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PII: S0223-5234(20)30141-0

DOI: https://doi.org/10.1016/j.ejmech.2020.112174

Reference: EJMECH 112174

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 25 November 2019

Revised Date: 14 February 2020

Accepted Date: 19 February 2020

Please cite this article as: T. Chen, L.-S. Zhuo, P.-F. Liu, W.-R. Fang, Y.-M. Li, W. Huang, Discovery of 1,6-naphthyridinone-based MET kinase inhibitor bearing quinoline moiety as promising antitumor drug candidate, *European Journal of Medicinal Chemistry* (2020), doi: https://doi.org/10.1016/j.ejmech.2020.112174.

Graphical Abstract

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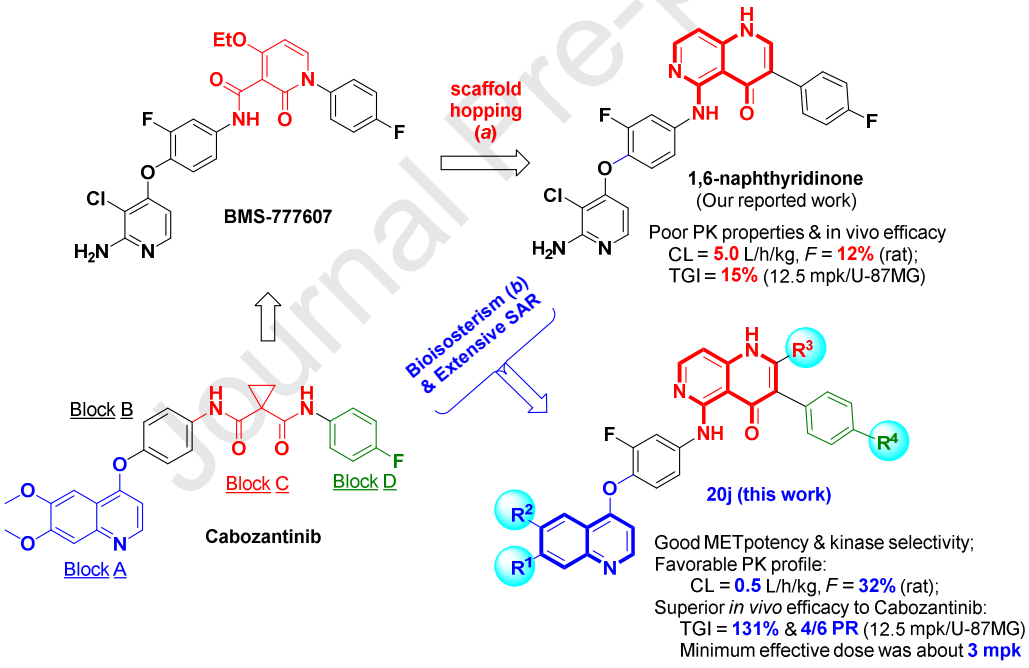
Tao Chen[1,†], Lin-Sheng Zhuo[2,†], Peng-Fei Liu[2], Wei-Rong Fang[1], Yun-Man Li[1,*], and Wei Huang[2,*]



Discovery of 1,6-Naphthyridinone-Based MET Kinase Inhibitor Bearing Quinoline Moiety as Promising Antitumor Drug Candidate

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ABSTRACT: A series of 1,6-naphthyridinone-based MET kinase inhibitors bearing quinoline moiety in block A were designed and synthesized based on the structures of Cabozantinib and our reported compound **IV**. Extensive SAR and DMPK studies led to the identification of **20j**, a potent and orally bioavailable MET kinase inhibitor with favorable kinase selectivity. More importantly, **20j** exhibited statistically significant tumor growth inhibition (Tumor growth inhibition/TGI of 131%, 4/6 partial regression/PR) in the U-87 MG xeograft model, which is superior to that of Cabozantinib (TGI of 97%, 2/6 PR), and significantly better than that of compound **IV** (TGI of 15%, 0/6 PR) at the same dose (12.5 mg/kg). Combined with favorable in vitro potency, kinase selectivity, pharmacokinetic profile and in vivo efficacy, the promising antitumor drug candidate **20j** has subsequently advanced into preclinical research.

KEYWORDS: 1,6-Naphthyridone, Quinoline, MET kinase inhibitor, Antitumor efficacy

1. Introduction

The MET receptor tyrosine kinase (RTK) is activated by its natural ligand, hepatocyte growth factor/scatter factor (HGF/SF) [1]. In a variety of human cancers, abnormalities in MET signaling (MET genomic amplification, MET overexpression, or MET mutations) have been reported to correlate with poor clinical outcomes [2]. Consequently, MET kinase has been considered as an attractive target for molecular targeted therapy in cancers [3,4]. Cabozantinib (**I**), the first small molecule MET inhibitor, was approved by FDA for the treatment of patients with progressive metastatic medullary thyroid cancer, advanced kidney cancer and liver cancer [5].

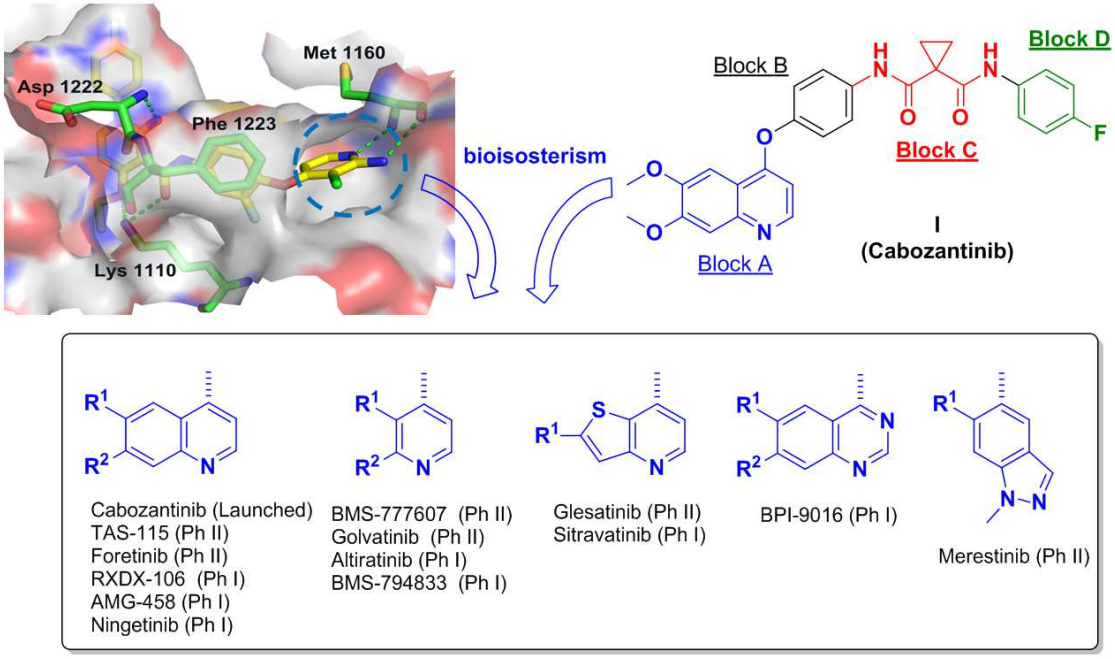


Figure 1. Reported block A of clinical candidates based on Cabozantinib (**I**)

As shown in Figure **1**, the molecular structure of Cabozantinib (**I**) was divided to block A, B, C and D. Recently, many derivatives of Cabozantinib (**I**) were reported. The main modification of these different series of derivatives was focused on the block C and block A. As the block A is directed towards the solvation region outside the binding pocket，the bioisosterism strategy of block A resulted in the discovery of many new MET inhibitors. More than a dozen drug candidates bearing diversified block A, such as quinoline moiety (TAS-115 [6], Foretinib [7], RXDX-106 [8], AMG-458 [9], Ningetinib [10]), pyridine moiety (BMS-777607 [11], Golvatinib [12], Altiratinib [13], BMS-794833 [14]), quinazoline moiety (BPI-9016 [15]), thieno[3,2-b]pyridine moiety (Glesatinib [16], Sitravatinib [17]), and indazole moiety (Merestinib [18]), have been advanced into clinical trials. Among them,

quinoline and pyridine moiety are the most common, indicating that they are the privileged scaffolds with favorable drug-likeness.

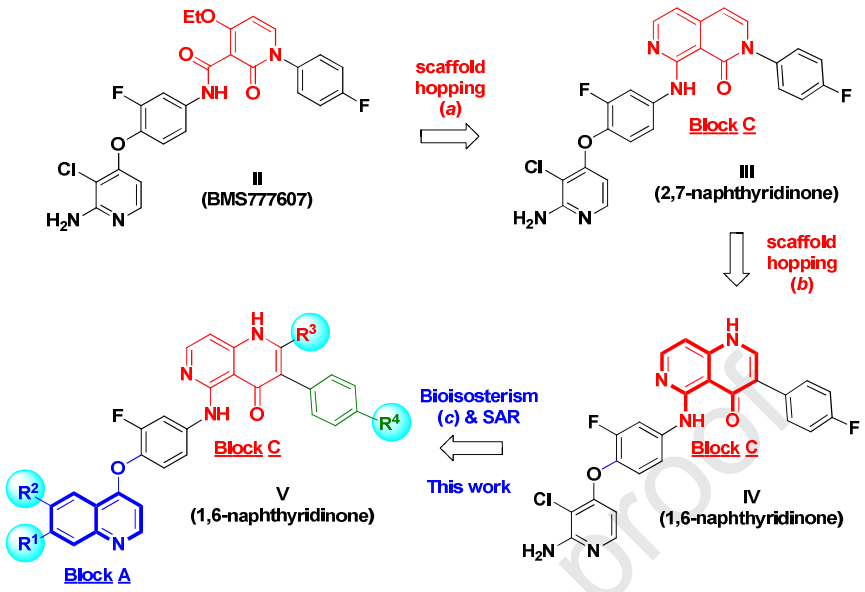
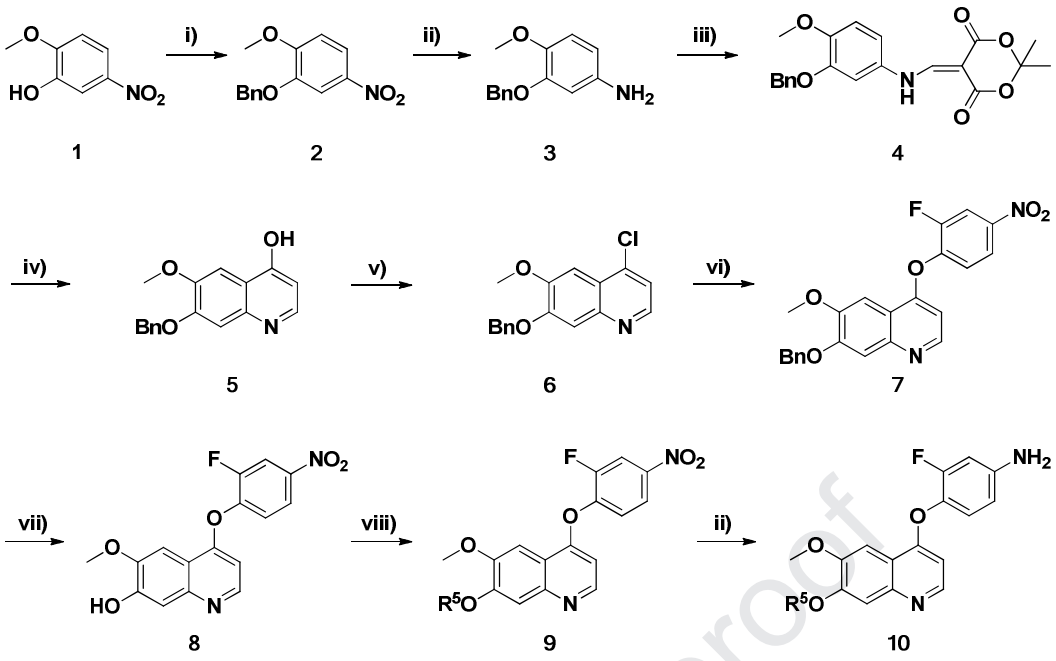


Figure 2. Design of 1,6-naphthyridinone derivatives bearing quinoline moiety in block A as new MET inhibitors

In our previous report, a novel 2,7-naphthyridone-based MET kinase inhibitor **III** [19] bearing the same block A (2-amino-3-chloropyridin-4-yl group) with **II** (BMS-777607) was discovered based on the scaffold hopping strategy *a* (cyclization & bioisosterism) of block C. A new 1,6-naphthyridone-based MET kinase inhibitor **IV** bearing pyridine moiety in block A was further designed via the scaffold hopping strategy *b* [20]. Unfortunately, compound **IV** displayed unfavorable PK properties ($AUC_{0-\infty}$ = 2.2 μg·h/m, $T_{1/2}$ = 1.0 h, CL = 5.0 L/h/kg after oral dose of 10 mg/kg) and poor in vivo antitumor efficacy (Tumor growth inhibition/TGI of 15% at 12.5 mg/kg Q.D.). Herein, we proposed a bioisosterism strategy *c* that replace pyridine moiety with quinoline moiety in block A of the molecule (Figure **2**). Furthermore, the extensive structure-activity relationship (SAR) studies of the block A, C and D were carried out to optimize the drug-likeness.

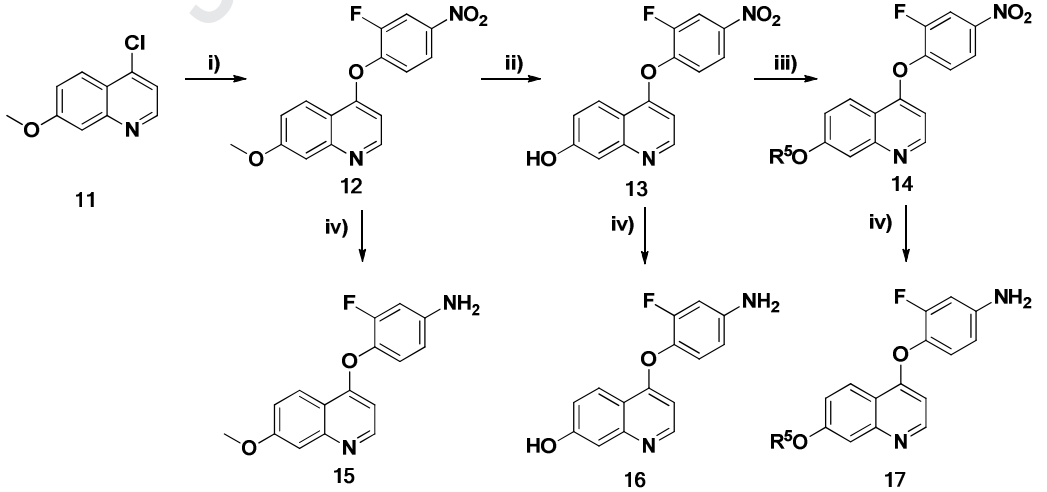
2. Chemistry

On the basis of our previous experience in the synthesis of compound **IV** [20], the assembly of chlorinated 1,6-naphthyridone (block C-D) with aromatic amine (block A-B) was designed to generate target molecule **V**. Diverse quinoline-based aromatic amine could be obtained by the modified reported methods [21-24].



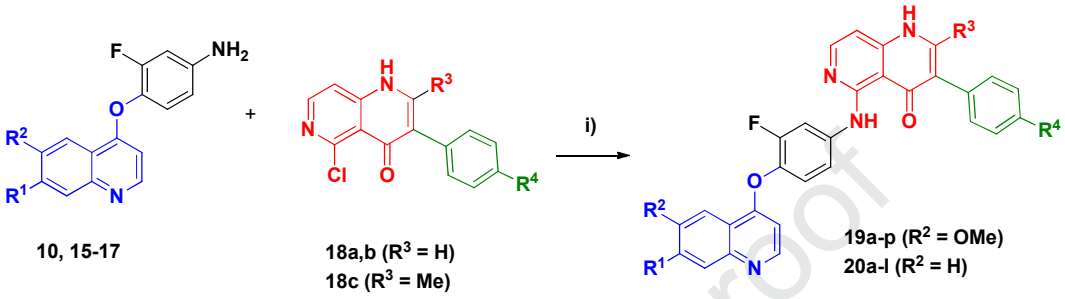
Scheme 1. Reaction conditions and reagents: (i) BnBr, K_2CO_3, DMF, R.T.~40°C, overnight; (ii) Fe, NH_4Cl, EtOH/H_2O=3/1, reflux, 1h; (iii)Triethyl orthoformate, Meldrum's acid, dry EtOH, reflux, 1h; (iv) 1,2-dichlorobenzene, 180°C, 5h; (v) $POCl_3$, toluene, reflux, 1.5h; (vi) 2-fluoro-4-nitrophenol, toluene, DIPEA, reflux, 72h; (vii) HBr (aq 40%), CH_3COOH, 80°C, 5h; (viii) R^5X, K_2CO_3, dry DMF, 70°C.

The synthesis of aromatic amine **10** bearing 6-methoxy-7-alkoxy-quinoline unit was shown in Scheme **1**. Firstly, the key intermediate 7-(benzyloxy)-4-chloro-6-methoxyquinoline **6** was produced by five steps reaction (protection-reduction-condensation-cyclization-chlorination) of **1**. Then the framework of block A-B (**7**) was constructed by a convenient nucleophilic substitution reaction of **6** and 2-fluoro-4-nitrophenol. The desired aromatic amine **10** was ultimately produced by a deprotection-substitution-reduction reaction of **7**.



Scheme 2. Reaction conditions and reagents: (i) DIPEA, toluene, reflux, 24 to 50h; (ii) BBr_3, dry DCM, TEBA, 20h; (iii) R^5X, K_2CO_3, dry DMF, 70°C, 7h; (iv) Fe, NH_4Cl, reflux, EtOH/H_2O=3/1, 1h.

The synthesis of other aromatic amine bearing 7-methoxy (**15**), 7-hydroxy (**16**) and 7-alkoxy (**17**) substituted quinoline unit was shown in Scheme **2**. The framework of block A-B (**12**) was conveniently constructed from the commercially available 4-chloro-7-methoxyquinoline **11** and 2-fluoro-4-nitrophenol. The deprotection and substitution can afford nitro-substituted block A-B **13** and **14**. The desired aromatic amines **15-17** can be obtained smoothly by subsequent reduction reaction of **12-14**.



Scheme 3. Reaction conditions and reagents: (i) PTSA, propan-2-ol, 90°C.

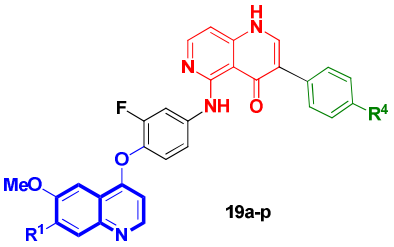
The chlorinated 1,6-naphthyridine **18a-c** were smoothly obtained using a modified method from a previous report [20]. With the desired quinoline-based aromatic amine **10**, **15-17** and chlorinated 1,6-naphthyridine **18** in hand, target compounds **19** and **20** were conveniently synthesized through an acid-catalyzed nucleophilic substitution reaction.

3. Results and discussion

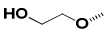
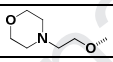
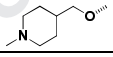
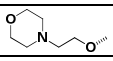
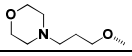
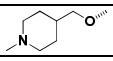
Firstly, the 6-R^2 group of quinoline moiety in block A was fixed in methoxy group and the SAR study of 7-R^1 group was performed (Table **1**). Compound **19a** bearing the same block A (6,7-dimethoxyquinolin-4-yl) with **I** (Cabozantinib) only displayed moderate MET inhibitory activity (IC_{50} of 76.6 nM). The replacement of the methyl group of OMe with *iso*-butyl group resulted in a 3.9-fold improvement of MET potency (IC_{50} of 19.7 nM, 2.3-fold lower potency compared with **I**). Interestingly, compound **19c** and **19d** which replaced the methyl with hydroxyethyl and methoxyethyl group displayed comparable MET inhibitory activity (IC_{50} of 5.7 and 8.3 nM) to that of **I** (Cabozantinib). Compounds **19c** and **19d** were screened in preliminary rat microsomal metabolic stability and showed moderate half-life ($T_{1/2}$ = 88.9 and 63.4 min). To further improve the drug-likeness, mono-methyl or di-methyl group was introduced into the hydroxyethyl or methoxyethyl group, the resulted compounds **19e-g** exhibited good inhibitory activity (IC_{50} of 12.1 to 19.4 nM). More importantly, compound **19f** displayed a longer half-life ($T_{1/2}$ of 310.2 min). After the alicyclic amines (morpholine, pyrrolidine, piperidine) were introduced in 7-R^1 group, compounds **19h-k** all showed comparable inhibitory activity (IC_{50} of 10.1 to 17.8 nM) to that of hydroxyethyl and

methoxyethyl substituted compounds. When the R^4 group in block D was replaced from F to H, the resulted compounds **19l-p** all displayed good MET inhibitory activity (IC_{50} of 7.7 to 20.1 nM).

Table 1. Activity of **19a-p** against MET[a] and microsomal metabolic stability (rat)



19a-p

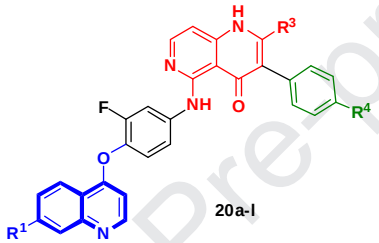
Compd	R^1	R^4	MET, IC_{50} (nM)	Metabolic stability ($T_{1/2}$, min)
19a	OMe	F	76.6	
19b		F	19.7	-
19c		F	5.7	88.9
19d		F	8.3	63.4
19e		F	15.6	-
19f		F	19.4	310.2
19g		F	12.1	-
19h		F	18.1	-
19i		F	17.8	-
19j		F	13.2	-
19k		F	10.1	-
19l		H	7.7	-
19m		H	20.1	-
19n		H	10.5	-
19o		H	10.1	-
19p		H	9.4	-
I (Cabozantinib)			8.4	-
III [19]			9.9	-
IV [20]			9.8	-

[a] In vitro kinase assay were performed with the indicated purified recombinant MET kinase domain (nM).

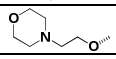
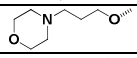
Moreover, the 6-methoxy group of quinoline moiety in block A was moved to further investigate the SAR and drug-likeness (Table **2**). Similar with the SAR of compounds **19a-p**, the hydroxyethyl, methoxyethyl and alicyclic amines derivatives **20c-h** and **20j-k** all displayed

excellent MET inhibitory activity (IC_{50} of 5.7 to 13.3 nM). Interestingly, compound **20i** with 7-hydrxoy group showed comparable inhibitory activity (IC_{50} of 5.0 nM) to that of **I** (Cabozantinib). The introduction of methyl group into the 2-position of 1,6-naphthyridinone resulted in a slight loss of activity (**20l**, IC_{50} of 40.3 nM, 5.4-fold lower potency compared with **20j**). The structure–pharmacokinetic relationship (SPR) of compounds **20** were studied based on the screen of rat microsomal metabolic stability. The morpholine substituted compounds **20h** and **20k** exhibited high clearance rates in rat microsomes ($T_{1/2}$ < 20 min), while alkoxy derivatives displayed moderate to low clearance rates ($T_{1/2}$ > 50 min). More importantly, compounds **20f** and **20j** showed longer half-life ($T_{1/2}$ = 248.4 and 322.3 min), which proposed the side chain of 7-hydroxyethoxy group was a key metabolic site.

Table 2. Activity of **20a-l** against MET[a] and microsomal metabolic stability (rat)



20a-l

Compd	R^1	R^3	R^4	MET, IC_{50} (nM)	Metabolic stability ($T_{1/2}$, min)
20a	OMe	H	F	41.4	-
20b		H	F	27.8	90.1
20c		H	F	6.8	90.6
20d		H	F	8.4	103.8
20e		H	F	13.3	85.4
20f		H	F	7.6	248.4
20g		H	F	13.1	86.8
20h		H	F	10.9	6.6
20i	OH	H	F	5.0	53.6
20j		H	H	7.4	322.3
20k		H	H	5.7	17.8
20l		Me	H	40.3	-

[a] In vitro kinase assay were performed with the indicated purified recombinant MET kinase domain (nM).

Molecular docking experiments were further performed to determine the SAR of block C. As shown in Figure **3A**, compound **20j** was located deep in the MET pocket, and since three key H-bond interactions were observed in the binding mode: one was established between the carbonyl group in block C and residue Asp1222, another formed between the N-methyl group in block C and Glu1127, the third formed between N atom in block A and Met1160, **20j**

displayed comparable MET enzymatic activity to that of **I**. As shown in Figure **3B-C**, the introduction of a C(3) methyl group in block C of **20j** resulted in a rotation of residue Glu1127, which led to a disappearance of the H-bond interaction between N-methyl group in block C of **20l** and the residue Glu1127. As a result, **20j** showed 5.4-fold higher potency compared with **20l**.

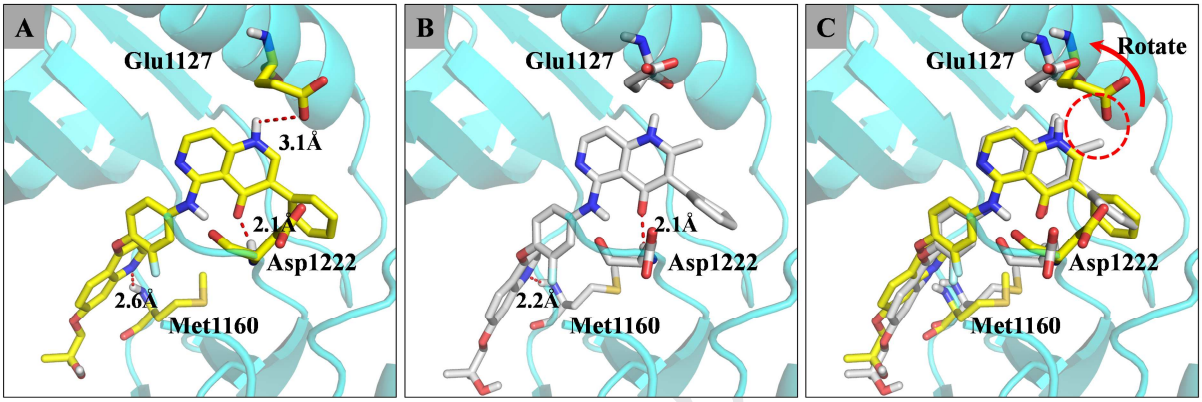


Figure 3. (A)The proposed binding mode of **20j** with MET; (B) The proposed binding mode of **20l** with MET; (C) The binding mode overlay of **20j** (yellow) and **20l** (gray) with MET. Each dashed red line represents hydrogen bonds between residues with **20j** and **20l**.

The inhibitory activity of compound **20j** against a panel of forty eight other kinases was also assayed (Figure **4**). In contrast to its high potency against MET (IC_{50} of 7.4 nM), **20j** only exhibited high inhibitory effects against AXL, Flt4, KDR, Mer, TEK and TYRO3 (inhibitory rate > 80% in 1 μM). The IC_{50} of **20j** agsinst these six kinases was shown in Table **3**. These kinase profiling data suggested that compound **20j** is a more selective kinase inhibitor than **I** (cabozantnib) [25]. More importantly, it provided a novel scaffold for further kinase selectivity enhancement.

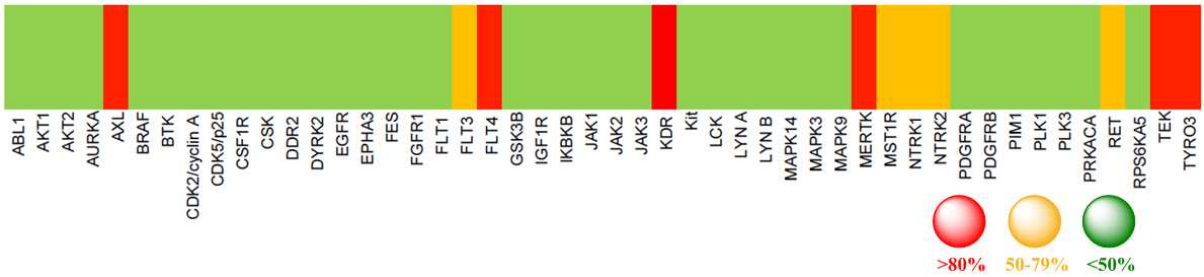


Figure 4. Preliminary results of kinase profile of **20j** (Inhibitory rate in 1μM)

Table 3. Activity of **20j** against AXL, Flt4, KDR, Mer, TEK and TYRO3

N.O.	Kinase	IC_{50}, nM
1	AXL	32.3
2	Flt4	116

3	KDR	198
4	Mer	16.5
5	TEK	19.0
6	TYRO3	91.6

Antiproliferative activities of the selected compounds (good MET inhibitory activity and favorable microsomal metabolic stability) against U-87 MG (human glioblastoma), NIH-H460 (human lung cancer), HT-29 (human colorectal cancer), MKN-45 (human gastric cancer) cell lines were also evaluated *in vitro* using compound **I** (Cabozantinib) as a positive control. As shown in Table **4**, most of the selected compounds except **20g** displayed good and broad-spectrum antiproliferative activity (IC_{50} of 1.4-8.5 μM) against the tested cancer cell lines, which is comparable to that of compound **I** (Cabozantinib, IC_{50} of 3.2-5.8 μM) .

Table 4. Antiproliferative activity of selected compounds against U-87 MG, NIH-H460, HT-29 and MKN-45 cell lines.

Compds.	IC_{50} (μM)			
	U-87MG	NIH-H460	HT-29	MKN-45
19c	4.1	2.0	2.9	1.6
19d	5.2	3.0	4.6	3.1
19f	2.6	1.7	2.1	1.4
20c	4.9	3.5	5.5	4.7
20d	5.1	4.3	6.5	5.6
20e	8.5	3.4	3.9	3.1
20f	4.7	3.2	3.4	2.7
20g	16.4	4.4	4.8	5.5
20i	7.2	4.3	5.9	5.0
20j	4.5	3.6	4.2	2.9
I	5.8	3.6	5.3	3.2

The PK properties of potent lead compound **20j** was further evaluated in rats. As summarized in Table **5**, the chemical structure of block A (quinoline or pyridine-based) had a significant influence on the PK properties after oral administration in rats. Compound **20j** displayed favorable overall PK profiles, with maximal plasma concentration (C_{max} = 1.5 μg/mL, 5-fold higher to that of **IV**), plasma exposure ($AUC_{0-\infty}$ = 10.7 μg·h/mL, 9.7-fold higher to that of **IV**), half-life ($T_{1/2}$ = 4.9 h, 4.9-fold longer to that of **IV**), total clearance CL (0.5 L/h/kg; 10-fold lower to that of **IV**), and oral bioavailability (F = 32%, 2.7-fold higher

to that of **IV**) after oral dose of 5 mg/kg (10 mg/kg for **IV**).

Table 5. In vivo PK profiles of compound **20j** in rat[a,b]

Compd.	route	Dose (mg/kg)	C_{max} (μg/mL)	T_{max}	$T_{1/2}$	$AUC_{0-\infty}$ (μg* h /mL)	CL (L/h/kg)	*Vz* (L/kg)	*F* (%)
20j	p.o.	5	1.5	4.0	4.9	10.7	0.5	3.3	32
	i.v.	1	0.5	-	4.0	6.6	0.2	0.9	-
IV [20]	p.o.	10	0.6	2.7	1.0	2.2	5.0	7.5	12
	i.v.	2.5	16.4	-	0.5	4.5	0.6	10.4	-

[a] Vehicle: 70% PEG400-30% water. $C_{max,}$ maximum concentration; T_{max}, time of maximum concentration; $T_{1/2}$, half-lif; $AUC_{0-\infty}$, area under the plasma concentration time curve; CL, clearance; V_Z, volume of distribution; *F*, oral bioavailability. [b] Data reported as the average of three animals.

As a representative MET-positive tumor cell line, U-87 MG human glioblastoma xenograft model [9] was selected to evaluated the in vivo antitumor efficacy of compound **20j** (Table **6** & Figure **5**). When administered orally Q.D., compound **20j** induced dose-dependent tumor growth inhibition. The minimum effective dose (MED, 50% inhibition of tumor growth) of **20j** was about 3 mg/kg. And, more importantly, **20j** displayed an excellent in vivo efficacy (TGI of 131%, 4/6 PR) superior to that of compound **I** (Cabozantinib, TGI of 97%, 2/6 PR), whereas compound **III** and **IV** only showed moderate or weak efficacy (TGI of 53% or 15%) at the same dose (12.5 mg/kg). All tested animals displayed tumor regressions at higher dose (37.5 mg/kg) of **20j** (TGI of 172%, 6/6 PR).

Table 6. In vivo tumor growth inhibition activity in U-87 MG xenograft model

Model	Compd.	Dose [a] (mg/kg)	TGI (%)[b]	PR[c]
U-87 MG	**20j**	37.5	172**	6/6
		12.5	131**	4/6
		6	57	0/6
		3	47	0/6
	I (Cabozantinib)	12.5	97**	3/6
	III [19]	12.5	53	0/6
	IV [20]	12.5	15	0/6

[a]1Q.D.×21/70% PEG-400/H_2O/p.o.; [b]TGI, Tumor growth inhibition value; **: P<0.01; [c]PR, partial regression.

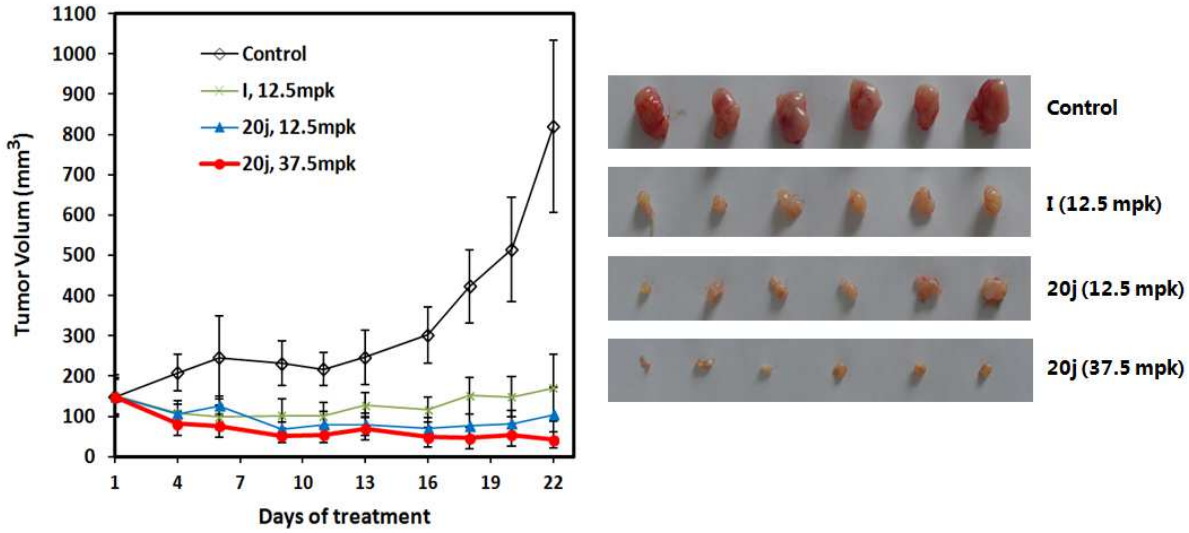


Figure 5. Antitumor efficacy of compound **20j** in the U-87 MG xenograft model. Tumor-bearing nude mice were randomly divided into groups when the tumor volume reached 100-200 mm^3 and given corresponding compounds p.o. at the indicated dose levels or vehicle alone over the designated treatment schedule. Data are presented as the mean (± SEM; n = 6 mice per group).

4. Conclusions

In the present work, we described the design, synthesis, and biological evaluation of a series of 1,6-naphthyridinone-based class II MET kinase inhibitors bearing quinoline moiety in block A based on the structures of Cabozantinib and our reported compound **IV** with pyridine moiety in block A. Extensive SAR and DMPK studies led to the identification of **20j**, a potent and orally bioavailable MET kinase inhibitor with favorable kinase selectivity. More importantly, **20j** exhibited statistically significant tumor growth inhibition (TGI of 131%, 4/6 PR) in the U-87 MG xenograft model, which is superior to that of Cabozantinib (TGI of 97%, 2/6 PR), and significantly better than that of compound **IV** (TGI of 15%, 0/6 PR) at the same dose (12.5 mg/kg). Combined with favorable in vitro potency, kinase selectivity, pharmacokinetic profile and in vivo efficacy, the promising antitumor drug candidate **20j** has subsequently advanced into preclinical research.

5. Experimental

5.1. General methods

Unless otherwise noted, all chemical reagents were commercially available and treated with standard methods. Silica gel column chromatography (CC). silica gel (200-400 Mesh; Qingdao Makall Group Co., Ltd; Qingdao; China). Solvents were dried in a routine way and redistilled. Melting points of compounds were measured on a Melt-Temp II apparatus

and uncorrected. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker BioSpin AG (Ultrashield Plus AV 400) spectrometer as deuterochloroform ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) solutions using tetramethylsilane (TMS) as an internal standard (δ = 0) unless noted otherwise. MS spectra were obtained on an Agilent technologies 6120 quadrupole LC/MS (ESI). High-resolution mass spectra (HR-MS) were obtained on an Agilent 6224 TOF LC/MS (USA). All reactions were monitored using thin-layer chromatography (TLC) on silica gel plates. Yields were of purified compounds and were not optimized.

5.2. General procedures for the synthesis of intermediates

The intermediates **2-18** were prepared according to reported methods [21-24]

*5.2.1 2-(benzyloxy)-1-methoxy-4-nitrobenzene (**2**)*

A mixture of 2-methoxy-5-nitrophenol **1** (20 g, 118 mmol), benzyl bromide (177 mmol) and K_2CO_3 (355 mmol) in DMF (200 mL) was stirred at 90°C for 5 hours. The reaction was cooled to room temperature and poured into a mixture of ice and water (1000 mL). The solid was collected by filtration, washed with water and dried in vacuo to give the title compound. **2** as a white solid (28.8 g, 94%). m.p.: 93-94 °C (91-92°C, ref 26); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (dd, J = 8.8, 2.6 Hz, 1H, Ar-H), 7.83 (d, J = 2.6 Hz, 1H, Ar-H), 7.45 (d, J = 7.2 Hz, 2H, Ar-H), 7.40 (t, J = 7.2 Hz, 2H, Ar-H), 7.35 (d, J = 7.0 Hz, 1H, Ar-H), 7.18 (d, J = 9.0 Hz, 1H, Ar-H), 5.21 (s, 2H, $PhCH_2$-), 3.91 (s, 3H, -OCH_3). MS (ESI) m/z: 260.1 $[M+H]^+$.

*5.2.2 3-(benzyloxy)-4-methoxyaniline (**3**)*

A mixture of iron powder (755 mmol), ammonium chloride (324 mmol), 2-(benzyloxy)-1-methoxy-4-nitrobenzene **2** (28 g, 108 mmol), ethanol (150 ml) and water (50 ml) was refluxed for 3 hours. The mixture was filtered through celite and washed with EtOAc. The organic layer was washed with water and Sat. NaCl, dried over Na_2SO_4, and concentrated to afford the title compound **3** as a pale-yellow solid (22.2 g, 90%). m.p.: 97-99 °C (100-101 °C, ref 26); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 6.0 Hz, 2H, Ar-H), 7.35 (t, J = 6.9 Hz, 2H, Ar-H), 7.30 (d, J = 6.6 Hz, 1H, Ar-H), 6.73 (d, J = 7.8 Hz, 1H, Ar-H), 6.32 (s, 1H, Ar-H), 6.25 (d, J = 7.2 Hz, 1H, Ar-H), 5.10 (s, 2H, $PhCH_2$-), 3.81 (s, 3H, -OCH_3), 3.37 (s, 2H, -NH_2). MS (ESI) m/z: 230.1 $[M+H]^+$.

5.2.3

*5-{[(3-(benzyloxy)-4-methoxyphenyl)amino]methylene}-2,2-dimethyl-1,3-dioxane-4,6-dione (**4**)*

To a stirred solution of 3-(benzyloxy)-4-methoxyaniline **3** (22 g, 96 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (115.2 mmol) in absolute ethanol (55 mL) was added drop-wise triethyl orthoformate (115.2 mmol). Upon the completion of addition, the reaction mixture was heated at 80 °C for 1 h. The mixture was cooled and poured into ice-water. The mixture was filtrated and washed with water, and then dried to give the title compound **4** as a pale-green solid (33.8 g, 92%). m.p.: 84-85 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.16 (d, J = 13.8 Hz, 1H, NH), 8.48 (d, J = 14.4 Hz, 1H, Ar-H), 7.46 (d, J = 7.2 Hz, 2H, Ar-H), 7.40 (t, J = 7.2 Hz, 2H, Ar-H), 7.34 (t, J = 6.9 Hz, 1H, Ar-H), 6.91 (d, J = 8.4 Hz, 1H, Ar-H), 6.81 (d, J = 9.0 Hz, 1H, Ar-H), 6.79 (s, 1H, -CH=C-), 5.17 (s, 2H, $PhCH_2$-), 3.91 (s, 3H, $-OCH_3$), 1.75 [s, 6H, $-(CH_3)_2$]. MS (ESI) m/z: 384.1 $[M+H]^+$.

*5.2.4 7-(benzyloxy)-6-methoxyquinolin-4-ol (**5**)*

A mixture of 5-(((3-(benzyloxy)-4-methoxyphenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **4** (33 g, 86 mmol) in 1,2-dichlorobenzene (200 mL) was stirred at 180°C for 7 hours, subsequently the mixture was cooled to room temperature and was stirred at 0°C for 3 hours. The mixture was filtrated and washed with cooled 1,2-dichlorobenzene and diethyl ether, and then dried to give the title compound **5** as a pale-yellow solid (13.1 g, 54%). m.p.: 238-239 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.57 (s, 1H, -OH), 7.77 (s, 1H, , Ar-H), 7.54 – 7.45 (m, 3H, Ar-H), 7.45 – 7.35 (m, 3H, Ar-H), 7.06 (s, 1H, Ar-H), 5.95 (d, J = 6.6 Hz, 1H, Ar-H), 5.19 (s, 2H, $PhCH_2$-), 3.84 (s, 3H, $-OCH_3$). MS (ESI) m/z: 282.2 $[M+H]^+$.

*5.2.5 7-(benzyloxy)-4-chloro-6-methoxyquinoline (**6**)*

A solution of 7-(benzyloxy)-6-methoxyquinolin-4-ol **5** (13 g, 46 mmol) and DMF (2d) in $POCl_3$ (50 mL) was heated at 100 °C for 1 hour. The mixture was evaporated under reduced pressure and the residue was added to ice water, and then extracted with DCM. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4. The residue was purified by chromatography (PE/EA = 30:1) to yield the title compound **6** as a yellow solid (12.4 g, 90%). m.p.: 132-133 °C (135-136 °C, ref 27); ^{1}H NMR (600 MHz,

DMSO-d_6) δ 8.61 (d, J = 4.2 Hz, 1H, Ar-H), 7.57 (s, 2H, Ar-H), 7.52 (d, J = 7.2 Hz, 2H, Ar-H), 7.43 (t, J = 7.2 Hz, 2H, Ar-H), 7.45 – 7.35 (m, 2H, Ar-H), 5.32 (s, 2H, $PhCH_2$-), 3.98 (s, 3H, -OCH_3). MS (ESI) m/z: 300.1 $[M+H]^+$.

*5.2.6 7-(benzyloxy)-4-(2-fluoro-4-nitrophenoxy)-6-methoxyquinoline (**7**)*

A solution of 7-(benzyloxy)-4-chloro-6-methoxyquinoline **6** (12 g, 40 mmol), 2-fluoro-4-nitrophenol (60 mmol) and DIPEA (120 mmol) in toluene (150 mL) was refluxed for 8 hour, then cooled to room temperature. The reaction mixture was concentrated under reduced pressure, and purified by chromatography (PE/EA = 30:1) to yield the title compound **7** as a yellow solid (13.4 g, 80%). m.p.: 169-170 °C (170-171 °C, ref 24); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, J = 5.1 Hz, 1H, Ar-H), 8.19 (dd, J = 9.6, 2.4 Hz, 1H, Ar-H), 8.15– 8.10 (m , 1H, Ar-H), 7.52 (d, J = 7.2 Hz, 2H, Ar-H), 7.50 (s, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.40 (t, J = 7.5 Hz, 2H, Ar-H), 7.34 (t, J = 8.4 Hz, 2H, Ar-H), 6.54 (d, J = 5.1 Hz, 1H, Ar-H), 5.34 (s, 2H, $PhCH_2$-), 4.04 (s, 3H, -OCH_3). MS (ESI) m/z: 421.1 $[M+H]^+$.

*5.2.7 4-(2-fluoro-4-nitrophenoxy)-6-methoxyquinolin-7-ol (**8**)*

A solution of 7-(benzyloxy)-4-(2-fluoro-4-nitrophenoxy)-6-methoxyquinoline **7** (13 g, 31 mmol) and TFA (310 mmol) in DCM (150 mL) was stirred at room temperature for 30 min. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The resulting suspension was filtered and the solid dried to afford the title compound **8** as a yellow solid (9.2 g, 90%). m.p.: 216-217 °C (219-220 °C, ref 24); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H, OH), 8.85 (d, J = 6.4 Hz, 1H, Ar-H), 8.56 (dd, J = 10.0, 2.6 Hz, 1H, Ar-H), 8.31 (dd, J = 9.6, 1.8 Hz, 1H, Ar-H), 7.89 (t, J = 8.4 Hz, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 7.13 (d, J = 6.6 Hz, 1H, Ar-H), 4.03 (s, 3H, -OCH_3). MS (ESI) m/z: 331.1 $[M+H]^+$.

*5.2.8 4-(2-fluoro-4-nitrophenoxy)-6-methoxy-7-(substituted alkoxy)quinoline (**9**)*

A solution of 4-(2-fluoro-4-nitrophenoxy)-6-methoxyquinolin-7-ol **8** (500 mg, 1.5 mmol) and K_2CO_3 (4.5 mmol) in CH_3CN (25 mL) was stirred at room temperature for 30 min. various alkyl halides (2.3 mmol) was added to the reaction mixture and subsequently refluxed for 4 hours. The reaction mixture was concentrated under reduced pressure, and purified by chromatography (PE/EA = 10:1) to yield the title compound **9**.

4-(2-fluoro-4-nitrophenoxy)-6,7-dimethoxyquinoline (**9a**): yield: 80%; m.p.: 152-153 °C (150-151 °C, ref 24); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.58 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.47 (dd, *J* = 10.3, 1.9 Hz, 1H, Ar-H), 8.21 (d, *J* = 8.9 Hz, 1H, Ar-H), 7.63 (t, *J* = 8.5 Hz, 1H, Ar-H), 7.46 (s, 2H, Ar-H), 6.79 (d, *J* = 5.1 Hz, 1H, Ar-H), 3.97 (s, 3H, -OCH_3), 3.93 (s, 3H, -OCH_3).

4-(2-fluoro-4-nitrophenoxy)-7-isobutoxy-6-methoxyquinoline (**9b**): yield: 83%; m.p.: 145-146 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.53 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.42 (dd, *J* = 10.4, 2.4 Hz, 1H, Ar-H), 8.16 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.58 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.40 (s, 1H, Ar-H), 6.75 (d, *J* = 5.2 Hz, 1H, Ar-H), 3.94 (d, *J* = 6.8 Hz, 2H, -CH_2-), 3.92 (s, 3H, -OCH_3), 2.18 – 2.07 (m, 1H, -CH-), 1.04 [d, *J* = 6.8 Hz, 6H, -$(CH_3)_2$].

2-((4-(2-fluoro-4-nitrophenoxy)-6-methoxyquinolin-7-yl)oxy)ethan-1-ol (**9c**): yield: 75%; m.p.: 144-145 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.53 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.43 (dd, *J* = 10.4, 2.6 Hz, 1H, Ar-H), 8.17 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.59 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.43 (s, 2H, Ar-H), 6.75 (d, *J* = 5.2 Hz, 1H, Ar-H), 4.94 (t, *J* = 5.2 Hz, 1H, OH), 4.20 – 4.15 (m, 2H, -CH_2-),3.92 (s, 3H, -OCH_3), 3.84 – 3.80 (m, 2H, -CH_2-).

4-(2-fluoro-4-nitrophenoxy)-6-methoxy-7-(2-methoxyethoxy)quinoline (**9d**): yield: 86%; m.p.: 154-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.54 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.16 (dd, *J* = 9.6, 2.6 Hz, 1H, Ar-H), 8.11 (dd, *J* = 8.8, 1.2 Hz, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.41 (s, 1H, Ar-H), 7.3 (t, *J* = 8.8 Hz, 1H, Ar-H), 6.53 (d, *J* = 4.8 Hz, 1H, Ar-H), 4.43 (t, *J* = 4.8 Hz, 2H, -CH_2-), 4.00 (s, 3H, -OCH_3), 3.90 (t, *J* = 4.8 Hz, 2H, -CH_2-), 3.48 (s, 3H, -OCH_3).

1-((4-(2-fluoro-4-nitrophenoxy)-6-methoxyquinolin-7-yl)oxy)propan-2-ol (**9e**): yield: 85%; m.p.: 158-159 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.9 Hz, 1H, Ar-H), 8.20 (d, *J* = 9.5 Hz, 1H, Ar-H), 8.15 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.36 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 6.56 (d, *J* = 4.9 Hz, 1H, Ar-H), 4.93 (s, 1H, -OH), 4.10 – 3.98 (m, 3H), 3.94 (s, 3H, -OCH_3), 1.21 (d, *J* = 6.0 Hz, 3H, -CH_3).

1-((4-(2-fluoro-4-nitrophenoxy)-6-methoxyquinolin-7-yl)oxy)-2-methylpropan-2-ol (**9f**): yield: 88%; m.p.: 154-155 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.57 (d, *J* = 5.2 Hz,

1H, Ar-H), 8.46 (dd, *J* = 10.4, 2.7 Hz, 1H, Ar-H), 8.20 (dd, *J* = 8.5, 2.3 Hz, 1H, Ar-H), 7.62 (t, *J* = 8.5 Hz, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 6.78 (d, *J* = 5.1 Hz, 1H, Ar-H), 4.71 (s, 1H, -OH), 3.94 (s, 3H, -OCH_3), 3.92 (s, 2H, -CH_2-), 1.27 [s, 6H, -$(CH_3)_2$].

4-(2-fluoro-4-nitrophenoxy)-6-methoxy-7-(2-methoxy-2-methylpropoxy)quinoline (**9g**): yield: 83%; m.p.: 141-142 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 5.1 Hz, 1H, Ar-H), 8.42 (dd, *J* = 10.4, 2.7 Hz, 1H, Ar-H), 8.17 (d, *J* = 8.9 Hz, 1H, Ar-H), 7.58 (t, *J* = 8.5 Hz, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 6.75 (d, *J* = 5.1 Hz, 1H, Ar-H), 4.03 (s, 2H, -CH_2-), 3.92 (s, 3H, -OCH_3), 3.19 (s, 3H, -OCH_3), 1.27 [s, 6H, -$(CH_3)_2$].

4-(2-((4-(2-fluoro-4-nitrophenoxy)-6-methoxyquinolin-7-yl)oxy)ethyl)morpholine (**9h**) [24]: yield: 81%; m.p.: 153-154 °C; ^{1}H NMR (600 MHz, DMSO-d_6) *δ* 8.57 (d, *J* = 5.1 Hz, 1H, Ar-H), 8.47 (dd, *J* = 10.2, 2.1 Hz, 1H, Ar-H), 8.21 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.62 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 6.78 (d, *J* = 5.1 Hz, 1H, Ar-H), 4.29 (t, *J* = 5.4 Hz, 2H, -CH_2-), 3.93 (s, 3H, -OCH_3), 3.64 – 3.56 (m, 4H, -CH_2-), 2.80 (t, *J* = 5.4 Hz, 2H, -CH_2-), 2.56 – 2.52 (m, 4H, -CH_2-).

4-(3-((4-(2-fluoro-4-nitrophenoxy)-6-methoxyquinolin-7-yl)oxy)propyl)morpholine (**9i**) [24]: yield: 77%; m.p.: 135-136°C (137-139 °C, ref 24); ^{1}H NMR (600 MHz, DMSO-d_6) *δ* 8.57 (d, *J* = 5.1 Hz, 1H, Ar-H), 8.47 (dd, *J* = 10.2, 2.4 Hz, 1H, Ar-H), 8.20 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.62 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.45 (d, *J* = 3.0 Hz, 2H, Ar-H), 6.78 (d, *J* = 5.1 Hz, 1H, Ar-H), 4.21 (t, *J* = 6.6 Hz, 2H, -CH_2-), 3.93 (s, 3H, -OCH_3), 3.59 (t, *J* = 3.9 Hz, 4H, -CH_2-), 2.47 (t, *J* = 6.9 Hz, 2H, -CH_2-), 2.43 – 2.36 (m, 4H, -CH_2-), 2.01 – 1.96 (m, 2H, -CH_2-).

4-(2-fluoro-4-nitrophenoxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinoline (**9j**) [28]: yield: 82%; m.p.: 142-143 °C (140-141 °C, ref 29); ^{1}H NMR (600 MHz, DMSO-d_6) *δ* 8.57 (d, *J* = 4.8 Hz, 1H, Ar-H), 8.46 (dd, *J* = 10.2, 1.8 Hz, 1H, Ar-H), 8.20 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.62 (t, *J* = 8.7 Hz, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 6.78 (d, *J* = 4.8 Hz, 1H, Ar-H), 4.22 (t, *J* = 6.0 Hz, 2H, -CH_2-), 3.93 (s, 3H, -OCH_3), 2.62 (t, *J* = 6.0 Hz, 2H, -CH_2-), 2.54 – 2.47 (m, 4H, -CH_2-), 2.03 – 1.98 (m, 2H, -CH_2-), 1.74 – 1.68 (m, 4H, -CH_2-).

4-(2-fluoro-4-nitrophenoxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinolin e (**9k**) [30]: yield: 88%; m.p.: 156-157 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.57 (d, *J* = 3.9

Hz, 1H, Ar-H), 8.19 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.14 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.35 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.56 (d, *J* = 3.6 Hz, 1H, Ar-H), 4.09 (d, *J* = 5.4 Hz, 2H, -CH_2-), 4.01 (s, 3H, -OCH_3), 3.22 (d, *J* = 9.6 Hz, 2H, -CH_2-), 2.53 (s, 3H, -NCH_3), 2.44 – 2.32 (m, 2H, -CH_2-), 2.20 – 2.10 (m, 1H, -CH-), 2.06 (d, *J* = 12.3 Hz, 2H, -CH_2-), 1.81 – 1.69 (m, 2H, -CH_2-).

*5.2.9 3-fluoro-4-{[6-methoxy-7-(substituted alkoxy)quinolin-4-yl]oxy}aniline (**10**)*

Prepared according to the procedure for the preparation of **3**, from **9**, to yield the title compound **10**.

4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline (**10a**): yield: 88%; m.p.: 191-192 °C (191-193 °C, ref 24); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 4.4 Hz, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 7.41 (s, 1H, Ar-H), 7.11 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.58 (dd, *J* = 13.2, 2.6 Hz, 1H, Ar-H), 6.50 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.42 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.55 (s, 2H, -NH_2), 3.97 (ovl, s, 6H, -OCH_3).

3-fluoro-4-((7-isobutoxy-6-methoxyquinolin-4-yl)oxy)aniline (**10b**): yield: 87%; m.p.: 182-183 °C ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.41 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.33 (s, 1H, Ar-H), 7.04 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.53 (dd, *J* = 13.2, 2.4 Hz, 1H, Ar-H), 6.44 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 6.36 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.46 (s, 2H, -NH_2), 3.94 (s, 3H, -OCH_3), 3.91 (d, *J* = 6.6 Hz, 2H, -CH_2-), 2.18 – 2.06 (m, 1H, -CH-), 1.03 [d, *J* = 6.6 Hz, 6H, -$(CH_3)_2$].

2-((4-(4-amino-2-fluorophenoxy)-6-methoxyquinolin-7-yl)oxy)ethan-1-ol (**10c**): yield: 90%; m.p.: 197-198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.42 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 7.05 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.53 (dd, *J* = 13.2, 2.4 Hz, 1H, Ar-H), 6.45 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 6.37 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.46 (s, 2H, -NH_2), 4.93 (t, *J* = 5.2 Hz, 1H, OH), 4.15 (t, *J* =5.0 Hz, 2H, -CH_2-), 3.94 (s, 3H, -OCH_3), 2.84 – 3.77 (m, 2H, -CH_2-).

3-fluoro-4-((6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl)oxy)aniline (**10d**): yield: 89%; m.p.: 185-186 °C; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.47 (d, *J* = 4.5 Hz, 1H, Ar-H), 7.58 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H), 7.03 (t, *J* = 8.4 Hz, 1H, Ar-H), 6.56 (d, *J* = 12.0 Hz, 1H, Ar-H), 6.50 (d, *J* = 7.8 Hz, 1H, Ar-H), 6.41 (d, *J* = 4.2 Hz, 1H, Ar-H), 4.36 – 4.32 (m, 2H, -CH_2-), 4.03 (s, 3H, -OCH_3), 3.93 – 3.88 (m, 2H, -CH_2-), 3.84 (s, 2H, -NH_2), 3.49 (s, 3H,

-OCH_3).

1-((4-(4-amino-2-fluorophenoxy)-6-methoxyquinolin-7-yl)oxy)propan-2-ol (**10e**): yield: 94%; m.p.: 192-193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.05 (t, *J* = 8.9 Hz, 1H, Ar-H), 6.53 (d, *J* = 13.2 Hz, 1H, Ar-H), 6.45 (d, *J* = 8.6 Hz, 1H, Ar-H), 6.37 (d, *J* = 4.8 Hz, 1H, Ar-H), 5.47 (s, 2H, -NH_2), 4.93 (s, 1H, -OH), 4.10 – 3.98 (m, 3H), 3.94 (s, 3H, -OCH_3), 1.21 (d, *J* = 5.9 Hz, 3H, -CH_3).

1-((4-(4-amino-2-fluorophenoxy)-6-methoxyquinolin-7-yl)oxy)-2-methylpropan-2-ol (**10f**): yield: 89%; m.p.: 188-189 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.45 (d, *J* = 5.0 Hz, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 7.09 (d, *J* = 8.9 Hz, 1H, Ar-H), 6.56 (d, *J* = 13.1 Hz, 1H, Ar-H), 6.47 (d, *J* = 8.3 Hz, 1H, Ar-H), 6.39 (d, *J* = 4.9 Hz, 1H, Ar-H), 5.51 (s, 2H, -NH_2), 4.71 (s, 1H, -OH), 3.96 (s, 3H, -OCH_3), 3.89 (s, 2H, -CH_2-), 1.27 [s, 6H, -$(CH_3)_2$].

3-fluoro-4-((6-methoxy-7-(2-methoxy-2-methylpropoxy)quinolin-4-yl)oxy)aniline (**10g**): yield: 90%; m.p.: 184-185 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.1 Hz, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.38 (s, 1H, Ar-H), 7.05 (t, *J* = 8.9 Hz, 1H, Ar-H), 6.53 (dd, *J* = 13.2, 2.3 Hz, 1H, Ar-H), 6.45 (dd, *J* = 8.3, 1.6 Hz, 1H, Ar-H), 6.37 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.46 (s, 2H, -NH_2), 4.01 (s, 2H, -CH_2-), 3.94 (s, 3H, -OCH_3), 3.20 (s, 3H, -OCH_3), 1.27 [s, 6H, -$(CH_3)_2$].

3-fluoro-4-((6-methoxy-7-(2-morpholinoethoxy)quinolin-4-yl)oxy)aniline (**10h**) [24]: yield: 91%; m.p.: 179-180 °C (180-181 °C, ref 24); ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.42 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 7.05 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.53 (dd, *J* = 13.2, 2.4 Hz, 1H, Ar-H), 6.44 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-H), 6.37 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.48 (s, 2H, -NH_2), 4.25 (t, *J* = 5.6 Hz, 2H, -CH_2-), 3.93 (s, 3H, -OCH_3), 3.64 – 3.52 (m, 4H, -CH_2-), 2.78 (t, *J* = 5.6 Hz, 2H, -CH_2-), 2.55 – 2.51 (m, 4H, -CH_2-).

3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)aniline (**10i**) [24]: yield: 91%; m.p.: 120-121 °C (119-121 °C, ref 24); ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.41 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.35 (s, 1H, Ar-H), 7.03 (d, *J* = 8.8 Hz, 1H, Ar-H), 6.53 (dd, *J* = 13.2, 2.4 Hz, 1H, Ar-H), 6.44 (dd, *J* = 8.4, 1.6 Hz, 1H, Ar-H), 6.36 (d,

J = 4.8 Hz, 1H, Ar-H), 5.48 (s, 2H, -NH_2), 4.17 (t, *J* = 6.2 Hz, 2H, -CH_2-), 3.93 (s, 3H, -OCH_3), 3.62 – 3.51 (m, 2H, -CH_2-), 2.48 – 2.43 (m, 2H, -CH_2-), 2.41 – 2.35 (m, 4H, -CH_2-), 2.02 – 1.92 (m, 2H, -CH_2-).

3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)aniline (**10j**) [28]: yield: 89%; m.p.: 165-166 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.45 (d, *J* = 4.5 Hz, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 7.07 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.55 (d, *J* = 12.9 Hz, 1H, Ar-H), 6.47 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.39 (d, *J* = 4.5 Hz, 1H, Ar-H), 5.52 (s, 2H, -NH_2), 4.29-4.16 (m, 2H, -CH_2-), 3.95 (s, 3H, -OCH_3), 3.00 – 2.80 (m, 6H, -CH_2-), 2.15 – 2.07 (m, 2H, -CH_2-), 1.82 (s, 4H, -CH_2-).

3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinolin-4-yl)oxy)aniline (**10k**) [30]: yield: 93%; m.p.: 178-179 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.48 (s, 1H, Ar-H), 7.68 (s, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 7.07 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.67 – 6.54 (m, 3H, Ar-H), 4.14 (s, 2H, -NH_2), 4.02 (s, 3H, -OCH_3), 3.66 – 3.54 (m, 2H, -CH_2-), 3.20 – 3.08 (m, 2H, -CH_2-), 2.91 (s, 3H, -NCH_3), 2.35 – 2.25 (m, 1H, -CH-), 2.21 (d, *J* = 13.8 Hz, 2H, -CH_2-), 1.90 – 1.76 (m, 2H, -CH_2-).

*5.2.10 4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinoline (**12**)[9]*

Prepared according to the procedure for the preparation of **7**, from 4-chloro-7-methoxyquinoline **11** (10 g, 52 mmol), to yield the title compound **12** as a yellow solid (13.5 g, 83%). m.p.: 142-143 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.70 (d, *J* = 5.1 Hz, 1H, Ar-H), 8.46 (dd, *J* = 10.2, 2.4 Hz, 1H, Ar-H), 8.19 (dd, *J* = 9.0, 2.1 Hz, 1H, Ar-H), 8.14 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.63 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.46 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.32 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-H), 6.77 (d, *J* = 5.1 Hz, 1H, Ar-H), 3.93 (s, 3H, -OCH_3); MS (ESI) m/z: 315.1 $[M+H]^+$.

*5.2.11 4-(2-fluoro-4-nitrophenoxy)quinolin-7-ol (**13**) [24]*

To a solution of 4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinoline **12** (8 g, 25.4 mmol) in DCM (80 mL) was added drop-wise a solution of boron tribromide (76.4 mmol) in DCM (30 mL) at -50°C and subsequently stirred for 1 hour. And then the mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into ice-water slowly and alkalized to pH 12 with saturated sodium hydroxide solution cautiously. After the organic layer was separated, the aqueous phase was acidated to pH 6 with 1N HCl with

solid precipitated. The resulting suspension was filtered the solid dried to afford the title compound **13** as a yellow solid (4.6 g, 60%); m.p.: 248-250 °C (250-252 °C, ref 24); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H, -OH), 9.00 (d, J = 6.4 Hz, 1H, Ar-H), 8.56 (dd, J = 10.0, 1.6 Hz, 1H, Ar-H), 8.43 (d, J = 9.6 Hz, 1H, Ar-H), 8.31 (d, J = 8.8 Hz, 1H, Ar-H), 7.91 (t, J = 8.4 Hz, 1H, Ar-H), 7.61 – 7.38 (m, 2H, Ar-H), 7.10 (d, J = 6.4 Hz, 1H, Ar-H); MS (ESI) m/z: 301.3 $[M+H]^+$.

*5.2.12 4-(2-fluoro-4-nitrophenoxy)-7-(substituted alkoxy)quinoline (**14**)*

Prepared according to the procedure for the preparation of **9**, from 4-(2-fluoro-4-nitrophenoxy)quinolin-7-ol **13**, to yield the title compound **14**.

4-(2-fluoro-4-nitrophenoxy)-7-isobutoxyquinoline (**14a**): yield 84%; m.p.: 133-134 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.71 (d, J = 5.1 Hz, 1H, Ar-H), 8.47 (d, J = 10.3 Hz, 1H, Ar-H), 8.20 (d, J = 9.0 Hz, 1H, Ar-H), 8.15 (d, J = 9.0 Hz, 1H, Ar-H), 7.64 (t, J = 8.4 Hz, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 7.34 (d, J = 9.0 Hz, 1H, Ar-H), 6.79 (d, J = 5.1 Hz, 1H, Ar-H), 3.96 (d, J = 6.3 Hz, 2H, -CH_2-), 2.15 – 2.07 (m, 1H, -CH-), 1.04 [d, J = 6.6 Hz, 6H, -$(CH_3)_2$].

2-((4-(2-fluoro-4-nitrophenoxy)quinolin-7-yl)oxy)ethan-1-ol (**14b**): yield 83%; m.p.: 143-144 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, J = 4.8 Hz, 1H, Ar-H), 8.43 (dd, J = 10.4, 2.6 Hz, 1H, Ar-H), 8.17 (d, J = 9.0 Hz, 1H, Ar-H), 8.13 (d, J = 9.0 Hz, 1H, Ar-H), 7.61 (t, J = 8.4 Hz, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.32 (dd, J = 9.0, 2.2 Hz, 1H, Ar-H), 6.76 (d, J = 5.2 Hz, 1H, Ar-H), 4.94 (t, J = 5.4 Hz, 1H, -OH), 4.18 (t, J = 4.8 Hz, 2H, -CH_2-), 3.80 (q, J = 4.8 Hz, 2H, -CH_2-).

4-(2-fluoro-4-nitrophenoxy)-7-(2-methoxyethoxy)quinoline (**14c**): yield 79%; m.p.: 132-133 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J = 5.0 Hz, 1H, Ar-H), 8.47 – 8.38 (m, 1H, Ar-H), 8.17 (d, J = 9.0 Hz, 1H, Ar-H), 8.13 (d, J = 9.2 Hz, 1H, Ar-H), 7.62 (t, J = 8.4 Hz, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.33 (d, J = 9.0 Hz, 1H, Ar-H), 6.77 (d, J = 4.8 Hz, 1H, Ar-H), 4.37 – 4.20 (m, 2H, -CH_2-), 3.82 – 3.68 (m, 2H, -CH_2-), 3.35 (s, 3H, -OCH_3).

1-((4-(2-fluoro-4-nitrophenoxy)quinolin-7-yl)oxy)propan-2-ol (**14d**): yield 77%; m.p.: 140-141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, J = 4.9 Hz, 1H, Ar-H), 8.20 (d, J = 9.5 Hz, 1H, Ar-H), 8.15 (d, J = 8.7 Hz, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.36 (t, J = 8.2 Hz, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 6.56 (d, J = 4.9 Hz, 1H, Ar-H), 4.93 (s, 1H,

-OH), 4.10 – 3.98 (m, 3H), 1.21 (d, *J* = 6.0 Hz, 3H, -CH_3)

1-((4-(2-fluoro-4-nitrophenoxy)quinolin-7-yl)oxy)-2-methylpropan-2-ol (**14e**) [22]: yield 84%; m.p.: 135-136 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.72 (d, *J* = 5.0 Hz, 1H, Ar-H), 8.48 (d, *J* = 10.1 Hz, 1H, Ar-H), 8.20 (d, *J* = 9.1 Hz, 1H, Ar-H), 8.16 (d, *J* = 9.1 Hz, 1H, Ar-H), 7.64 (t, *J* = 8.6 Hz, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.36 (d, *J* = 9.1 Hz, 1H, Ar-H), 6.80 (d, *J* = 4.9 Hz, 1H, Ar-H), 4.76 (s, 1H, -OH), 3.93 (s, 2H, -CH_2-), 1.27 [s, 6H, -$(CH_3)_2$].

4-(2-fluoro-4-nitrophenoxy)-7-(2-methoxy-2-methylpropoxy)quinoline (**14f**): yield 88%; m.p.: 116-117 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.72 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.47 (d, *J* = 10.5 Hz, 1H, Ar-H), 8.20 (d, *J* = 9.4 Hz, 1H, Ar-H), 8.15 (dd, *J* = 8.9, 0.5 Hz, 1H, Ar-H), 7.64 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.37 (d, *J* = 9.1 Hz, 1H, Ar-H), 6.80 (d, *J* = 5.2 Hz, 1H, Ar-H), 4.06 (s, 2H, -CH_2-), 3.20 (s, 3H, -OCH_3), 1.27 [s, 6H, -$(CH_3)_2$].

4-(2-((4-(2-fluoro-4-nitrophenoxy)quinolin-7-yl)oxy)ethyl)morpholine (**14g**): yield 90%; m.p.: 138-139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.68 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.43 (dd, *J* = 10.4, 2.8 Hz, 1H, Ar-H), 8.17 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.11 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.60 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.47 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.31 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-H), 6.77 (d, *J* = 5.2 Hz, 1H, Ar-H), 4.28 (t, *J* = 5.6 Hz, 2H, -CH_2-), 3.64 – 3.52 (m, 4H, -CH_2-), 2.78 (t, *J* = 5.6 Hz, 2H, -CH_2-), 2.57 – 2..44 (m, 4H, -CH_2-).

4-(3-((4-(2-fluoro-4-nitrophenoxy)quinolin-7-yl)oxy)propyl)morpholine (**14h**): yield 84%; m.p.: 111-112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.66 (d, *J* = 4.8 Hz, 1H, Ar-H), 8.20 – 8.02 (m, 3H, Ar-H), 7.43 (s, 1H, Ar-H), 7.31 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.28 – 7.21 (m, 1H, Ar-H), 6.51 (d, *J* = 4.8 Hz, 1H, Ar-H), 4.20 (t, *J* = 6.0 Hz, 2H, -CH_2-), 3.83 – 3.64 (m, 4H, -CH_2-), 2.64 – 2.55 (m, 2H, -CH_2-), 2.49 – 2.35 (m, 4H, -CH_2-), 2.13 – 2.01 (m, 2H, -CH_2-).

*5.2.13 3-fluoro-4-[(7-methoxyquinolin-4-yl)oxy]aniline (**15**)* [9]

Prepared according to the procedure for the preparation of **3**, from 4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinoline **12** (300 mg, 0.95 mmol), to yield the title compound **15** as s yellow solid (234 mg, 86%); m.p.: 188-189 °C; ^{1}H NMR (600 MHz, DMSO-d_6) *δ* 8.60 (d, *J* = 5.1 Hz, 1H, Ar-H), 8.21 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.40 (d, *J* =

1.8 Hz, 1H, Ar-H), 7.28 (dd, *J* = 9.0, 1.8 Hz, 1H, Ar-H), 7.09 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.56 (dd, *J* = 13.2, 1.8 Hz, 1H, Ar-H), 6.48 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.41 (d, *J* = 5.1 Hz, 1H, Ar-H), 5.52 (s, 2H, -NH_2), 3.94 (s, 3H, -OCH_3); MS (ESI) m/z: 285.1 $[M+H]^+$.

*5.2.14 4-(4-amino-2-fluorophenoxy)quinolin-7-ol (**16**)* [24]

Prepared according to the procedure for the preparation of **3**, from 4-(2-fluoro-4-nitrophenoxy)quinolin-7-ol **13** (300 mg, 1 mmol), to yield the title compound **16** as s yellow solid (237 mg, 88%); m.p.: 267-268 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.25 (s, 1H, -OH), 8.49 (d, *J* = 5.1 Hz, 1H, Ar-H), 8.14 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 7.16 (dd, *J* = 9.0, 1.8 Hz, 1H, Ar-H), 7.05 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.53 (d, *J* = 13.2 Hz, 1H, Ar-H), 6.44 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.29 (d, *J* = 5.1 Hz, 1H, Ar-H), 5.50 (s, 2H, -NH_2); MS (ESI) m/z: 271.1 $[M+H]^+$.

*5.2.15 3-fluoro-4-((7-(substituted alkoxy)quinolin-4-yl)oxy)aniline (**17**)*

Prepared according to the procedure for the preparation of **3**, from **14**, to yield the title compound **17**.

3-fluoro-4-((7-isobutoxyquinolin-4-yl)oxy)aniline (**17a**): yield 88%; m.p.: 168-169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.17 (d, *J* = 9.2 Hz, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.25 (dd, *J* = 9.2, 2.4 Hz, 1H, Ar-H), 7.05 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.53 (dd, *J* = 13.2, 2.4 Hz, 1H, Ar-H), 6.44 (dd, *J* = 8.8, 2.0 Hz, 1H, Ar-H), 6.37 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.50 (s, 2H, -NH_2), 3.92 (d, *J* = 6.4 Hz, 2H, -CH_2-), 2.18 – 2.04 (m, 1H, -CH-), 1.03 [d, *J* = 6.6 Hz, 6H, -$(CH_3)_2$].

2-((4-(4-amino-2-fluorophenoxy)quinolin-7-yl)oxy)ethan-1-ol (**17b**) [22]: yield 89%; m.p.: 175-176 °C;^{1}H NMR (600 MHz, DMSO-d_6) δ 8.60 (d, *J* = 4.8 Hz, 1H, Ar-H), 8.22 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.40 (s, 1H, Ar-H), 7.30 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.09 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.57 (d, *J* = 13.2 Hz, 1H, Ar-H), 6.48 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.42 (d, *J* = 4.8 Hz, 1H, Ar-H), 5.63 (s, 2H, -NH_2), 4.99 (s, 1H, -OH), 4.18 (s, 2H, -CH_2-), 3.81 (s, 2H, -CH_2-).

3-fluoro-4-((7-(2-methoxyethoxy)quinolin-4-yl)oxy)aniline (**17c**): yield 84%; m.p.: 159-160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, *J* = 5.0 Hz, 1H, Ar-H), 8.18 (d, *J* = 9.2 Hz, 1H, Ar-H), 7.38 (s, 1H, Ar-H), 7.26 (dd, *J* = 9.0, 2.0 Hz, 1H, Ar-H), 7.05 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.54 (dd, *J* = 13.2, 1.6 Hz, 1H, Ar-H), 6.45 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.38

(d, *J* = 5.0 Hz, 1H, Ar-H), 5.48 (s, 2H, -NH_2), 4.30 – 4.21 (m, 2H, -CH_2-), 3.77 – 3.69 (m, 2H, -CH_2-), 3.34 (s, 3H, -OCH_3).

1-((4-(4-amino-2-fluorophenoxy)quinolin-7-yl)oxy)propan-2-ol (**17d**): yield 83%; m.p.: 168-169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.05 (t, *J* = 8.9 Hz, 1H, Ar-H), 6.53 (d, *J* = 13.2 Hz, 1H, Ar-H), 6.45 (d, *J* = 8.6 Hz, 1H, Ar-H), 6.37 (d, *J* = 4.8 Hz, 1H, Ar-H), 5.47 (s, 2H, -NH_2), 4.93 (s, 1H, -OH), 4.10 – 3.98 (m, 3H), 1.21 (d, *J* = 6.0 Hz, 3H, -CH_3).

1-((4-(4-amino-2-fluorophenoxy)quinolin-7-yl)oxy)-2-methylpropan-2-ol (**17e**) [22]: yield 87%; m.p.: 171-172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, *J* = 4.0 Hz, 1H, Ar-H), 8.18 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.28 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.06 (t, *J* = 8.8 Hz, 1H, Ar-H), 6.53 (d, *J* = 12.9 Hz, 1H, Ar-H), 6.45 (d, *J* = 8.6 Hz, 1H, Ar-H), 6.38 (d, *J* = 4.7 Hz, 1H, Ar-H), 5.51 (br, s, 2H, -NH_2), 4.72 (s, 1H, -OH), 3.89 (s, 2H, -CH_2-), 1.26 [s, 6H, -$(CH_3)_2$].

3-fluoro-4-((7-(2-methoxy-2-methylpropoxy)quinolin-4-yl)oxy)aniline (**17f**): yield 83%; m.p.: 167-168 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.18 (d, *J* = 9.1 Hz, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 7.28 (d, *J* = 9.1 Hz, 1H, Ar-H), 7.06 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.54 (d, *J* = 13.1 Hz, 1H, Ar-H), 6.45 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.38 (d, *J* = 5.1 Hz, 1H, Ar-H), 5.49 (br, s, 2H, -NH_2), 4.02 (s, 2H, -CH_2-), 3.19 (s, 3H, -OCH_3), 1.27 [s, 6H, -$(CH_3)_2$].

3-fluoro-4-((7-(2-morpholinoethoxy)quinolin-4-yl)oxy)aniline (**17g**): yield 89%; m.p.: 164-165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.17 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.38 (s, 1H, Ar-H), 7.25 (dd, *J* = 9.0, 2.2 Hz, 1H, Ar-H), 7.05 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.53 (dd, *J* = 13.2, 2.2 Hz, 1H, Ar-H), 6.44 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.38 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.47 (s, 2H, -NH_2), 4.26 (t, *J* = 5.6 Hz, 2H, -CH_2-), 3.64 – 3.52 (m, 4H, -CH_2-), 2.77 (t, *J* = 5.6 Hz, 2H, -CH_2-), 2.56 – 2..43 (m, 4H, -CH_2-).

3-fluoro-4-((7-(3-morpholinopropoxy)quinolin-4-yl)oxy)aniline (**17h**) [31]: yield 85%; m.p.: 118-119 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.56 (d, *J* = 5.4 Hz, 1H, Ar-H), 8.18 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 7.24 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-H), 7.06 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.53 (dd, *J* = 13.2, 2.4 Hz, 1H, Ar-H), 6.45 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.37 (d, *J* = 4.8 Hz, 1H, Ar-H), 5.50 (s, 2H, -NH_2), 4.17 (t, *J* = 6.0 Hz, 2H, -CH_2-), 3.66 –

3.50 (m, 4H, -CH_2-), 4.45 (t, *J* = 6.0 Hz, 2H, -CH_2-), 2.41 – 2.32 (m, 4H, -CH_2-), 2.00 – 1.87 (m, 2H, -CH_2-).

*5.3. General procedures for the synthesis of targets **19a-19p** and **20a-l.***

General Procedure A:

To the solution of aromatic amine (0.7 mmol) and the corresponding chlorinated 1,6-naphthyridine (0.7 mmol) in isopropanol (10 mL), HCl (20 mmol%) was added drop-wise, and then heated to 90 °C under nitrogen for 2 h. The mixture was filtered, and the solid was dissolved in ethyl acetate. The solution was stired with K_2CO_3 (1 mmol) at r.t. for 1h and filtered. The filtrate was concentrated in vacuum and purified by flash chromatography (CH_2Cl_2/MeOH = 20:1) to yield the corresponding targets.

General Procedure B:

A solution of aromatic amine (0.7 mmol), the corresponding chlorinated 1,6-naphthyridine (0.7 mmol) and PTSA (0.5 mmol) in isopropanol (10 mL) was heated to 90 °C under nitrogen for 2 h. The mixture was filtered, and the solid was washed with ice-cold ethanol to yield the corresponding targets.

*5.3.1 5-{[4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one (**19a**)*

Prepared according to general procedure A. Yellow solid; yield: 85%; m.p.: 279-281 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ13.22 (s, 1H, -NH), 12.50 (s, 1H, -NH), 8.52 – 8.47 (m, 1H, Ar-H), 8.46 – 8.39 (m, 1H, Ar-H), 8.25 – 8.16 (m, 2H, Ar-H), 7.77 – 7.70 (m, 2H, Ar-H), 7.59 – 7.49 (m, 2H, Ar-H), 7.46 – 7.37 (m, 2H, Ar-H), 7.27 (t, *J* = 8.4 Hz, 2H, Ar-H), 6.88 (d, *J* = 5.2 Hz, 1H, Ar-H), 6.53 – 6.45 (m, 1H, Ar-H), 3.96 (s, 6H, -OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.49 (C=O), 155.46 (d, *J* = 196.4 Hz, 3-F-Ph), 148.99, 146.78, 139.09, 131.32, 130.16, 123.66, 115.27, 107.55, 104.60, 99.02, 56.75 (-OCH_3), 56.51 (-OCH_3)(Remark: some chemical shifts do not appear in the spectra due to the use of insufficient quantities of the substance); HRMS(ESI): calcd for $C_{31}H_{23}F_2N_4O_4$ $[M+H]^+$ 553.1681, Found 553.1679.

*5.3.2 5-{[3-fluoro-4-((7-isobutoxy-6-methoxyquinolin-4-yl)oxy)phenyl]amino}-3-(4-fluoro-phenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19b**)*

Prepared according to general procedure B. White solid; yield: 87%; m.p.: 234-236 °C;

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.34 (s, 1H, -NH), 12.93 (s, 1H, -NH), 8.83 (d, J = 6.4 Hz, 1H, Ar-H), 8.33 – 8.19 (m, 2H, Ar-H), 8.12 – 8.03 (m, 1H, Ar-H), 7.77 – 7.68 (m, 3H, Ar-H), 7.67 – 7.55 (m, 3H, Ar-H), 7.48 – 7.42 (m, 2H, Ar-H), 7.29 – 7.21 (m, 2H, Ar-H), 7.19 – 7.04 (m, 3H, Ar-H), 7.02 – 6.94 (m, 1H, Ar-H), 4.05 (s, 3H, -OCH_3), 4.02 – 3.99 (m, 2H, -OCH_2-), 2.27 (s, 3H, -CH_3), 2.22 – 2.14 (m, 1H, -CH-), 1.05 [d, J = 6.8 Hz, 6H, -$(CH_3)_2$]. ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.79 (C=O), 164.57, 162.51 (d, J = 246.7 Hz, 4-F-Ph), 155.62 (d, J = 226.1 Hz, 3-F-Ph), 154.39, 154.12, 152.74, 151.50, 147.11, 144.93, 143.02, 138.88, 138.20, 137.09, 130.92 (d, J = 8.3 Hz),130.13, 128.29, 125.52, 124.85, 124.22, 115.05 (d, J = 22.8 Hz), 114.86, 106.62, 104.02, 103.30, 100.29, 100.11, 75.24, 56.61, 27.46, 20.84 (-CH_3Ph), 18.99 [-$(CH_3)_2$]; HRMS(ESI): calcd for $C_{34}H_{29}F_2N_4O_4$ $[M+H]^+$ 595.2151, Found 595.2159.

*5.3.3 5-{[3-fluoro-4-((7-(2-hydroxyethoxy)-6-methoxyquinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19c**)*

Prepared according to general procedure B. White solid; yield: 81%; m.p.: 241-243 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.34 (s, 1H, -NH), 12.92 (s, 1H, -NH), 8.84 (d, J = 6.4 Hz, 1H, Ar-H), 8.33 – 8.22 (m, 2H, Ar-H), 8.09 (d, J = 6.2 Hz, 1H, Ar-H), 7.76 (s, 1H, Ar-H), 7.73 (d, J = 5.6 Hz, 1H, Ar-H), 7.71 (d, J = 5.6 Hz, 1H, Ar-H), 7.69 (s, 1H, Ar-H), 7.62 – 7.55 (m, 2H, Ar-H), 7.46 (d, J = 8.0 Hz, 2H, Ar-H), 7.26 (t, J = 8.8 Hz, 2H, Ar-H), 7.15 (d, J = 6.4 Hz, 1H, Ar-H), 7.09 (d, J = 8.0 Hz, 2H, Ar-H), 6.99 (d, J = 6.2 Hz, 1H, Ar-H), 4.29 – 4.22 (m, 2H, $HOCH_2$-),4.05 (s, 3H, -OCH_3), 3.89 – 3.83 (m, 2H, -OCH_2-), 2.28 (s, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.80 (C=O), 164.56, 162.48 (d, J = 243.2 Hz, 4-F-Ph), 154.36, 154.13 (d, J = 233.7 Hz, 3-F-Ph), 152.73, 151.43, 147.09, 144.99, 142.95, 138.80, 138.15, 137.05, 130.90 (d, J = 8.0 Hz), 130.15, 128.26, 125.51, 124.79, 124.17, 115.02 (d, J = 20.7 Hz), 106.62, 103.99, 103.35, 100.33, 100.13, 71.35, 59.06, 56.49 , 20.82 (-CH_3Ph); HRMS(ESI): calcd for $C_{32}H_{25}F_2N_4O_5$ $[M+H]^+$ 583.1787, Found 583.1792.

*5.3.4 5-{[3-fluoro-4-((6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19d**)*

Prepared according to general procedure B. White solid; yield: 80%; m.p.: 235-236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H, -NH), 12.86 (s, 1H, -NH), 8.84 (d, J = 6.8

Hz, 1H, Ar-H), 8.39 – 8.27 (m, 1H, Ar-H), 8.25 (d, *J* = 5.6 Hz, 1H, Ar-H), 8.10 (d, *J* = 6.4 Hz, 1H, Ar-H), 7.76 (s, 1H, Ar-H), 7.75 – 7.51 (m, 5H, Ar-H), 7.45 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.31 – 7.20 (m, 2H, Ar-H), 7.18 – 7.12 (m, 1H, Ar-H), 7.09 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.01 – 6.90 (m, 1H, Ar-H), 4.36 (t, *J* = 4.4 Hz, 2H, -OCH_2-), 4.04 (s, 3H, -OCH_3), 3.80 (t, *J* = 4.4 Hz, 2H, -OCH_2-), 3.35 (s, 3H, -OCH_3), 2.28 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.84 (C=O), 164.62, 162.49 (d, *J* = 243.4 Hz, 4-F-Ph), 155.45 (d, *J* = 234.2 Hz, 3-F-Ph), 154.36, 152.71, 151.39, 147.05, 145.09, 143.06, 138.83, 138.12, 137.00, 130.92 (d, *J* = 7.4 Hz), 130.22, 128.26, 125.53, 124.73, 124.11, 115.02 (d, *J* = 20.1 Hz), 106.67, 103.99, 103.37, 100.43 (d, *J* = 32.1 Hz), 69.77, 68.81, 58.36, 56.55, 20.83 (-CH_3Ph); HRMS(ESI): calcd for $C_{33}H_{27}F_2N_4O_5[M+H]^+$ 597.1944, Found 597.1940.

*5.3.5 5-{[3-fluoro-4-((7-(2-hydroxypropoxy)-6-methoxyquinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19e**)*

Prepared according to general procedure B. White solid; yield: 80%; m.p.: 236-237 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ13.22 (s, 1H, -NH), 12.47 (s, 1H, -NH), 8.67 (d, *J* = 6.8 Hz, 1H, Ar-H), 8.44 (d, J = 13.6 Hz, 1H, Ar-H), 8.23 – 8.10 (m, 2H, Ar-H), 7.79 – 7.62 (m, 3H, Ar-H), 7.61 – 7.36 (m, 5H, Ar-H), 7.31 – 7.17 (m, 2H, Ar-H), 7.16 – 7.02 (m, 3H, Ar-H), 6.92 – 6.84 (m, 1H, Ar-H), 6.82 – 6.75 (m, 1H, Ar-H), 5.10 (m, 1H), 4.13 – 3.96 (m, 5H), 2.28 (s, 3H, -CH_3), 1.22 (d, *J* = 6.0 Hz, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.01 (C=O), 162.61, 162.21 (d, *J* = 243.6 Hz, 4-F-Ph), 155.52, 154.06 (d, *J* = 244.1 Hz, 3-F-Ph), 150.61, 148.31, 146.01, 145.57, 145.22, 140.93, 139.91, 138.38, 138.01, 133.37, 131.06, 130.80 (d, *J* = 7.4 Hz), 128.20, 125.55, 123.79, 122.78, 116.38, 114.83 (d, *J* = 19.1 Hz), 108.00, 106.95, 103.87, 103.44, 102.47, 99.72, 74.23, 64.27, 56.19, 20.82 (-CH_3Ph), 20.24 (-CH_3). HRMS(ESI): calcd for $C_{33}H_{27}F_2N_4O_5[M+H]$+ 597.1944, Found 597.1926.

*5.3.6 5-{[3-fluoro-4-((7-(2-hydroxy-2-methylpropoxy)-6-methoxyquinolin-4-yl)oxy)phenyl]-amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19f**)*

Prepared according to general procedure B. White solid; yield: 84%; m.p.: 232-233 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.40 (s, 1H, -NH), 12.97 (s, 1H, -NH), 8.89 (d, *J* = 6.8 Hz, 1H, Ar-H), 8.36 – 8.24 (m, 2H, Ar-H), 8.17 – 8.06 (m, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 7.77 – 7.57 (m, 5H, Ar-H), 7.48 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.29 (t, *J* = 8.4 Hz, 2H, Ar-H),

7.21 – 7.15 (m, 1H, Ar-H), 7.12 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.04 – 6.98 (m, 1H, Ar-H), 4.07 (s, 3H, -CH_3), 3.99 (s, 2H, -CH_2-), 2.28 (s, 3H, -CH_3), 1.29 [s, 6H, -$(CH_3)_2$]. ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.09 (C=O), 164.87, 162.75 (d, *J* = 243.9 Hz, 4-F-Ph), 156.07, 154.63 (d, *J* = 244.7 Hz, 3-F-Ph), 151.85, 147.35, 145.33, 143.30, 139.12, 138.37, 137.35, 131.15, 130.47 (d, *J* = 7.4 Hz), 128.52, 125.79, 125.02, 124.42, 115.22, 114.36 (d, *J* = 21.1 Hz), 106.93 , 104.27 , 103.58 , 100.77 , 100.46 , 77.48 , 68.88, 56.96, 26.90 [-$(CH_3)_2$], 21.10 (-CH_3Ph). HRMS(ESI): calcd for $C_{34}H_{28}F_2N_4O_5$ $[M+H]^+$611.2100, Found 611.2106.

5.3.7

*5-{[3-fluoro-4-((6-methoxy-7-(2-methoxy-2-methylpropoxy)quinolin-4-yl)oxy)phenyl]-amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19g**)*

Prepared according to general procedure B. White solid; yield: 86%; m.p.: 241-242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.34 (s, 1H, -NH), 12.86 (s, 1H, -NH), 8.84 (d, *J* = 6.8 Hz, 1H, Ar-H), 8.32 – 8.21 (m, 2H, Ar-H), 8.08 (d, *J* = 6.4 Hz, 1H, Ar-H), 7.76 (s, 1H, Ar-H), 7.72 (d, *J* = 5.6 Hz, 1H, Ar-H), 7.70 (d, *J* = 5.6 Hz, 1H, Ar-H), 7.67 (s, 1H, Ar-H), 7.65 – 7.55 (m, 2H, Ar-H), 7.46 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.26 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.13 (d, *J* = 6.8 Hz, 1H, Ar-H), 7.09 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.97 (d, *J* = 6.4 Hz, 1H, Ar-H), 4.11 (s, 2H, -OCH_2-), 4.06 (s, 3H, -OCH_3), 3.20 (s, 3H, -OCH_3), 2.27 (s, 3H, -CH_3), 1.30 [s, 6H, -$(CH_3)_2$]; ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.79 (C=O), 164.59, 162.47 (d, *J* = 243.2 Hz, 4-F-Ph), 155.58 (d, *J* = 213.6 Hz, 3-F-Ph), 154.34, 152.70, 151.54, 147.07, 144.99, 143.11, 138.85, 138.12, 137.00, 130.89 (d, *J* = 7.7 Hz), 130.15, 128.24, 125.50, 124.76, 124.17, 114.86 (d, *J* = 20.6 Hz), 106.62, 103.99, 103.33, 100.60, 100.20, 74.44, 73.70, 56.70, 49.36, 21.94 [-$(CH_3)_2$], 20.80 (-CH_3Ph) ; HRMS(ESI): Calcd for $C_{35}H_{31}F_2N_4O_5$ $[M+H]^+$625.2257, Found 625.2260.

*5.3.8 5-{[3-fluoro-4-((6-methoxy-7-(2-morpholinoethoxy)quinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19h**)*

Prepared according to general procedure B. White solid; yield: 86%; m.p.: 241-242 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.32 (s, 1H, -NH), 12.66 (s, 1H, -NH), 11.04 (s, 1H, -SO_2OH), 8.91 – 8.80 (m, 1H, Ar-H), 8.45 (d, *J* = 12.2 Hz, 1H, Ar-H), 8.26 – 8.09 (m, 2H, Ar-H), 7.81 (s, 1H, Ar-H), 7.76 – 7.71 (m, 3H, Ar-H), 7.64 – 7.60 (m, 1H, Ar-H), 7.58 – 7.53 (m, 1H, Ar-H), 7.48 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.30 – 7.24 (m, 2H, Ar-H), 7.10 (d, *J* =

6.8 Hz, 2H, Ar-H), 7.05 (s, 1H, Ar-H), 6.95 (s, 1H, Ar-H), 4.76 – 4.70 (m, 2H), 4.07 (s, 3H, -OCH_3), 4.03 – 3.99 (m, 2H), 3.86 – 3.79 (m, 2H), 3.76 – 3.72 (m, 2H), 3.62 – 3.55 (m, 2H), 3.35 – 3.26 (m, 2H), 2.28 (s, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.00 (C=O), 164.66, 161.49 (d, J = 242.1 Hz, 4-F-Ph), 154.43 (d, J = 214.7 Hz, 3-F-Ph), 154.15, 153.97, 152.34, 151.15, 146.27, 145.14, 143.77, 138.55, 138.05, 137.19, 130.61 (d, J = 6.5 Hz), 128.23, 125.51, 123.97, 123.12, 115.41, 114.83 (d, J = 20.9 Hz), 106.92, 103.70, 103.23, 101.60, 100.50, 64.39, 63.33, 56.76, 54.72, 52.18, 20.82 (-CH_3Ph); HRMS(ESI): calcd for $C_{36}H_{32}F_2N_5O_5[M+H]^+$ 652.2366, Found 652.2358.

5.3.9

*5-{[3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19i**)*

Prepared according to general procedure B. Pale-yellow solid; yield: 70%; m.p.: 238-240 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.33 (s, 1H, -NH), 12.68 (s, 1H, -NH), 10.51 (s, 1H, -SO_2OH), 8.86 (d, J = 6.4 Hz, 1H, Ar-H), 8.45 (d, J = 13.2 Hz, 1H, Ar-H), 8.26 – 8.14 (m, 2H, Ar-H), 7.80 (s, 1H, Ar-H), 7.77 – 7.65 (m, 3H, Ar-H), 7.66 – 7.53 (m, 2H, Ar-H), 7.49 (d, J = 7.2 Hz, 2H, Ar-H), 7.32 – 7.22 (m, 2H, Ar-H), 7.11 (d, J = 7.2 Hz, 2H, Ar-H), 7.07 (d, J = 6.4 Hz, 1H, Ar-H), 6.96 (d, J = 6.0 Hz, 1H, Ar-H), 4.43 – 4.29 (m, 2H,-CH_2-), 4.06 (s, 3H, -OCH_3), 4.04 – 3.95 (m, 2H, -CH_2-), 3.79 (t, J = 12.4 Hz, 2H, -CH_2-), 3.57 – 3.49 (m, 2H, -CH_2-), 3.38 – 3.27 (m, 2H, -CH_2-), 3.19 – 3.07 (m, 2H, -CH_2-), 2.41 – 2.32 (m, 2H, -CH_2-), 2.28 (s, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.96 (C=O), 164.74, 161.52 (d, J = 242.7 Hz, 4-F-Ph), 154.56 (d, J = 214.3 Hz, 3-F-Ph), 152.41, 151.27, 146.41, 145.05, 143.32, 138.13, 137.07, 130.83 (d, J = 7.8 Hz), 128.33, 128.20, 125.52 (d, J = 11.0 Hz), 124.43, 123.31, 115.08, 114.87, 114.72, 106.87, 103.67, 103.06, 100.76, 100.30, 66.99, 63.35, 56.62, 53.60, 51.29, 22.76, 20.83 (-CH_3Ph); HRMS(ESI): Calcd for $C_{37}H_{34}F_2N_5O_5$ $[M+H]^+$ 666.2522, Found 666.2507.

*5.3.10 5-{[3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl]-amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19j**)*

Prepared according to general procedure B. Pale-yellow solid; yield: 70%; m.p.: 177-178 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.37 (s, 1H, -NH), 12.88 (s, 1H, -NH), 10.50 (s, 1H, -SO_2OH), 8.87 (d, J = 6.6 Hz, 1H, Ar-H), 8.32 (dd, J = 18.0, 8.4 Hz, 1H,

Ar-H), 8.26 (d, *J* = 5.4 Hz, 1H, Ar-H), 8.13 (d, *J* = 5.4 Hz, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.78 – 7.68 (m, 3H, Ar-H), 7.61 (s, 2H, Ar-H), 7.47 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.28 (t, *J* = 9.0 Hz, 2H, Ar-H), 7.15 (d, *J* = 6.0 Hz, 1H, Ar-H), 7.10 (d, *J* = 7.8 Hz, 2H, Ar-H), 6.99 (d, *J* = 6.0 Hz, 1H, Ar-H), 4.40 – 4.34 (m, 2H, -CH_2-), 4.07 (s, 3H, -OCH_3), 3.66 – 3.56 (m, 2H, -CH_2-), 3.40 – 3.29 (m, 2H, -CH_2-), 3.12 – 2.98 (m, 2H, -CH_2-), 2.35 – 2.29 (m, 2H, -CH_2-), 2.28 (s, 3H, -CH_3), 2.10 – 1.98 (m, 2H, -CH_2-), 1.96 – 1.82 (m, 2H, -CH_2-); ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.88 (C=O), 164.70, 161.64 (d, *J* = 243.1 Hz, 4-F-Ph), 154.86 (d, *J* = 213.6 Hz, 3-F-Ph), 154.49, 152.61, 151.35, 146.88, 145.09, 143.21, 138.80, 138.09, 136.99, 130.92, 130.64 (d, *J* = 6.7 Hz), 128.24, 125.51, 124.57, 123.94, 115.08, 115.02 (d, *J* = 21.3 Hz), 109.62, 106.74, 103.94, 103.32, 100.58, 100.27, 66.87, 56.67, 53.21, 51.25, 24.95, 22.74, 20.84 (-CH_3Ph); HRMS(ESI): calcd for $C_{37}H_{34}F_2N_5O_4$ $[M+H]^+$ 650.2573, Found 650.2558.

5.3.11 5-{[3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinolin-4-yl)oxy)-phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate ***(19k)***

Prepared according to general procedure B. white solid; yield: 80%; m.p.: 180-182 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.22 (s, 1H, -NH), 12.75 (s, 1H, -NH), 10.32 (s, 1H, -SO_2OH), 8.49 (s, 1H, Ar-H), 8.41 (d, *J* = 14.4 Hz, 1H, Ar-H), 8.17 (s, 2H, Ar-H), 7.72 (s, 2H, Ar-H), 7.65 – 7.36 (m, 6H, Ar-H), 7.25 (s, 2H, Ar-H), 7.12 (s, 2H, Ar-H), 6.94 (s, 1H, Ar-H), 6.50 (s, 1H, Ar-H), 4.10 – 4.01 (m, 2H, -CH_2-), 3.96 (s, 3H, -OCH_3), 3.54 – 3.42 (m, 2H, -CH_2-), 3.09 – 2.94 (m, 2H, -CH_2-), 2.73 (s, 3H, -NCH_3), 2.28 (s, 3H, -CH_3), 2.21 – 2.08 (m, 1H), 2.02 (d, *J* = 10.2 Hz, 2H, -CH_2-), 1.66 (d, *J* = 9.0 Hz, 2H, -CH_2-); ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.04 (C=O), 162.20 (d, *J* = 242.1 Hz), 159.80, 155.62 (d, *J* = 214.2 Hz), 152.75, 151.87, 149.60, 148.71, 148.40, 146.07, 145.42, 139.30, 138.31, 137.89, 134.09, 131.14, 130.82 (d, *J* = 7.8 Hz), 128.18, 125.56, 123.94, 122.77, 116.27, 114.70 (d, *J* = 22.2 Hz), 108.46, 108.01, 106.96, 103.33, 102.11, 99.27, 71.89, 55.93, 52.91, 42.73, 32.58, 26.01, 20.83 (-CH_3Ph); HRMS(ESI): calcd for $C_{37}H_{34}F_2N_5O_4$ $[M+H]^+$ 650.2578，Found 650.2570.

5.3.12 5-{[3-fluoro-4-((6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl)oxy)phenyl]amino}-3-phenyl-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate ***(19l)***

Prepared according to general procedure B. white solid; yield: 85%; m.p.: 239-240 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.45 (s, 1H, -NH), 12.95 (s, 1H, -NH), 8.88 (d, J = 6.6 Hz, 1H, Ar-H), 8.35 – 8.23 (m, 2H, Ar-H), 8.10 (d, J = 6.4 Hz, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 7.72 – 7.57 (m, 5H, Ar-H), 7.51 – 7.41 (m, 4H, Ar-H), 7.41 – 7.34 (m, 1H, Ar-H), 7.21 – 7.15 (m, 1H, Ar-H), 7.11 (d, J = 7.2 Hz, 2H, Ar-H), 7.03 – 6.97 (m, 1H, Ar-H), 4.37 (t, J = 4.4 Hz, 2H, -OCH_2-), 4.06 (s, 3H, -OCH_3), 3.81 (t, J = 4.4 Hz, 2H, -OCH_2-), 3.36 (s, 3H, -OCH_3), 2.28 (s, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.92 (C=O), 164.60, 155.45 (d, J = 185.7 Hz, 3-F-Ph), 154.35, 152.71, 151.38, 147.06, 145.02, 143.09, 138.97, 138.13, 136.98, 133.87, 128.86 (d, J = 9.6 Hz), 128.30, 128.20, 128.13, 127.74, 125.55 (d, J = 10.7 Hz), 114.98, 106.69, 104.85, 104.01, 103.24, 100.48, 100.24, 69.75, 68.80, 58.34, 56.54, 20.82 (-CH_3Ph); HRMS(ESI): calcd for $C_{33}H_{28}FN_4O_5[M+H]^+$ 579.2038, Found 579.2038.

*5.3.13 5-{[3-fluoro-4-((7-(2-hydroxy-2-methylpropoxy)-6-methoxyquinolin-4-yl)oxy)phenyl]-amino}-3-phenyl-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19m**)*

Prepared according to general procedure B. white solid; yield: 86%; m.p.: 234-236 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.45 (s, 1H, -NH), 12.93 (s, 1H, -NH), 8.89 (d, J = 6.6 Hz, 1H, Ar-H), 8.35 – 8.22 (m, 2H, Ar-H), 8.11 (d, J = 6.2 Hz, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 7.76 – 7.58 (m, 5H, Ar-H), 7.53 – 7.42 (m, 4H, Ar-H), 7.41 – 7.32 (m, 1H, Ar-H), 7.21 – 7.14 (m, 1H, Ar-H), 7.12 (d, J = 7.2 Hz, 2H, Ar-H), 7.01 (d, J = 6.6 Hz, 1H, Ar-H), 4.07 (s, 3H, -OCH_3), 3.99 (s, 2H, -OCH_2-), 2.28 (s, 3H, -CH_3), 1.29 (s, 6H, -$(CH_3)_2$). ^{13}C NMR (150 MHz, d_6) δ 176.89 (C=O), 164.57, 155.78 (d, J = 234.1 Hz, 3-F-Ph), 154.32, 152.67, 151.55, 147.03, 145.06, 143.02, 138.82, 138.04, 137.05, 133.84, 128.81, 128.21 (d, J = 18.7 Hz), 127.65, 125.48, 125.22, 124.75, 114.90, 106.67, 103.98, 103.26, 100.49, 100.17, 77.18, 68.57, 56.66, 26.60 [-$(CH_3)_2$], 20.80 (-CH_3Ph). HRMS(ESI): calcd for $C_{34}H_{29}FN_4O_5$ $[M+H]^+$ 593.2194, Found 593.2197.

*5.3.14 5-{[3-fluoro-4-((6-methoxy-7-(2-morpholinoethoxy)quinolin-4-yl)oxy)phenyl]-amino}-3-phenyl-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19n**)*

Prepared according to general procedure B. white solid; yield: 71%; m.p.: 260-262 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.37 (s, 1H, -NH), 12.66 (s, 1H, -NH), 11.05 (s, 1H,

-SO_2OH), 8.86 (d, *J* = 6.6 Hz, 1H, Ar-H), 8.47 (d, *J* = 13.4 Hz, 1H, Ar-H), 8.25 – 8.14 (m, 2H, Ar-H), 7.81 (s, 1H, Ar-H), 7.74 – 7.64 (m, 3H, Ar-H), 7.64 – 7.59 (m, 1H, Ar-H), 7.59 – 7.53 (m, 1H, Ar-H), 7.51 – 7.40 (m, 4H, Ar-H), 7.36 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.11 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.04 (d, *J* = 6.6 Hz, 1H, Ar-H), 6.95 (d, *J* = 6.0 Hz, 1H, Ar-H), 4.72 (t, *J* = 4.4 Hz, 2H, -OCH_2-), 4.06 (s, 3H, -OCH_3), 4.05 – 3.95 (m, 2H, -CH_2-), 3.88 – 3.77 (m, 2H, -CH_2-), 3.77 – 3.70 (m, 2H, -CH_2-), 3.64 – 3.56 (m, 2H, -CH_2-), 3.34 – 3.27 (m, 2H, -CH_2-), 2.28 (s, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.09 (C=O), 164.46, 155.33, 153.14 (d, *J* = 249.9 Hz, 3-F-Ph), 151.04, 147.04, 146.16, 145.12, 143.93, 139.76, 138.47, 138.04, 137.50, 134.63, 133.51, 128.87, 128.22 (d, *J* = 30.2 Hz), 127.24, 125.50, 124.06 (d, *J* = 27.6 Hz), 117.20, 115.37, 106.96, 103.64, 103.15, 101.84, 100.42, 64.35, 63.31, 56.71, 54.69, 52.16, 20.81 (-CH_3Ph); HRMS(ESI): calcd for $C_{36}H_{33}FN_5O_5[M+H]^+$ 634.2460, Found 634.2458.

*5.3.15 5-{[3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl]-amino}-3-phenyl-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19o**)*

Prepared according to general procedure B. white solid; yield: 67%; m.p.: 223-225 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H, -NH), 12.60 (s, 1H, -NH), 10.52 (s, 1H, --SO_2OH), 8.82 (d, *J* = 6.4 Hz, 1H, Ar-H), 8.44 (d, *J* = 13.8 Hz, 1H, Ar-H), 8.19 (d, *J* = 5.8 Hz, 1H, Ar-H), 8.16 (d, *J* = 5.8 Hz, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 7.68 – 7.63 (m, 3H, Ar-H), 7.60 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.54 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.45 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.41 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.33 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.08 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.03 (d, *J* = 5.2 Hz, 1H, Ar-H), 6.93 (d, *J* = 6.0 Hz, 1H, Ar-H), 4.35 (t, *J* = 5.2 Hz, 2H, -OCH_2-), 4.05 (s, 3H, -OCH_3), 4.00 (d, *J* = 10.4 Hz, 2H), 3.77 (t, *J* = 11.6 Hz, 2H, -NCH_2-), 3.62 – 3.39 (m, 4H, -CH_2-), 3.20 – 3.05 (m, 2H, -CH_2-), 2.40 – 2.31 (m, 2H, -CH_2-), 2.27 (s, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.07 (C=O), 164.69, 155.19, 155.00, 153.14 (d, *J* = 244.2 Hz, 3-F-Ph), 151.22, 146.29, 145.10, 143.35, 138.54, 138.06, 137.15, 134.52, 128.87, 128.13 (d, *J* = 28.2 Hz), 127.32, 125.51, 124.23 (d, *J* = 32.2 Hz), 115.06, 106.93, 103.72, 103.07, 100.79, 100.24, 66.95, 63.33, 56.61, 53.57, 51.27, 22.74, 20.83 (-CH_3Ph); HRMS(ESI): calcd for $C_{37}H_{35}FN_5O_5[M+H]^+$ 648.2616, Found 648.2610.

5.3.16 5-{[3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinolin-4-yl)oxy)-

*phenyl]amino}-3-phenyl-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**19p**)*

Prepared according to general procedure B. White solid; yield: 60%; m.p.: 240-242 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.42 (s, 2H, -NH), 10.89 (s, 1H, -NH), 8.84 (d, J = 6.6 Hz, 1H, Ar-H), 8.36 – 8.16 (m, 2H, Ar-H), 8.09 (d, J = 3.0 Hz, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.69 (d, J = 7.2 Hz, 2H, Ar-H), 7.64 (d, J = 8.1 Hz, 1H, Ar-H), 7.59 (d, J = 8.1 Hz, 1H, Ar-H), 7.48 (d, J = 7.8 Hz, 2H, Ar-H), 7.44 (t, J = 7.2 Hz, 2H, Ar-H), 7.36 (t, J = 7.2 Hz, 1H, Ar-H), 7.31 – 7.20 (m, 1H, Ar-H), 7.12 (d, J = 7.2 Hz, 3H, Ar-H), 4.12 (d, J = 5.4 Hz, 2H, -OCH_2-), 4.06 (s, 3H, -OCH_3), 3.43 (d, J = 10.8 Hz, 2H, -CH_2-), 3.03 (dd, J = 21.9, 10.8 Hz, 2H, -CH_2-), 2.71 (d, J = 3.6 Hz, 3H), 2.28 (s, 3H, -CH_3), 2.22 – 2.13 (m, 1H), 2.02 (d, J = 12.6 Hz, 2H), 1.73 (q, J = 12.0 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.93 (C=O), 164.58, 155.15, 154.37, 154.24 (d, J = 228.5 Hz, 3-F-Ph), 151.34, 146.99, 144.97, 142.78, 142.71, 138.60, 138.18, 136.94, 133.92, 129.14, 128.82, 128.67, 128.27 (d, J = 18.2 Hz), 127.66, 125.54, 125.07, 124.75, 115.00, 106.64, 103.90, 103.52, 100.44, 100.20, 72.66, 56.67, 52.68, 42.66, 32.38, 25.79, 20.86 (-CH_3Ph); HRMS(ESI): Calcd for $C_{37}H_{35}FN_5O_4[M+H]^+$ 632.2667，Found 632.2668.

*5.3.17 5-{[3-fluoro-4-((7-methoxyquinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one (**20a**)*

Prepared according to general procedure A. White solid; yield: 83%; m.p.: 247-249 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.23 (s, 1H, -NH), 12.65 (s, 1H, -NH), 8.82 (d, J = 6.0 Hz, 1H, Ar-H), 8.53 – 8.30 (m, 2H, Ar-H), 8.17 (t, J = 6.0 Hz, 2H, Ar-H), 7.78 – 7.63 (m, 2H, Ar-H), 7.63 – 7.37 (m, 4H, Ar-H), 7.24 (t, J = 8.8 Hz, 2H, Ar-H), 6.91 (d, J = 6.0 Hz, 1H, Ar-H), 6.82 (d, J = 6.0 Hz, 1H, Ar-H), 3.99 (s, 3H, -OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.16 (d, J = 241.5 Hz, 4-F-Ph), 155.98, 152.24, 151.57, 146.39, 138.70, 131.34 (d, J = 7.4 Hz), 124.21, 123.17, 119.23, 116.59, 115.11 (d, J = 23.5 Hz), 107.77, 107.31, 103.59, 101.99, 55.90 (-OCH_3) (Remark: some chemical shifts do not appear in the spectra due to the use of insufficient quantities of the substance); HRMS(ESI): calcd for $C_{30}H_{21}F_2N_4O_3$ $[M+H]^+$ 523.1576, Found 523.1583.

5.3.18

5-{[3-fluoro-4-((7-isobutoxyquinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-

*naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**20b**)*

Prepared according to general procedure B. White solid; yield: 81%; m.p.: 244-246 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.39 (s, 1H, -NH), 12.99 (s, 1H, -NH), 9.01 (d, J = 6.6 Hz, 1H, Ar-H), 8.51 (d, J = 9.6 Hz, 1H, Ar-H), 8.33 – 8.19 (m, 2H, Ar-H), 8.08 (d, J = 5.4 Hz, 1H, Ar-H), 7.73 (d, J = 6.0 Hz, 1H, Ar-H), 7.72 (d, J = 6.0 Hz, 1H, Ar-H), 7.69 – 7.60 (m, 3H, Ar-H), 7.58 (d, J = 8.4 Hz, 1H, Ar-H), 7.47 (d, J = 7.8 Hz, 2H, Ar-H), 7.27 (t, J = 8.7 Hz, 1H, Ar-H), 7.17 (d, J = 5.2 Hz, 1H, Ar-H), 7.10 (d, J = 7.8 Hz, 2H, Ar-H), 7.00 (d, J = 6.0 Hz, 1H, Ar-H), 4.01 (d, J = 6.6 Hz, 2H, -OCH_2-), 2.26 (s, 3H, -CH_3), 2.20 – 2.10 (m, 1H), 1.04 [d, J = 6.6 Hz, 6H, -$(CH_3)_2$]; ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.92 (C=O), 166.51, 164.11, 163.64, 161.57 (d, J = 243.0 Hz, 4-F-Ph), 154.73, 154.46, 152.01, 146.74, 146.68, 145.47, 141.96, 138.74, 137.79, 130.91 (d, J = 8.1 Hz), 130.53, 128.12, 125.50, 124.73, 124.25, 123.66, 121.90, 114.98 (d, J = 21.2 Hz), 114.30, 106.80, 103.84, 102.82, 100.48, 74.85, 27.47 [-(CH)Me_2], 20.79 (-CH_3Ph), 18.88 [-$(CH_3)_2$]; HRMS(ESI): Calcd for $C_{33}H_{27}F_2N_4O_3[M+H]^+$ 565.2045, Found 565.2047

*5.3.19 5-{[3-fluoro-4-((7-(2-hydroxyethoxy)quinolin-4-yl)oxy)phenyl]amino}-3-(4-fluoro-phenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**20c**)*

Prepared according to general procedure B. White solid; yield: 95%; m.p.: 235-237 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.41 (s, 1H, -NH), 13.10 (s, 1H, -NH), 9.03 (d, J = 6.3 Hz, 1H, Ar-H), 8.53 (d, J = 9.0 Hz, 1H, Ar-H), 8.30 (d, J = 4.2 Hz, 1H, Ar-H), 8.24 (d, J = 9.6 Hz, 1H, Ar-H), 8.08 (d, J = 6.0 Hz, 1H, Ar-H), 7.80 – 7.73 (m, 2H, Ar-H), 7.71 – 7.66 (m, 2H, Ar-H), 7.65 (d, J = 9.3 Hz, 1H, Ar-H), 7.60 (d, J = 8.7 Hz, 1H, Ar-H), 7.49 (d, J = 7.2 Hz, 2H, Ar-H), 7.29 (t, J = 8.4 Hz, 2H, Ar-H), 7.23 (d, J = 5.4 Hz, 1H, Ar-H), 7.12 (d, J = 7.2 Hz, 2H, Ar-H), 7.04 (d, J = 5.4 Hz, 1H, Ar-H), 4.27 (t, J = 4.8 Hz, 2H, -OCH_2-), 3.85 (t, J = 4.8 Hz, 2H, -OCH_2-), 2.28 (s, 3H, -OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.90 (C=O), 166.49, 163.68, 162.78 (d, J = 242.9 Hz, 4-F-Ph), 154.64, 154.48, 152.03, 146.70, 145.46, 141.91, 138.72, 137.77, 130.89 (d, J = 8.0 Hz), 130.47, 128.10, 125.48, 124.70, 124.28, 124.03, 123.71, 121.86, 114.96 (d, J = 21.0 Hz), 114.30, 106.77, 103.85, 102.85, 100.58, 70.95, 59.18, 20.77 (-CH_3Ph) ; HRMS(ESI): calcd for $C_{31}H_{23}F_2N_4O_4[M+H]^+$ 553.1681, Found 553.1710.

5.3.20 5-{[3-fluoro-4-((7-(2-methoxyethoxy)quinolin-4-yl)oxy)phenyl]amino}-3-(4-fluoro-

*phenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**20d**)*

Prepared according to general procedure B. White solid; yield: 84%; m.p.: 237-238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.34 (s, 1H, -NH), 12.90 (s, 1H, -NH), 8.98 (d, J = 6.4 Hz, 1H, Ar-H), 8.49 (d, J = 10.0 Hz, 1H, Ar-H), 8.33 – 8.18 (m, 2H, Ar-H), 8.06 (d, J = 6.4 Hz, 1H, Ar-H), 7.80 – 7.67 (m, 2H, Ar-H), 7.67 – 7.52 (m, 4H, Ar-H), 7.52 – 7.41 (m, 2H, Ar-H), 7.31 – 7.21 (m, 2H, Ar-H), 7.14 (d, J = 6.4 Hz, 1H, Ar-H), 7.08 (d, J = 7.8 Hz, 2H, Ar-H), 6.98 (d, J = 6.4 Hz, 1H, Ar-H), 4.41 – 4.32 (m, 2H, -CH_2-), 3.83 – 3.70 (m, 2H, -CH_2-), 3.34 (s, 3H, -OCH_3), 2.27 (s, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.80 (C=O), 166.43, 163.45, 162.49 (d, J = 243.2 Hz, 4-F-Ph), 157.83, 154.28, 154.14, 152.63, 147.10, 146.72, 145.03, 141.81, 138.85, 138.13, 136.68, 130.90 (d, J = 6.8 Hz), 128.26, 125.52, 124.73, 124.20, 121.89, 115.02 (d, J = 21.2 Hz), 114.36, 106.63, 104.03, 103.07, 100.54, 69.91, 68.37, 58.31, 20.82 (-CH_3Ph); HRMS(ESI): calcd for $C_{32}H_{25}F_2N_4O_4[M+H]^+$ 567.1838, Found 567.1843.

*5.3.21 5-{[3-fluoro-4-((7-(2-hydroxypropoxy)quinolin-4-yl)oxy)phenyl]amino}-3-(4-fluoro-phenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**20e**)*

Prepared according to general procedure B. White solid; yield: 80%; m.p.: 183-185 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.41 (s, 1H, -NH), 13.03 (s, 1H, -NH), 9.03 (d, J = 6.6 Hz, 1H, Ar-H), 8.54 (d, J = 9.2 Hz, 1H, Ar-H), 8.35 – 8.22 (m, 2H, Ar-H), 8.10 (d, J = 6.4 Hz, 1H, Ar-H), 7.81 – 7.72 (m, 2H, Ar-H), 7.71 – 7.57 (m, 4H, Ar-H), 7.49 (d, J = 7.6 Hz, 2H, Ar-H), 7.29 (t, J = 8.6 Hz, 2H, Ar-H), 7.23 – 7.17 (m, 1H, Ar-H), 7.12 (d, J = 7.6 Hz, 2H, Ar-H), 7.06 – 6.99 (m, 1H, Ar-H), 4.13 – 4.07 (m, 2H), 4.06 – 4.00 (m, 1H), 2.29 (s, 3H, -CH_3), 1.24 (d, J = 4.8 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.92 (C=O), 166.51, 163.64, 162.75 (d, J = 243.2 Hz, 4-F-Ph), 154.77, 151.98, 146.76, 146.63, 145.50, 141.92, 138.69, 137.74, 130.89 (d, J = 7.8 Hz), 128.08, 125.48, 124.70, 124.19, 123.60, 121.85, 114.94 (d, J = 21.4 Hz), 114.31, 106.80, 103.81, 103.48, 102.79, 102.02, 101.73, 100.67, 74.21, 64.24, 20.76 (-CH_3Ph), 19.89 (-CH_3); HRMS(ESI): calcd for $C_{32}H_{25}F_2N_4O_4$ $[M+H]^+$ 567.1838, Found 567.1829.

*5.3.22 5-{[3-fluoro-4-((7-(2-hydroxy-2-methylpropoxy)quinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one (**20f**)*

Prepared according to general procedure A. White solid; yield: 88%; m.p.: 194-195 °C;

^{1}H NMR (600 MHz, DMSO-d_6): δ 13.41 (s, 2H, -NH), 9.03 (d, J = 6.0 Hz, 1H, -NH), 8.54 (d, J = 9.0 Hz, 1H, Ar-H), 8.30 (d, J = 3.6 Hz, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 8.06 (d, J = 4.8 Hz, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.77 – 7.72 (m, 2H, Ar-H), 7.72 – 7.63 (m, 2H, Ar-H), 7.59 (d, J = 8.4 Hz, 1H, Ar-H), 7.33 (s, 1H, Ar-H), 7.29 (t, J = 8.4 Hz, 2H, Ar-H), 7.10 (d, J = 5.4 Hz, 1H, Ar-H), 4.00 (s, 2H, -OCH_2-), 1.29 [s, 6H, , -$(CH_3)_2$]. ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.37 (C=O), 161.74 (d, J = 242.4 Hz, 4-F-Ph), 161.12 ,160.76 , 155.96 , 154.65 , 153.03 , 152.19 , 151.52 , 148.76 , 146.36 , 139.64 , 138.62 , 134.36 , 131.48 , 131.17 (d, J = 8.0 Hz), 124.13 , 123.08 , 119.51 , 116.55 , 115.06 (d, J = 21.4 Hz), 108.47 , 107.30 , 103.55 , 101.94 , 76.62 , 69.00 , 27.01 [-$(CH_3)_2$]. HRMS(ESI): calcd for $C_{33}H_{26}F_2N_4O_4$ $[M+H]^+$581.1994, Found 581.1996.

5.3.23 *5-{[3-fluoro-4-((7-(2-methoxy-2-methylpropoxy)quinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**20g**)*

Prepared according to general procedure B. White solid; yield: 90%; m.p.: 237-239 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.39 (s, 1H, -NH), 12.92 (s, 1H, -NH), 9.03 (d, J = 6.6 Hz, 1H, Ar-H), 8.54 (d, J = 9.0 Hz, 1H, Ar-H), 8.37 – 8.25 (m, 2H, Ar-H), 8.11 (d, J = 6.0 Hz, 1H, Ar-H), 7.75 (d, J = 5.7 Hz, 1H, Ar-H), 7.74 (d, J = 5.7 Hz, 1H, Ar-H), 7.70 – 7.63 (m, 3H, Ar-H), 7.61 (d, J = 8.7 Hz, 1H, Ar-H), 7.48 (d, J = 7.8 Hz, 2H, Ar-H), 7.29 (t, J = 8.4 Hz, 2H, Ar-H), 7.17 (d, J = 5.6 Hz, 1H, Ar-H), 7.12 (d, J = 7.8 Hz, 1H, Ar-H), 7.00 (d, J = 6.0 Hz, 1H, Ar-H), 4.14 (s, 2H, -OCH_2-), 3.21 (s, 3H, -OCH_3), 2.28 (s, 3H, -CH_3), 1.29 [s, 6H, , -$(CH_3)_2$]; ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.92 (C=O), 166.51, 163.57, 162.78 (d, J = 242.4 Hz, 4-F-Ph), 154.75, 151.99, 146.86, 146.66, 145.49, 141.90, 138.73, 137.76, 130.90 (d, J = 8.0 Hz), 130.51, 128.10, 125.48, 124.73, 124.22, 123.62, 121.82, 114.96 (d, J = 21.2 Hz), 114.39, 106.80, 103.83, 102.85, 100.81, 73.93, 73.66, 49.25, 21.88 [-$(CH_3)_2$], 20.77 (-CH_3Ph)； HRMS(ESI): calcd for $C_{34}H_{29}F_2N_4O_4$[M+H]$^+$ 595.2151, Found 595.2154.

*5.3.24 5-{[3-fluoro-4-((7-(2-morpholinoethoxy)quinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**20h**)*

Prepared according to general procedure B. Yellow solid; yield: 94%; m.p.: 232-234 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H, -NH), 12.55 (s, 1H, -NH), 10.24 (s, 1H, -SO_2OH), 8.94 (d, J = 6.6 Hz, 1H, Ar-H), 8.55 – 8.33 (m, 2H, Ar-H), 8.25 – 8.09 (m, 2H, Ar-H), 7.75 – 7.65 (m, 2H, Ar-H), 7.65 – 7.35 (m, 7H, Ar-H), 7.30 – 7.18 (m,

2H, Ar-H), 7.13 – 7.03 (m, 3H, Ar-H), 7.01 – 6.96 (m, 1H, Ar-H), 6.91 (d, *J* = 6.0 Hz, 1H, Ar-H), 4.72 – 4.54 (m, 2H, -CH_2-), 4.08 – 3.91 (m, 2H, -CH_2-), 3.83 – 3.67 (m, 4H, -CH_2-), 3.63 – 3.50 (m, 2H, -CH_2-), 3.31 – 3.22 (m, 2H, -CH_2-), 2.27 (s, 3H, -CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 176.99 (C=O), 166.06, 162.01 (d, *J* = 242.4 Hz, 4-F-Ph), 155.26, 153.88, 153.29, 152.25, 147.71, 146.23, 145.04, 142.65, 138.54, 138.11, 133.50, 130.87 (d, *J* = 6.8 Hz), 128.24, 125.50, 124.59, 123.82, 123.08, 121.41, 114.87 (d, *J* = 21.2 Hz), 106.92, 103.68, 102.86, 101.98, 63.27, 54.87, 51.88, 45.73, 20.80 (-CH_3Ph); HRMS(ESI): Calcd for $C_{35}H_{30}F_2N_5O_4[M+H]^+$ 622.2260, Found 622.2257.

*5.3.25 5-{[3-fluoro-4-((7-hydroxyquinolin-4-yl)oxy)phenyl]amino}-3-(4-fluorophenyl)-1,6-naphthyridin-4(1H)-one 4-methylbenzenesulfonate (**20i**)*

Prepared according to general procedure B. White solid; yield: 80%; m.p.: 246-248 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H, -NH), 12.96 (s, 1H, -NH), 11.85 (s, 1H, -OH), 8.93 (d, *J* = 6.6 Hz, 1H, Ar-H), 8.49 (d, *J* = 9.2 Hz, 1H, Ar-H), 8.35 – 8.23 (m, 2H, Ar-H), 8.11 (d, *J* = 6.0 Hz, 1H, Ar-H), 7.75 (d, *J* = 5.8 Hz, 1H, Ar-H), 7.73 (d, *J* = 5.8 Hz, 1H, Ar-H), 7.68 – 7.56 (m, 3H, Ar-H), 7.51 (d, *J* = 9.6 Hz, 1H, Ar-H), 7.48 (d, *J* =8.0 Hz, 2H, Ar-H), 7.28 (t, *J* = 8.8 Hz, 2H, Ar-H), 7.11 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.08 (d, *J* = 6.6 Hz, 1H, Ar-H), 7.01 (d, *J* = 6.4 Hz, 1H, Ar-H), 2.28 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.79 (C=O), 166.38, 163.74, 162.54 (d, *J* = 242.4 Hz, 4-F-Ph), 154.42, 154.00, 152.77, 147.25, 146.15, 144.96, 141.96, 138.90, 138.21, 130.93 (d, *J* = 7.8 Hz), 130.07, 128.32, 125.55, 125.02, 124.90, 124.36, 122.20, 115.07 (d, *J* = 21.2 Hz), 113.33, 106.60, 104.07, 102.25, 102.06, 20.87 (-CH_3Ph); HRMS(ESI): calcd for $C_{29}H_{19}F_2N_4O_3[M+H]^+$ 509.1419, Found 509.1425.

*5.3.26 5-{[3-fluoro-4-((7-(2-hydroxy-2-methylpropoxy)quinolin-4-yl)oxy)phenyl]amino}-3-phenyl-1,6-naphthyridin-4(1H)-one (**20j**)*

Prepared according to general procedure A. Yellow solid; yield: 84%; m.p.: 213-214 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.45 (s, 1H, -NH), 13.27 (s, 1H, -NH), 9.03 (d, *J* = 6.6 Hz, 1H, Ar-H), 8.54 (d, *J* = 9.6 Hz, 1H, Ar-H), 8.28 (d, *J* = 5.6 Hz, 1H, Ar-H), 8.27 – 8.20 (m, 1H, Ar-H), 8.07 (d, *J* = 6.6 Hz, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 7.74 – 7.64 (m, 4H, Ar-H), 7.63 – 7.56 (m, 1H, Ar-H), 7.46 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.38 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.34 – 7.25 (m, 1H, Ar-H), 7.08 (d, *J* = 6.6 Hz, 1H, Ar-H), 4.00 (s, 2H,

-OCH_2-), 1.29 [s, 6H, -$(CH_3)_2$]. ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.10 (C=O), 160.70, 160.38, 155.62, 154.65, 153.44 (d, J = 243.0 Hz, 3-F-Ph), 151.78, 151.08, 148.36, 145.98, 139.32, 139.22, 138.26, 134.76, 134.13, 134.00, 128.81, 127.88, 127.03, 123.82 (d, J = 6.5 Hz), 122.62, 119.10, 116.19, 114.57, 108.10, 106.94, 103.17, 101.58, 76.23, 68.56, 26.57 [-$(CH_3)_2$]. HRMS(ESI): calcd for $C_{33}H_{27}FN_4O_4$ $[M+H]^+$ 563.2089, Found 563.2086.

*5.3.27 5-{[3-fluoro-4-((7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl]amino}-3-phenyl-1,6-naphthyridin-4(1H)-one (**20k**)*

Prepared according to general procedure A. Yellow solid; yield: 78%; m.p.: 148-150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (s, 1H, -NH), 12.38 (s, 1H, -NH), 8.57 (d, J = 4.6 Hz, 1H, Ar-H), 8.38 (d, J = 13.6 Hz, 1H, Ar-H), 8.20 (d, J = 9.2 Hz, 1H, Ar-H), 8.17 – 8.10 (m, 2H, Ar-H), 7.65 (d, J = 6.8 Hz, 1H, Ar-H), 7.50 (d, J = 8.8 Hz, 1H, Ar-H), 7.44 – 7.35 (m, 4H, Ar-H), 7.32 (d, J = 6.8 Hz, 1H, Ar-H), 7.27 (d, J = 8.4 Hz, 1H, Ar-H), 6.85 (d, J = 5.6 Hz, 1H, Ar-H), 6.46 (d, J = 4.0 Hz, 1H, Ar-H), 4.24 – 4.14 (m, 2H, -CH_2-), 3.64 – 3.50 (m, 4H, -CH_2-), 2.49 – 2.43 (m, 2H, -CH_2-), 2.43 – 2.30 (m, 4H, -CH_2-), 2.02 – 1.90 (m, 2H, -CH_2-); ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.17 (C=O), 160.78, 160.14, 155.69, 153.44 (d, J = 243.0 Hz, 3-F-Ph), 151.91, 151.16, 148.46, 146.06, 139.33, 138.37, 134.83, 134.04, 128.91, 128.67, 127.99, 127.81, 127.15, 123.90, 122.74, 119.07, 116.27, 114.60, 108.22, 108.05, 107.02, 103.27, 101.63, 66.19, 54.84, 53.37, 25.70 (-CH_2-); HRMS(ESI): calcd for $C_{36}H_{33}FN_5O_4$[M+H]$^+$ 618.2511, Found 618.2512.

*5.3.28 5-{[3-fluoro-4-((7-(2-hydroxy-2-methylpropoxy)quinolin-4-yl)oxy)phenyl]amino}-2-methyl-3-phenyl-1,6-naphthyridin-4(1H)-one (**20l**)*

Prepared according to general procedure A. Yellow solid; yield: 72%; m.p.: 153-155 °C; ^{1}H NMR (600 MHz,DMSO-d_6) δ 13.18 (s, 1H, -NH), 12.11 (s, 1H, -NH), 8.61 (d, J = 4.8 Hz, 1H, Ar-H), 8.40 (dd, J = 13.8, 1.6 Hz, 1H, Ar-H), 8.25 (d, J = 9.0 Hz, 1H, Ar-H), 8.19 (d, J = 5.4 Hz, 1H, Ar-H), 7.49 (d, J = 8.0 Hz, 1H, Ar-H), 7.47 – 7.42 (m, 3H, Ar-H), 7.40 (d, J = 12.0 Hz, 2H, Ar-H), 7.37 (d, J = 7.2 Hz, 1H, Ar-H), 7.34 (d, J = 10.8 Hz, 1H, Ar-H), 7.28 (d, J = 7.8 Hz, 2H, Ar-H), 6.85 (d, J = 5.4 Hz, 1H, Ar-H), 6.48 (d, J = 4.8 Hz, 1H, Ar-H), 4.75 (s, 1H, -OH), 3.91 (s, 2H, -OCH_2-), 2.22 (s, 3H, -CH_3), 1.26 [s, 6H, , -$(CH_3)_2$]. ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.77 (C=O), 155.75, 151.47, 148.72, 146.21, 131.17, 128.39, 119.53, 108.42, 103.28, 76.62, 68.99, 27.01 [-$(CH_3)_2$], 18.92 (-CH_3Ar).

(Remark: some chemical shifts do not appear in the spectra due to the use of insufficient quantities of the substance). HRMS(ESI): calcd for $C_{34}H_{29}FN_4O_4$ $[M+H]^+$ 577.2245, Found 577.2244.

5.4. Biochemical Kinase Assays.

The ability of compounds to inhibit the activity of a wide variety of kinases was tested *in vitro*. Enzyme assays were run in homogeneous time-resolved fluorescence (HTRF) format in 384-well microtiter plates using purified kinases purchased from Invitrogen. The HTRF KinEASE TK kit (contains substrate-biotin, antibody-cryptate, streptavidin-XL665, 5×enzymatic buffer and detection buffer) was purchased from Cisbio, and the kinase assays were performed according to manufacture's instructions. After the kinases and the compounds incubated at 25~30 °C for 5 min, the reactions were initiated by the addition of 2 μl of mixed substrate solution [mixed solution of ATP (Sigma) and substrate-biotin]. The final concentrations of kinases were at EC_{80} and the total reaction volume was 8 μl. Plates were incubated at 30 °C for 30~60 min, then the reactions were quenched by the addition 8 μl mixed detection solution (mixed solution of antibody-cryptate and streptavidin-XL665 in detection buffer). The fluorescence at 665 nm and 620 nm was measured with PHERAstar FS plate reader (BMG) using a time delay of 50 μs. All kinases assays were conducted using ATP concentrations below the enzyme K_{mapp} and kinase-specific biotinylated substrate peptides.

The data for dose responses were plotted as percent inhibition calculated with the data reduction formula $100 \times [1 - (U_1 - C_2) / (C_1 - C_2)]$ versus concentration of compound, where U is the emission ratio of 665 nm and 620 nm of test sample, C_1 is the average value obtained for solvent control (2% DMSO), and C_2 is the average value obtained for no reaction control (no kinase sample). Inhibition curves were generated by plotting percentage control activity versus $\log_{10}$ of the concentration of each kinase. The IC_{50} values were calculated by nonlinear regression with Graphpad Prism 5.

5.5. Molecular docking.

The three dimensional (3D) structure of the MET kinase complex (PDB code: 3F82) was obtained from PDB database. All water molecules and ligand were removed from the

complex structure and hydrogen atoms were added with pH equaling to 7.0 using Sybyl-X. The AutoDock 4.2 [32] program was applied to docking compound **20j** and **20l** into the binding site of MET kinase. The Gasteiger charges were used for this inhibitors. In the docking process, a conformational search was performed for the ligand using the Solis and Wets local search method, and the Lamarckian genetic algorithm (LGA) [33-34] was applied for the conformational search of the binding complex of ligand with the kinase. Among a series of docking parameters, the grid size was set to be 70x70x80 in 3F82, and the used grid space was the default value of 0.375 Å. Among a set of 100 candidates of the docked complex structures, the best one was first selected according to the interaction energy.

5.6. Cell Proliferation Assay.

Cells were seeded in 96-well tissue culture plates. On the next day, cells were exposed to various concentrations of compounds and further cultured for 72 h. Finally, cell proliferation was determined using thiazolyl blue tetrazolium bromide (MTT, Sigma) assay.

5.7. Pharmacokinetic profiles in SD rats

Compound **20j** were dissolved in 70% PEG-400 solution and administered to 3 male SD rats (weight ranging from 180 g to 220 g) for i.v. (1 mg/kg) and p.o. (5 mg/kg) administration. The dosing volume was 2.5 mL/kg (i.v.) or 12.5 mL/kg (p.o.). After administration, blood samples were collected at the point including 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h and 24 h (i.v.) or 15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h and 24 h (p.o.) for analyses, the collected blood samples were centrifuged at 8000 rpm for 5 min at 4 ^{o}C, and then analyzed after protein precipitation. LC/MS/MS analysis of compound **20j** was performed under optimized conditions to obtain the best sensitivity and selectivity of the analyte in selected reaction monitoring mode (SRM) containing an internal standard. Plasma concentration-time data were measured by a noncompartmental approach using the software WinNonlin Enterprise, version 5.2 (Pharsight Co., Mountain View, CA).

5.8. In Vivo Antitumor Activity Assay.

Female nude mice (4-6 weeks old) were housed and maintained under specific-pathogen free conditions. Animal experiments were performed according to institutional ethical guidelines of animal care. Tumor cells were inoculated into the flanks of athymic nude mice (2×10^6 cells/mouse). When the tumor volume reached about 100-200 mm^3, the mice were randomly assigned into control and treatment groups. Control groups were given vehicle alone, and treatment groups received corresponding compounds as indicated doses via p.o. administration 7 days per week for 3 weeks. The sizes of the tumors were measured three times per week using microcaliper. The tumour volume (V) was calculated as follows: V =[length (mm) $\times$width^2 (mm^2)]/2. Percent (%) inhibition values (TGI) were measured on the final day of study for drug treated compared with vehicle-treated mice andwere calculated as $100\% \times (1- ((\text{treated}^{\text{final day}}-\text{treated}^{\text{day 0}})/(\text{control}^{\text{final day}}-\text{control}^{\text{day 0}}))$. Significant differences between the treated versus the control groups ($P \leq 0.01$) were determined using Student's.

Acknowledgement

This work was supported by the National Major Scientific and Technological Special Project for "Significant New Drugs Development" during the Thirteenth Five-year Plan Period (No. 2016ZX09101031) and the "Double First-Class" Construction Technology Innovation Team Project of China Pharmaceutical University (No. CPU2018GY23 and CPU2018GY24).

Appendix A. Supplementary data

Supplementary data related to this article can be found online at.

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Highlights:

Discovery of 1,6-Naphthyridinone-Based MET Kinase Inhibitor Bearing Quinoline Moiety as Promising Antitumor Drug Candidate

- A series of 1,6-naphthyridinone-based MET kinase inhibitors bearing quinoline moiety were designed based on Cabozantinib and our reported compound.
- Extensive SAR studies led to the identification of **20j** as a promising antitumor drug candidate.
- **20j** displayed favorable MET potency, kinase selectivity, PK profile, and in vivo efficacy, and has advanced into preclinical research.