European Journal of Medicinal Chemistry 75 (2014) 96–105

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Discovery of 2-methoxy-3-phenylsulfonamino-5-(quinazolin-6-yl or quinolin-6-yl)benzamides as novel PI3K inhibitors and anticancer agents by bioisostere

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ARTICLE INFO

Article history:
Received 3 August 2013
Received in revised form
17 December 2013
Accepted 25 January 2014
Available online 29 January 2014

Keywords:
Benzamide
Quinazoline
PI3K inhibitor
Antiproliferative activity
Anticancer effect
Bioisostere

ABSTRACT

2-Substituted-3-sulfonamino-5-(quinazolin-6-yl or quinolin-6-yl)benzamides have been proposed as novel structures of PI3K inhibitors and anticancer agents based on bioisostere. In the present study, 2-substituted-3-sulfonamino-5-(4-morpholinoquinazolin-6-yl)benzamides and 2-methoxy-3-sulfonamino-5-(4-morpholinoquinolin-6-yl)benzamides were synthesized. Their antiproliferative activities in vitro were evaluated via MTT assay against four human cancer cell lines, including A549, HCT-116, U-87 MG and KB. The SAR of the title compounds was preliminarily discussed. Compound **1a** with potent antiproliferative activity was tested for its inhibitory activity against PI3K and mTOR and its effect on the AKT and p-AKT^{473}. The anticancer effect of **1a** was evaluated in established nude mice U-87 MG xenograft model. The results suggest that compound **1a** can significantly inhibit PI3K/AKT/mTOR pathway and tumor growth. These findings strongly support the assumption that title compounds are potent PI3K inhibitors and anticancer agents.

1. Introduction

Cancer is characterized by uncontrolled cell growth and proliferation, which usually results from the abnormal activation of some enzymes. In many cancers, the PI3K/AKT/mTOR signal transduction pathway is dysregulated, contributing to cellular transformation and tumor growth [1]. Thus, the phosphatidylinositol 3-kinase (PI3K, a family of lipid kinases) signaling pathway plays a crucial role in cell growth, proliferation and survival. Genomic aberrations in the PI3K pathway such as mutational activation of PI3Kα or dysfunction of tumor suppressor PTEN are closely linked to the development and progression of a wide range of cancers, including cancers of colon, breast, head and neck, and non-small cell lung. Hence, inhibition of the key targets in the pathway, e.g. PI3K, AKT or mTOR (mammalian target of rapamycin), has great potential for the treatment of cancer. Therefore, PI3Kα and mTOR have become the targets of quest research for anticancer drug [2,3]. In recent years, a remarkable progress has been made on the design, synthesis and evaluation of PI3Kα and mTOR dual inhibitors [4–11], and thereupon the pharmacophore of the dual inhibitors has been put forward [12]. Among the reported PI3K and mTOR dual inhibitors, *N*-(5-(quinolin-6-yl)pyridin-3-yl)phenylsulfonamide is a class of important active compounds. In these structures, the two ring nitrogen atoms in pyridine and quinoline are the main components of pharmacophore. *N*-(2-Methoxy-5-(4-pyridazin-4-yl)quinolin-6-ylpyridin-3-yl)-2,4-difluorophenylsulfonamide, GSK2126458, was identified by GlaxoSmithKline as a potent, orally bioavailable dual inhibitor of PI3Kα and mTOR [13]. Having designed, synthesized and evaluated several classes of *N*-(2,5-disubstituted-pyridin-3-yl) phenylsulfonamides, Amgen Inc discovered that *N*-(2-chloro-5-(4-morpholinoquinolin-6-yl)pyridine-3-yl)-4-fluorophenylsulfonamide [14], *N*-(2-chloro-5-(2-acetylaminobenzo[*d*]thiazol-6-yl)pyridine-3-yl)-4-fluoro phenylsulfonamide [15] and *N*-(2-chloro-5-(2-acetylaminoimidazo[1,2-b]pyridazin-6-yl)pyridine-3-yl)-4-fluorophenylsulfonamide [16] were effective PI3Kα and mTOR dual inhibitors. Recently, they have reported that AMG 511 is a potent PI3Kα selective inhibitor [17]. Our group synthesized a series of [1,2,4]triazolo[1,5-α]pyridinylpyridines and evaluated their anticancer activity [18]. Meanwhile, other group reported 3D-

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http://dx.doi.org/10.1016/j.ejmech.2014.01.053

QSAR and docking studies of 3-pyridinyl heterocyclic derivatives as potent PI3K/mTOR inhibitors [19]. The first PI3Kα/mTOR dual inhibitor, BEZ235 developed by Novartis, is being in clinical trials [20]. The pharmacophore of PF-04691502 and PF-04979064 is similar to that of GSK2126458. They are also PI3Kα/mTOR dual inhibitors, developed by Pfizer in phase I/II clinical trials for treating solid tumors [21–23]. (Fig. 1).

The co-crystal of GSK2126458 with PI3Kγ protein has clarified the interaction of GSK2126458 with PI3K [13]. In the co-crystal structure, we find that the nitrogen atom in the pyridine ring can form two hydrogen bonds at the affinity pocket in PI3K kinase with the aid of a water molecule. One hydrogen atom in water molecule forms a hydrogen bond with the nitrogen atom in pyridine ring, the other hydrogen atom forms a hydrogen bond with the carboxyl in Asp841 and the oxygen atom in water molecule forms a hydrogen bond with the phenolic hydroxyl in Tyr867. Meanwhile, the nitrogen atom at 1-position in the quinoline ring can form a hydrogen bond with the Val882 at the hinge region in PI3K kinase. The interaction is outlined in Fig. 2.

In order to obtain a novel scaffold of anticancer agents, we propose that the complex of pyridine with a water molecule be replaced by the structure of benzamide on the basis of bioisostere (Fig. 2). In this way, benzamide can replace the pyridine ring in GSK2126458 to produce a novel scaffold of PI3K inhibitors. In this novel scaffold, we suspect that the oxygen atom in benzamide can form a hydrogen bond with the phenolic hydroxyl in Tyr867, and the hydrogen atom in benzamide can form a hydrogen bond with the carboxyl in Asp841 as well, which might indicate that 2-methoxy-3-phenylsulfonylamino-5-(quinolin-6-yl)benzamide shares the same pharmacophore (denoted as red in Fig. 2) with GSK2126458. In other words, 2-methoxy-3-phenylsulfonylamino-5-(quinazolin-6-yl or quinolin-6-yl)benzamides might interact with PI3K without the aid of water molecule, serve as a novel scaffold of PI3K inhibitors and exhibit potential anticancer effect. Thus, we further assume that this design may help us discover the novel PI3K inhibitors with a scaffold of 2-substituted-3-phenylsulfonylamino-5-(quinazolin-6-yl) benzamide by using bioisostere principle. Hereafter in this paper, we describe the synthesis of 2-substituted-3-phenylsulfonylamino-5-(quinazolin-6-yl or quinolin-6-yl)benzamides, and the evaluation of their bioactivity, anticancer effect *in vivo* as well.

2. Chemistry

The synthetic route for the title compounds **1a**–**h** and **2a**–**b** is outlined in Scheme 1.

The commercially available 5-bromo-3-nitro-2-methoxybenzoic acid **3a** was converted into corresponding intermediate **4a**–**d** with the conventional steps. Reduction of **4** with stannous chloride in concentrated hydrochloric acid produced corresponding amines. Without further purification, the amines were converted into sulfamides **5a**–**h**. The commercially available 6-bromo-4-hydroxyquinozoline or 6-bromo-4-hydroxyquinoline was converted into 6-bromo-4-chloroquinozoline or 6-bromo-4-chloroquinoline by reaction with thionyl chloride and phosphorus oxychloride. Without further purification, the reaction of 4-chloroquinozoline or 6-bromo-4-chloroquinoline with morpholine produced intermediate **6a** or **6b**. Catalyzed by $PdCl_2$(dppf), **6a** or **6b** was reacted with bis(pinacolato) diboron to produce arylboronic esters. Without isolation of arylboronic esters, intermediate **5**, $PdCl_2$(dppf), water and sodium carbonate were added to the above reaction mixture. The resulted mixture was refluxed for 1–2 h to produce the title compounds **1** or **2**. The preparation of arylboronic esters and Suzuki coupling were completed in one pot. 1,2-dimethoxyethane was used as solvent to improve the yield.

To investigate the different activity of substituted groups at 2-position in the benzamide ring, 5-bromo-2-chloro-3-nitrobenzoic acid and 5-bromo-3-nitrobenzoic acid were used as starting materials to synthesize the compounds **1i**–**k**. The synthetic route for the compounds is shown in Scheme 2. The synthetic procedure is similar to that of **1a**.

3. Pharmacology

3.1. Antiproliferative assays in vitro

We evaluated antiproliferative activities of compounds **1a**–**k**, **2a** and **2b** against four human cancer cell lines, including human lung adenocarcinoma epithelial cell line (A549), human colon carcinoma cell line (HCT-116), human glioblastoma-astrocytoma epithelial-like cell line (U-87 MG) and human epidermis mouth carcinoma cell line (KB) by applying the MTT colorimetric assay. The PI3K and mTOR dual inhibitor BEZ235 was used as the positive control.

3.2. PI3K and mTOR enzymatic activity assay

Selected compound **1a** was evaluated for its PI3K and mTOR enzymatic activity using a ATP depletion assay [24]. BEZ235 was used as the positive drug. Compounds **1a** and BEZ235 were dissolved in DMSO and tested at final concentrations of 1.0, 3.3, 10, 33, 100, 333, 1000, 3333, 10,000 nM. IC_{50}s of compounds were calculated according to inhibitory rates using GraphPad Prism5.

3.3. Western blot assay

To further determine whether these compounds affect the PI3K/AKT/mTOR signaling pathway, we evaluated the suppressive effects of compound **1a** at 10 μM and positive compound BEZ235 at 10 μM on AKT and p-AKT^{473} in HCT-116 cells through Western blot.

3.4. Anticancer effects in established nude mouse U-87 MG xenograft model in vivo

To preliminarily test the anticancer effects of the synthesized compounds *in vivo*, a test using U-87 MG xenograft model was performed. Compound **1a** displayed evident activities against the

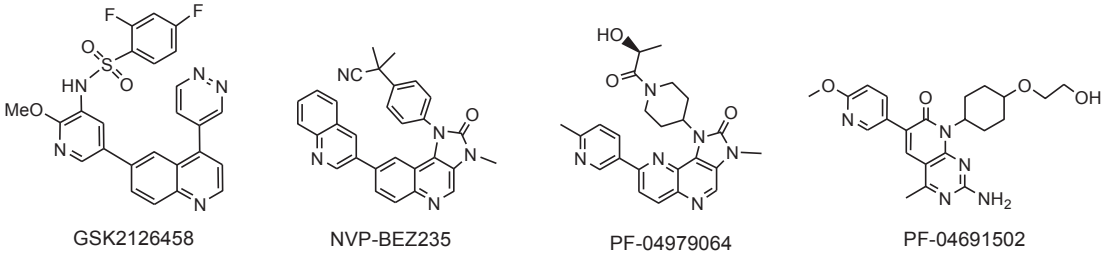


Fig. 1. Some structures of PI3Kα and mTOR dual inhibitors developing in clinical trials.

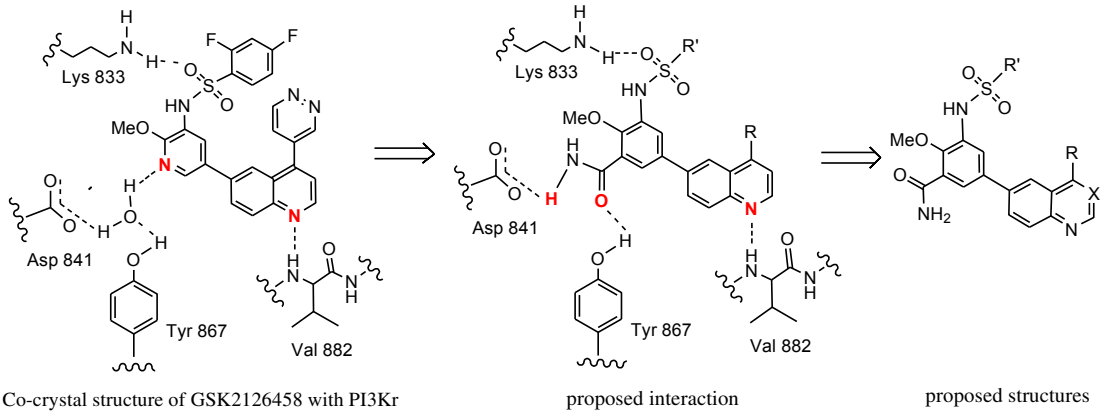
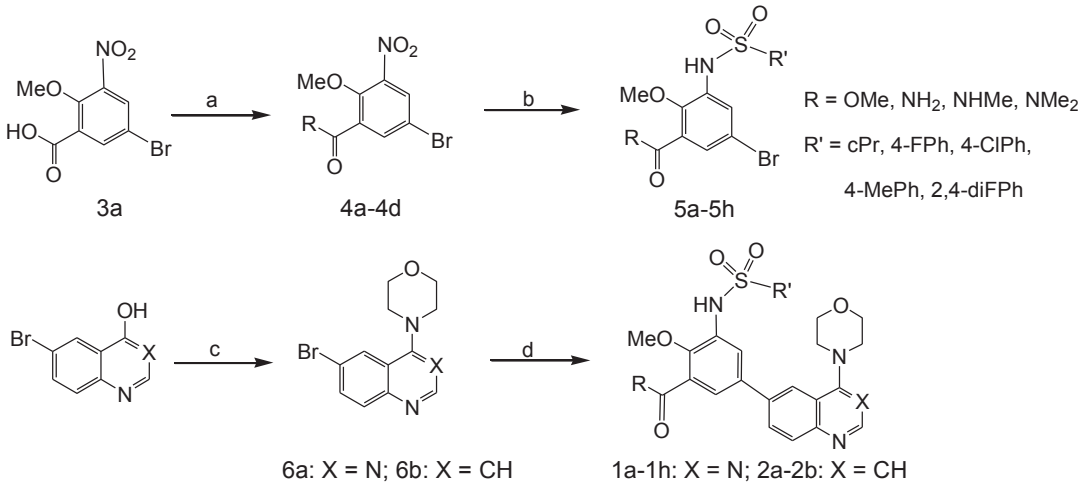


Fig. 2. The design idea of the research subject. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

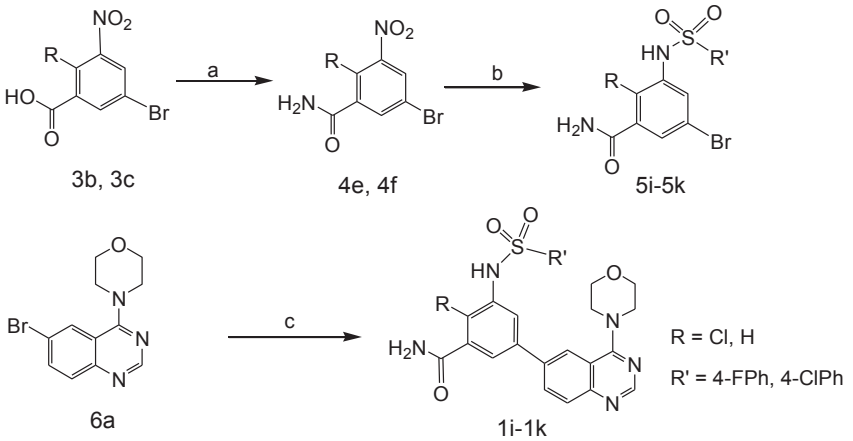


Scheme 1. a) i: Me_2SO_4, K_2CO_3, acetone; or ii: $SOCl_2$, DMF, toluene, reflux, 2 h; then amine, THF, r.t, 1 h. b) i: $SnCl_2{\cdot}2H_2O$, conc. HCl, r.t, overnight; ii: sulfonyl chloride, pyridine, 0 °C-r.t, overnight. c) i: $POCl_3$, $SOCl_2$, toluene, DMF, reflux, 4 h; ii: morpholine, isopropanol, reflux, 1 h. d) i: bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), 1,2-dimethoxyethane, reflux, 2 h; ii: 5, H_2O, Na_2CO_3, $PdCl_2$(dppf), reflux, 2 h.

four carcinoma cell lines and was thus chosen to evaluate its anti-cancer effect *in vivo*. BEZ235 (20 mg/kg) was used as positive drug. **1a** was dosed orally at 20 mg/kg or 50 mg/kg once a day for 12 days. The control group was administrated orally the solvent only.

3.5. Docking studies

We performed docking analysis by utilizing the C-DOCKER program within Discovery Studio 2.5 software package to further



Scheme 2. a) i: $SOCl_2$, DMF, toluene, reflux, 1 h; ii: aqueous ammonia, THF, r.t, 1 h. b) i: $SnCl_2{\cdot}2H_2O$, conc. HCl, r.t, overnight; ii: sulfonyl chloride, pyridine, 0 °C-r.t, overnight. c) i: bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), 1,2-dimethoxyethane, reflux, 2 h; ii: **5**, H_2O, Na_2CO_3, $PdCl_2$(dppf), reflux, 2 h.

look into the binding mode of the compound **1a**. Docking simulations were performed on human PI3Kγ (PDB code 3L08) [10].

4. Results and discussion

4.1. Chemistry

All the newly synthesized compounds show satisfactory analyses for the proposed structures, which were characterized on the basis of their ^{1}H NMR, ^{13}C NMR and HRMS. The structures of reported compounds were characterized by ^{1}H NMR and HRMS.

4.2. Antiproliferative assays in vitro

The results of the antiproliferative activities are summarized in Table 1. Firstly, compounds **1a**–**e** exhibited significant activities against the four cancer cell lines, especially against HCT-116, which might be related to PI3Kα mutant in HCT-116. The fact that compound **1a** (IC_{50} = 0.54 μM against HCT-116) was more potent than compound **1i** (IC_{50} = 31.60 μM against HCT-116) and **1j** (IC_{50} = 20.26 μM against HCT-116) indicates that the title compound with a methoxy at 2-position (R^2) of benzamide ring may improve the antiproliferative activity. To further investigate the structure–activity relationship (SAR) of compound **1**, we synthesized compounds **1f**, **1g** and **1h** by changing substituent R^1. As we had expected, almost all the activities of compounds **1f** and **1g** (IC_{50} > 50 μM) were weaken or disappeared. The activity of **1h** distinctly decreased compared with **1a** against the four cancer call lines. These results strongly support our design idea that amino group at R^1 position is essential to maintain the interactions of inhibitor with PI3K protein. Compound **1e** (IC_{50} = 3.74 μM against HCT-116) was less potent than **1a**, **1b** and **1c** (IC_{50} = 0.54–0.85 μM against HCT-116), indicating that aromatic group at position of R^3 is more beneficial to activity than cyclopropyl group. When 4-fluorophenyl (**1a** and **2a**) was replaced by 2,4-difluorophenyl (**1d** and **2b**) at position of R^3, the antiproliferative activities of compounds did not improve. The activities of **1a** (IC_{50} = 0.54 μM against HCT-116) and **1d** (IC_{50} = 1.92 μM against HCT-116) were more potent than those of **2a** (IC_{50} = 3.84 μM against HCT-116) and **2b** (IC_{50} = 4.71 μM against HCT-116), which suggests that a fragment of quinazoline at 5-position of benzamide is favorable to maintain the activity. From the above mentioned results we could detect a SAR in which amino at R^1, methoxy at R^2 and aryl at R^3 are favorable for antiproliferative activity. In its antiproliferative activity, the IC_{50} of compound **1a** is comparable to that of PI3K and mTOR dual inhibitor BEZ235. Therefore, we further investigated compound **1a**.

Table 2
Enzymatic activities of compound **1a** against PI3K and mTORC1 (IC_{50}, nM).

Kinase	**1a**	BEZ235
mTORC1	65	18
PI3Kα	14	58
PI3Kβ	190	15
PI3Kγ	56	65
PI3Kδ	74	97

4.3. PI3K and mTOR enzymatic activity assay

The results of the PI3K and mTOR enzymatic activity are summarized in Table 2.

Compound **1a** exhibited significant activities against PI3K and mTORC1. The activity against PI3Kα is four-fold higher than the other kinases tested. These results suggest that compound **1a** is a selective PI3Kα inhibitor.

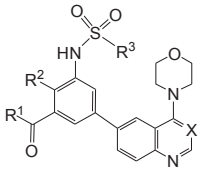
4.4. Western blot assay

As shown in Fig. 3, the suppressive effect of compound **1a** on p-AKT^{473} was a slightly stronger than that of BEZ235. The results suggest compound **1a** inhibit the PI3K/AKT/mTOR pathway and thus is a potential PI3K inhibitor.

4.5. Anticancer effects in established nude mouse U-87 MG xenograft model in vivo

The change in the tumor volumes was observed in Fig. 4 (A). In this model, treatment groups with compound **1a** at 20 mg/kg or 50 mg/kg significantly inhibit tumor growth by 30.05% and 57.20%, compared to

Table 1
Antiproliferative activities of compounds **1a**–**k** and **2a**, **2b** against four human cancer cell lines ($\bar{x} \pm s$, n = 3).



Compds	R^1	R^2	R^3	X	IC_{50} (μM)			
					A549	HCT-116	U87 MG	KB
1a	NH_2	OMe	4-FPh	N	4.32 ± 1.52	0.54 ± 0.28	1.37 ± 0.40	4.45 ± 2.82
1b	NH_2	OMe	4-ClPh	N	3.85 ± 1.52	0.96 ± 0.02	1.12 ± 0.07	14.61 ± 3.68
1c	NH_2	OMe	4-MePh	N	2.18 ± 1.10	0.85 ± 0.16	1.06 ± 0.57	3.59 ± 0.75
1d	NH_2	OMe	2,4-diFPh	N	5.52 ± 2.14	1.92 ± 1.08	2.88 ± 1.66	2.69 ± 1.41
1e	NH_2	OMe	cPr	N	9.80 ± 1.36	3.74 ± 1.03	5.21 ± 1.87	4.02 ± 0.98
1f	NHMe	OMe	4-FPh	N	>50	>50	>50	>50
1g	NMe_2	OMe	4-FPh	N	>50	>50	>50	>50
1h	OMe	OMe	4-FPh	N	35.19 ± 7.13	26.60 ± 4.38	7.80 ± 1.53	5.96 ± 2.02
1i	NH_2	Cl	4-FPh	N	>50	31.60 ± 5.12	>50	33.62 ± 4.16
1j	NH_2	H	4-FPh	N	>50	20.26 ± 4.09	20.80 ± 4.83	16.76 ± 3.88
1k	NH_2	H	4-ClPh	N	>50	12.31 ± 3.13	11.85 ± 3.65	10.74 ± 3.01
2a	NH_2	OMe	4-FPh	H	4.85 ± 1.87	3.84 ± 0.88	3.28 ± 1.61	4.00 ± 0.69
2b	NH_2	OMe	2,4-diFPh	H	6.49 ± 1.77	4.71 ± 2.49	5.09 ± ± 2.77	4.47 ± 2.98
BEZ235					0.54 ± 0.36	1.16 ± 0.15	1.32 ± 0.41	3.34 ± 2.43

the control group, respectively. BEZ235 group displayed a delay in tumor growth by 42.44% with 20 mg/kg. These results suggest that **1a** display significant inhibitory effect on the tumor growth.

The change in mouse body weights in the four groups is outlined in Fig 4 (B). The loss of weight in the tested animals was observed in two dosages groups of **1a** and BEZ235 group, indicating that compound **1a** and BEZ235 display some toxicity at the dosage administered. After the medicative was stopped, mouse body weights recovered gradually.

4.6. Docking studies

The docking result of compound **1a** with PI3Kγ (Fig. 5) has the following three indications: (a) 1-position of quinazoline group can form a hydrogen bond with Val882; (b) The oxygen atom of benzamide can form one hydrogen bond with Tyr867. The hydrogen atom of benzamide can form a hydrogen bond with Asp841. These interactions indicate that benzamide can replace the complex of pyridine ring in the structure of GSK2126458 with water molecule; (c) The oxygen of sulfonylamide and methoxy group at 2-position of benzamide can form two hydrogen bonds with Lys833. As for compound **1i** or **1j**, chloride or hydrogen atom at 2-position of benzamide cannot form hydrogen bond with Lys833, which suggest that the methoxy group is a more suitable substitute group than chloride in compound **1**.

5. Conclusion

The present study proves that 2-substituted-3-sulfonamino-5-(quinazolin-6-yl or quinolin-6-yl)benzamide can serve as a novel structure of PI3K inhibitors and anticancer agents. Thirteen compounds were synthesized, whose structures were characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The results of antiproliferative activities indicate that title compounds exhibit significant activity against the four cancer cell lines, especially against HCT-116. The SAR of these compounds indicates that a methoxy at 2-position of benzamide ring can improve the inhibitory activity of title compounds. The PI3K and mTOR enzymatic activity assay and Western blot assay results of compound **1a** suggest that **1a** can block the PI3K/AKT/mTOR pathway. Furthermore, compound **1a** significantly exhibited inhibitory effect on tumor growth in established nude mice U-87 MG xenograft model. These findings strongly support our hypothesis that the structure of benzamide can replace the complex of pyridine with a water molecule to design novel PI3K inhibitors and anticancer agents.

6. Experimental protocols

6.1. 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 Beijing micromelting-point apparatus and thermometer was uncorrected. ^{1}H NMR spectra and ^{13}C 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 exact mass measurements were performed using electrospray ionization (positive mode) on a quadrupole time-of-flight (QTOF) mass spectrometer (Maxis Q-TOF, Bruker Inc.).

6.1.1. Methyl 5-bromo-2-methoxy-3-nitrobenzate (*4a*)

To a solution of compound **3a** (8.0 g, 29.0 mmol) in acetone (100 ml) were added K_2CO_3 (6.5 g, 47.0 mmol) and Me_2SO_4 (4.5 ml, 45.0 mmol). The reaction mixture was refluxed with stirring for 6 h, cooled to room temperature and filtrated. The filtrate was concentrated in vacuum and the residue was suspended in water1 (100 ml). The mixture was extracted with ethyl acetate (40 ml ×3). The combined organic phase was washed with saturated solution of Na_2CO_3 and brine, dried over anhydrous Na_2SO_4 and concentrated to afford title compound (7.7 g, 87.0%) as an oil, which was solidified in one day keeping. mp 60.0–60.5 °C. ^{1}H NMR ($CDCl_3$) δ: 8.17 (1H, d, J = 2.4 Hz, Ar–H), 8.05 (1H, d, J = 2.4 Hz, Ar–H), 4.02 (3H, s, OCH_3), 3.99 (3H, s, OCH_3). ESI-HRMS m/z: calcd for $C_9H_8BrNO_5$ $[M + H]^+$: 288.9586; found 288.9590, 290.9568.

6.1.2. 5-Bromo-2-methoxy-3-nitrobenzamide (*4b*)

The mixture of 5-bromo-2-methoxy-3-nitrobenzoic acid **3a** (7.2 g, 26.0 mmol), thionyl chloride (10 ml, 137.0 mmol), toluene (20 ml) and DMF (3 drops) was refluxed for 2 h. The volatile was removed in vacuum to afford a brown oil which was diluted with dry THF (20 ml). The obtained solution was added dropwise to the stirred ammonia water cooled by an ice-water bath. The reaction mixture was stirred at room temperature for 30 min. THF was removed in vacuum and the resultant solid was collected by filtration, washed with water and dried to yield **4b** (6.9 g, 96.2%) as a yellow solid. mp: 150.0–153.0 °C. ^{1}H NMR (DMSO-d_6) δ: 8.25 (1H, d, J = 2.4 Hz, Ar–H), 8.04 (1H, s, $CONH_2$), 7.91 (1H, d, J = 2.4 Hz, Ar–H), 7.87 (1H, s, $CONH_2$), 3.87 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ: 165.60, 149.26, 145.26, 136.14, 134.97, 128.59, 115.42, 63.78. ESI-HRMS m/z: calcd for $C_8H_8BrN_2O_4$ $[M + H]^+$: 274.9667; found 274.9665, 276.9644.

Compounds **4b** and **4f** were synthesized according to the procedure described in **4a**.

6.1.3. N-Methyl-5-bromo-2-methoxy-3-nitrobenzamide (*4c*)

Yield 84.4%, mp 142.0–142.5 °C. ^{1}H NMR ($CDCl_3$) δ: 8.41 (1H, d, J = 2.4 Hz, Ar–H), 8.05 (1H, d, J = 2.4 Hz, Ar–H), 7.35 (1H, s, NH), 3.98 (3H, s, OCH_3), 3.08 (3H, d, J = 5.2 Hz, NCH_3). ^{13}C NMR (DMSO-d_6) δ: 164.23, 149.27, 145.20, 136.23, 134.82, 128.57, 115.41, 63.72,

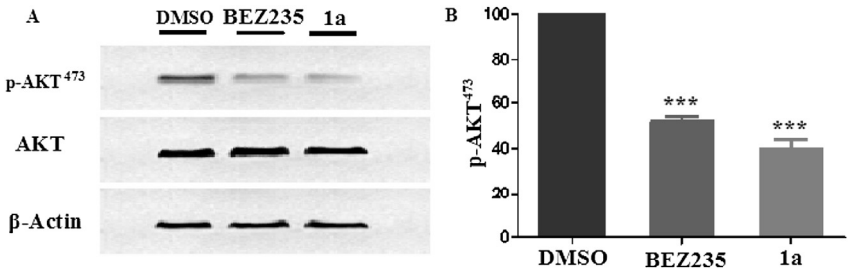


Fig. 3. Effects of BEZ235 and compound **1a** on AKT in HCT-116 cells. (A) Effect of BEZ235 and compound **1a** on the AKT and p-AKT^{473}. (B) The quantified effect of BEZ235 and compound **1a** on the AKT and p-AKT^{473}. Results are $\bar{x} \pm s$ for three independent experiments each performed in duplicate. ***$P < 0.001$*vs* DMSO.

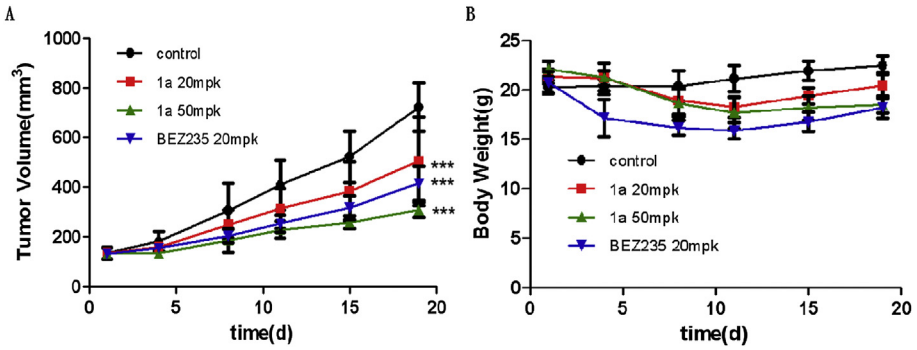


Fig. 4. *In vivo* efficacy of **1a** in U-87 MG xenograft tumor model on a once daily dosing schedule. (A) the change of tumor volume; (B) the change of mouse body weight. ***, $p < 0.001$ compared with the control group.

26.74. ESI-HRMS *m/z*: calcd for $C_9H_{10}BrN_2O_4$ $[M + H]^+$: 288.9824; found 288.9820, 290.9801.

*6.1.4. N,N-Dimethyl-5-bromo-2-methoxy-3-nitrobenzamide (**4d**)*

Yield 87.3%, mp 96.0–98.0 °C. ^{1}H NMR ($CDCl_3$) δ: 8.00 (1H, d, $J = 2.4$ Hz, Ar–H), 7.65 (1H, d, $J = 2.4$ Hz, Ar–H), 3.95 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 2.91 (3H, s, NCH_3). ^{13}C NMR (DMSO-d_6) δ: 164.93, 148.26, 144.65, 135.33, 134.84, 128.24, 115.64, 63.11, 38.50, 34.87. ESI-HRMS *m/z*: calcd for $C_{10}H_{12}BrN_2O_4$ $[M + H]^+$: 302.9980; found 302.9976; 302.9956.

*6.1.5. 5-Bromo-2-chloro-3-nitrobenzamide (**4e**)*

Yield 91.6%, mp 191.0–192.0 °C. ^{1}H NMR (DMSO-d_6) δ: 8.41 (1H, s, Ar–H), 8.17 (1H, s, $CONH_2$), 8.01 (1H, s, Ar–H), 7.95 (1H, s, $CONH_2$). ^{13}C NMR (DMSO-d_6) δ: 165.55, 149.61, 141.38, 134.58, 128.10, 121.14, 120.85. ESI-HRMS *m/z*: calcd for $C_7H_5BrClN_2O3$ $[M + H]^+$: 278.9172; found 278.9170, 280.9148.

*6.1.6. 5-Bromo-3-nitrobenzamide (**4f**)*

Yield 84.2%, mp 188.0–190.5 °C. ^{1}H NMR (DMSO-d_6): 8.63 (1H, s, Ar–H), 8.51 (1H, s, Ar–H), 8.44 (1H, s, Ar–H), 8.10 (2H, s, $CONH_2$). ^{13}C NMR (DMSO-d_6) δ: 164.76, 149.10, 137.72, 136.71, 128.98, 122.61, 121.98. ESI-HRMS *m/z*: calcd for $C_7H_6BrN_2O_3$ $[M + H]^+$: 244.9562; found 244.9560, 246.9538.

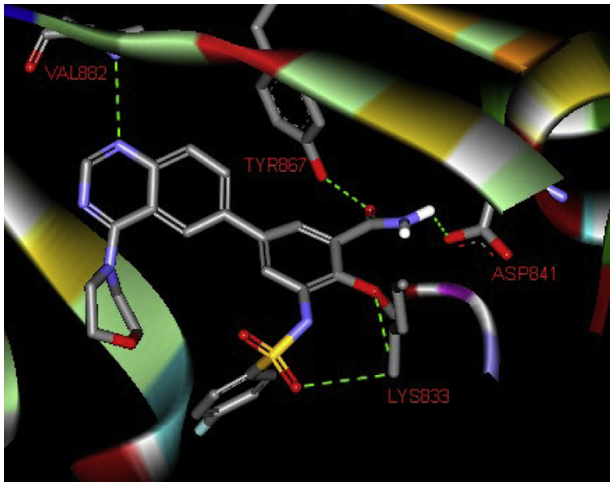


Fig. 5. Docking mode of compound **1a** with PI3Kγ. Selected residues Val882, Tyr867, Lys833, Asp841 and Asp964 are shown. Green dashed lines indicate hydrogen bond. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

*6.1.7. 5-Bromo-2-methoxy-3-(4-fluorophenylsulfonamino) benzamide (**5a**)*

To a suspension of compound **4a** (6.9 g, 25.0 mmol) in concentrated HCl (30 ml) was added $SnCl_2 \cdot 2H_2O$ (20.0 g, 88.0 mmol) in portions. After addition, the mixture was stirred at room temperature overnight, basified to pH 11 with saturated NaOH solution and extracted with ethyl acetate (70 ml ×4). The combined organic phase was washed with brine (100 ml ×3), dried over Na_2SO_4 and concentrated in vacuum to give reduced compound (6.1 g, quantitative) as light-yellow solid. To a solution of reduced product in pyridine (70 ml) was added 4-fluorophenylsulfonyl chloride (5.4 g, 27.5 mmol) in portions at 0 °C. Then the mixture was stirred at room temperature overnight. Pyridine was removed under reduced pressure to give a residue, which was solidified by adding H_2O (70 ml). The solid was filtered, washed with H_2O and dried to give a brown solid, which was recrystallized in ethanol to afford **5a** (8.6 g, 85.3%) as white solid. mp 186.0–188.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.18 (1H, s, SO_2NH), 7.89 (2H, dd, $J = 8.8$, 4.2 Hz, Ar–H), 7.79 (1H, s, $CONH_2$), 7.63 (1H, s, $CONH_2$), 7.48 (1H, d, $J = 1.6$ Hz, Ar–H), 7.46 (2H, t, $J = 9.0$ Hz, Ar–H), 7.34 (1H, d, $J = 1.6$ Hz, Ar–H), 3.45 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ: 166.64, 164.94 (d, $J_{C-F} = 250$ Hz), 149.09, 136.74, 132.75, 132.44, 130.25, 130.15, 128.14, 126.73, 117.19, 116.96, 115.23, 61.99. ESI-HRMS *m/z*: calcd for $C_{14}H_{13}BrFN_2O_4S$ $[M + H]^+$: 402.9763; found 402.9760, 402.9740.

Compounds **5b**–**k** were synthesized according to the procedure described in 5**a**.

*6.1.8. 5-Bromo-2-methoxy-3-(4-chlorophenylsulfonamino) benzamide (**5b**)*

Yield 84.3%, mp 177.5–178.5 °C. ^{1}H NMR (DMSO-d_6) δ: 10.26 (1H, s, SO_2NH), 7.82 (2H, d, $J = 8.8$ Hz, Ar–H), 7.81 (1H, s, $CONH_2$), 7.70 (2H, d, $J = 8.8$ Hz, Ar–H), 7.64 (1H, s, $CONH_2$), 7.48 (1H, d, $J = 2.4$ Hz, Ar–H), 7.34 (1H, d, $J = 2.4$ Hz, Ar–H), 3.45 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ: 166.64, 149.15, 139.24, 138.54, 132.77, 132.31, 130.02, 129.02, 128.25, 126.83, 115.22, 61.98. ESI-HRMS *m/z*: calcd for $C_{14}H_{13}BrClN_2O_4S$ $[M + H]^+$: 418.9468; found 418.9466, 420.9443.

*6.1.9. 5-Bromo-2-methoxy-3-(4-methylphenylsulfonamino) benzamide (**5c**)*

Yield 87.4%, mp 169.0–170.5 °C. ^{1}H NMR (DMSO-d_6) δ: 10.11 (1H, s, SO_2NH), 7.81 (1H, s, $CONH_2$), 7.72 (2H, d, $J = 8.0$ Hz, Ar–H), 7.64 (1H, s, $CONH_2$), 7.50 (1H, d, $J = 2.4$ Hz, Ar–H), 7.41 (2H, d, $J = 8.4$ Hz, Ar–H), 7.29 (1H, d, $J = 2.4$ Hz, Ar–H), 3.44 (3H, s, OCH_3), 2.36 (3H, s, Ar–CH_3). ^{13}C NMR (DMSO-d_6) δ: 166.65, 148.58, 144.16, 137.42, 132.88, 132.76, 130.28, 127.55, 127.14, 125.82, 115.29, 62.01, 21.46. ESI-HRMS *m/z*: calcd for $C_{15}H_{16}BrN_2O_4S$ $[M + H]^+$: 399.0014; found 399.0010, 400.9990.

*6.1.10. 5-Bromo-2-methoxy-3-(2,4-difluorophenylsulfonamino) benzamide (**5d**)*

Yield 75.4%, mp 152.0–153.0 °C. ^{1}H NMR ($CDCl_3$) δ: 8.05 (1H, m, Ar–H), 7.81 (1H, d, J = 1.6 Hz, Ar–H), 7.73 (1H, d, J = 1.6 Hz, Ar–H), 7.47 (1H, s, CONH), 7.09 (1H, m, Ar–H), 7.05 (1H, s, CONH), 7.00 (1H, m, Ar–H), 5.84 (1H, s, SO_2NH), 3.82 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ: 166.90, 159.58 (d, J_{C-F} = 256 Hz), 155.51 (d, J_{C-F} = 227 Hz), 150.13, 132.69, 132.47, 131.82, 128.94, 128.42, 125.21, 125.07, 115.00, 112.88, 112.69, 106.90, 106.65, 106.38, 61.89. ESI-HRMS m/z: calcd for $C_{14}H_{12}BrF_2N_2O_4S$ $[M + H]^+$: 420.9669; found 420.9667, 422.9646.

*6.1.11. 5-Bromo-2-methoxy-3-cyclopropylsulfonaminobenzamide (**5e**)*

Yield 57.5%, mp 175.5–177.0 °C. ^{1}H NMR (DMSO-d_6) δ: 9.55 (1H, s, SO_2NH), 7.85 (1H, s, $CONH_2$), 7.69 (1H, s, $CONH_2$), 7.64 (1H, d, J = 2.4 Hz, Ar–H), 7.39 (1H, d, J = 2.4 Hz, Ar–H), 3.77 (3H, s, OCH_3), 2.82 (1H, m, CH), 0.99 (4H, m, $2CH_2$). ^{13}C NMR (DMSO-d_6) δ: 166.66, 149.26, 133.44, 132.76, 127.78, 127.15, 115.42, 62.28, 30.96, 5.73 ($2CH_2$). ESI-HRMS m/z: calcd for $C_{11}H_{14}BrN_2O_4S$ $[M + H]^+$: 348.9858; found 348.9860, 350.9834.

*6.1.12. Methyl 5-bromo-2-methoxy-3-(4-fluorophenylsulfonamino) benzoate (**5f**)*

Yield 77.8%, mp 147.0–147.5 °C. ^{1}H NMR ($CDCl_3$) δ: 7.93 (1H, d, J = 2.8 Hz, Ar–H), 7.89 (2H, dd, J = 4.8, 8.8 Hz, Ar–H), 7.69 (1H, d, J = 2.4 Hz, Ar–H), 7.31 (1H, s, SO_2NH), 7.19 (2H, t, J = 8.8 Hz, Ar–H), 3.91 (3H, s, OCH_3), 3.63 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ: 164.71, 164.94 (d, J_{C-F} = 251 Hz), 151.18, 136.70, 133.41, 130.22, 130.13, 129.47, 129.09, 127.04, 117.20, 116.99, 115.33, 62.49, 53.13. ESI-HRMS m/z: calcd for $C_{15}H_{14}BrFNO_5S$ $[M + H]^+$: 417.9760; found 417.9764, 419.9748.

*6.1.13. N-Methyl-5-bromo-2-methoxy-3-(4-fluorophenylsulfonamino)benzamide (**5g**)*

Yield 83.6%, mp 170.5–171.5 °C. ^{1}H NMR ($CDCl_3$) δ: 7.88 (2H, dd, J = 5.2, 8.8 Hz, Ar–H), 7.82 (1H, s, Ar–H), 7.75 (1H, s, SO_2NH), 3.07 (3H, s, NCH_3), 7.19 (3H, t, J = 8.4 Hz, Ar–H), 6.94 (1H, s, NH), 3.51 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ: 165.33, 164.93 (d, J_{C-F} = 251 Hz), 149.01, 136.73, 132.78, 132.36, 130.24, 130.14, 128.11, 126.61, 117.19, 116.97, 115.20, 61.90, 26.65. ESI-HRMS m/z: calcd for $C_{15}H_{15}BrFN_2O_4S$ $[M + H]^+$: 416.9920; found 416.9918, 418.9896.

*6.1.14. N,N-Dimethyl-5-bromo-2-methoxy-3-(4-fluorophenylsulfonamino)benzamide (**5h**)*

Yield 89.1%, mp 169.0–170.0 °C. ^{1}H NMR ($CDCl_3$) δ: 7.86 (2H, dd, J = 4.8, 8.8 Hz, Ar–H), 7.79 (1H, d, J = 2.4 Hz, Ar–H), 7.17 (2H, t, J = 8.8 Hz, Ar–H), 7.15 (1H, s, SO_2NH), 7.13 (1H, d, J = 2.4 Hz, Ar–H), 3.54 (3H, s, OCH_3), 3.09 (3H, s, NCH_3), 2.75 (3H, s, NCH_3). ^{13}C NMR (DMSO-d_6) δ: 166.17, 165.08 (d, J_{C-F} = 246 Hz), 148.17, 136.53, 132.60, 131.77, 130.28, 130.18, 127.51, 127.31, 117.03, 116.81, 115.39, 61.61, 38.10, 34.68. ESI-HRMS m/z: calcd for $C_{16}H_{17}BrFN_2O_4S$ $[M + H]^+$: 431.0076; found 431.0074, 433.0053.

*6.1.15. 5-Bromo-2-chloro-3-(4-fluorophenylsulfonamino) benzamide (**5i**)*

Yield 75.1%, mp 228.0–229.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.47 (1H, s, SO_2NH), 7.96 (1H, s, $CONH_2$), 7.82 (2H, dd, J = 5.2, 8.8 Hz, Ar–H), 7.70 (1H, s, $CONH_2$), 7.47 (1H, s, Ar–H), 7.45 (2H, t, J = 8.8 Hz, Ar–H), 7.41 (1H, d, J = 2.0 Hz, Ar–H). ^{13}C NMR (DMSO-d_6) δ: 166.68, 165.00 (d, J_{C-F} = 251 Hz), 140.59, 136.90, 135.88, 130.29, 130.19, 129.86, 128.68, 125.41, 119.74, 117.21, 116.98. ESI-HRMS m/z: calcd for $C_{13}H_{10}BrClFN_2O_3S$ $[M + H]^+$: 406.9268; found 406.9264, 408.9244.

*6.1.16. 5-Bromo-3-(4-fluorophenylsulfonamino)benzamide (**5j**)*

Yield 83.1%, mp 238.0–240.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.77 (1H, s, SO_2NH), 8.06 (1H, s, Ar–H), 7.84 (2H, dd, J = 8.8, 5.2 Hz, Ar–H), 7.74 (1H, s, $CONH_2$), 7.60 (1H, s, Ar–H), 7.56 (1H, s, $CONH_2$), 7.44 (2H, t, J = 8.8 Hz, Ar–H), 7.38 (1H, s, Ar–H). ^{13}C NMR (DMSO-d_6) δ: 166.24, 164.86 (d, J_{C-F} = 250 Hz), 139.69, 137.81, 135.79, 130.26, 130.16, 125.95, 124.96, 122.12, 118.79, 117.32, 117.10. ESI-HRMS m/z: calcd for $C_{13}H_{11}BrFN_2O_3S$ $[M + H]^+$: 372.9658; found 372.9655, 374.9635.

*6.1.17. 5-Bromo-3-(4-chlorophenylsulfonamino)benzamide (**5k**)*

Yield 95.0%, mp 206.5–208.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.82 (1H, s, SO_2NH), 8.06 (1H, s, Ar–H), 7.78 (2H, d, J = 8.8 Hz, Ar–H), 7.76 (1H, s, $CONH_2$), 7.68 (2H, d, J = 8.8 Hz, Ar–H), 7.61 (1H, s, Ar–H), 7.56 (1H, s, $CONH_2$), 7.39 (1H, s, Ar–H). ^{13}C NMR (DMSO-d_6) δ: 166.20, 139.57, 138.69, 138.30, 137.83, 130.16, 129.03, 126.04, 125.01, 122.14, 118.82. ESI-HRMS m/z: calcd for $C_{13}H_{11}BrClN_2O_3S$ $[M + H]^+$: 388.9362; found 388.9360, 390.9340.

*6.1.18. 6-Bromo-4-morpholinoquinazoline (**6a**)*

To a mixture of 6-bromo-4-hydroxyquinazoline (7.9 g, 35.1 mmol) in $POCl_3$ (60 ml) was added DMF (1 ml). Then the mixture was heated to reflux under N_2 for 6 h. The dark clear solution was cooled to room temperature and concentrated in vacuum to produce a brown solid. To the mixture of above brown solid in 2-propanol (150 ml) was added morpholine (12.2 ml, 140.5 mmol). Then the mixture was heated to reflux under N_2 for 1 h, concentrated in vacuum to give a residue which was dissolved in ethyl acetate (200 ml). The ethyl acetate solution was washed with brine (80 ml ×5), dried over Na_2SO_4 and concentrated to give a brown oil, which was solidified on keeping to produce **6a** (8.9 g). Yield 85.7%, mp 112.0–114.0 °C. ^{1}H NMR ($CDCl_3$) δ: 8.75 (1H, s, Ar–H), 8.00 (1H, d, J = 1.6 Hz, Ar–H), 7.82 (1H, d, J = 8.8 Hz, Ar–H), 7.80 (1H, dd, J = 9.2, 2.0 Hz, Ar–H), 3.90 (4H, t, J = 4.4 Hz, NCH_2), 3.79 (4H, t, J = 4.4 Hz, OCH_2). ESI-HRMS m/z: calcd for $C_{12}H_{12}BrClN_3O$ $[M + H]^+$: 293.0164; found 293.0166, 295.0140.

*6.1.19. 6-Bromo-4-morpholinoquinoline (**6b**)*

Yield 88.1%, mp: 72.0–73.0 °C. ^{1}H NMR ($CDCl_3$) δ: 8.76 (1H, d, J = 4.8 Hz, Ar–H), 8.17 (1H, d, J = 1.6 Hz, Ar–H), 8.00 (1H, d, J = 8.8 Hz, Ar–H), 7.76 (1H, dd, J = 1.6, 8.8 Hz, Ar–H), 6.91 (1H, d, J = 4.8 Hz, Ar–H), 4.02 (4H, t, J = 4.4 Hz, OCH_2), 3.26 (4H, t, J = 4.4 Hz, NCH_2). ESI-HRMS m/z: calcd for $C_{13}H_{11}BrClN_2O_3S$ $[M + H]^+$: 388.9362; found 388.9360, 390.9340.

*6.1.20. 3-(4-Fluorophenylsulfonamino)-2-methoxy-5-(4-morpholinoquinazolin-6-yl)benzamide (**1a**)*

The mixture of **6a** (1.0 g, 3.4 mmol), bis(pinacolato)diboron (1.0 g, 4.1 mmol), potassium acetate (5.0 g, 10.2 mmol), $PdCl_2$(dppf) (126 mg, 0.16 mmol) and 1,2-dimethoxyethane (25 ml) was reflux for 2 h under nitrogen atmosphere, cooled to room temperature. To the resulted mixture were added **5a** (1.4 g, 3.4 mmol), Na_2CO_3 (1.1 g, 10.4 mmol), $PdCl_2$(dppf) (126 mg, 0.16 mmol) and water (12 ml). The reaction mixture was refluxed under nitrogen atmosphere for 2 h. The volatiles were removed in vacuum and the residue was purified through a column chromatography on silica with chloroform/methanol (V:V = 30:1) as eluent to produce **1a** (1.49 g, 81.4%). mp 168.5–170.5 °C. ^{1}H NMR (DMSO-d_6) δ: 10.13 (1H, s, SO_2NH), 8.67 (1H, s, Ar–H), 8.04 (1H, d, J = 8.8 Hz, Ar–H), 8.03 (1H, s, Ar–H), 7.92 (1H, d, J = 8.8 Hz, Ar–H), 7.91 (2H, dd, J = 8.8, 5.2 Hz, Ar–H), 7.85 (1H, s, $CONH_2$), 7.74 (1H, d, J = 2.0 Hz, Ar–H), 7.63 (1H, s, $CONH_2$), 7.60 (1H, d, J = 2.0 Hz, Ar–H), 7.45 (2H, t, J = 8.8 Hz, Ar–H), 3.80 (8H, s, OCH_2, NCH_2), 3.49 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ: 167.96, 164.83 (d, J_{C-F} = 250 Hz), 164.25, 154.24, 151.22, 149.99, 137.20, 136.31, 134.65, 131.83, 131.27, 130.23, 130.13, 129.41, 124.71, 123.55,

122.83, 117.10, 116.88, 116.42, 66.45 ($2CH_2$), 61.91, 50.23 ($2CH_2$). ESI-HRMS *m/z*: calcd for $C_{26}H_{24}FN_5O_5S$ $[M + H]^+$: 538.1560; found 538.1557.

Compounds **1b**–**k**, **2a** and **2b** were synthesized according to the procedure described in **1a**.

*6.1.21. 3-(4-Chlorophenylsulfonamino)-2-methoxy-5-(4-morpholinoquinazolin-6-yl)benzamide (**1b**)*

Yield 68.5%, mp 134.0–137.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.19 (1H, s, SO_2NH), 8.67 (1H, s, Ar–H), 8.04 (2H, m, Ar–H), 7.92 (1H, d, J = 8.8 Hz, Ar–H), 7.85 (3H, m, Ar–H), 7.73 (1H, d, J = 2.4 Hz, Ar–H), 7.70 (1H, s, $CONH_2$), 7.68 (1H, s, Ar–H), 7.63 (1H, s, $CONH_2$), 7.61 (1H, d, J = 2.4 Hz, Ar–H), 3.81 (8H, s, OCH_2, NCH_2), 3.51 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ: 167.96, 164.24, 154.24, 151.23, 150.09, 139.70, 138.33, 136.28, 134.64, 131.84, 131.29, 131.15, 129.95, 129.40, 129.04, 124.82, 123.68, 122.84, 116.41, 66.45 ($2CH_2$), 61.90, 50.23 ($2CH_2$). ESI-HRMS *m/z*: calcd for $C_{26}H_{24}ClN_5O_5S$ $[M + H]^+$: 554.1265; found 554.1260.

*6.1.22. 3-(4-Methylphenylsulfonamino)-2-methoxy-5-(4-morpholinoquinazolin-6-yl)benzamide (**1c**)*

Yield 72.1%, mp 146.0–147.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.00 (1H, s, SO_2NH), 8.67 (1H, s, Ar–H), 8.02 (1H, s, Ar–H), 8.01 (1H, d, J = 8.0 Hz, Ar–H), 7.92 (1H, d, J = 9.2 Hz, Ar–H), 7.85 (1H, s, $CONH_2$), 7.75 (2H, d, J = 8.4 Hz, Ar–H), 7.74 (1H, d, J = 2.4 Hz, Ar–H), 7.61 (1H, s, $CONH_2$), 7.57 (1H, d, J = 2.4 Hz, Ar–H), 7.45 (2H, d, J = 8.0 Hz, Ar–H), 3.80 (8H, s, OCH_2, NCH_2), 3.51 (3H, s, OCH_3), 2.35 (3H, s, Ar–CH_3). ^{13}C NMR (DMSO-d_6) δ: 167.95, 164.25, 154.25, 151.23, 149.58, 143.91, 137.91, 136.39, 134.60, 131.81, 131.75, 131.27, 130.21, 129.43, 127.16, 124.15, 122.74, 122.64, 116.43, 66.47 ($2CH_2$), 61.94, 50.23 ($2CH_2$), 21.43. ESI-HRMS *m/z*: calcd for $C_{27}H_{27}N_5O_5S$ $[M + H]^+$: 534.1811; found 534.1809.

*6.1.23. 3-(2,4-Difluorophenylsulfonamino)-2-methoxy-5-(4-morpholinoquinazolin-6-yl)benzamide (**1d**)*

Yield 61.5%, mp 112.0–116.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.44 (1H, b, SO_2NH) 8.73 (1H, d, J = 5.2 Hz, Ar–H), 8.14 (1H, d, J = 2.0 Hz, Ar–H), 8.05 (1H, d, J = 8.8 Hz, Ar–H), 7.96 (1H, m, Ar–H), 7.89 (1H, s, CONH), 7.85 (1H, m, Ar–H), 7.76 (1H, d, J = 2.4 Hz, Ar–H), 7.66 (1H, d, J = 2.4 Hz, Ar–H), 7.62 (1H, s, CONH), 7.57 (1H, m, Ar–H), 7.28 (1H, m, Ar–H), 7.07 (1H, d, J = 4.8 Hz, Ar–H), 3.91 (4H, t, J = 4.4 Hz, NCH_2), 3.58 (3H, s, OCH_3), 3.23 (4H, d, J = 3.6 Hz, OCH_2). ^{13}C NMR (DMSO-d_6) δ: 167.97, 165.44 (d, J_{C-F} = 250 Hz), 164.24, 164.18, 159.42 (d, J_{C-F} = 249 Hz), 154.24, 151.22, 150.96, 136.23, 134.56, 132.42, 131.86, 131.20, 130.77, 129.40, 125.41, 125.13, 122.84, 121.50, 116.42, 112.70, 106.64, 66.44 ($2CH_2$), 61.81, 50.22 ($2CH_2$). ESI-HRMS *m/z*: calcd for $C_{27}H_{24}F_2N_4O_5S$ $[M + H]^+$: 555.1514; found 555.1519.

*6.1.24. 3-Cyclopropylsulfonamino-2-methoxy-5-(4-morpholinoquinazolin-6-yl)benzamide (**1e**)*

Yield 72.2%, mp 189.0–192.0 °C. ^{1}H NMR (DMSO-d_6) δ: 9.44 (1H, s, SO_2NH), 8.67 (1H, s, Ar–H), 8.12 (1H, d, J = 9.2 Hz, Ar–H), 8.09 (1H, s, Ar–H), 7.93 (1H, d, J = 8.8 Hz, Ar–H), 7.88 (2H, s, Ar–H, $CONH_2$), 7.67 (1H, s, Ar–H), 7.66 (1H, s, $CONH_2$), 3.86 (3H, s, OCH_3), 3.80 (8H, s, OCH_2, NCH_2), 1.99 (1H, s, CH), 1.01 (4H, m, $2CH_2$). ^{13}C NMR (DMSO-d_6) δ: 167.98, 164.28, 154.23, 151.21, 150.12, 136.52, 134.85, 132.26, 131.97, 131.31, 129.37, 124.28, 123.86, 122.91, 116.42, 66.46 ($2CH_2$), 62.26, 50.25 ($2CH_2$), 30.95, 5.75 ($2CH_2$). ESI-HRMS *m/z*: calcd for $C_{23}H_{25}N_5O_5S$ $[M + H]^+$: 484.1655; found 484.1652.

*6.1.25. N-Methyl-3-(4-fluorophenylsulfonamino)-2-methoxy-5-(4-morpholinoquinazolin-6-yl)benzamide (**1f**)*

Yield 43.5%, mp 199.5–201.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.12 (1H, s, SO_2NH), 8.67 (1H, s, Ar–H), 8.34 (1H, d, J = 4.4 Hz, Ar–H), 8.04 (1H, d, J = 6.4 Hz, Ar–H), 8.03 (1H, s, Ar–H), 7.92 (2H, dd, J = 8.6, 2.4 Hz, Ar–H), 7.90 (1H, s, CONH), 7.75 (1H, d, J = 1.6 Hz, Ar–H), 7.56 (1H, d, J = 2.4 Hz, Ar–H), 7.49 (2H, t, J = 8.8 Hz, Ar–H), 3.80 (8H, s, OCH_2, NCH_2), 3.45 (3H, s, OCH_3), 2.77 (3H, d, J = 4.8 Hz, NCH_3). ^{13}C NMR (DMSO-d_6) δ: 166.64, 164.82 (d, J_{C-F} = 250 Hz), 164.23, 154.24, 151.22, 149.84, 137.20, 136.26, 134.67, 131.83, 131.40, 131.20, 130.22, 130.12, 129.39, 124.60, 123.35, 122.81, 117.11, 116.89, 116.40, 66.45 ($2CH_2$), 61.83, 50.23 ($2CH_2$), 26.59. ESI-HRMS *m/z*: calcd for $C_{27}H_{26}FN_5O_5S$ $[M + H]^+$: 552.1717; found 552.1725.

*6.1.26. N,N-Dimethyl-3-(4-fluorophenylsulfonamino)-2-methoxy-5-(4-morpholinoquinazolin-6-yl)benzamide (**1g**)*

Yield 39.7%, mp 103.0–103.5 °C. ^{1}H NMR (DMSO-d_6) δ: 10.07 (1H, s, SO_2NH), 8.67 (1H, s, Ar–H), 8.06 (1H, m, Ar–H), 8.04 (1H, s, Ar–H), 7.90 (1H, d, J = 5.6 Hz, Ar–H), 7.85 (2H, dd, J = 8.8, 5.2 Hz, Ar–H), 7.73 (1H, d, J = 2.0 Hz, Ar–H), 7.43 (2H, t, J = 8.0 Hz, Ar–H), 7.41 (1H, d, J = 9.2 Hz, Ar–H), 3.81 (8H, s, OCH_2, NCH_2), 3.43 (3H, s, OCH_3), 2.99 (3H, s, NCH_3), 2.67 (3H, s, NCH_3). ^{13}C NMR ($CDCl_3$) δ: 168.10, 165.38, 164.68 (d, J_{C-F} = 251 Hz), 154.23, 151.30, 145.91, 136.53, 136.39, 135.17, 131.54, 130.16, 129.86, 129.77 (2CH), 129.46, 123.16, 122.63, 120.56, 116.63 (2CH), 116.41, 66.71 ($2CH_2$), 61.80, 50.37 ($2CH_2$), 38.23, 35.06. ESI-HRMS *m/z*: calcd for $C_{28}H_{28}FN_5O_5S$ $[M + H]^+$: 566.1873; found 566.1879.

*6.1.27. Methyl 3-(4-fluorophenylsulfonamino)-2-methoxy-5-(4-morpholinoquinazolin-6-yl)benzoate (**1h**)*

Yield 47.7%, mp > 250.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.20 (1H, s, SO_2NH), 8.68 (1H, s, Ar–H), 8.04 (2H, s, Ar–H), 7.89–7.93 (4H, m, Ar–H), 7.82 (1H, s, Ar–H), 7.45 (2H, t, J = 8.2 Hz, Ar–H), 3.86 (3H, s, OCH_3), 3.81 (8H, s, OCH_2, NCH_2), 3.46 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ: 166.04, 164.83 (d, J_{C-F} = 251 Hz), 164.20, 154.30, 151.73, 151.25, 137.12, 135.82, 134.97, 132.23, 131.79, 130.20, 130.10, 129.38, 125.94, 125.80, 125.69, 123.01, 117.11, 116.88, 116.34, 66.44 ($2CH_2$), 62.41, 53.00, 50.20 ($2CH_2$). ESI-HRMS *m/z*: calcd for $C_{27}H_{25}FN_4O_6S$ $[M + H]^+$: 553.1557; found 553.1552.

*6.1.28. 2-Chloro-3-(4-fluorophenylsulfonamino)-5-(4-morpholinoquinazolin-6-yl)benzamide (**1i**)*

Yield 62.7%, mp 223.0–225.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.43 (1H, s, SO_2NH), 8.67 (1H, s, Ar–H), 8.08 (1H, s, Ar–H), 8.06 (1H, d, J = 8.8 Hz, Ar–H), 7.97 (1H, s, $CONH_2$), 7.92 (1H, d, J = 8.8 Hz, Ar–H), 7.85 (2H, dd, J = 8.4, 5.2 Hz, Ar–H), 7.68 (3H, d, J = 2.8 Hz, 2Ar–H, $CONH_2$), 7.45 (2H, t, J = 8.8 Hz, Ar–H), 3.81 (8H, d, J = 4.8 Hz, OCH_2, NCH_2). ^{13}C NMR (DMSO-d_6) δ: 167.97, 164.90 (d, J_{C-F} = 251 Hz), 164.16, 154.42, 151.48, 139.45, 138.52, 137.41, 135.39, 135.20, 131.65, 130.28, 130.18, 129.41, 126.17, 125.76, 124.77, 123.43, 117.11, 116.38, 116.32, 66.43 ($2CH_2$), 50.17 ($2CH_2$). ESI-HRMS *m/z*: calcd for $C_{25}H_{21}ClFN_5O_4S$ $[M + H]^+$: 542.1065; found 542.1071.

*6.1.29. 3-(4-Fluorophenylsulfonamino)-5-(4-morpholinoquinazolin-6-yl)benzamide (**1j**)*

Yield 47.2%, mp 142.0–144.5 °C. ^{1}H NMR (DMSO-d_6) δ: 10.68 (1H, s, SO_2NH), 8.68 (1H, s, Ar–H), 8.14 (1H, s, Ar–H), 8.10 (1H, s, Ar–H), 8.08 (1H, d, J = 2.4 Hz, Ar–H), 7.97 (1H, s, $CONH_2$), 7.94 (1H, d, J = 9.2 Hz, Ar–H), 7.88 (2H, dd, J = 8.8, 5.2 Hz, Ar–H), 7.65 (1H, s, $CONH_2$), 7.63 (1H, s, Ar–H), 7.52 (1H, s, Ar–H), 7.43 (2H, t, J = 8.8 Hz, Ar–H), 3.81 (8H, s, OCH_2, NCH_2). ^{13}C NMR (DMSO-d_6) δ: 167.53, 164.86 (d, J_{C-F} = 251 Hz), 164.24, 154.37, 151.50, 140.54, 139.03, 136.80, 136.40, 136.18, 132.05, 130.25, 130.15, 129.39, 123.23, 122.03, 121.37, 119.35, 117.24, 117.02, 116.35, 66.54($2CH_2$), 50.21($2CH_2$). ESI-HRMS *m/z*: calcd for $C_{25}H_{22}FN_5O_4S$ $[M + H]^+$: 508.1455; found 508.1452.

*6.1.30. 3-(4-Chlorophenylsulfonamino)-5-(4-morpholinoquinazolin-6-yl)benzamide (**1k**)*

Yield 43.1%, mp 146.0–148.5 °C. ^{1}H NMR (DMSO-d_6) δ: 10.75 (1H, s, SO_2NH), 8.68 (1H, s, Ar–H), 8.16 (1H, s, Ar–H), 8.10 (1H, m,

Ar–H), 8.08 (1H, s, Ar–H), 7.98 (1H, s, $CONH_2$), 7.94 (1H, d, J = 9.2 Hz, Ar–H), 7.81 (2H, d, J = 8.8 Hz, Ar–H), 7.67 (2H, d, J = 8.8 Hz, Ar–H), 7.66 (1H, s, $CONH_2$), 7.63 (1H, s, Ar–H), 7.54 (1H, s, Ar–H), 3.81 (8H, s, OCH_2, NCH_2). ^{13}C NMR (DMSO-d_6) δ: 167.50, 164.23, 154.37, 151.50, 140.57, 138.89, 138.65, 136.82, 136.38, 132.04, 132.07, 129.38, 129.11, 129.05, 123.24, 122.14, 121.42, 119.39, 116.35, 66.45 ($2CH_2$), 50.21 ($2CH_2$). ESI-HRMS m/z: calcd for $C_{25}H_{22}ClN_5O_4S$ $[M + H]^+$: calcd 524.1159; found 524.1151.

6.1.31. 3-(4-Fluorophenylsulfonamino)-2-methoxy-5-(4-morpholinoquinolin-6-yl)benzamide (**2a**)

Yield 69.8%, mp 141.0–142.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.17 (1H, s, SO_2NH), 8.73 (1H, d, J = 5.2 Hz, Ar–H), 8.15 (1H, s, Ar–H), 8.05 (1H, d, J = 8.8 Hz, Ar–H), 7.96 (1H, s, $CONH_2$), 7.91 (2H, dd, J = 8.6, 5.6 Hz, Ar–H), 7.89 (1H, s, Ar–H), 7.81 (1H, s, Ar–H), 7.64 (1H, s, $CONH_2$), 7.62 (1H, d, J = 1.6 Hz, Ar–H), 7.45 (2H, t, J = 8.8 Hz, Ar–H), 7.07(1H, d, J = 4.8 Hz, Ar–H), 3.92 (4H, s, OCH_2), 3.50 (3H, s, OCH_3), 3.23 (4H, s, NCH_2). ^{13}C NMR (DMSO-d_6) δ: 168.00, 164.80 (d, J_{C-F} = 250 Hz), 156.63, 151.63, 149.79, 148.95, 137.29, 135.95, 135.01, 131.51, 131.19, 131.00, 130.14, 130.04, 128.14, 124.38, 123.24, 123.21, 121.25, 117.11, 116.88, 110.05, 66.56 ($2CH_2$), 61.91, 52.77 ($2CH_2$). ESI-HRMS m/z: calcd for $C_{27}H_{25}FN_4O_5S$ $[M + H]^+$: 537.1608; found 537.1616.

6.1.32. 3-(2,4-Difluorophenylsulfonamino)-2-methoxy-5-(4-morpholinoquinolin-6-yl) benzamide (**2b**)

Yield 52.8%, mp 111.0–116.0 °C. ^{1}H NMR (DMSO-d_6) δ: 10.44 (1H, b, SO_2NH), 8.73 (1H, d, J = 5.2 Hz, Ar–H), 8.14 (1H, d, J = 2.0 Hz, Ar–H), 8.05 (1H, d, J = 8.8 Hz, Ar–H), 7.96 (1H, m, Ar–H), 7.89 (1H, s, CONH), 7.85 (1H, m, Ar–H), 7.76 (1H, d, J = 2.4 Hz, Ar–H), 7.66 (1H, d, J = 2.4 Hz, Ar–H), 7.62 (1H, s, CONH), 7.57 (1H, m, Ar–H), 7.28 (1H, m, Ar–H), 7.07 (1H, d, J = 4.8 Hz, Ar–H), 3.91 (4H, t, J = 4.4 Hz, OCH_2), 3.58 (3H, s, OCH_3), 3.23 (4H, d, J = 3.6 Hz, NCH_2). ^{13}C NMR (DMSO-d_6) δ: 168.02, 165.43, 160.66, 158.17, 156.67, 151.56, 150.72, 148.86, 135.88, 134.94, 132.30, 131.85, 131.14, 130.92, 128.19, 125.10, 124.78, 124.0, 123.21, 121.29, 112.70, 110.02, 106.70, 66.54 ($2CH_2$), 61.82, 52.76 ($2CH_2$). ESI-HRMS m/z: calcd for $C_{27}H_{24}F_2N_4O_5S$ $[M + H]^+$: 555.1514; found 555.1519.

6.2. Biological assay methods

6.2.1. Cell culture

The human cell lines A549, HCT-116, U-87 MG or KB were maintained as a monolayer culture in DMEM, supplemented with 10% FBS in a humidified atmosphere (5% CO_2) at 37 °C.

6.2.2. Antiproliferative activity

3-[4,5-Dimethyl-2-thiazolyl]-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) was purchased from Sigma (St. Louis, MO, USA). Cellular chemosensitivity was determined by using a modified MTT method assay in vitro. Cell numbers were titrated to keep cells growing in the exponential phase throughout the 48 h incubation period. In brief, HCT-116, U-87 MG, A549 or KB cells in 100 μl culture medium were seeded into 96-well microplates at 3000–5000 cells per well respectively and cultured in DMEM 10% FBS, incubated at 37 °C for 24 h prior to drug exposure. Compounds were prepared in DMSO and then diluted with medium to the desired concentrations. Cells were treated with final concentrations of 100.0, 10.0, 1.0, 0.1 and 0.01 μM of tested compounds simultaneously and incubated for 72 h and then 20 μl of MTT solution (5 mg/ml in medium) was added to each well and incubated for 4 h. The formed blue formazan crystals were dissolved in 200 μl of DMSO. The optical density at 490 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 was calculated according to the inhibition ratios.

6.2.3. PI3K and mTOR enzymatic activity assay

PI3K and mTOR enzymatic activity assay was performed according to process described in supporting information of Ref. [24]. Briefly, different enzyme phosphorylate different substrates, the concentration of kinases and corresponding substrates was different. The enzyme reaction buffer contained 40 mM Tris–HCl, pH 7.4, 10 mM $MgCl_2$, 0.1 mg/ml BSA, 1 mM DTT, 10 μM ATP, enzyme and substrate. Various concentration of compounds was added to this enzyme reaction buffer, and the final reaction volume was 50 μl. The reaction mixture was incubated at 30 °C for 40 min, and then stopped by the addition of 25 μL of KinaseGlo solution. The stopped reaction was incubated for 5 min and the remaining ATP was then detected via luminescence.

6.2.4. Western blot assay

The suppressive activity of AKT and p-AKT^{473} in HCT-116 cells was determined by western blot. HCT-116 cells were seeded into six-well plates at 1×10^6 cells per well respectively and cultured in DMEM 10% FBS, incubated at 37 °C for 16 h prior to drug exposure. Cells were treated with final concentrations of 10 μM of compounds **1a**, BEZ235 and DMSO and incubated at 37 °C for 1 h. Cells were washed twice with ice-cold PBS and scraped into ice-cold cell lysis buffer. Then the cell lysates were clarified by centrifugation at 12,000 rpm for 20 min at 4 °C and the supernatant was collected. Protein content was measured by BCA protein Assay Kit and the proteins were separated on SDS-PAGE and then transferred onto nitrocellulose membranes. The membranes were incubated with antibodies against AKT (Cell Signaling Technology), p-Ser473 AKT (Cell Signaling Technology) and β-Acin (Santa Cruz), washed by TBST and then incubated with Mouse and rabbit horseradish peroxidase-conjugated secondary antibodies. The protein–antibody complexes were detected by chemiluminescence with a GeneGnome5 system (Syngene, UK). Protein bands were quantified using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

6.2.5. Anticancer effects in established nude mouse U-87 MG xenograft model in vivo

Mice (BALB/C, SPF grade, male, 18–20 g) were purchased from Shanghai Slakey Laboratory Animal Co., LTD and fed at Shanghai Institute of Pharmaceutical Industry. The experimental protocol was approved by Ethic Committee of Shanghai Institute of Pharmaceutical Industry.

U-87 MG cells at 3×10^6 were injected subcutaneously into the flank. Once the tumor xenografts reached 100 mm^3, all tumor-bearing nude mice were randomly divided into four groups, with 8 mice in control group and 5 mice in each drug group. In the control group, the same volume of solvent was administered orally. BEZ235 and **1a** were dissolved in NMP/PEG300 (1: 9). BEZ235 was dosed orally at 20 mg/kg to positive group. **1a** was dosed orally at 20 mg/kg and 50 mg/kg for the low and high dosage groups once a day for 12 days, respectively. Tumor volumes and body weights were recorded at intervals of 3 or 4 days. Tumor volume was calculated as length × width × width/2 and is reported in mm^3. Results are expressed as the mean ± standard error. The mice were anesthetized and sacrificed on day 21. The weights of the body, the neoplasm, and the volumes of neoplasm, were measured and inhibitory ratios for tumor volume and weight was calculated.

6.3. Molecular modeling

The protein–ligand complex crystal structure of GSK2126458 bound to PI3Kγ was chosen as the template to compare the docking

mode between compound **1a** bound to PI3Kγ and **1a** 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 GSK2126458. GSK2126458 and water molecule were removed and compound **1a** was placed. After end of molecular docking, ten docking poses were scored and selected based on calculated C-DOCKER energy.

Acknowledgments

Financial support from National Natural Science Foundation of China (Grant No. 21072156 and 81272448) is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.01.053.

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