Accepted Manuscript

Design, synthesis, and evaluation of hinge-binder tethered 1,2,3-triazolylsalicylamide derivatives as Aurora kinase inhibitors

Yunkyung Jeong, Jooyeon Lee, Jae-Sang Ryu

PII: S0968-0896(16)30199-7
DOI: http://dx.doi.org/10.1016/j.bmc.2016.03.042
Reference: BMC 12891

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 15 March 2016
Revised Date: 22 March 2016
Accepted Date: 25 March 2016

Please cite this article as: Jeong, Y., Lee, J., Ryu, J-S., Design, synthesis, and evaluation of hinge-binder tethered 1,2,3-triazolylsalicylamide derivatives as Aurora kinase inhibitors, *Bioorganic & Medicinal Chemistry* (2016), doi: http://dx.doi.org/10.1016/j.bmc.2016.03.042

Bioorganic & Medicinal Chemistry
journal homepage: www.elsevier.com

Design, synthesis, and evaluation of hinge-binder tethered 1,2,3-triazolylsalicylamide derivatives as Aurora kinase inhibitors

Yunkyung Jeong, Jooyeon Lee, and Jae-Sang Ryu*

College of Pharmacy & Graduate School of Pharmaceutical Sciences, Ewha Womans University, 52 Ewhayeodae-gil, Seodaemun-gu, Seoul, 03760, Republic of Korea

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Aurora kinase
Click chemistry
Hinge-binder
1,2,3-Triazole
Anticancer

ABSTRACT

A series of hinge-binder tethered 1,2,3-triazolylsalicylamide derivatives were designed, synthesized, and evaluated for the Aurora kinase inhibitory activities. The novel hinge-binder tethered 1,2,3-triazolylsalicylamide scaffold was effectively assembled by Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC). A variety of alkynes with hinge binders were used to search proper structures–binding relationship to the hinge region. The synthesized 1,2,3-triazolylsalicylamide derivatives showed significant Aurora kinase inhibitory activity. In particular, **8a** inhibited Aurora A kinase with an IC_{50} value of 0.284 μM, whereas **8m** inhibited Aurora B kinase with an IC_{50} value of 0.364 μM.

1. Introduction

Aurora kinases are the members of serine/threonine kinases and have attracted significant attention as promising anticancer targets up to date.[1] Both Aurora A and B are commonly overexpressed in human tumor cells and play important roles in various organ tumors including the colon, breast, pancreatic, gastric, and prostate cancer. The overexpression of Aurora A causes aberrant phosphorylation of normal cell cycle targets and cytoplasmic targets, leading to chromosomal instability, oncogenic transformation, tumor progression, and development of chemoresistance.[2] Similarly, the overexpression of Aurora B increases the phosphorylation of histone H3, forming more aggressive tumors in transgenic mouse models.[3]

Mechanistically, Aurora kinases (A, B, and C) are regulatory proteins and play key roles in the mitotic events of cell division.[4] Aurora A associates with the spindle poles and regulates centrosome duplication, maturation, and mitotic spindle assembly;[5] Aurora B is involved in chromatin remodeling, phosphorylation of histone H3 at Ser-10, centrosome separation, chromosome segregation, and cytokinesis;[6] the third isozyme, Aurora C is believed to have overlapping function with Aurora B and similar localization patterns; however, its function is not yet clearly understood.[7]

Over the past decade, extensive research has been directed toward the discovery of Aurora-selective small-molecule

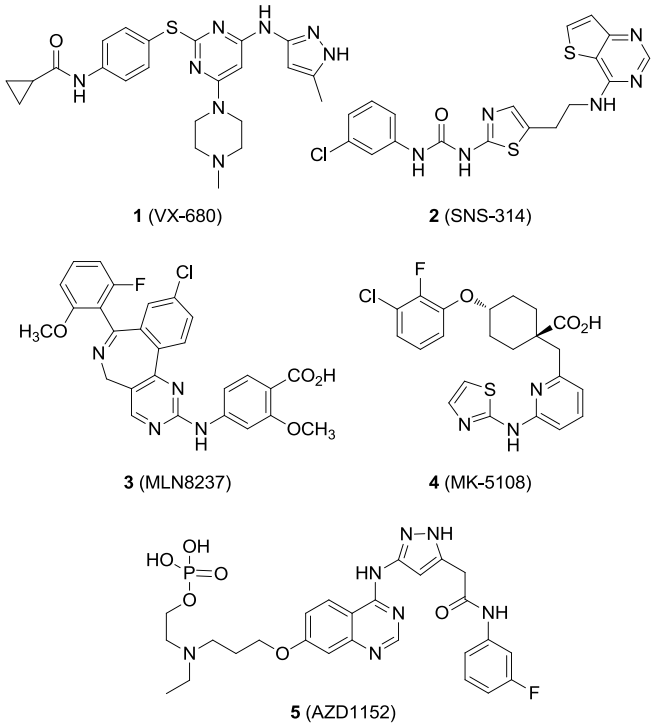


Figure 1. Aurora kinase inhibitors in clinical trials.

* Corresponding author. Tel.: +82-2-3277-3008; fax: +82-2-3277-2851; e-mail: ryuj@ewha.ac.kr

inhibitors. As a result, a handful of Aurora inhibitors has been identified. Among them, **1** (VX-680)[8] and **2** (SNS-314)[9] have entered human clinical trials as pan-Aurora kinase inhibitors (Fig 1), and **3** (MLN8237)[10] and **4** (MK-5108)[11] are undergoing clinical assessment as Aurora A specific inhibitors. As another clinical candidate drug, **5** (AZD1152)[12] has been also reported to selectively inhibit Aurora B. Although several Aurora inhibitors have currently reached the clinical evaluation stage, the ideal inhibitor profile for therapeutic use has not yet been defined. As a part of our ongoing effort to develop Aurora kinase inhibitors, herein, we describe the design, synthesis, and biochemical evaluation of hinge-binder tethered 1,2,3-triazolylsalicylamide inhibitors.

2. Results and Discussion

2.1. Design

Previously, we constructed a small molecule library mimicking a natural kinase inhibitor, lavendustin, using a rapid 'click fragment assembly' and screening method, leading to the identification of antiproliferative agent **6** (Fig 2).[13] Later, following study to improve the potency and selectivity of compound **6** led to the discovery of an effective Aurora A kinase inhibitor **7** through a systematic synthesis of 1,2,3-triazolylsalicylamide small molecules.[14] The identified 1,2,3-triazolylsalicylamide **7** inhibited Aurora A kinase with an IC_{50} value of 0.375 μM. The molecular modeling study also exhibited that the salicylamide moiety of compound **7** interacts with Lys175 and Glu194 of Aurora A through hydrogen-bonding network: the carbonyl group of the salicylamide plays an important role as a hydrogen bond acceptor, and both the phenolic OH and amide NH as hydrogen bond donors interact with the carboxylate of Glu194 (Fig 3). According to the co-crystal structure of humanized mouse Aurora A and compound **2** (SNS-314),[15] the urea moiety of compound **2** interacts with Lys175 and Glu194 as well. In addition, the thienopyrimidine N1 of compound **2** forms a hydrogen bond with the main chain NH of Ala226 in the hinge region. Therefore, we scrutinized the structural difference of compounds **2** and **7**. The extensive examination of their binding mode guided us to incorporate a functional group capable of forming hydrogen bond in the hinge region.

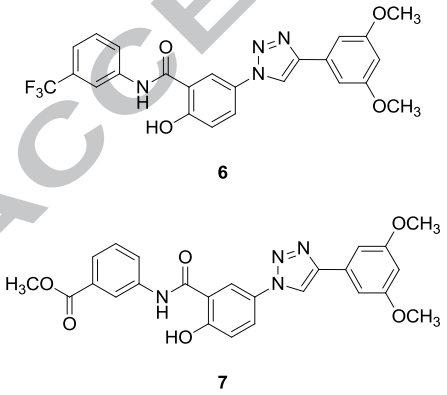


Figure 2. 1,2,3-Triazolylsalicylamide Aurora kinase inhibitors.

Structurally, the ATP-binding pocket of kinase is located deep inside of the cleft between the N- and C- terminal lobes.[16] The 'hinge' is a single string amino acid segment connecting these two lobes. The ATP adenine ring binds to the hinge string through two hydrogen bonds: one with the NH and the other with the carbonyl group in the amide backbone of the hinge. Most of the marketed kinase inhibitors mimic this interaction and form one to three hydrogen bonds to the hinge. In this study, we introduced functional groups being able to form hydrogen bonds with the hinge region to the 1,2,3-triazole moiety. The functional groups include nitrophenyl, quinoxalin-6-yl, 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl, benzo[*d*][1,3]dioxol-5-yl, aminophenyl, and morphorinyl group to form one hydrogen bonding as well as ((5-methylisoxazol-3-yl)amino)methyl, ((6-methylpyridin-2-yl)amino)methyl, (pyrimidin-2-ylamino)methyl, and (thieno[3,2-*d*]pyrimidin-4-ylamino)methyl groups to make two or more hydrogen bonds. In addition, the length between the 1,2,3-triazole and the hydrogen-bonding site was also varied to get an insight of the distance between the 1,2,3-triazole and the hinge.

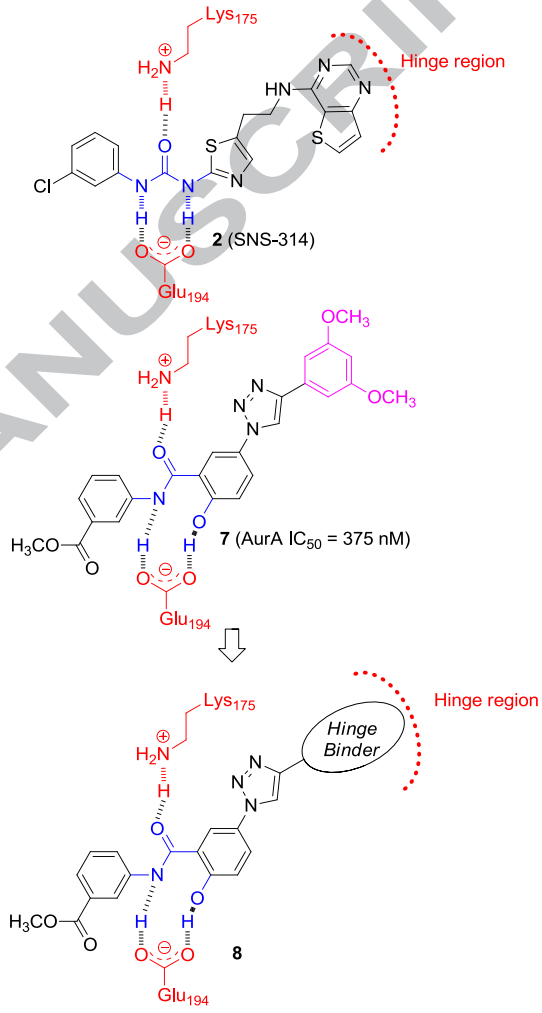
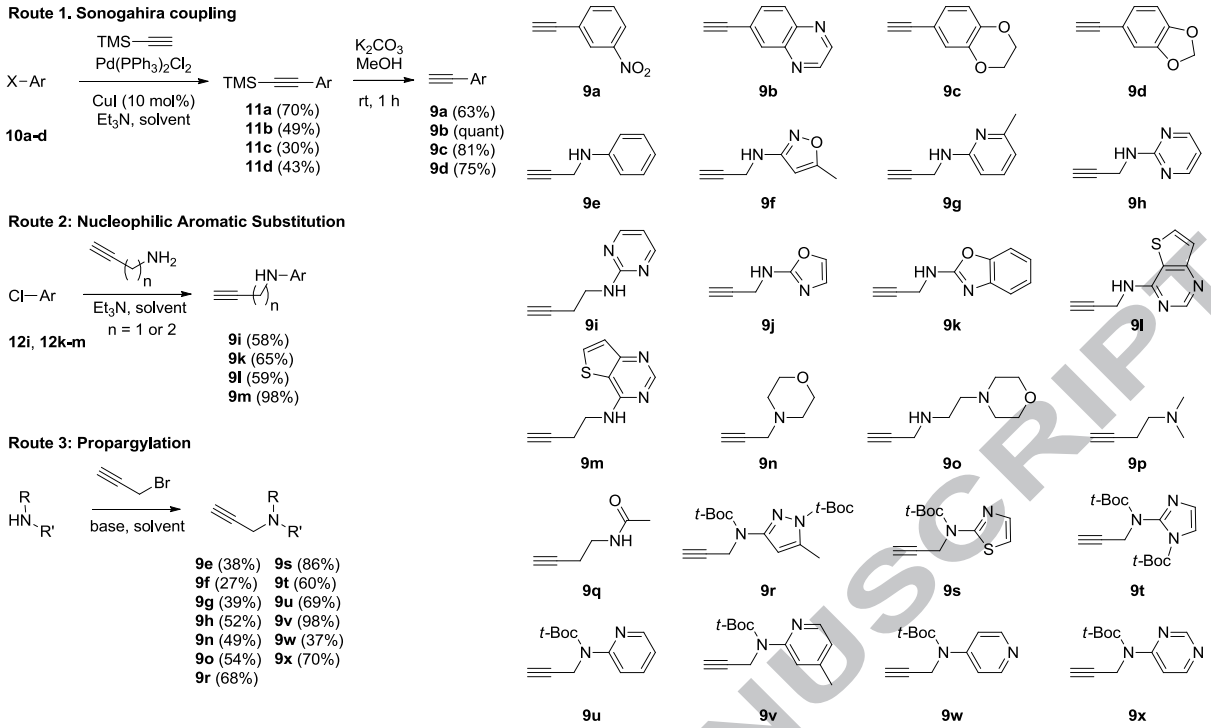


Figure 3. Design of 1,2,3-triazolylsalicylamide derivatives

2.2. Synthesis

For the installation of hinge binders on the inhibitors, click chemistry was used because it offers a number of attractive benefits for the development of kinase inhibitors:[17] (i) the resulting 1,2,3-triazole scaffold is a mimic of the purine of ATP and a bioisostere of flat heteroaromatic rings such as imidazole, pyrazole, and oxazole observed in many kinase inhibitor drugs; (ii) the structure of the substituent can be easily varied by using readily available alkynes. Hence, we envisioned that 1,2,3-triazolylsalicylamide derivatives bearing hinge-binding functionalities could be synthesized via the Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) of azidosalicylamide and various alkynes with hydrogen-bonding donor/acceptor. Twenty-four alkyne building blocks **9a–x** bearing hydrogen-bonding donor/acceptor were prepared via



Scheme 1. Synthesis of alkyne building blocks **9a–x**.

three different synthetic routes, as shown in Scheme 1. First, aryl acetylenes **9a–d** were obtained by the Sonogashira cross-coupling reaction of TMS acetylene and aryl halides **10** (route 1 in Scheme 1), followed by the subsequent TMS deprotection of alkyne **11a–d** by K_2CO_3. The resulting alkynes **9a–d** carry one or two hydrogen-bonding acceptors in the *meta* or *para* position. Second, alkynes **9i** and **9k–m** were synthesized by the nucleophilic aromatic substitution reactions of electron-deficient aryl chlorides **12i** and **12k–m** using propargyl/homopropargyl amine according to route 2 in Scheme 1. Lastly, most of the alkynes were synthesized through the propargylation of various amines: alkynes **9e–h**, **9j**, **9n**, and **9o** were obtained from the propargylation of the unprotected amines, whereas alkynes **9r–x** were obtained from the propargylation of Boc-protected amines because of the unexpected side reactions.

Next, we commenced the synthesis of azidosalicylamide **15** from commercially available 5-aminosalicylic acid (**13**) (Scheme 2). The addition of $NaNO_2$ to a sulfuric acid solution of **13** converted the amino group into the diazonium salt, which was then substituted with NaN_3 to form 5-azidosalicylic acid (**14**) in 99% yield. The CDI coupling reaction of acid **14** and substituted aniline containing an electron-withdrawing ester group was sluggish and afforded the corresponding amide **15** in a low yield (21%), because of the poor nucleophilicity of aniline nitrogen. However, after extensive screening of several coupling reagents, the desired azidosalicylamides **15** was obtained in 64% yield in the presence of 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT).

With azide **15** and alkyne building blocks **9a–x** in hand, CuAAC reactions were performed under the standard click condition: i) CuI in DMF, or ii) $CuSO_4$, sodium ascorbate in *t*-BuOH/H_2O. Under these click conditions, all the reactions smoothly produced the corresponding hinge-binder tethered 1,2,3-triazolylsalicylamides **8a–x** in 35–98% yields. Twenty-four hinge-binder tethered 1,2,3-triazolylsalicylamide derivatives were obtained, and the Boc protecting groups of seven compounds (**8r–x**) were then removed in the presence of trifluoroacetic acid solution in CH_2Cl_2 to afford **8r′–x′**.

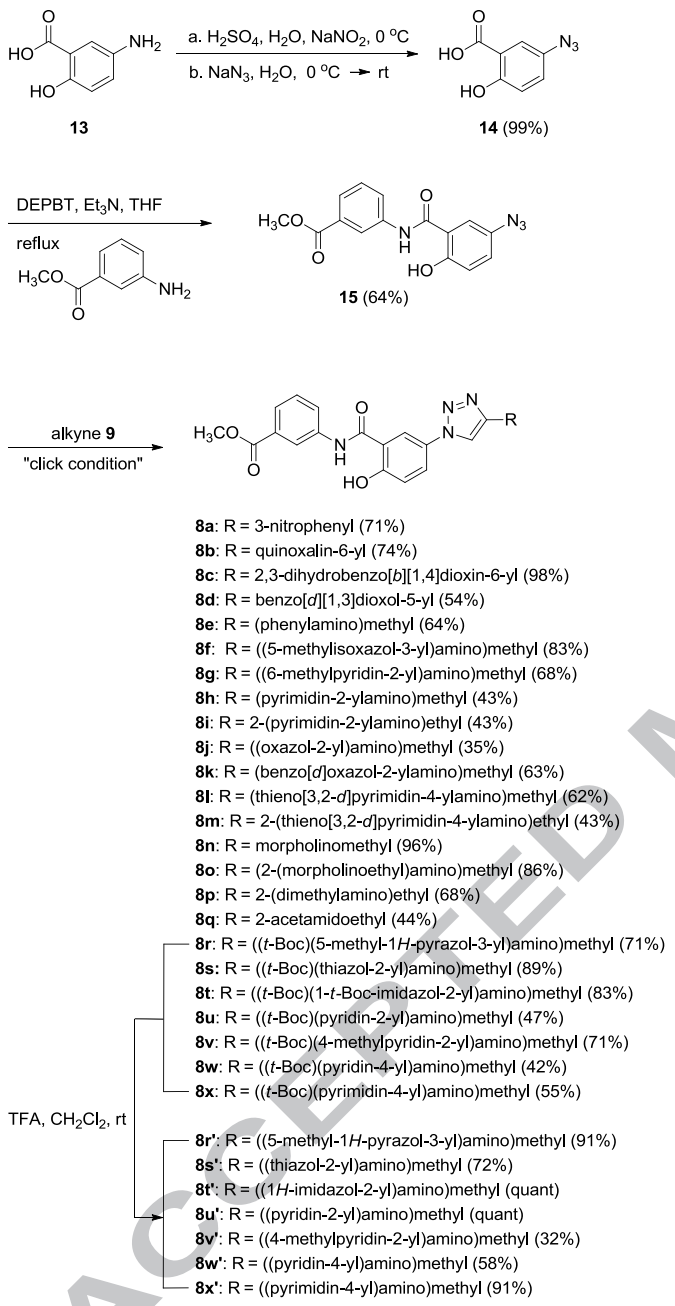
2.3. Biological Screening

To assess the synthesized 1,2,3-triazolylsalicylamide compounds as the Aurora kinase inhibitors, a single-dose in vitro kinase assay was performed at a concentration of 10 μM against Aurora A and B. This assay was duplicated, and the known non-selective kinase inhibitor, staurosporine, was used as the positive control. The % inhibition data of Aurora kinase activity are shown in Table 1 as the average of two independent experiments. Among the twenty-four 1,2,3-triazolylsalicylamides, ten analogs (**8a**, **8d, 8e**, **8f**, **8i**, **8k**, **8m**, **8r′**, **8u′**, and **8v′**) showed higher potency than compound **7** against Aurora A, whereas the mean % inhibitions were moderate for the rest of the compounds. Interestingly, these analogs were relatively less active against Aurora B (19.3%–37.3% inhibition at 10 μM) except **8m** (73.7%), showing the highest % inhibition against Aurora B.

After the single-dose preliminary screening data were analyzed, thirteen 1,2,3-triazolylsalicylamides (**8a**, **8b**, **8d–f**, **8h**, **8i**, **8k–m**, **8r′**, **8u′,** and **8v′**) showing high % inhibition against Aurora A and/or Aurora B were selected for further study (Table 2). The IC_{50} values for these selected compounds were determined in a 10-dose IC_{50} mode with 3-fold serial dilution starting at 30 μM as listed in Table 2. Most of the compounds inhibited Aurora A with IC_{50} values in the nanomolar to low micromolar range. Especially, compounds **8a**, **8b**, **8d** and **8l** revealed nanomolar IC_{50} values, and three compounds (**8a**, **8b**, and **8d**) exhibited lower IC_{50} values against Aurora A than compound **7**. Among the series of compounds, compound **8a** carrying *m*–NO_2 group was the best analog, exhibiting an IC_{50} value of 0.284 μM against Aurora A kinase.

The distance between 1,2,3-triazole moiety and hinge binder was also studied by using various linker sizes such as an aminomethyl or an aminoethyl linker. 1,2,3-Triazole compounds directly connected to the aryl moiety exhibited lower IC_{50} values than those tethered with flexible linkers (**8a**, **8b**, **8d** vs **8e**, **8f**, **8h**, **8i**, **8k–m**, **8r′**, **8u′**, and **8v′**). However, direct comparison of aminomethyl linker and aminoethyl linker was not clear: **8h** carrying (pyrimidylamino)methyl group showed higher IC_{50}

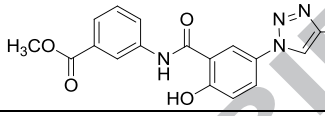
value than **8i** having (pyrimidylamino)ethyl group against Aurora A (IC_{50} = 15.4 μM vs 7.67 μM), whereas **8l** carrying (thienopyrimidinylamino)methyl group showed lower IC_{50} value than **8m** having (thienopyrimidinylamino)ethyl group against Aurora A (IC_{50} = 0.801 μM vs 2.97 μM).



Scheme 2. Synthesis of **8a–x** and **8r′–x′**.

Interestingly, compound **8m** revealed a nanomolar IC_{50} value against Aurora B. (Thienopyrimidinylamino)ethyl group may be an important part of Aurora B kinase inhibitor as shown in compound **2** (SNS-314, IC_{50} for AurB = 31 nM), which was reported as a pan-Aurora inhibitor. Compound **8a** showed the highest potency toward Aurora A (IC_{50} = 0.284 μM), and compound **8m** showed the highest potency toward Aurora B (IC_{50} = 0.364 μM). Most of the compounds except **8m** showed better inhibitory activities against Aurora A than against Aurora B (2–25 times). Only **8m** was approximately 8 times more active against Aurora B than against Aurora A. It is worth noting that the compound tethered with thienopyrimidinylamino group showed better selectivity for either Aurora A or Aurora B than the other hinge binding groups: **8l** tethered with (thienopyrimidinylamino)methyl group was 25 times more potent against Aurora A than against Aurora B (IC_{50} for AurA = 0.801 μM vs. IC_{50} for AurB = 20.1 μM), whereas **8m** tethered with (thienopyrimidinylamino)ethyl group was 8 times more potent against Aurora B than against Aurora A (IC_{50} for AurB = 0.364 μM vs IC_{50} for AurA = 2.97 μM). This selectivity inversion may provide useful structural insight of Aurora A and Aurora B for the Aurora A/B selective inhibitor development.

Table 1. Inhibitory activity of 1,2,3-triazolylsalicylamides **8a–q** and **8r′–v′** against AurA and AurB.[a]



Compd	R	%inhibition[b]	
		AurA	AurB
8a	3-nitrophenyl	77.0	32.3
8b	quinoxalin-6-yl	62.3	29.4
8c	2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl	61.7	24.6
8d	benzo[*d*][1,3]dioxol-5-yl	67.9	26.0
8e	(phenylamino)methyl	64.7	20.4
8f	((5-methylisoxazol-3-yl)amino)methyl	71.8	19.3
8g	((6-methylpyridin-2-yl)amino)methyl	55.9	16.7
8h	(pyrimidin-2-ylamino)methyl	29.2	20.2
8i	2-(pyrimidin-2-ylamino)ethyl	70.2	23.9
8j	((oxazol-2-yl)amino)methyl	0.00	3.54
8k	(benzo[*d*]oxazol-2-ylamino)methyl	75.4	37.3
8l	(thieno[3,2-*d*]pyrimidin-4-ylamino)methyl	62.5	-3.61
8m	2-(thieno[3,2-*d*]pyrimidin-4-ylamino)ethyl	69.1	73.7
8n	morpholinomethyl	11.7	12.6
8o	(2-(morpholinoethyl)amino)methyl	15.3	6.04
8p	2-(dimethylamino)ethyl	6.44	6.51
8q	2-acetamidoethyl	13.2	10.3
8r′	((5-methyl-1*H*-pyrazol-3-yl)amino)methyl	66.9	15.5
8s′	((thiazol-2-yl)amino)methyl	54.1	13.8
8t′	((1*H*-imidazol-2-yl)amino)methyl	30.0	10.9
8u′	((pyridin-2-yl)amino)methyl	79.6	22.6
8v′	((4-methylpyridin-2-yl)amino)methyl	75.3	19.8
8w′	((pyridin-4-yl)amino)methyl	9.25	6.16
8x′	((pyrimidin-4-yl)amino)methyl	29.5	11.7
7	3,5-dimethoxyphenyl	64.1	39.6
Staurosporine IC_{50} (μM)		< 0.001	0.001

[a]Enzymatic assay was conducted by Reaction Biology Corporation (http://www.reactionbiology.com).

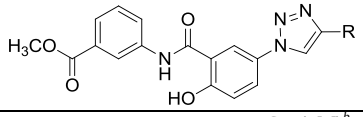
[b]Compounds were tested at 10 μM in the presence of 1 μM ATP. Data shown are the average of duplicated assays. % Inhibition was calculated by subtracting the % enzyme activity from 100.

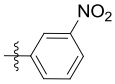
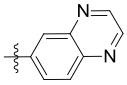
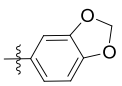
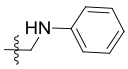
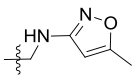
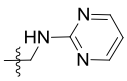
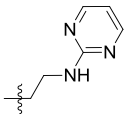
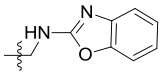
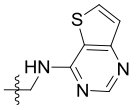
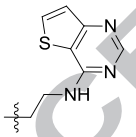
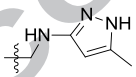
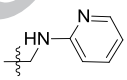
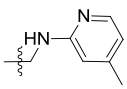
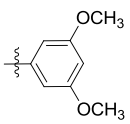
3. Conclusions

In conclusion, we developed a series of novel hinge binder tethered 1,2,3-triazolylsalicylamide Aurora kinase inhibitors. Various alkynes capable of interacting with the hinge through hydrogen bonds were introduced by facile CuAAC click chemistry. Click chemistry offered rapid access to the diverse hinge binding structures. The representative compound **8a** exhibited inhibitory activity against Aurora A kinase with an IC_{50} value of 0.284 μM, and **8m** showed an IC_{50} value of 0.364 μM

against Aurora B kinase. We believe that these compounds can be good candidates for further design of potent and selective antiproliferative agents targeting Aurora kinases.

Table 2. IC_{50} of selected 1,2,3-triazolylsalicylamides over AurA and AurB.[a]



Compd	R	IC_{50} (μM)[b]	
		AurA	AurB
8a		0.284	1.33
8b		0.607	7.30
8d		0.638	2.19
8e		5.15	36.5
8f		12.4	54.8
8h		15.4	40.7
8i		7.67	15.2
8k		3.52	10.2
8l		0.801	20.1
8m		2.97	0.364
8r′		13.7	49.5
8u′		6.43	32.1
8v′		6.07	16.3
7		0.768	5.94
Staurosporine		0.002	0.007

[a]Enzymatic assay was conducted by Reaction Biology Corporation (http://www.reactionbiology.com).

[b]IC_{50} was determined in the presence of 10 μM ATP.

4. Experimental

4.1. Chemistry

4.1.1. General

All reactions were performed in flame-dried glassware fitted with a glass stopper under positive pressure of Ar with magnetic stirring, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with cerium ammonium molybdenate (CAM), potassium permanganate ($KMnO_4$) or *p*-anisaldehyde. Flash chromatography was performed on E. Merck 230–400 mesh silica gel 60. Reagents were purchased from commercial suppliers, and used without further purification unless otherwise noted. Solvents were distilled from proper drying agents (CaH_2 or Na wire) under Ar atmosphere at 760 mm Hg. All moisture- and/or oxygen-sensitive solids were handled and stored in a glove box under N_2. NMR spectra were recorded on Varian Unity 400 instruments at 24 °C. Chemical shifts are expressed in ppm relative to TMS (^{1}H, 0 ppm), $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.2 ppm), DMSO-d_6 (^{1}H, 2.50 ppm; ^{13}C, 39.5 ppm), acetone-d_6 (^{1}H, 2.05 ppm; ^{13}C, 206.3, 29.9 ppm), benzene-d_6 (^{1}H, 7.15 ppm; ^{13}C, 128.5 ppm), CD_3OD (^{1}H, 3.31 ppm; ^{13}C, 49.1 ppm); coupling constants are expressed in Hz. High resolution mass spectra electrospray ionization (HRMS-ESI) was obtained on an Agilent technologies 6220 TOF LC/MS spectrometer.

4.1.2. Synthesis of azide 15.

4.1.2.1. 5-Azido-2-hydroxybenzoic acid (14).

5-Aminosalicylic acid (**13**) (1.05 g, 6.53 mmol) was dissolved in a mixture of conc. H_2SO_4 (5 mL) and H_2O (26.1 mL). The mixture was cooled to 0 °C and a solution of $NaNO_2$ (557 mg, 7.84 mmol) in H_2O (5 mL) was added dropwise. After stirring for 1.5 h at 0 °C, a solution of NaN_3 (722 mg, 11.1 mmol) in H_2O (4.0 mL) was added dropwise. The resulting suspension was stirred at 0 °C for 1.5 h and at rt for 13 h. The reaction mixture was extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. Evaporation under reduced pressure afforded compound **14** (1.16 g, 99%) as a red solid.

TLC: R_f 0.31 (5:1 EtOAc/MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.75 (brs, 1H), 11.30 (brs, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.15 (dd, J = 8.8, 2.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 158.3, 130.2, 126.6, 119.7, 118.9, 113.9.

4.1.2.2. Methyl 3-(5-azido-2-hydroxybenzamido)benzoate (15).

Methyl 3-aminobenzoate (751 mg, 4.87 mmol), Et_3N (1.54 mL, 11.0 mmol) and DEPBT (2.00 g, 6.68 mmol) were added to a solution of **14** (1.00 g, 5.58 mmol) in THF (5.4 mL) at 0 °C under argon atmosphere. After stirring for 5 h at 70 °C, the reaction mixture was quenched with distilled water (28 mL) and treated with saturated aqueous $NaHCO_3$ (54 mL). CH_2Cl_2 (40 mL) was added and the phases were then separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by column chromatography (4:1 hexanes/EtOAc) to afford **15** (968 mg, 64%) as a brown solid.

TLC: R_f 0.33 (4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.60 (brs, 1H), 10.61 (brs, 1H), 8.40 (t, J = 1.2 Hz, 1H), 7.94 (dm, J = 8.0 Hz, 1H), 7.74 (dt, J = 8.0, 1.2 Hz,

1H), 7.65 (d, *J* = 2.8 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.5, 155.4, 138.5, 130.4, 130.2, 129.3, 125.3, 124.8, 124.5, 121.2, 119.3, 119.0, 118.8, 52.3.

4.1.3. Synthesis of 1,2,3-triazolylsalicylamides 8a–x [Click reactions].

4.1.3.1. Methyl 3-[2-hydroxy-5-(4-(3-nitrophenyl)-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8a).

To a screw cap vial were added azide **15** (62.5 mg, 200 μmol), alkyne **9a** (40.0 mg, 272 μmol), CuI (19.5 mg, 100 μmol), and anhydrous DMF (0.4 mL) at rt. The reaction mixture was stirred at 80 °C for 16 h. Upon completion of the reaction, the reaction mixture was cooled to rt. Purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8a** (65.3 mg, 71%) as an ivory solid.

TLC: R_f 0.34 (40:1 CH_2Cl_2/MeOH (×2)). mp: 278.0−280.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1H), 10.71 (brs, 1H), 9.55 (s, 1H), 8.77 (t, *J* = 2.0 Hz, 1H), 8.45−8.44 (m, 2H), 8.41 (dt, *J* = 8.0, 1.2 Hz, 1H), 8.25 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 8.01 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.99 (dm, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.1, 157.7, 148.4, 145.2, 138.6, 132.0, 131.3, 130.7, 130.2, 129.3, 128.5, 125.3, 125.1, 124.8, 122.7, 121.3, 121.0 (2C), 119.6, 119.6, 118.4, 52.2. HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N_5O_6^+$ ([M + H]$^+$) 460.1252, found 460.1246.

4.1.3.2. Methyl 3-[2-hydroxy-5-(4-(quinoxalin-6-yl)-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8b).

To a screw cap vial were added azide **15** (46.9 mg, 150 μmol), alkyne **9b** (34.8 mg, 225 μmol), CuI (14.6 mg, 75.1 μmol), and anhydrous DMF (0.3 mL) at rt. The reaction mixture was stirred at 80 °C for 15 h. Upon completion of the reaction, the reaction mixture was cooled to rt. Purification by column chromatography (2:1 hexanes/EtOAc → 40:1 CH_2Cl_2/MeOH) yielded **8b** (51.8 mg, 74%) as an off-white solid.

TLC: R_f 0.21 (20:1 CH_2Cl_2/MeOH). mp: 270.1−272.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1H), 10.71 (s, 1H), 9.59 (s, 1H), 9.00 (d, *J* = 1.6 Hz, 1H), 8.97 (d, *J* = 1.6 Hz, 1H), 8.65 (d, *J* = 1.6 Hz, 1H), 8.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.48−8.45 (m, 2H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.03 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.2, 158.1, 146.4, 146.0, 145.6, 142.6, 142.1, 138.6, 131.9, 130.2, 130.0, 129.3, 128.4, 127.6, 125.4, 125.1, 124.7, 124.5, 121.4, 121.2, 121.0, 119.5, 118.5, 52.2. HRMS (ESI) *m/z* calcd for $C_{25}H_{19}N_6O_4^+$ ([M + H]$^+$) 467.1462, found 467.1464.

4.1.3.3. Methyl 3-[5-(4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8c).

To a screw cap vial were added azide **15** (62.5 mg, 200 μmol), alkyne **9c** (48.1 mg, 300 μmol), CuI (19.5 mg, 100 μmol), and anhydrous DMF (0.4 mL) at rt. The reaction mixture was stirred at 80 °C for 16 h. Upon completion of the reaction, the reaction mixture was cooled to rt. Purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8c** (92.5 mg, 98%) as an ivory solid.

TLC: R_f 0.18 (40:1 CH_2Cl_2/MeOH). mp: 246.1−247.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H), 10.69 (brs, 1H), 9.14 (s, 1H), 8.44 (t, *J* = 2.0 Hz, 1H), 8.41 (d, *J* = 2.8 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.97 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 7.42 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 6.97 (dt, *J* = 8.8, 1.2 Hz, 1H), 4.29 (s, 4H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.4, 158.1, 146.9, 143.7, 143.5, 138.6, 130.2, 129.2, 128.5, 125.2, 125.2, 124.8, 123.7, 121.1 (2C), 119.1, 119.0, 118.5, 118.4, 117.6, 113.9, 64.1, 52.2. HRMS (ESI) *m/z* calcd for $C_{25}H_{21}N_4O_6^+$ ([M + H]$^+$) 473.1456, found 473.1455.

4.1.3.4. Methyl 3-[5-(4-(benzo[d][1,3]dioxol-5-yl)-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8d).

To a screw cap vial were added azide **15** (68.4 mg, 219 μmol), alkyne **9d** (48.0 mg, 328 μmol), CuI (20.9 mg, 110 μmol), and anhydrous DMF (0.44 mL) at rt. The reaction mixture was stirred at 80 °C for 15 h. Upon completion of the reaction, the reaction mixture was cooled to rt. Purification by column chromatography (10:1 hexanes/EtOAc → 20:1 CH_2Cl_2/MeOH) yielded **8d** (54.0 mg, 54%) as an ivory solid.

TLC: R_f 0.28 (20:1 CH_2Cl_2/MeOH). mp: 271.3−273.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.83 (s, 1H), 10.68 (s, 1H), 9.14 (s, 1H), 8.44 (t, *J* = 2.0 Hz, 1H), 8.40 (d, *J* = 2.8 Hz, 1H), 7.99 (dm, *J* = 8.0 Hz, 1H), 7.96 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.49−7.46 (m, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.08 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.3, 158.3, 147.8, 147.2, 147.1, 138.7, 130.2, 129.3, 128.3, 125.3, 125.1, 124.7, 124.4, 121.2, 121.0, 119.3, 119.0, 119.0, 118.6, 108.8, 105.7, 101.2, 52.2. HRMS (ESI) *m/z* calcd for $C_{24}H_{19}N_4O_6^+$ ([M + H]$^+$) 459.1299, found 459.1295.

4.1.3.5. Methyl 3-[2-hydroxy-5-(4-(phenylamino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8e).

Azide **15** (50.0 mg, 160 μmol), alkyne **9e** (21.0 mg, 160 μmol) and TBTA (4.3 mg, 5 mol%) were dissolved in 1:1 *t*-BuOH/H_2O (380 μL). $CuSO_4$ (1 M solution, 3.2 μL, 2 mol%) and sodium ascorbate (1 M solution, 16.0 μL, 10 mol%) were added and the reaction mixture was stirred at 80 °C for 2 h. After completion of the reaction, the mixture was concentrated, basified with saturated aqueous $NaHCO_3$ (3 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the crude product as a brown solid. Purification by column chromatography (60:1 CH_2Cl_2/MeOH) yielded **8e** (45.3 mg, 64%) as a light brown solid.

TLC: R_f 0.27 (20:1 CH_2Cl_2/MeOH). mp: 166.0−168.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85 (brs, 1H), 10.66 (brs, 1H), 8.62 (s, 1H), 8.41 (t, *J* = 1.6 Hz, 1H), 8.35 (d, *J* = 2.8 Hz, 1H), 7.98 (dm, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.08 (dd, *J* = 7.6, 1.2 Hz, 2H), 6.67 (d, *J* = 7.6 Hz, 2H), 6.55 (t, *J* = 7.6 Hz, 1H), 6.13 (m, 1H), 4.37 (d, *J* = 4.8 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 167.2, 166.7, 160.1, 147.5, 147.4, 137.8, 130.9, 129.4, 129.3, 129.1, 126.3, 126.1, 126.0, 122.3, 120.6, 120.4, 119.2, 118.4, 116.8, 113.4, 52.4, 39.8. HRMS (ESI) *m/z* calcd for $C_{24}H_{22}N_5O_4^+$ ([M + H]$^+$) 444.1666, found 444.1669.

4.1.3.6. Methyl 3-[2-hydroxy-5-(4-((5-methylisoxazol-3-yl)amino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8f).

Azide **15** (68.8 mg, 220 μmol), alkyne **9f** (30.0 mg, 220 μmol), $CuSO_4$ (7.0 mg, 44.1 μmol) and sodium ascorbate (43.6 mg, 220 μmol) were dissolved in 1:1 *t*-BuOH/H_2O (2.2 mL). The

reaction mixture was stirred at rt for 24 h. After completion of the reaction, the suspension was filtered, washed with H_2O (20 mL), and dried (solid A) *in vacuo*. The filtrate was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation (residue B). The solid A and residue B were combined. Purification by column chromatography (100:1 → 80:1 CH_2Cl_2/MeOH) yielded **8f** (82.2 mg, 83%) as a cherry solid.

TLC: R_f 0.16 (40:1 CH_2Cl_2/MeOH). mp: 161.2−163.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1H), 10.67 (s, 1H), 8.58 (s, 1H), 8.41 (t, *J* = 2.0 Hz, 1H), 8.35 (d, *J* = 2.8 Hz, 1H), 7.98 (dm, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.55 (t, *J* = 6.0 Hz, 1H), 5.68 (d, *J* = 2.8 Hz, 1H), 4.35 (d, *J* = 9.2 Hz, 2H), 3.88 (s, 3H), 2.22 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 170.1, 169.9, 166.1, 166.1, 159.6, 136.9, 136.8, 130.1, 129.8, 128.2, 127.8, 125.4, 125.1, 125.0, 121.5, 121.4, 119.3, 118.4, 115.4, 51.4, 38.6, 28.7. HRMS (ESI) *m/z* calcd for $C_{22}H_{21}N_6O_5^+$ ([M + H]$^+$) 449.1568, found 449.1573.

4.1.3.7. Methyl 3-[2-hydroxy-5-(4-((6-methylpyridin-2-yl)amino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8g).

Azide **15** (119 mg, 380 µmol), alkyne **9g** (140 mg, 960 µmol), $CuSO_4$ (12.3 mg, 77.3 µmol) and sodium ascorbate (76.4 mg, 390 µmol) were dissolved in 1:1 *t*-BuOH/H_2O (8 mL). The reaction mixture was stirred at rt for 20 h. After completion of the reaction, the suspension was filtered, washed with H_2O (30 mL), and dried (solid A) *in vacuo*. The filtrate was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporation (residue B). The solid A and residue B were combined. Purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8g** (118 mg, 68%) as a white solid.

TLC: R_f 0.17 (20:1 CH_2Cl_2/MeOH). mp: 183.7−185.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1H), 10.76 (brs, 1H), 8.54 (s, 1H), 8.40 (t, *J* = 2.0 Hz, 1H), 8.34 (d, *J* = 2.8 Hz, 1H), 7.97 (dm, *J* = 8.0 Hz, 1H), 7.90 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.74 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 8.8, 7.2 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.86 (brt, *J* = 5.6 Hz, 1H), 6.38 (d, *J* = 7.2 Hz, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 4.57 (d, *J* = 5.6 Hz, 2H), 3.88 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 167.3, 166.7, 160.2, 157.2, 155.1, 146.6, 139.9, 137.9, 130.9, 129.3, 129.2, 126.4, 126.1, 126.0, 122.4, 120.9, 120.7, 119.2, 116.9, 113.1, 104.8, 52.4, 37.9, 23.0. HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_6O_4^+$ ([M + H]$^+$) 459.1775, found 459.1780.

4.1.3.8. Methyl 3-[2-hydroxy-5-(4-(pyrimidin-2-ylamino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8h).

Azide **15** (93.8 mg, 300 µmol), alkyne **9h** (40.0 mg, 300 µmol), $CuSO_4$ (9.4 mg, 60.1 µmol) and sodium ascorbate (59.5 mg, 300 µmol) were dissolved in 1:1 *t*-BuOH/H_2O (3.2 mL). The mixture was stirred at rt for 20 h. After an additional **9h** (16.0 mg, 120 µmol) was added, the mixture was stirred rt for an additional 24 h. The resulting suspension was filtered, washed with H_2O (20 mL), and dried (solid A) *in vacuo*. The filtrate was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation (residue B). The solid A and residue B were combined. Purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8h** (57.9 mg, 43%) as a light brown solid.

TLC: R_f 0.21 (20:1 CH_2Cl_2/MeOH). mp: 162.0−164.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85 (brs, 1H), 10.66 (brs, 1H), 8.52 (s, 1H), 8.40 (t, *J* = 1.6 Hz, 1H), 8.34 (d, *J* = 2.8 Hz, 1H), 8.31 (d, *J* = 4.8 Hz, 2H), 7.98 (dm, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* =8.8, 2.8 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.63 (t, *J* = 6.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.62 (t, *J* = 4.8 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 167.2, 166.6, 161.7, 160.0, 158.2, 146.6, 137.8, 130.8, 129.2, 129.1, 126.3, 126.0, 125.9, 122.3, 120.7, 120.6, 119.1, 116.8, 111.2, 52.4, 36.7. HRMS (ESI) *m/z* calcd for $C_{22}H_{20}N_7O_4^+$ ([M + H]$^+$) 446.1571, found 446.1572.

4.1.3.9. Methyl 3-[2-hydroxy-5-(4-(2-(pyrimidin-2-ylamino)ethyl)-1H-1,2,3-triazol-1-yl)-benzamido]benzoate (8i).

To a screw cap vial were added azide **15** (62.5 mg, 200 µmol), alkyne **9i** (44.2 mg, 300 µmol), CuI (19.5 mg, 100 µmol), and anhydrous DMF (0.4 mL) at rt. The reaction mixture was stirred at rt for 2 h. After completion of the reaction, purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8i** (39.2 mg, 43%) as an ivory solid**.**

TLC: R_f 0.38 (10:1 CH_2Cl_2/MeOH). mp: 226.9−228.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.83 (s, 1H), 10.67 (s, 1H), 8.56 (s, 1H), 8.42 (t, *J* = 1.6 Hz, 1H), 8.35 (d, *J* = 2.8 Hz, 1H), 8.28 (d, *J* = 4.4 Hz, 2H), 7.99 (dm, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.30 (brt, *J* = 6.4 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.57 (t, *J* = 4.8 Hz, 1H), 3.88 (s, 3H), 3.61 (q, *J* = 7.2 Hz, 2H), 2.98 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.5, 162.2, 157.9, 157.7, 145.7, 138.5, 130.2, 129.3, 128.9, 125.4, 125.2, 124.8, 121.2, 120.9, 120.7, 119.0, 118.3, 110.1, 52.2, 40.4, 25.3. HRMS (ESI) *m/z* calcd for $C_{23}H_{22}N_7O_4^+$ ([M + H]$^+$) 460.1728, found 460.1733.

4.1.3.10. Methyl 3-[2-hydroxy-5-(4-(oxazol-2-ylamino)methyl-1H-1,2,3-triazol-1-yl)-benzamido]benzoate (8j).

To a screw cap vial were added 2-aminooxazole (78.9 mg, 901 µmol), anhydrous DMF (0.9 mL), and propargyl bromide (120 mg, 991 µmol) was added. The reaction mixture was heated to 80 °C and stirred for 24 h. Upon completion of the reaction, the reaction mixture was cooled to rt. Azide **15** (62.5 mg, 200 µmol), CuI (19.5 mg, 100 µmol), and DIPEA (106 mg, 901 µmol) were added and the reaction mixture was stirred at rt for 2 h. After completion of the reaction, purification by column chromatography (20:1 CH_2Cl_2/MeOH) yielded **8j** (30.7 mg, 35%) as a beige solid.

TLC: R_f 0.24 (5:1 CH_2Cl_2/MeOH (× 2)). mp: 189.1−191.1 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 8.48 (s, 1H), 8.43 (t, *J* = 1.6 Hz, 1H), 8.30 (s, 1H), 7.94 (dm, *J* = 8.0 Hz, 1H), 7.78 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.71 (dm, *J* = 8.8 Hz, 1H), 7.63 (s, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 5.25 (s, 2H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 166.2, 165.7, 157.2, 140.8, 140.0, 138.9, 132.6, 130.2, 129.3, 125.1, 124.2, 123.4, 122.0, 121.7, 121.0, 120.2, 118.9, 118.4, 52.2, 40.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_6O_5^+$ ([M + H]$^+$) 435.1411, found 435.1411.

4.1.3.11. Methyl 3-[5-(4-(benzo[d]oxazol-2-ylamino)methyl-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8k).

To a screw cap vial were added azide **15** (62.5 mg, 200 µmol), alkyne **9k** (51.7 mg, 300 µmol), CuI (19.5 mg, 100 µmol), and anhydrous DMF (0.4 mL) at rt. The reaction mixture was stirred

at rt for 2 h. After completion of the reaction, purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8k** (61.4 mg, 63%) as an ivory solid.

TLC: R_f 0.21 (40:1 CH_2Cl_2/MeOH). mp: 246.0−246.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85 (brs, 1H), 10.65 (brs, 1H), 8.68 (s, 1H), 8.51 (t, *J* = 2.4 Hz, 1H), 8.40 (t, *J* = 1.6 Hz, 1H), 8.36 (d, *J* = 2.4 Hz, 1H), 7.97 (dm, *J* = 8.0 Hz, 1H), 7.93 (dd, *J* = 8.8, 3.2 Hz, 1H), 7.74 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.12 (td, *J* = 8.0, 1.2 Hz, 1H), 7.00 (td, *J* = 8.0, 1.2 Hz, 1H), 4.67 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.6, 162.3, 158.0, 148.3, 145.7, 143.1, 138.5, 130.2, 129.3, 128.7, 125.5, 125.2, 124.8, 123.6, 121.4, 121.2, 121.1, 120.3, 118.9, 118.4, 115.7, 108.7, 52.2, 37.8. HRMS (ESI) *m/z* calcd for $C_{25}H_{21}N_6O_5^+$ ([M + H]$^+$) 485.1568, found 485.1569.

4.1.3.12. Methyl 3-[2-hydroxy-5-(4-(thieno[3,2-d]pyrimidin-4-ylamino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8l).

To a screw cap vial were added azide **15** (62.5 mg, 200 μmol), alkyne **9l** (56.8 mg, 300 μmol), CuI (19.5 mg, 100 μmol), and anhydrous DMF (0.4 mL) at rt. The reaction mixture was stirred at rt for 5 h. After completion of the reaction, purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8l** (62.2 mg, 62%) as an ivory solid.

TLC: R_f 0.33 (15:1 CH_2Cl_2/MeOH (× 2)). mp: 240.3−242.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.83 (brs, 1H), 10.65 (brs, 1H), 8.61 (s, 1H), 8.50 (s, 1H), 8.47 (t, *J* = 5.6 Hz, 1H), 8.40 (t, *J* = 1.6 Hz, 1H), 8.34 (d, *J* = 2.4 Hz, 1H), 8.11 (d, *J* = 5.2 Hz, 1H), 7.97 (dm, *J* = 8.0 Hz, 1H), 7.84 (dd, *J* = 8.8, 3.2 Hz, 1H), 7.74 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 5.2 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 4.85 (d, *J* = 5.6 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.6, 159.3, 157.9, 156.6, 154.5, 146.0, 138.5, 133.2, 130.0, 129.3, 128.7, 125.5, 125.2, 124.8, 124.3, 121.4, 121.2, 121.1, 118.9, 118.3, 114.9, 52.2, 35.7. HRMS (ESI) *m/z* calcd for $C_{24}H_{20}N_7O_4S^+$ ([M + H]$^+$) 502.1292, found 502.1287.

4.1.3.13. Methyl 3-[2-hydroxy-5-(4-(2-(thieno[3,2-d]pyrimidin-4-ylamino)ethyl)-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8m).

To a screw cap vial were added azide **15** (62.5 mg, 200 μmol), alkyne **9m** (61.0 mg, 300 μmol), CuI (19.5 mg, 100 μmol), and anhydrous DMF (0.4 mL) at rt. The reaction mixture was stirred at 40 °C for 24 h. Upon completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$ (30 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8m** (44.7 mg, 43%) as a pale green solid.

TLC: R_f 0.14 (20:1 CH_2Cl_2/MeOH (× 2)). mp: 194.7−196.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (brs, 1H), 10.69 (brs, 1H), 8.59 (s, 1H), 8.48 (s, 1H), 8.42 (t, *J* = 2.0 Hz, 1H), 8.35 (d, *J* = 2.8 Hz, 1H), 8.09 (d, *J* = 5.6 Hz, 1H), 8.04 (t, *J* = 5.6 Hz, 1H), 7.98 (dm, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 5.6 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.84 (m, 2H), 3.09 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.5, 159.3, 158.6, 156.8, 154.5, 145.4, 138.7, 132.9, 130.2, 129.3, 128.3, 125.3, 125.1, 124.7, 124.4, 121.1, 121.0, 120.8, 118.9, 118.6, 114.8, 52.2, 40.0, 25.2. HRMS (ESI) *m/z* calcd for $C_{25}H_{22}N_7O_4S^+$ ([M + H]$^+$) 516.1448, found 516.1445.

4.1.3.14. Methyl 3-[2-hydroxy-5-(4-(N-morpholino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8n).

To a screw cap vial were added azide **15** (62.5 mg, 200 μmol), alkyne **9n** (37.6 mg, 300 μmol), CuI (19.5 mg, 100 μmol), and anhydrous DMF (0.4 mL) at rt. The reaction mixture was stirred at rt for 2 h. After completion of the reaction, purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8n** (84.4 mg, 96%) as an ivory solid.

TLC: R_f 0.28 (20:1 CH_2Cl_2/MeOH). mp: 204.0−206.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (brs, 1H), 10.72 (s, 1H), 8.64 (s, 1H), 8.42 (s, 1H), 8.38 (s, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.94 (dm, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.67 (s, 2H), 3.59 (s, 4H), 2.52 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.7, 158.3, 144.0, 138.5, 130.2, 129.3, 128.7, 125.5, 125.2, 124.8, 122.3, 121.2, 121.0, 118.6, 66.0 (2C), 52.7, 52.2. HRMS (ESI) *m/z* calcd for $C_{22}H_{24}N_5O_5^+$ ([M + H]$^+$) 438.1772, found 438.1772.

4.1.3.15. Methyl 3-[2-hydroxy-5-(4-((2-(N-morpholino)ethyl)amino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8o).

To a screw cap vial were added azide **15** (62.5 mg, 200 μmol), alkyne **9o** (53.0 mg, 300 μmol), CuI (19.5 mg, 100 μmol), and anhydrous DMF (0.4 mL) at rt. The reaction mixture was heated to 80 °C and stirred for 14 h. Upon completion of the reaction, the reaction mixture was cooled to rt. Purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8o** (86.8 mg, 86%) as an ivory solid.

TLC: R_f 0.09 (10:1 CH_2Cl_2/MeOH). mp: 174.5−176.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H), 8.28 (s, 1H), 8.03 (d, *J* = 3.2 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.37 (dm, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 8.8 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 2H), 3.56 (t, *J* = 4.8 Hz, 4H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.41 (t, *J* = 6.0 Hz, 2H) 2.33 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD + $CDCl_3$): δ 170.0, 168.2, 167.8, 146.0, 140.1 (2C), 131.2, 129.5, 126.6, 125.8, 125.1, 123.3, 122.9, 122.1, 121.9, 119.2, 67.4, 58.0, 54.2, 52.5, 45.2, 44.3. HRMS (ESI) *m/z* calcd for $C_{24}H_{29}N_6O_5^+$ ([M + H]$^+$) 481.2194, found 481.2195.

4.1.3.16. Methyl 3-[5-(4-(2-(N,N-dimethyl)aminoethyl)-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8p).

To a screw cap vial was added K_2CO_3 (429 mg, 3.10 mmol), dimethylamine solution (2 M in methanol, 1 mL, 2.07 mmol), and 4-bromobut-1-yne (200 μL, 2.07 mmol) under argon atmosphere. The reaction mixture was heated to 60 °C and stirred for 24 h. Upon completion of the reaction, the reaction mixture was cooled to rt. Azide **15** (62.5 mg, 200 μmol), CuI (19.5 mg, 100 μmol), and anhydrous DMF (0.4 mL) were added and the reaction mixture was stirred at rt for 2 h. Upon completion of the reaction, the reaction mixture was concentrated by rotary evaporation rt, diluted with CH_2Cl_2 (10 mL), and washed with water (3 × 7 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH (10:1, 10 × 10 mL), the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. Purification by column chromatography (20:1 CH_2Cl_2/MeOH) yielded **8p** (55.2 mg, 68%) as an ivory solid.

TLC: R_f 0.17 (10:1 CH_2Cl_2/MeOH). mp: 195.0−197.0 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ 8.50 (d, *J* = 2.4 Hz, 1H), 8.49 (t, *J* = 2.0 Hz, 1H), 8.32 (s, 1H), 8.11 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H),

7.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.82 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 3.91 (s, 3H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 165.7, 163.5, 144.4, 139.5, 130.2, 129.3, 125.5, 125.1, 124.6, 123.9, 121.3, 120.7, 120.5, 120.0, 118.4, 57.0, 52.2, 43.6, 22.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_5O_4^+$ ([M + H]$^+$) 410.1823, found 410.1829.

4.1.3.17. Methyl 3-[5-(4-(2-acetamidoethyl)-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8q).

To a screw cap vial were added azide **15** (44.4 mg, 142 μmol), alkyne **9q** (33.4 mg, 300 μmol), CuI (13.8 mg, 71.1 μmol), anhydrous DMF (0.3 mL), and DIPEA (16.6 mg, 142 μmol) at rt. The reaction mixture was stirred at rt for 16 h. After completion of the reaction, purification by column chromatography (10:1 CH_2Cl_2/MeOH) yielded **8q** (23.2 mg, 44%) as a white solid.

TLC: R_f 0.35 (10:1 CH_2Cl_2/MeOH). mp: 226.2−228.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.83 (s, 1H), 10.70 (brs, 1H), 8.53 (s, 1H), 8.42 (t, *J* = 2.0 Hz, 1H), 8.34 (d, *J* = 2.8 Hz, 1H), 7.99−7.97 (m, 2H), 7.90 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.37 (td, *J* = 7.2, 6.0 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.2, 166.0, 165.5, 157.6, 145.5, 138.5, 130.2, 129.3, 128.9, 125.3, 125.2, 124.8, 121.1, 121.0, 120.8, 119.1, 118.3, 52.2, 38.3, 25.6, 22.6. HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_5O_5^+$ ([M + H]$^+$) 424.1615, found 424.1623.

4.1.3.18. Methyl 3-[2-hydroxy-5-(4-(N-(tert-butoxycarbonyl)-N-(5-methyl-1H-pyrazol-3-yl)amino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8r).

To a screw cap vial were added azide **15** (31.3 mg, 100 μmol), alkyne **9r** (50.4 mg, 150 μmol), CuI (9.7 mg, 50 μmol), and anhydrous DMF (0.2 mL) at rt. The reaction mixture was stirred at rt for 2 h. After completion of the reaction, purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8r** (38.8 mg, 71%) as an ivory solid.

TLC: R_f 0.32 (20:1 CH_2Cl_2/MeOH). mp: 145.6−147.6 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ 12.25 (brs, 1H), 11.23 (brs, 1H), 10.27 (s, 1H), 8.43−8.42 (m, 2H), 8.24 (s, 1H), 8.07 (dm, *J* = 8.0 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.83 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.25 (brs, 1H), 5.17 (s, 2H), 3.91 (s, 3H), 2.26 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0 (2C), 165.6, 157.9, 152.6, 145.9, 138.5 (2C), 130.2, 129.3, 128.7, 125.7, 125.3, 124.9, 121.2 (2C), 121.1, 118.8, 118.3, 97.6, 80.4, 52.2, 42.2, 27.9, 10.7. HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_7O_6^+$ ([M + H]$^+$) 548.2252, found 548.2246.

4.1.3.19. Methyl 3-[5-(4-(N-(tert-butoxycarbonyl)thiazol-2-ylamino)methyl-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8s).

To a screw cap vial were added azide **15** (62.5 mg, 200 μmol), alkyne **9s** (71.5 mg, 300 μmol), CuI (19.5 mg, 100 μmol), and anhydrous DMF (0.4 mL) at rt. The reaction mixture was stirred at rt for 2 h. After completion of the reaction, purification by column chromatography (80:1 CH_2Cl_2/MeOH) yielded **8s** (98.2 mg, 89%) as a pale brown solid.

TLC: R_f 0.20 (40:1 CH_2Cl_2/MeOH). mp: 114.1−116.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.82 (s, 1H), 10.65 (brs, 1H), 8.56 (s, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 3.6 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 5.40 (s, 2H), 3.88 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 166.1, 165.9, 160.7, 159.3, 151.5, 143.5, 136.8, 135.3, 129.8, 128.2, 128.0, 125.4, 125.1, 125.0, 121.4, 120.4, 119.5, 118.2, 115.5, 113.9, 84.0, 51.4, 41.5, 27.1. HRMS (ESI) *m/z* calcd for $C_{26}H_{27}N_6O_6S^+$ ([M + H]$^+$) 551.1707, found 551.1702.

4.1.3.20. Methyl 3-[5-(4-(N-(tert-butoxycarbonyl)-N-(1-(tert-butoxycarbonyl)imidazol-2-yl)amino)methyl-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8t).

To a screw cap vial were added azide **15** (15.5 mg, 49.6 μmol), alkyne **9t** (23.9 mg, 74.4 μmol), CuI (4.8 mg, 24.8 μmol), and anhydrous DMF (0.1 mL) at rt. The reaction mixture was stirred at rt for 45 h. After completion of the reaction, purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8t** (26.0 mg, 83%) as a yellow solid.

TLC: R_f 0.52 (20:1 CH_2Cl_2/MeOH (× 2)). mp: 144.7−146.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1H), 8.55 (s, 1H), 8.41 (s, 1H), 8.29 (s, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 7.84 (s, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.10 (s, 1H), 6.90 (s, 1H), 4.85 (s, 2H), 3.88 (s, 3H), 1.47 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.4, 162.3, 157.8, 153.1, 152.7, 146.1, 138.5, 130.2, 129.3, 128.6, 126.3, 125.3, 124.8, 122.0, 121.2, 121.0, 118.7, 118.4, 85.2, 80.7, 52.2, 43.2, 35.7, 30.7, 27.7, 27.2. HRMS (ESI) *m/z* calcd for $C_{31}H_{36}N_7O_8^+$ ([M + H]$^+$) 634.2620, found 634.2626.

4.1.3.21. Methyl 3-[5-(4-(N-(tert-butoxycarbonyl)pyridin-2-ylamino)methyl-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8u).

Azide **15** (50.0 mg, 160 μmol), alkyne **9u** (37.2 mg, 160 μmol) and TBTA (4.3 mg, 5 mol%) were dissolved in 1:1 *t*-BuOH/H_2O (0.38 mL). $CuSO_4$ (0.25 M solution, 12.8 μL, 2 mol%) and sodium ascorbate (0.25 M solution, 64.0 μL, 10 mol%) were added and the reaction mixture was stirred at 80 °C for 30 min. After completion of the reaction, the reaction mixture was concentrated, basified with saturated aqueous $NaHCO_3$ (3 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the crude product as a brown solid. Purification by column chromatography (100:1 → 80:1 → 70:1 CH_2Cl_2/MeOH) yielded **8u** (41.3 mg, 47%) as a brown solid.

TLC: R_f 0.20 (40:1 CH_2Cl_2/MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.82 (brs, 1H), 10.65 (brs, 1H), 8.50 (s, 1H), 8.41 (d, *J* = 2.8 Hz, 1H), 8.39 (m, 2H), 8.32 (d, *J* = 2.8 Hz, 1H), 7.97 (dm, *J* = 8.0 Hz, 1H), 7.90 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.77 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.22 (s, 2H), 3.88 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 167.2, 160.6, 154.0, 153.6, 147.1, 146.4, 138.5, 137.8, 130.9, 129.2, 129.1, 126.3, 126.2, 126.1, 122.6, 122.5, 121.3, 120.5, 120.3, 120.2, 119.3, 116.4, 82.8, 52.4, 42.9, 28.2. HRMS (ESI) *m/z* calcd for $C_{28}H_{29}N_6O_6^+$ ([M + H]$^+$) 545.2143, found 545.2142.

4.1.3.22. Methyl 3-[5-(4-(N-(tert-butoxycarbonyl)-N-(4-methylpyridin-2-yl)amino)methyl-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8v).

Azide **15** (50.0 mg, 160 μmol), alkyne **9v** (78.9 mg, 320 μmol), CuI (30.5 mg, 160 μmol) and DIPEA (27.7 μL, 160 μmol)

were dissolved in DMF (0.57 mL). The reaction mixture was stirred at rt for 50 min. After completion of the reaction, 10% ammonia water was added and stirred at rt for 20 min. The mixture was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the crude product as a brown solution. Purification by column chromatography (40:1 CH_2Cl_2/MeOH) yielded **8v** (63.2 mg, 71%) as an orange solid.

TLC: R_f 0.24 (30:1 CH_2Cl_2/MeOH). mp: 81.3−83.3 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ 10.32 (brs, 1H), 8.44 (s, 1H), 8.43 (s, 1H), 8.32 (s, 1H), 8.24 (d, *J* = 5.2 Hz, 1H), 8.07 (dm, *J* = 8.0 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.83 (ddd, *J* = 8.0, 1.6, 0.8 Hz, 1H), 7.61 (s, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.95 (dm, *J* = 5.2 Hz, 1H), 5.31 (d, *J* = 0.4 Hz, 2H), 3.91 (s, 3H), 2.35 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 167.1, 166.3, 159.6, 154.0, 153.5, 150.2, 146.6, 146.2, 137.8, 130.7, 129.2, 129.1, 126.2, 126.0, 125.9, 122.3, 122.2, 121.9, 121.2, 120.9, 118.9, 117.0, 82.4, 52.2, 42.9, 28.0, 21.0. HRMS (ESI) *m/z* calcd for $C_{29}H_{31}N_6O_6^+$ ([M + H]$^+$) 559.2300, found 559.2294.

4.1.3.23. Methyl 3-[5-(4-(N-(tert-butoxycarbonyl)pyridin-4-ylamino)methyl-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8w).

Azide **15** (75.0 mg, 240 μmol), alkyne **9w** (83.7 mg, 360 μmol) and TBTA (6.4 mg, 5 mol%) were dissolved in 1:1 *t*-BuOH/H_2O (0.6 mL). $CuSO_4$ (0.25 M solution, 19.2 μL, 2 mol%) and sodium ascorbate (0.25 M solution, 96.0 μL, 10 mol%) were added and the reaction mixture was stirred at 80 °C for 2 h. After completion of the reaction, the mixture was concentrated, basified with saturated aqueous $NaHCO_3$ (6 mL), and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the crude product as a brown solid. Purification by column chromatography (30:1 CH_2Cl_2/MeOH) yielded **8w** (54.8 mg, 42%) as an ivory solid.

TLC: R_f 0.16 (30:1 CH_2Cl_2/MeOH). mp: 198.5−200.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ 8.58 (d, *J* = 6.0 Hz, 2H), 8.42-8.41 (m, 2H), 8.34 (t, *J* = 1.6 Hz, 1H), 8.17 (d, *J* = 6.0 Hz, 1H), 7.95 (ddd, *J* = 8.0, 2.4, 1.2 Hz, 1H), 7.87 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.83 (ddd, *J* = 8.0, 1.6, 1.2 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 5.28 (s, 2H), 3.93 (s, 3H), 1.57 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 166.2, 165.3, 159.0, 152.3, 149.3, 148.7, 144.1, 136.9, 129.8, 128.3, 128.0, 125.3, 125.0, 124.9, 121.2, 120.4, 120.0, 118.2, 118.0, 116.2, 82.2, 51.4, 43.7, 27.2. HRMS (ESI) *m/z* calcd for $C_{28}H_{29}N_6O_6^+$ ([M + H]$^+$) 545.2143, found 545.2141.

4.1.3.24. Methyl 3-[5-(4-(N-(tert-butoxycarbonyl)pyrimidin-4-ylamino)methyl-1H-1,2,3-triazol-1-yl)-2-hydroxybenzamido]benzoate (8x).

To a screw cap vial were added azide **15** (63.0 mg, 202 μmol), alkyne **9x** (94.0 mg, 404 μmol), CuI (38.5 mg, 202 μmol), and anhydrous DMF (0.72 mL) at rt. Then, the reaction mixture was stirred at rt for 2 h. Upon completion of the reaction, the reaction mixture was diluted with EtOAc (15 mL) and washed with water (3 × 5 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Purification by column chromatography (80:1 CH_2Cl_2/MeOH) yielded **8x** (61.2 mg, 55%) as a dark brown solid.

TLC: R_f 0.37 (20:1 CH_2Cl_2/MeOH). mp: 107.2−109.2 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ 10.52 (brs, 1H), 8.90 (s, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 8.45 (s, 2H), 8.41 (s, 1H), 8.07 (dd, *J* = 6.0, 1.2 Hz, 1H), 8.05 (s, 1H), 7.93 (brs, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 6.0 Hz, 1H), 5.45 (s, 2H), 3.91 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6): δ 168.6, 167.0, 162.1, 160.6, 158.7, 157.9, 153.9, 146.8, 139.1, 131.9, 130.1, 127.6, 126.6, 126.5, 123.0, 123.0, 122.0, 121.0, 120.0, 116.7, 114.1, 83.7, 52.6, 41.6, 28.3. HRMS (ESI) *m/z* calcd for $C_{27}H_{28}N_7O_6^+$ ([M + H]$^+$) 546.2096, found 546.2103.

4.1.4. Synthesis of 1,2,3-triazolylsalicylamides 8r'–x' [t-Boc deprotection].

4.1.4.1. Methyl 3-[2-hydroxy-5-[4-((5-methyl-1H-pyrazol-3-yl)amino)methyl-1H-1,2,3-triazol-1-yl]benzamido]benzoate (8r').

To a screw cap vial were added **8r** (19.6 mg, 35.8 μmol) and CH_2Cl_2 (0.36 mL) at rt. A solution of TFA (20% v/v in CH_2Cl_2, total 1.2 mL) was added at rt dropwise while checking by TLC. Upon completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (3 mL), basified with saturated aqueous $NaHCO_3$ (3 mL) to pH 8, and stirred for 30 min. The resulting suspension was filtered, and the filtrate extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Purification of filtered solid and crude residue by column chromatography (20:1 CH_2Cl_2/MeOH) yielded **8r'** (14.6 mg, 91%) as an ivory solid.

TLC: R_f 0.24 (10:1 CH_2Cl_2/MeOH). mp: 198.2−200.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85 (brs, 1H), 11.21 (brs, 1H), 8.44 (s, 1H), 8.40 (t, *J* = 1.6 Hz, 1H), 8.27 (s, 1H), 7.96 (dm, *J* = 8.0 Hz, 1H), 7.80 (brd, *J* = 5.2 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.04 (brs, 1H), 5.42 (s, 1H), 5.30 (s, 1H), 4.30 (d, *J* = 5.6 Hz, 2H), 3.88 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 165.8, 162.1, 161.2, 147.4, 139.3 (2C), 130.1, 129.2, 126.3, 125.2, 124.8, 124.1, 121.1, 120.7 (2C), 119.7, 118.3, 90.0, 52.2, 38.5, 10.7. HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N_7O_4^+$ ([M + H]$^+$) 448.1728, found 448.1729.

4.1.4.2. Methyl 3-[2-hydroxy-5-(4-(thiazol-2-ylamino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8s').

To a screw cap vial were added **8s** (52.5 mg, 95.4 μmol) and CH_2Cl_2 (0.96 mL) at rt. A solution of TFA (20% v/v in CH_2Cl_2, total 2.4 mL) was added at rt dropwise while checking by TLC. Upon completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (3 mL), basified with saturated aqueous $NaHCO_3$ (5 mL) to pH 8, and stirred for 30 min. The resulting suspension was filtered, and the filtrate was extracted with $CHCl_3$/IPA (4:1, 3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Purification of filtered solid and crude residue by column chromatography (30:1 CH_2Cl_2/MeOH) yielded **8s'** (31.1 mg, 72%) as a pale yellow solid.

TLC: R_f 0.41 (10:1 CH_2Cl_2/MeOH). mp: 137.0−139.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1H), 10.68 (s, 1H), 8.61 (s, 1H), 8.41 (s, 1H), 8.35 (d, *J* = 2.8 Hz, 1H), 8.04 (d, *J* = 5.6 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 4.0 Hz, 1H), 6.65 (d, *J* = 4.0 Hz, 1H), 4.58 (d, *J* = 5.6 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 167.2, 164.3, 163.2, 156.6, 142.8, 135.0, 134.9, 127.8, 126.2, 126.1, 123.4, 123.0, 119.4, 119.3, 118.2, 118.1, 116.0, 114.3, 104.1, 49.3, 37.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_6O_4S^+$ ([M + H]$^+$) 451.1183, found 451.1183.

4.1.4.3. Methyl 3-[2-hydroxy-5-(4-(imidazol-2-ylamino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8t').

To a screw cap vial were added **8t** (20.6 mg, 32.5 μmol) and CH_2Cl_2 (0.33 mL) at rt. A solution of TFA (20% v/v in CH_2Cl_2, total 1.6 mL) was added at rt dropwise while checking by TLC. Upon completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (3 mL), basified with saturated aqueous $NaHCO_3$ (5 mL) to pH 8, and stirred for 30 min. The resulting suspension was filtered, and the filtrate was extracted with $CHCl_3$/IPA (4:1, 3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Purification of the filtered solid and the crude residue by column chromatography (10:1 CH_2Cl_2/MeOH) yielded **8t'** (14.7 mg, quantitative yield) as an ivory solid.

TLC: R_f 0.14 (5:1 CH_2Cl_2/MeOH (× 2)). mp: 153.0−155.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 2H), 8.56 (s, 1H), 8.40 (t, *J* = 1.2 Hz, 1H), 8.23 (d, *J* = 2.8 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 2H), 4.56 (d, *J* = 6.0 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 165.5, 147.4, 144.6, 139.0, 130.2, 129.2, 125.3, 124.7, 124.1, 121.6, 121.4, 121.2, 120.7, 119.7, 118.8, 115.8, 114.3, 52.2, 38.0. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}N_7O_4^+$ ([M + H]$^+$) 434.1571, found 434.1569.

4.1.4.4. Methyl 3-[2-hydroxy-5-(4-(pyridin-2-ylamino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8u').

To a solution of **8u** (40.0 mg, 73.5 μmol) in CH_2Cl_2 (0.7 mL) was added TFA (168 μL, 2.20 mmol) at 0 °C dropwise and stirred at rt for 1.5 h. After completion of the reaction, water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporation. Purification by column chromatography (15:1 CH_2Cl_2/MeOH) yielded **8u'** (35.1 mg, quantitative yield) as an ivory solid.

TLC: R_f 0.45 (10:1 CH_2Cl_2/MeOH). mp: 140.0−142.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1H), 10.75 (brs, 1H), 8.54 (s, 1H), 8.40 (t, *J* = 2.0 Hz, 1H), 8.34 (d, *J* = 2.8 Hz, 1H), 8.01 (dm, *J* = 4.8 Hz, 1H), 7.97 (dm, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 8.8, 3.2 Hz, 1H), 7.74 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.39 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.99 (brt, *J* = 5.6 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.51 (ddd, *J* = 6.8, 5.2, 1.2 Hz, 1H), 4.59 (d, *J* = 5.2 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 167.1, 166.9, 160.5, 158.0, 147.2, 146.9, 138.1, 137.8, 130.8, 129.2, 129.0, 126.3, 126.1, 126.0, 122.3, 120.7, 120.3, 119.3, 116.4, 113.5, 108.5, 52.4, 37.2. HRMS (ESI) *m/z* calcd for $C_{23}H_{21}N_6O_4^+$ ([M + H]$^+$) 445.1619, found 445.1617.

4.1.4.5. Methyl 3-[2-hydroxy-5-(4-((4-methylpyridin-2-yl)amino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8v').

To a solution of **8v** (60.0 mg, 107 μmol)) in CH_2Cl_2 (1 mL) was added TFA (246 μL, 3.22 mmol) at 0 °C dropwise and stirred at rt for 1.5 h. After completion of the reaction, saturated aqueous $NaHCO_3$ (5 mL) was added at 0 °C to pH 7, basified with 1 *N* NaOH (0.4 mL) to pH 10, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporation. Purification by column chromatography (20:1 CH_2Cl_2/MeOH) yielded **8v'** (15.7 mg, 32%) as a light yellow solid.

TLC: R_f 0.19 (20:1 CH_2Cl_2/MeOH). mp: 132.0−134.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1H), 10.73 (brs, 1H), 8.52 (s, 1H), 8.40 (t, *J* = 1.6 Hz, 1H), 8.34 (d, *J* = 2.8 Hz, 1H), 7.97 (dm, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.87 (d, *J* = 6.0 Hz, 1H), 7.74 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.91 (brt, *J* = 6.0 Hz, 1H), 6.38−6.37 (m, 2H), 4.58 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 167.3, 167.2, 160.9, 158.2, 149.6, 147.1, 146.8, 137.8, 130.9, 129.3, 129.0, 126.4, 126.2, 126.1, 122.4, 120.6, 119.9, 119.5, 116.2, 115.3, 108.6, 52.4, 37.4, 21.2. HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_6O_4^+$ ([M + H]$^+$) 459.1775, found 459.1779.

4.1.4.6. Methyl 3-[2-hydroxy-5-(4-(pyridin-4-ylamino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8w').

To a solution of **8w** (50.0 mg, 91.8 μmol) in CH_2Cl_2 (0.9 mL) was added TFA (229 μL, 2.75 mmol) at 0 °C dropwise and stirred at rt for 1.5 h. After completion of the reaction, saturated aqueous $NaHCO_3$ (5 mL) was added at 0 °C to pH 7, the resulting suspension was filtered and washed with water. The solid was dried in vacuo to afford **8w'** (23.6 mg, 58%) as a light pink solid.

TLC: R_f 0.15 (10:1 CH_2Cl_2/MeOH). mp: 143.0−145.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ 8.31 (d, *J* = 2.8 Hz, 1H), 8.28 (s, 1H), 8.24 (t, *J* = 1.6 Hz, 1H), 7.91 (m, 1H), 7.90 (d, *J* = 7.2 Hz, 2H), 7.81 (dd, *J* = 8.8, 2,8 Hz, 1H), 7.76 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 2H), 4.57 (s, 2H), 3.86 (s, 3H). No ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 165.4, 161.6, 156.8, 143.8, 142.0, 139.2, 130.2, 129.3, 126.3, 125.3, 124.7, 124.2, 121.5, 121.4, 120.7, 119.5, 118.9, 107.6, 52.2, 37.4. HRMS (ESI) *m/z* calcd for $C_{23}H_{21}N_6O_4^+$ ([M + H]$^+$) 445.1619, found 445.1623.

4.1.4.7. Methyl 3-[2-hydroxy-5-(4-(pyrimidin-4-ylamino)methyl-1H-1,2,3-triazol-1-yl)benzamido]benzoate (8x').

To a screw cap vial were added **8x** (30.4 mg, 55.7 μmol) and CH_2Cl_2 (0.56 mL) at rt. A solution of TFA (20% v/v in CH_2Cl_2, total 1.8 mL) was added at rt dropwise while checking by TLC. Upon completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (3 mL), basified with saturated aqueous $NaHCO_3$ (5 mL) to pH 8, and stirred for 30 min. The resulting suspension was filtered, and the filtrate was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Purification of the filtered solid and the crude residue by column chromatography (20:1 CH_2Cl_2/MeOH) yielded **8x'** (22.6 mg, 91%) as a white solid.

TLC: R_f 0.15 (20:1 CH_2Cl_2/MeOH). mp: 231.2−233.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1H), 8.59 (s, 1H), 8.46 (s, 1H), 8.40 (t, *J* = 2.0 Hz, 1H), 8.32 (s, 1H), 8.07 (brs, 1H), 7.97 (dm, *J* = 8.0 Hz, 1H), 7.94−7.84 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.14 (brs, 1H), 6.56 (d, *J* = 6.0 Hz, 1H), 4.63 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.5, 161.5, 158.1, 154.0, 145.7, 138.6, 130.2, 129.3, 128.3, 125.5, 125.2 (2C), 124.7, 121.2, 121.1 (2C), 118.9, 118.5, 52.2, 35.2. HRMS (ESI) *m/z* calcd for $C_{22}H_{20}N_7O_4^+$ ([M + H]$^+$) 446.1571, found 446.1576.

4.2. Enzyme screening

The kinase assays were conducted by 'HotSpot' kinase assay platform at Reaction Biology Corporation (Malvern, PA, USA). Following base reaction buffer was used: 20 mM Hepes (pH 7.5), 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.02 mg/mL BSA, 0.1 mM Na_3VO_4, 2mM DTT, 1% DMSO. The reaction procedure used is as follows: the required cofactor for the enzymatic reaction was added to a freshly prepared buffer solution, followed by the addition of the Aurora kinase at a concentration of 20 μM. The contents were mixed gently, and the compound dissolved in DMSO was added to the reaction mixture at 10 μM concentration. Compounds were evaluated in a 10-dose IC_{50} mode with 3-fold serial dilution starting at 30 μM for IC_{50} determination. ^{33}P-ATP (specific activity 10 μCi/L) was added to the mixture to initiate the reaction, and the mixture was incubated at room temperature for 2 h. Staurosporine was used as the control compound in a five-dose IC_{50} mode with 10-fold serial dilutions starting at 20 μM, and the reaction was carried out at 10 μM ATP concentration.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and future Planning (NRF-2015R1A2A2A01004511).

References and notes

1. Pollard, J. R.; Mortimore, M. *J. Med. Chem.* **2009**, *52*, 2629.
2. Carvajal, R. D.; Tse, A.; Schwartz, G. K. *Clin. Cancer Res.* **2006**, *12*, 6869.
3. (a) Katayama, H.; Brinkley, W. R.; Sen, S. *Cancer Metastasis Rev.* **2003**, *22*, 451; (b) Ota, T.; Suto, S.; Katayama, H.; Han, Z.-B.; Suzuki, F.; Maeda, M.; Tanino, M.; Terada, Y.; Tatsuka, M. *Cancer Res.* **2002**, *62*, 5168.
4. (a) Carmena, M.; Earnshaw, W. C. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 842; (b) Marumoto, T.; Zhang, D.; Saya, H. *Nat. Rev. Cancer* **2005**, *5*, 42.
5. Lee, E. C. Y.; Frolov, A.; Li, R.; Ayala, G.; Greenberg, N. M. *Cancer Res.* **2006**, *66*, 4996.
6. (a) Murnion, M. E.; Adams, R. R.; Callister, D. M.; Allis, C. D.; Earnshaw, W. C.; Swedlow, J. R. *J. Biol. Chem.* **2001**, *276*, 26656; (b) Adams, R. R.; Wheatleya, S. P.; Gouldsworthy, A. M.; Kandels-Lewis, S. E; Carmena, M.; Smythe, C.; Gerloff, D. L.; Earnshaw, W. C. *Curr. Biol.* **2000**, *10*, 1075.
7. Sasai, K.; Katayama, H.; Stenoien, D. L.; Fujii, S.; Honda, R.; Kimura, M.; Okano, Y.; Tatsuka, M.; Suzuki, F.; Nigg, E. A.; Earnshaw, W. C.; Brinkley, W. R.; Sen, S. *Cell Motil. Cytoskeleton* **2004**, *59*, 249.
8. Harrington, E. A.; Bebbington, D.; Moore, J.; Rasmussen, R. K.; Ajose-Adeogun, A. O.; Nakayama, T.; Graham, J. A.; Demur, C.; Hercend, T.; Diu-Hercend, A.; Su, M.; Golec, J. M.; Miller, K. M. *Nat. Med.* **2004**, *10*, 262.
9. (a) Oslob, J. D.; Yu, C. H. PCT Int. Pat. Appl. WO2007013964, 2007.; (b) Lew, W.; Baskaran, S.; Oslob, J. D.; Yoburn, J. C.; Zhong, M. PCT Int. Pat. Appl. WO2006036266, 2006.
10. Sloane, D. A.; Trikic, M. Z.; Chu, M. L.; Lamers, M. B.; Mason, C. S.; Mueller, I.; Savory, W. J.; Williams, D. H.; Eyers, P. A. *ACS Chem. Biol.* **2010**, *5*, 563.
11. Shimomura, T.; Hasako, S.; Nakatsuru, Y.; Mita, T.; Ichikawa, K.; Kodera, T.; Sakai, T.; Nambu, T.; Miyamoto, M.; Takahashi, I.; Miki, S.; Kawanishi, N.; Ohkubo, M.; Kotani, H.; Iwasawa, Y. *Mol. Cancer Ther.* **2010**, *9*, 157.
12. Mortlock, A. A.; Foote, K. M.; Heron, N. M.; Jung, F. H.; Pasquet, G.; Lohmann, J. J.; Warin, N.; Renaud, F.; De Savi, C.; Roberts, N. J.; Johnson, T.; Dousson, C. B.; Hill, G. B.; Perkins, D.; Hatter, G.; Wilkinson, R. W.; Wedge, S. R.; Heaton, S. P.; Odedra, R.; Keen, N. J.; Crafter, C.; Brown, E.; Thompson, K.; Brightwell, S.; Khatri, L.; Brady, M. C.; Kearney, S.; McKillop, D.; Rhead, S.; Parry, T.; Green, S. *J. Med. Chem.* **2007**, *50*, 2213.
13. Yoon, J.; Ryu, J.-S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3930.
14. Song, D.; Park, Y.; Yoon, J.; Aman, W.; Hah, J.-M.; Ryu, J.-S. *Bioorg. Med. Chem.* **2014**, *22*, 4855.
15. Oslob, J. D.; Romanowski, M. J.; Allen, D. A.; Baskaran, S.; Bui, M.; Elling, R. A.; Flanagan, W. M.; Fung, A. D.; Hanan, E. J.; Harris, S.; Heumann, S. A.; Hoch, U.; Jacobs, J. W.; Lam, J.; Lawrence, C. E.; McDowell, R. S.; Nannini, M. A.; Shen, W.; Silverman, J. A.; Sopko, M. M.; Tangonan, B. T.; Teague, J.; Yoburn, J. C.; Yu, C. H.; Zhong, M.; Zimmerman, K. M.; O'Brien, T.; Lew, W. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 4880.
16. Zhang, J.; Yang, P. L.; Gray, N. S. *Nat. Rev. Cancer* **2009**, *9*, 28.
17. Li, F.; Park, Y.; Hah, J.-M.; Ryu, J.-S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1083.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at.

Click here to remove instruction text...

Graphical Abstract

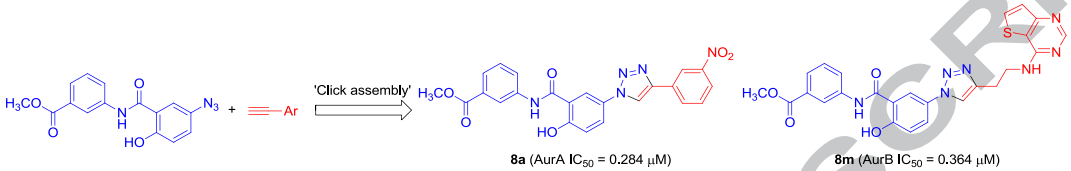
To create your abstract, type over the instructions in the template box below.

Design, synthesis, and evaluation of hinge-binder tethered 1,2,3-triazolylsalicylamide derivatives as Aurora kinase inhibitors

Leave this area blank for abstract info.

Yunkyung Jeong, Jooyeon Lee, and Jae-Sang Ryu*

College of Pharmacy & Graduate School of Pharmaceutical Sciences, Ewha Womans University, 52 Ewhayeodae-gil, Seodaemun-gu, Seoul, 03760, Republic of Korea



Fonts or abstract dimensions should not be changed or altered.