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Identification of 3-amidoquinoline derivatives as PI3K/mTOR dual inhibitors with potential for cancer therapy†

Jiankang Zhang,^{‡,b} Xiaodong Ma,^{‡,c} Xiaoqing Lv,^{*a} Ming Li,^a Yanmei Zhao,^b Guoqiang Liu^a and Shuyu Zhan^aReceived 18th November 2016
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A new series of 3-amidoquinoline derivatives were designed, synthesized and evaluated as PI3K/mTOR dual inhibitors. Among them, five compounds showed potent PI3K α inhibitory activities ($IC_{50} < 10$ nM) and anti-proliferative activities ($IC_{50} < 1$ μ M). The representative compound **15a** can significantly inhibit other class I PI3Ks, mTOR and phosphorylation of pAkt(Ser473) at low nanomolar level, suggesting that **15a** was a potent PI3K/mTOR dual inhibitor. Moreover, **15a** displayed favorable pharmacokinetic properties *in vivo*.

1 Introduction

Hyperactivation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signalling pathway is common in cancer.^{1–4} There is abundant evidence demonstrating that genomic aberrations of PI3K and PTEN (PI3K negative regulator) are closely linked to the development and progression of a wide range of human cancers, including breast, colon, ovarian, prostate cancer and glioblastoma *etc.*^{5–8} In addition, mTOR-related multiple negative feedback loops, especially mTOR–S6K1–PI3K signalling, have been thought to contribute directly to the reactivation of this pathway, which results in the recrudescence of cancer.^{9,10} Given the pivotal role of PI3K and mTOR in cancer biology, combined targeting of PI3K and mTOR have been considered as an attractive anti-cancer strategy and is expected to effectively block signal transduction, overcome

negative feedbacks and reduce possibility of drug resistance.^{11–16} To date, several of PI3K and mTOR dual inhibitors have been advanced into clinical trials, such as GSK2126458, BEZ235, NVP-BGT226 and PF-06491502 (Fig. 1).^{9,17–21}

2 Rational design of PI3K/mTOR inhibitors

In our previous work, quinoline derivatives were identified as mTOR inhibitors and PI3K/mTOR dual inhibitors with high potency against cancer cells.^{22,23} Herein, we describe continued efforts in this field to pursue the novel PI3K/mTOR dual inhibitors through structural modification of GSK2126458.¹⁸ As a PI3K/mTOR dual inhibitor under clinical trials, GSK2126458 displayed remarkable *in vitro* and *in vivo* potency. To guide these efforts, we docked GSK2126458 into PI3K α protein (PDB code 4JPS) which is currently available.²⁴ As illustrated in Fig. 1, three hydrogen bonds are formed between the molecule and residues (Val851, Lys802, Asp810 and Tyr836). However, the pyridazine ring is not involved in the hydrogen-bonding interaction as it in the crystal structure of GSK2126458 binds to PI3K γ . The C-3 position of the quinoline ring pointed to the residue Ser854 in space. Therefore, our strategy is removal of pyridazine ring and introduction of various substituents onto the C-3 position of the quinoline ring to explore potential interactions with the residue Ser854. Based on these assumptions, a series of 3-amidoquinoline derivatives were designed and prepared (Fig. 2).

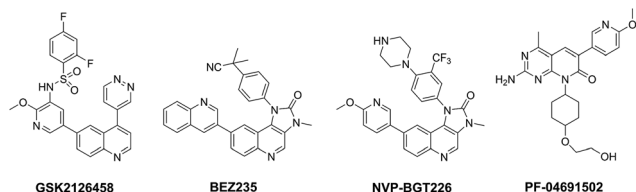


Fig. 1 Structures of clinical PI3K/mTOR dual inhibitors.

^aCollege of Medicine, Jiaxing University, Jiaxing 314001, Zhejiang Province, China. E-mail: lxqd1@126.com; Fax: +86-573-8364-1678; Tel: +86-573-8364-3848

^bDepartment of Pharmaceutical Preparation, Hangzhou Xixi Hospital, Hangzhou 310023, Zhejiang Province, China

^cDepartment of Medicinal Chemistry, School of Pharmacy, Anhui University of Chinese Medicine, Hefei 230031, Anhui Province, China

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‡ These authors contributed equally to this work.

3 Results and discussion

Synthesis

The synthetic route for 3-substituted quinolines **5**, **10**, **13** and **15a–l** is outlined in Scheme 1. Reaction of 4-chloroquinoline **1** with KI provided 4-iodoquinoline **2**, which was treated with

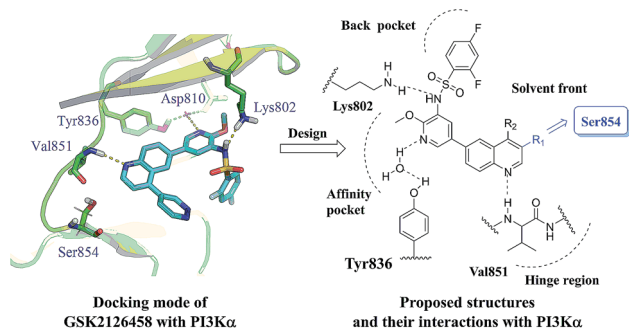


Fig. 2 The design concept based on the docking study.

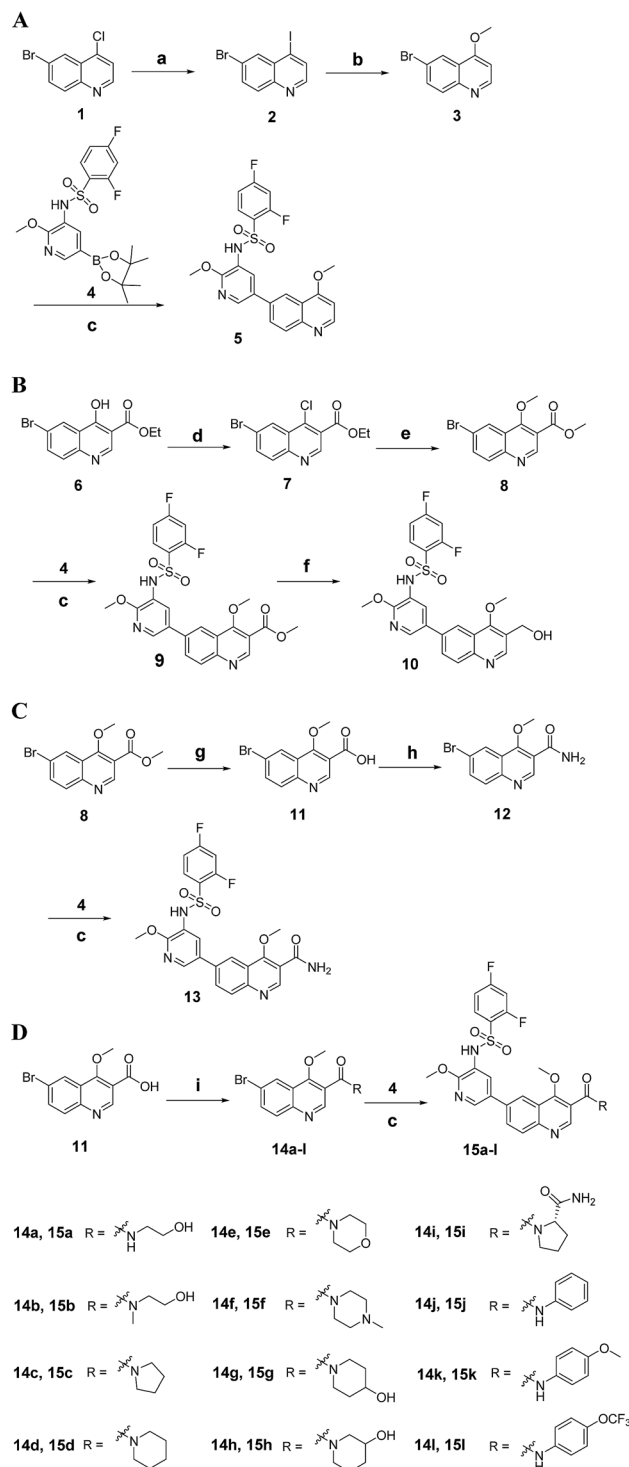
CH₃ONa to give 4-methoxyquinoline **3**. Coupling **3** with boric acid ester **4** via Suzuki reaction yielded corresponding target compound **5**. Following halogenation of 4-hydroxyquinoline derivative **6** with POCl₃, the newly formed 4-chloroquinoline derivative **7** was treated with CH₃ONa, leading to the generation of 4-methoxyquinoline derivative **8**. Coupling **8** with **4** afforded compound **9**, then reduction of **9** in the presence of DIBAL gave target compound **10**. Hydrolysis of **8** with NaOH produced quinoline-3-carboxylic acid derivative **11**, which was treated with ethyl chloroformate and NH₃·H₂O successively to afford the quinoline-3-carboxamide derivative **12**. Coupling **12** with **4** gave target compound **13**. Compound **11** can also be treated with amines in the presence of EDCI and HOBt to give other quinoline-3-carboxamide derivatives **14a–l**. Coupling **14a–l** with **4** yielded corresponding target compounds **15a–l**.

Biological evaluation

Enzymatic and anti-proliferative assays *in vitro*. Firstly, all derivatives were evaluated for their PI3K α inhibitory activities and exhibited moderate to potent activities (Table 1). Among them, compounds **10**, **13** and **15a** were more potent in PI3K α enzymatic assay than compounds **5** and **15b–i**. To illustrate their structure–activity relationships (SARs), docking analysis of **15a** bound to PI3K α (PDB code 4JPS) was performed utilizing the Discovery Studio 2.1 software package. As speculated, compound **15a** formed an additional hydrogen bond with the residue Ser854 *via* its hydrogen on the amide bond at the C-3 position of quinoline (Fig. 3).

In contrast, compounds **15b–i** without hydrogen proton on the amide bond lost the ability to form hydrogen bond with Ser854, leading to the reduction in enzymatic activities. As for **15j–l**, compounds **15k** and **15l** with methoxyl or trifluoromethoxyl group at C-4 position of phenyl group displayed 2–14 fold drop in enzymatic potency compared to **15j**. It suggested that substitution at C-4 position of phenyl is sensitive to the inhibitory activity and relatively large substituents had negative impact on enzymatic potency. Similarly, the evaluated derivatives showed moderate to potent mTOR activities as well.

The results of anti-proliferative assay showed that these derivatives displayed moderate to potent activities against PC-3 cell line (Table 1). Half of them with cellular activities below 1.0 μ M displayed better or equivalent anti-proliferation activities compared to that of BEZ235. In particular, compound **15a** with



Scheme 1 (A) The synthetic route for target compounds **5**, **10**, **13** and **15a–l**. Reagents and conditions (A–D): (a) HCl/EA, rt, 30 min, then KI, MeCN, reflux, 48 h; (b) NaOCH₃, CH₃OH, 50 °C, 12 h; (c) Pd(dppf)₂Cl₂, K₂CO₃, dioxane/H₂O, 100 °C, 10 h; (B) reagents and conditions: (d) POCl₃, 120 °C, 6 h; (e) NaOCH₃, CH₃OH, rt, 24 h; (f) DIBAL, rt, 6 h; (g) 2 N NaOH, rt, 2 h, then 2 N HCl; (h) ethyl chloroformate, NMM, THF, 30 min, then NH₃·H₂O, rt, 4 h; (i) amine, EDCI, HOBt, rt, 2 h.

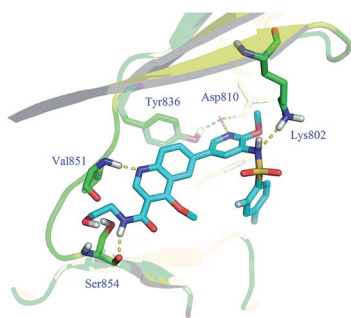
potent activities in both enzymatic and anti-proliferative assays, can be used as a promising lead compound for further biological evaluation.



Table 1 Enzymatic activities and anti-proliferative activities of compounds **5**, **10**, **13** and **15a–l**

Compd	IC ₅₀ ^a			
	PI3K α	mTOR	PC3	HCT116
5	8.6	116	3.41	4.46
10	1.0	8.9	0.90	1.16
13	2.6	1.5	1.29	0.15
15a	1.6	1.8	0.42	1.35
15b	7.9	13	3.54	5.90
15c	26	30	2.80	2.43
15d	27	36	0.93	3.67
15e	33	27	0.57	2.51
15f	60	46	0.55	2.13
15g	12	13	0.27	2.08
15h	13	15	0.79	5.55
15i	28	27	16.24	10.07
15j	5.4	189	0.96	5.05
15k	11	279	1.39	6.70
15l	72	246	1.44	10.41
BEZ235	35	21	0.51	0.22

^a IC₅₀ values (nM) for PI3K α and mTOR inhibitory activities; IC₅₀ values (μ M) for anti-proliferative activities; values are means of three experiments.

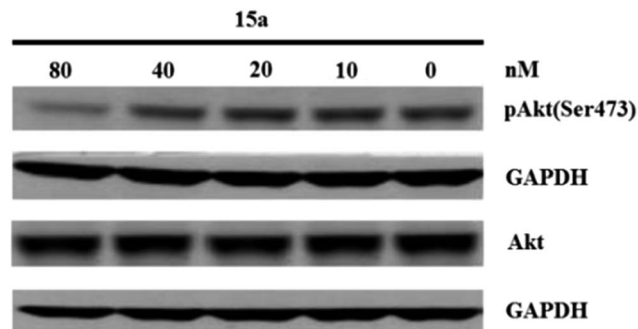
**Fig. 3** Docking mode of **15a** with PI3K α .

Class I PI3Ks enzymatic assays *in vitro*. Compound **15a** was further screened for its activities against other class I PI3Ks. As shown in Table 2, compound **15a** displayed significant inhibitory activities with IC₅₀ values at low nanomolar level, which was more potent than that of the positive control BEZ235, suggesting that **15a** was a potent PI3K/mTOR dual inhibitor.

Table 2 Enzymatic activities of compound **15a** against class I PI3Ks and mTOR (IC₅₀, nM)^a

Enzyme	Compd	
	15a	BEZ235
PI3K α	1.6	35
PI3K β	2.8	16
PI3K γ	4.4	26
PI3K δ	1.3	89
mTOR	1.8	21

^a Values are means of three experiments.

**Fig. 4** The suppressive effect of **15a** on pAkt(Ser473) in PC-3 cells.

Western blot assay *in vitro*. PC-3 prostate carcinoma cell have a mutation in PTEN that results in a constitutively activated PI3K signaling pathway. These cells were used to examine if **15a** could inhibit pAkt(Ser473) as a measure of inhibition of PI3K signaling. GAPDH was used as the internal control. After western blot assay, it demonstrates that **15a** significantly inhibits PI3K/Akt/mTOR signaling in PC-3 cells at the concentration of 80 nM (Fig. 4).

Pharmacokinetics study *in vivo*. On the basis of this promising profile, **15a** was further characterized through PK studies conducted in fasted male mice. PK parameters obtained in mice after oral administration at 5 mg kg⁻¹ as a crystalline suspension in 0.5% methylcellulose. Compound **15a** showed favorable *in vivo* plasma clearance (CL, 0.13 L h⁻¹ kg⁻¹), volume of distribution (V_d, 0.94 L kg⁻¹), mean residence time (MRT, 7.5 h), exposure (AUC, 39 722 h ng⁻¹ mL⁻¹), peak plasma concentration (C_{max}, 4624 ng mL⁻¹), and plasma terminal half-life (t_{1/2}, 5.2 h).

4 Conclusion

A new series of 3-amidoquinoline derivatives were designed by the docking analysis. Several synthesized target compounds exhibited strong enzymatic activities and anti-proliferative activities. Through the biological evaluation, **15a** was identified as a potentially interesting lead molecule, which significantly inhibited other class I PI3Ks and mTOR, as well as the phosphorylation of pAkt(Ser473) at low nanomolar level. Furthermore, compound **15a** exhibited favorable pharmacokinetic properties in the established mice model. These findings strongly support our hypothesis that incorporation of suitable substituents at the C-3 position of the quinoline ring could suppress PI3K/AKT/mTOR pathway effectively and achieve potent PI3K/mTOR dual inhibitors for cancer therapy.

5 Experimental section

Chemistry and chemical methods

¹H NMR and ¹³C NMR spectra were recorded on the Bruker 500 and 400 NMR instruments. Chemical shifts are given in ppm (δ) relative to TMS as internal standard, coupling constants (*J*) are in hertz (Hz), and signals are using the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, doublet of triplets; q, quartet; m,



multiplet, *etc.* Mass spectra (MS) and high resolution mass spectra (HRMS) were measured on Esquire-LC-00075 spectrometer and Waters GCT Premier spectrometer, respectively. IR (KBr disks) spectra were recorded on a Brüker Tensor 27 spectrometer. Melting points were determined with a B-540 Büchi melting-point apparatus. The purity of compounds was determined by Agilent 1260 HPLC system. Column chromatography and thin layer chromatography (TLC) were carried out using silica gel ZCX-3 and GF-254 (Qingdao Haiyang Chemical Co., Ltd.), respectively. Reagents and solvents were commercially available without further purification.

6-Bromo-4-iodoquinoline (2). To a solution of 6-bromo-4-chloroquinoline (**1**) (3.50 g, 14.46 mmol) in anhydrous EtOAc (20 mL) was added HCl-saturated EtOAc (40 mL) and a white precipitate formed immediately. After stirring for 30 min, the suspension was concentrated under vacuum to afford 6-bromo-4-chloroquinoline hydrochloride as an off white solid (3.91 g, 14.14 mmol).

A two-neck flask was charged with 6-bromo-4-chloroquinoline hydrochloride (3.91 g, 14.14 mmol), anhydrous potassium iodide (9.76 g, 70.70 mmol) and anhydrous acetonitrile (100 mL). The resulting slurry was stirred at reflux for 48 h and allowed to cool to room temperature. Saturated aqueous NaHCO₃ solution (40 mL) was added to the mixture, followed by 20 mL of a 5% sodium sulfite solution. The reaction mixture was extracted with CH₂Cl₂ (200 mL × 2). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to give the crude product, which was further purified by silica gel column chromatography (25% ethyl acetate/petroleum ether) to give the title compound (4.42 g, 13.27 mmol, 94% yield) as an off-white solid.¹⁸ ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.51 (d, *J* = 4.5 Hz, 1H, Ar-H), 8.21 (d, *J* = 4.5 Hz, 1H, Ar-H), 8.11 (t, *J* = 1.5 Hz, 1H, Ar-H), 7.97–7.91 (m, 2H, Ar-H). ESI-MS: *m/z* = 334 [M + H]⁺.

6-Bromo-4-methoxyquinoline (3). To a solution of **2** (200 mg, 0.60 mmol) in anhydrous methanol (10 mL) was added sodium methoxide (65 mg, 1.20 mmol) at 0 °C. The reaction mixture was then heated to 50 °C and stirred for 12 h. After the completion of reaction, the mixture was filtered and the precipitate was washed with water. The obtained solids were then dried under reduced pressure to give the title compound (120 mg, 0.51 mmol, 85% yield) as a white solid.²⁵ ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.78 (d, *J* = 5.0 Hz, 1H, Ar-H), 8.25 (d, *J* = 2.0 Hz, Ar-H), 7.90 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.86 (dd, *J* = 9.0, 2.0 Hz, 1H, Ar-H), 7.09 (d, *J* = 5.0 Hz, 1H, Ar-H), 4.05 (s, 3H, OCH₃). ESI-MS: *m/z* = 238 [M + H]⁺.

2,4-Difluoro-*N*-(2-methoxy-5-(4-methoxyquinolin-6-yl)pyridin-3-yl)benzenesulfonamide (5). To a three-neck round bottom flask was added **3** (36 mg, 0.15 mmol), commercially available 2,4-difluoro-*N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (**4**) (64 mg, 0.15 mmol),¹⁸ Pd(dppf)₂Cl₂ (11 mg, 0.015 mmol) and K₂CO₃ (62 mg, 0.45 mmol) in dioxane/H₂O (3/1). The flask was fitted with a N₂ inlet adaptor and purged with N₂ for 15 min. The reaction mixture was then sealed under an atmosphere of N₂ and stirred at 100 °C for 10 h. The crude mixture was concentrated under reduced pressure and the residue was dissolved in CH₂Cl₂, washed with water

twice, then the organic phase was dried over magnesium sulfate. The crude product was purified by silica gel column chromatography (2% CH₃OH/CH₂Cl₂) to give the title compound (19 mg, 0.042 mmol, 28% yield) as a white solid. Mp 180–181 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.37 (s, 1H, NH), 8.76 (d, *J* = 5.0 Hz, 1H, Ar-H), 8.45 (d, *J* = 2.5 Hz, 1H, Ar-H), 8.24 (d, *J* = 1.5 Hz, 1H, Ar-H), 8.06–8.01 (m, 2H, Ar-H), 7.95 (d, *J* = 2.5 Hz, 1H, Ar-H), 7.79 (m, 1H, Ar-H), 7.60 (m, 1H, Ar-H), 7.24 (td, *J* = 8.5, 2.5 Hz, 1H, Ar-H), 7.08 (d, *J* = 5.0 Hz, 1H, Ar-H), 4.10 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.6 (dd, *J*_{C-F} = 252.5, 11.5 Hz), 162.1, 159.9 (dd, *J*_{C-F} = 256.2, 16.6 Hz), 158.0, 152.4, 148.4, 142.9, 134.3, 133.9, 132.4 (d, *J*_{C-F} = 10.6 Hz), 130.1, 129.6, 128.8, 125.5 (dd, *J*_{C-F} = 14.0, 3.5 Hz), 121.4, 120.3, 118.9, 112.4 (d, *J*_{C-F} = 21.7, 3.7 Hz), 106.3 (t, *J*_{C-F} = 26.0 Hz), 102.0, 56.7, 53.9. IR (KBr) ν 3422, 3262, 2928, 2851, 1601, 1488, 1468, 1384, 1308, 1160, 1145 cm⁻¹. MS (ESI) *m/z* = 458 [M + H]⁺, HRMS (ESI) *m/z* calcd for C₂₂H₁₈F₂N₃O₄S [M + H]⁺ 458.0980, found 458.0986. HPLC purity = 97.8%.

Ethyl 6-bromo-4-chloroquinoline-3-carboxylate (7). To a 100 mL round-bottomed flask was added ethyl 6-bromo-4-hydroxyquinoline-3-carboxylate (**6**) (10.0 g, 33.90 mmol), POCl₃ (100 mL) and DMF (2 mL). The mixture was stirred at reflux for 6 h. After cooling to room temperature, the reaction mixture was poured into ice water (100 mL) and stirred for 1 h. Then the pH of the mixture was adjusted to 8 using saturated aqueous NaHCO₃. The mixture was extracted with EtOAc and the organic phase was dried over sodium sulfate and concentrated *in vacuo* to give the title compound (8.82 g, 28.18 mmol, 83% yield) as a brown solid.²² ESI-MS: *m/z* = 314 [M + H]⁺.

Methyl 6-bromo-4-methoxyquinoline-3-carboxylate (8). To a solution of **7** (8.0 g, 25.56 mmol) in anhydrous methanol (200 mL) was added sodium methoxide (2.76 g, 51.12) at 0 °C. The reaction mixture was stirred for 24 h at room temperature. After the completion of reaction, the mixture was filtered and the precipitate was washed with water. The obtained solids were then dried under reduced pressure to give the title compound (6.53 g, 22.14 mmol, 87% yield) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.04 (s, 1H, Ar-H), 8.40 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.02 (dd, *J* = 9.0, 2.0 Hz, 1H, Ar-H), 7.99 (d, *J* = 9.0 Hz, 1H, Ar-H), 4.10 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃). ESI-MS: *m/z* = 296 [M + H]⁺.

Methyl 6-(5-((2,4-difluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)-4-methoxyquinoline-3-carboxylate (9). This compound was prepared from **8** (221 mg, 0.75 mmol) and **4** (320 mg, 0.75 mmol) according to the general synthesis procedure of **5** to afford the title compound (90 mg, 0.18 mmol, 23% yield) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.37 (s, 1H, NH), 9.03 (s, 1H, Ar-H), 8.47 (s, 1H, Ar-H), 8.36 (s, 1H, Ar-H), 8.14 (m, 2H, Ar-H), 7.99 (s, 1H, Ar-H), 7.80 (m, 1H, Ar-H), 7.57 (m, 1H, Ar-H), 7.22 (m, 1H, Ar-H), 4.14 (s, 3H, OCH₃), 3.97 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃). ESI-MS: *m/z* = 516 [M + H]⁺.

2,4-Difluoro-*N*-(5-(3-(hydroxymethyl)-4-methoxyquinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide (10). DIBAL (300 μ L, 0.48 mmol) was added to a solution of **9** (60 mg, 0.12 mmol) in CH₂Cl₂ under an atmosphere of N₂ and stirred for 6 h at room temperature. After the completion of reaction, 1 N NaOH (4 mL) was added to the mixture and then stirred for 10 min. The



mixture was extracted with CH_2Cl_2 and the organic phase was dried over sodium sulfate. The crude product was purified by silica gel column chromatography (5% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give the title compound (9 mg, 0.018 mmol, 15% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H, NH), 8.89 (s, 1H, Ar-H), 8.42 (s, 1H, Ar-H), 8.19 (d, $J = 1.5$ Hz, 1H, Ar-H), 8.09 (d, $J = 9.0$ Hz, 1H, Ar-H), 7.99 (dd, $J = 9.0, 2.0$ Hz, 1H, Ar-H), 7.94 (s, 1H, Ar-H), 7.80 (m, 1H, Ar-H), 7.55 (m, 1H, Ar-H), 7.22 (td, $J = 8.5, 2.0$ Hz, 1H, Ar-H), 5.42 (t, $J = 7.0$ Hz, 1H, OH), 4.77 (d, $J = 7.0$ Hz, 2H, CH_2), 4.09 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3). MS (ESI) $m/z = 488$ $[\text{M} + \text{H}]^+$.

6-Bromo-4-methoxyquinoline-3-carboxylic acid (11). Methyl 6-bromo-4-methoxyquinoline-3-carboxylate **8** (6.0 g, 19.42 mmol) and 2 N NaOH (200 mL) were charged in a 500 mL round-bottomed flask. The mixture was stirred at reflux for 2 h. After cooling to room temperature, the pH of the mixture was adjusted to 5 using 2 N HCl and the resulting solid was filtered and washed with water. The filter cake was then dried under reduced pressure to afford the title compound (5.12 g, 18.22 mmol, 94% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 13.69 (s, 1H, COOH), 9.03 (s, 1H, Ar-H), 8.38 (m, Ar-H), 7.97 (m, 2H, Ar-H), 4.11 (s, 3H, OCH_3). ESI-MS: $m/z = 282$ $[\text{M} + \text{H}]^+$.

6-Bromo-4-methoxyquinoline-3-carboxamide (12). A solution of **11** (200 mg, 0.71 mmol), ethyl chloroformate (85 mg, 0.78 mmol) and *N*-methylmorpholine (79 mg, 0.78 mmol) in dry THF was stirred at room temperature for 30 min. Then, $\text{NH}_3 \cdot \text{H}_2\text{O}$ (0.3 mL) was added and stirred for 4 h. The mixture was washed with NaHSO_3 and water, respectively. The organic phase was dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product, which was further purified by silica gel column chromatography (50% ethyl acetate/petroleum ether) to give the title compound (155 mg, 0.55 mmol, 77% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.80 (s, 1H, Ar-H), 8.37 (d, $J = 1.0$ Hz, 1H, Ar-H), 8.19 (s, 1H, NH_2), 7.96–7.93 (m, 2H, Ar-H), 7.91 (s, 1H, NH_2), 4.15 (s, 3H, OCH_3). ESI-MS: $m/z = 281$ $[\text{M} + \text{H}]^+$.

6-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)-4-methoxyquinoline-3-carboxamide (13). This compound was prepared from **12** (42 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (12 mg, 0.024 mmol, 16% yield) as a white solid. Mp 207–208 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.39 (s, 1H, NH), 8.82 (s, 1H, Ar-H), 8.47 (s, 1H, Ar-H), 8.33 (s, 1H, Ar-H), 8.16 (s, 1H, NH_2), 8.10 (s, 2H, Ar-H), 7.99 (d, $J = 2.0$ Hz, 1H, Ar-H), 7.89 (s, 1H, NH_2), 7.80 (m, 1H, Ar-H), 7.59 (m, 1H, Ar-H), 7.24 (td, $J = 8.5, 2.0$ Hz, 1H, Ar-H), 4.19 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3). IR (KBr) ν 3458, 3389, 3254, 3190, 2938, 2853, 1660, 1602, 1509, 1475, 1421, 1433, 1172, 1153 cm^{-1} . MS (ESI) $m/z = 501$ $[\text{M} + \text{H}]^+$, HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{19}\text{F}_2\text{N}_4\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 501.1044, found 501.1042. HPLC purity = 95.3%.

General procedure A for synthesis of intermediates (14a–l)

A solution of **11** (1.0 equiv.), EDCI (1.5 equiv.) and HOBt (1.0 equiv.) in dry CH_2Cl_2 was stirred at room temperature for 2 h. Triethylamine (3.0 equiv.) and amine (2.0 equiv.) were then

added and stirred for 1 h. The mixture was washed with 1 N NaOH and water, respectively. The organic phase was dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product, which was further purified by silica gel column chromatography to give the desired compounds.

6-Bromo-*N*-(2-hydroxyethyl)-4-methoxyquinoline-3-carboxamide (14a). This compound was prepared from **11** (100 mg, 0.36 mmol) and 2-aminoethan-1-ol (44 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (92 mg, 0.28 mmol, 79% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.74 (s, 1H, Ar-H), 8.71 (t, $J = 5.5$ Hz, 1H, NH), 8.33 (m, 1H, Ar-H), 7.94–7.90 (m, 2H, Ar-H), 4.78 (t, $J = 5.5$ Hz, 1H, OH), 4.10 (s, 3H, OCH_3), 3.55 (q, $J = 5.5$ Hz, 2H, CH_2), 3.37 (q, $J = 5.5$ Hz, 2H, CH_2). ESI-MS: $m/z = 325$ $[\text{M} + \text{H}]^+$.

6-Bromo-*N*-(2-hydroxyethyl)-4-methoxy-*N*-methylquinoline-3-carboxamide (14b). This compound was prepared from **11** (100 mg, 0.36 mmol) and 2-(methylamino)ethan-1-ol (54 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (88 mg, 0.26 mmol, 72% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.62 (s, 1H, Ar-H), 8.37–8.33 (m, 1H, Ar-H), 7.95–7.91 (m, 2H, Ar-H), 4.87 (t, $J = 5.0$ Hz, 0.5H, OH), 4.80 (t, $J = 5.0$ Hz, 0.5H, OH), 4.08 (s, 3H, OCH_3), 3.69 (d, $J = 5.0$ Hz, 1H, CH_2), 3.57–3.41 (m, 2H, CH_2), 3.33–3.26 (m, 1H, CH_2), 3.09 (s, 1.5H, CH_3), 2.97 (s, 1.5H, CH_3). ESI-MS: $m/z = 339$ $[\text{M} + \text{H}]^+$.

(6-Bromo-4-methoxyquinolin-3-yl)(pyrrolidin-1-yl)methanone (14c). This compound was prepared from **11** (100 mg, 0.36 mmol) and pyrrolidine (51 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (86 mg, 0.26 mmol, 72% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.64 (s, 1H, Ar-H), 8.33 (t, $J = 1.0$ Hz, 1H, Ar-H), 7.91 (m, 2H, Ar-H), 4.03 (s, 3H, OCH_3), 3.52 (t, $J = 6.5$ Hz, 2H, CH_2), 3.24 (t, $J = 6.5$ Hz, 2H, CH_2), 1.89 (q, $J = 6.5$ Hz, 2H, CH_2), 1.84 (q, $J = 6.5$ Hz, 2H, CH_2). ESI-MS: $m/z = 335$ $[\text{M} + \text{H}]^+$.

(6-Bromo-4-methoxyquinolin-3-yl)(piperidin-1-yl)methanone (14d). This compound was prepared from **11** (100 mg, 0.36 mmol) and piperidine (61 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (78 mg, 0.22 mmol, 62% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.59 (s, 1H, Ar-H), 8.32 (brs, 1H, Ar-H), 7.92 (m, 2H, Ar-H), 4.04 (s, 3H, OCH_3), 3.80–3.71 (m, 1H, CH_2), 3.62–3.54 (m, 1H, CH_2), 3.27–3.22 (m, 2H, CH_2), 1.64–1.55 (m, 4H, $\text{CH}_2 \times 2$), 1.46 (m, 2H, CH_2). ESI-MS: $m/z = 349$ $[\text{M} + \text{H}]^+$.

(6-Bromo-4-methoxyquinolin-3-yl)(morpholino)methanone (14e). This compound was prepared from **11** (100 mg, 0.36 mmol) and morpholine (63 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (89 mg, 0.25 mmol, 69% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.63 (s, 1H, Ar-H), 8.35–8.30 (m, 1H, Ar-H), 7.92 (m, 2H, Ar-H), 4.06 (s, 3H, OCH_3), 3.71 (m, 4H, $\text{CH}_2 \times 2$), 3.54 (q, $J = 5.0$ Hz, 2H, CH_2), 3.32 (q, $J = 5.0$ Hz, 2H, CH_2). ESI-MS: $m/z = 351$ $[\text{M} + \text{H}]^+$.

(6-Bromo-4-methoxyquinolin-3-yl)(4-methylpiperazin-1-yl)methanone (14f). This compound was prepared from **11** (100 mg, 0.36 mmol) and *N*-methylpiperazine (72 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (95 mg, 0.26 mmol, 72% yield) as a white



solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.59 (s, 1H, Ar-H), 8.32 (m, 1H, Ar-H), 7.92 (m, 2H, Ar-H), 4.04 (s, 3H, OCH_3), 3.70 (t, J = 5.0 Hz, 2H, CH_2), 3.33–3.29 (m, 2H, CH_2), 2.40 (m, 2H, CH_2), 2.27 (t, J = 5.0 Hz, 2H, CH_2), 2.20 (s, 3H, CH_3). ESI-MS: m/z = 364 $[\text{M} + \text{H}]^+$.

(6-Bromo-4-methoxyquinolin-3-yl)(4-hydroxypiperidin-1-yl)methanone (14g). This compound was prepared from **11** (100 mg, 0.36 mmol) and 4-hydroxypiperidine (72 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (99 mg, 0.27 mmol, 75% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.62 (d, J = 3.0 Hz, 1H, Ar-H), 8.34 (d, J = 4.0 Hz, 1H, Ar-H), 7.97–7.90 (m, 2H, Ar-H), 4.82 (t, J = 3.5 Hz, 1H, OH), 4.15 (m, 0.5H, CH), 4.06 (m, 3.5H, OCH_3 + CH), 3.84–3.73 (m, 1H, CH_2), 3.54–3.39 (m, 2H, CH_2), 3.17 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 1.69 (m, 1H, CH_2), 1.53–1.41 (m, 1H, CH_2), 1.41–1.30 (m, 1H, CH_2). ESI-MS: m/z = 365 $[\text{M} + \text{H}]^+$.

(6-Bromo-4-methoxyquinolin-3-yl)(3-hydroxypiperidin-1-yl)methanone (14h). This compound was prepared from **11** (100 mg, 0.36 mmol) and 3-hydroxypiperidine (72 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (105 mg, 0.29 mmol, 81% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.63 (s, 0.27H, Ar-H), 8.59–8.55 (m, 0.74H, Ar-H), 8.33 (s, 0.32H, Ar-H), 8.32 (s, 0.65H, Ar-H), 7.91 (s, 2H, Ar-H), 5.02 (m, 0.48H, OH), 4.83 (d, J = 3.5 Hz, 0.33H, OH), 4.80 (d, J = 3.5 Hz, 0.25H, OH), 4.06 (m, 3H, OCH_3), 3.78 (s, 0.39H, CH), 3.65 (m, 0.61H, CH), 3.58 (m, 1H, CH_2), 3.46 (m, 0.39H, CH_2), 3.36 (m, 0.73H, CH_2), 3.23 (m, 0.34H, CH_2), 3.20–3.15 (m, 0.27H, CH_2), 3.10 (m, 0.65H, CH_2), 3.04 (m, 0.63H, CH_2), 1.80 (m, 1.56H, CH_2), 1.63 (m, 0.54H, CH_2), 1.52–1.35 (m, 2H, CH_2). ESI-MS: m/z = 365 $[\text{M} + \text{H}]^+$.

(S)-1-(6-Bromo-4-methoxyquinoline-3-carbonyl)pyrrolidine-2-carboxamide (14i). This compound was prepared from **11** (100 mg, 0.36 mmol) and (S)-pyrrolidine-2-carboxamide (82 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (95 mg, 0.25 mmol, 69% yield) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.69 (s, 1H, Ar-H), 8.40 (d, J = 2.0 Hz, 1H, Ar-H), 7.94 (d, J = 9.0 Hz, 1H, Ar-H), 7.82 (dd, J = 9.0, 2.0 Hz, 1H, Ar-H), 6.81 (s, 1H, NH_2), 5.52 (s, 1H, NH_2), 4.77 (dd, J = 7.5, 3.5 Hz, 1H, CH), 3.48 (m, 1H, CH_2), 3.31 (m, 1H, CH_2), 2.49–2.39 (m, 1H, CH_2), 2.17–2.12 (m, 2H, CH_2), 1.95–1.89 (m, 1H, CH_2). ESI-MS: m/z = 378 $[\text{M} + \text{H}]^+$.

6-Bromo-4-methoxy-N-phenylquinoline-3-carboxamide (14j). This compound was prepared from **11** (100 mg, 0.36 mmol) and aniline (67 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (76 mg, 0.21 mmol, 58% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.77 (s, 1H, NH), 8.88 (s, 1H, Ar-H), 8.41 (d, J = 2.0, 1H, Ar-H), 8.03–7.94 (m, 2H, Ar-H), 7.75 (d, J = 7.5 Hz, 2H, Ar-H), 7.39 (t, J = 8.0 Hz, 2H, Ar-H), 7.15 (t, J = 7.5 Hz, 1H, Ar-H), 4.14 (s, 3H, OCH_3). ESI-MS: m/z = 357 $[\text{M} + \text{H}]^+$.

6-Bromo-4-methoxy-N-(4-methoxyphenyl)quinoline-3-carboxamide (14k). This compound was prepared from **11** (100 mg, 0.36 mmol) and 4-methoxyaniline (89 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (72 mg, 0.19 mmol, 53% yield) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.62 (s, 1H, NH), 8.86 (s, 1H, Ar-H), 8.40 (d, J = 2.0, 1H, Ar-H), 8.00–7.91 (m, 2H, Ar-H), 7.70–

7.62 (d, J = 9.0 Hz, 2H, Ar-H), 7.00–6.92 (d, J = 9.0 Hz, 2H, Ar-H), 4.14 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3). ESI-MS: m/z = 387 $[\text{M} + \text{H}]^+$.

6-Bromo-4-methoxy-N-(4-(trifluoromethoxy)phenyl)quinoline-3-carboxamide (14l). This compound was prepared from **11** (100 mg, 0.36 mmol) and 4-(trifluoromethoxy)aniline (127 mg, 0.72 mmol) according to the general synthesis procedure A to afford the title compound (80 mg, 0.18 mmol, 50% yield) as a white solid. ESI-MS: m/z = 441 $[\text{M} + \text{H}]^+$.

6-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)-N-(2-hydroxyethyl)-4-methoxyquinoline-3-carboxamide (15a). This compound was prepared from **14a** (49 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (21 mg, 0.039 mmol, 26% yield) as a white solid. Mp 215–216 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H, NH), 8.75 (s, 1H, Ar-H), 8.69 (t, J = 5.5 Hz, 1H, NH), 8.47 (d, J = 2.0 Hz, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 8.07 (s, 2H, Ar-H), 7.98 (d, J = 2.0 Hz, 1H, Ar-H), 7.76 (m, 1H, Ar-H), 7.58 (m, 1H, Ar-H), 7.21 (td, J = 8.5, 2.0 Hz, 1H, Ar-H), 4.79 (t, J = 5.5 Hz, 1H, OH), 4.14 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.57 (q, J = 5.5 Hz, 2H, CH_2), 3.39 (q, J = 5.5 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 166.1, 165.6 (dd, $J_{\text{C-F}}$ = 252.8, 11.6 Hz), 160.2, 159.9 (dd, $J_{\text{C-F}}$ = 256.4, 14.0 Hz), 158.1, 151.7, 148.9, 143.0, 135.0, 134.3, 132.3 (d, $J_{\text{C-F}}$ = 10.6 Hz), 130.2, 129.8, 129.4, 125.6 (dd, $J_{\text{C-F}}$ = 15.0, 3.5 Hz), 122.8, 120.0, 118.3, 112.4 (dd, $J_{\text{C-F}}$ = 21.1, 3.4 Hz), 106.3 (t, $J_{\text{C-F}}$ = 26.1 Hz), 61.4, 60.0, 53.9, 42.7. IR (KBr) ν 3356, 3050, 2953, 2851, 2785, 1651, 1602, 1487, 1163, 1073 cm^{-1} . MS (ESI) m/z = 545 $[\text{M} + \text{H}]^+$, HRMS (ESI) m/z calcd for $\text{C}_{25}\text{H}_{22}\text{F}_2\text{N}_4\text{O}_6\text{NaS}$ $[\text{M} + \text{Na}]^+$ 567.1126, found 567.1120. HPLC purity = 97.5%.

6-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)-N-(2-hydroxyethyl)-4-methoxy-N-methylquinoline-3-carboxamide (15b). This compound was prepared from **14b** (51 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (23 mg, 0.041 mmol, 27% yield) as a white solid. Mp 224–225 °C. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.38 (s, 1H, NH), 8.60 (s, 1H, Ar-H), 8.46 (s, 1H, Ar-H), 8.31 (d, J = 5.5 Hz, 1H, Ar-H), 8.07 (d, J = 5.0 Hz, 2H, Ar-H), 7.97 (s, 1H, Ar-H), 7.79 (m, 1H, Ar-H), 7.59 (m, 1H, Ar-H), 7.23 (t, J = 9.0 Hz, 1H, Ar-H), 4.88 (t, J = 5.0 Hz, 0.5H, OH), 4.81 (t, J = 5.0 Hz, 0.5H, OH), 4.13 (s, 3H, OCH_3), 3.70 (m, 1H, CH_2), 3.69 (s, 3H, OCH_3), 3.50 (m, 2H, CH_2), 3.32–3.26 (m, 1H, CH_2), 3.10 (s, 1.5H, CH_3), 3.00 (s, 1.5H, CH_3). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 167.8, 167.6, 165.6 (dd, $J_{\text{C-F}}$ = 251.5, 12.8 Hz), 159.9 (dd, $J_{\text{C-F}}$ = 255.6, 13.3 Hz), 158.4, 158.1, 158.1, 151.3, 150.7, 148.4, 148.3, 143.0, 134.9, 134.9, 134.3, 132.3 (d, $J_{\text{C-F}}$ = 10.8 Hz), 130.1, 129.6, 129.5, 129.4, 125.6 (dd, $J_{\text{C-F}}$ = 13.8, 3.7 Hz), 122.5, 119.9, 116.8, 116.7, 112.3 (dd, $J_{\text{C-F}}$ = 22.1, 3.3 Hz), 106.3 (t, $J_{\text{C-F}}$ = 23.0 Hz), 60.0, 58.6, 58.3, 53.9, 53.3, 49.9, 38.3, 32.8. IR (KBr) ν 3384, 3102, 2949, 2850, 1650, 1602, 1488, 1342, 1176, 1148 cm^{-1} . MS (ESI) m/z = 559 $[\text{M} + \text{H}]^+$, HRMS (ESI) m/z calcd for $\text{C}_{26}\text{H}_{24}\text{F}_2\text{N}_4\text{O}_6\text{NaS}$ $[\text{M} + \text{Na}]^+$ 581.1282, found 581.1273. HPLC purity = 97.9%.

2,4-Difluoro-N-(2-methoxy-5-(4-methoxy-3-(pyrrolidine-1-carbonyl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide (15c). This compound was prepared from **14c** (50 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis



procedure of **5** to afford the title compound (31 mg, 0.056 mmol, 37% yield) as a white solid. Mp 213–214 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 10.36 (s, 1H, NH), 8.64 (s, 1H, Ar-H), 8.47 (d, J = 2.0 Hz, 1H, Ar-H), 8.32 (brs, 1H, Ar-H), 8.08 (brs, 2H, Ar-H), 7.98 (d, J = 2.0 Hz, 1H, Ar-H), 7.79 (m, 1H, Ar-H), 7.59 (m, 1H, Ar-H), 7.23 (td, J = 10.5, 2.5 Hz, 1H, Ar-H), 4.10 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃), 3.56 (t, J = 6.5 Hz, 2H, CH₂), 3.28 (t, J = 6.5 Hz, 2H, CH₂), 1.93 (q, J = 6.5 Hz, 2H, CH₂), 1.88 (q, J = 6.5 Hz, 2H, CH₂). ^{13}C NMR (100 MHz, DMSO- d_6) δ 165.6 (dd, $J_{\text{C-F}}$ = 252.2, 11.4 Hz), 165.5, 159.8 (dd, $J_{\text{C-F}}$ = 253.6, 11.2 Hz), 158.5, 158.1, 150.7, 148.5, 143.1, 134.9, 134.4, 132.4, 132.3, 130.1, 129.6, 129.4, 125.5 (dd, $J_{\text{C-F}}$ = 13.5, 2.8 Hz), 122.6, 120.3, 119.9, 117.7, 112.4 (dd, $J_{\text{C-F}}$ = 22.6, 3.5 Hz), 106.3 (t, $J_{\text{C-F}}$ = 25.8 Hz), 74.0, 60.3, 53.9, 48.4, 46.2, 25.8, 25.4, 24.5. IR (KBr) ν 3331, 3102, 3080, 2974, 2876, 1626, 1602, 1487, 1434, 1342, 1177, 1147 cm⁻¹. MS (ESI) m/z = 555 [M + H]⁺, HRMS (ESI) m/z calcd for C₂₇H₂₄F₂N₄O₅NaS [M + Na]⁺ 577.1333, found 577.1327. HPLC purity = 95.5%.

2,4-Difluoro-N-(2-methoxy-5-(4-methoxy-3-(piperidine-1-carbonyl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide (15d). This compound was prepared from **14d** (52 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (20 mg, 0.035 mmol, 23% yield) as a white solid. Mp 225–226 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 10.35 (s, 1H, NH), 8.62 (s, 1H, Ar-H), 8.45 (d, J = 2.0 Hz, 1H, Ar-H), 8.32 (brs, 1H, Ar-H), 8.08 (brs, 2H, Ar-H), 7.98 (d, J = 2.0 Hz, 1H, Ar-H), 7.81 (m, 1H, Ar-H), 7.56 (m, 1H, Ar-H), 7.22 (td, J = 10.5, 2.5 Hz, 1H, Ar-H), 4.10 (s, 3H, OCH₃), 3.68 (s, 3H, OCH₃), 3.78–3.66 (m, 2H, CH₂), 3.65–3.55 (m, 2H, CH₂), 1.65 (m, 2H, CH₂), 1.58 (m, 4H, CH₂ × 2). ^{13}C NMR (100 MHz, DMSO- d_6) δ 165.6 (dd, $J_{\text{C-F}}$ = 253.6, 12.0 Hz), 165.6, 159.8 (dd, $J_{\text{C-F}}$ = 255.5, 15.0 Hz), 158.6, 158.1, 150.5, 148.4, 143.1, 135.0, 134.4, 132.4 (d, $J_{\text{C-F}}$ = 10.9 Hz), 130.2, 129.6, 129.4, 125.6 (dd, $J_{\text{C-F}}$ = 14.2, 2.9 Hz), 122.5, 120.4, 119.9, 116.8, 112.4 (dd, $J_{\text{C-F}}$ = 22.3, 3.6 Hz), 106.3 (t, $J_{\text{C-F}}$ = 26.1 Hz), 66.8, 60.4, 53.9, 48.3, 42.5, 26.0, 25.5, 24.4. IR (KBr) ν 3417, 3102, 3080, 2974, 2877, 1625, 1602, 1487, 1435, 1342, 1177, 1147 cm⁻¹. MS (ESI) m/z = 569 [M + H]⁺, HRMS (ESI) m/z calcd for C₂₈H₂₆F₂N₄O₅NaS [M + Na]⁺ 591.1490, found 591.1485. HPLC purity = 94.1%.

2,4-Difluoro-N-(2-methoxy-5-(4-methoxy-3-(morpholine-4-carbonyl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide (15e). This compound was prepared from **14e** (53 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (25 mg, 0.044 mmol, 29% yield) as a white solid. Mp 219–220 °C. ^1H NMR (500 MHz, CDCl₃) δ 8.68 (s, 1H, Ar-H), 8.27 (d, J = 2.0 Hz, 1H, Ar-H), 8.21 (d, J = 2.0 Hz, 1H, Ar-H), 8.15 (d, J = 9.0 Hz, 1H, Ar-H), 8.07 (d, J = 2.0 Hz, 1H, Ar-H), 7.87 (m, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 6.95 (m, 2H, Ar-H), 4.18 (s, 3H, OCH₃), 3.98 (m, 2H, CH₂), 3.97 (s, 3H, OCH₃), 3.83 (m, 2H, CH₂), 3.68 (m, 2H, CH₂), 3.43–3.34 (m, 2H, CH₂). IR (KBr) ν 3442, 3104, 2958, 2923, 2856, 1636, 1604, 1488, 1463, 1434, 1347, 1178, 1152, 1119, 1017 cm⁻¹. MS (ESI) m/z = 571 [M + H]⁺, HRMS (ESI) m/z calcd for C₂₇H₂₄F₂N₄O₆NaS [M + Na]⁺ 593.1282, found 591.1279. HPLC purity = 95.7%.

2,4-Difluoro-N-(2-methoxy-5-(4-methoxy-3-(4-methylpiperazine-1-carbonyl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide (15f). This compound was prepared from **14f** (54 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis

procedure of **5** to afford the title compound (13 mg, 0.022 mmol, 15% yield) as a white solid. Mp 231–233 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 10.34 (s, 1H, NH), 8.57 (s, 1H, Ar-H), 8.43 (d, J = 2.5 Hz, 1H, Ar-H), 8.31–8.24 (m, 1H, Ar-H), 8.10–8.04 (m, 2H, Ar-H), 7.94 (d, J = 2.5 Hz, 1H, Ar-H), 7.76 (m, 1H, Ar-H), 7.61–7.55 (m, 1H, Ar-H), 7.20 (td, J = 8.5, 2.5 Hz, 1H, Ar-H), 4.08 (s, 3H, OCH₃), 3.73 (m, 2H, CH₂), 3.66 (s, 3H, OCH₃), 3.34 (m, 2H, CH₂), 2.45 (m, 2H, CH₂), 2.33 (m, 2H, CH₂), 2.23 (s, 3H, OCH₃). ^{13}C NMR (100 MHz, DMSO- d_6) δ 165.4 (dd, $J_{\text{C-F}}$ = 252.5, 11.8 Hz), 165.9, 158.9, 159.8 (dd, $J_{\text{C-F}}$ = 255.9, 13.2 Hz), 158.1, 150.5, 148.5, 142.5, 135.1, 133.8, 132.3 (d, $J_{\text{C-F}}$ = 11.0 Hz), 130.2, 129.7, 129.4, 125.9 (dd, $J_{\text{C-F}}$ = 14.4, 3.6 Hz), 122.5, 121.1, 119.8, 116.4, 112.3 (dd, $J_{\text{C-F}}$ = 21.7, 3.0 Hz), 106.25 (t, $J_{\text{C-F}}$ = 26.2 Hz), 60.6, 54.7, 54.4, 53.9, 47.2, 45.9, 41.7. IR (KBr) ν 3423, 3071, 2943, 2853, 2796, 1632, 1602, 1486, 1461, 1363, 1344, 1175, 1148, 1119, 1073 cm⁻¹. MS (ESI) m/z = 584 [M + H]⁺, HRMS (ESI) m/z calcd for C₂₈H₂₇F₂N₅O₅NaS [M + Na]⁺ 606.1599, found 606.1592. HPLC purity = 97.0%.

2,4-Difluoro-N-(5-(3-(4-hydroxypiperidine-1-carbonyl)-4-methoxyquinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide (15g). This compound was prepared from **14g** (55 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (24 mg, 0.041 mmol, 27% yield) as a white solid. Mp 241–242 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 10.38 (s, 1H, NH), 8.59 (d, J = 2.5 Hz, 1H, Ar-H), 8.46 (brs, 1H, Ar-H), 8.31 (brs, 1H, Ar-H), 8.08 (brs, 2H, Ar-H), 7.97 (brs, 1H, Ar-H), 7.79 (m, 1H, Ar-H), 7.59 (m, 1H, Ar-H), 7.23 (t, J = 8.0 Hz, 1H, Ar-H), 4.85 (s, 1H, OH), 4.19 (s, 1H, CH), 4.12 (s, 1.5H, OCH₃), 4.08 (s, 1.5H, OCH₃), 3.79 (s, 1H, CH₂), 3.69 (s, 3H, OCH₃), 3.46 (m, 2H, CH₂), 3.24–3.14 (m, 1H, CH₂), 1.87 (m, 1H, CH₂), 1.71 (s, 1H, CH₂), 1.43 (m, 2H, CH₂). ^{13}C NMR (100 MHz, DMSO- d_6) δ 166.3 (dd, $J_{\text{C-F}}$ = 252.8, 12.0 Hz), 165.7, 165.6, 159.8 (dd, $J_{\text{C-F}}$ = 255.9, 13.3 Hz), 158.8, 158.6, 158.1, 150.5, 150.4, 148.5, 143.1, 135.0, 134.4, 132.4 (d, $J_{\text{C-F}}$ = 11.0 Hz), 130.2, 129.6, 129.4, 125.5 (dd, $J_{\text{C-F}}$ = 14.9, 4.1 Hz), 122.6, 122.5, 120.3, 119.9, 116.8, 116.7, 112.4 (dd, $J_{\text{C-F}}$ = 22.2, 3.6 Hz), 106.3 (t, $J_{\text{C-F}}$ = 26.0 Hz), 65.9, 65.5, 60.5, 60.3, 60.2, 53.9, 45.1, 44.8, 39.1, 34.6, 34.3, 34.1, 33.8, 21.2, 14.5. IR (KBr) ν 3384, 3102, 2997, 2947, 2857, 1646, 1603, 1487, 1460, 1364, 1343, 1176, 1155, 1121, 1073, 1017 cm⁻¹. MS (ESI) m/z = 585 [M + H]⁺, HRMS (ESI) m/z calcd for C₂₈H₂₆F₂N₄O₆NaS [M + Na]⁺ 607.1439, found 607.1430. HPLC purity = 99.1%.

2,4-Difluoro-N-(5-(3-(3-hydroxypiperidine-1-carbonyl)-4-methoxyquinolin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide (15h). This compound was prepared from **14h** (55 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (28 mg, 0.048 mmol, 32% yield) as a white solid. Mp 238–239 °C. ^1H NMR (500 MHz, DMSO- d_6) δ 10.36 (s, 1H, NH), 8.61 (s, 0.25H, Ar-H), 8.57–8.52 (m, 0.73H, Ar-H), 8.46 (m, 1H, Ar-H), 8.30 (m, 1H, Ar-H), 8.06 (m, 2H, Ar-H), 7.96 (m, 1H, Ar-H), 7.76 (m, 1H, Ar-H), 7.61–7.52 (m, 1H, Ar-H), 7.21 (td, J = 8.5, 2.0 Hz, 1H, Ar-H), 5.03 (m, 0.44H, OH), 4.86 (d, J = 3.5 Hz, 0.29H, OH), 4.81 (d, J = 3.5 Hz, 0.24H, OH), 4.10 (m, 3H, OCH₃), 3.86 (m, 0.32H, CH), 3.68 (m, 0.77H, CH), 3.66 (s, 3H, OCH₃), 3.62–3.52 (m, 1H, CH₂), 3.40 (m, 1H, CH₂), 3.26 (m, 0.30H, CH₂), 3.19 (m, 0.28H, CH₂), 3.13 (m, 0.62H, CH₂), 3.05 (m, 0.62H, CH₂), 1.81 (m, 1.61H, CH₂),



1.66 (m, 0.50H, CH₂), 1.53–1.35 (m, 2H, CH₂). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 166.2, 166.1, 165.6 (dd, *J*_{C-F} = 252.4, 12.1 Hz), 159.8 (dd, *J*_{C-F} = 268.3, 13.2 Hz), 158.6, 158.1, 150.6, 148.4, 143.0, 135.0, 134.4, 132.4 (d, *J*_{C-F} = 10.7 Hz), 130.2, 129.6, 129.4, 125.6 (dd, *J*_{C-F} = 15.4, 2.4 Hz), 122.5, 120.4, 119.9, 117.0, 116.5, 115.7, 112.3 (dd, *J*_{C-F} = 21.8, 3.1 Hz), 106.3 (t, *J*_{C-F} = 25.9 Hz), 74.0, 65.4, 65.2, 65.2, 64.8, 60.6, 60.5, 60.2, 59.7, 54.4, 54.1, 53.9, 48.8, 48.6, 47.6, 41.9, 41.9, 32.9, 32.6, 32.4, 25.4, 24.9, 22.9, 22.8, 22.1, 21.7. IR (KBr) ν 3373, 3232, 3097, 2944, 2859, 1646, 1602, 1488, 1464, 1364, 1341, 1177, 1147, 1119, 1072, 1013 cm⁻¹. MS (ESI) *m/z* = 585 [M + H]⁺, HRMS (ESI) *m/z* calcd for C₂₈H₂₆F₂N₄O₆NaS [M + Na]⁺ 607.1439, found 607.1430. HPLC purity = 98.4%.

(S)-1-(6-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxy-pyridin-3-yl)-4-methoxyquinoline-3-carbonyl)pyrrolidine-2-carboxamide (15i). This compound was prepared from **14i** (57 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (38 mg, 0.064 mmol, 43% yield) as a white solid. Mp 242–243 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.32 (s, 1H, NH), 8.66 (s, 0.69H, Ar-H), 8.50 (s, 0.30H, Ar-H), 8.43 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.29 (m, 1H, Ar-H), 8.08–8.00 (m, 2H, Ar-H), 7.94 (m, 1H, Ar-H), 7.81–7.73 (m, 1H, Ar-H), 7.60–7.52 (m, 1H, Ar-H), 7.51 (s, 0.65H, NH₂), 7.20 (t, *J* = 8.5 Hz, 1H, Ar-H), 7.12 (s, 0.32H, NH₂), 6.99 (s, 0.65H, NH₂), 6.76 (s, 0.30H, NH₂), 4.48 (dd, *J* = 8.5, 4.0 Hz, 0.70H, CH), 4.20 (m, 0.35H, CH), 4.15 (s, 2.1H, OCH₃), 4.12 (s, 0.9H, OCH₃), 3.67 (s, 3H, OCH₃), 3.41 (m, 1H, CH₂), 3.37–3.31 (m, 1H, CH₂), 2.31–2.16 (m, 1H, CH₂), 1.96–1.89 (m, 2H, CH₂), 1.87–1.77 (m, 1H, CH₂). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 173.7, 173.5, 165.5 (dd, *J*_{C-F} = 252.1, 11.3 Hz), 166.3, 166.2, 165.9, 165.8, 159.8 (dd, *J*_{C-F} = 256.5, 12.8 Hz), 158.7, 158.6, 158.1, 158.1, 150.9, 150.7, 150.6, 149.1, 148.4, 143.0, 134.9, 134.3, 132.4 (d, *J*_{C-F} = 10.0 Hz), 131.0, 130.9, 130.1, 129.6, 129.5, 129.4, 129.1, 127.1, 127.0, 125.6 (dd, *J*_{C-F} = 15.4, 4.6 Hz), 123.0, 123.0, 122.5, 122.5, 122.2, 122.2, 120.5, 120.0, 116.8, 116.4, 112.4 (dd, *J*_{C-F} = 22.3, 3.0 Hz), 106.3 (t, *J*_{C-F} = 26.4 Hz), 61.3, 61.3, 60.7, 60.6, 60.1, 53.9, 49.5, 47.3, 32.0, 30.4, 24.8, 23.0, 23.07. IR (KBr) ν 3389, 3197, 2953, 2877, 1684, 1618, 1603, 1487, 1450, 1430, 1377, 1343, 1175, 1156 cm⁻¹. MS (ESI) *m/z* = 598 [M + H]⁺, HRMS (ESI) *m/z* calcd for C₂₈H₂₅F₂N₅O₆NaS [M + Na]⁺ 620.1391, found 620.1397. HPLC purity = 95.7%.

6-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxy-pyridin-3-yl)-4-methoxy-N-phenylquinoline-3-carboxamide (15j). This compound was prepared from **14j** (53 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (22 mg, 0.038 mmol, 25% yield) as a white solid. Mp 230–231 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.76 (s, 1H, NH), 10.37 (s, 1H, NH), 8.87 (s, 1H, Ar-H), 8.49 (d, *J* = 2.0, 1H, Ar-H), 8.38 (s, 1H, Ar-H), 8.13 (s, 2H, Ar-H), 8.01 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.79 (m, 3H, Ar-H), 7.58 (m, 1H, Ar-H), 7.40 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.16 (t, *J* = 7.5 Hz, 1H, Ar-H), 4.18 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.6 (dd, *J*_{C-F} = 254.5, 10.4 Hz), 164.8, 160.1, 159.8 (dd, *J*_{C-F} = 255.8, 13.4 Hz), 158.1, 151.3, 149.0, 143.1, 139.3, 135.1, 134.4, 132.3 (d, *J*_{C-F} = 10.4 Hz), 130.3, 130.0, 129.5, 129.4, 125.6 (dd, *J*_{C-F} = 14.6, 4.0 Hz), 124.6, 122.8, 120.4, 120.3, 120.0, 118.7, 112.4 (dd, *J*_{C-F} = 20.8, 3.6 Hz), 106.3 (t, *J*_{C-F} = 25.9 Hz), 61.5, 54.0. IR (KBr) ν 3364,

3261, 3104, 2952, 2837, 1656, 1603, 1511, 1486, 1243, 1176, 1149 cm⁻¹. MS (ESI) *m/z* = 577 [M + H]⁺, HRMS (ESI) *m/z* calcd for C₂₉H₂₂F₂N₄O₅NaS [M + Na]⁺ 599.1177, found 599.1177. HPLC purity = 94.0%.

6-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxy-pyridin-3-yl)-4-methoxy-N-(4-methoxyphenyl)quinoline-3-carboxamide (15k). This compound was prepared from **14k** (58 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (20 mg, 0.033 mmol, 22% yield) as a white solid. Mp 235–236 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.61 (s, 1H, NH), 10.37 (s, 1H, NH), 8.85 (s, 1H, Ar-H), 8.50 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.38 (s, 1H, Ar-H), 8.12 (s, 2H, Ar-H), 8.01 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.80 (m, 1H, Ar-H), 7.69 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.62–7.55 (m, 1H, Ar-H), 7.24 (td, *J* = 8.5, 2.0 Hz, 1H, Ar-H), 6.97 (d, *J* = 9.0 Hz, 2H, Ar-H), 4.18 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.6 (dd, *J*_{C-F} = 252.1, 11.2 Hz), 164.3, 160.0, 158.1, 159.9 (dd, *J*_{C-F} = 255.7, 12.7 Hz), 156.3, 151.4, 148.9, 143.1, 135.0, 134.4, 132.4, 132.3 (d, *J*_{C-F} = 11.2 Hz), 130.2, 129.9, 129.4, 125.6 (dd, *J*_{C-F} = 12.7, 4.6 Hz), 122.8, 121.8, 120.4, 120.0, 118.8, 114.5, 112.4 (dd, *J*_{C-F} = 22.8, 26.1 Hz), 106.3 (t, *J*_{C-F} = 26.1 Hz), 61.3, 55.7, 54.0. IR (KBr) ν 3363, 3256, 3072, 2951, 2837, 1658, 1603, 1541, 1511, 1343, 1242, 1176, 1149 cm⁻¹. MS (ESI) *m/z* = 607 [M + H]⁺, HRMS (ESI) *m/z* calcd for C₃₀H₂₄F₂N₄O₆NaS [M + Na]⁺ 629.1282, found 629.1284. HPLC purity = 94.3%.

6-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxy-pyridin-3-yl)-4-methoxy-N-(4-(trifluoromethoxy)phenyl)quinoline-3-carboxamide (15l). This compound was prepared from **14l** (66 mg, 0.15 mmol) and **4** (64 mg, 0.15 mmol) according to the general synthesis procedure of **5** to afford the title compound (25 mg, 0.038 mmol, 25% yield) as a white solid. Mp 249–251 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.96 (s, 1H, NH), 10.37 (s, 1H, NH), 8.88 (s, 1H, Ar-H), 8.51 (d, *J* = 2.5 Hz, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.13 (d, *J* = 1.0 Hz, 2H, Ar-H), 8.02 (d, *J* = 2.5 Hz, 1H, Ar-H), 7.89 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.80 (m, 1H, Ar-H), 7.63–7.56 (m, 1H, Ar-H), 7.42 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.24 (td, *J* = 8.5, 2.0 Hz, 1H, Ar-H), 4.18 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.6 (dd, *J*_{C-F} = 252.4, 11.7 Hz), 165.0, 160.3, 159.9 (dd, *J*_{C-F} = 256.1, 13.5 Hz), 158.2, 151.2, 149.0, 144.6, 143.2, 138.5, 135.1, 134.4, 132.3 (d, *J*_{C-F} = 10.7 Hz), 130.3, 130.1, 129.3, 125.6 (dd, *J*_{C-F} = 13.6, 2.9 Hz), 122.7, 122.3, 121.7, 120.4 (d, *J*_{C-F} = 206.2 Hz), 120.4, 120.0, 118.4, 112.4 (dd, *J*_{C-F} = 22.0, 3.6 Hz), 106.3 (t, *J*_{C-F} = 25.6 Hz), 61.6, 54.0. IR (KBr) ν 3358, 3106, 2952, 2854, 1675, 1604, 1509, 1483, 1345, 1251, 1175, 1151 cm⁻¹. MS (ESI) *m/z* = 661 [M + H]⁺, HRMS (ESI) *m/z* calcd for C₃₀H₂₁F₅N₄O₆NaS [M + Na]⁺ 683.1000, found 683.0995. HPLC purity = 94.6%.

6 Pharmacokinetic study

Fasted male mice were dosed orally at 5 mg kg⁻¹ using a dosing formulation consisting of 0.5% methylcellulose. Blood samples were collected and placed into chilled tubes containing EDTA as the anticoagulant. The samples were centrifuged at 10 000 rpm for 10 min, and plasma was collected and stored frozen until analysis. **15a** was extracted from the plasma samples by protein



precipitation, and the plasma concentration of **15a** was assessed by UPLC-MS/MS (Waters). Pharmacokinetic analysis was conducted using Winnolin software. Mean plasma concentration values for each time point were used to generate plasma clearance [CL (L h⁻¹ kg⁻¹)], mean residence time [MRT (h)], peak plasma concentration [C_{\max} (ng mL⁻¹)], plasma terminal half-life [$t_{1/2}$ (h)], volume of distribution [V_d (L kg⁻¹)], and exposure [AUC (h ng⁻¹ mL⁻¹)]. Animal study was approved by the Animal Research Committee at Jiaying University (log number JXU2015120812), and animal care was provided in accordance with institutional guidelines.

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References

- 1 L. C. Cantley, *Science*, 2002, **296**, 1655–1657.
- 2 B. Vanhaesebroeck, L. Stephens and P. Hawkins, *Nat. Rev. Mol. Cell Biol.*, 2012, **13**, 195–203.
- 3 J. U. Flanagan and P. R. Shepherd, *Biochem. Soc. Trans.*, 2014, **42**, 120–124.
- 4 J. A. Engelman, *Nat. Rev. Cancer*, 2009, **9**, 550–562.
- 5 K. Okkenhaug and R. Roychoudhuri, *Sci. Signaling*, 2015, **8**, pe3.
- 6 A. E. Yueh, S. N. Payne, A. A. Leystra, D. R. Van De Hey, T. M. Foley, C. A. Pasch, L. Clipson, K. A. Matkowskyj and D. A. Deming, *PLoS One*, 2016, **11**, e0148730.
- 7 M. S. Song, L. Salmena and P. P. Pandolfi, *Nat. Rev. Mol. Cell Biol.*, 2012, **13**, 283–296.
- 8 C. H. Huang, D. Mandelker, O. Schmidt-Kittler, Y. Samuels, V. E. Velculescu, K. W. Kinzler, B. Vogelstein, S. B. Gabelli and L. M. Amzel, *Science*, 2007, **318**, 1744–1748.
- 9 A. Carracedo, L. Ma, J. Teruya-Feldstein, F. Rojo, L. Salmena, A. Alimonti, A. Egia, A. T. Sasaki, G. Thomas, S. C. Kozma, A. Papa, C. Nardella, L. C. Cantley, J. Baselga and P. P. Pandolfi, *J. Clin. Invest.*, 2008, **118**, 3065–3074.
- 10 X. Lv, X. Ma and Y. Hu, *Expert Opin. Drug Discovery*, 2013, **8**, 991–1012.
- 11 W. Peng, Z. C. Tu, Z. J. Long, Q. Liu and G. Lu, *Eur. J. Med. Chem.*, 2016, **108**, 644–654.
- 12 F. Lei, C. Sun, S. Xu, Q. Wang, Y. OuYang, C. Chen, H. Xia, L. Wang, P. Zheng and W. Zhu, *Eur. J. Med. Chem.*, 2016, **116**, 27–35.
- 13 T. Saurat, F. Buron, N. Rodrigues, M. L. de Tauzia, L. Colliandre, S. Bourg, P. Bonnet, G. Guillaumet, M. Akssira, A. Corlu, C. Guillouzo, P. Berthier, P. Rio, M. L. Jourdan, H. Benedetti and S. Routier, *J. Med. Chem.*, 2014, **57**, 613–631.
- 14 M. M. Stec, K. L. Andrews, Y. Bo, S. Caenepeel, H. Liao, J. McCarter, E. L. Mullady, T. San Miguel, R. Subramanian, N. Tamayo, D. A. Whittington, L. Wang, T. Wu, L. P. Zalameda, N. Zhang, P. E. Hughes and M. H. Norman, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4136–4142.
- 15 F. Han, S. Lin, P. Liu, J. Tao, C. Yi and H. Xu, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4538–4541.
- 16 H. Cheng, C. Li, S. Bailey, S. M. Baxi, L. Goulet, L. Guo, J. Hoffman, Y. Jiang, T. O. Johnson, T. W. Johnson, D. R. Knighton, J. Li, K. K. Liu, Z. Liu, M. A. Marx, M. Walls, P. A. Wells, M. J. Yin, J. Zhu and M. Zientek, *ACS Med. Chem. Lett.*, 2012, **4**, 91–97.
- 17 Y. N. Liu, R. Z. Wan and Z. P. Liu, *Mini-Rev. Med. Chem.*, 2013, **13**, 2047–2059.
- 18 S. D. Knight, N. D. Adams, J. L. Burgess, A. M. Chaudhari, M. G. Darcy, C. A. Donatelli, J. I. Luengo, K. A. Newlander, C. A. Parrish, L. H. Ridgers, M. A. Sarpong, S. J. Schmidt, G. S. Van Aller, J. D. Carson, M. A. Diamond, P. A. Elkins, C. M. Gardiner, E. Garver, S. A. Gilbert, R. R. Gontarek, J. R. Jackson, K. L. Kershner, L. Luo, K. Raha, C. S. Sherk, C. M. Sung, D. Sutton, P. J. Tummino, R. J. Wegrzyn, K. R. Auger and D. Dhanak, *ACS Med. Chem. Lett.*, 2010, **1**, 39–43.
- 19 S. M. Maira, F. Stauffer, J. Bruegggen, P. Furet, C. Schnell, C. Fritsch, S. Brachmann, P. Chene, A. De Pover, K. Schoemaker, D. Fabbro, D. Gabriel, M. Simonen, L. Murphy, P. Finan, W. Sellers and C. Garcia-Echeverria, *Mol. Cancer Ther.*, 2008, **7**, 1851–1863.
- 20 K. Y. Chang, S. Y. Tsai, C. M. Wu, C. J. Yen, B. F. Chuang and J. Y. Chang, *Clin. Cancer Res.*, 2011, **17**, 7116–7126.
- 21 H. M. Cheng, S. Bagrodia, S. Bailey, M. Edwards, J. Hoffman, Q. Y. Hu, R. Kania, D. R. Knighton, M. A. Marx, S. Ninkovic, S. X. Sun and E. Zhang, *Med. Chem. Commun.*, 2010, **1**, 139–144.
- 22 X. Ma, X. Lv, N. Qiu, B. Yang, Q. He and Y. Hu, *Bioorg. Med. Chem.*, 2015, **23**, 7585–7596.
- 23 X. Lv, H. Ying, X. Ma, N. Qiu, P. Wu, B. Yang and Y. Hu, *Eur. J. Med. Chem.*, 2015, **99**, 36–50.
- 24 P. Furet, V. Guagnano, R. A. Fairhurst, P. Imbach-Weese, I. Bruce, M. Knapp, C. Fritsch, F. Blasco, J. Blanz, R. Aichholz, J. Hamon, D. Fabbro and G. Caravatti, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3741–3748.
- 25 W. Kevin, A. Michael, L. Kathryn, W. Catherine and D. Matthew, Patent WO2012009194A1, 2012.

