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PII: S0968-0896(15)30150-4
DOI: http://dx.doi.org/10.1016/j.bmc.2015.11.027
Reference: BMC 12675

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 26 October 2015
Revised Date: 17 November 2015
Accepted Date: 20 November 2015

Please cite this article as: Zhang, H., Xin, M-H., Xie, X-X., Mao, S., Zuo, S-J., Lu, S-M., Zhang, S-Q., Synthesis and antitumor activity evaluation of PI3K inhibitors containing 3-substituted quinazolin-4(*3H*)-one moiety, *Bioorganic & Medicinal Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bmc.2015.11.027

Synthesis and antitumor activity evaluation of PI3K inhibitors containing 3-substituted quinazolin-4(*3H*)-one moiety

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Abstract

In present study, a series of *N*-(2-methoxy-5-(3-substituted quinazolin-4(*3H*)-one-6-yl)-pyridin-3-yl)phenylsulfonamide were synthesized. Their antiproliferative activities *in vitro* were evaluated via MTT assay against HCT116 and MCF-7 cancer cell lines. The SAR of title compounds was discussed. The compounds **(*S*)-C5** and **(*S*)-C8** displayed potent inhibitory activity against PI3Ks and mTOR, especially against PI3Kα. In addition, compound **(*S*)-C5** can efficaciously inhibit tumor growth in a mice S-180 model. These findings suggest that our designed compounds can serve as potent PI3K inhibitors and effective anticancer agents.

Key Words quinazolin-4(*3H*)-ones ∗ synthesis ∗ PI3K inhibitor ∗ antitumor activity

1. Introduction

PI3K/AKT/mTOR signal transduction pathway is an important signaling pathway, playing key regulatory roles in many cellular processes, including cell growth, proliferation, differentiation, motility and survival.[1] Dysregulated expression of PI3K/AKT/mTOR signal transduction pathway is linked to development of many cancers.[2] Therefore, the compounds that inhibit the PI3K/AKT/mTOR signal transduction pathway has been regarded to have great potential for treatment of malignant tumors. PI3Kα and mTOR are the key nodes of the PI3K/AKT/mTOR pathway, which have been identified as promising druggable targets in this pathway for cancer therapy.[3,4] Recently, several PI3K inhibitors and PI3K/mTOR dual inhibitors have been in clinical development.[5,6] Among the reported PI3K/mTOR dual inhibitors, *N*-(5-(quinilin-6-yl)-pyridin-3-yl)phenylsulfonamide derivatives are a class of PI3K/mTOR dual inhibitors with potent anticancer activity *in vitro* and *in vivo*. The two ring nitrogen atoms in pyridine and quinoline ring are the main components of pharmacophore. GlaxoSmithKline discovered GSK2126458 (Figure 1) as a potent, orally bioavailable PI3Kα and mTOR dual inhibitor.[7] Amgen designed, synthesized and evaluated several classes of *N*-(2,5-disubstituted-pyridin-3-yl) phenylsulfonamides, and discovered that compound **A** (Figure 1) is potent PI3K/mTOR dual inhibitor.[8] According to the X-ray co-crystal structure of PI3Kγ with GSK2126458, we proposed that the structure of an amide group may take the place of the water molecule bridge. Thereupon, we synthesized a series of 2-substituted-3- phenylsulfonylamino-5-(quinazolin-6-yl or quinolin-6-yl)benzamides as novel PI3K/mTOR inhibitors.[9] Later, we discovered another novel PI3K/mTOR inhibitors as potent anticancer agents by combining of the benzamide moiety with 2-aminobenzothiazole.[10] However, the emerging clinical data show limited single-agent activity of the inhibitors targeting PI3K, AKT or mTOR at tolerated doses.[11] Some candidates displayed off-target effects or dose-limiting toxicities.[12] Recently, we disclosed the structures of PI3K/mTOR dual inhibitors with low toxicity.[13,14] It has been reported that PI3K/mTOR dual inhibitor VS-5584 can

preferentially targets cancer stem cells.[15] This discovery may potentially bring a breakthrough to the treatment of cancer with PI3K/mTOR dual inhibitor. Therefore, The development of new PI3K/mTOR dual inhibitors with reduced toxicity and increased efficacy is still needed.

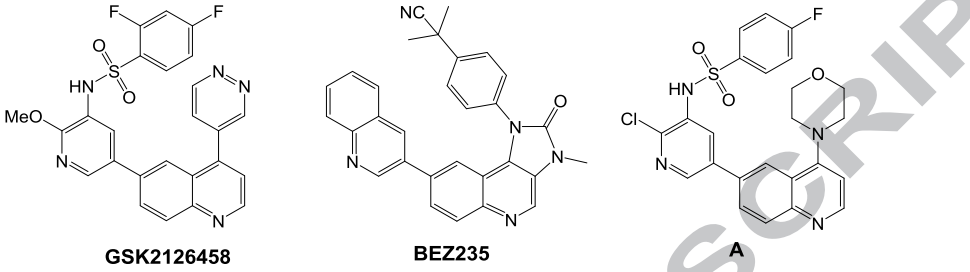


Figure 1. The structures of PI3K and mTOR dual inhibitors

Quinazoline and quinazolin-4(*3H*)-one have been regarded as two important drug scaffolds in drug discovery. Many launched drugs or clinical drug candidates contain quinazoline and quinazolin-4(*3H*)-one framework, such as gefitinib, erlotinib, lapatinib, and several other clinical EGFR-TKIs.[16,17] Furthermore, the quinazolin-4(3*H*)-one derivatives are reported to exhibit a broad spectrum of biological activities, such as antitumor, antimicrobial, antifungal, anti-inflammatory, anticonvulsant, antidiabetic and antihypertensive activities.[18-22] Recently, Several PI3K inhibitors bearing a quinazolin-4(*3H*)-one moiety were mentioned.[23] In an attempt to develop novel anticancer agents, we intend to replace the quinoline moiety in compound **A** with 3-substituted quinazolin-4(*3H*)-one to search for the novel PI3K/mTOR dual inhibitors containing 3-substituted quinazolin-4(*3H*)-one moiety and probe their structure-activity relationship (Figure 2). In this paper, we describe the synthesis, biological activities evaluation of *N*-(2-methoxy-5-(3-substituted quinazolin-4(*3H*)- one-6-yl)-pyridin-3-yl)phenylsulfonamide *in vitro* and *in vivo*.

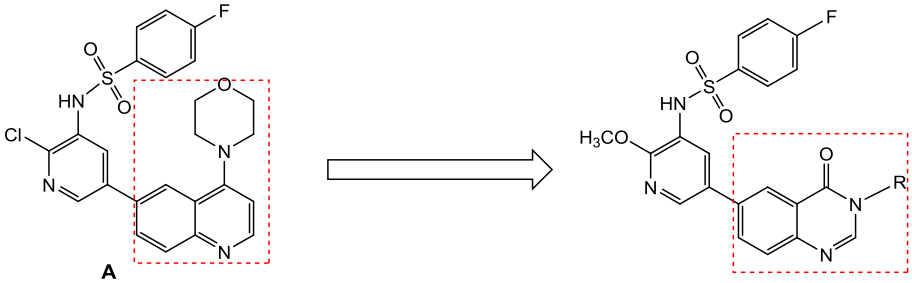
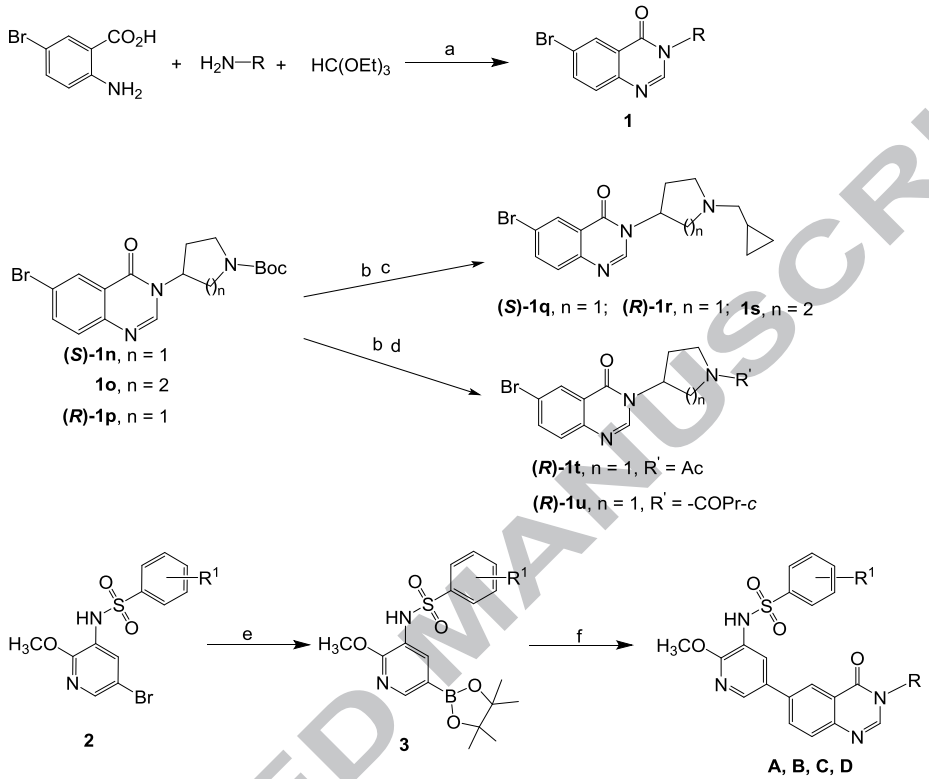


Figure 2. The design of title compounds

2. Results and discussion

2.1. Synthesis of designed compounds

The synthetic route of compounds **A**, **B**, **C** and **D** is outlined in Scheme 1.

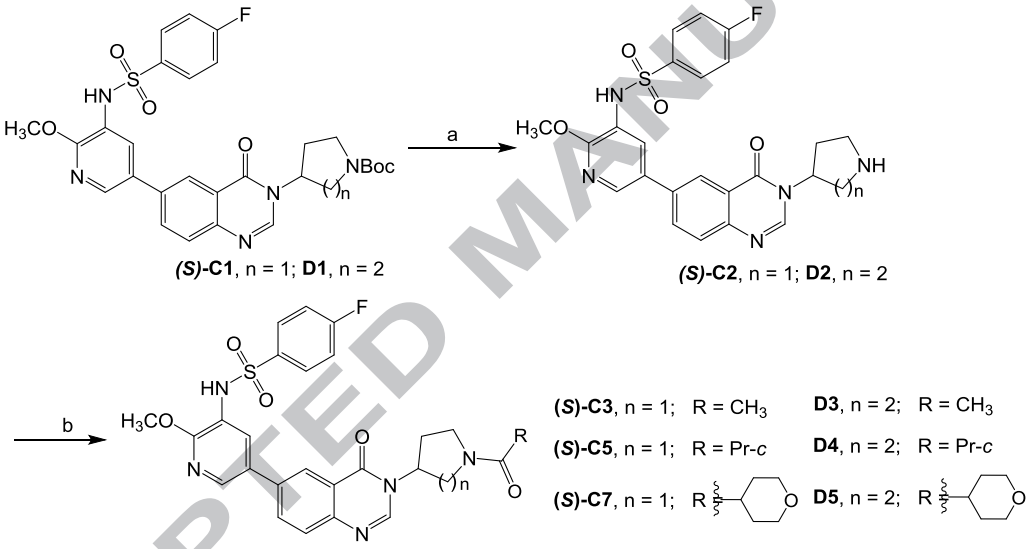


Scheme 1. Reagents and conditions: (a) EtOH, I_2, reflux, 4–6 h, 45.2%–83.4%; (b) TFA/DCM, r.t., 2 h; (c) cyclopropylformaldehyde, $NaBH(OAc)_3$, AcOH, DCE, r.t., overnight, 37.7%–90.6% (two steps); (d) AcOH or *c*-$PrCO_2H$, HATU, DIPEA, DCM, reflux, 2 h, 75.0%–86.0% (two steps); (e) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, 1,4-dioxane, reflux, 2 h; (f) **1a**–(*R*)-**1u,** $PdCl_2$(dppf), Na_2CO_3 or K_2CO_3, DME/H_2O, reflux, 4–6 h, 42.5%–83.1% (two steps).

Commercially available 2-amino-5-bromobenzoic acid, triethyl orthoformate and amine were refluxed in ethanol for 4-6 h to produce the intermediates **1a**–**1m, (*S*)-1n, 1o, (*R*)-1p**.[22] The intermediates **(*S*)-1q**, **(*R*)-1r**, and **1s** was prepared, respectively, from intermediates **(*S*)-1n**, **1o** and **(*R*)-1p** by the remove of *N*-Boc with TFA and reductive amination with cyclopropylformaldehyde in the presence of sodium triacetoxyborohydride. Similarly, intermediates **(*R*)-1t** and **(*R*)-1u** was synthesized by the remove of *N*-Boc in intermediate **(*R*)-1p** with TFA and acylation with acetic acid or cyclopropyl formic acid in the presence of HAUT and DIPEA, respectively. The phenylsulfonamides **2** were prepared from 2-amino-5-bromopyridine according to the steps reported in our previous work.[24] Catalyzed by $PdCl_2$(dppf), intermediate **2** reacted with bis(pinacolato)diboron to yield corresponding arylboronic esters **3**.

Without isolation of the **3**, intermediate **1**, $PdCl_2$(dppf), water and potassium carbonate as well were added to the above reaction mixture. The resulted mixture was refluxed to produce the designed compounds **A**, **B**, **C** or **D**. The preparation of arylboronic esters and Suzuki coupling were completed in one pot.

Compound **(*S*)-C1** and **D1** were synthesized according to the scheme 1. The remove of *N*-Boc in **(*S*)-C1** and **D1** with TFA produced, respectively, **(*S*)-C2** and **D2**, which were acylated with acetic acid, cyclopropyl formic acid or tetrahydro-*2H*-pyran-4-carboxylic acid to produce title compounds **(*S*)-C3, (*S*)-C5, (*S*)-C7** and **D3**–**D5** (Scheme 2).



Scheme 2. Reagents and conditions: (a) TFA/DCM, r.t., 2 h, 46.0%–61.7%.; (b) RCO_2H, HATU, DIPEA, DCM, reflux, 2 h, 45.8%–94.9%.

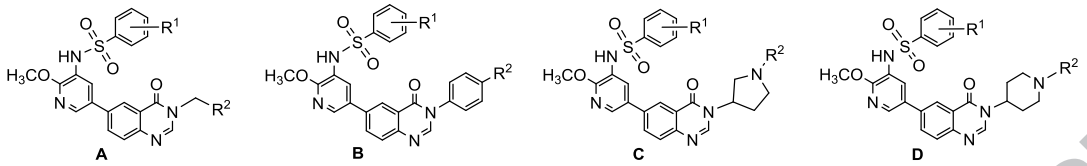
The newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.

2.2. Biological evaluations

2.2.1. Antiproliferative assays *in vitro*

We first evaluated the antiproliferative activities of synthesized compounds against human colon carcinoma cell line (HCT-116, PI3CA mutant: H1047R), human breast adenocarcinoma carcinoma cell line (MCF-7, PI3CA mutant: E545K) by applying the MTT colorimetric assay. The PI3K/mTOR dual inhibitors **BEZ235** was used as the positive controls. The results are summarized in Table 1.

Table 1 Antiproliferative activities of compounds **A**, **B**, **C** and **D** ($\bar{x} \pm s$, n = 3)



Compds	R^1	R^2	IC_{50} (μM)	
			HCT-116	MCF-7
A1	4-F	$CH_2CH_2CH_3$	4.06±0.72	3.93±0.20
A2	4-F	$CH_2N(CH_3)_2$	2.69±0.16	3.72±0.32
A3	4-F	$CH_2N(CH_2CH_3)_2$	1.20±0.25	2.34±0.20
A4	4-F	$CH_2N(CH_2CH_2)_2O$	1.82±0.24	3.20±0.13
A5	4-F	$CH_2N(CH_2CH_2)_2NCH_3$	1.45±0.28	3.00±0.25
A6	4-F	$CH_2N(CH_2)_4$	2.64±0.27	3.82±0.26
A7	4-F	$CH_2N(CH_2)_5$	2.75±0.15	2.95±0.18
A8	4-Cl	$CH_2N(CH_2CH_2)_2O$	2.02±0.16	4.14±0.61
A9	4-CH_3	$CH_2N(CH_2CH_2)_2O$	1.35±0.17	3.48±0.24
A10	2,4-di-F	$CH_2N(CH_2CH_3)_2$	1.03±0.18	2.59±0.21
A11	F	Ph	4.74±0.36	5.90±0.78
A12	F	Ph-4-OCH_3	2.80±0.41	3.34±0.28
A13	F	Py-4	2.95±0.52	1.84±0.33
A14	F	Py-3	1.29±0.23	1.78±0.20
B1	F	$CH_2N(CH_2CH_2)_2O$	1.42±0.32	3.49±0.57
B2	F	$CH_2N(CH_2CH_2)_2NCH_3$	1.25±0.06	4.60±0.95
(*S*)-C1	F	Boc	0.66±0.10	2.73±0.50
(*S*)-C2	F	H	1.46±0.16	2.77±0.24
(*S*)-C3	F	Ac	1.25±0.21	2.52±0.17
(*R*)-C4	F	Ac	4.72±0.71	2.45±0.11
(*S*)-C5	F	COPr-c	0.71±0.03	2.36±0.25
(*R*)-C6	F	COPr-c	6.09±1.04	2.26±0.20
(*S*)-C7	F	$COCH(CH_2CH_2)_2O$	0.60±0.14	1.62±0.30
(*S*)-C8	F	CH_2Pr-c	0.67±0.07	1.03±0.21
(*R*)-C9	F	CH_2Pr-c	4.88±0.34	2.03±0.03
D1	F	Boc	1.53±0.13	4.36±0.44
D2	F	H	1.15±0.12	1.67±0.17
D3	F	Ac	1.30±0.25	2.63±0.30
D4	F	COPr-c	1.35±0.09	2.73±0.41
D5	F	$COCH(CH_2CH_2)_2O$	0.96±0.06	2.90±0.23
D6	F	CH_2Pr-c	1.22±0.06	2.26±0.20
BEZ235			0.56±0.06	1.09±0.15

As expected, all compounds exhibited significant antiproliferative activities

against HCT-116 and MCF-7 with an IC_{50} of 0.41–6.09 μM and 1.62–5.90 μM, respectively. Compared with compound **A1** (IC_{50} = 4.06 μM against HCT-116, 3.93 μM against MCF-7), compounds **A2**–**A7** (IC_{50} = 1.20–2.75 μM against HCT-116, 2.34–3.82 μM against MCF-7) with tertiary amines at the 3-position of quinazolin-4(3*H*)-one displayed a slight increase in cell-based activity against both HCT-116 and MCF-7. This data indicate that polar group were preferred in this region. As the lipophilicity of the substituent R^2 increased in going from dimethylaminoethyl (**A2**, IC_{50} = 2.69 μM against HCT-116, 3.72 μM against MCF-7) to phenyl (**A11**, IC_{50} = 4.74 μM against HCT-116, 5.90 μM against MCF-7), the drops of cellular activity was observed. However, substituted phenyl (**A12**, **B1** and **B2**) or pyridinyl (**A13** and **A14**) at the 3-position of quinazolin-4(3*H*)-one were well tolerated. This results suggest that the reducing lipophilicity of the substitutes at the 3-position of quinazolin-4(3*H*)-one may improve the antiproliferative activity. When the R^1 in compounds **A** changed from 4-F (**A3**, **A4**) to 4-Cl (**A8**), 4-CH_3 (**A9**) and 2,4-di-F (**A10**), the compounds displayed the similar potency. These results are consistent with the observation in our previous work.[30] Compounds **C** with different 1-substituted pyrrolidin-3-yl attached to the 3-position of quinazolin-4(3*H*)-one moiety displayed significantly different antiproliferative activity. The compounds **((*S*)-C3**, (*S*)-C5 and **(*S*)-C8**) with a (*S*)-1-substituted pyrrolidin-3-yl exhibit higher activity than the compounds (**(*R*)-C4**, **(*R*)-C6** and **(*R*)-C9**) with a (*R*)-1-substituted pyrrolidin-3-yl. We also noticed that the activity of compound **(*S*)-C8** displayed 8-fold to compound **(*R*)-C9** against HCT-116 cell. The replacement of cyclopropylcarbonyl in **(*S*)-C5** with cyclopropylmethyl produced compounds **(*S*)-C8**, which showed an improved antiproliferative activity against HCF-7 cells. Furthermore, the replacement of pyrrolid-3-yl in compounds C with piperid-4-yl gave compounds D, which displayed a drop in cell-based activity. Building on the discussions above, we consider that (*S*)-1-substituted pyrrolidin-3-yl moiety is the suitable substituent at the 3-position of quinazolin-4(*3H*)-one moiety. To be worth mention, the potency of compounds **(*S*)-C5**, and **(*S*)-C8** are comparable to that of positive drug **BEZ235** against HCT-116. Therefore, we investigated these compounds in next study.

2.2.2. PI3K and mTOR enzymatic activity assay

Next, to elucidate the mechanism of antiproliferative activities of title compounds, compounds **(*S*)-C5** and **(*S*)-C8** were selected to evaluate their inhibitory activity against PI3Ks and mTOR by performing an ATP depletion assay.[25,26] **BEZ235** was used as the positive drug. The data are listed in Table 2.

Table 2 Inhibitory activity of **(*S*)-C5** and **(*S*)-C8** against PI3Ks and mTOR (n = 2)

Compds	IC_{50} (nM)				
	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ	mTOR
(*S*)-C5	7.3	209	116	106	208
(*S*)-C8	6.7	24	181	21	114
BEZ235	89	421	169	204	97

The data in Table 2 indicated compounds **(*S*)-C5** and **(*S*)-C8** displayed remarkable potency against PI3Ks and mTOR, especially against PI3Kα. The inhibitory activities of compounds **(*S*)-C5** and **(*S*)-C8** against PI3Kα were 7.3 nM and 6.7 nM respectively, which are approximately 10-fold more potent than that of **BEZ235**. The replacement of cyclopropylcarbonyl in **(*S*)-C5** with cyclopropylmethyl produced compounds **(*S*)-C8**, which displayed an improved inhibitory activity against PI3Kβ, PI3Kδ and mTOR. These results suggest that compounds **(*S*)-C5** and **(*S*)-C8** are potent selective PI3Kα inhibitors.

Considering PIK3CA mutations in both HCT-116 and MCF-7, the excellent potency of compounds **(*S*)-C5** and **(*S*)-C8** on PI3Kα further supported the significant antiproliferative activities of compounds **(*S*)-C5** and **(*S*)-C8** against HCT-116 and MCF-7. Compounds **(*S*)-C5** and **(*S*)-C8** exhibited more potent activities than **BEZ235** in enzyme-based activities, but similar activities in cell based-activity. These differences may relate to other property of compounds **(*S*)-C5** and **(*S*)-C8**, such as their undesirable cell permeability.

2.2.3. Anticancer effect in the mice S-180 homograft models *in vivo*

Compound **(*S*)-C5** displayed potent antiproliferative activity and inhibitory activity against PI3Kα. Thus, we evaluated whether compound **(*S*)-C5** could inhibit tumor growth *in vivo*. A study using mice bearing sarcoma S-180 was performed. Compound **(*S*)-C5** was dissolved in DMSO : PEG400 : 5% glucose injection (1 : 7 : 2, V/V/V) and dosed orally at 20 mg/kg or 40 mg/kg once a day for 8 days. Considering that it is difficult to measure the volumes of S-180 tumor, tumor weights were used as evaluating indicators. The tumor weights and daily body weights were depicted in Figure 3. The inhibitory ratios of compound **(*S*)-C5** at 20 mg/kg and 40 mg/kg were 34.5% and 58.0%, respectively. In addition, the body weight of two dose groups dropped a little in the first few days. These results suggested that compound **(*S*)-C5** is an effective anticancer agent *in vivo*.

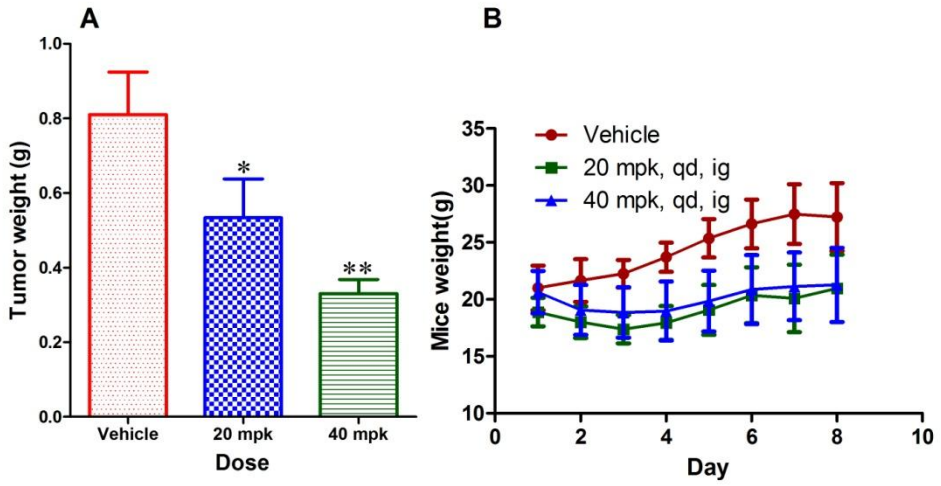


Figure 3. (A) The anticancer effect of compound **(*S*)-C5** in establishing mice S-180 homograft model. $^{*}P < 0.05$ *vs* vehicle; $^{**}P < 0.01$ *vs* vehicle. (B) The change of tested mice body weights. Mice bearing subcutaneous cancers were orally administered solvent, compound **(*S*)-C5** (20 mg/kg or 40 mg/kg) once daily for 8 days (mpk: mg/kg).

2.3. Docking studies

To further explain the potent activities of compounds **(*S*)-C5** and **(*S*)-C8**, we performed a docking analysis utilizing the C-DOCKER program within Discovery Studio 2.5 software package. Docking simulations were carried out on human PI3Kγ (PDB code 3S2A)[8] with compound **(*S*)-C5** or **(*S*)-C8**, and the results were depicted in Figure 4. From the docking results, we observed that: (1) the nitrogen atom of pyridine ring formed hydrogen bonds via an ordered water molecule with Tyr867 and

Asp841; (2) the two oxygen atoms at 2-position and 3-sulfonamido of pyridine ring simultaneously formed hydrogen bonds with Lys833; (3) the hydrogen atom at the 3-amino of pyridine ring formed a hydrogen bond with Asp964; (4) the 1-nitrogen atom of quinazolin-4(*3H*)-one moiety formed a hydrogen bond with Val882; (5) the oxygen atom from cyclopropylcarbonyl in **(*S*)-C5** formed a hydrogen bond with Lys890 (**Figure 4a**). These formation of hydrogen bonds suggest that both **(*S*)-C5** and **(*S*)-C8** can exactly interact with the catalytic domain of PI3K.

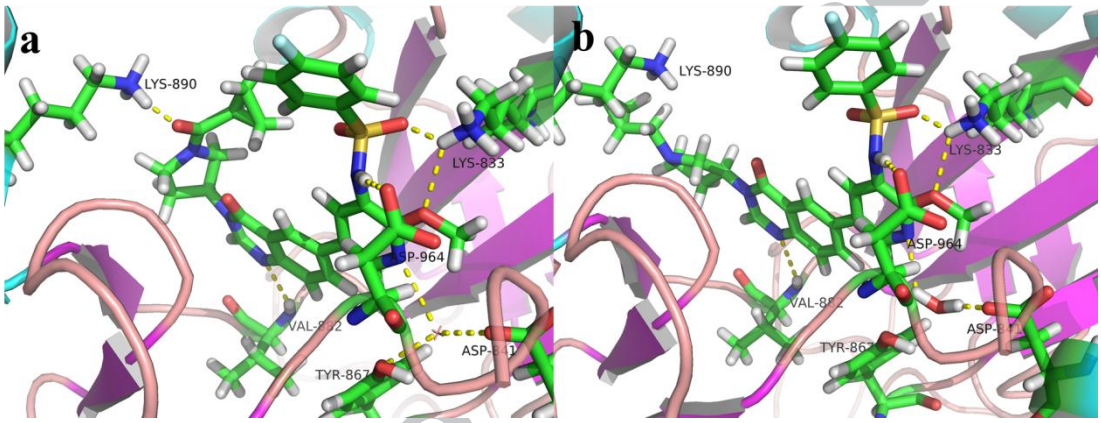


Figure 4. (a) Compound **(*S*)-C5** docked into the ATP-binding site of PI3Kγ (PDB code: 3S2A). (b) Compound **(*S*)-C8** docked into the ATP-binding site of PI3Kγ. **(*S*)-C5** and **(*S*)-C8** is shown as sticks. Hydrogen bonds within 2.5 Å are shown as yellow dashed lines.

3. Conclusion

In present study, a series of *N*-(2-methoxy-5-(3-substituted quinazolin-4(*3H*)-one-6-yl)-pyridin-3-yl)-phenyl sulfonamides were synthesized and characterized. All compounds exhibited significant antiproliferative activities against HCT-116 and MCF-7. The discussion of SAR revealed that the antiproliferative activity is closely related to the substituted group at the 3-position of quinazolin-4(*3H*)-one moiety. The compounds **(*S*)-C5** and **(*S*)-C8** displayed potent inhibitory activity against PI3Ks and mTOR, especially against PI3Kα. In addition, compound **(*S*)-C5** can efficaciously inhibit tumor growth in a mice S-180 model. These results suggest that our designed compounds can serve as potent PI3K inhibitors and effective anticancer agents.

4. Experimental

4.1. Chemistry and chemical methods

Unless specified otherwise, all starting materials, reagents and solvents were commercially available. All reactions were monitored by thin-layer chromatography on silica gel plates (GF-254) and visualized with UV light. All the melting points were determined on a Shanghai micro melting-point apparatus (model: SGW® X-4B) and thermometer was uncorrected. NMR spectra were recorded on a 400 Bruker NMR spectrometer with tetramethylsilane (TMS) as an internal reference. All chemical shifts are reported in parts per million (ppm). High-resolution mass measurements were performed using electrospray ionization (positive mode) on a quadrupole time-of-flight (QTOF) mass spectrometer (Maxis Q-TOF, Bruker Inc.).

4.1.1. General procedures for the synthesis of intermediates 1a-1p

The mixture of 2-amino-5-bromobenzoic acid (1.00 g, 4.63 mmol), triethyl orthoformate (1.00 mL, 6.02 mmol), amine (6.02 mmol), iodine (0.12 g, 0.046 mmol) and anhydrous ethanol (20 mL) was refluxed under nitrogen atmosphere for 4–6 h, then concentrated under vacuum to give a residue which was dissolved in ethyl acetate (90 mL). The ethyl acetate solution was washed with 1 N aqueous sodium hydroxide (20 mL×3) and brine (30 mL×3), dried over anhydrous sodium sulfate and concentrated to give a white or light yellow solid.

4.1.1.1. 6-Bromo-3-butylquinazolin-4(*3H*)-one (1a)

White solid; Yield 56.2%; mp: 112.0–113.5 °C. ^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.59 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.00 (t, *J* = 7.4 Hz, 2H, CH_2), 1.81–1.73 (m, 2H, CH_2), 1.47–1.35 (m, 2H, CH_2), 0.97 (t, *J* = 7.3 Hz, 3H, CH_3). ESI-MS *m/z*: 280.9 $[M + H]^+$.

4.1.1.2. 6-Bromo-3-(2-(dimethylamino)ethyl)quinazolin-4(*3H*)-one (1b)

Light yellow solid; Yield 83.9%; mp: 58.9–60.5 °C. ^{1}H NMR ($CDCl_3$) δ 8.43 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.06 (s, 1H, Ar-H), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.57 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.07 (t, *J* = 6.0 Hz, 2H, CH_2), 2.65 (t, *J* = 6.0 Hz, 2H, CH_2), 2.29 (s, 6H, $NCH_3\times2$). ESI-MS *m/z*: 295.9 $[M + H]^+$.

4.1.1.3. 6-Bromo-3-(2-(diethylamino)ethyl)quinazolin-4(*3H*)-one (1c)

White solid; Yield 78.0%; mp: 57.9–59.8 °C. ^{1}H NMR ($CDCl_3$) δ: 8.44 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.06 (s, 1H, Ar-H), 7.81 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.57 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.00 (t, *J* = 5.8 Hz, 2H, CH_2), 2.74 (t, *J* = 5.8 Hz, 2H, CH_2), 2.52 (q, *J* = 7.1 Hz, 4H, $C\underline{H}_2CH_3$), 0.91 (t, *J* = 7.1 Hz, 6H, $CH_2C\underline{H}_3$). ESI-MS *m/z*: 324.0 $[M + H]^+$.

4.1.1.4. 6-Bromo-3-(2-(4-morpholino)ethyl)quinazolin-4(*3H*)-one (1d)

Light yellow solid; Yield 81.4%; mp: 109.0–111.0 °C. ^{1}H NMR ($CDCl_3$) δ: 8.43 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.06 (s, 1H, Ar-H), 7.83 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.58 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.10 (t, 2H, NCH_2), 3.78–3.56 (m, 4H, $OCH_2\times2$), 2.72 (t, 2H, NCH_2), 2.52 (s, 4H, $NCH_2\times2$). ESI-MS *m/z*: 338.0 $[M + H]^+$.

4.1.1.5. 6-Bromo-3-(2-(4-methylpiperazin-1-yl)ethyl)quinazolin-4(*3H*)-one (1e)

Light yellow solid; Yield 28.7%; mp: 103.2–105.4 °C. ^{1}H NMR ($CDCl_3$) δ: 8.43 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 7.82 (dd, *J* = 8.7, 2.2 Hz, 1H, Ar-H), 7.58 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.07 (t, *J* = 5.8 Hz, 2H, CH_2), 2.70 (t, *J* = 5.8 Hz, 2H, CH_2), 2.65–2.31 (m, 8H, NCH_2), 2.28 (s, 3H, NCH_3). ESI-MS *m/z*: 351.1 $[M + H]^+$.

4.1.1.6. 6-Bromo-3-(2-(pyrrolidin-1-yl)ethyl)quinazolin-4(*3H*)-one (1f)

White solid; Yield 80.5%; mp: 82.3–84.4 °C. ^{1}H NMR ($CDCl_3$) δ 8.43 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.57 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.11 (t, *J* = 6.2 Hz, 2H, CH_2), 2.84 (t, *J* = 6.2 Hz, 2H, CH_2), 2.58 (t, 4H, NCH_2), 1.83–1.72 (m, 4H, CH_2). ESI-MS *m/z*: 322.0 $[M + H]^+$.

4.1.1.7. 6-Bromo-3-(2-(piperidin-1-yl)ethyl)quinazolin-4(*3H*)-one (1g)

White solid; Yield 80.1%; mp: 62.6–64.8 °C. ^{1}H NMR ($CDCl_3$) δ 8.43 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.57 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.07 (t, *J* = 5.9 Hz, 2H, CH_2), 2.64 (t, *J* = 5.9 Hz, 2H, CH_2), 2.43 (t, 4H, NCH_2), 1.58–1.50 (m, 4H, CCH_2), 1.46–1.37 (m, 2H, CH_2). ESI-MS *m/z*: 336.1 $[M + H]^+$.

4.1.1.8. 3-Benzyl-6-bromoquinazolin-4(*3H*)-one (1h)

White solid; Yield 48.63%; mp: 126.0–128.0 °C. ^{1}H NMR ($CDCl_3$) δ 8.37 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 7.74 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.50 (d, *J*

= 8.7 Hz, 1H, Ar-H), 7.33–7.14 (m, 5H, Ar-H), 5.11 (s, 2H, CH_2). ESI-MS *m/z*: 314.9 $[M + H]^+$.

4.1.1.9. 6-Bromo-3-(4-methoxybenzyl)quinazolin-4(*3H*)-one (1i)

White solid; Yield 75.0%; mp: 129.6–131.7 °C. ^{1}H NMR ($CDCl_3$) δ 8.45 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.57 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.31 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.91–6.85 (m, 2H, Ar-H), 5.12 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3). ESI-MS *m/z*: 345.0 $[M + H]^+$.

4.1.1.10. 6-Bromo-3-(pyridin-4-ylmethyl)quinazolin-4(*3H*)-one (1j)

White solid; Yield 71.43%; mp: 116.5–118.6 °C. ^{1}H NMR (DMSO-d_6) δ 8.61 (s, 1H, Ar-H), 8.53 (dd, *J* = 4.6, 1.4 Hz, 1H, Ar-H), 8.24 (d, *J* = 2.4 Hz, 2H, Ar-H), 8.02 (dd, *J* = 8.7, 2.4 Hz, 1H, Ar-H), 7.69 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.30 (d, *J* = 6.0 Hz, 2H, Ar-H), 5.25 (s, 2H, CH_2). ESI-MS *m/z*: 315.9 $[M + H]^+$.

4.1.1.11. 6-Bromo-3-(pyridin-3-ylmethyl)quinazolin-4(*3H*)-one (1k)

White solid; Yield 76.1%; mp: 158.0–159.8 °C. ^{1}H NMR ($CDCl_3$) δ 8.69 (s, 1H, Ar-H), 8.60 (d, *J* = 4.1 Hz, 1H, Ar-H), 8.44 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 7.84 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.74 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.59 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.31 (dd, *J* = 7.8, 4.8 Hz, 1H, Ar-H), 5.20 (s, 2H, CH_2). ESI-MS *m/z*: 315.9 $[M + H]^+$.

4.1.1.12. 6-Bromo-3-(4-(morpholinomethyl)phenyl)quinazolin-4(*3H*)-one (1l)

White solid; Yield 16.22%; mp: 152.1–153.9 °C. ^{1}H NMR ($CDCl_3$) δ: 8.49 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 7.88 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.64 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.55 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.37 (d, *J* = 8.3 Hz, 2H, Ar-H), 3.76 (s, 4H, OCH_2), 3.60 (s, 2H, NCH_2), 2.52 (s, 4H, , NCH_2). ESI-MS *m/z*: 400.1 $[M+H]^+$. ESI-MS *m/z*: 400.0 $[M + H]^+$.

4.1.1.13. 6-Bromo-3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)quinazolin-4(*3H*)-one (1m)

Light yellow solid; Yield 66.5%; mp: 119.8–122.5 °C. ^{1}H NMR ($CDCl_3$) δ: 8.48 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 7.88 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.64 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.52 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.3 Hz, 2H, Ar-H), 3.58 (s, 2H, CH_2), 2.52–2.43 (m, 8H, NCH_2), 2.31 (s, 3H, NCH_3). ESI-MS *m/z*:

413.0 $[M + H]^+$.

4.1.1.14. *t*-Butyl (*S*)-3-(6-bromo-4-oxoquinazolin-3(*4H*)-yl)pyrrolidine-1-carboxylate ((*S*)-1n)

White solid; Yield 46.15%; mp: 115.0–117.0 °C. ^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.12–8.06 (m, 1H, Ar-H), 7.85 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.61 (d, *J* = 8.7 Hz, 1H, Ar-H), 5.50–5.32 (m, 1H, CH_2), 3.87 (dd, *J* = 12.3, 7.1 Hz, 1H, CH_2), 3.74–3.68 (m, 1H, CH), 3.59 (s, 2H, CH_2), 2.46–2.36 (m, 1H, CH_2), 2.22 (s, 1H, CH_2), 1.48 (s, 9H, $CH_3\times3$). ESI-MS *m/z*: 394.0 $[M + H]^+$.

4.1.1.15. *t*-Butyl 4-(6-bromo-4-oxoquinazolin-3(*4H*)-yl)piperidine-1-carboxylate (1o)

White solid; Yield 42.54%; mp: 166.8–169.4 °C. ^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 7.84 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.59 (d, *J* = 8.7 Hz, 1H, Ar-H), 5.04–4.89 (m, 1H, CH), 4.35 (s, 2H, CH_2), 2.91 (s, 2H, CH_2), 2.01–1.91 (m, 2H, CH_2), 1.91–1.73 (m, 2H, CH_2), 1.49 (s, 9H, $CH_3 \times 3$). ESI-MS *m/z*: 408.0 $[M + H]^+$.

4.1.1.16. *t*-Butyl (*R*)-3-(6-bromo-4-oxoquinazolin-3(*4H*)-yl)pyrrolidine-1-carboxylate ((*R*)-1p)

White solid; Yield 36.6%; ^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.04–8.12 (m, 1H, Ar-H), 7.85 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.61 (d, *J* = 8.7 Hz, 1H, Ar-H), 5.03–4.87 (m, 1H, CH), 3.87 (dd, *J* = 12.3, 7.1 Hz, 1H, CH_2), 3.75–3.65 (m, 1H, CH_2), 3.59 (s, 2H, CH_2), 2.51–2.33 (m, 1H, CH_2), 2.20 (s, 1H), 1.47 (s, 9H, $CH_3\times3$). ESI-MS *m/z*: 394.1 $[M + H]^+$.

4.1.17. (*S*)-6-Bromo-3-(1-(cyclopropylmethyl)pyrrolidin-3-yl)quinazolin-4(*3H*)-one ((*S*)-1q)

To a solution of **(*S*)-1n** (250 mg, 0.63 mmol) in dichloromethane (DCM, 10 mL), trifluoroacetic acid (TFA, 2 mL) was added. The resulting mixture was stirred at room temperature for 2 h, concentrated under vacuum to give a yellow product, which was dissolved in 1, 2-dichloroethane (DCE, 10 mL), and then cyclopropylformaldehyde (44 mg, 0.63 mmol), $NaBH(OAc)_3$ (200 mg, 0.95 mmol) and AcOH (38 mg, 0.63 mmol) were added. The resulted suspension was stirred overnight, quenched with

aqueous sodium hydrogen carbonate and extracted with DCM twice (30 mL×2). The combined organic phase was washed with brine, and dried over Na_2SO_4, filtered, concentrated in vacuum. The residue was purified by column chromatography on silica gel to produce **(*S*)-1q** as light yellow oil. Yield 90.6%; ^{1}H NMR ($CDCl_3$) δ 8.43 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 7.84 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.59 (d, *J* = 8.6 Hz, 1H, Ar-H), 5.06–4.96 (m, 1H, CH), 3.40–3.30 (m, 2H), 2.44–2.34 (m, 2H, CH_2), 2.12–2.01 (m, 2H), 1.25–1.18 (m, 2H), 0.95–0.83 (m, 1H, cPr-CH), 0.70–0.60 (m, 2H, cPr-CH_2), 0.14–0.12 (m, 2H, cPr-CH_2). ESI-MS *m/z*: 348.0 $[M + H]^+$.

Intermediates **(*R*)-1r** and **1s** were prepared according to the process described in **(*S*)-1q**.

4.1.18. (*R*)-6-Bromo-3-(1-(cyclopropylmethyl)pyrrolidin-3-yl)quinazolin-4(3H)-one ((*R*)-1r)

Light yellow oil; Yield 37.7%; ^{1}H NMR ($CDCl_3$) δ 8.43 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 7.84 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.59 (d, *J* = 8.6 Hz, 1H, Ar-H), 4.98-4.88 (m, 1H, CH), 3.38–3.30 (m, 2H), 2.34–2.30 (m, 2H, CH_2), 2.03–1.97 (m, 2H), 1.25–1.20 (m, 2H), 0.91–0.88 (m, 1H, *c*-Pr-CH), 0.62–0.57 (m, 2H, cPr-CH_2), 0.14–0.12 (m, 2H, cPr-CH_2). ESI-MS *m/z*: 348.0 $[M + H]^+$.

4.1.19. 6-Bromo-3-(1-(cyclopropylmethyl)piperidin-4-yl)quinazolin-4(3H)-one (1s)

White solid; Yield 82.0%; mp: 176.8–178.6 °C. ^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.18 (s, 1H, Ar-H), 7.83 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-H), 7.57 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.90-4.84 (m, 1H, CH), 3.28 (d, *J* = 11.9 Hz, 2H, CH_2), 2.34 (d, *J* = 6.5 Hz, 2H, CH_2), 2.23–2.19 (m, 2H, CH_2), 2.02–1.98 (m, 4H, CH_2), 0.92–0.88 (m, 1H, CH), 0.58–0.53 (m, 2H, CH_2), 0.14–0.12 (m, 2H, CH_2). ESI-MS *m/z*: 362.0 $[M + H]^+$.

4.1.20. (*R*)-3-(1-Acetylpyrrolidin-3-yl)-6-bromoquinazolin-4(3H)-one ((*R*)-1t)

To a solution of **(*R*)-1p** (150 mg, 0.38 mmol) in DCM (8 mL), trifluoroacetic acid (2 mL) was added. The resulting solution was stirred at room temperature for 2 h, concentrated under vacuum to produce crude product, which was dissolved in DCM

(15 mL). Then, acetic acid (30 mg, 0.50 mmol), HATU (570 mg, 1.5 mmol), and DIPEA (1.2 mL) was added. The resulted mixture was refluxed for 2 h. The solvent were removed under vacuum and the residue was purified through a column chromatography on silica gel to produce **(*R*)-1t** as a light yellow solid. Yield 86.0%; mp: 89.0–91.5 °C. ^{1}H NMR ($CDCl_3$) δ 8.43 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.03 (d, *J* = 27.5 Hz, 1H, Ar-H), 7.86 (ddd, *J* = 8.6, 5.0, 2.3 Hz, 1H, Ar-H), 7.59 (dd, *J* = 8.7, 5.5 Hz, 1H, Ar-H), 5.38–5.30 (m, 1H, CH), 4.05–3.99 (m, 1H, CH_2), 3.87–3.82 (m, 1H, CH_2), 3.71–3.66 (m, 2H, CH_2), 2.46–2.41 (m, 2H, CH_2), 2.11 (d, *J* = 18.7 Hz, 3H, $COCH_3$). ESI-MS *m/z*: 335.9 $[M + H]^+$.

Intermediates **(*R*)-1u** was synthesized according to the process described in **(*S*)-1t**.

4.1.20. (*R*)-6-Bromo-3-(1-(cyclopropanecarbonyl)pyrrolidin-3-yl)quinazolin-4(*3H*)-one ((*R*)-1u)

Light yellow oil; Yield 75.0%; ^{1}H NMR ($CDCl_3$) δ 8.43 (s, 1H, Ar-H), 8.06 (d, *J* = 27.7 Hz, 1H, Ar-H), 7.84 (d, *J* = 5.8 Hz, 1H, Ar-H), 7.59 (dd, *J* = 8.2, 5.3 Hz, 1H, Ar-H), 5.42 (s, 1H, CH), 3.99–3.93 (m, 4H, CH_2), 2.48–2.43 (m, 2H, CH_2), 1.63–1.58 (m, 1H, cPr-CH), 1.04–1.02 (m, 2H, *c*-Pr-CH_2), 0.91–0.87 (m, 2H, *c*-Pr-CH_2). ESI-MS *m/z*: 361.9 $[M + H]^+$.

4.2.1. *N*-(5-(3-Butyl-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide (A1)

N-(5-Bromo-2-methoxypyridin-3-yl)-4-arylsulfonamide was prepared as our reported steps.[24] The mixture of *N*-(5-Bromo-2-methoxypyridin-3-yl)-4-fluoro phenylsulfonamide (100 mg, 0.28 mmol), bis(pinacolato)diboron (78 mg, 0.31 mmol), potassium acetate (82 mg, 0.84 mmol), $PdCl_2$(dppf) (16 mg, 0.021 mmol) and 1,4-dioxane (10 mL) was reflux under nitrogen atmosphere for 2 h, then concentrated in vacuum. To the resulted residue was added **1a** (63 mg, 0.25 mmol), K_2CO_3 (116 mg, 0.84 mmol), $PdCl_2$(dppf) (16 mg, 0.021 mmol), 1,2-dimethoxyethane (DME, 10 mL) and water (4 mL). The obtained mixture was refluxed under nitrogen atmosphere for 4 h. The volatile was removed under vacuum and the residue was purified through a column chromatography on silica gel with

dichloromethane /methanol (V:V = 40:1) as eluent to produce **A1** as white solid. yield 61.1%; mp: 176.0–178.0 °C. ^{1}H NMR (DMSO-d_6): δ 10.13 (s, 1H, SO_2NH), 8.45 (s, 1H, Ar-H), 8.39 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.27 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.09 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-H), 7.93 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.85-7.80 (m, 2H, Ar-H), 7.78 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.43 (t, *J* = 8.8 Hz, 2H, Ar-H), 4.01 (t, *J* = 7.2 Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 1.78–1.64 (m, 2H, CH_2), 1.41-1.26 (m, 2H, CH_2), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.5, 157.2, 148.7, 147.8, 142.0, 137.0, 135.4, 132.8, 132.1, 130.3, 130.2, 128.9, 128.6, 123.5, 122.4, 121.0, 116.8, 116.6, 54.0, 46.2, 31.2, 19.8, 14.0. ESI-HRMS *m/z*: calc'd for $C_{24}H_{23}FN_4O_4S$ $[M+H]^+$: 483.1497; found 483.1497.

Compounds **A2**–**A14**, **B1**, **B2**, **(*S*)-C1, (*R*)-C4, (*R*)-C6, (*S*)-C8, (*R*)-C9**, **D1** and **D6** were synthesized according to the process described in **A1**.

4.2.2. *N*-(5-(3-(2-(Dimethylamino)ethyl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide (A2)

Yield 61.18%; mp: 172.0–174.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.09 (s, 1H, SO_2NH), 8.39–8.33 (m, 2H, Ar-H), 8.26 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.08 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.92 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.86–7.79 (m, 2H, Ar-H), 7.77 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.42 (t, *J* = 8.8 Hz, 2H, Ar-H), 4.12 (t, *J* = 5.9 Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 2.61 (t, *J* = 5.9 Hz, 2H, CH_2), 2.23 (s, 6H, CH_3×2). ^{13}C NMR (DMSO-d_6) δ 164.73 (d, J_{C-F} = 250 Hz), 160.6, 157.1, 148.9, 147.7, 141.4, 137.3, 137.2, 135.4, 132.8, 131.5, 130.3, 130.2, 128.8, 128.5, 123.5, 122.4, 121.7, 116.7, 116.5, 57.6, 54.0, 45.6(CH_3×2), 43.87. ESI-HRMS *m/z*: calc'd for $C_{24}H_{25}FN_5O_4S$ $[M+H]^+$: 498.1606; found 498.1606.

4.2.3. *N*-(5-(3-(2-(Diethylamino)ethyl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide (A3)

Yield 74.43%; mp: 157.0–159.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.04 (s, 1H, SO_2NH), 8.37 (d, *J* = 1.6 Hz, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 8.27 (d, 1H, Ar-H), 8.08 (dd, *J* = 8.4 Hz, 1H, Ar-H), 7.92 (d, *J* = 1.6 Hz, 1H, Ar-H), 7.82 (dd, *J* = 8.3, 5.3 Hz, 2H, Ar-H), 7.77 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.42 (t, *J* = 8.7 Hz, 2H, Ar-H), 4.05 (t, *J* = 5.4 Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 2.71 (t, *J* = 5.3 Hz, 2H, CH_2), 0.86 (t, *J* = 7.0 Hz,

6H, CH_3×2). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.7, 157.1, 149.1, 147.7, 141.4, 137.1, 135.3, 132.8, 131.5, 130.3, 130.2, 128.7, 128.5, 123.3, 122.3, 121.6, 116.7, 116.5, 54.0, 50.7, 49.1, 47.2, 44.7, 12.1(CH_3×2). ESI-HRMS *m/z*: calc'd for $C_{26}H_{29}FN_5O_4S$ $[M + H]^+$: 526.1919; found 526.1919.

4.2.4. 4-Fluoro-*N*-(2-methoxy-5-(3-(2-morpholinoethyl)-4-oxo-3,4-dihydroquinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (A4)

Yield 44.35%; mp: 202.0–204.0 °C. ^{1}H NMR (DMSO-d_6): δ 10.06 (s, 1H, SO_2NH), 8.34 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 8.22 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.04 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.88 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.81-7.75 (m, 2H, Ar-H), 7.73 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.37 (t, *J* = 8.8 Hz, 2H, Ar-H), 4.08 (t, *J* = 5.8 Hz, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.53–3.44 (m, 4H, OCH_2×2), 2.59 (t, *J* = 5.8 Hz, 2H, CH_2), 2.41 (s, 4H, NCH_2×2). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.5, 157.2, 149.0, 147.8, 142.0, 137.1, 135.3, 132.8, 132.1, 130.3, 130.2, 128.9, 128.6, 123.6, 122.4, 121.0, 116.8, 116.6, 66.7 (CH_2×2), 56.8, 54.0, 53.7 (CH_2×2), 43.2. ESI-HRMS *m/z*: calc'd for $C_{26}H_{27}FN_5O_5S$ $[M+H]^+$: 540.1705; found 540.1711.

4.2.5. 4-Fluoro-*N*-(2-methoxy-5-(3-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-3,4-dihydroquinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (A5)

Yield 58.75%; mp: 151.0–153.0 °C. ^{1}H NMR (DMSO-d_6) δ 8.37-8.31 (m, *J* = 2.4 Hz, 2H, Ar-H), 8.26 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.08 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.90 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.82 (dd, *J* = 8.8, 5.2 Hz, 2H, Ar-H), 7.77 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.41 (t, *J* = 8.8 Hz, 2H, Ar-H), 4.11 (t, *J* = 5.8 Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 2.64 (t, *J* = 5.8 Hz, 2H, CH_2), 2.42 (s, 4H, CH_2×2), 2.24 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6) δ 172.5, 164.7 (d, J_{C-F} = 250 Hz), 160.5, 157.2, 149.0, 147.8, 141.0, 137.5, 135.5, 132.8, 131.3, 130.2, 130.1, 128.8, 128.6, 123.5, 122.4, 122.2, 116.7, 116.5, 56.1, 54.9 (CH_2×2), 53.9, 52.5 (CH_2×2), 45.5, 43.4. ESI-HRMS *m/z*: calc'd for $C_{27}H_{30}FN_6O_4S$ $[M+H]^+$: 553.2028; found 553.2028.

4.2.6. 4-Fluoro-*N*-(2-methoxy-5-(4-oxo-3-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydroquinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (A6)

Yield 67.04%; mp: 187.0–189.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.08 (s, 1H, SO_2NH), 8.41-8.33 (m, 2H, Ar-H), 8.26 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.08 (dd, *J* = 8.5, 2.2 Hz, 1H,

Ar-H), 7.91 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.82 (dd, *J* = 8.8, 5.2 Hz, 2H, Ar-H), 7.77 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.41 (t, *J* = 8.8 Hz, 2H, Ar-H), 4.14 (t, *J* = 6.0 Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 2.82 (t, *J* = 5.9 Hz, 2H, CH_2), 2.58 (t, 4H, CH_2×2), 1.75–1.63 (m, 4H, CH_2×2). ^{13}C NMR (DMSO-d_6) δ 164.7 (d, J_{C-F} = 250 Hz), 160.6, 157.2, 148.8, 147.7, 141.2, 137.4, 135.5, 132.8, 131.4, 130.2, 130.1, 128.8, 128.6, 123.5, 122.4, 121.9, 116.7, 116.5, 54.2 (CH_2×2), 54.1, 53.9, 45.1, 23.6 (CH_2×2). ESI-HRMS *m/z*: calc'd for $C_{26}H_{27}FN_5O_4S$ $[M+H]^+$: 524.1763; found 524.1762.

4.2.7. 4-Fluoro-*N*-(2-methoxy-5-(4-oxo-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydro quinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (A7)

Yield 62.64%; mp: 195.0–197.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.06 (s, 1H, SO_2NH), 8.36 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.33 (s, 1H, Ar-H), 8.26 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.08 (dd, *J* = 8.5, 2.1 Hz, 1H, Ar-H), 7.92 (d, *J* = 2.2 Hz, 1H, Ar-H), 7.83 (dd, *J* = 8.8, 5.2 Hz, 2H, Ar-H), 7.77 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.42 (t, *J* = 8.8 Hz, 2H, Ar-H), 4.12 (t, *J* = 5.9 Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 2.61 (t, *J* = 5.9 Hz, 2H, CH2), 2.44 (s, 4H, CH_2×2), 1.50–1.41 (m, *J* = 4.7 Hz, 4H, CH_2×2), 1.40–1.31 (m, *J* = 4.5 Hz, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.5, 157.1, 149.0, 147.8, 141.8, 137.2, 135.4, 132.8, 131.7, 130.3, 130.2, 128.8, 128.6, 123.5, 122.4, 121.5, 116.8, 116.5, 56.9, 54.4 (CH_2×2), 54.0, 43.5, 26.0 (CH_2×2), 24.3. ESI-HRMS *m/z*: calc'd for $C_{27}H_{29}FN_5O_4S$ $[M+H]^+$: 538.1919; found 538.1919.

4.2.8. 4-Chloro-*N*-(2-methoxy-5-(3-(2-morpholinoethyl)-4-oxo-3,4-dihydro quinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (A8)

Yield 44.1%; mp: 214.0–216.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.20 (s, 1H, SO_2NH), 8.40 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.37 (s, 1H, Ar-H), 8.28 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.09 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.94 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.77 (dd, *J* = 11.8, 5.1 Hz, 3H, Ar-H), 7.66 (d, *J* = 8.7 Hz, 2H, Ar-H), 4.13 (t, *J* = 5.9 Hz, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.54 (t, 4H, OCH_2×2), 2.64 (t, *J* = 5.8 Hz, 2H, CH_2), 2.46 (s, 4H, NCH_2×2). ^{13}C NMR (DMSO-d_6) δ 160.5, 157.2, 149.0, 147.8, 142.1, 139.5, 138.3, 135.3, 132.8, 132.3, 129.7 (Ar-C×2), 129.1 (Ar-C×2), 128.9, 128.6, 123.6, 122.4, 120.9, 66.7 (CH_2×2), 56.8, 54.0, 53.7 (CH_2×2), 43.1. ESI-HRMS *m/z*: calc'd for $C_{26}H_{27}ClN_5O_5S$ $[M+H]^+$: 556.1416; found 556.1416.

4.2.9. *N*-(2-methoxy-5-(3-(2-morpholinoethyl)-4-oxo-3,4-dihydro quinazolin-6-yl)pyridin-3-yl)-4-methylphenylsulfonamide (A9)

Yield 71.3%; mp: 212.0–214.0 °C. ^{1}H NMR (DMSO-d_6) δ 9.99 (s, 1H, SO_2NH), 8.37 (s, 1H, Ar-H), 8.34 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.23 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.06 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.87 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.77 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.67 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.2 Hz, 2H, Ar-H), 4.13 (t, *J* = 5.9 Hz, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.54 (t, 4H, OCH_2×2), 2.63 (t, *J* = 5.9 Hz, 2H, CH_2), 2.46 (s, 4H, NCH_2×2), 2.36 (s, 3H, Ar-CH_3). ^{13}C NMR (DMSO-d_6) δ 160.5, 156.8, 149.0, 147.8, 143.9, 141.3, 137.6, 135.4, 132.8, 130.7 (Ar-C×2), 130.0, 128.7, 128.6, 127.2 (Ar-C×2), 123.4, 122.4, 121.5, 66.7 (CH_2×2), 56.8, 54.0, 53.7 (CH_2×2), 43.1, 21.4. ESI-HRMS *m/z*: calc'd for $C_{27}H_{30}N_5O_5S$ $[M+H]^+$: 536.1963; found 536.1962.

4.2.10. *N*-(5-(3-(2-(diethylamino)ethyl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-2,4-difluorophenylsulfonamide (A10)

Yield 63.9%; mp: 177.5–179.5 °C. ^{1}H NMR (DMSO-d_6) δ 10.26 (s, 1H, SO_2NH), 8.38 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 8.28 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.09 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.93 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.82–7.73 (m, 2H, Ar-H), 7.60–7.51 (m, 1H, Ar-H), 7.25–7.16 (m, *J* = 8.5, 2.3 Hz, 1H, Ar-H), 4.07 (t, *J* = 5.9 Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 2.75 (t, *J* = 5.9 Hz, 2H, CH_2), 2.59–2.52 (m, 4H, NCH_2×2), 0.88 (t, *J* = 7.1 Hz, 6H, CH_3×2). ^{13}C NMR (DMSO-d_6) δ 165.40 (d, $J_{C\text{-}F}$ = 252 Hz), 160.7, 159.9 (d, $J_{C\text{-}F}$ = 255 Hz), 158.0, 149.1, 147.8, 141.8, 135.3, 133.2, 132.8, 132.3, 128.8, 128.5, 123.4, 122.4, 121.6, 112.3, 112.1, 106.2, 53.9, 50.8, 47.2 (CH_2×2), 44.6, 12.1 (CH_3×2). ESI-HRMS *m/z*: calc'd for $C_{26}H_{27}F_2N_5NaO_4S$ $[M+Na]^+$: 632.1950; found 632.1950.

4.2.11. *N*-(5-(3-benzyl-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide (A11)

Yield 61.1%; mp: 211.5–213.5 °C. ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H, SO_2NH), 8.64 (s, 1H, Ar-H), 8.39 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.27 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.10 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.94 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.84–7.78 (m, 3H, Ar-H), 7.45–7.27 (m, 7H, Ar-H), 5.24 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3). ^{13}C NMR

(DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.5, 157.2, 148.7, 147.8, 142.1, 137.2, 137.0, 135.6, 133.0, 132.2, 130.3, 130.2, 129.1 (Ar-C×2), 128.8, 128.7, 128.2 (Ar-C×3), 123.6, 122.6, 120.9, 116.8, 116.6, 54.0, 49.5. ESI-HRMS *m/z*: calc'd for $C_{27}H_{22}FN_4O_4S$ $[M+H]^+$: 517.1341; found 517.1340.

4.2.12. 4-Fluoro-*N*-(2-methoxy-5-(3-(4-methoxybenzyl)-4-oxo-3,4-dihydro quinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (A12)

Yield 83.1%; mp: 219.0–221.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H, SO_2NH), 8.63 (s, 1H, Ar-H), 8.39 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.27 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.09 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.94 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.85–7.76 (m, 3H, Ar-H), 7.46–7.33 (m, 4H, Ar-H), 6.92 (d, *J* = 8.7 Hz, 2H, Ar-H), 5.16 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.5, 159.3, 157.2, 148.5, 147.7, 142.1, 137.0, 136.9, 135.5, 132.9, 132.2, 130.3, 129.9 (Ar-C×2), 129.2, 128.8, 128.7, 123.6, 122.6, 121.0, 116.8, 116.6, 114.5 (Ar-C×2), 55.5, 54.0, 48.9. ESI-HRMS *m/z*: calc'd for $C_{28}H_{23}FN_4NaO_5S$ $[M+Na]^+$: 569.1266; found 569.1265.

4.2.13. 4-Fluoro-*N*-(2-methoxy-5-(4-oxo-3-(pyridin-4-ylmethyl)-3,4-dihydro quinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (A13)

Yield 43.8%; mp: 215.0–217.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H, SO_2NH), 8.62 (s, 1H, Ar-H), 8.54 (d, *J* = 4.6 Hz, 2H Ar-H), 8.40 (d, *J* = 2.1 Hz, 1H Ar-H), 8.27 (d, *J* = 1.8 Hz, 1H Ar-H), 8.13 (dd, *J* = 8.5, 1.9 Hz, 1H Ar-H), 7.94 (d, *J* = 2.1 Hz, 1H Ar-H), 7.86–7.78 (m, 3H Ar-H), 7.42 (t, *J* = 8.8 Hz, 2H Ar-H), 7.32 (d, *J* = 5.1 Hz, 2H Ar-H), 5.28 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.6, 157.2, 150.3 (Ar-C×2), 148.7, 147.8, 146.0, 142.1, 137.0, 136.9, 135.7, 133.1, 132.2, 130.3, 130.2, 128.8, 128.7, 123.6, 122.8, 122.5, 121.0, 116.8, 116.6, 54.0, 48.8. ESI-HRMS *m/z*: calc'd for $C_{26}H_{21}FN_5O_4S$ $[M+H]^+$: 518.1293; found 518.1293.

4.2.14. 4-Fluoro-*N*-(2-methoxy-5-(4-oxo-3-(pyridin-3-ylmethyl)-3,4-dihydro quinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (A14)

Yield 54.31%; mp: 215.0–217.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H, SO_2NH), 8.71 (s, 1H, Ar-H), 8.69 (s, 1H, Ar-H), 8.53 (d, *J* = 4.2 Hz, 1H, Ar-H), 8.39 (d, *J* = 2.2

Hz, 1H, Ar-H), 8.26 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.11 (dd, *J* = 8.5, 2.1 Hz, 1H, Ar-H), 7.93 (d, *J* = 2.2 Hz, 1H, Ar-H), 7.87–7.78 (m, 4H, Ar-H), 7.42 (dd, *J* = 11.8, 5.7 Hz, 3H, Ar-H), 5.27 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.6, 157.2, 149.3, 148.9, 148.5, 147.7, 142.1, 137.0, 136.9, 136.7, 135.6, 133.0, 132.2, 130.3, 130.2, 128.7, 128.7, 124.5, 123.6, 122.5, 120.9, 116.8, 116.6, 54.0, 47.5. ESI-HRMS *m/z*: calc'd for $C_{26}H_{21}FN_5O_4S$ $[M+H]^+$: 518.1293; found 518.1293.

4.2.15. 4-Fluoro-*N*-(2-methoxy-5-(3-(4-(morpholinomethyl)phenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (B1)

Yield 61.1%; mp: 217.0–219.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H, SO_2NH), 8.40 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.29 (d, *J* = 1.8 Hz, 1H, Ar-H), 8.14 (dd, *J* = 8.5, 1.9 Hz, 1H, Ar-H), 7.93 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.86–7.79 (m, 3H, Ar-H), 7.51 (s, *J* = 9.5 Hz, 4H, Ar-H), 7.42 (t, *J* = 8.8 Hz, 2H, Ar-H), 3.68 (s, 3H, OCH_3), 3.61 (t, *J* = 3.9 Hz, 4H, OCH_2×2), 3.56 (s, 2H, CH_2), 2.41 (s, 4H, NCH_2×2). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.4, 157.2, 147.9, 147.6, 142.0, 139.1, 137.0, 136.8, 135.8, 133.2, 131.9, 130.3, 130.2, 130.0 (Ar-C×2), 128.8, 127.7 (Ar-C×2), 123.9, 122.8, 121.1, 116.8, 116.6, 66.7 (CH_2×2), 62.2, 54.0, 53.6 (CH_2×2). ESI-HRMS *m/z*: calc'd for $C_{31}H_{29}FN_5O_5S$ $[M+H]^+$: 602.1868; found 602.1868.

4.2.16. 4-Fluoro-*N*-(2-methoxy-5-(3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (B2)

Yield 16.82%; mp: 218.5–220.5 °C. ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H, SO_2NH), 8.38 (s, 1H, Ar-H), 8.32 (d, 1H), 8.28 (s, 1H), 8.13 (dd, *J* = 7.9 Hz, 1H), 7.89 (s, 1H), 7.82 (dd, *J* = 11.1, 6.2 Hz, 3H), 7.55–7.46 (m, 4H, Ar-H), 7.40 (t, *J* = 8.7 Hz, 2H, Ar-H), 3.69 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2), 2.49–2.30 (m, 8H, CH_2×4), 2.23 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6) δ 164.6 (d, J_{C-F} = 250 Hz), 160.4, 157.2, 147.8, 147.5, 140.8, 139.6, 137.7, 136.7, 136.1, 133.2, 131.0, 130.2, 130.1, 129.9, 128.7, 128.7, 127.7, 123.8, 122.8, 122.5, 116.7, 116.5, 61.8, 55.0 (CH_2×2), 53.9, 52.7 (CH_2×2), 45.8. ESI-HRMS *m/z*: calc'd for $C_{32}H_{32}FN_6O_4S$ $[M+H]^+$: 615.2185; found 615.2184.

4.2.17. *t*-Butyl (*S*)-3-(6-(5-((4-fluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)-4-oxoquinazolin-3(*4H*)-yl)pyrrolidine-1-carboxylate ((*S*)-C1)

Yield 42.54%; mp: 137.0–139.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H, SO_2NH), 8.39 (d, J = 2.3 Hz, 1H, Ar-H), 8.35 (s, 1H, Ar-H), 8.27 (d, J = 2.1 Hz, 1H, Ar-H), 8.10 (dd, J = 8.5, 2.2 Hz, 1H, Ar-H), 7.93 (d, J = 2.3 Hz, 1H, Ar-H), 7.86–7.80 (m, 2H, Ar-H), 7.78 (d, J = 8.5 Hz, 1H, Ar-H), 7.47–7.39 (m, 2H, Ar-H), 5.29–5.15 (m, 1H, CH), 3.82–3.73 (m, J = 8.8 Hz, 1H, CH_2), 3.68 (s, 3H, OCH_3), 3.60–3.50 (m, 2H, CH_2), 3.45–3.38 (m, 1H, CH_2), 2.46–2.26 (m, 2H, CH_2), 1.43 (d, J = 7.3 Hz, 9H, CH_3×3). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.7, 157.2, 153.9, 147.2, 145.9, 142.0, 137.0, 137.0, 135.5, 133.0, 132.1, 130.3, 128.8, 128.5, 123.7, 122.3, 121.0, 116.8, 116.6, 79.2, 54.8, 54.0, 49.6, 44.5, 28.9, 28.6 (CH_3×3). ESI-HRMS *m/z*: calc'd for $C_{29}H_{31}FN_5O_6S$ $[M+H]^+$: 596.1974; found 596.1974.

4.2.18. (*R*)-N-(5-(3-(1-acetylpyrrolidin-3-yl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylnesulfonamide ((*R*)-C4)

Yield 75.1%; mp: 118.0–120.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H, SO_2NH), 8.41–8.34 (m, 2H, Ar-H), 8.28 (t, J = 2.6 Hz, 1H, Ar-H), 8.11 (dt, J = 8.5, 2.3 Hz, 1H, Ar-H), 7.98–7.92 (m, J = 2.1, 1.0 Hz, 1H, Ar-H), 7.87–7.81 (m, 3H, Ar-H), 7.43 (t, J = 8.8 Hz, 2H, Ar-H), 5.33–5.20 (m, 1H, CH), 3.90–3.80 (m, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.55–3.42 (m, 2H, CH_2), 2.45–2.32 (m, 2H, CH_2), 2.00 (d, J = 14.9 Hz, 3H, $COCH_3$). ^{13}C NMR (DMSO-d_6) δ 164.9 (d, J_{C-F} = 250 Hz), 160.7, 157.2, 147.2, 145.9, 141.9, 135.5, 133.0, 132.0, 130.3, 130.2, 128.8, 128.5, 123.7, 122.3, 121.1, 116.8, 116.6, 54.9, 54.0, 53.9, 50.5, 49.1, 45.6, 44.1, 30.4, 28.8, 22.8, 22.4. ESI-HRMS *m/z*: calc'd for $C_{26}H_{25}FN_5O_5S$ $[M+H]^+$: 538.1555; found 538.1555.

4.2.19. (*R*)-*N*-(5-(3-(1-(cyclopropanecarbonyl)pyrrolidin-3-yl)-4-oxo-3,4-dihydro quinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide ((*R*)-C6)

Yield 63.0%; mp: 236.0–238.0 °C.^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H, SO_2NH), 8.40–8.35 (m, J = 17.4, 15.6 Hz, 2H, Ar-H), 8.30–8.22 (m, 1H, Ar-H), 8.15–8.05 (m, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.83–7.74 (m, 3H, Ar-H), 7.43 (t, J = 8.8 Hz, 2H, Ar-H), 5.30–5.20 (m, 1H, CH), 3.82–3.72 (m, 7H, OCH_3+CH_2×2), 2.45–2.35 (m, 2H, CH_2), 1.82–1.75 (m, 1H, cPr-CH), 0.79–0.74 (m, 4H, cPr-CH_2×2). ^{13}C NMR (DMSO-d_6) δ 164.9 (d, J_{C-F} = 250 Hz), 160.7, 157.2, 147.2, 146.0, 145.9, 142.0, 137.0, 135.5, 133.0, 132.0, 130.3, 130.2, 128.8, 128.5, 123.7, 122.3, 121.0, 116.8, 116.6,

74.0, 54.9, 54.0, 53.7, 49.8, 49.5, 45.0, 44.5, 30.3, 28.4, 25.4, 12.5, 12.13, 7.6 (CH_2×2). ESI-HRMS *m/z*: calc'd for $C_{28}H_{27}FN_5O_5S$ $[M+H]^+$: 586.1531; found 586.1540.

4.2.20. (*S*)-*N*-(5-(3-(1-(cyclopropylmethyl)pyrrolidin-3-yl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide ((*S*)-C8)

Yield 38.7%; mp: 203.0–205.0 °C.^{1}H NMR (DMSO-d_6) δ 10.10 (s, 1H, SO_2NH), 8.65 (s, 1H, Ar-H), 8.35 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.25 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.08 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.90 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.85–7.79 (m, 3H, Ar-H), 7.42 (t, *J* = 8.8 Hz, 2H, Ar-H), 5.34 (s, 1H, CH), 3.69 (s, 3H, OCH_3), 3.21–3.10 (m, 2H, CH_2), 2.71 (dd, *J* = 10.5, 7.3 Hz, 1H, CH_2), 2.44–2.34 (m, 4H, CH_2), 1.99–1.88 (m, 1H, CH_2), 0.90–0.85 (m, 1H, cPr-CH), 0.49–0.43 (m, 2H, cPr-CH_2), 0.15–0.12 (m, 2H, cPr-CH_2). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.3, 157.1, 147.2, 146.3, 141.3, 137.4, 135.6, 132.8, 131.4, 130.3, 130.2, 128.8, 128.5, 123.7, 122.1, 121.8, 116.8, 116.5, 59.9, 59.4, 53.9, 53.4, 53.0, 32.0, 10.0, 4.1 (CH_2 × 2). ESI-HRMS *m/z*: calc'd for $C_{28}H_{29}FN_5O_4S$ $[M+H]^+$: 550.1919; found 550.1928.

4.2.21. (*R*)-*N*-(5-(3-(1-(cyclopropylmethyl)pyrrolidin-3-yl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide ((*R*)-C9)

Yield 38.0%; mp: 195.0–197.0 °C.^{1}H NMR (DMSO-d_6) δ 10.10 (s, 1H, SO_2NH), 8.66 (s, 1H, Ar-H), 8.33 (s, 1H, Ar-H), 8.25 (s, 1H, Ar-H), 8.08 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.85–7.77 (m, 4H, Ar-H), 7.41 (t, *J* = 8.7 Hz, 2H, Ar-H), 5.38–5.27 (m, 1H, CH), 3.70 (s, 3H, OCH_3), 3.22–3.11 (m, 2H, CH_2), 2.71–2.65 (m, 1H, CH_2), 2.42–2.36 (m, 4H, CH_2), 1.94–1.88 (m, *J* = 8.2 Hz, 1H, CH_2), 0.95–0.90 (m, 1H, cPr-CH), 0.49 (d, *J* = 7.4 Hz, 2H, cPr-CH_2), 0.15 (d, *J* = 4.4 Hz, 2H, cPr-CH_2). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.3, 157.1, 147.2, 146.3, 141.3, 137.4, 135.6, 132.8, 131.4, 130.3, 130.2, 128.8, 128.5, 123.7, 122.1, 121.8, 116.8, 116.5, 59.9, 59.4, 53.9, 53.4, 53.0, 32.0, 10.0, 4.1 (CH_2×2).ESI-HRMS *m/z*: calc'd for $C_{28}H_{29}FN_5O_4S$ $[M+H]^+$: 550.1919; found 550.1935.

4.2.22. t-Butyl4-(6-(5-((4-fluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)-4-oxoquinazolin-3(*4H*)-yl)piperidine-1-carboxylate (D1)

Yield 71.3%; mp: 219.5–221.5 °C. ^{1}H NMR (DMSO-d_6) δ 10.13 (s, 1H, SO_2NH), 8.52 (s, 1H, Ar-H), 8.38 (s, 1H, Ar-H), 8.26 (s, 1H, Ar-H), 8.10 (m, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.83 (dd, *J* = 8.2, 5.4 Hz, 2H, Ar-H), 7.78 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.43 (t, *J* = 8.7 Hz, 2H, Ar-H), 4.87–4.76 (m, 1H, CH), 4.15 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 2.92 (s, 2H, CH_2), 1.99–1.90 (m, 2H, CH_2), 1.86–1.79 (m, 2H, CH_2), 1.44 (s, 9H, CH_3×3). ^{13}C NMR (DMSO-d_6) δ 164.8 (d, J_{C-F} = 250 Hz), 160.2, 157.1, 154.2, 147.1, 146.2, 141.7, 137.1, 135.5, 132.9, 131.8, 130.3, 130.2, 128.8, 128.5, 123.7, 122.2, 121.3, 116.8, 116.6, 79.4 (CH_2×2), 63.5, 54.0 (CH_2×2), 52.8, 30.7, 28.6 (CH_3×3). ESI-HRMS *m/z*: calc'd for $C_{30}H_{32}FN_5NaO_6S$ $[M + Na]^+$: 632.1950; found 632.1950.

4.2.23. *N*-(5-(3-(1-(cyclopropylmethyl)piperidin-4-yl)-4-oxo-3,4-dihydro quinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide (D6)

Yield 84.4%; mp: 217.0–219.0 °C.^{1}H NMR (DMSO-d_6) δ 10.06 (s, 1H, SO_2NH), 8.51 (s, 1H, Ar-H), 8.33 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.25 (d, *J* = 1.6 Hz, 1H, Ar-H), 8.08 (dd, *J* = 8.5, 1.8 Hz, 1H, Ar-H), 7.89 (d, *J* = 2.1 Hz, 1H, Ar-H), 7.83 (dd, *J* = 8.7, 5.2 Hz, 2H, Ar-H), 7.77 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.42 (t, *J* = 8.8 Hz, 2H, Ar-H), 4.69–4.60 (m, 1H, CH), 3.69 (s, *J* = 7.9 Hz, 3H, OCH_3), 3.20–3.10 (m, 2H, CH_2), 2.32 (d, *J* = 6.6 Hz, 2H, CH_2), 2.19–2.11 (m, 4H, CH_2), 1.90–1.80 (m, 2H, CH_2), 0.90–0.80 (m, 1H, CH), 0.51–0.42 (m, 2H, cPr-CH_2), 0.16–0.13 (m, 2H, cPr-CH_2). ^{13}C NMR (DMSO-d_6) δ 164.7 (d, J_{C-F} = 250 Hz), 160.3, 157.1, 147.1, 146.0, 141.1, 137.5, 135.6, 132.9, 131.2, 130.2, 130.1, 128.8, 128.5, 123.7, 122.2, 116.7, 116.5, 62.7, 53.9, 52.9 (CH_2×2), 52.8, 30.5 (CH_2×2), 8.7, 4.3 (CH_2×2). ESI-HRMS *m/z*: calc'd for $C_{28}H_{29}FN_5O_4S$ $[M+H]^+$: 564.2075; found 564.2080.

4.2.24. (*S*)-4-fluoro-*N*-(2-methoxy-5-(4-oxo-3-(pyrrolidin-3-yl)-3,4-dihydro quinazolin-6-yl)pyridin-3-yl)phenylsulfonamide ((*S*)-C2)

To a solution of **(*S*)-C1** (480 mg, 8.63 mmol) in DCM (5 mL), trifluoroacetic acid (2 mL) was added. The resulting solution was stirred at room temperature for 2 h, concentrated under vacuum and neutralized by slow addition of a saturated aqueous sodium carbonate solution at 0°C, and then extracted with DCM (30 mL×2). The organic phase was dried over anhydrous sodium sulfate, followed by filtration,

concentration, and drying to produce **(*S*)-C2** as off-white solid. Yield 46.0%; mp: 130.0-133.0 °C. ^{1}H NMR (DMSO-d_6) δ 13.58 (s, 1H, SO_2NH), 8.44 (s, 1H, Ar-H), 8.20 (d, J = 2.1 Hz, 1H, Ar-H), 8.01 (dd, J = 8.6, 2.1 Hz, 2H, Ar-H), 7.83–7.79 (m, 2H, Ar-H), 7.75 (d, J = 8.5 Hz, 1H, Ar-H), 7.73 (d, J = 2.2 Hz, 1H, Ar-H), 7.34–7.29 (m, 2H, Ar-H), 5.27–5.16 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 3.44–3.42 (m, 1H, CH_2), 3.38–3.35 (m, 1H, CH_2), 3.19–3.06 (m, 2H, CH_2), 2.45–2.37 (m, 1H, CH_2), 2.25–2.13 (m, 1H, CH_2). ^{13}C NMR (DMSO-*d*6) δ 164.0 (d, J_{C-F} = 247 Hz), 160.9, 157.2, 147.1, 146.9, 140.1, 136.7, 136.4, 132.8, 129.9, 129.8, 128.5, 128.4, 126.9, 123.2, 122.3, 116.2, 116.0, 56.3, 53.7, 50.0, 46.0, 30.7. ESI-HRMS *m/z*: calc'd for $C_{24}H_{23}FN_5O_4S$ $[M+H]^+$: 496.1450; found 496.1449.

Compounds **D2** were synthesized according to the procedure described in **(*S*)-C2**.

4.2.25. 4-Fluoro-N-(2-methoxy-5-(4-oxo-3-(piperidin-4-yl)-3,4-dihydro quinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (D2)

Yield 61.7%; mp: 146.0–148.0 °C. ^{1}H NMR (DMSO-d_6) δ 8.36 (s, 1H, Ar-H), 8.19 (s, 1H, Ar-H), 8.01 (d, J = 9.0 Hz, 2H, Ar-H), 7.91–7.70 (m, 4H, Ar-H), 7.33 (t, J = 8.6 Hz, 2H, Ar-H), 4.92–4.75 (m, 1H, CH), 3.75 (s, 3H, OCH_3), 3.34–3.24 (m, 2H, CH_2), 2.95–2.85 (m, 2H, CH_2), 2.19–2.09 (m, 2H, CH_2), 2.02–1.92(m, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 163.8 (d, J_{C-F} = 247 Hz), 160.3, 157.1, 146.8, 145.7, 140.5, 140.4, 136.9, 135.5, 132.8, 130.0, 129.8, 128.5, 128.4, 126.1, 123.4, 122.3, 116.1, 115.9, 53.7, 51.9, 44.5 (CH_2×2), 29.1 (CH_2×2). ESI-HRMS *m/z*: calc'd for $C_{25}H_{24}FN_5O_4S$ $[M+H]^+$: 510.1606; found 510.1606.

4.2.26. (*S*)-*N*-(5-(3-(1-acetylpyrrolidin-3-yl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide ((*S*)-C3)

The mixture of **(*S*)-C2** (60 mg, 0.12 mmol), acetic acid (36 mg, o.6 mmol), HATU (90 mg, 0.24 mmol), DIPEA (0.5 mL) and DCM (15 mL) was refluxed for 2 h. The volatile were removed under vacuum and the residue was purified through a column chromatography on silica gel with dichloromethane /methanol (V:V = 30:1) as eluent to produce **(*S*)-C3** as light yellow solid. Yield 32.87%; mp: 116.0–118.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.01 (s, 1H, SO_2NH), 8.43–8.30 (m, 2H, Ar-H), 8.27 (s, 1H, Ar-H), 8.13–8.07 (m, 1H, Ar-H), 7.92 (d, J = 1.7 Hz, 1H, Ar-H), 7.88–7.73 (m, 3H,

Ar-H), 7.42 (t, J = 8.8 Hz, 2H, Ar-H), 5.37–5.20 (m, 1H, CH), 3.95–3.73 (m, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.65–3.61 (m, 1H, CH_2), 3.48–3.39 (m, 1H, CH_2), 2.48–2.30 (m, 2H, CH_2), 2.00 (s, 3H, $COCH_3$). ^{13}C NMR (DMSO-d_6) δ 169.0, 168.8, 164.8 (d, J_{C-F} = 250 Hz), 160.7, 157.2, 147.1, 145.9, 141.7, 137.2, 135.6, 133.0, 131.8, 130.3, 130.2, 128.8, 128.5, 123.7, 122.3, 116.8, 116.6, 54.9, 54.0, 53.9, 50.5, 49.1, 45.6, 44.1, 30.38, 28.8, 22.8. ESI-HRMS *m/z*: calc'd for $C_{26}H_{24}FN_5NaO_5S$ $[M+Na]^+$: 560.1375; found 560.1374.

Compounds **(*S*)-C5, (*S*)-C7** and **D3-D5** were synthesized according to the process described in **(*S*)-C2**.

4.2.27. (*S*)-*N*-(5-(3-(1-(cyclopropanecarbonyl)pyrrolidin-3-yl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide ((*S*)-C5)

Yield 93.42%; mp: 82.0–84.0 °C. ^{1}H NMR (DMSO-d_6) δ 9.53 (s, 1H, SO_2NH), 8.43–8.32 (m, 2H, Ar-H), 8.28 (s, 1H, Ar-H), 8.13–8.08 (m, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.85–.76 (m, 3H, Ar-H), 7.42 (t, J = 8.8 Hz, 2H, Ar-H), 5.40–5.20 (m, 1H, CH), 4.01–3.92 (m, 1H, CH_2), 3.90–3.77 (m, 1H, CH_2), 3.72–3.68 (s, 3H, OCH_3), 3.68–3.61 (m, 1H, CH_2), 3.50–3.39 (m, 1H, CH_2), 2.49–2.28 (m, 2H, CH_2), 1.89–1.73 (m, 1H, COCH), 0.81–0.70 (m, J = 8.2 Hz, 4H, *c*-Pr-H). ^{13}C NMR (DMSO-d_6) δ 171.65, 164.72 (d, J_{C-F} = 250 Hz), 160.7, 157.2, 147.1, 146.0, 145.9, 141.4, 137.4, 135.7, 133.0, 131.6, 130.3, 130.2, 128.8, 128.5, 123.6, 122.3, 117.1, 116.6, 54.0, 53.7, 53.4, 45.0, 41.9, 30.3, 18.1, 13.1, 12.5, 12.1, 7.6. ESI-HRMS *m/z*: calc'd for $C_{28}H_{26}FN_5NaO_5S$ $[M+Na]^+$: 586.1533; found 586.1531.

4.2.28. (*S*)-4-fluoro-*N*-(2-methoxy-5-(4-oxo-3-(1-(tetrahydro-*2H*-pyran-4-carbonyl)pyrrolidin-3-yl)-3,4-dihydroquinazolin-6-yl)pyridin-3-yl)phenylsulfonamide ((*S*)-C7)

Yield 94.3%; mp: 113.0–116.0 °C. ^{1}H NMR (DMSO-d_6) δ 9.90 (s, 1H, SO_2NH), 8.39–8.30 (m, 2H, Ar-H), 8.29–8.25 (m, 1H, Ar-H), 8.12–8.08 (m, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.85–7.77 (m, 3H, Ar-H), 7.43 (t, J = 8.8 Hz, 2H, , Ar-H), 5.36–5.21 (m, 1H, CH), 3.93–3.90 (m, 1H, CH_2), 3.90–3.82 (m, 4H, OCH_2×2), 3.71 (s, 1H), 3.48–3.38 (m, 1H), 2.81–2.68 (m, 1H), 2.47–2.41 (m, 1H, CH_2), 2.39–2.33 (m, 1H, CH), 1.64–1.58 (m, 4H, CH_2×2). ^{13}C NMR (DMSO) δ 174.6, 172.9, 164.7 (d, J_{C-F} =

250 Hz), 160.7, 157.2, 147.2, 146.0, 141.9, 140.0, 137.1, 135.6, 133.0, 132.0, 130.3, 130.2, 130.2, 128.8, 128.5, 123.7, 122.2, 121.3, 121.2, 116.8, 116.6, 66.8, 54.9, 54.0, 53.7, 49.4, 44.7, 42.1, 38.6, 30.4, 28.8. ESI-HRMS *m/z*: calc'd for $C_{30}H_{30}FN_5NaO_6S$ $[M+Na]^+$: 630.1794; found 630.1793.

4.2.29. *N*-(5-(3-(1-acetylpiperidin-4-yl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide (D3)

Yield 55.1%; mp: 143.0–146.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H, SO_2NH), 8.51 (s, 1H, Ar-H), 8.38 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.26 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.10 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.92 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.86–7.80 (m, 2H, Ar-H), 7.78 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.43 (t, *J* = 8.8 Hz, 2H, Ar-H), 4.99–4.84 (m, 1H, CH), 4.65–4.55 (m, 1H, CH_2), 4.05–3.95 (m, 1H, CH_2), 3.68 (s, 3H, OCH_3), 3.51–3.38 (m, 1H, CH_2), 2.74–2.63 (m, 1H, CH_2), 2.07 (s, 3H, OCH_3), 1.96–1.83 (m, 4H,CH_2). ^{13}C NMR (DMSO-d_6) δ 168.6, 164.8 (d, J_{C-F} = 250 Hz), 160.2, 157.1, 147.1, 146.2, 142.0, 137.0, 135.5, 132.9, 132.0, 130.3, 130.2, 128.8, 128.5, 123.8, 122.2, 121.0, 116.8, 116.6, 56.5, 54.0, 52.6, 43.4, 45.8, 40.9, 30.9, 31.2, 30.6, 21.8, 19.0. ESI-HRMS *m/z*: calc'd for $C_{27}H_{26}FN_5NaO_5S$ $[M+Na]^+$: 574.1531; found 574.1531.

4.2.30. *N*-(5-(3-(1-(cyclopropanecarbonyl)piperidin-4-yl)-4-oxo-3,4-dihydroquinazolin-6-yl)-2-methoxypyridin-3-yl)-4-fluorophenylsulfonamide (D4)

Yield 48.9%; mp: 165.0–167.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H, SO_2NH), 8.53 (s, 1H, Ar-H), 8.39 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.27 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.10 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 7.92 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.83 (dd, *J* = 8.8, 5.2 Hz, 2H, Ar-H), 7.78 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.43 (t, *J* = 8.8 Hz, 2H, Ar-H), 5.03–4.87 (m, 1H, CH), 4.67–4.41 (m, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.32–3.22 (m, 1H, CH_2), 2.78–2.70 (m, 1H, CH_2), 2.14–2.01 (m, 2H, CH_2), 2.01–1.93 (m, 2H, CH_2), 1.89 (s, 1H, COCH), 0.83–0.74 (m, 4H, coPr-H). ^{13}C NMR (DMSO-d_6) δ 171.3, 164.8 (d, J_{C-F} = 250 Hz), 160.2, 157.1, 147.1, 146.2, 141.9, 137.0, 135.4, 132.9, 132.0, 130.3, 130.2, 128.8, 128.5, 123.8, 122.2, 121.0, 116.8, 116.6, 54.0 (CH_2×2), 52.9, 43.3, 31.0, 10.9 (CH_2×2), 7.5, 7.4. ESI-HRMS *m/z*: calc'd for $C_{29}H_{29}FN_5O_5S$ $[M+H]^+$: 578.1868; found 578.1868.

4.2.31. 4-Fluoro-*N*-(2-methoxy-5-(4-oxo-3-(1-(tetrahydro-*2H*-pyran-4-carbonyl)

piperidin-4-yl)-3,4-dihydroquinazolin-6-yl)pyridin-3-yl)phenylsulfonamide (D5)

Yield 78.5%; mp: 237.0–239.0 °C. ^{1}H NMR (DMSO-d_6) δ 10.14 (s, 1H, SO_2NH), 8.51 (s, 1H, Ar-H), 8.38 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.26 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.10 (dd, *J* = 8.5, 2.1 Hz, 1H, Ar-H), 7.92 (d, *J* = 2.2 Hz, 1H, Ar-H), 7.83 (dd, *J* = 8.8, 5.2 Hz, 2H, Ar-H), 7.78 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.43 (t, *J* = 8.8 Hz, 2H, Ar-H), 4.99–4.85 (m, 1H, CH), 4.63–4.53 (m, 1H, CH_2), 4.25–4.15 (m, 1H, CH_2), 3.87–3.77(m, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.42–3.32(m, 2H, CH_2), 3.22 (t, *J* = 12.0 Hz, 1H, CH_2), 3.00–2.90 (m, 1H, CH_2), 2.70 (t, *J* = 11.1 Hz, 1H, CH_2), 2.10–1.85 (m, 4H, CH_2×2), 1.74–1.52 (m, 4H, CH_2×2). ^{13}C NMR (DMSO-d_6) δ 172.6, 164.8 (d, J_{C-F} = 250 Hz), 160.2, 157.1, 147.1, 146.2, 141.9, 137.0, 135.5, 132.9, 132.0, 130.3, 130.2, 128.8, 128.5, 123.8, 122.2, 121.1, 116.8, 116.6, 66.8 (CH_2×2), 54.0 (CH_2×2), 52.9, 43.0, 44.7, 41.2, 36.8 (CH_2×2), 31.1, 31.6, 30.6, 29.5 (CH_2×2). ESI-HRMS *m/z*: calc'd for $C_{31}H_{33}FN_5O_6S$ $[M+H]^+$: 622.2131; found 622.2130.

4.3. Biology assay methods

4.3.1. Cell Culture

The human cell lines HCT-116 and MCF-7 were maintained as a monolayer culture in DMEM, supplemented with 10% FBS in a humidified atmosphere (5% CO_2) at 37 °C.

4.3.2. Antiproliferative assays

BEZ235 was purchased from Shanghai Biochempartner Company (Purity: 99%, HPLC). 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyl-*2H*-tetrazolium bromide (MTT) was purchased from Sigma (St. Louis, MO, USA). Cellular chemosensitivity was determined by using a modified MTT method assay in vitro. In brief, HCT-116, MCF-7 cells in 200 μL culture medium were seeded into 96-well microplates at 3000-5000 cells per well respectively and cultured in DMEM with 10% FBS or RPMI-1640 with 10% calf serum, incubated at 37 ℃ for 24 h prior to drug exposure. Cell numbers were titrated to keep control cells growing in the exponential phase throughout the 72 h incubation period. Cells were treated with final concentrations of 10.0, 5.0, 1.0 and 0.5 μM of tested compounds simultaneously and incubated for 72 h

and then 20 μL of MTT solution (5 mg/mL in PBS) was added to each well at lucifugal condition and incubated for 4 h at 37 °C. The formed purple formazan crystals were pelleted at the bottom of the well, separated from the supernatant, and dissolved in 200 μL of DMSO. The optical density at 570 nm was determined by Varioskan Flash Multimode Reader (Thermo scientific). Three separate experiments with triplicate data were performed to obtain mean cell viability. The IC_{50} value, that is, the concentration (μM) of a compound was able to cause 50% cell death with respect to the control culture, was calculated according to the inhibition ratios.

4.3.3. PI3K enzymatic activity assay

PI3K and mTOR enzymatic activity assay was performed according to process described in reference.[25,26] Briefly, compounds **(*S*)-C5**, **(*S*)-C8** and **BEZ235** were dissolved in DMSO and diluted to a series of concentrations. Different concentrations of compounds were added to the enzyme reaction buffer containing 40 mM Tris-HCl, pH 7.4, 10 mM $MgCl_2$, 0.1 mg/mL BSA, 1 mM DTT, 2.5 μM ATP, PI3K (p110α/p85α, p110β/p85α, p110γ/PIK3R5 or p110δ/p85α), mTOR and L-α-phosphatidylinositol. The final reaction volume was 50 μL. After incubation for 40 min at 30 °C, the reaction was terminated by addition of stop solution. The amount of ADP was then detected via luciferase assay. After incubation for 5 min, the luminescence signal was determined by the multimode reader (MD-SpectraMax M5). The signal intensity is proportional to the enzyme activity.

The percentage of inhibition was calculated based on the following equation

$$\% \text{ inhibition rate} = [1 - (Lu_{compound} - Lu_{min})/(Lu_{max} - Lu_{min})] \times 100\%,$$

Where $Lu_{compound}$ is the signal at a given compound concentration, Lu_{max} is the signal of PI3Ks without compound and Lu_{min} is the signal of background in the absence of enzyme and compound. The IC_{50} values were calculated according to the fit of the dose -response curves by using GraphPad Prism5.

4.3.4. Anticancer effect in established mice S-180 homograft models *in vivo*

Mice (19.5 ± 1.8 g) were purchased from Experiment Animal Center of Xi′an Jiaotong University Health Science Center and fed in the same place. The experimental protocol was approved by Ethic Committee of Xi′an Jiaotong

University.

3×10^6 S-180 cells were injected subcutaneously into the flank of the mice. All tumor-bearing mice were randomly divided into three groups, with 8 mice in each group. The next day, compound **(*S*)-C5** was dissolved in DMSO : PEG400 : 5% glucose injection (1 : 7 : 2, V/V/V) and dosed orally at 20 mg/kg and 40 mg/kg for the low and high dosage groups once a day for 8 days, respectively. In the solvent group, the same volume of solvent was administered orally. Body weights were recorded per day. The mice were anesthetized and sacrificed on Day 9. The weights of the body and the neoplasm were measured and inhibitory ratios of tumor weight were calculated.

5. Molecular modeling

The protein-ligand complex crystal structure of compound **A** bound to PI3Kγ was chosen as the template to compare the docking mode between compound **(*S*)-C5** bound to PI3Kγ and **(*S*)-C8** bound to PI3Kγ. The molecular docking procedure was performed by using C-DOCKER protocol within Discovery Studio 2.5. For enzyme preparation, the hydrogen atoms were added. The whole PI3Kγ enzyme was defined as a receptor and the site sphere was selected on the basis of the ligand binding location of compound **A**. Compound A was removed and compound **(*S*)-C5** or **(*S*)-C8** was placed. After end of molecular docking, ten docking poses was scored and selected based on calculated C-DOCKER energy. Figure 4 was prepared using PyMOL.

Acknowledgment

Financial supports from National Natural Science Foundation of China (81272448) and China Postdoctoral Science Foundation (2014M560793) are gratefully acknowledged.

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Figure and scheme Legend

Figure 1. The structures of PI3K and mTOR dual inhibitors

Figure 2. The design of title compounds

Figure 3. (A) The anticancer effect of compound **(*S*)-C5** in establishing mice S-180 homograft model. $^{*}P < 0.05$ *vs* vehicle; $^{**}P < 0.01$ *vs* vehicle. (B) The change of tested mice body weights. Mice bearing subcutaneous cancers were orally administered solvent, compound **(*S*)-C5** (20 mg/kg or 40 mg/kg) once daily for 8 days (mpk: mg/kg).

Figure 4. (a) Compound **(*S*)-C5** docked into the ATP-binding site of PI3Kγ (PDB code: 3S2A). (b) Compound **(*S*)-C8** docked into the ATP-binding site of PI3Kγ. **(*S*)-C5** and **(*S*)-C8** is shown as sticks. Hydrogen bonds within 2.5 Å are shown as yellow dashed lines.

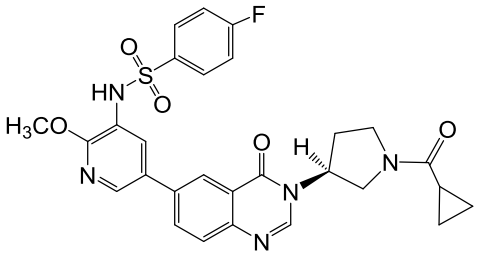
Scheme 1. Reagents and conditions: (a) EtOH, I_2, reflux, 4–6 h, 45.2%–83.4%; (b) TFA/DCM, r.t., 2 h; (c) cyclopropylformaldehyde, $NaBH(OAc)_3$, AcOH, DCE, r.t., overnight, 37.7%–90.6% (two steps); (d) AcOH or *c*-$PrCO_2H$, HATU, DIPEA, DCM, reflux, 2 h, 75.0%–86.0% (two steps); (e) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, 1,4-dioxane, reflux, 2 h; (f) **1a**–(*R*)-**1u,** $PdCl_2$(dppf), Na_2CO_3 or K_2CO_3, DME/H_2O, reflux, 4–6 h, 42.5%–83.1% (two steps).

Scheme 2. Reagents and conditions: (a) TFA/DCM, r.t., 2 h, 46.0%–61.7%.; (b) RCO_2H, HATU, DIPEA, DCM, reflux, 2 h, 45.8%–94.9%.

Table 1 Antiproliferative activities of compounds **A**, **B**, **C** and **D** ($\bar{x} \pm s$, n = 3)

Table 2 Inhibitory activity of **(*S*)-C5** and **(*S*)-C8** against PI3Ks and mTOR (n = 2)

Graphical abstract



(*S*)-C5

	IC_{50}(nM)
PI3Kα:	7.3
PI3Kβ:	209
PI3Kγ:	116
PI3Kδ:	106