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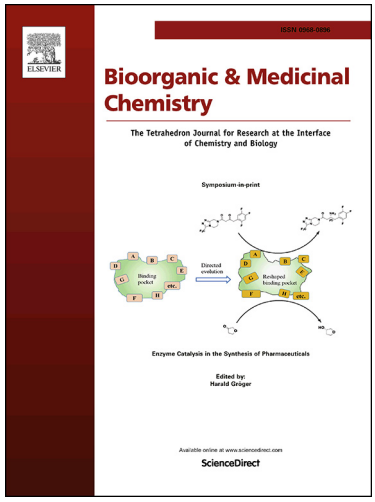

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2-Aminoquinazolin-4(3H)-one based plasmepsin inhibitors with improved hydrophilicity and selectivity

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Abstract: 2-Aminoquinazolin-4(3H)-ones were previously discovered as perspective leads for antimalarial drug development targeting the plasmepsins. Here we report the lead optimization studies with the aim to reduce inhibitor lipophilicity and increase selectivity versus the human aspartic protease Cathepsin D. Exploiting the solvent exposed area of the enzyme provides an option to install polar groups (R^1) the 5-position of 2-aminoquinazolin-4(3H)-one to inhibitors such as carboxylic acid without scarifying enzymatic potency. Moreover, introduction of R^1 substituents increased selectivity factors of compounds in this series up to 100-fold for Plm II, IV *vs* CatD inhibition. The introduction of flap pocket substituent (R^2) at 7-postion of 2-aminoquinazolin-4(3H)-one allows to remove Ph group from THF ring without notably impairing Plm inhibitory potency. Based on these findings, inhibitors were developed, which show Plm II and IV inhibitory potency in low nanomolar range and remarkable selectivity against Cathepsin D along with decreased lipophilicity and increased solubility.

Key words: Plasmepsins; Malaria; *Plasmodium* Falciparum; Cathepsin D; Inhibitors; 2-Aminoquinazolin-4(3H)-ones

1. Introduction

Malaria is a life threatening infectious disease caused by *Plasmodium* parasites, of which *Plasmodium falciparum* is the most lethal [1]. The treatment and prophylaxis of Malaria has been improved over the recent decades, considerably reducing the infection cases and mortality [2]. However, these efforts are in danger due to an alarming spread of drug-resistant malaria [3-5]. To address this problem, new drugs targeting the life cycle of the parasite by yet unexploited mechanisms of action are required [2,3]. Malarial aspartic proteases – plasmepsins (Plms) have been explored

as potential drug targets for decades, [6-11], nevertheless, so far no plasmepsin inhibitor has been developed to a clinical candidate.

Out of the 10 plasmepsins encoded in the *Plasmodium falciparum* genome, the most attention has been paid to the digestive plasmepsins (Plm I, II, IV and HAP), which are involved in the processing of haemoglobin to amino acids. However, their inhibition may not be sufficient to kill the parasite as the haemoglobin digestion by plasmepsins has redundant mechanisms [11-14]. On the other hand, certain digestive plasmepsin inhibitors show parasite growth inhibition in red blood cells (RBC) at nanomolar concentration [15,16] which is likely achieved by (co)-targeting the non-digestive plasmepsins. Of these, only Plm V, IX and X subtypes are expressed in the blood stages of the parasite. The subtype Plm V [17,18] is more distant from Plm I, II, IV, while Plm IX and X share high sequence homology. It has been recently shown that Plm IX is involved in merozoite invasion of RBC while Plm X is involved in both, the invasion and the egress of merozoites [19,20]. Moreover, inhibitors of Plm IX and Plm X were demonstrated which showed antiplasmodial activity in RBC assays. These findings reinforce the importance of plasmepsins as targets for antimalarial drug development. However, production of recombinant Plm IX and X has only been possible in higher eukaryotic protein expression systems, such as insect or mammalian cells [19,20]. For this reason, the more easily accessible digestive plasmepsins [21-23] are still useful as model proteins for inhibitor development.

In the last decade, a notable focus has been on the search for non-peptidomimetic plasmepsin inhibitors [10,24-28]. These inhibitors are more drug-like and also show an improved selectivity profile against human aspartic proteases (e.g. Cathepsin D) as compared to peptidomimetic inhibitors. Recently, we reported 2-aminoquinazolin-4(3H)-ones **1** as non-peptidomimetic Plm I, II, IV inhibitors (Figure 1) [29].

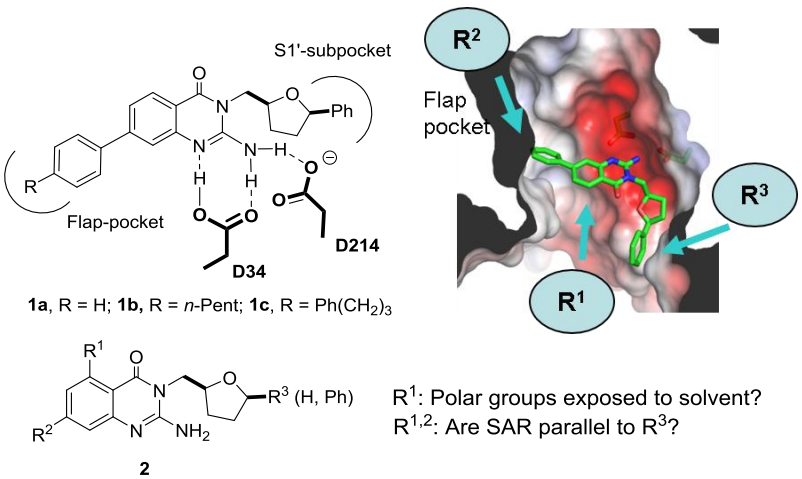


Figure 1. Crucial binding interactions of inhibitors **1** with Plm II according to X-ray of the complex (PDB ID 4z22) and proposed SAR study for evaluating substituents at positions R^{1-3} in the follow-up inhibitor series **2**. The pockets are labeled according to protease nomenclature.

According to the X-ray structure of the complex of **1a** and Plm II, these inhibitors bind to the open-flap conformation of the enzyme. The major interactions involve the 2-aminoquinazolinone *N*1 and 2-amino groups, which form hydrogen bond interactions with the catalytic aspartates, the Ph-THF moiety, which targets the S1' sub-pocket and the 7-Ph substituent, which makes hydrophobic and stacking interactions with residues in the flap-pocket. The inhibitor **1b** bearing *n*-pentylphenyl group as flap-pocket substituent showed similar inhibitory potency against subtypes Plm I,II,IV while inhibitor **1c** with phenylpropylphenyl substituent turned out to be selective Plm IV inhibitor. Both compounds **1b,c** inhibited *Plasmodium* growth at low micromolar concentrations. However, due to their high lipophilicity the compounds were poorly water-soluble, which limited their optimization. This prompted us to generate a follow-up series of inhibitors **2** aimed at reducing lipophilicity without sacrificing potency.

2. Results and discussion

2.1. SAR studies

Our strategy for reducing the inhibitor lipophilicity was to install hydrophilic substituents in positions that are facing polar protein surfaces or are solvent-exposed. Guided by the co-crystal structure of **1a** and Plm II (Figure 1), we modified the position R^1 facing solvent exposed area. For 2-aminoquinazolinones bearing R^1 substituents, two sets of compounds were tested – one with Ph group at THF, and one with unsubstituted THF (compounds **3a,b** and **2a-g**, respectively, Table 1). Substitution of THF (analogues **3a,b** vs **2a-g**) improved only Plm I and Plm IV inhibition, while the potency against Plm II remained very similar. This is opposite to the previous observation that the addition of Ph group at THF improved Plm II inhibition five-fold (inhibitors **2h** vs **1a**, Table 1).

Compounds **2a-g** with various R^1 substituents showed a flat SAR as could be expected by their situation in an area exposed to the solvent. Also, compounds **3a,b**

showed very similar activity to the parent compound **1a** suggesting that the R^1 group does not form specific interactions with the protein. This is in line with results from molecular docking, which show that the R^1 substituents may only form hydrogen bond interactions with surface exposed backbone amide and side chain hydroxyl groups of Val78 and Tyr192 (Figure 2) or with solvent molecules. Minor differences in the compound activities could be attributed to positioning and electron donor properties of functional groups in R^1, where groups with better electron donor (H-bond acceptor) properties are favoured. The slightly higher activities against Plm II over Plm I, IV and CatD can be explained by a Tyr192Phe substitution in the latter, which abolishes interactions with the THF oxygen and the propionate groups of **2b** and **3b**. Importantly, selectivity factors of compounds in this series for Plm II, IV *vs* CatD inhibition was increased up to 100-fold indicating that the selectivity against CatD can be improved by introduction of R^1 substituents.

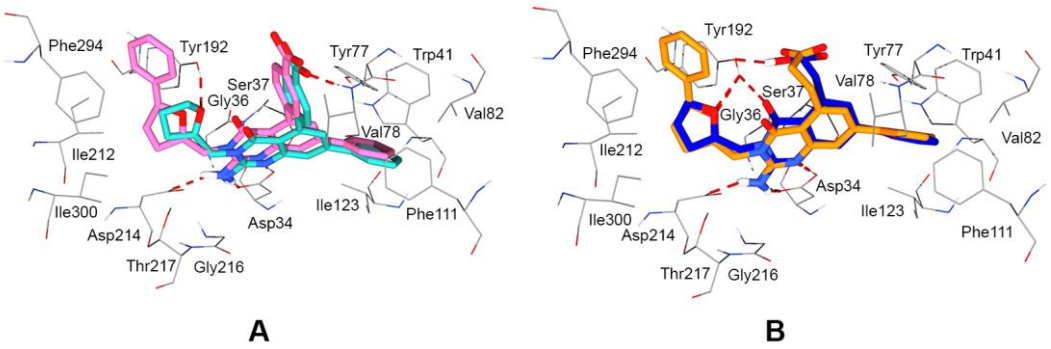
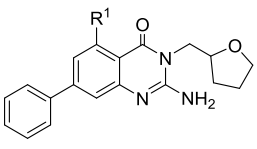
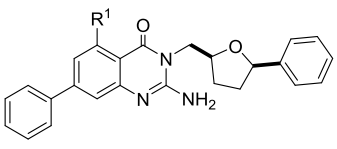


Figure 2. Docked poses of compounds **2a**, **3a** (A) and **2b**, **3b** (B). Protein residues are shown with thin sticks and labelled. Dashed red lines indicate hydrogen bonds with aspartates and Val78 or Tyr192. Docking was performed on the crystal structure of Plm II – **1a** complex (PDB ID 4Z22) using Schrödinger Glide software.

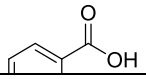
Table 1. SAR of R^1 Substituents in Inhibitors **1a**, **2a-h** and **3a,b**

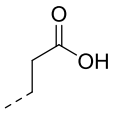
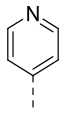
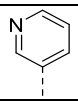
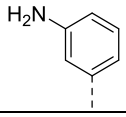
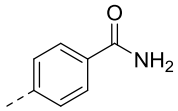
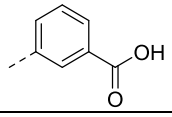


2a-h



1a, 3a,b

Compd.	**R^1**	**PlmI, IC_{50} (μM)[a]**	**PlmII, IC_{50} (μM)[a]**	**PlmIV, IC_{50} (μM)[a]**	**CatD, IC_{50} (μM)[a]**	**clogP[c]**	**PSA (Å^2)[c]**	**LiPE[d]**
2a		3.50 ± 0.04	0.33 ± 0.02	1.4 ± 0.2	~100	3.6	113.3	2.3

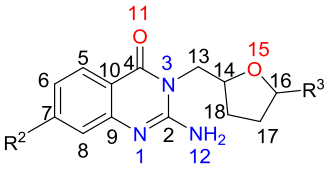
3a		0.6 ± 0.1	0.28 ± 0.02	0.50 ± 0.08	20.0 ± 1.2	4.8	111.2	1.5
2b		11.5 ± 1	0.50 ± 0.06	6.0 ± 0.5	>100	2.8	114.1	2.4
3b		1.0 ± 0.2	0.40 ± 0.03	0.6 ± 0.1	11.0 ± 0.8	4.3	111.4	1.9
2c		5.0 ± 0.5	1.00 ± 0.06	2.4 ± 0.2	>100	3.5	77.3	2.1
2d		3.0 ± 0.2	0.48 ± 0.04	1.5 ± 0.1	71 ± 2	3.5	77.6	2.3
2e		2.0 ± 0.5	0.82 ± 0.08	1.0 ± 0.3	93 ± 2	3.4	93.4	2.6
2f		3.4 ± 0.2	0.60 ± 0.08	2.5 ± 0.6	>100	2.8	117.8	2.8
2g		1.0 ± 0.4	0.50 ± 0.02	1.5 ± 0.1	98 ± 2	3.6	116.1	2.2
2h[b]	H	6.0 ± 0.3	2.3 ± 0.1	1.30 ± 0.06	53.4 ± 0.8	2.7	65.7	3.1
1a[b]		1.30 ± 0.06	0.57 ± 0.02	0.60 ± 0.03	13.8 ± 0.6	4.4	67.5	1.9

[a]Plm I,II,IV and CatD inhibitory activity was determined by enzymatic FRET assay in triplicate experiments; [b]Data from ref. [29]. [c] Calculated using Schrödinger QikProp software for pH 7; [d]LipE calculated using IC_{50} values of Plm IV inhibition.

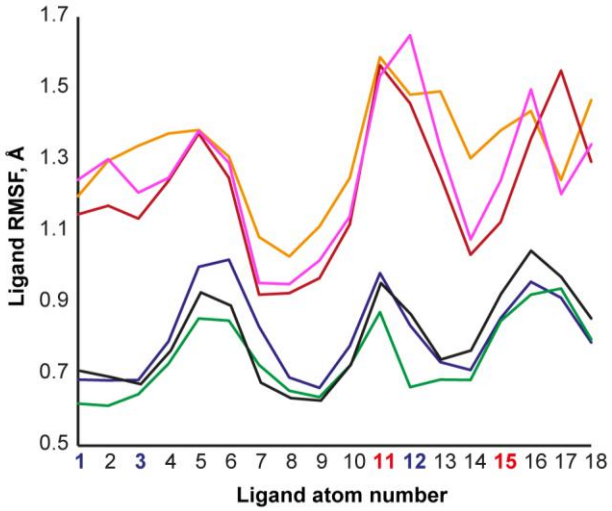
Next, we explored the possibility of removing the Ph substituent from the THF ring. Docking and molecular dynamics (MD) simulations of inhibitors containing the flap pocket substituent and either Ph-substituted THF or unsubstituted THF group showed that the presence of Ph substituent in this position affects inhibitor mobility in the binding pocket. During the MD simulation, compounds **1a-c** were conformationally locked and exhibited high rigidity, while compounds **2h, 4a-b** lacking the Ph substituent were more flexible (Fig. 3A). In the case of phenylpropylphenyl as flap pocket substituent, the Ph-THF group additionally caused a slight misalignment of the inhibitor (**1c**) with respect to the binding pose of compound **4b** (Fig. 3B). Based on these data we hypothesized that the benefit of the Ph-THF group in compounds containing a flap pocket substituent may be diminished due to a larger entropic penalty associated with constraining the ligand flexibility and/or due to ligand inability to maintain an optimal binding pose, when both terminal

groups are locked in hydrophobic pockets (flap pocket and S1' sub-pocket). Experimentally it was found that compound **4a** lacking the Ph substituent at THF exhibits a very similar inhibitory potency against Plms I,II and IV and CatD compared to the parent compound **1b** (Table 2). Phenylpropylphenyl group, previously found as Plm IV subtype selectivity inducing group, was added as R^2 substituent (compound **4b**). Again, this compound lacking Ph substituent at THF ring did not reduce the activity against Plm IV compared to the parent compound **1c**, however, the subtype selectivity against Plm I, II was decreased. Attachment of *n*-octyl chain directly to the 7-position of quinazolinone scaffold also led to potent Plms I,II and IV inhibitors **4c** and **5** irrespective of the substitution at THF ring. However, the introduction of this flap pocket substituent significantly reduced selectivity against CatD.

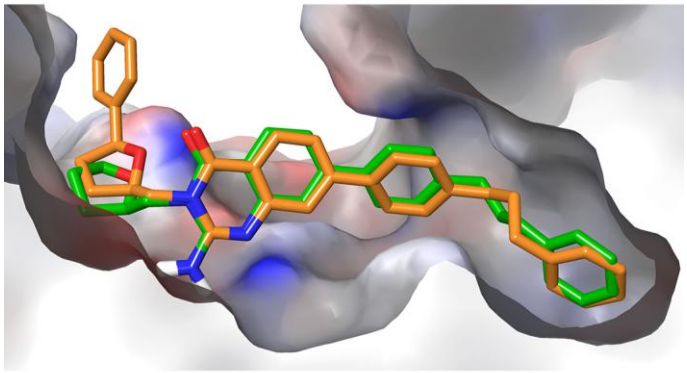
The results from SAR studies of compound series **2** and **4** suggested to introduce ionisable substituent at 5-position and to remove the phenyl substituent from THF group which would lead to increased selectivity and hydrophilicity (Table 1). At the same time, addition of flap-pocket substituents at 7-position of quinazolinone lacking Ph group at THF ring is beneficial to achieve high inhibitory potency against plasmepsins (compounds **4a-c**, Table 2). Based on these considerations, quinazolinone derivatives **6a-c** and **7a,b** were prepared bearing the carboxyethyl and carboxyphenyl groups at the 5-position (Table 3). Compound **6a** containing pentylphenyl group as a flap-pocket substituent and carboxyethyl group at the 5-position showed high inhibitory potency against all Plm subtypes. In the case of carboxyphenyl analogue **7a**, the potency was high only against Plms II and IV subtypes. Notably, selectivity for these compounds **6a**,**7a** against CatD was retained at very high level. Introduction of phenylpropylphenyl as flap-pocket substituent induced remarkable Plm IV subtype selectivity only in the case of carboxyphenyl group containing analogue **7b**. In the case of carboxyethyl substituent (compound **6b**) the potency was relatively high against all Plms subtypes. Introduction of *n*-octyl group at 7-position and carboxyethyl group at 5-position of quinazolinone led to potent inhibitor **6c** for Plm I,II,IV subtypes, however the selectivity against CatD was lost.



1a R^2 = Ph; R^3 = Ph
1b R^2 = Ph-*n*-pentyl; R^3 = Ph
1c R^2 = Ph-$(CH_2)_3$Ph; R^3 = Ph
2h R^2 = Ph; R^3 = H
4b R^2 = Ph-$(CH_2)_3$Ph; R^3 = H
4a R^2 = Ph-*n*-pentyl; R^3 = H



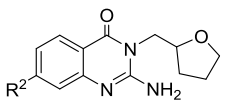
A



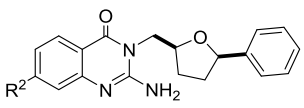
B

Figure 3. Influence of the Ph substituent at the THF ring on bound inhibitor flexibility and binding pose. (A) Root mean square fluctuations (RMSF) of inhibitor atoms during a 70 ns MD simulation. The atom numbering used is shown on the structure above the plot. (B) Comparison of docked poses of inhibitors **1c** and **4b**. The protein active site cavity is mapped with electrostatic potential surface. Docking was performed on the crystal structure of Plm II – **1a** complex (PDB ID 4Z22) using Schrödinger Glide software.

Table 2 SAR of R^2 Substituents in Inhibitors **1b,c**,**4a-c**,**5**

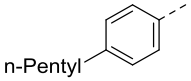
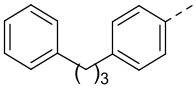


4a-c



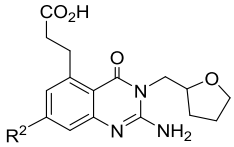
1b,c and **5**

Compd.	R^2	PlmI, IC_{50} (μM)[a]	PlmII, IC_{50} (μM)[a]	PlmIV, IC_{50} (μM)[a]	CatD IC_{50} (μM)[a]	clogP[c]	PSA (Å^2)[c]	LiPE

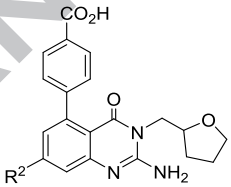
4a		0.70 ± 0.04	0.075 ± 0.004	0.092 ± 0.005	3.20 ± 0.16	4.4	71.4	2.6
1b[b]		0.30 ± 0.01	0.15 ± 0.01	0.10 ± 0.01	5.0 ± 0.2	6.2	68.0	0.8
4b		1.30 ± 0.08	0.70 ± 0.03	0.10 ± 0.04	>100	5.4	68.8	1.6
1c[b]		3.2 ± 0.1	10.0 ± 0.5	0.13 ± 0.03	6.0 ± 0.3	7.7	66.3	-0.8
4c	*n*-octyl	0.090 ± 0.004	0.093 ± 0.005	0.155 ± 0.007	2.70 ± 0.14	4.0	69.5	2.8
5		0.08 ± 0.02	0.088 ± 0.003	0.11 ± 0.02	0.40 ± 0.04	5.8	68.9	1.2

[a]*Plm I,II,IV and CatD inhibitory activity was determined by enzymatic FRET assay in triplicate experiments;* [b]*Data from ref. [29]* [c] *Calculated using Schrödinger QikProp software for pH 7;* [d]*LipE calculated using IC_{50} values of Plm IV inhibition*.

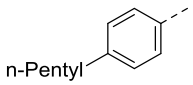
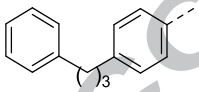
Table 3 SAR of R^2 Substituents in Inhibitors **6a-c**;**7a,b**



6a-c



7a,b

Comp.	**R^2**	**PlmI, IC_{50} (μM)**[a]	**PlmII, IC_{50} (μM)**[a]	**PlmIV, IC_{50} (μM)**[a]	**CatD, IC_{50} (μM)**[a]	**clogP**[b]	**PSA ($Å^2$)**[b]	**LiPE**[c]
6a		0.050 ± 0.003	0.027 ± 0.002	0.042 ± 0.002	21.0 ± 1.1	4.6	116.4	2.8
7a		2.40 ± 0.12	0.023 ± 0.001	0.045 ± 0.002	29.0 ± 1.4	5.3	113.5	2.0
6b		0.74 ± 0.04	0.080 ± 0.004	0.030 ± 0.002	13.00 ± 0.65	5.5	113.5	2.0
7b		16.7 ± 0.8	0.90 ± 0.05	0.027 ± 0.001	25.0 ± 1.2	6.3	113.5	1.2
6c	*n*-octyl	0.020 ± 0.001	0.022 ± 0.001	0.110 ± 0.006	0.43 ± 0.02	4.1	115.8	2.9

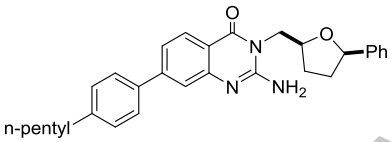
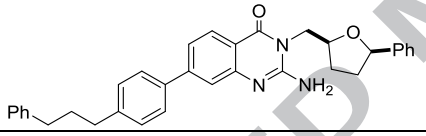
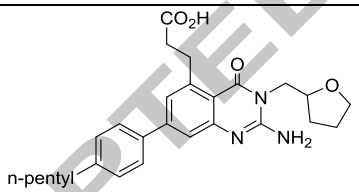
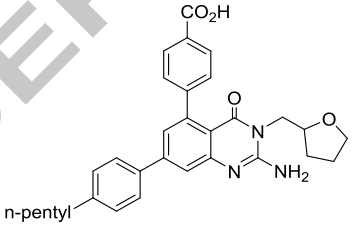
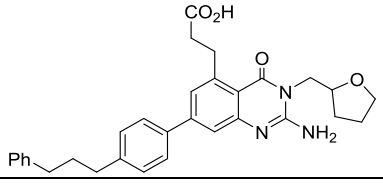
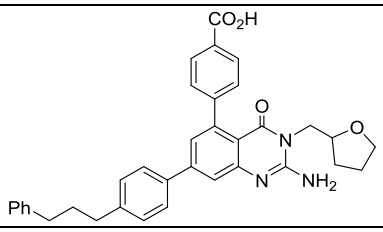
[a]*Plm I,II,IV and CatD inhibitory activity was determined by enzymatic FRET assay in triplicate experiments.* [b]*Calculated using Schrödinger QikProp software for pH 7;* [c]*LipE calculated using IC_{50} values of Plm IV inhibition*.

The most notable effect on reducing lipophilicity and consequently improving LiPE was achieved by removal of Ph substituent from THF group (e.g. compounds **2a** *vs*, **3a**, **2b** *vs*, **3b**, **2h** *vs* **1a**, Table 1 and **4a** *vs* **1b, 4b** *vs* **1c**, Table 2). Introduction of oxycarbonylethyl group at 5th position of quinazolinone practically did not change the

lipophilicity (compounds **6a** *vs* **4a** and **6c** *vs* **4c**, Tables 2,3) while introduction of carboxyphenyl group in this position had negative impact (compounds **7a** *vs* **4a**, Tables 2,3).

Selected compounds were tested for the solubility **1b,c**, **6a,b** and **7a,b** at physiological pH (Table 4). These data indicate that removal of phenyl group from tetrahydrofurane and the installation of ionazable group at the 5-position was beneficial for improving solubility of inhibitors **6a,b** and **7a,b** compared to parent compounds **1b,c**, however the solubility was found to be still very low.

Table 4 Solubility of Inhibitors **1b,c**, **6a,b** and **7a,b** in 0.05 M TRIS buffer at pH 7.4

Entry	**Compound**	Solubility[a]
1b		<10 μg/L[b]
1c		<10 μg/L[b]
6a		100 μg/L
7a		30 μg/L
6b		10 μg/L
7b		170 μg/L

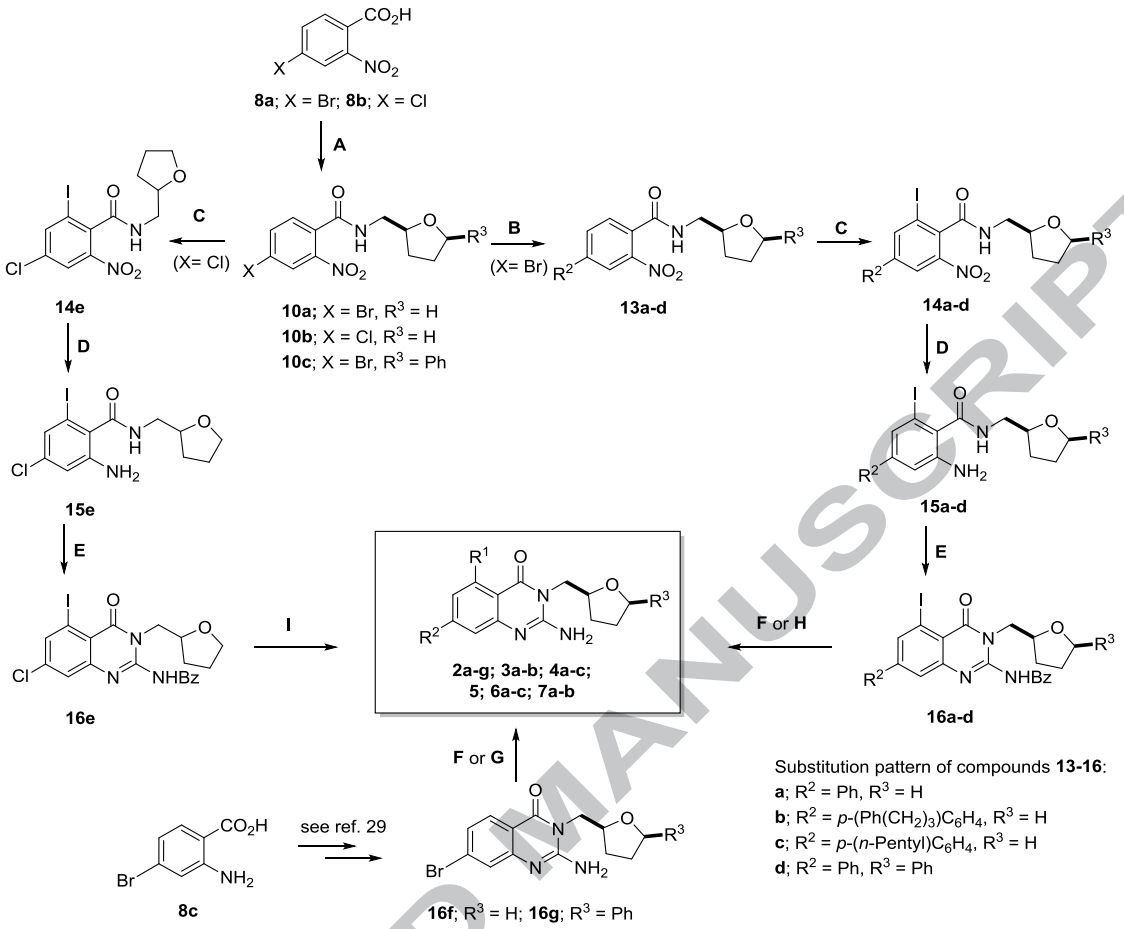
[a]Solubility was determined by HPLC as the residual compound concentration after its precipitation with aqueous TRIS-buffer (pH=7.4) from DMSO stock solution; [b]detection limit

2.2. Chemistry

The previously reported strategy was applied to prepare 2-aminoquinazolin-4(3H)-ones **2-7** using 4,6-substituted 2-aminobenzamides **15a-e** as key intermediates (Scheme 1) [29]. Commercially available 4-bromo- or 4-chloro-2-nitrobenzoic acids (**8a,b**) were coupled with 2-aminomethyltetrahydrofuran derivatives **9a** (R^3 = Ph) or **9b** (R^3 = H) to give amides **10a-c**. Two of intermediates **10a,c** bearing bromide were subjected to Suzuki–Miyaura reaction with corresponding boronic acid **11** or pinacolboranes **12a,b** to give the coupling products **13a**,**d** (R^2 = Ph); **13b**, (R^2 = *p*-(Ph$(CH_2)_3$)C_6H_4) and **13c**, (R^2 = *p*-(*n*-Pentyl)C_6H_4). This was followed by directed *ortho*-C-H activation/iodination in the presence of catalytic amount of $Pd(OAc)_2$ providing iodides **14a-d**. Reduction of nitro group in compounds **14a-d** provided the desired 2-aminobenzamides **15a-d**. Formation of thiourea intermediate from aniline **15a-d** with BzSCN and subsequent cyclisation afforded protected 2-aminoquinazolin-4(3H)-one building blocks **16a-d**. Last steps involved Suzuki–Miyaura or Mizoroki-Heck reactions to install R^1 substituents. Benzoyl group cleavage was achieved with hydrazine hydrate which served also as hydrogen transfer reagent for hydrogenation of unsaturated bonds in the presence of Pd/C catalyst to give the final products **2a-g**; **3a-b**; **6a-b**; **7a-b**.

Intermediate **10b** bearing chloride substituent was converted to 2-aminoquinazolin-4(3H)-one building block **16e** in three step sequence which involved directed *ortho*-C-H activation/iodation of **10b** to give amide **14e**. The reduction of nitro group in this compound provided 4,6-substituted 2-aminobenzamide **15e**, which was cyclised to give building block **16e**. Selective Sonogashira reaction with chloride **16e** was used to install alkynyl group in R^2 position and Mizoroki-Heck reaction with *t*-butyl acrylate was used to introduce substituent in R^1 position. Subsequent cleavage of *t*-butyl and benzoyl groups followed by *in situ* saturation of unsaturated bonds provided product **6c**.

Products **4a-b** were synthesized from known building block **16f** [29] using Suzuki–Miyaura reaction with pinacolboranes **12a,b** and subsequent benzoyl group cleavage with hydrazine hydrate. Sonogashira reaction with building blocks **16f,g** [29], benzoyl group cleavage and *in situ* saturation of alkynyl group provided final products **4c**, **5**.



Scheme 1 Synthesis of 2-aminoquinazolin-4(3H)-ones. Reagents and conditions: **A)** $(COCl)_2$, cat. DMF, DCM, then Et_3N, amine **9a,b**, DCM; **B)** R^2-$B(OH)_2$ **11** or R^2-B(Pin) **12a,b**, $Pd(PPh_3)_4$, K_2CO_3, THF, H_2O; **C)** $PhI(OAc)_2$, I_2, $Pd(OAc)_2$, DMF; **D)** $Na_2S.9H_2O$, THF, MeOH; **E)** BzSCN, Et_2O, then EDCI*HCl, Et_3N, DCM; **F)** boronic acid **11b-g** or R^2-B(Pin) **12a,b**, $Pd(PPh_3)_4$, K_2CO_3, DMF, then N_2H_4*H_2O, EtOH; **G)** 1-octyne, $Pd[(PPh_3)Cl]_2$, Et_3N, CuI, DMF, then N_2H_4*H_2O, Pd/C, EtOH; **H)** *t*-butyl acrylate, $Pd(PPh_3)_4$, Et_3N, DMF, then TFA, DCM, then N_2H_4*H_2O, Pd/C, EtOH; **I)** *t*-butyl acrylate, Pd(dppf)Cl_2*DCM, K_2CO_3, DMF, then 1-octyne, Pd(Amphos)Cl_2, Cs_2CO_3, DMF, then TFA, DCM, then N_2H_4*H_2O, Pd/C, EtOH.

3. SUMMARY

In summary, we have shown that exploiting the solvent exposed area of enzyme provides an option to install polar groups (R^1) in the 5-position of 2-aminoquinazolin-4(3H)-one inhibitors such as carboxylic acid or pyridine without sacrificing enzymatic potency. Moreover, introduction of R^1 substituents increased selectivity factors of

compounds in this series up to 100-fold for Plm II, IV *vs* CatD inhibition. It was found that the introduction of flap pocket substituent (R^2) at 7-postion of 2-aminoquinazolin-4(3H)-one allows to remove the Ph group from THF ring without notably impairing Plm inhibitory potency. Taken these findings together, inhibitors **6a,b** and **7a,b** were developed which show Plm II and IV inhibitory potency in low nanomolar range and remarkable selectivity against Cathepsin D. These modifications were also beneficial to decrease the lipophilicity and increase the aqueous solubility.

4. EXPERIMENTAL SECTION

4.1. General

Reagents and starting materials were purchased from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. Flash chromatography was carried out using Kieselgel (35−70μm) silica gel. TLC was performed on Kieselgel 60 F254 (Merck) and was visualized by staining with $KMnO_4$ or UV. NMR spectra were recorded on 300 and 400 MHz spectrometers with chemical shift values (δ) in ppm using the residual solvent signal as an internal refercence. Exact molecular masses (HRMS) were determined on a hybrid quadrupole time-of-flight mass spectrometer equipped with an electrospray ion source. The purity for all compounds tested in bioassays was 95+%, determined by UPLC analysis on a Waters Acquity column: Acquity UPLC BEH-C18 (2.1 mm×50 mm, 1.7μm, (30.0±5.0)°C); gradient, 0.01% TFA in water/CH_3CN 90%/10% to 10%/90%;flow rate, 0.5 mL/min; run time, 8 min; detector, PDA (photodiode matrix), 220−320 nm.

*4.2. General procedure **A** for the synthesis of compounds **10a-c***

$(COCl)_2$ (1.5 equiv.) was added dropwise to the solution of benzoic acid (5 mmol, 1 equiv.) and few drops of DMF in DCM (20 mL) at 0 ^oC. Reaction mixture was stirred at r. t. for 4 h, then solvent evaporated. Obtained crude benzoyl chloride was dissolved in DCM (20 mL). Et_3N (3 equiv.) and amine (1.1 equiv.) was added and mixture stirred at r. t. overnight. Then 5% aq. $KHSO_4$ solution was added and product extracted with DCM, dried over anh. Na_2SO_4. Purification by column chromatography.

*4.2.1. rac-4-Bromo-2-nitro-N-((tetrahydrofuran-2-yl)methyl)benzamide (**10a**)*

Prepared from benzoic acid **8a** and amine **9b**. Yield 1.3 g (79%), white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19 (d, J = 1.9 Hz, 1H), 7.79 (dd, J = 8.1, 1.9 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 6.19 (s, 1H), 4.09 (qd, J = 7.2, 3.3 Hz, 1H), 3.89 – 3.73 (m, 3H), 3.33 (ddd, J = 13.8, 7.4, 4.8 Hz, 1H), 2.12 – 1.87 (m, 3H), 1.72 – 1.63 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.5, 146.9, 136.4, 131.6, 129.9, 127.4, 123.6, 77.3, 68.0, 43.6, 28.5, 25.8. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}BrN_2O_4$ 329.0137; Found 329.0143.

*4.2.2. rac-4-Chloro-2-nitro-N-((tetrahydrofuran-2-yl)methyl)benzamide (**10b**)*

Prepared from acid **8b** and amine **9b.** Yield 4.59 g (88%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, J = 1.9 Hz, 1H), 7.62 (dd, J = 8.1, 1.9 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 6.36 (brs, 1H), 4.06 (qd, J = 7.2, 3.4 Hz, 1H), 3.86 – 3.78 (m, 1H), 3.78 – 3.67 (m, 2H), 3.35 – 3.25 (m, 1H), 2.03 (m, 1H), 1.92 (m, 2H), 1.71 – 1.59 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.7, 147.2, 136.5, 133.7, 131.4, 130.0, 125.0, 77.5, 68.3, 43.9, 28.7, 26.0. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}ClN_2O_4$ 285.0642; Found 285.0645.

4.2.3. 4-Bromo-2-nitro-N-(((2S,5R*)-5-phenyltetrahydrofuran-2-yl)methyl)benzamide (**10c**)*

Prepared from acid **8a** and amine **9a.** Yield 2.85 g (59%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, J = 1.9 Hz, 1H), 7.70 (dd, J = 8.1, 1.9 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.28 – 7.24 (m, 4H), 7.23 – 7.17 (m, 1H), 6.35 (brs, 1H), 4.86 (dd, J = 7.7, 6.7 Hz, 1H), 4.31 – 4.09 (m, 1H), 3.87 (ddd, J = 13.7, 6.9, 3.4 Hz, 1H), 3.40 (ddd, J = 13.8, 7.5, 4.6 Hz, 1H), 2.38 – 2.24 (m, 1H), 2.19 – 2.05 (m, 1H), 1.94 – 1.73 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.8, 147.1, 142.2, 136.7, 131.7, 130.0, 128.6, 127.7, 126.0, 124.0, 81.7, 78.1, 44.3, 34.0, 29.0. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}BrN_2O_4$ 405.0450; Found 405.0445.

*4.3. General procedure **B** for the synthesis of compounds **13a-d***

To a solution of bromobenzene (3 mmol, 1 equiv.) in THF (10 mL) and H_2O (2 mL), boronic acid (1.2 equiv.) or pinacolborane (1.2 equiv.), $Pd(PPh_3)_4$ (2.5 mol%), and K_2CO_3 (3 equiv.) were added. The resulting mixture was heated at 80 °C. After the

reaction was completed (monitored by TLC), the solution was cooled to r. t. and then partitioned between H_2O and EtOAc. The organic layer was concentrated in vacuo and product purified by column chromatography.

*4.3.1. rac-3-Nitro-N-((tetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**13a**)*

Prepared from bromobenzene **10a** and phenylboronic acid **11**. Yield 0.91 g (92%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.66-1.75 (m, 1H), 1.91-1.99 (m, 2H), 2.03-2.11 (m, 1H), 3.35-3.42 (m, 1H), 3.74-3.90 (m, 3H), 4.09-4.15 (m, 1H), 6.24 (brs, 1H), 7.43-7.53 (m, 3H), 7.58-7.62 (m, 3H), 7.86 (dd, J = 2.0 Hz, 7.8 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.6, 147.3, 144.1, 137.9, 131.9, 131.5, 129.4, 129.3, 129.1, 127.3, 123.1, 77.6, 68.3, 43.9, 28.8, 26.1. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}N_2O_4$ 327.1345; Found 327.1353.

*4.3.2. rac-3-Nitro-4'-(3-phenylpropyl)-N-((tetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**13b**)*

Prepared from bromide **10a** pinacolborane **12a.** Yield 1.3 g (86%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, J = 1.7 Hz, 1H), 7.84 (dd, J = 7.9, 1.8 Hz, 1H), 7.55 (dd, J = 16.4, 8.1 Hz, 4H), 7.35 – 7.25 (m, 3H), 7.21 (d, J = 0.7 Hz, 3H), 6.29 – 6.21 (m, 1H), 4.17 – 4.06 (m, 1H), 3.89 – 3.71 (m, 4H), 3.38 (ddd, J = 13.8, 7.3, 4.9 Hz, 1H), 2.70 (dt, J = 11.8, 7.7 Hz, 4H), 2.11 – 1.90 (m, 4H), 1.76 – 1.65 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.6, 147.3, 144.0, 143.6, 142.1, 135.4, 131.6, 131.2, 129.5, 129.2, 128.6, 128.5, 127.2, 126.0, 122.8, 77.6, 68.3, 43.8, 35.5, 35.2, 32.9, 28.7, 26.1. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{27}H_{29}N_2O_4$ 445.2127; Found 445.2124.

*4.3.3. rac-3-Nitro-4'-pentyl-N-((tetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**13c**)*

Prepared from bromide **10a** pinacolborane **12b** in DMF. Yield 1.5 g (75%), white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, J = 1.7 Hz, 1H), 7.83 (dd, J = 7.9, 1.7 Hz, 1H), 7.54 (dd, J = 13.7, 8.0 Hz, 3H), 7.30 (d, J = 8.1 Hz, 2H), 6.37 (t, J = 5.7 Hz, 1H), 4.14 – 4.04 (m, 1H), 3.88 – 3.71 (m, 3H), 3.37 (ddd, J = 13.7, 7.3, 4.9 Hz, 1H), 2.71 – 2.63 (m, 2H), 1.98 – 1.87 (m, 2H), 1.75 – 1.59 (m, 3H), 1.35 (h, J =

3.7, 3.2 Hz, 4H), 1.25 (td, *J* = 7.2, 0.6 Hz, 1H), 0.94 – 0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 166.7, 147.3, 144.3, 144.0, 135.2, 131.6, 131.1, 129.5, 129.2, 127.1, 122.7, 77.6, 68.3, 43.8, 35.7, 31.6, 31.2, 28.7, 26.1, 22.7, 14.1. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{23}H_{29}N_2O_4$ 397.2127; Found 397.2135.

4.3.4. 3-Nitro-N-(((2S,5R*)-5-phenyltetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**13d**)*

Prepared from bromide **10c** and boronic acid **11.** Yield 1.7 g (85 %), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.16 (d, *J* = 1.8 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.50 – 7.35 (m, 4H), 7.30 – 7.20 (m, 4H), 7.22 – 7.13 (m, 1H), 6.28 (t, *J* = 5.9 Hz, 1H), 4.85 (t, *J* = 7.0 Hz, 1H), 4.23 (tdd, *J* = 7.2, 6.3, 3.4 Hz, 1H), 3.89 (ddd, *J* = 13.8, 6.9, 3.4 Hz, 1H), 3.43 (ddd, *J* = 13.8, 7.4, 4.7 Hz, 1H), 2.36 – 2.22 (m, 1H), 2.19 – 2.04 (m, 1H), 1.94 – 1.76 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 166.6, 147.2, 144.1, 142.3, 137.9, 131.9, 131.4, 129.4, 129.2, 129.1, 128.6, 127.7, 127.3, 126.1, 123.1, 81.6, 78.3, 44.3, 34.1, 29.0. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{24}H_{23}N_2O_4$ 403.1658; Found 403.1660.

*4.4. General procedure **C** for the synthesis of compounds **14a-e***

Mixture of benzamide (1 mmol, 1 equiv.), $PhI(OAc)_2$ (1 equiv.), I_2 (1 equiv.) and $Pd(OAc)_2$ (10 mol%) in DMF (5 mL) was heated at 100 ^{o}C. After 24 h saturated aq. $NaHCO_3$ added, and mixture extracted with EtOAc. Organic layer washed with 10% aq. $Na_2S_2O_3$, brine and dried over anh. Na_2SO_4. Purification by column chromatography.

*4.4.1. rac-3-Iodo-5-nitro-N-((tetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**14a**)*

Prepared from benzamide **13a**. Yield 0.27 g (65%), white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.72.-1.79 (m, 1H), 1.91-1.99 (m, 2H), 2.04-2.13 (m, 1H), 3.37-3.43 (m, 1H), 3.75-3.80 (m, 1H), 3.85-3.91 (m, 2H), 4.16-4.22 (m, 1H), 6.14 (brs, 1H), 7.44-7.54 (m, 3H), 7.56-7.60 (m, 2H), 8.33 (d, *J* = 2.0 Hz, 1H), 8.34 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 166.5, 146.9, 144.6, 143.2, 136.6, 136.3, 129.5, 127.3, 123.0, 96.0, 77.3, 68.3, 43.8, 28.9, 26.1. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}IN_2O_4$ 453.0311; Found 453.0313.

*4.4.2. rac-3-Iodo-5-nitro-4'-(3-phenylpropyl)-N-((tetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**14b**)*

Prepared from benzamide **13b**. Yield 1.3 g (76%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (qd, J = 1.7, 0.6 Hz, 2H), 7.55 – 7.45 (m, 2H), 7.34 – 7.27 (m, 4H), 7.24 – 7.16 (m, 3H), 6.18 – 6.13 (m, 1H), 4.18 (qd, J = 7.1, 3.5 Hz, 1H), 3.92 – 3.83 (m, 2H), 3.77 (dt, J = 8.2, 6.8 Hz, 1H), 3.40 (ddd, J = 13.6, 7.3, 4.7 Hz, 1H), 2.70 (dt, J = 13.5, 7.7 Hz, 4H), 2.13 – 2.05 (m, 1H), 2.03 – 1.89 (m, 4H), 1.76 (ddt, J = 12.1, 8.5, 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.4, 146.7, 144.4, 144.0, 142.8, 141.9, 135.8, 133.9, 129.5, 128.42, 128.36, 127.1, 125.9, 122.6, 95.8, 77.2, 68.2, 43.7, 35.4, 35.0, 32.8, 28.7, 25.9. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{27}H_{28}IN_2O_4$ 571.1094; Found 571.1093.

*4.4.3. rac-3-Iodo-5-nitro-4'-pentyl-N-((tetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**14c**)*

Prepared from benzamide **13c**. Yield 1.1 g (57%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (d, J = 1.7 Hz, 1H), 8.31 (d, J = 1.7 Hz, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.13 (t, J = 5.1 Hz, 1H), 4.19 (qd, J = 7.0, 3.3 Hz, 1H), 3.92 – 3.84 (m, 2H), 3.80 – 3.73 (m, 1H), 3.40 (ddd, J = 13.7, 7.3, 4.7 Hz, 1H), 2.67 (t, J = 7.5 Hz, 2H), 2.14 – 2.03 (m, 1H), 2.00 – 1.91 (m, 2H), 1.82 – 1.70 (m, 1H), 1.65 (m, 2H), 1.37 – 1.31 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.4, 146.7, 144.7, 144.5, 142.8, 135.8, 133.8, 129.4, 127.0, 122.6, 95.8, 77.2, 68.2, 43.7, 35.6, 31.4, 31.0, 28.7, 25.9, 22.5, 14.0. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{23}H_{28}IN_2O_4$ 523.1094; Found 523.1091.

4.4.4. 3-Iodo-5-nitro-N-(((2S,5R*)-5-phenyltetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**14d**)*

Prepared from benzamide **13d**. Yield 0.15 g (56 %, 75 % brsm), white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25 (s, 2H), 7.54 – 7.36 (m, 5H), 7.31 – 7.07 (m, 5H), 6.15 (dd, J = 7.1, 4.3 Hz, 1H), 4.85 (t, J = 7.0 Hz, 1H), 4.30 (qd, J = 7.2, 3.4 Hz, 1H), 3.95 (ddd, J = 13.7, 7.1, 3.5 Hz, 1H), 3.44 (ddd, J = 13.7, 7.6, 4.3 Hz, 1H), 2.36 – 2.23 (m, 1H), 2.22 – 2.08 (m, 1H), 1.97 – 1.79 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.6, 146.8, 144.6, 143.1, 142.3, 136.6, 136.2, 129.5, 128.6, 127.7, 127.3,

126.1, 123.0, 96.0, 81.7, 77.9, 44.4, 34.1, 29.2. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{24}H_{22}IN_2O_4$ 529.0624; Found 529.0599.

*4.4.5. rac-4-Chloro-2-iodo-6-nitro-N-((tetrahydrofuran-2-yl)methyl)benzamide (**14e**)*

Prepared from benzamide **10b**.Yield 1.8 g (31 %), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (m, 2H), 6.09 (brs, 1H), 4.16 (qd, J = 7.2, 3.4 Hz, 1H), 3.92 – 3.81 (m, 2H), 3.81 – 3.67 (m, 1H), 3.35 (ddd, J = 13.7, 7.4, 4.6 Hz, 1H), 2.14 – 2.01 (m, 1H), 1.94 (m, 2H), 1.87 – 1.63 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.67, 146.65, 144.36, 136.54, 136.50, 124.87, 95.82, 77.36, 68.32, 43.90, 28.88, 26.06. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{12}H_{13}ClIN_2O_4$ 410.9609; Found 410.9612.

*4.5. General procedure **D** for the synthesis of compounds **15a-e***

Mixture of nitrobenzene (1.5 mmol, 1 equiv.) and $Na_2S.9H_2O$ (3 equiv.) in THF (15 mL) and MeOH (15 mL) was refluxed for 1 – 2 h then solvents evaporated in vacuo. Residue partitioned between H_2O and EtOAc. The organic layer was washed 2 times with H_2O, brine and dried over anh. Na_2SO_4. After evaporation of solvent crude product washed with PE/EtOAc (4:1), filtered.

*4.5.1. rac-3-Amino-5-iodo-N-((tetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**15a**)*

Prepared from nitrobenzene **14a**. Yield 0.52 g (83%), light yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65-1.74 (m, 1H), 1.86-2.09 (m, 3H), 3.37-3.44 (m, 1H), 3.71-3.79 (m, 2H), 3.86-3.91 (m, 1H), 4.09-4.16 (m, 1H), 4.39 (brs, 2H), 6.29 (brs, 1H), 6.83 (d, J = 1.6 Hz, 1H), 7.33-7.44 (m, 4H), 7.47-7.51 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.1, 146.0, 144.8, 139.3, 128.9, 128.2, 128.1, 127.2, 126.2, 114.7, 93.90, 77.4, 68.2, 43.5, 29.0, 26.0. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}IN_2O_2$ 423.0569; Found 423.0563.

*4.5.2. rac-3-Amino-5-iodo-4'-(3-phenylpropyl)-N-((tetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**15b**)*

Prepared from nitrobenzene **14b**. Yield 1.0 g (96%), light yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (dd, J = 4.9, 3.4 Hz, 3H), 7.32 – 7.26 (m, 2H),

7.25 – 7.16 (m, 5H), 6.83 (d, *J* = 1.5 Hz, 1H), 6.26 (t, *J* = 5.9 Hz, 1H), 4.33 (brs, 2H), 4.14 (qd, *J* = 7.1, 3.6 Hz, 1H), 3.89 (ddd, *J* = 8.4, 7.0, 6.3 Hz, 1H), 3.79 – 3.73 (m, 2H), 3.41 (ddd, *J* = 13.8, 7.3, 5.3 Hz, 1H), 2.72 – 2.63 (m, 4H), 2.10 – 1.87 (m, 5H), 1.74 – 1.65 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 168.9, 145.8, 144.5, 142.4, 142.1, 136.6, 128.9, 128.4, 128.3, 127.8, 126.9, 125.83, 125.76, 114.3, 93.7, 77.6, 68.1, 43.4, 35.4, 35.0, 32.8, 28.8, 25.8. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{27}H_{30}IN_2O_2$ 541.1352; Found 541.1371.

*4.5.3. rac-3-Amino-5-iodo-4'-pentyl-N-((tetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**15c**)*

Prepared from nitrobenzene **14c**. Yield 0.79 g (84%), light yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.40 (dt, *J* = 7.5, 1.7 Hz, 3H), 7.25 – 7.16 (m, 2H), 6.83 (d, *J* = 1.6 Hz, 1H), 6.23 (t, *J* = 5.9 Hz, 1H), 4.36 (brs, 2H), 4.14 (qd, *J* = 7.1, 3.7 Hz, 1H), 3.89 (dt, *J* = 8.4, 6.6 Hz, 1H), 3.81 – 3.67 (m, 2H), 3.41 (ddd, *J* = 13.8, 7.3, 5.3 Hz, 1H), 2.63 (dd, *J* = 8.7, 6.7 Hz, 2H), 2.12 – 1.84 (m, 3H), 1.78 – 1.53 (m, 3H), 1.39 – 1.26 (m, 4H), 0.95 – 0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 169.0, 145.8, 144.6, 143.1, 136.4, 128.9, 127.9, 126.8, 125.8, 114.3, 93.7, 77.3, 68.1, 43.4, 35.6, 31.5, 31.1, 28.8, 25.8, 22.5, 14.0. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}IN_2O_2$ 493.1352; Found 493.1352.

4.5.4. 3-Amino-5-iodo-N-(((2S,5R*)-5-phenyltetrahydrofuran-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (**15d**)*

Prepared from nitrobenzene **14d**. Yield 0.41 g (59%), yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.52 – 7.20 (m, 11H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.30 (t, *J* = 6.0 Hz, 1H), 4.92 (t, *J* = 7.1 Hz, 1H), 4.42 – 4.24 (m, 3H), 3.91 (ddd, *J* = 13.7, 6.7, 3.7 Hz, 1H), 3.52 (ddd, *J* = 13.2, 7.7, 4.8 Hz, 1H), 2.42 – 2.28 (m, 1H), 2.25 – 2.09 (m, 1H), 1.99 – 1.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 169.1, 146.0, 144.8, 142.3, 139.3, 128.9, 128.6, 128.2, 128.1, 127.6, 127.2, 126.1, 126.0, 114.7, 93.9, 81.7, 77.9, 44.2, 34.3, 29.3. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}IN_2O_2$ 499.0882; Found 499.0893.

*4.5.5. rac-2-Amino-4-chloro-6-iodo-N-((tetrahydrofuran-2-yl)methyl)benzamide (**15e**)*

Prepared from nitrobenzene **14e**. Yield 1.6 g (96%), light yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.17 (d, J = 1.8 Hz, 1H), 6.64 (d, J = 1.8 Hz, 1H), 6.16 (brs, 1H), 4.39 (brs, 2H), 4.11 (qd, J = 7.1, 3.5 Hz, 1H), 3.94 – 3.83 (m, 1H), 3.82 – 3.61 (m, 2H), 3.47 – 3.21 (m, 1H), 2.10 – 1.86 (m, 3H), 1.74 – 1.57 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.4, 146.4, 136.4, 128.2, 125.8, 115.7, 93.4, 77.3, 68.2, 43.6, 29.0, 25.9. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}ClIN_2O_2$ 380.9867; Found 380.9865.

*4.6. General procedure **E** for the synthesis of compounds **16a-e***

Benzoyl isothiocyanate (1 equiv.) was added dropwise to the solution of benzamide (2 mmol, 1 equiv.) in Et_2O (10 mL), and the mixture was stirred at r. t. for 2 h. The solid was collected, giving the corresponding thiourea intermediate that was dissolved in dry DCM (20 mL). Et_3N (3 equiv.) and EDCI*HCl (1.2 equiv.) added and the solution was stirred at r. t. overnight. Then solvent evaporated and product washed with MeOH, filtered.

*4.6.1. rac-N-(5-Iodo-4-oxo-7-phenyl-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-2-yl)benzamide (**16a**)*

Prepared from benzamide **15a**. Yield 0.45 g (44 %), white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.79-2.17 (m, 4H), 3.71-3.79 (m, 1H), 3.93-4.01 (m, 1H), 4.28-4.33 (m, 1H), 4.57-4.75 (m, 2H), 7.41-7.64 (m, 9H), 8.22-8.29 (m, 3H), 14.51 (brs, 1H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ: 168.9, 167.1, 151.4, 142.2, 138.3, 135.2, 134.5, 133.1, 132.1, 132.0, 129.1, 128.6, 128.3, 127.3, 126.9, 120.0, 94.5, 76.6, 67.2, 43.3, 28.9, 25.2. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{26}H_{23}IN_3O_3$ 552.0784; Found 552.0791.

*4.6.2. rac-N-(5-Iodo-4-oxo-7-(4-(3-phenylpropyl)phenyl)-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-2-yl)benzamide (**16b**)*

Prepared from benzamide **15b**. Yield 0.52 g (42%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, J = 7.3 Hz, 2H), 8.21 (s, 1H), 7.57 – 7.38 (m, 7H), 7.34 – 7.18 (m, 7H), 4.70 (dd, J = 12.6, 8.4 Hz, 1H), 4.65 – 4.57 (m, 1H), 4.30 (dd, J = 12.6, 4.6 Hz, 1H), 4.00 – 3.93 (m, 1H), 3.80 – 3.73 (m, 1H), 2.76 – 2.63 (m, 4H), 2.14

– 1.79 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 179.2, 159.0, 153.8, 148.0, 144.2, 142.1, 138.7, 138.1, 137.2, 134.5, 132.5, 129.5, 128.6, 128.5, 128.3, 127.3, 126.0, 114.9, 114.3, 94.9, 75.7, 68.1, 45.8, 35.5, 35.2, 32.9, 29.5, 25.6. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{35}H_{33}IN_3O_3$ 670.1567; Found 670.1557.

*4.6.3. rac-N-(5-Iodo-4-oxo-7-(4-pentylphenyl)-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-2-yl)benzamide (**16c**)*

Prepared from benzamide **15c**. Yield 0.39 g (41%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, J = 7.6 Hz, 2H), 8.21 (d, J = 1.6 Hz, 1H), 7.53 (d, J = 7.9 Hz, 3H), 7.49 – 7.43 (m, 3H), 7.39 (brs, 1H), 7.32 – 7.26 (m, 2H), 4.76 – 4.53 (m, 2H), 4.30 (d, J = 12.6 Hz, 1H), 4.00 – 3.90 (m, 1H), 3.75 (d, J = 7.2 Hz, 1H), 2.71 – 2.61 (m, 2H), 2.14 – 2.03 (m, 2H), 1.98 – 1.75 (m, 2H), 1.65 (p, J = 7.5 Hz, 2H), 1.38 – 1.32 (m, 4H), 0.94 – 0.86 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 178.9, 158.9, 153.5, 147.8, 144.8, 138.7, 138.0, 137.0, 134.2, 132.4, 129.4, 128.2, 127.1, 114.8, 114.3, 94.7, 75.7, 68.1, 45.8, 35.7, 31.6, 31.1, 29.5, 25.5, 22.6, 14.1. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{31}H_{33}IN_3O_3$ 622.1567; Found 622.1570.

4.6.4. N-(5-Iodo-4-oxo-7-phenyl-3-(((2S,5R*)-5-phenyltetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-2-yl)benzamide (**16d**)*

Prepared from benzamide **15d**. Yield 0.21 g (20%), white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 14.52 (brs, 1H), 8.29 (d, J = 7.1 Hz, 2H), 8.21 (d, J = 1.7 Hz, 1H), 7.64 – 7.35 (m, 11H), 7.23 – 7.14 (m, 3H), 5.00 – 4.85 (m, 2H), 4.80 – 4.70 (m, 1H), 4.52 (dd, J = 12.7, 5.1 Hz, 1H), 2.40 – 2.11 (m, 2H), 2.07 – 1.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 179.3, 159.1, 153.8, 148.2, 142.7, 138.8, 138.3, 137.1, 132.5, 129.7, 129.6, 129.4, 128.4, 128.3, 127.4, 127.3, 126.0, 115.3, 114.6, 94.9, 81.8, 76.2, 46.5, 34.8, 29.9. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{32}H_{27}IN_3O_3$ 628.1097; Found 628.1073.

*4.6.5. rac-N-(7-Chloro-5-iodo-4-oxo-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-2-yl)benzamide (**16e**)*

Prepared from benzamide **15e** Yield 0.20 g (30%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, J = 7.1 Hz, 2H), 7.96 (d, J = 1.9 Hz, 1H), 7.61 – 7.42 (m, 3H), 7.24 (d, J = 1.9 Hz, 1H), 4.68 (dd, J = 12.7, 8.6 Hz, 1H), 4.62 – 4.52 (m, 1H), 4.25 (dd, J = 12.7, 4.4 Hz, 1H), 4.00 – 3.90 (m, 1H), 3.79 – 3.70 (m, 1H), 2.08

(m, 2H), 2.00 – 1.86 (m, 1H), 1.85 – 1.75 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 179.3, 158.4, 153.6, 141.0, 138.9, 138.7, 136.8, 132.6, 129.4, 128.2, 116.8, 114.4, 95.0, 75.4, 68.0, 45.8, 29.4, 25.4. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}ClIN_3O_3$ 510.0081; Found 510.0095.

*4.7. General procedure **F** for the synthesis of compounds **2a,c-g; 3a; 4a-b; 7a-b***

To a solution of iodobenzene or bromobenzene (0.15 mmol, 1 equiv.) in DMF (1.5 mL), benzoic acid or pinacolborane (1.3 equiv.), $Pd(PPh_3)_4$ (5 mol%), and K_2CO_3 (3 equiv.) were added. The resulting mixture was heated at 80 °C. After the reaction was completed (TLC), the solution was cooled to r. t., concentrated in vacuo and filtered through a pad of silica gel with EtOAc:DCM = 1:1 to afford protected intermediate that was used in the next step without additional purification. To a suspension of protected intermediate (1 equiv.) in EtOH (5 mL), hydrazine hydrate (0.1 mL) was added and the mixture was refluxed for 4 h. Solvent was evaporated, water was added, product filtered, washed with wet MeOH, filtered or purified by column chromatography.

*4.7.1. rac-4-(2-Amino-4-oxo-7-phenyl-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)benzoic acid (**2a**)*

Prepared from iodobenzene **16a** and 4-boronobenzoic acid. Yield 33 mg (52%), white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.49-1.58 (m, 1H), 1.72-1.95 (m, 3H), 3.60-3.65 (m, 1H), 3.76-3.80 (m, 1H), 3.95-4.12 (m, 3H), 6.91 (brs, 2H), 7.09 (d, J =1.6 Hz, 1H), 7.42-7.50 (m, 6H), 7.75 (d, J = 7.4 Hz, 2H), 7.91 (d, J = 8.2 Hz, 2H), 12.9 (brs, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 24.9, 28.5, 45.0, 67.3, 76.3, 112.2, 121.4, 123.0, 127.0, 128.1, 128.3, 128.7, 128.8, 129.0, 138.8, 142.7, 144.4, 147.0, 151.4, 152.8, 160.7, 167.3. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}N_3O_4$ 442.1767 ; Found 442.1771.

*4.7.2. rac-2-Amino-7-phenyl-5-(pyridin-4-yl)-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3H)-one (**2c**)*

Prepared from iodobenzene **16a** and pyridin-4-ylboronic acid. Yield 14 mg (39%), white solid. $T_{decomp.}$ = 180 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51-1.61 (m, 1H), 1.87-1.95 (m, 2H), 2.07-2.14 (m, 1H), 3.78 (q, J = 7.0 Hz, 1H), 3.90-3.96 (m, 2H),

4.13 (q, *J* = 7.0 Hz, 1H), 4.45 (d, *J* = 14.9 Hz, 1H), 5.89 (brs, 2H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.28 (d, *J* = 5.9 Hz, 2H), 7.38-7.48 (m, 3H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 2H), 8.64 (d, *J* = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 25.6, 28.9, 46.7, 68.5, 79.4, 112.9, 123.0, 123.7, 124.8, 127.3, 128.5, 129.0, 139.3, 141.4, 146.0, 148.8, 150.8, 150.9, 153.7, 161.7. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{24}H_{23}N_4O_2$ 399.1821; Found 399.1821.

*4.7.3. rac-2-Amino-7-phenyl-5-(pyridin-3-yl)-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3H)-one (**2d**)*

Prepared from iodobenzene **16a** and pyridin-3-ylboronic acid. Yield 13 mg (36%), white solid. $T_{decomp.}$ = 192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.51-1.60 (m, 1H), 1.87-1.94 (m, 2H), 2.05-2.14 (m, 1H), 3.78 (dd, *J* =7.0 Hz, 14.9 Hz, 1H), 3.89-3.97 (m, 2H), 4.13 (q, *J* = 7.4 Hz, 1H), 4.43 (d, *J* =14.9 Hz, 1H), 5.89 (brs, 2H), 7.22 (d, *J* =1.2 Hz, 1H), 7.32-7.41 (m, 2H), 7.44-7.48 (m, 2H), 7.61 (d, *J* =1.6 Hz, 1H), 7.69 (m, 3H), 8.61 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 25.6, 28.9, 46.6, 68.4, 79.4, 113.3, 122.2, 122.9, 125.6, 127.3, 128.4, 128.9, 135.9, 138.1, 139.3, 140.4, 145.9, 148.0, 149.2, 150.9, 153.7, 161.9. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{24}H_{23}N_4O_2$ 399.1821; Found 399.1825.

*4.7.4. rac-2-Amino-5-(3-aminophenyl)-7-phenyl-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3H)-one (**2e**)*

Prepared from iodobenzene **16a** and (3-aminophenyl)boronic acid. Yield 29 mg (39%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.51-1.61 (m, 1H), 1.82-1.95 (m, 2H), 1.99-2.13 (m, 1H), 3.74-3.80 (m, 1H), 3.86-3.96 (m, 2H), 4.08-4.16 (m, 1H), 4.46-4.49 (m, 1H), 5.85 (brs, 2H), 6.67-6.77 (m, 3H), 7.15-7.23 (m, 2H), 7.35-7.46 (m, 5H), 7.53-7.57 (m, 1H), 7.64-7.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 25.6, 28.9, 46.6, 68.5, 79.5, 113.4, 113.8, 115.4, 119.4, 121.7, 125.3, 127.2, 127.3, 128.2, 128.8, 128.9, 139.6, 143.8, 144.6, 145.5, 145.6, 153.5, 161.5. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{25}H_{25}N_4O_2$ 413.1978; Found 413.1971.

*4.7.5. rac-4-(2-Amino-4-oxo-7-phenyl-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)benzamide (**2f**)*

Prepared from iodobenzene **16a** and (4-carbamoylphenyl)boronic acid. Yield 12 mg (19%), light yellow amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 1.52-1.61

(m, 1H), 1.73-1.98 (m, 3H), 3.62-3.67 (m, 1H), 3.74-3.80 (m, 1H), 3.99-4.11 (m, 3H), 7.25 (d, *J* =1.6 Hz, 1H), 7.37 (brs, 1H), 7.40-7.56 (m, 6H), 7.77 -7.88 (m, 6H), 8.01 (brs, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 25.0, 28.5, 45.1, 67.3, 75.9, 111.5, 123.4, 124.5, 126.4, 127.0, 128.4, 128.7, 129.1, 132.3, 132.6, 138.2, 143.3, 144.3, 145.1, 152.2, 159.5, 167.7. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}N_4O_3$ 441.1927; Found 441.1923.

*4.7.6. rac-3-(2-Amino-4-oxo-7-phenyl-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)benzoic acid (**2g**)*

Prepared from iodobenzene **16a** and 3-boronobenzoic acid. Yield 60 mg (75%), white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.50-1.61 (m, 1H), 1.72-1.98 (m, 3H), 3.59-3.66 (m, 1H), 3.72-3.82 (m, 1H), 3.98-4.13 (m, 3H), 7.27 (brs, 2H), 7.43-7.62 (m, 6H), 7.76-7.79 (m, 2H), 7.87-7.94 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 25.5, 29.0, 45.8, 67.9, 75.6, 111.0, 114.1, 126.8, 127.6, 127.7, 128.3, 128.6, 129.7, 129.8, 130.5, 133.4, 137.8, 139.6, 141.0, 144.1, 146.7, 152.0, 158.5, 167.7. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}N_3O_4$ 442.1767; Found 442.1771.

4.7.7. 4-(2-Amino-4-oxo-7-phenyl-3-(((2S,5R*)-5-phenyltetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)benzoic acid (**3a**)*

Prepared from iodobenzene **16d** and 4-boronobenzoic acid. Yield 18 mg (77%), white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.65-1.77 (m, 2H), 2.01-2.09 (m, 1H), 2.19-2.28 (m, 1H), 4.12-4.27 (m, 3H), 4.77 (t, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 1.6 Hz, 1H), 7.24-7.36 (m, 5H), 7.41-7.52 (m, 5H), 7.59-7.64 (m, 3H), 7.74-7.76 (m, 2H), 7.93 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 28.6, 33.7, 45.2, 76.3, 80.8, 112.0, 125.8, 127.0, 128.1, 128.1, 128.6, 128.7, 128.8, 129.0, 131.3, 131.4, 132.0, 133.1, 138.5, 142.3, 142.9, 144.7, 146.7, 152.5, 160.3, 167.3. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{32}H_{28}N_3O_4$ 518.2080; Found 518.2079.

*4.7.8. rac-2-Amino-7-(4-pentylphenyl)-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3H)-one (**4a**)*

Prepared from bromobenzene **16f** [29] and pinacolborane **12b**. Yield 19 mg (69%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, *J* = 7.0 Hz, 3H), 1.29-1.39 (m, 4H), 1.59-1.75(m, 3H), 1.80-1.98 (m, 2H), 2.08-2.26 (m, 1H), 2.64 (dd, *J* = 6.5 Hz, 14.1 Hz, 2H), 3.73-3.81 (m, 1H), 3.90 (dt, *J* = 7.1, 14.2 Hz, 1H), 4.10-4.28

(m, 2H), 4.48 (d, *J* = 14.5 Hz, 1H), 5.85 (brs, 2H), 7.18-7.34 (m, 2H), 7.42 (dd, *J* = 1.7, 8.3 Hz, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 8.13 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 14.0, 22.5, 25.7, 28.7, 31.1, 31.5, 35.6, 46.4, 68.4, 79.5, 115.7, 122.0, 122.1, 127.1, 127.5, 128.9, 137.4, 143.2, 147.2, 149.3, 153.4, 163.0. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{24}H_{30}N_3O_2$ 392.2338; Found 392.2336.

*4.7.9. rac-2-Amino-7-(4-(3-phenylpropyl)phenyl)-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3H)-one (**4b**)*

Prepared from bromobenzene **16f** [29] and pinacolborane **12a**. Yield 18 mg (75%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.59-1.71 (m, 1H), 1.87-2.04 (m, 4H), 2.09-2.23 (m, 1H), 2.68 (dd, *J* = 6.6, 15.0 Hz, 4H), 3.72-3.82 (m, 1H), 3.85-3.96 (m, 1H), 4.08-4.32 (m, 2H), 4.48 (d, *J* = 14.5 Hz, 1H), 5.83 (brs, 2H), 7.14-7.21 (m, 3H), 7.24-7.33 (m, 4H), 7.43 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.52 (dd, *J* = 0.5 Hz, 1.7 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 8.14 (dd, *J* = 0.5, 8.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 25.7, 28.8, 32.8, 35.1, 35.4, 46.4, 68.4, 79.5, 115.8, 122.0, 122.1, 125.7, 127.2, 127.6, 128.3, 128.4, 129.0, 137.6, 142.1, 142.5, 147.1, 149.2, 153.4, 162.9. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{28}H_{30}N_3O_2$ 440.2338; Found 440.2337.

*4.7.10. rac-4-(2-Amino-4-oxo-7-(4-pentylphenyl)-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)benzoic acid (**7a**)*

Prepared from iodobenzene **16c** and 4-boronobenzoic acid. Yield 20 mg (24%), white amorphous solid.^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 12.82 (brs, 1H), 7.93 – 7.89 (m, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.40 (m, 3H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 1.9 Hz, 1H), 6.88 (brs, 2H), 4.11 – 4.04 (m, 1H), 3.99 – 3.97 (m, 2H), 3.77 (dt, *J* = 8.3, 6.9 Hz, 1H), 3.63 (td, *J* = 7.8, 5.6 Hz, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.96 – 1.73 (m, 3H), 1.63 – 1.49 (m, 3H), 1.36 – 1.21 (m, 4H), 0.91 – 0.83 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 167.4, 160.8, 152.9, 151.5, 147.2, 144.4, 142.8, 142.7, 136.2, 129.0, 128.9, 128.7, 128.2, 126.9, 123.0, 121.1, 112.1, 76.4, 67.3, 45.0, 34.7, 30.9, 30.5, 28.6, 25.0, 22.0, 13.9. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{31}H_{34}N_3O_4$ 512.2549; Found 512.2548.

*4.7.11. rac-4-(2-Amino-4-oxo-7-(4-(3-phenylpropyl)phenyl)-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)benzoic acid (**7b**)*

Prepared from iodobenzene **16b** and 4-boronobenzoic acid using $Pd(dppf)Cl_2*CH_2Cl_2$ as a catalyst. Yield 10 mg (46%), white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.92 – 7.82 (m, 2H), 7.69 – 7.60 (m, 2H), 7.39 (d, J = 1.9 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.29 – 7.22 (m, 4H), 7.20 – 7.11 (m, 3H), 7.04 (d, J = 1.9 Hz, 1H), 6.83 (brs, 2H), 4.07 – 4.00 (m, 1H), 3.98 – 3.91 (m, 2H), 3.77 – 3.70 (m, 1H), 3.62 – 3.55 (m, 1H), 2.65 – 2.55 (m, 4H), 1.95 – 1.71 (m, 5H), 1.58 – 1.45 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 160.8, 152.9, 151.6, 144.3, 143.1, 142.4, 141.9, 136.4, 135.2, 134.3, 129.0, 128.6, 128.3, 128.2, 127.0, 125.7, 123.0, 121.1, 112.2, 76.4, 67.4, 45.1, 34.8, 34.4, 32.5, 28.6, 25.1. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{35}H_{34}N_3O_4$ 560.2549; Found 560.2535.

*4.8. General procedure **G** for the synthesis of compounds **4c, 5***

To a solution of bromobenzene (0.15 mmol, 1 equiv.) in DMF (0.5 mL), 1-octyne (1.1 equiv.), $Pd[(PPh_3)Cl]_2$ (10 mol%), Et_3N (3 equiv.) and CuI (40 mol%) were added. The resulting mixture was stirred at r. t. After the reaction was completed (TLC), the solution was concentrated in vacuo and filtered through a pad of silica gel with EtOAc/PE = 1:4 to afford alkyne intermediate that was used in the next step without additional purification. To a suspension of protected intermediate (1 equiv.) in EtOH (5 mL), hydrazine hydrate (0.1 mL) and 10% Pd/C (5 mg) was added and the mixture was refluxed overnight. Solvent was evaporated and product purified by column chromatography.

4.8.1. 2-Amino-7-octyl-3-(((2S,5R*)-5-phenyltetrahydrofuran-2-yl)methyl)quinazolin-4(3H)-one (**5**)*

Prepared from bromobenzene **16g** [29]. Yield 32 mg (66%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.0 Hz, 3H), 1.63-1.39 (m, 10H), 1.60-1.70 (m, 2H), 1.84-1.96 (m, 2H), 2.19-2.41 (m, 2H), 2.66 (t, J = 7.0 Hz, 2H), 4.18 (dd, J = 7.1, 14.7 Hz, 1H), 4.33-4.42 (m, 1H), 4.65 (dd, J = 1.6, 14.8 Hz, 1H), 4.87-4.91 (m, 1H), 5.58 (brs, 2H), 7.04 (dd, J = 1.6, 8.1 Hz, 1H), 7.12 (d, J = 1.0 Hz, 1H), 7.22-7.38 (m, 5H), 8.03 (d, J = 8.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 10.1, 22.6, 28.8, 29.2, 29.4, 30.9, 31.9, 33.3, 36.2, 46.4, 79.8, 82.0, 115.0, 123.5, 124.2, 126.0, 126.9, 127.9,

128.6, 141.4, 149.0, 150.4, 153.0, 163.0. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{27}H_{36}N_3O_2$ 434.2808; Found 434.2805.

*4.8.2. rac-2-Amino-7-octyl-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3H)-one (**4c**)*

Prepared from bromobenzene **16f** [29]. Yield 15 mg (25%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 1.5 Hz, 1H), 7.03 (dd, J = 8.2, 1.6 Hz, 1H), 5.71 (brs, 2H), 4.47 (d, J = 14.4 Hz, 1H), 4.27 – 4.10 (m, 2H), 3.98 – 3.84 (m, 1H), 3.84 – 3.71 (m, 1H), 2.67 (t, J = 7.5 Hz, 2H), 2.22 – 2.07 (m, 1H), 2.04 – 1.82 (m, 2H), 1.75 – 1.49 (m, 3H), 1.35 – 1.19 (m, 10H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.1, 153.3, 150.6, 149.1, 127.1, 124.3, 123.6, 115.1, 79.7, 68.6, 46.5, 36.4, 32.0, 31.0, 29.6, 29.4, 28.9, 25. 9, 22.8, 14.3. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{21}H_{32}N_3O_2$ 358.2495; Found 358.2493.

*4.9. General procedure **H** for the synthesis of compounds **2b; 3b; 6a-b***

To a solution of iodobenzene (0.15 mmol, 1 equiv.) in DMF (1 mL), Et_3N (3 equiv.), *t*-butyl acrylate (1.3 equiv.) and $Pd(PPh_3)_4$ (5 mol%) were added. The resulting mixture was heated at 80 °C. After the reaction was completed (TLC), the solution was cooled to r. t., and then partitioned between H_2O and EtOAc. The organic layer was concentrated in vacuo and product washed with MeOH to afford protected intermediate that was used in the next step. To a suspension of protected intermediate (1 equiv.) in DCM (5 mL), TFA (0.1 mL) added and mixture stirred at r. t. for 16 h. Then reaction mixture concentrated in vacuo, EtOH (10 mL) and hydrazine hydrate (0.1 mL), 10 % Pd/C (5 mg) was added and the mixture was refluxed for 6 h. Solvent was evaporated, water was added resulting product filtered and washed with MeOH or purified by column chromatography.

*4.9.1. rac-3-(2-Amino-4-oxo-7-phenyl-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)propanoic acid (**2b**)*

Prepared from iodobenzene **16a**. Yield 16 mg (36%), white amorphous solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 1.55-1.64 (m, 1H), 1.73-1.82 (m, 1H), 1.83-2.01 (m, 2H), 2.52 (t, J = 7.6 Hz, 2H), 3.37 (t, J = 7.6 Hz, 2H), 3.59-3.64 (m, 1H), 3.76-3.81

(m, 1H), 4.06-4.17 (m, 3H), 7.27 (m, 3H), 7.32-7.49 (m, 4H), 7.69 (d, *J* = 7.0 Hz, 2H), 11.99 (brs, 1H). ^{13}C NMR (101 MHz, DMSO-*d6*) *δ*: 25.5, 29.0, 30.9, 35.6, 45.5, 67.8, 76.6, 113.1, 119.0, 123.9, 127.4, 128.9, 129.5, 139.3, 144.3, 145.5, 152.6, 152.6, 161.5, 174.4. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}N_3O_4$ 394.1767; Found 394.1770.

4.9.2. 3-(2-Amino-4-oxo-7-phenyl-3-(((2S,5R*)-5-phenyltetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)propanoic acid (**3b**)*

Prepared from iodobenzene **16d**. Yield 29 mg (97%), white solid. T_m = 124 – 126 ^{o}C. ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.67-1.82 (m, 2H), 2.01-2.13 (m, 1H), 2.20-2.30 (m, 1H), 2.44 (m, 2H), 3.37 (t, *J* = 7.43 Hz, 2H), 4.20-4.35 (m, 3H), 4.74-4.78 (m, 1H), 6.80 (brs, 2H), 7.17 (d, *J* =1.6 Hz, 1H), 7.20-7.23 (m, 2H), 7.29 (t, *J* = 7.0 Hz, 2H), 7.35-7.38 (m, 3H), 7.44 (t, *J* = 7.0 Hz, 2H), 7.66 (d, *J* = 7.4 Hz, 2H), 8.28 (brs, 1H). ^{13}C NMR (101 MHz, DMSO-*d6*) *δ*: 28.7, 30.6, 33.8, 35.4, 45.1, 76.5, 80.9, 113.1, 120.1, 122.6, 125.8, 126.8, 127.1, 128.1, 128.9, 139.2, 142.3, 143.6, 144.5, 151.7, 152.3, 161.7, 174.1. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}N_3O_4$ 470.2080; Found 470.2094.

*4.9.3. rac-3-(2-Amino-4-oxo-7-(4-pentylphenyl)-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)propanoic acid (**6a**)*

Prepared from iodobenzene **16c**. Yield 28 mg (46%), white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 11.98 (brs, 1H), 7.62 (d, *J* = 7.7 Hz, 2H), 7.34 – 7.12 (m, 4H), 6.77 (brs, 2H), 4.22 – 4.04 (m, 3H), 3.89 – 3.77 (m, 1H), 3.70 – 3.60 (m, 1H), 3.44 – 3.35 (m, 2H), 2.67 – 2.59 (m, 2H), 2.03 – 1.75 (m, 4H), 1.67 – 1.55 (m, 4H), 1.39 – 1.24 (m, 4H), 0.92 – 0.82 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 174.1, 161.8, 152.4, 151.8, 144.6, 143.4, 142.6, 136.6, 128.9, 126.8, 122.5, 119.9, 112.9, 76.5, 67.4, 45.0, 35.4, 34.7, 30.9, 30.57, 30.56, 28.6, 25.1, 22.0, 13.9. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{27}H_{34}N_3O_4$ 464.2549; Found 464.2540.

*4.9.4. rac-3-(2-Amino-4-oxo-7-(4-(3-phenylpropyl)phenyl)-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)propanoic acid (**6b**)*

Prepared from iodobenzene **16b**. Yield 24 mg (48%), white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 11.78 (brs, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.22 (m, 5H), 7.21 – 7.15 (m, 4H), 6.74 (brs, 2H), 4.15 – 4.03 (m, 3H), 3.79 (q, *J* = 7.2 Hz,

1H), 3.64 – 3.55 (m, 1H), 3.36 (t, *J* = 7.6 Hz, 2H), 2.61 (m, 4H), 2.54 – 2.48 (m, 2H), 1.96 – 1.78 (m, 4H), 1.62 –1.53 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 174.1, 161.8, 152.4, 151.8, 144.5, 143.4, 142.2, 141.9, 136.7, 129.0, 128.3, 126.8, 125.7, 122.5, 119.9, 112.9, 112.6, 76.5, 67.4, 45.0, 35.4, 34.8, 34.4, 32.5, 30.6, 28.6, 25.1. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{31}H_{34}N_3O_4$ 512.2549; Found 512.2549.

*4.10. Procedure **I** for the synthesis rac-3-(2-Amino-7-octyl-4-oxo-3-((tetrahydrofuran-2-yl)methyl)-3,4-dihydroquinazolin-5-yl)propanoic acid (**6c**)*

Procedure I: To a solution of iodobenzene **16e** (323 mg, 1 equiv.) in DMF (10 mL), K_2CO_3 (262 mg, 3 equiv.), *t*-butyl acrylate (0.111 mL, 1.2 equiv.) and Pd(dppf)Cl_2*DCM (50 mg, 10 mol%) were added. The resulting mixture was heated at 100°C. After the reaction was completed, the solution was cooled to r. t., and partitioned between 5% aq. $KHSO_4$ and DCM. The organic layer was concentrated in vacuo and alkene intermediate isolated by column chromatography (EtOAc/DCM/PE = 1/1/4). To a solution of alkene intermediate (130 mg, 1 equiv.) in DMF (0.5 mL), 1-octyne (0.045 mL, 1.2 equiv.), Pd(Amphos)Cl_2 (3.6 mg, 2 mol%) and Cs_2CO_3 (249 mg, 3 equiv.) were added. The resulting mixture was stirred at 100 ^{o}C for 2 days. Then solution was concentrated in vacuo and mixture separated by column chromatography EtOAc/PE = 1/8 to afford protected alkyne intermediate that was dissolved in DCM (10 mL), TFA (0.1 mL) added and mixture stirred at r. t. for 48 h. Then reaction mixture concentrated in vacuo, EtOH (5 mL), hydrazine hydrate (0.5 mL) and 10% Pd/C (5 mg) was added and the mixture was refluxed for 3 days. Solvent was evaporated and product **6c** washed with wet MeOH, filtered. Yield 19 mg (44%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.12 (brs, 1H), 7.39 (brs, 2H), 7.02 (s, 1H), 6.90 (s, 1H), 4.47 (d, *J* = 14.5 Hz, 1H), 4.22 – 4.14 (m, 1H), 4.03 – 3.97 (m, 1H), 3.95 – 3.87 (m, 1H), 3.82 – 3.74 (m, 1H), 3.51 (t, *J* = 7.4 Hz, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.23 – 2.09 (m, 1H), 1.92 (p, *J* = 6.9 Hz, 2H), 1.67 – 1.53 (m, 3H), 1.35 – 1.15 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 178.6, 161.8, 153.9, 150.2, 147.9, 143.7, 126.8, 119.9, 112.0, 79.2, 68.5, 46.6, 36.5, 36.0, 31.8, 31.2, 30.8, 29.4, 29.3, 29.2, 28.9, 25.7, 22.6, 14.1. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{24}H_{36}N_3O_4$ 430.2706; Found 430.2702.

4.11. Biological assays

4.11.1. Bioassay

A fluorescence resonance energy transfer (FRET) assay was performed to evaluate ability of compounds to inhibit PlmI,II,IV, and CatD. K_m of the substrate was determined for each enzyme: PlmII = 2 ± 0.2 μM; PlmI = 2.7 ± 0.3μM; PlmIV = 2.8 ± 0.2μM; CatD = 1.8 ± 0.2 μM. A solution of compounds for testing (concentration 0.01−100 μM) on 96-well plate was added to the enzyme (PlmI,II,IV, or CatD) in buffer (0.1 M NaOAc, pH = 4.5, 10% glycerol). The mixture was incubated for 30 min at 37 °C. Substrate (DABCYL-Glu-Arg-Nle-Phe-Leu-Ser-Phe-Pro-EDANS, AnaSpec Inc.) was then added to reach a final concentration of 5 μM. Hydrolysis of the substrate was detected as an increase in fluorescence (Em 490 nm, Ex 336 nm) at 37 °C. The data points were collected every 1 min within 8−15 min. For the rate calculation, only the linear interval was used, which was slightly different for each enzyme. Compounds were tested in triplicate experiments. IC_{50} values were calculated using software Graph Pad Prism 5.0. Pepstatin A (IC_{50} = 0.42 ±0.02 nM (Plm II); IC_{50} = 0.9 ±0.02 nM (Plm I); IC_{50} = 0.3 ±0.04 nM (Plm IV)) and resveratrol (IC_{50} = 138 μM) were used as positive controls.

4.12. Computational studies

4.12.1. Docking

The crystal structure of Plm II and **1a** complex (PDB ID 4z22) was prepared for docking using the protein preparation wizard tool in Maestro 11.3.016 [30]. Hydrogen atoms were added, and bond orders were assigned. Hydrogen bond networks were optimized by choosing optimal orientations of hydroxyl groups, water molecules, and amide groups of Asn and Gln and by selecting appropriate states and orientations of histidine imidazoles. Inhibitors were prepared for docking using the standard protocol implemented in LigPrep. The stereochemistry of the THF moiety's 2- and 5-carbon atoms was R and S, respectively [29]. The ligand and protein protonation states were adjusted to pH 4.6, and Asp214 was [29, 31] protonated as this generally provided better docking poses.

Docking was performed using the standard precision protocol in Glide [32]. Docked complexes were further refined with Prime MM-GBSA (Molecular Mechanics/Generalized Born Surface Area) method [33] using VSGB solvation model [34] and OPLS3 force field [35]. For MM-GBSA calculations, a 7-Å active

region around the ligands for full molecular mechanics minimization was used. Results were visualized using UCSF Chimera v1.12 [36] and Maestro.

4.12.2. Molecular dynamics (MD)

Molecular systems for running MD simulations were prepared using the System builder tool in Maestro. Protein ligand complexes were solvated in an orthogonal box of water molecules (SPC solvent model) [37] with buffer width of 10 Å. Na^+ and Cl^- ions were added to maintain physiological salinity (0.15 M) and to obtain a neutral total charge for the system. The complete systems were relaxed and equilibrated using the default Desmond relaxation protocol. All MD simulations were performed for 70 ns at constant pressure (1.0 bar), maintained using a Martyna-Tobias-Klein barostat[38, 39], and at constant temperature (300 K) maintained using Nose-Hoover thermostat [40,41]. OPLS3 force field [35] was used for all simulations. The pressure and temperature control used a relaxation time of 5.0 ps. All simulations used a RESPA integrator with a 2.0 fs time step [42]. The MD simulations were analyzed using Maestro built in MD analysis tools.

4.13. Solubility determination

The procedure for solubility determination of lipophilic organic compounds in 0.05 M TRIS-buffer solution (pH=7.4) containing 0.5% of DMSO was used. The working concentration range of the procedure is from ≈0.005 mg/mL to 0.05 mg/mL. A stock solution (c≈10 mg/mL) in DMSO of the compounds to be studied was prepared. For preparation of calibration standard solutions the stock was diluted with methanol to obtain c≈0,05 mg/mL. For preparation of the analytical samples 10 μL of stock above was diluted with 2 mL of 0.05M TRIS-buffer (pH=7.4) and incubated in shaker for 16 h at 25°C. The precipitate was filtered off and the concentration of resulting solution was determined against the calibration standard solution. The concentration was measured by peak area in HPLC chromatograms (column, Apollo-C18, 5 μm; 150x4.6 mm; linear gradient from 40% of MeCN in 0.1% H_3PO_4 to 100% of MeCN - 15 min + isocratic run 100% of MeCN - 5 min, Detector: UV 210nm or 254nm; injection volume: 25μL)

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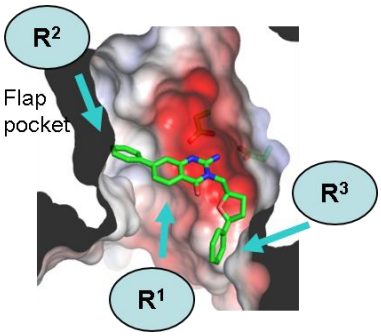
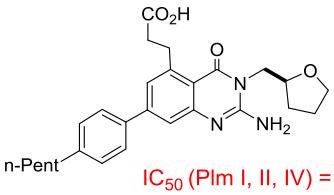
TOC graphic



R^1: increased polarity and selectivity against CatD
R^2: substitution allows removal of Ph (**R**^{3}) from THF



IC_{50} (Plm I, II, IV) = 0.03-0.05 uM
IC_{50} (Cat D) = 21 uM