). A typical incubation mixture (100 μL total volume) for metabolic stability studies contained 1 μM test compounds, 1.0 mg/mL microsomal protein, 0.1M phosphate buffer saline (pH 7.4), and 1mM NADPH. After preincubation at 37 °C for 5 min, the reactions were started by addition of test compounds and further incubated for another 0, 10, 20, 30 min. The reactions were terminated by adding 400 μL of ice-cold methanol containing internal standard (1 μM), followed by centrifugation at 15000g for 10 min to obtain the supernatant. Aliquots (100μL) of the supernatant were taken, which were subsequently analyzed by a Shimadzu

LC/MS-2020 mass spectrometer. The peak area response ratio to internal standard (PARR) of the compounds at different time point was compared to the PARR at 0 min to determine the percent of test compounds remaining.

4.3. Molecular modeling

Docking calculations were performed using the Glide module in Schrodinger (version 11.1) with the default option [32, 33]. The X-ray crystal structure of the proteasome (PDB entry: 3MG6) was used as the docking template, and it was prepared by the protein preparation Wizard in Schrodinger by adding hydrogens and disulfide bridges, removing crystallographic waters and ions, fixing bond orders, assigning partial charges with the OPLS force field. The ligand **18x** was prepared using the Ligprep module in Schrodinger. The binding box with the size of 10 Å × 10 Å × 10 Å centered on the centroid of the ligand in the crystal structure of 3MG6. For the docking calculations of **18x**, the standard precision (SP) scoring function of Glide was used. All graphical images were created using Pymol.

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- A series of novel phenol ether derivatives were designed and synthesized as non-covalent proteasome inhibitors.
- Most compounds exhibited moderate to excellent proteasome inhibitory activity.
- Compound **18x** exhibited a 2-fold higher potency compared to the reported PI-1840.
- Docking studies were carried out to predict the binding mode of compound **18x** within proteasome.
- These compounds exhibited excellent metabolic stability and selective anti-proliferative activity against solid cancer cell lines including HepG2 and HGC27.