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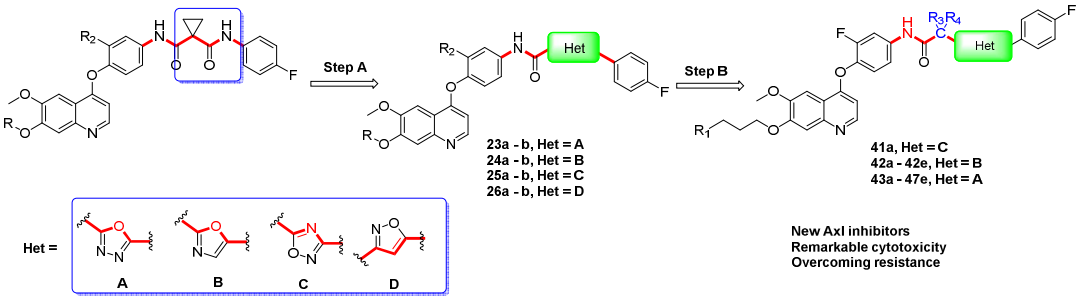

Design, synthesis and biological evaluation of new Axl kinase inhibitors containing 1,3,4-oxadiazole acetamide moiety as novel linker

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Abstract

Using the principle of bioisosteric replacement, we present a structure-based design approach to obtain new Axl kinase inhibitors with significant activity at the kinase and cellular levels. Through a stepwise structure-activity relationships exploration, a series of 6,7-disubstituted quinoline derivatives, which contain 1,3,4-oxadiazol acetamide moiety as novel Linker, were ultimately synthesized with Axl as the primary target. Most of them exhibited moderate to excellent activity, with IC_{50} values ranging from 0.032 to 1.54 μM against the tested cell lines. Among them, the most promising compound **47e**, as an Axl kinase inhibitor (IC_{50} = 10 nM), shows remarkable cytotoxicity against A549, HT-29, PC-3, MCF-7, H1975 and MDA-MB-231 cell lines. More importantly, **47e** also shows a significant inhibitory effect on EGFR-TKI resistant NSCLC cell lines H1975/gefitinib. Meanwhile, this study provides a novel type of linker for Axl kinase inhibitors, namely 1,3,4-oxadiazol acetamide moiety, which is out of the scope of the "5- atoms role ".

Keywords: Axl, EGFR, drug resistance, 1,3,4-oxadiazole, Isosteresis

1. Introduction

Lung cancer remains one of the most common malignant cancers worldwide, with approximately 1.8 million new cases diagnosed annually. Among them, non-small cell lung cancer (NSCLC) accounts for about 85%. NSCLC targeted therapy has now become critically important, and the epidermal growth factor receptor (EGFR) tyrosine kinase is a particular popular target, but its drug resistance has become a major challenge in the targeted treatment of NSCLC. The receptor tyrosine kinase Axl is one of most phosphorylated RTKs in over 50% of non-small cell lung cancer cells (NSCLCs). Accumulating evidence suggests that Axl is an effective target for the treatment of non-small cell lung cancer and overcoming the drug resistance of EGFR-TKI[1-3].

Axl belongs to the TAM family as Mer and Tyro-3[4]. Upon activation by its endogenous ligand

growth arrest-specific 6 (Gas6)[5], Axl exhibits a key role in many fundamental cellular processes, including survival[6], adhesion, proliferation[7], differentiation[8], migration, invasion and angiogenesis though activating the downstream signaling pathways. Apart from NSCLC, overexpression of Axl has been observed in a wide range of tumor types, both liquid and solid, such as prostate carcinoma[9], breast cancer[10], pancreatic cancer[11], leukemia[12], and in most cases high Axl expression correlates with a poorer patient prognosis.

Moreover, overexpression and/or overactivation of Axl are considered as an important mechanism of drug-resistance in NSCLC[13]. It has been reported that treatment of resistant cell lines with Axl inhibitors restored the sensitivity of the cells to some targeted drugs[14]. Thus, Axl becomes a new promising molecular target for anticancer drug discovery.

In the past decade, several well-characterized receptor tyrosine kinase inhibitors were discovered as Axl inhibitors with low IC_{50} values, which were reported as multitarget kinase inhibitors. Cabozantinib[15] (Cometriq^{TM}, **1**), a Met/VEGFR2 inhibitor, was approved by FDA in 2012 for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC). While identified as c-MET and VEGFR2 inhibitor, Cabozatinib inhibits other kinases such as Axl at the low nanomolar level (IC_{50} = 7 nM in cell free assay)[16]. In addition, Liu, L. has reported that Cabozatinib almost inhibited Axl phosphorylation completely in lapatinib-resistance breast cancer cells at 100 nM and restored sensitivity to lapatinib in treated cells, suggesting that activation of Axl might be a mechanism of drug resistance [17]. Also as quinoline derivatives, Foretinib is an extremely potent VEGFR2 inhibitor (IC_{50} = 0.035 nM, in cell-free assays) that also inhibits a wide number of kinases, including Met, Kit, Ret, and Axl (IC_{50}= 11 nM, in cell-free assays) in the low nanomolar range [18]. Other inhibitors such as NPS-1034, LY2801663 and MGCD265 are also multitarget kinase inhibitors. R428 (BGB324, **3**) is recognized as a first selective Axl inhibitor with an IC_{50} value of 14.0 nM. However, recent reports suggest that R428 also inhibit other kinases (e.g. RET, VEGFR2 and Flt3) as potently as Axl[19, 20].

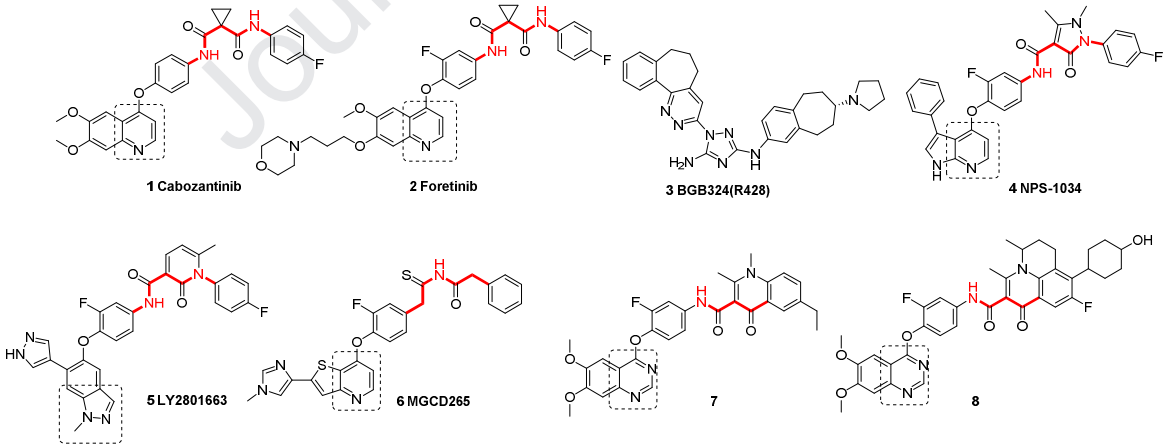


Figure 1. The representative small-molecule Axl inhibitors

Although increasing attention has been focused on the development of Axl kinase inhibitors, improving the selectivity of Axl inhibitors is still an urgent problem to be solved. Ke Ding' team developed a series of 6,7-dimethoxyquinazolin derivatives exhibiting considerable selectivity[20, 21]. However, there is a lack of

further investigation on the antitumor activity and overcoming drug resistance of these compounds. Thus, in this paper, we developed a class of new inhibitors primarily targeting Axl, and explored their antitumor activity and overcoming EGFR-TKI resistance.

2. Results and discussion

2.1 Design strategy of the new compounds

As shown in Figure 1, significant structural similarities are found in Cabozatinib, Forotinib and other related multitarget kinase inhibitors such as NPS-1034 (**4**), LY2801663 (**5**), MGCD265 (**6**), **7**[20]and **8**[21]. These inhibitors include three chemical moieties: the hinge-binding heterocycles at the left side; middle **linker** highlighted in red; the terminal *para*-F phenyl ring.

The SAR studies[22] about these compounds suggested that hinge-binding heterocycles and terminal phenyl ring (usually 4-fluorophenyl) appear to be critical for kinase activity. Hence, at the beginning of this study, we introduced five-membered azole heterocycles as bioisosteres into the linker to meet our previous study "5-atoms role"[23] and got four series of compounds (**23a-b, 24a-b, 25a-b and 26a-b** in Figure 2 **Step A**). With the goal of targeting Axl, these compounds were evaluated for their in *vitro* inhibitory activity against Axl kinase. The results indicated that they did not show excellent Axl kinase inhibitory activity, but it can be seen that the cycloamino substituted propoxy substituent at position 7 of quinolines plays a role in the interaction with the active site of Axl (shown in Table 1). In the molecular docking experiment, it was found that the cyclic amino group was embedded in the hydrophilic pocket of Axl kinase, which increased the affinity. (shown in Figure S1 in SI).

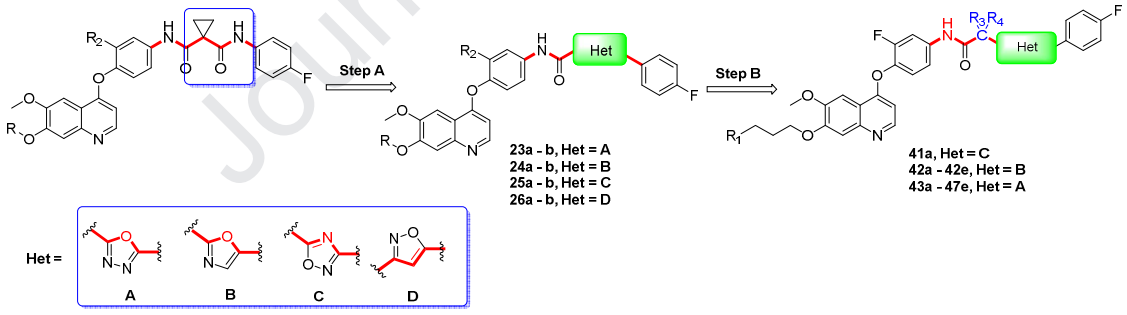


Figure 2. The design strategy of target compounds. (**Step A):** Based on the principle of bioisosteric replacement, the amide bond is replaced by various five-membered azole heterocycles. (**Step B):** CAD-based and SAR-based drug design.

Based on the result above, an assumption was drawn that the replacement of amides with five-membered heterocycles and the removal of methylene to meet the "5-atoms role" would lead to an increase in the rigidity of the **Linker**, which would be detrimental for target compounds into the Axl kinase binding site. From this assumption, one carbon atom was added at the carbonyl alpha position to increase molecular flexibility and several alkyl groups were introduced to limit conformations (Figure 2 **Step B**).

As proof of this concept, two compounds were docked to the binding sites of with AXL (PDB code:

5u6b) to gain an insight into the possible binding modes (shown in Figure 3). The simulation showed a clear difference in the ligand positioning between the two subtypes. Compared with **23b** without "methylene", compound **42a** containing the "methylene" is shown to interact with multiple residues in the binding site, such as Arg727, Asn728, Lys619, Met674 and Leu593 and the extension length and flexibility enhances its affinity and selectivity (**Figure 3B**). On the other hand, compound 42a with the "methylene" exhibits a "V" conformation that is more suitable for embedding into the Axl protein to improve affinity. Namely, the quinoline fragment occupies the intermediate active site, and the cyclic amino substituted propoxy group is embedded in the hydrophilic pocket A as well as (4-fluorophenyl)-1,3,4-oxadiazol moiety into the active pocket B. (Figure 3B and Figure S1). The experiments are in good agreement with the results obtained from the Axl % Inhibition experiment.

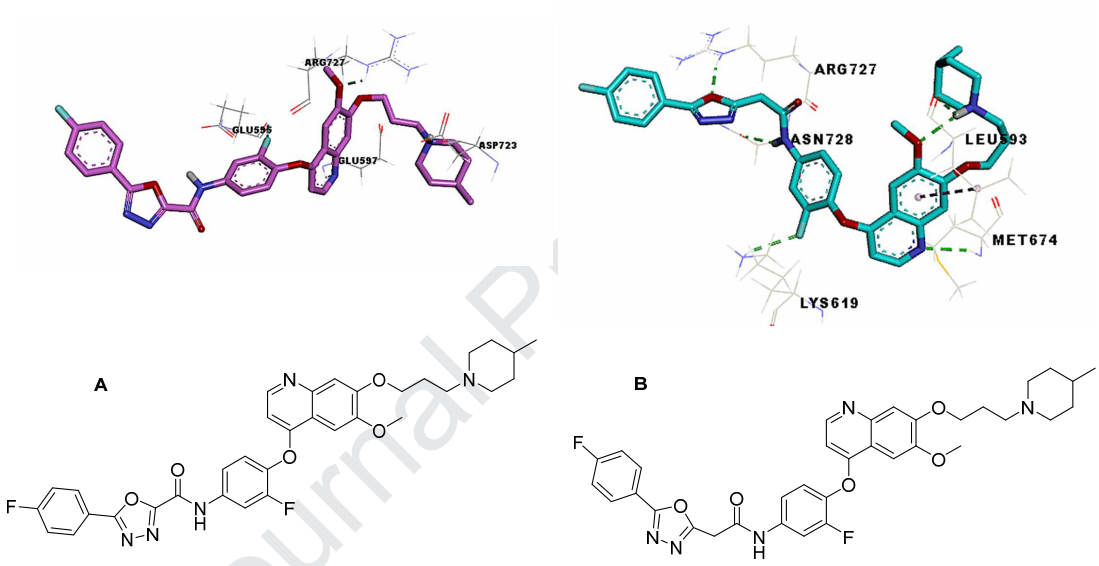


Figure 3. Docking studies of AXL (PDB code: 5u6b) and two compounds. (**A**): Compound **23b** without methylene in the binding site of Axl. (**B**): Docking poses of compound **42a** containing the "methylene" in the binding site of Axl.

As a result, other three series compounds (**41a**, **42a-42e** and **43a-47e** in Figure 2B) were designed and synthesized, in which, a novel **Linker** has been developed. Afterwards, a three-carbon tether which contained different cyclic tertiary amines were introduced at the 7-position of quinolines. After a stepwise structure-activity relationships (SAR) exploration, a series of 6,7-disubstituted-4-benzyloxyquinoline derivatives, which contain 1,3,4-oxadiazol acetamide moiety were ultimately synthesized as Axl inhibitors. 1,3,4-oxadiazole is commonly utilized pharmacophore has been subjected to extensive study[24-26] due to their metabolic profile[27] and pharmacokinetic property[28, 29]. In addition, 1,3,4-oxadiazol acetamide moiety enhances hydrogen bonding with the Axl protein and affects the conformation of the compounds so that the compounds can sufficiently occupy the active pocket (Figure 3 and Figure S1). Hence, 1,3,4-oxadiazol acetamide moiety may be a novel type of linker for Axl kinase inhibitors.

2.2 Chemistry

Compounds **23a-26a** and **23b-26b** were synthesized according to the routes respectively outlined in scheme 1. The key intermediates **9** and **10a-e**, as shown in Figure 4, were synthesized using a convenient procedure starting from 1-(3,4-dimethoxyphenyl) ethanone or 1-(4-hydroxy-3-methoxyphenyl)ethanone, which was illustrated in detail in our previous study[23, 30]. Intermediate **11** was obtained from commercially available substituted benzoate *via* hydrazinolysis with 80% hydrazine monohydrate. Subsequently, condensation with ethyl oxalyl monochloride[31] acnd the intramolecular cyclization[32] in the presence of $POCl_3$ afforded the ethyl 5-aryl-1,3,4-oxadiazole-2-carboxylate **12**. **12** was hydrolyzed and then reacted with oxalyl chloride to give the key intermediate 5-aryl-1,3,4-oxadiazole-2-carbonyl chloride **13**, which underwent a condensation reaction with intermediate 6,7-disubstituted-4-phenoxyquinolines **9** and **10c** respectively to give access to the desired target compounds **23a-b**. In this way, **24a-b**, **25a-b** and **26a-b** were prepared *via* cyclization, hydrolysis, acyl chlorination and condensation from **14**, **17** and **20** respectively. Substituted benzonitrile reacted with hydroxylamine hydrochloride in EtOH to give intermediate *N*-hydroxybenzimidamide **17**[33]. **14** was obtained from substituted acetophenone *via* substitution, ammonolysis[34]. **20** was obtained from substituted acetophenone after reaction with ethyl oxalate in the presence of *t*-BuOK in THF[35].

Scheme 2 depicts the preparation of compounds **41a-47e**. Intermediate **17**, obtained by conventional synthesis as described in Scheme 1, reacted with malonate monoethyl ester to afford amide intermediate, which transformed to oxazole acetate **27**. **27** was hydrolyzed and acylated with oxalyl chloride to give the key intermediate **28**, which underwent a condensation reaction with intermediate 6,7-disubstituted-4-phenoxyquinolines **10** to yield the desired target compound **41a**. The target compounds **42a-42e** and **43a-47e** were similarly prepared from compounds 14 or 11 respectively**.**

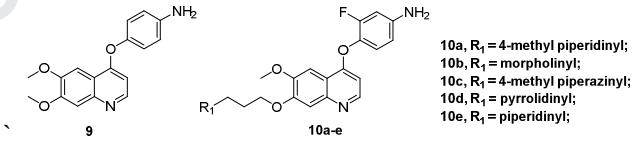
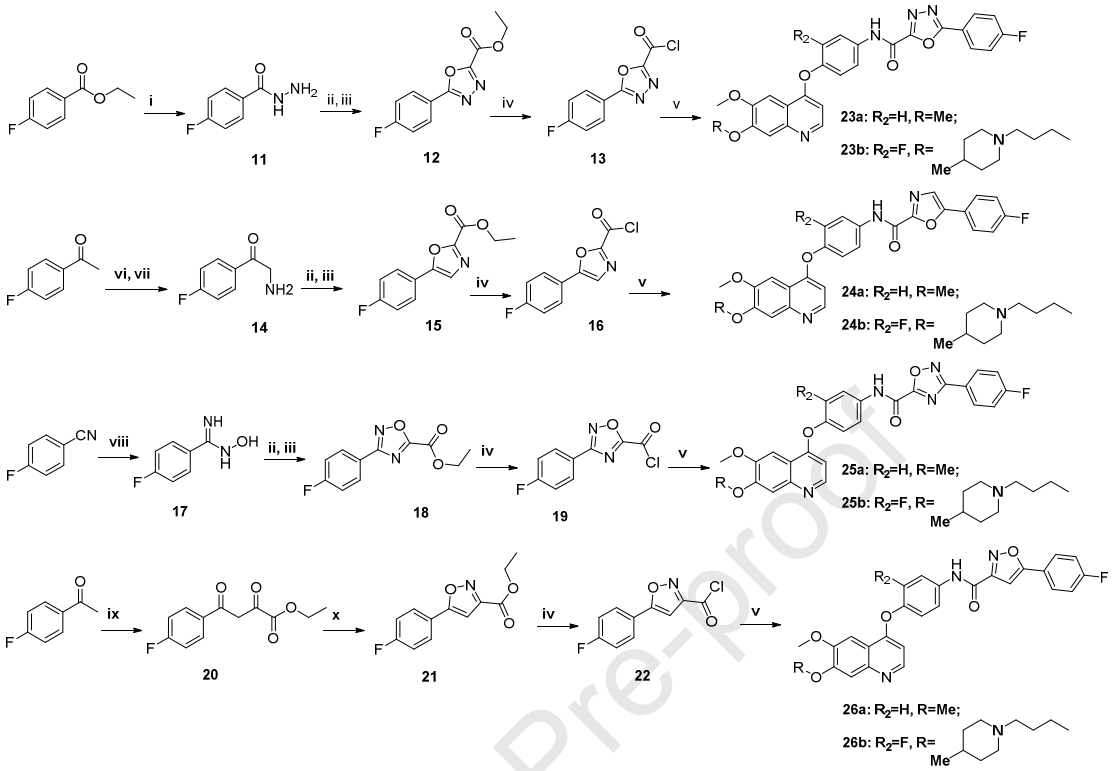
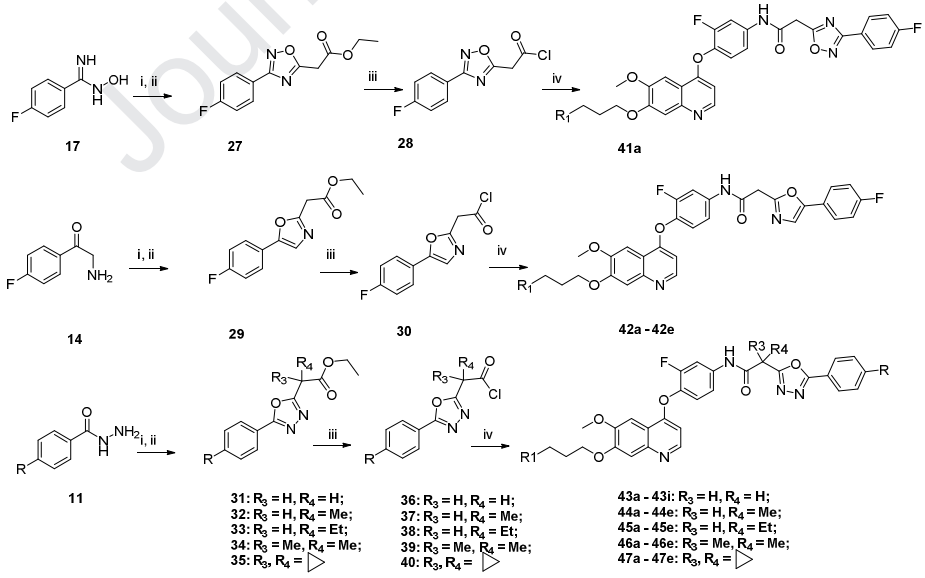


Figure 4. The structure of intermediates **9** and **10a-e**



Scheme 1. Reagents and conditions: (i) 80% hydrazine monohydrate, EtOH, reflux; (ii) ethyl oxalyl monochloride, TEA, DCM, 0 ^{o}C to rt; (iii) $POCl_3$, 85 ^{o}C; (iv) 1) LiOH, MeOH/THF, H_2O; 2) oxalyl chloride, DCM; (v) **9** or **10c**, TEA, DCM; (vi) NBS, DCM; (vii) hexamethylenetetramine, 6N HCl; (viii) $NH_2OH{\cdot}HCl$, TEA, EtOH; (ix) diethyl oxalate, *t*-BuOK, THF; (x) $NH_2OH{\cdot}HCl$, MeOH, 60 ^{o}C.



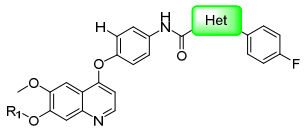
Scheme 2. Reagents and conditions: (i) monoethyl 2-substituted malonate, EDCI, DCM, 0 °C to rt; (ii) $POCl_3$, 85°C; (iii) 1) LiOH, MeOH/THF, H_2O; 2) oxalyl chloride, DCM; (iv) **10**, TEA, DCM, 0 °C to rt.

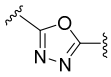
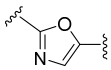
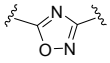
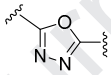
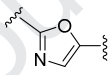
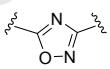
2.3 In vitro cytotoxicity and structure-activity relationships

Target compounds **23a-26a** and **23b-26b** were evaluated for their in *vitro* inhibitory activity against Axl kinase by Mobility shift assay with ATP concentration at Km at 1.0 μM. The cytotoxicity of the eight prepared compounds were evaluated *in vitro* against three cancer cell lines, including, HT-29 (human colon cancer), A549 (human lung adenocarcinoma) and PC-3 (human prostate cancer cell).

Table 1.

The antiproliferative activities and Axl inhibition of target compounds **23a-26b**.



Compd.	R_1	Het	IC_{50} (μmol/L) ± SD			Axl % Inhibition at 1 μM
			A549	HT-29	PC-3	
23a	Me		5.14 ± 0.06	52.29±3.62	>100	-2.0±0.4
24a	Me		5.59±0.03	>100	21.91±0.56	21.5±0.6
25a	Me		10.30±0.02	39.74±0.75	>100	-4.5±0.5
26a	Me		40.37±0.13	>100	29.44±1.01	-2.2±0.9
23b			**2.73±0.05**	7.89±0.16	**3.81±0.08**	73.2±1.4
24b			**0.24±0.04**	**1.89±0.04**	**0.72±0.01**	80.9±2.9
25b			**0.87±0.01**	6.38±0.07	**1.04±0.02**	36.6±2.7
26b			**3.34±0.06**	24.56±1.10	**2.04±0.03**	11.0±0.0
Cabozantinib[b]	-	-	3.75±0.01	4.56± 0.08	8.25 ± 0.63	**93.8±0.85**
Foretinib[b]	-	-	0.21	0.25 ± 0.01	0.81± 0.09	ND

[a]ND = not determined;

[b]Used as the positive control;

[c]Bold values show the IC_{50} values of the target compounds lower than the values of the positive control;

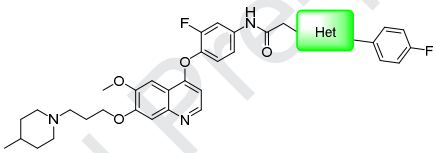
This first screening results are listed in Table 1. None of compounds **23a-26a** bearing 6,7-dimethoxyquinolin moiety (contained in the structure of Cabozantinib), exhibits inhibitory activity on Axl at 1μM. Interestingly, their analogues (**23b-26b**) bearing the cyclic amino propanoxy group (similar to Foretinib) exhibited a higher inhibitory activity against Axl. Especially, compound **24b** with the oxazole as bioisostere exhibited the highest inhibitory activity with the IC_{50} values of 0.24 ± 0.04 μM, 1.89 ± 0.04 μM

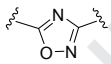
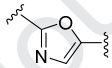
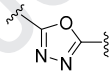
and 0.72 ± 0.01 μM against A549, HT-29 and PC-3 cell lines respectively and a percent inhibition close to 81% at 1.0 μM, which indicated the cyclic amino propanoxy group seemed to play an important role in the interaction with the active site of Axl. Compounds **23b** and **24b** exhibited better Axl kinase inhibitory activity compared to **25b** and **26b**, which indicated 1,3,4-oxadiazole and oxazole moiety are more suitable as isosteres in this study. Interesting, compounds **25b** and **26b** showed almost no inhibitory activity against Axl, but exhibited better cytotoxicity against A549 and PC-3 cell lines than Cabozantinib. To explore the cause of this phenomenon, we tested the inhibition rate of **26b** against five other kinases. The result **(Table S1 in SI)** indicated that **26b** showed good inhibitory activity against FLT3 and KDR at a concentration of 100 nM. Even, **26b** had a percent inhibition 87% at 100 nM against c-Met, which suggested **26b** may be a potential c-Met inhibitor.

Meanwhile, the flexibility of the **Linker** was investigated by evaluating the target compounds **41a-43a**. In this screening whose results were reported in Table 2, further enhanced activity was observed for compound **42a** and **43a** with lower IC_{50} values than the values of the positive control. The results showed that the activity benefits from the presence of the "methylene".

Table 2.

The anti-tumor activities and Axl inhibition of target compounds **41a-43a.**



Compd.	Het	IC_{50} (μmol/L) ± SD			Axl % Inhibition at 1 μM
		A549	HT-29	PC-3	
41a		**0.106±0.002**	1.16 ± 0.04	**0.33 ± 0.15**	68.0±1.8
42a		**0.105±0.001**	**0.109±0.004**	**0.54±0.09**	83.1±2.4
43a		**0.082±0.004**	**0.238 ± 0.006**	**0.28 ± 0.08**	88.1±6.0
Cabozantinib	-	3.75±0.01	4.56± 0.08	8.25 ± 0.63	**93.8±0.85**
Foretinib	-	0.21	0.25 ± 0.011	0.81± 0.09	ND

[a]ND = not determined;

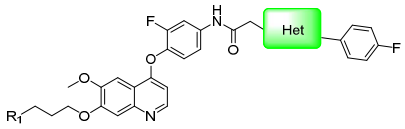
Based on the preliminary SAR, we decided to focus our screening on some target compounds bearing cyclic amino propanoxy group at position 7 of quinoline. As shown in Table 3, when the cyclic amino was morpholinyl group, compound **42b** (a percent inhibition only 24% at 100 nM) afforded lower activities in the anti-Axl activities compared to **42c-42e**. The same trend was observed for compounds **43b-43e**. In addition, compounds containing the 1,3,4-oxadiazole moiety (**43b-43e**) have better activity than compounds containing an oxazole moiety (**42b-42e**). The results suggested that the 1,3,4-oxadiazole moiety was a privileged scafford for anti-Axl activities.

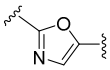
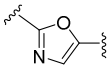
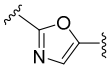
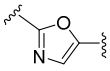
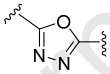
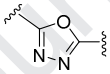
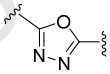
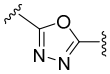
Encouraged by the observations described above, further investigations were performed to study the

cytotoxic activity of different substituents on the position 4 of phenyl ring. As seen from Table 4, among these compounds (**43f-43i**), only **43f** (containing 4-bromophenyl fragment) exhibited better cytotoxic activity than Foretinib, but the activity was still weaker than compound **43a**, which bear 4-fluorophenyl moiety. Accordingly, 4-fluorophenyl derivatives were further studied in our work.

Table 3.

The anti-tumor activities and Axl inhibition of target compounds **42b-42e** and **43b-43e.**



Compd.	R_1	Het	IC_{50} (μmol/L) ± SD			Axl % Inhibition at 100 nM
			A549	HT-29	PC-3	
42b			0.596±0.022	13.74±0.75	2.41±0.17	24.0±2.7
42c			0.254±0.013	2.52±0.03	**0.57±0.06**	55.5±3.2
42d			**0.178±0.005**	4.17±0.07	**0.34±0.03**	49.0±1.3
42e			1.042±0.006	1.042±0.021	**0.53±0.03**	37.0±0.28
43b			**0.103±0.007**	4.3±0.12	**0.68±0.07**	27.5±3.7
43c			**0.071±0.014**	3.48±0.07	**0.41±0.03**	66.0±0.09
43d			**0.091±0.011**	2.37±0.16	**0.21±0.02**	61.5±3.5
43e			0.813±0.004	0.813±0.041	**0.40±0.01**	58.5±1.9
Cabozantinib	-	-	3.75±0.01	4.56± 0.08	8.25 ± 0.63	**93.0±0.4**
Foretinib	-	-	0.21	0.25 ± 0.011	0.81± 0.09	ND

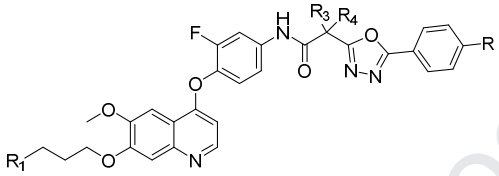
[a]ND = not determined;

Our final modification focused on the R_3 and R_4 group of the methylene at the *alpha* position of the carbonyl group. As shown in Table 4, most of them displayed excellent cytotoxicity against four cancer cells lines (especially in the inhibition of A549 cell line) with potency from single-digit μM to nanomole range, which were more potent than Foretinib against one or more cell lines. Three compounds (**44a**, **45a** and **47e**) were found to have 1.8-8.4 fold, 1.1-2.9 fold, 1.38-2.0 fold and 2.0-6.5 fold increase in activity cytotoxic activity than the positive control Foretinib against A549, HT-29, PC-3 and MCF-7 cell lines in *vitro* respectively. In order to further summarize the structure-activity relationship, Axl inhibition activity of

those compounds were evaluated. The results showed that most of those compounds exhibit moderate to excellent anti-Axl activities with Axl % Inhibition at 100 nM > 50%. In addition, there was a positive correlation between cytotoxicity and Axl kinase inhibitory activity. As for Cyclic amino (R_1), compounds with morpholinyl groups are much weaker in terms of cell and kinase activity, which is consistent with the above conclusion.

Table 4.

Cytotoxicity of compounds **43f-43i** and **44a-47e** against A549, HT-29, PC-3 and MCF-7.



Entry	R_1	R_3	R_4	R	IC_{50}(μM)				Axl % Inhibition at 100 nM
					A549	HT-29	PC-3	MCF-7	
43f		H	H	Br	**0.102±0.006**	**0.583±0.01**	**0.68±0.02**	ND [a]	ND
43h		H	H	Cl	0.63±0.02	2.46±0.03	0.36±0.05	ND	ND
43g		H	H	H	0.92±0.06	7.81±0.04	4.73±0.03	ND	ND
43i		H	H	OMe	1.56±0.07	7.52±0.04	**0.41±0.06**	ND	ND
44a		**H**	**Me**	**F**	**0.032±0.001**	**1.46±0.10**	**0.53±0.01**	**1.00±0**	**83.2±0.0**
44b		H	Me	F	**0.052±0.004**	2.54±0.33	1.18±0.02	**1.05±0.04**	47.9±1.2
44c		H	Me	F	**0.075±0.003**	1.96±0.01	1.70±0.03	**1.63±0.03**	**80.0±0.8**
44d		H	Me	F	**0.076±0.002**	**1.27±0.04**	1.08±0.04	2.70±0.03	79.3±2.7
44e		H	Me	F	**0.086±0.002**	**1.00±0.08**	1.26±0.04	**1.04±0.02**	69.7±0.3
45a		**H**	**Et**	**F**	**0.119±0.009**	**0.554±0.03**	**0.40±0.02**	**0.46±0.03**	**78.7±0.5**
45b		H	Et	F	**0.049±0.007**	2.02±0.03	2.53±0.06	2.69±0.15	48.9±2.3
45c		H	Et	F	**0.038±0.006**	**1.54±0.07**	0.97±0.03	2.22±0.32	76.0±0.2
45d		H	Et	F	**0.078±0.001**	**0.570±0.016**	1.42±0.06	**1.04±0.09**	75.3±1.1
45e		H	Et	F	**0.092±0.099**	**1.08±0.05**	1.47±0.02	**0.41±0.03**	**80.1±1.5**
46a		Me	Me	F	0.42±0.02	**0.648±0.009**	1.49±0.02	**0.37±0.08**	69.9±0.0
46b		Me	Me	F	**0.275±0.0035**	2.48±0.11	1.79±0.08	**1.60±0.13**	42.7±0.1
46c		Me	Me	F	0.597±0.0125	**1.08±0.02**	1.90±0.01	2.48±0.07	76.3±0.0
46d		Me	Me	F	0.263±0.03	**1.03±0.10**	1.05±0.07	ND	70.3±0.2
46e		Me	Me	F	**0.215±0.011**	**0.871±0.002**	1.76±0.05	**0.47±0.09**	73.7±1.0
47a				F	**0.120±0.007**	**0.442±0.003**	2.18±0.03	**0.74±0.03**	**87.9±0.5**
47b				F	1.66±0.03	9.33±0.42	12.95±0.13	>100	42.7±0.7
47c				F	**0.143±0.006**	**1.05±0.07**	1.67±0.02	2.61±0.22	82.3±0.3
47d				F	**0.150±0.008**	**0.779±0.015**	2.34±0.07	**0.31±0.07**	79.3±0.2
47e				**F**	**0.053±0.008**	**1.03±0.13**	**0.59±0.04**	**1.01±0.011**	**93.7±0.2**
Foretinib	-	-	-	-	0.27±0.04	1.62±0.07	0.82±0.11	2.00±0.06	88.0**±0.1**

[a]ND = not determined.

To explore the contribution of Axl kinase inhibition to cytotoxicity, we also tested Axl overexpressing human breast cancer cell line MDA-MB-231[10, 20, 36] and human noncancerous cell line WI-38. The results indicated 47e had a significant inhibitory effect on the proliferation of MDA-MB-231, which was much stronger than that on normal cells (Table S2 in SI).

2.4 In vitro enzymatic assays

As shown in Table 5, compounds **44a**, **45a** and **47e** all exhibited excellent Axl enzymatic potency, suggesting that the inhibition of Axl may be a mechanism for the antitumor effect of these derivatives. Compounds **45a** and **47e** showed the potent activity with an IC_{50} value of 0.036 and 0.010 μM against Axl respectively, which was comparable to that of the positive control, **Foretinib** (IC_{50}=0.014 μM), indicating that these compounds deserve further study with regard to its application in the treatment of cancer.

Table 5.

Inhibitory activities of **44a**, **45a**, **47e** and Foretinib against Axl *in vitro*.

Compd.	IC_{50} on Axl (μM)[a]
44a	0.036
45a	0.077
47e	**0.010**
Foretinib	0.014

[a] The values are an average of two separate determinations.

2.5 Enzymatic selectivity assays

Compounds **44a** and **47e** were screened against other 7 tyrosine kinases to examine their selectivity on Axl over other kinases (Table 6). Compared with its high potency against Axl (IC_{50}=0.036 and 0.010 μM), **47e** exhibited inferior inhibitory effects against c-Met (IC_{50} = 0.071 μM), VEGFR-2 (IC_{50} = 0.081 μM) and c-kit (IC_{50} = 0.063μM). Compound **47e** showed inhibitory potency against Flt-3, PDGFRβ, Mer and Tyro3 lower (>10 fold) than that of Axl. These data suggested that compound **47e** seem to be an Axl kinase inhibitor with some selectivity. To identify other kinase targets of **47e**, profiling studies were conducted to evaluate its selectivity toward Axl (Figure 4). Except for Axl, **47e** also shows considerable activity against the other three kinases (Aurora-B, Flt4 and Ron, % Inhibition at 200 nM > 80%).

Table 6.

Inhibition of tyrosine kinases by compound **44a** and **47e**.

Compd.	IC_{50}(μM)[a]							
	Axl	c-Met	VEGFR-2	c-Kit	Flt-3	PDGFRβ	Mer	Tyro3
44a	0.036	0.062	0.040	0.047	>0.2	>0.2	>0.2	0.190

47e	0.010	0.071	0.081	0.063	0.103	>0.2	>0.2	>0.2

[a] The values are an average of two separate determinations.

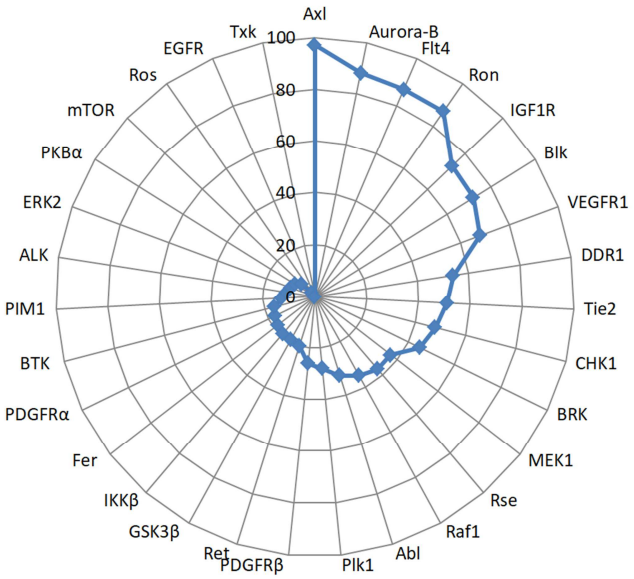


Figure 4. Compound **47e** was profiled against a panel of 30 kinases at 200 nM using Eurofins's SelectScreen kinase profiling service.

2.6 Study on overcoming drug resistance of EGFR-TKI.

Since Axl inhibitor **47e** was obtained after multiple optimizations, the anti-EGFR-TKI resistance activity was investigated as shown in Table 7. The Axl inhibitor **47e** exhibits prominent inhibition against both H1975 and gefitinib- resistant H1975.

Table 7.

Anti-proliferative activity towards H1975 and H1975/Gefitinib.

Entry	**IC_{50}(μM)**	
	H1975	**H1975/Gefitinib**
47e	**0.099±0.008**	**0.107±0.031**
Gefitinib	6.5±0.14	78.7±1. 7

3. Conclusion

In summary, through a stepwise structure-activity relationship analysis, a series of 6,7-disubstituted quinoline derivatives containing 1,3,4-oxadiazole acetamide moiety were synthesized and evaluated for their Axl kinase inhibition and cytotoxicity against A549, HT-29, PC-3 and MCF-7 cancer cell lines in *vitro*. Most compounds exhibited moderate to excellent activity, with IC_{50} values ranging from 0.032 to 1.54 μM against A549, HT-29, PC-3 and MCF-7 respectively. Some selected compounds (**44a**, **45a** and **47e**) were evaluated for the activity against Axl kinase, and compounds **44a** and **47e** were further evaluated for other seven tyrosine kinases (c-Met, VEGFR-2, c-Kit, Flt-3, PDGFRβ, Mer and Tyro3) to test the enzyme-based selectivity. The studies of SARs indicated that the presence of a carbonyl alpha-methylene was of

significant importance to the inhibition potency and selectivity. In a sense, this study provides a novel type of linker for Axl kinase inhibitors, namely 1,3,4-oxadiazole acetamide moiety, which equipped more suitable length and flexibility to improve activity. Moreover, the introduction of a three-carbon tether contained cyclic amino (R_1) into the 7-position of quinolines was advantageous to the potency. To our delight, the most promising compound **47e**, as a Axl kinase inhibitor, showed the better cytotoxic activities than Foretinib with 1.9 fold, 1.57 fold, 1.54 fold and 2.0 fold increases in activity against A549, HT-29, PC-3 and MCF-7 cell lines in *vitro* respectively. What's more, compound **47e** exhibits prominent inhibition against both H1975 and gefitinib- resistant NSCLC cell line H1975/ gefitinib.

4. Experimental protocols

4.1 Chemistry

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were uncorrected. The IR spectra were recorded by means of the KBr pellet technique on a Bruker FTS 135 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were generated on a Bruker ARX-300 or ARX-600 spectrometers (Bruker Bioscience, Billerica, MA, USA). Column chromatography was carried out on silica gel (200-300 mesh). Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, USA). Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy).

4.2. Preparation of aromatic-substituted heterocyclic carboxylate esters (**12**, **15**, **18** and **21**)

4.2.1. The preparation of 4-fluorobenzohydrazide (**11**)

To a stirred solution of 4-fluoroethylbenzoate (4.5g, 26.7mmol) in EtOH (30mL) was added $NH_2NH_2{\cdot}H_2O$ (6.67g, 133.5mmol) (80% in H_2O) at room temperature and refluxed at 85°C for 10 h. The reaction was cooled to room temperature, and evaporated *in vacuo* to afford a crude reside which was washed with *n*-hexane (50mL) and then dried to obtain compound. Yield: (4.2g, quantitative yield), white solid. MS (ESI) m/z (%): 155.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.85 (s, 1H), 7.86 (dd, 2H), 7.25 (t, 3H), 4.46 (s, 1H), 3.47 (br s, 1H).

4.2.2. The preparation of ethyl 5-(4-fluorophenyl)-1,3,4-oxadiazole-2-carboxylate (**12**)

Ethyl oxalyl monochloride (0.64g, 5.25mmol) was added drop-wise to a solution of 4-fluorobenzohydrazide (**11**, 0.78g, 5.0mmol) and triethylamie (1.01g, 10.0mmol) in DCM in an ice bath. Upon completion of the addition, the reaction mixture was removed from the ice bath and placed in room temperature for 8h and monitored by thin-layer chromatography (TLC). The mixture was washed with 10% K_2CO_3 (150 mL×3) followed by brine (150 mL×1), and the organic phase was separated, dried, and evaporated to yield ethyl 2-(2-(4-fluorobenzoyl)hydrazinyl)-2-oxoacetate as yellow solid, Yield: 83%; MS (ESI)m/z(%): 255.4 $[M+Na]^+$.

Ethyl 2-(2-(4-fluorobenzoyl)hydrazinyl)-2-oxoacetate (2.06g) was added to $POCl_3$ 150mL and then

heated to 85 ^{o}C for 3h. The reaction mixture was evaporated and then poured into water, basified with sodium hydroxide to PH = 7, and extracted with dichloromethane (200 mL × 3). The combined extracts were washed with brine (200 mL×2), dried over anhydrous Na_2SO_4, and concentrated in vacuum to give the corresponding ethyl 5-(4-fluorophenyl)-1,3,4-oxadiazole-2-carboxylate (**12**) as white solid; MS (ESI) m/z(%): 237.4 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J*=8.6, 5.3 Hz, 2H), 7.13 (t, *J*= 8.5 Hz, 2H), 4.40 (q, *J*= 7.1 Hz, 2H), 1.40 (t, *J*= 7.1 Hz, 3H).

4.2.3. The preparation of 2-amino-1-(4-fluorophenyl)ethanone hydrochloride (**14**)

To a solution of 1-(4-fluorophenyl)ethan-1-one (15.0mmol, 1.0 equiv) in 8 mL of dichloromethane were added NBS (2.72g, 15.3mmol, 1.02equiv) and *p*-toluenesulfonic acid (2.85g, 15.0mmol, 1.0 equiv). The reaction mixture was stirred for 24 h at 50 °C. After that time, the solvent was evaporated under reduced pressure. A water solution of saturated $NaHCO_3$ (30 mL) was then added, and the solution was extracted with dichloromethane (3 × 30 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated, and the residue was subjected to column chromatography (silica gel) using hexanes/CH_2Cl_2 (from 9:1 to 4:1) as eluent to obtain 2-bromo-1-(4-fluorophenyl)ethan-1-one. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05-8.00 (m, 2H), 7.19-7.13 (m, 2H), 4.41 (s, 2H).

A solution of hexamethylenetetramine (1.42g, 10.1mmol) in $CHCl_3$ was added drop-wise over 30 min to a solution of 2-bromo-4-fluoroacetophenone (2.0g, 9.2mmol) in dry $CHCl_3$ 40 mL at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. After completion of the reaction the solid precipitate was collected by filtration and washed with $CHCl_3$. The solid obtained was suspended in EtOH 40mL and conc. HCl 4 mL was added. The mixture was heated to 80 °C for 3 h, cooled to room temperature, and the solid formed was filtered off. The clear filtrate was concentrated. 2-amino-1-(4-fluorophenyl)ethanone hydrochloride (**14**, 1.5g) as yellow solid. MS (ESI) m/z(%): 154.3$[M+H]^+$; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.15 (m, 2 H), 7.44 (m, 2 H), 4.65 (m, 2 H).

4.2.4. The preparation of ethyl 5-(4-fluorophenyl)oxazole-2-carboxylate (**15**)

Ethyl oxalyl monochloride (0.64g, 5.25mmol) was added drop-wise to a solution of 2-Amino-1-(4-fluorophenyl)ethanone hydrochloride (**14**, 0.78g, 5.0mmol) and triethylamie (1.01g, 10.0mmol) in dichloromethane in an ice bath. Upon completion of the addition, the reaction mixture was removed from the ice bath and placed in room temperature for 8h and monitored by thin-layer chromatography (TLC). The mixture was washed with 10% K_2CO_3 (150 mL×3) followed by brine (150 mL×1), and the organic phase was separated, dried, and evaporated to yield Ethyl 2-((2-(4-fluorophenyl)-2-oxoethyl)amino)-2-oxoacetate as white solid;

Ethyl 2-((2-(4-fluorophenyl)-2-oxoethyl)amino)-2-oxoacetate (2.06g) was added to $POCl_3$ 15mL and then heated to 85^{o}C for 3h. The reaction mixture was evaporated and then poured into water, basified with sodium hydroxide to PH 7, and extracted with dichloromethane (200 mL × 3). The combined extracts were washed with brine (200 mL×2), dried over anhydrous Na_2SO_4, and concentrated in vacuum to give the ethyl 5-(4-fluorophenyl)-1,3,4-oxadiazole-2-carboxylate (**15**) as white solid; MS (ESI) m/z(%): 236.3$[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.76 (dd, *J*=8.7,5.2 Hz, 2H), 7.48 (s,1H), 7.17(t, J=8.6 Hz, 2H), 4.50(q, *J*=7.1 Hz, 2H),1.46(t, *J*=7.1 Hz, 3H).

4.2.5. The preparation of 4-fluoro-*N*-hydroxybenzimidamide (**17**)

To a solution of 4-fluoro benzonitrile (4.84g, 40mmol) in ethanol (50mL), was added hydroxylamine hydrochloride (6.5g, 100mmol), followed by addition of triethylamine (5.5g, 52mmol). The reaction mass was refluxed for 8 h. Excess of solvent was removed under vacuum and the reaction mass was diluted with water, acidified with dilute HCl and filtered to afford the desired product. MS (ESI) m/z (%): 189.1 $[M + H]^+$; ^{1}H NMR (DMSO-d_6): δ 5.95 (s, 2H), 7.42 (t, *J* = 8.7 Hz, 1H), 7.69 (m, 1H), 7.83 (dd, 1H), 9.80 (s, 1H).

4.2.6. The preparation of ethyl 3-(4-fluorophenyl)-1,2,4-oxadiazole-5-carboxylate (**18**)

Ethyl oxalyl monochloride (0.64g, 5.25mmol) was added drop-wise to a solution of 4-fluoro-*N*-hydroxybenzimidamide (**17**, 0.78g, 5.0mmol) and triethylamie (1.01g, 10.0mmol) in dichloromethane in an ice bath. Upon completion of the addition, the reaction mixture was removed from the ice bath and placed in room temperature for 8h and monitored by thin-layer chromatography (TLC). The mixture was washed with 10% K_2CO_3 (150 mL×3) followed by brine (150 mL×1), and the organic phase was separated, dried, and evaporated to yield Ethyl 2-(2-(4-fluorobenzoyl)hydrazinyl)-2-oxoacetate as yellow solid. MS (ESI) m/z (%): 255.1 $[M + H]^+$.

Ethyl 2-(2-(4-fluorobenzoyl)hydrazinyl)-2-oxoacetate (2.06g) was added to $POCl_3$ 15mL and then heated to 95 ^oC for 3h. The reaction mixture was evaporated and then poured into water, basified with sodium hydroxide to PH = 7, filtered and obtain the ethyl 5-(4-fluorophenyl)-1,3,4-oxadiazole -2-carboxylate as yellow solid. MS (ESI) m/z (%): 238.1 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J*= 8.4 Hz，2H), 7.66 (d, *J*= 8.6 Hz，2H), 4.37 (q, *J*= 7.1 Hz, 2H), 1.42 (t, *J*= 7.2 Hz, 3H).

4.2.7. The preparation of ethyl 4-(4-fluorophenyl)-2,4-dioxobutanoate (**20**)

In a three-necked flask acetophenone (5g, 41.61mmol) and diethyl oxalate (6.76mL, 50mmol) were dissolved in anhydrous DMF 65mL at 0°C and *t*-BuOK (2g, 83.25mmol) was slowly added, the mixture was stirred at 0°C for 15 min and 30 min more at room temperature before heating at 45 °C for 1h. Reaction was poured into water-acetic acid and product extracted with ethyl acetate. Organic layers were combined, washed with water and brine, dried over magnesium sulphate, filtered and concentrated to yield the title compound. MS (ESI) m/z (%): 237.2 $[M - H]^+$

4.2.8. The preparation of ethyl 5-(4-fluorophenyl)isoxazole-3-carboxylate (**21**)

A mixture of **20** (3 g, 11.03 mmol) and NH_2-OH·HCl (2.28 g, 33.09 mmol) in MeOH (50 mL) was heated to reflux overnight. The MeOH was then evaporated and the residue was extracted with ethyl acetate, dried over Na_2SO_4. After filtration and concentration *in vacuo*, the crude residue was purified by column to afford **21**; MS (ESI) m/z (%): 236.1$[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.85-7.78 (m, 2H), 7.20(t, *J*=8.6 Hz, 2H), 6.89(s, 1H), 4.01(s, 3H).

4.3. General procedure for preparation of aromatic ring-substituted heterocycliccarbonyl chloride (**13**, **16**, **19** and **22**)

The corresponding aromatic ring-substituted heterocycliccarbonyl esters (**12**, **15**, **18** and **21**, 10mmol)

was dissolved in THF 10mL and methanol 40mL. A solution of lithium hydroxide (0.6g, 30mmol) in water 3mL was slowly added. The reaction mixture was stirred at room temperature for 5 h and monitored by thin-layer chromatography (TLC). The reaction was extracted with dichloromethane (40 mL × 3) and the aqueous phase was acidified with 1N HCl and the corresponding aromatic ring-substituted heterocycliccarboxylic acid was isolated as white solid.

Thoroughly dried aromatic ring-substituted heterocyclic carboxylic acid 3.5mmol, DMF 1 drops, anhydrous dichloromethane was added in a three-neck flask under a N_2 atomosphere. Oxalyl chloride (4.2mmol) was drop-wise added at 0 ^oC. The reaction mixture was stirred at room temperature for 4h. And the reaction was then removed *in vacuo*. The resulting aromatic ring-substituted heterocycliccarbonyl chloride (**13**, **16**, **19** and **22**) was used immediately without further purification.

4.4. General procedure for preparation of target compounds (**23a-b**, **24a-b**, **25a-b** and **26a-b**)

A mixture of corresponding carbonyl chloride (**13**, **16**, **19** and **22**, 1.5eq.) in DCM was added to a solution of triethylamine (0.2g, 2.0mmol) and **9** or **10c** (0.493g, 1.0mmol) in DCM 10 mL. The reaction mixture was placed at room temperature for 2 h. The solvent was concentrated in vacuum and the residue was resolved with DCM (100 mL), washed with water (30 mL× 3), brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography to afford the target compounds (**23a-b**, **24a-b**, **25a-b** and **26a-b**).

4.4.1. *N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole-2-carboxamide* (**23a**)

Yield: 62%; m.p. 224 - 126^{o}C; MS (ESI) m/z (%): 487.3 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.52 (d, *J* = 5.9 Hz, 1H), 8.22 (dd, *J* = 8.6, 5.2 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.86 (s, 1H), 7.61 (s, 1H), 7.32 - 7.25 (m, 4H), 6.64 (d, *J* = 6.0 Hz, 1H), 4.13 (s, 3H), 4.10 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 165.05, 165.03 (d, *J* = 251.0 Hz), 160.17, 159.03, 153.07, 151.92, 151.10, 149.86, 149.32, 146.96, 135.45, 130.47 (d, *J* = 9.5 Hz), 123.14, 121.90, 117.37 (d, *J* = 22.4 Hz), 115.68, 108.34, 103.85, 99.57, 56.21, 56.19. Anal. calcd. for $C_{26}H_{19}FN_4O_5$ (%): C, 64.20; H, 3.94; F, 3.91; N, 11.52; O, 16.44. Found (%): C, 64.21; H, 3.93; N, 11.51.

4.4.2. *N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole-2-carboxamide* (**23b**)

Yield: 61%; m.p. 122 - 123 ^{o}C; MS (ESI) m/z (%): 630.1 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO) δ 11.28 (s, 1H), 8.49 (d, *J* = 5.1 Hz, 1H), 8.09 (m, 2H), 7.91 (d, *J* = 12.7 Hz, 1H), 7.61-7.47（m, 6H）, 6.54 (d, *J* = 5.0 Hz, 1H), 4.21 (t, *J* = 6.1 Hz, 2H), 3.98 (s, 3H), 3.14-2.96(m, 2H), 2.78 – 2.58(m, 2H), 2.07(d, *J* = 17.0 Hz, 4H), 1.68 (d, *J* = 12.3 Hz, 2H), 1.48 (s, 1H), 1.25(s, 2H), 0.93 (d, *J* = 6.4 Hz, 3H). Anal. calcd. for $C_{34}H_{33}F_2N_5O_5$ (%): C, 64.86; H, 5.28; F, 6.03; N, 11.12; O, 12.70. Found (%): C, 64.85; H, 5.24; N, 11.15.

4.4.3. *N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)oxazole-2-carboxamide* (**24a**)

Yield: 54%; m.p. 242 - 243 °C; MS (ESI) m/z (%): 486.1 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.06 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 1.8 Hz, 2H), 7.43 (dd, *J* = 15.9, 7.0 Hz, 3H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.50 (d, *J* = 5.3 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H).^{13}C NMR (101 MHz, DMSO) δ 170.19, 163.92 (d, J = 249.9 Hz), 160.40, 160.26, 157.64, 153.04, 150.67, 149.82, 149.31, 146.95, 135.97, 128.93 (d, J = 8.9 Hz), 123.46, 122.83, 121.86, 117.02 (d, J = 22.4 Hz), 115.64, 108.34, 103.71, 100.64, 99.56, 56.19. Anal. calcd. for $C_{27}H_{20}FN_3O_5$ (%): C, 66.80; H, 4.15; F, 3.91; N, 8.66; O, 16.48. Found (%): C, 66.76; H, 4.12; N, 8.62.

4.4.4. *N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)oxazole-2-carboxamide (**24b**)

Yield: 57%; m.p. 211 - 213 °C; MS (ESI) m/z (%): 629.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 11.17 (s, 1H), 8.48 (d, *J* = 5.2 Hz, 1H), 8.11 - 7.99 (m, 3H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.57 - 7.38 (m, 6H), 6.48 (d, *J* = 5.2 Hz, 1H), 4.19 (t, *J* = 6.0 Hz, 2H), 3.96 (s, 3H), 2.92 - 2.78 (m, 2H), 2.47 - 2.37 (m, 2H), 2.04 - 1.81 (m, 5H), 1.65 - 1.52 (m, 2H), 1.40 - 1.26 (m, 2H), 0.89 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.54, 162.54, 159.88, 154.52 (d, *J* = 250.2 Hz), 154.01 (d, *J* = 53.0 Hz), 152.69, 152.31, 149.91, 148.73, 146.94, 137.99 (d, J = 12.5 Hz), 135.55 (d, J = 9.6 Hz), 127.18 (d, *J* = 8.4 Hz), 124.02, 122.93 (d, *J* = 3.4 Hz), 122.44, 116.44 (d, *J* = 22.3 Hz), 116.09 (d, *J* = 3.4 Hz), 115.47, 109.49 (d, *J* = 23.2 Hz), 108.81, 102.28, 99.51, 67.52, 56.15, 55.41, 53.94, 33.99, 30.66, 26.28, 21.79. Anal. calcd. for $C_{35}H_{34}F_2N_4O_5$ (%): C, 66.87; H, 5.45; F, 6.04; N, 8.91; O, 12.72. Found (%): C, 66.84; H, 5.43; N, 8.93.

4.4.5. *N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole-5-carboxamide* (**25a**)

Yield: 61%; m.p. 247 - 249°C; MS (ESI) m/z (%): 487.2 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.71 (d, *J* = 5.9 Hz, 1H), 8.17 (dd, *J* = 8.6, 5.2 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.86 (s, 1H), 7.61 (s, 1H), 7.42 - 7.35 (m, 4H), 6.64 (d, *J* = 6.0 Hz, 1H), 4.11 (s, 3H), 4.09 (s, 3H). Anal. calcd. for $C_{26}H_{19}FN_4O_5$ (%): C, 64.20; H, 3.94; F, 3.91; N, 11.52; O, 16.44. Found (%): C, 64.13; H, 3.98; N, 11.51.

4.4.6. *N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole-5-carboxamide* (**25b**)

Yield: 61%; m.p. 136 - 137 °C; MS (ESI) m/z (%): 630.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 11.64 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.19 (dd, *J* = 8.7, 5.5 Hz, 2H), 8.05 (dd, *J* = 12.8, 2.3 Hz, 1H), 7.84 (d, *J* = 9.3 Hz, 1H), 7.60 - 7.37 (m, 6H), 6.52 (d, *J* = 5.0 Hz, 1H), 4.24 (t, *J* = 6.4 Hz, 3H), 3.97 (s, 3H), 2.96 (dd, *J* = 12.2, 5.1 Hz, 2H), 2.15 (s, 2H), 1.80 - 1.67 (m, 3H), 1.60 - 1.44 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 3H). Anal. calcd. for $C_{34}H_{33}F_2N_5O_5$ (%): C, 64.86; H, 5.28; F, 6.03; N, 11.12; O, 12.70. Found (%): C, 64.84; H, 5.23; N, 11.14.

4.4.7. *N*-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)isoxazole-3-carboxamide (**26a**)

Yield: 43%; m.p. 204 – 205 °C; MS (ESI) m/z (%): 486.1 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.04 - 7.92 (m, 5H), 7.52 (s, 1H), 7.42 (dd, *J* = 11.3, 6.3 Hz, 3H), 7.32 (d, *J* = 8.9 Hz, 2H), 6.50 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 163.08 (d, J = 247.6 Hz), 160.24, 154.42, 153.48, 153.02, 152.66, 150.69, 149.81, 149.30, 146.95, 135.88,

127.65 (d, J = 8.6 Hz), 124.18, 123.80, 123.77, 122.93, 121.81, 116.87 (d, J = 22.3 Hz), 115.64, 108.33, 103.72, 99.55, 56.18, 56.15. Anal. calcd. For $C_{27}H_{20}FN_3O_5$ (%): C, 66.80; H, 4.15; F, 3.91; N, 8.66; O, 16.48. Found (%): C, 66.82; H, 4.12; N, 8.63.

4.4.8. *N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)isoxazole-3-carboxamide (**26b**)

Yield: 61%; m.p. 197 – 199 ^{o}C; MS (ESI) m/z (%): 629.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 11.23 (s, 1H), 8.48 (d, *J* = 5.2 Hz, 1H), 8.06 (dd, *J* = 11.9, 3.3 Hz, 2H), 7.95 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.59 - 7.48 (m, 2H), 7.45 - 7.37 (m, 3H), 6.49 (d, *J* = 5.2 Hz, 1H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.96 (s, 3H), 2.88 (s, 2H), 2.51 - 2.37 (m, *J* = 1.6 Hz, 11H), 2.10 - 1.79 (m, 4H), 1.59 (d, *J* = 11.5 Hz, 2H), 1.41 - 1.27 (m, 1H), 1.22 - 1.10 (m, *J* = 11.7 Hz, 2H), 0.89 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 167.04, 160.78 (d, *J* = 225.9 Hz), 153.75 (d, *J* = 244.9 Hz), 154.12, 153.67, 152.89, 152.21, 150.00, 149.39, 146.77, 137.38 (d, *J* = 9.9 Hz), 137.00 (d, *J* = 11.9 Hz), 132.50 (d, *J* = 9.4 Hz), 127.72 (d, *J* = 8.2 Hz), 124.39 (d, *J* = 27.9 Hz), 123.71, 116.91 (d, *J* = 22.3 Hz), 116.51 (d, *J* = 294.0 Hz), 115.94 (d, *J* = 22.5 Hz), 109.90 (d, *J* = 22.6 Hz), 109.13, 102.67, 99.56, 66.91, 56.29, 54.49, 53.05, 32.73, 29.57, 25.28, 21.76. Anal. calcd. for $C_{35}H_{34}F_2N_4O_5$ (%): C, 66.87; H, 5.45; F, 6.04; N, 8.91; O, 12.72. Found (%): C, 66.86; H, 5.46; N, 8.95.

4.5.1 The preparation of ethyl 2-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)acetate (**27**)

Ethyl hydrogen malonate (0.70g, 5.25mmol) was added drop-wise to a solution of 4-fluoro-*N*-hydroxybenzimidamide (**17**, 0.78g, 5.0mmol), EDCI (1.5eq.) and triethylamine (1.01g, 10.0mmol) in dichloromethane in an ice bath. Upon completion of the addition, the reaction mixture was removed from the ice bath and placed in room temperature for 8h and monitored by thin-layer chromatography (TLC). The mixture was washed with 10% K_2CO_3 (150 mL×3) followed by brine (150 mL×1), and the organic phase was separated, dried and evaporated to yield ethyl 3-((4-fluorobenzimidamido)oxy)-3-oxopropanoate as yellow solid. MS (ESI) m/z (%): 269.1 $[M + H]^+$.
The intermidate was added to $POCl_3$ 15mL and then heated to 95 ^{o}C for 3h. The reaction mixture was evaporated and then poured into water, basified with sodium hydroxide to PH = 7, filtered and obtain the ethyl 2-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)acetate as yellow solid. MS (ESI) m/z (%): 251.3 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J*= 3.2, 3.4 Hz 2H), 7.42 (t, *J*= 8.4 Hz, 2H), 4.36 (s, 2H), 4.17 (q, *J*= 7.4 Hz 2H), 1.20 (t, *J*= 7.2 Hz 3H).

4.5.2 The preparation of 2-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)acetyl chloride (**28**)

The ethyl 2-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)acetate (**27**, 12.5g, 50mmol) was dissolved in THF 200mL added methanol and a solution of LiOH (1.8g, 75mmol) in water 15mL. The reaction mixture was stirred at room temperature for 5 h and monitored by thin-layer chromatography (TLC). The reaction was extracted with dichloromethane (70 mL × 3) and the aqueous phase was acidified with 1N HCl and the corresponding aromatic ring-substituted heterocyclic carboxylic acid was isolated as white solid.

2-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)acetic acid (7.7g, 35mmol), DMF (2 drops), anhydrous dichlromethane were added under a N_2 atomosphere. Oxalyl chloride (5.28g, 42mmol) was drop-wise added at 0 ^{o}C. The reaction mixture was stirred at room temperature for 4h. The mixture was then removed

in vacuo, and the resulting 5-(4-fluorophenyl)-1,3,4-oxadiazole-2-carbonyl chloride (**28**) was used immediately without further purification.

4.5.3 The preparation of *N*-(3-fluoro-4-((6-methoxy-7- (3-(4-methylpiperidin-1-yl)propoxy)quin-olin-4-yl) oxy)phenyl)-2-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)acetamide (**41a**)

Triethylamine (0.2g, 2.0mmol) was added to a solution of 5-(4-fluorophenyl)-1,3,4-oxadiazole-2-carbonyl chloride **29** and **10** (0.493g, 1.0mmol) in DCM. The reaction mixture was placed at room temperature for 2 h. The solvent was concentrated in vacuum and the residue was resolved with dichloromethane (20 mL), washed with water (10 mL× 3), brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was purified by column chromatography to afford the target compound. Yield: 51%; m.p. 214 - 216 ^oC; MS (ESI) m/z (%): 644.2 $[M + H]^+$; ^1H NMR (600 MHz, DMSO) δ 11.26 (s, 1H), 8.53 (d, J = 4.1 Hz, 1H), 8.09 (m, 2H), 7.90 (d, J = 12.7 Hz, 1H), 7.59 (s, 1H), 7.48 (m, 5H), 6.54 (d, J = 3.4 Hz, 1H), 4.41 (s, 2H), 4.28 (t, J = 5.2 Hz, 2H), 3.98 (s, 3H), 3.51 (d, J = 11.6 Hz, 2H), 3.21 (s, 3H), 2.94 (dd, J = 21.9, 10.7 Hz, 2H), 2.32 (s, 2H), 1.79 (d, J = 13.4 Hz, 2H), 1.63 (s, 1H), 1.51 (dd, J = 24.2, 11.9 Hz, 2H), 0.93 (d, J = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 175.48, 32.7332.7350, 164.52, 164.45 (d, *J* = 249.3 Hz), 159.93, 153.85 (d, *J* = 245.7 Hz), 152.12, 150.00, 149.16, 138.13 (d, *J* = 9.8 Hz), 136.31 (d, *J* = 11.9 Hz), 130.03 (d, *J* = 9.0 Hz), 124.68, 123.10, 117.08, 116.86, 115.87 (d, *J* = 141.7 Hz), 109.04, 108.54 (d, *J* = 23.0 Hz), 102.66, 99.66, 66.59, 56.35, 54.06, 52.41, 35.48, 31.26, 28.64, 23.72, 21.58; Anal. calcd. for $C_{35}H_{35}F_2N_5O_5$ (%): C, 65.31; H, 5.48; F, 5.90; N, 10.88; O, 12.43. Found (%): C, 65.25; H, 5.35; N, 10.80.

4.6 General preparation of **42a~42e**.

Starting from 2-amino-1-(4-fluorophenyl)ethan-1-one (**14**), the target compounds were prepared by the method metioned above.

4.6.1

N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluoro phenyl)oxazol-2-yl)acetamide (**42a**)

Yield: 55%; m.p. 221 - 223 ^oC; MS (ESI) m/z (%): 643.1 $[M + H]^+$; ^1H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 7.87 (d, *J* = 13.1 Hz, 1H), 7.76 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.64 (s, 1H), 7.54 (s, 1H), 7.49 - 7.29 (m, 5H), 6.46 (d, *J* = 4.9 Hz, 1H), 4.22 (t, *J* = 6.0 Hz, 2H), 4.07 (s, 2H), 3.95 (s, 3H), 3.24 - 2.96 (m, 4H), 2.19 - 1.99 (m, 2H), 1.76 - 1.61 (m, 2H), 1.45 (s, 2H), 1.34 - 1.15 (m, *J* = 15.6, 8.2 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H). Anal. calcd. for $C_{36}H_{36}F_2N_4O_5$ (%): C, 67.28; H, 5.65; F, 5.91; N, 8.72; O, 12.45. Found (%): C, 67.13; H, 5.60; N, 8.73.

4.6.2

N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)oxaz ol-2-yl)acetamide (**42b**)

Yield: 56%; m.p. 157 - 158 ^oC; MS (ESI) m/z (%): 631.2 $[M + H]^+$; ^1H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 7.87 (d, *J* = 12.7 Hz, 1H), 7.76 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.64 (s, 1H), 7.53 (s, 1H), 7.46 (d, *J* = 4.2 Hz, 1H), 7.41 (s, 1H), 7.34 (t, *J* = 8.9 Hz, 1H), 6.45 (d, *J* = 5.2 Hz, 1H),

4.21 (t, *J* = 6.1 Hz, 1H), 4.07 (s, 2H), 3.95 (s, 2H), 3.61 (s, 4H), 2.47 (m, *6*H), 2.00 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 165.87, 161.97 (d, *J* = 452.7 Hz), 161.16, 158.68, 154.57 (d, *J* = 203.2 Hz), 152.29, 150.71, 150.02, 149.33, 146.76, 137.61, 137.44, 136.30, 136.19, 126.63, 126.54, 124.67, 123.06, 119.38, 116.77, 116.56, 116.45, 114.98, 109.05, 108.58, 108.35, 102.51, 99.98, 99.53, 75.08, 66.99, 66.06, 56.28, 55.05, 53.35, 37.09; Anal. calcd. for $C_{34}H_{32}F_2N_4O_6$ (%): C, 64.75; H, 5.11; F, 6.03; N, 8.88; O, 15.22. Found (%): C, 64.68; H, 5.10; N, 8.82;.

4.6.3

N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)oxazol-2-yl)acetamide (**42c**)

Yield: 58%; m.p. 168 - 169 ^{o}C; MS (ESI) m/z (%): 644.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 8.47 (d,*J* = 5.2 Hz, 1H), 7.87 (d, *J* = 12.9 Hz, 1H), 7.76 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.64 (s, 1H), 7.42 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.19 (t, *J* = 6.1 Hz, 2H), 4.07 (s, 2H), 3.95 (s, 3H), 2.70 - 2.52 (m, 8H), 2.34 (s, 3H), 2.04 - 1.95(m,2H). Anal. calcd. for $C_{35}H_{35}F_2N_5O_5$ (%): C, 65.31; H, 5.48; F, 5.90; N, 10.88; O, 12.43.Found(%):C, 65.20; H, 5.45; N, 10.78.

4.6.4 *N*-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)oxazol-2-yl)acetamide (**42d**)

Yield: 53%; m.p. 120 - 121^{o}C; MS (ESI) m/z (%): 615.2 [M + H]+ ; ^{1}H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 8.48 (d,*J* = 5.2 Hz, 1H), 7.87 (dd, *J* = 12.6, 0.7 Hz, 1H), 7.76 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.64 (s, 1H), 7.56 (s, 1H), 7.48 - 7.42 (m, 3H), 7.34 (t, *J* = 8.9 Hz, 2H), 6.47 (d, *J* = 4.8 Hz, 1H)， 4.26 (t, *J* = 6.0 Hz, 2H), 4.07 (s, 2H), 3.96 (s, 3H), 3.07 (dd, *J* = 13.9, 6.8 Hz, 5H), 2.25 - 2.13 (m, 2H), 1.98 - 1.86 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 165.89, 162.39 (d, *J* = 246.0 Hz), 159.77, 158.68, 153.88 (d, *J* = 246.5 Hz), 151.94, 150.71, 149.91, 149.45, 146.68, 138.23 (d, *J* = 10.1 Hz), 136.23 (d, *J* = 12.5 Hz), 132.56 (d, *J* = 10.0 Hz), 126.59 (d, *J* = 8.5 Hz), 124.65, 123.05, 116.67 (d, *J* = 22.3 Hz), 116.49, 115.17, 109.28, 108.49 (d, *J* = 22.8 Hz), 102.66, 99.63, 66.32, 56.36, 53.89, 52.15, 37.09, 25.66, 23.07; Anal. calcd. For $C_{34}H_{32}F_2N_4O_5$(%): C, 66.44; H, 5.25; F, 6.18; N, 9.12; O, 13.01. Found (%): C, 66.34; H, 5.26; N, 9.10.

4.6.5

N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)oxazol-2-yl)acetamide (**42e**)

Yield: 52%; m.p. 104 - 106^{o}C; MS (ESI) m/z (%): 629.7 [M + H]+; ^{1}H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 7.87 (d, *J* = 13.3 Hz, 1H), 7.76 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.64 (s, 1H), 7.54 (s, 1H), 7.47 (dd, *J* = 26.5, 22.0 Hz, 3H), 7.34 (t, *J* = 8.9 Hz, 2H), 6.46 (d, *J* = 5.0 Hz, 1H), 4.22 (t, *J* = 6.1 Hz, 2H), 4.07 (s, 2H), 3.96 (s, 3H), 2.61 (dd, *J* = 29.0, 16.6 Hz, 6H), 2.11 (s, 2H), 1.62 (s, 4H), 1.46 (s, 2H).Anal. calcd. for $C_{35}H_{34}F_2N_4O_5$ (%): C, 66.87; H, 5.45; F, 6.04; N, 8.91; O, 12.72. Found (%): C, 66.85; H, 5.40; N, 8.88.

4.7. General preparation of **43a~43i** and **44a~47e**.

Starting from 4-fluorobenzohydrazide (**11**), the compounds were prepared by the method mentioned above.

4.7.1 *N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide (**43a**)

Yield: 59%; m.p. 123 - 125°C; MS (ESI) m/z (%): 644.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 8.08 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.86 (d, *J* = 12.3 Hz, 1H), 7.56 - 7.37 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.29 (s, 2H), 4.20 (t, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 3.12 - 2.94 (m, 2H), 2.77 - 2.57 (m, 2H), 2.07 (d, *J* = 17.0 Hz, 4H), 1.64 (d, *J* = 12.3 Hz, 2H), 1.49 - 1.32 (m, 1H), 1.23 (s, 2H), 0.90 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 165.03, 164.58 (d, *J* = 250.4 Hz), 164.26, 162.35, 159.68, 153.90 (d, *J* = 246.1 Hz), 152.30, 150.02, 149.32, 146.82, 138.01 (d, *J* = 9.8 Hz), 136.39 (d, *J* = 12.2 Hz), 129.66 (d, *J* = 9.1 Hz), 124.70, 120.44 (d, *J* = 3.1 Hz), 117.36, 117.13, 115.76 (d, *J* = 158.1 Hz), 109.11, 108.56 (d, *J* = 23.2 Hz), 102.53, 99.53, 67.06, 56.28, 54.85, 53.47, 34.23, 28.46, 27.14, 26.11, 22.08; Anal. calcd. For $C_{35}H_{35}F_2N_5O_5$ (%): C, 65.31; H, 5.48; F, 5.90; N, 10.88; O, 12.43. Found (%): C, 65.25; H, 5.45; N, 10.83.

4.7.2 *N*-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide (**43b**)

Yield: 62%; m.p. 181- 183 °C; MS (ESI) m/z (%): 632.8 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.86 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.11 - 8.05 (m, *J* = 8.8, 5.4 Hz, 1H), 7.85 (d, *J* = 13.7 Hz, 1H), 7.55 - 7.38 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.28 (s, 2H), 4.21 (t, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 3.61 (s, 4H), 2.42 (m, 6H), 2.00 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 165.03, 164.58 (d, *J* = 248.9 Hz), 164.28, 162.34, 159.69, 153.89 (d, *J* = 246.2 Hz), 152.32, 150.03, 149.32, 146.78, 137.98 (d, *J* = 9.9 Hz), 136.40 (d, *J* = 11.8 Hz), 129.67 (d, *J* = 9.4 Hz), 124.70, 120.42 (d, *J* = 2.9 Hz), 117.35, 117.13, 115.76 (d, *J* = 160.1 Hz), 109.05, 108.59 (d, *J* = 23.6 Hz), 102.53, 99.52, 67.04, 66.15, 56.27, 55.11, 53.46, 34.21, 25.64; Anal. calcd. For $C_{33}H_{31}F_2N_5O_6$ (%): C, 62.75; H, 4.95; F, 6.02; N, 11.09; O, 15.20. Found (%): C, 62.73; H, 4.97; N, 11.05.

4.7.3 *N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide (**43c**)

Yield: 53%; m.p. 122 - 124 °C; MS (ESI) m/z (%): 645.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 8.47 (d, *J* = 5.0 Hz, 1H), 8.08 (m, 2H), 7.92 - 7.77 (m, 1H), 7.56 - 7.34 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.28 (s, 2H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.95 (s, 3H), 3.38 (dd, *J* = 14.0, 7.0 Hz, 3H), 2.40 (m, 8 H), 2.20 (s, 3H), 2.02 - 1.92 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 165.03, 164.58 (d, *J* = 250.3 Hz), 164.28, 162.34, 159.69, 154.00 (d, *J* = 224.8 Hz), 152.40, 150.04, 149.31, 146.80, 137.83 (d, *J* = 16.3 Hz), 136.41 (d, *J* = 12.3 Hz), 129.67 (d, *J* = 9.1 Hz), 124.71, 120.15 (d, *J* = 50.2 Hz), 117.36, 117.13, 115.74 (d, *J* = 163.6 Hz), 112.16, 108.97, 99.98, 99.50, 67.15, 56.27, 54.70, 54.60, 52.51, 34.21, 26.34, 18.99; Anal. calcd. For $C_{34}H_{34}F_2N_6O_5$ (%): C, 63.35; H, 5.32; F, 5.89; N, 13.04; O, 12.41. Found (%): C, 63.33; H, 5.30; N, 13.02.

4.7.4 *N*-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide (**43d**)

Yield: 51%; m.p. 131 - 133 °C; MS (ESI) m/z (%): 616.7 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.86 (s, 1H), 8.47 (d, *J* = 4.7 Hz, 1H), 8.08 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.86 (d, *J* = 13.7 Hz, 1H), 7.56 - 7.36

(m, 6H), 6.45 (d, *J* = 4.9 Hz, 1H), 4.28 (s, 2H), 4.22 (t, *J* = 6.2 Hz, 2H), 3.95 (s, 3H), 2.71 (d, *J* = 33.6 Hz, 6H), 2.08 - 1.98 (m, 2H), 1.76 (s, 4H); ^{13}C NMR (101 MHz, DMSO) δ 165.05, 164.59 (d, *J* = 250.6 Hz), 164.28, 162.35, 159.72, 152.39 (d, *J* = 58.4 Hz), 149.95, 149.40, 146.74, 138.37 (d, *J* = 62.7 Hz), 136.74 (d, *J* = 59.2 Hz), 129.67 (d, *J* = 8.6 Hz), 124.72, 120.43, 117.36, 117.14, 115.84 (d, *J* = 150.5 Hz), 108.95 (d, *J* = 48.2 Hz), 102.46, 99.57, 66.59, 56.33, 53.93, 52.29, 34.21, 26.51, 23.24; Anal. calcd. for $C_{33}H_{31}F_2N_5O_5$ (%): C, 64.38; H, 5.08; F, 6.17; N, 11.38; O, 12.99. Found (%): C, 64.35; H, 5.04; N, 11.35.

4.7.5 *N*-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide (**43e**)

Yield: 57%; m.p. 177 - 179 °C; MS (ESI) m/z (%): 630.3 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.08 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.86 (d, *J* = 13.9 Hz, 1H), 7.56 - 7.36 (m, 6H), 6.45 (d, *J* = 5.2 Hz, 1H), 4.29 (s, 2H), 4.21 (t, *J* = 6.2 Hz, 3H), 3.95 (s, 2H), 2.80 - 2.53 (m, 6H), 2.04 (s, 2H), 1.58 (s, 4H), 1.43 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.44 (d, *J* = 80.2 Hz), 164.28, 163.34, 162.35, 159.70, 153.66 (d, *J* = 291.7 Hz), 149.99, 149.36, 146.76, 138.00 (d, *J* = 7.4 Hz), 137.46 (d, *J* = 11.1 Hz), 129.67 (d, *J* = 9.2 Hz), 124.72, 120.43, 117.36, 117.13, 115.78 (d, *J* = 154.6 Hz), 109.13, 108.59 (d, *J* = 23.1 Hz), 102.56, 99.55, 66.95, 56.29, 54.95, 53.77, 34.22, 25.37, 24.71, 20.11 . Anal. calcd. For $C_{34}H_{33}F_2N_5O_5$(%): C, 64.86; H, 5.28; F, 6.03; N, 11.12; O, 12.70. Found (%): C, 64.83; H, 5.25; N, 11.14.

4.7.6 2-(5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)-*N*-(4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)acetamide (**43f**)

Yield: 65%; m.p. 131 - 132 °C; MS (ESI) m/z (%): 705.7 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO) δ 11.09 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.88 (dd, *J* = 12.9, 2.0 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.56 (s, 1H), 7.52 - 7.43 (m, 3H), 4.32 (s, 2H), 4.27 (t, *J* = 5.9 Hz, 2H), 3.96 (s, 3H), 3.51 (d, *J* = 11.1 Hz, 2H), 3.22 (s, 2H), 2.92 (dd, *J* = 36.2, 14.3 Hz, 2H), 2.30 (s, 2H), 1.80 (d, *J* = 13.5 Hz, 2H), 1.62 (s, 1H), 1.48 (dd, *J* = 24.4, 11.7 Hz, 2H), 0.93 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 165.03, 162.56, 162.00 (d, *J* = 452.5 Hz), 153.87 (d, *J* = 245.9 Hz), 151.98, 149.91, 149.37, 146.66, 138.12 (d, *J* = 10.0 Hz), 137.23, 136.30 (d, *J* = 12.2 Hz), 130.17, 128.76, 124.69, 122.61, 116.56, 115.14, 109.30, 108.54 (d, *J* = 23.1 Hz), 102.61, 99.61, 66.52, 56.32, 54.09, 52.46, 34.21, 31.33, 28.62, 23.78, 21.58; Anal. calcd. For $C_{35}H_{35}BrFN_5O_5$ (%): C, 59.66; H, 5.01; Br, 11.34; F, 2.70; N, 9.94; O, 11.35. Found (%): C, 59.63; H, 5.02; N, 9.95.

4.7.7 2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)acetamide (**43g**)

Yield: 64%; m.p. 96 - 98 °C; MS (ESI) m/z (%): 661.0 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO) δ 10.93 (s, 1H), 8.48 (d, *J* = 5.2 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.86 (dd, *J* = 3.0 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.54 (s, 1H), 7.49 - 7.40 (m, 3H), 6.46 (d, *J* = 5.1 Hz, 1H), 4.30 (s, 2H), 4.23 (t, *J* = 6.0 Hz, 2H), 3.96 (s, 3H), 3.21 (s, 2H), 3.11 - 2.98 (m, 2H), 2.97 - 2.76 (m, 2H), 2.14 (s, 2H), 1.71 (d, *J* = 11.0 Hz, 2H), 1.50 (s, 1H), 1.33 (d, *J* = 31.8 Hz, 2H), 0.92 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 165.00, 162.54, 161.97 (d, *J* = 458.3 Hz), 153.89 (d, *J* = 246.5 Hz), 152.15, 149.97, 149.35, 146.78, 138.05 (d, *J* = 9.8 Hz), 137.23, 136.36 (d, *J* = 12.2 Hz), 130.15, 128.74, 124.68, 122.61, 116.56, 115.04, 109.20, 108.56 (d, *J* =

22.7 Hz), 102.55, 99.56, 66.83, 56.28, 54.39, 52.90, 46.04, 34.23, 32.49, 29.41, 25.10, 21.69, 9.21; Anal. calcd. For $C_{35}H_{35}ClFN_5O_5$ (%):C, 63.68; H, 5.34; Cl, 5.37; F, 2.88; N, 10.61; O, 12.12. Found (%): C, 63.65; H, 5.36; N, 10.56.

4.7.8 *N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5 -phenyl-1,3,4-oxadiazol-2-yl)acetamide (**43h**)

Yield: 54%; m.p. 210 - 212 ^{o}C; MS (ESI) m/z (%): 626.9 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO) δ 11.33 (s, 1H), 8.63 (s, 1H), 8.02 (d, *J* = 6.9 Hz, 2H), 7.94 (dd, *J* = 12.9, 1.7 Hz, 1H), 7.68 - 7.57 (m, 6H), 6.68 (s, 1H), 4.34 (s, 2H), 4.30 (t, *J* = 5.9 Hz, 2H), 4.00 (s, 3H), 3.48 (d, *J* = 11.4 Hz, 2H), 3.25 - 3.19 (m, 2H), 2.96 - 2.87 (m, 2H), 2.38 - 2.31 (m, 2H), 1.87 - 1.77 (m, 4H), 1.75 - 1.68 (m, 1H), 0.92 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.20, 164.99, 162.37, 154.15 (d, *J* = 146.5 Hz), 152.43, 150.68, 146.91, 138.69 (d, *J* = 9.1 Hz), 135.74 (d, *J* = 13.1 Hz), 132.50, 129.97, 126.94, 124.59, 123.76, 116.66, 115.33, 108.67 (d, *J* = 1.0 Hz), 108.44, 102.96, 100.09, 66.95, 56.63, 53.86, 52.52, 34.19, 23.52, 22.83, 21.85; Anal. calcd. For $C_{35}H_{36}FN_5O_5$ (%): C, 65.31; H, 5.48; F, 5.90; N, 10.88; O, 12.43. Found (%): C, 65.32; H, 5.45; N, 10.85.

4.7.9 *N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5 -(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)acetamide (**43i**)

Yield: 65%; m.p. 119 - 121 ^{o}C; MS (ESI) m/z (%): 656.8 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO) δ 10.35 (s, 1H), 8.48 (d, *J* = 5.1 Hz, 1H), 7.87 (d, *J* = 13.9 Hz, 2H), 7.94 (dd, *J* = 12.9, 1.7 Hz, 1H), 7.55-7.48 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.32 (s, 2H), 4.25 (t, *J* = 5.9 Hz, 2H), 3.95 (s, 3H), 3.45 (d, *J* = 11.1 Hz, 2H), 3.16 (s, 2H), 2.88 (m, 2H), 2.23 (s, 2H), 1.78 (d, *J* = 11.5 Hz, 2H), 1.58 (s, 1H), 1.39 (dd, *J* = 21.4, 14.7 Hz, 2H), 0.93 (d, *J* = 5.0 Hz, 3H); Anal. calcd. For $C_{36}H_{38}FN_5O_6$ (%): C, 67.19; H, 5.80; F, 3.04; N, 11.19; O, 12.78. Found (%): C, 67.14; H, 5.81; N, 11.15.

4.7.10

N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluoro phenyl)-1,3,4-oxadiazol-2-yl)propanamide (**44a**)

Yield: 64%; m.p. 123 - 125 ^{o}C; MS (ESI) m/z (%): 658.2 $[M + H]^+$;^{1}H NMR (400 MHz, DMSO) δ 10.86 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 8.08 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.88 (d, *J* = 11.9 Hz, 1H), 7.56 - 7.36 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 1H), 4.19 (t, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 2.95 (d, *J* = 9.5 Hz, 2H), 2.57 (s, 2H), 2.16 - 1.94 (m, 4H), 1.71 (d, *J* = 7.1 Hz, 3H), 1.61 (d, *J* = 12.1 Hz, 2H), 1.36 (s, 1H), 1.21 - 1.09 (m, 2H), 0.89 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 168.64, 165.87, 163.35, 161.53 (d, *J* = 365.8 Hz), 153.90 (d, *J* = 245.8 Hz), 152.36, 150.04, 149.30, 146.82, 138.05 (d, *J* = 10.0 Hz), 136.44 (d, *J* = 12.1 Hz),129.72 (d, *J* = 9.0 Hz), 124.70, 120.41, 117.23 (d, *J* = 22.5 Hz), 116.71, 114.94, 109.02, 108.84, 108.61, 102.50, 99.50, 67.17, 56.26, 54.96, 53.67, 33.91, 30.46, 26.23, 22.12, 15.36. Anal. calcd. for $C_{36}H_{37}F_2N_5O_5$ (%): C, 65.74; H, 5.67; F, 5.78; N, 10.65; O, 12.16. Found (%): C, 65.70; H, 5.63; N, 10.63.

4.7.11

N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,

4-oxadiazol-2-yl)propanamide (**44b**)

Yield: 63%; m.p. 122 - 124 °C; MS (ESI) m/z (%): 646.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.91 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.08 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.88 (dd, *J* = 12.9, 1.8 Hz, 1H), 7.57 - 7.35 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.40 (t, *J* = 7.0 Hz, 1H), 4.21 (t, *J* = 6.3 Hz, 2H), 3.96 (s, 3H), 3.64 - 3.59 (m, 3H), 2.55 (m, 2H), 2.46 (s, 4H), 2.07 - 1.94 (m, 2H), 1.71 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 168.68, 165.87, 163.36, 161.96 (d, *J* = 445.4 Hz), 153.89 (d, *J* = 245.9 H) 152.38, 150.03, 149.31, 146.75, 138.02 (d, *J* = 10.1 Hz), 136.44 (d, *J* = 12.8 Hz), 129.72 (d, *J* = 9.0 Hz), 124.70, 120.40, 117.32, 117.21 (d, *J* = 22.5 Hz), 114.93, 108.93, 108.63, 102.50, 99.48, 67.11, 66.41, 56.26, 55.20, 53.64, 46.16, 25.87, 15.35, 9.06. Anal. calcd. for $C_{34}H_{33}F_2N_5O_6$(%): C, 63.25; H, 5.15; F, 5.88; N, 10.85; O, 14.87. Found (%): C, 63.23; H, 5.14; N, 10.84.

4.7.12 *N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)propanamide (**44c**)

Yield: 68%; m.p. 120 - 123 °C; MS (ESI) m/z (%): 669.0 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.11 - 8.05 (m, 2H), 7.89 (dd, *J* = 12.9, 2.0 Hz, 1H), 7.55 - 7.38 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 1H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.95 (s, 3H), 3.04 - 2.96 (m, 3H), 2.57 - 2.51 (m, 8H), 2.28 (s, 3H), 2.02 - 1.94 (m, 2H), 1.70 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 168.67, 165.89, 163.36, 161.67 (d, *J* = 443.3 Hz), 153.89 (d, *J* = 245.9 H), 152.38, 150.04, 149.31, 146.83, 138.11 (d, *J* = 10.3 Hz), 136.40 (d, *J* = 12.3 Hz), 129.73 (d, *J* = 9.0 Hz), 124.70, 120.45, 117.23 (d, *J* = 22.5 Hz, 3H), 116.71, 114.92, 109.00, 108.82, 108.59, 102.49, 99.50, 67.10, 56.27, 54.52, 52.23, 46.00, 45.19, 26.31, 15.38, 9.26; Anal.calcd. for $C_{36}H_{37}F_2N_5O_5$(%): C, 63.82; H, 5.51; F, 5.77; N, 12.76; O, 12.14. Found (%): C, 63.84; H, 5.46; N, 12.75.

4.7.13

N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)propanamide (**44d**)

Yield: 54%; m.p. 144 - 146 °C; MS (ESI) m/z (%): 630.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.99 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.12 - 8.05 (m, 2H), 7.90 (dd, *J* = 13.0, 1.7 Hz, 1H), 7.58 - 7.39 (m, 6H), 6.46 (d, *J* = 5.1 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 1H), 4.24 (t, *J* = 6.1 Hz, 2H), 3.96 (s, 3H), 2.99 (d, *J* = 6.9 Hz, 7H), 2.22 - 2.05 (m, 2H), 1.85 (s, 4H), 1.70 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 168.68, 165.89, 163.35, 161.92 (d, *J* = 441.7 Hz),153.89 (d, *J* = 246.1 Hz), 152.15, 149.96, 149.36, 146.78, 138.13 (d, *J* = 9.5 Hz), 136.39 (d, *J* = 11.8 Hz), 129.72 (d, *J* = 8.8 Hz), 124.70, 120.45, 117.23 (d, *J* = 22.4 Hz), 116.67, 115.05, 109.16, 108.81, 108.58, 102.56, 99.54, 66.70, 56.31, 53.84, 52.26, 46.01, 26.82, 23.33, 15.39; Anal. calcd. for $C_{34}H_{33}F_2N_5O_5$ (%): C, 65.06; H, 5.46; F, 3.03; N, 11.16; O, 15.29. Found (%): C, 65.02; H, 5.43; N, 11.12.

4.7.14

N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)propanamide (**44e**)

Yield: 52%; m.p. 119 - 120 °C; MS (ESI) m/z (%): 644.2 $[M + H]^+$;^{1}H NMR (400 MHz, DMSO) δ 10.91 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.15 - 8.03 (m, 2H), 7.88 (dd, *J* = 12.7, 1.2 Hz, 1H), 7.57 - 7.32 (m,

6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 1H), 4.20 (t, *J* = 6.2 Hz, 2H), 3.95 (s, 3H), 2.90 (dd, *J* = 16.4, 8.4 Hz, 2H), 2.59 (d, *J* = 4.1 Hz, 4H), 2.09 - 1.97 (m, 2H), 1.70 (d, *J* = 7.1 Hz, 3H), 1.61 - 1.51 (m, 4H), 1.42 (d, *J* = 3.8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ 168.64, 165.88, 163.37, 161.93 (d, *J* = 444.1 Hz, 1H), 153.90 (d, *J* = 246.7 Hz, 1H), 152.32, 150.03, 149.33, 146.82, 138.07 (d, *J* = 9.6 Hz, 0H), 136.43 (d, *J* = 13.3 Hz, 0H), 129.73 (d, *J* = 9.0 Hz, 2H), 124.71, 120.42, 117.24 (d, *J* = 22.3 Hz, 2H), 116.72, 114.96, 109.08, 108.83, 108.61, 102.52, 99.52, 67.09, 56.28, 55.20, 54.11, 46.10, 25.85, 25.32, 23.84, 15.37. Anal. calcd. for $C_{35}H_{35}F_2N_5O_5$ (%): C, 65.31; H, 5.48; F, 5.90; N, 10.88; O, 12.43. Found (%): C, 65.25; H, 5.44; N, 10.84.

4.7.15

N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluoro phenyl)-1,3,4-oxadiazol-2-yl)butanamide (**45a**)

Yield: 64%; m.p. 127 - 129°C; MS (ESI) m/z (%): 672.4 $[M + H]^+$; ^{1}H NMR (600 MHz, DMSO) δ 10.90 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.08 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.89 (dd, *J* = 12.9, 2.0 Hz, 1H), 7.54 (s, 1H), 7.52 - 7.44 (m, 4H), 7.42 (s, 1H), 6.47 (d, *J* = 5.1 Hz, 1H), 4.22 (t, *J* = 6.8 Hz, 3H), 3.96 (s, 3H), 3.39 (dd, *J* = 14.0, 7.0 Hz, 2H), 3.13 (s, 2H), 2.79 (s, 2H), 2.26 - 2.15 (m, 2H), 2.10 (s, 2H), 1.69 (d, *J* = 11.4 Hz, 2H), 1.47 (s, 1H), 1.25 (d, *J* = 13.8 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 167.67, 165.03, 164.61 (d, *J* = 250.1 Hz), 164.14, 153.90 (d, *J* = 245.0 Hz), 152.19, 149.98, 149.36, 146.78, 137.95 (d, *J* = 9.1 Hz), 136.48 (d, *J* = 12.5 Hz), 129.74 (d, *J* = 9.2 Hz), 124.70, 120.43, 117.24 (d, *J* = 22.5 Hz); 6.75, 115.01, 109.16, 108.87, 108.65, 102.60, 99.54, 66.89, 56.29, 54.55, 53.11, 46.41, 32.89, 29.61, 25.25, 23.47, 21.80, 12.10. Anal. calcd. for $C_{37}H_{39}F_2N_5O_5$(%): C, 66.16; H, 5.85; F, 5.66; N, 10.43; O, 11.91. Found (%): C, 66.12; H, 5.83; N, 10.42.

4.7.16

N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3, 4-oxadiazol-2-yl)butanamide (**45b**)

Yield: 53%; m.p. 128 - 129°C; MS (ESI) m/z (%): 660.2 $[M + H]^+$;^{1}H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 8.46 (d, *J* = 5.0 Hz, 1H), 8.07 (m, 2H), 7.89 (d, *J* = 13.7 Hz, 1H), 7.57 - 7.40 (m, 6H), 6.46 (d, *J* = 5.0 Hz, 1H), 4.21 (m, 4H), 3.95 (s, 3H), 3.64 (s, 4H), 3.09 (m, 2H), 2.19 (m, 3H), 2.03 (s, 2H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 167.65, 165.02, 164.61 (d, *J* = 249.9 Hz), 164.14, 153.91 (d, *J* = 245.5 Hz), 152.33, 150.03, 149.32, 146.82, 137.93 (d, *J* = 10.2 Hz), 136.51 (d, *J* = 12.1 Hz), 129.74 (d, *J* = 9.2 Hz), 124.70, 120.41, 117.24 (d, *J* = 22.3 Hz), 116.74, 114.96, 109.06, 108.89, 108.66, 102.57, 99.50, 67.04, 56.28, 55.13, 53.52, 46.42, 46.15, 23.47, 12.10, 9.08; Anal. calcd. For $C_{35}H_{35}F_2N_5O_6$ (%): C, 63.72; H, 5.35; F, 5.76; N, 10.62; O, 14.55. Found (%): C, 63.73; H, 5.33; N, 10.61.

4.7.17

N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluoro phenyl)-1,3,4-oxadiazol-2-yl)butanamide (**45c**)

Yield: 54%; m.p.154 - 155°C; MS (ESI) m/z (%): 673.7 $[M + H]^+$;^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.45 (t, *J* = 4.9 Hz, 1H), 8.07 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.89 (dd, *J* = 12.9, 1.7 Hz, 1H), 7.54 - 7.43 (m, 1H), 7.39 (s, 1H), 6.45 (d, *J* = 5.2 Hz, 1H), 4.21 - 4.15 (m, *J* = 10.2, 6.2 Hz, 3H), 3.95 (s, 3H), 2.51

- 2.31 (m, 10H), 2.28 - 2.13 (m, 7H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 167.67, 165.03, 164.60 (d, *J* = 249.6 Hz), 164.13, 153.90 (d, *J* = 245.7 Hz), 152.40, 150.05, 149.31, 146.84, 137.95 (d, *J* = 10.1 Hz), 136.50 (d, *J* = 12.2 Hz), 129.74 (d, *J* = 9.3 Hz), 124.70, 120.44, 117.24 (d, *J* = 22.6 Hz); 116.73, 114.92, 109.00, 108.88, 108.65, 102.01, 99.50, 67.15, 56.27, 54.81, 54.65, 52.64, 46.40, 46.08, 45.62, 26.40, 23.48, 12.09; Anal. calcd. For $C_{36}H_{38}F_2N_6O_5$(%): C, 64.27; H, 5.69; F, 5.65; N, 12.49; O, 11.89. Found (%): C, 64.23; H, 5.70; N, 12.45.

4.7.18

N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)butanamide (**45d**)

Yield: 55%; m.p. 133 - 134^{o}C; MS (ESI) m/z (%): 643.7 $[M + H]^+$;^{1}H NMR (400 MHz, DMSO) δ 10.91 (s, 1H), 8.46 (t, *J* = 4.8 Hz, 1H), 8.07 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.88 (dd, *J* = 14.2, 12.2 Hz, 1H), 7.56 - 7.36 (m, 6H), 6.46 (d, *J* = 5.1 Hz, 1H), 4.27 - 4.19 (m, 3H), 3.96 (s, 3H), 2.89 (d, *J* = 23.0 Hz, 6H), 2.25 - 2.14 (m, 2H), 2.14 - 2.04 (m, 2H), 1.82 (s, 4H), 1.04 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 167.67, 165.03, 164.61 (d, *J* = 251.0 Hz), 164.14, 153.90 (d, *J* = 247.6 Hz), 152.21, 150.00, 149.37, 146.81, 137.95 (d, *J* = 8.9 Hz), 136.50 (d, *J* = 11.6 Hz), 129.74 (d, *J* = 9.7 Hz), 124.71, 120.45, 117.24 (d, *J* = 22.3 Hz, 1H), 116.77, 115.02, 109.14, 108.90, 108.69, 102.07, 99.60 (d, *J* = 12.5 Hz, 1H), 66.80, 56.31, 53.96, 52.41, 46.42, 27.17, 23.47, 23.37, 12.10; Anal. calcd. For $C_{35}H_{35}F_2N_5O_5$ (%): C, 65.31; H, 5.48; F, 5.90; N, 10.88; O, 12.43. Found (%): C, 65.30; H, 5.45; N, 10.86.

4.7.19

N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl) butanamide (**45e**)

Yield: 53%; m.p. 132 - 134^{o}C; MS (ESI) m/z (%): 658.9 $[M + H]^+$;^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 8.47 (d, *J* = 4.8 Hz, 1H), 8.07 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.89 (d, *J* = 12.3 Hz, 1H), 7.55 (s, 1H), 7.51 - 7.40 (m, 5H), 6.47 (d, *J* = 5.1 Hz, 1H), 4.27 - 4.18 (m, 3H), 3.96 (s, 3H), 3.14 - 2.77 (m, 6H), 2.26 - 2.09 (m, 4H), 1.68 (s, 4H), 1.51 (s, 2H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 167.65, 165.02, 164.61 (d, *J* = 250.4 Hz), 164.14, 153.16 (d, *J* = 247.6 Hz), 152.10, 149.96, 149.39, 146.77, 137.93 (d, *J* = 8.9 Hz), 136.51 (d, *J* = 11.6 Hz), 129.74 (d, *J* = 9.7 Hz), 124.71, 120.44, 117.25 (d, *J* = 22.3 Hz, 1H), 116.76, 115.07, 109.26, 108.89, 108.67, 102.59, 99.56, 66.73, 56.31, 53.33, 46.42, 46.16, 24.17, 23.46, 12.10, 9.41, 9.21; Anal. calcd. For $C_{36}H_{37}F_2N_5O_5$ (%): C, 65.74; H, 5.67; F, 5.78; N, 10.65; O, 12.16. Found (%): C, 65.72; H, 5.65; N, 10.60.

4.7.20*N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropanamide (**46a**)

Yield: 70%; m.p. 126 - 128^{o}C; MS (ESI) m/z (%): 672.2 $[M + H]^+$;^{1}H NMR (400 MHz, DMSO) δ 10.02 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.10 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.88 (dd, *J* = 13.1, 2.2 Hz, 1H), 7.62 - 7.34 (m,6H), 6.44 (d, *J* = 5.1 Hz, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 3.95 (s, 4H), 3.38 (dd, *J* = 16.5, 9.5 Hz, 2H), 2.89 (d, *J* = 11.0 Hz, 2H), 2.47 (s, 2H), 2.05 - 1.89 (m, 4H), 1.92(s, 6H), 1.60 (t, *J* = 12.5 Hz, 2H), 1.41 - 1.27 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 171.19, 169.01, 164.60 (d, *J* = 249.8 Hz), 164.08, 159.71, 153.73 (d, *J* = 245.3 Hz), 152.36, 150.04, 149.31, 146.83, 138.06 (d, *J* = 9.4 Hz),

136.54 (d, *J* = 13.2 Hz), 129.76 (d, *J* = 9.2 Hz), 124.37, 120.54, 117.63, 117.21 (d, *J* = 22.7 Hz), 114.95, 109.63 (d, *J* = 23.1 Hz), 109.02, 102.54, 99.50, 67.17, 56.27, 54.97, 53.70, 44.97, 33.97, 30.46, 26.25, 24.25, 22.14; Anal. calcd. For $C_{37}H_{39}F_2N_5O_5$ (%): C, 66.16; H, 5.85; F, 5.66; N, 10.43; O, 11.91. Found (%): C, 66.12; H, 5.84; N, 10.41.

4.7.21

N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropanamide (**46b**)

Yield: 64%; m.p. 134 - 135°C; MS (ESI) m/z (%): 660.2 $[M + H]^+$;^{1}H NMR (400 MHz, DMSO) δ 10.11 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.10 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.90 (dd, *J* = 13.1, 1.8 Hz, 1H), 7.64 - 7.36 (m, 6H), 6.43 (t, *J* = 9.7 Hz, 1H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.95 (s, 3H), 3.64 - 3.53 (m, 4H), 2.95 (q, *J* = 7.1 Hz, 2H), 2.47 (t, *J* = 7.0 Hz, 2H), 2.39 (s, 4H), 2.03 - 1.92 (m, 2H), 1.81 (s, 6H); Anal. calcd. For $C_{35}H_{35}F_2N_5O_6$ (%): C, 63.72; H, 5.35; F, 5.76; N, 10.62; O, 14.55. Found (%): C, 63.70; H, 5.34; N, 10.63.

4.7.22

N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropanamide (**46c**)

Yield: 55%; m.p. 134 - 135°C; MS (ESI) m/z (%): 673.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.07 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.10 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.89 (d, *J* = 11.5 Hz, 1H), 7.63 - 7.33 (m, 6H), 6.44 (d, *J* = 5.0 Hz, 1H), 4.18 (t, *J* = 5.9 Hz, 2H), 3.95 (s, 3H), 3.62 (s, 4H), 2.49 (d, *J* = 7.6 Hz, 6H), 2.24 (s, 3H), 2.04 - 1.92 (m, 2H), 1.81 (s, 6H). Anal. calcd. for $C_{36}H_{38}F_2N_6O_5$ (%): C, 64.27; H, 5.69; F, 5.65; N, 12.49; O, 11.89. Found (%): C, 64.23; H, 5.64; N, 12.44.

4.7.23

N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropanamide (**46d**)

Yield: 65%; m.p. 145 - 146°C; MS (ESI) m/z (%): 644.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.05 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.10 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.89 (dd, *J* = 13.1, 2.0 Hz, 1H), 7.61 - 7.35 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.21 (t, *J* = 6.2 Hz, 2H), 3.95 (s, 3H), 2.69 (t, *J* = 6.9 Hz, 2H), 2.59 (s, 4H), 2.09 - 1.96 (m, 2H), 1.81 (s, 6H), 1.73 (s, 4H); ^{13}C NMR (101 MHz, DMSO) δ 171.23, 169.02, 164.59 (d, *J* = 250.5 Hz), 164.08, 159.73, 153.73 (d, *J* = 245.6 Hz), 152.33, 150.00, 149.30, 146.78, 138.05 (d, *J* = 10.0 Hz), 136.52 (d, *J* = 12.3 Hz), 129.75 (d, *J* = 9.1 Hz), 124.36, 120.53 (d, *J* = 3.0 Hz), 117.63, 117.19 (d, *J* = 22.4 Hz),114.94, 109.64 (d, *J* = 23.1 Hz), 108.95, 102.52, 99.47, 67.03, 56.26, 54.01, 52.56, 44.99, 27.91, 24.22, 23.47; Anal. calcd. For $C_{35}H_{35}F_2N_5O_5$ (%): C, 65.31; H, 5.48; F, 5.90; N, 10.88; O, 12.43. Found (%): C, 65.33; H, 5.44; N, 10.83.

4.7.24

N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-2-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-methylpropanamide (**46e**)

Yield: 53%; m.p. 126 - 127°C; MS (ESI) m/z (%): 658.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.02 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 8.10 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.88 (dd, *J* = 13.1, 2.2 Hz, 1H), 7.62

- 7.34 (m, 6H), 6.44 (d, *J* = 5.1 Hz, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 3.95 (s, 2H), 3.38 (dd, *J* = 16.5, 9.5 Hz, 2H), 2.89 (d, *J* = 11.0 Hz, 2H), 2.47 (s, 2H), 2.05 - 1.89 (m, 4H), 1.60 (t, *J* = 12.5 Hz, 2H), 1.41 - 1.27 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 171.22, 169.03, 164.59 (d, *J* = 250.3 Hz), 164.07, 159.71, 153.73 (d, *J* = 245.6 Hz), 152.37, 150.03, 149.27, 146.84, 138.09 (d, *J* = 9.8 Hz, 2H), 136.51 (d, *J* = 12.3 Hz), 129.74 (d, *J* = 9.1 Hz), 124.34, 120.57, 117.61, 117.18 (d, *J* = 22.4 Hz), 114.94, 109.62 (d, *J* = 23.0 Hz); 109.01, 102.51, 99.48, 67.19, 56.24, 55.38, 54.34, 46.04, 45.01, 26.22, 25.69, 24.23; Anal. calcd. For $C_{36}H_{37}F_2N_5O_5$ (%): C, 65.74; H, 5.67; F, 5.78; N, 10.65; O, 12.16. Found (%): C, 65.73; H, 5.65; N, 10.63.

4.7.25 *N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (**47a**)

Yield: 64%; m.p. 146 - 147°C; MS (ESI) m/z (%): 670.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.38 (s, 1H), 8.48 (s, 1H), 8.10 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.86 (dd, *J* = 13.0, 1.9 Hz, 1H), 7.58 - 7.34 (m, 6H), 6.46 (d, *J* = 4.9 Hz, 1H), 4.19 (t, *J* = 6.2 Hz, 2H), 3.95 (s, 3H), 2.93 (d, *J* = 10.8 Hz, 2H), 2.53 (d, *J* = 10.1 Hz, 2H), 2.10 - 1.92 (m, 4H), 1.85 - 1.67 (m, 4H), 1.60 (d, *J* = 11.7 Hz, 2H), 1.35 (s, 1H), 1.29 - 1.11 (m, *J* = 24.2, 12.1 Hz, 4H), 0.88 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 166.89, 165.69, 164.54 (d, *J* = 250.4 Hz), 164.00, 159.67, 153.78 (d, *J* = 245.2 Hz), 152.37, 150.03, 149.28, 146.88, δ137.93 (d, *J* = 9.9 Hz), 136.57 (d, *J* = 12.2 Hz), 129.76 (d, *J* = 9.0 Hz), 124.42, 120.69, 117.51, 117.14 (d, *J* = 22.5 Hz), 114.96, 109.59 (d, *J* = 22.7 Hz), 109.00, 102.53, 99.48, 67.19, 56.24, 55.02, 53.74, 34.07, 30.58, 26.36, 23.15, 22.17, 17.32; Anal. calcd. for $C_{37}H_{37}F_2N_5O_5$ (%): C, 65.94; H, 5.38; F, 5.79; N, 10.68; O, 12.20. Found (%): C, 65.93; H, 5.34; N, 10.64.

4.7.26

N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (**47b**)

Yield: 64%; m.p. 194 - 196°C; MS (ESI) m/z (%): 658.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.36 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 8.10 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.86 (d, *J* = 11.0 Hz, 1H), 7.58 - 7.36 (m, 6H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.20 (t, *J* = 6.3 Hz, 2H), 3.95 (s, 3H), 3.59 (t, *J* = 4.4 Hz, 4H), 2.51 - 2.44 (m, 2H), 2.40 (s, 4H), 2.04 - 1.94 (m, 2H), 1.81 - 1.67 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 166.89, 165.69, 164.67 (d, *J* = 226.9 Hz), 164.01, 159.67, 153.78 (d, *J* = 245.7 Hz), 152.42, 150.06, 149.31, 146.86, 137.93 (d, *J* = 9.2 Hz), 136.60 (d, *J* = 11.2 Hz), 129.78 (d, *J* = 9.2 Hz), 124.44, 120.73 (d, *J* = 2.9 Hz), 117.56, 117.16 (d, *J* = 22.4 Hz), 114.94, 109.60 (d, *J* = 23.3 Hz), 109.03, 102.54, 99.49, 66.68, 56.26, 55.28, 53.84, 46.09, 26.15, 23.16, 17.28; Anal. calcd. for $C_{35}H_{33}F_2N_5O_6$ (%): C, 63.92; H, 5.06; F, 5.78; N, 10.65; O, 14.60. Found (%): C, 63.91; H, 5.04; N, 10.64.

4.7.27

N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (**47c**)

Yield: 74%; m.p. 130 - 131°C; MS (ESI) m/z (%): 671.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.39 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.10 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.87 (dd, *J* = 13.0, 2.2 Hz, 1H), 7.55 - 7.38 (m, 6H), 6.46 (d, *J* = 5.1 Hz, 1H), 4.21 (t, *J* = 6.2 Hz, 2H), 3.95 (s, 3H), 3.37 (dd, *J* = 12.9, 5.6 Hz,

2H), 3.06 (q, *J* = 7.3 Hz, 4H), 2.58 (s, 4H), 2.03 (s, 2H), 1.84 - 1.67 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 166.92, 165.69, 164.55 (d, *J* = 250.2 Hz), 163.99, 159.69, 153.77 (d, *J* = 246.4 Hz), 152.33, 150.01, 149.34, 146.81, 137.97 (d, *J* = 9.8 Hz), 136.56 (d, *J* = 11.9 Hz), 129.77 (d, *J* = 9.6 Hz), 124.44, 120.74, 117.56, 117.16 (d, *J* = 22.2 Hz), 114.98, 109.60 (d, *J* = 22.2 Hz), 109.05, 102.56, 99.51, 66.95, 56.28, 54.04, 53.24, 50.66, 45.89, 23.18, 17.27, 8.97; Anal. calcd. for $C_{36}H_{36}F_2N_6O_5$ (%): C, 64.47; H, 5.41; F, 5.67; N, 12.53; O, 11.93. Found (%): C, 64.45; H, 5.40; N, 12.52.

4.7.28

N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (**47d**)

Yield: 64%; m.p. 135 - 136°C; MS (ESI) m/z (%): 642.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.37 (s, 1H), 8.47 (d, *J* = 4.5 Hz, 1H), 8.10 (dd, *J* = 8.7, 5.4 Hz, 3H), 7.86 (dd, *J* = 12.9, 1.9 Hz, 1H), 7.56 - 7.37 (m, 6H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.21 (t, *J* = 6.3 Hz, 2H), 3.95 (s, 3H), 2.79 - 2.63 (m, 2H), 2.58 (s, 4H), 2.08 - 1.96 (m, 2H), 1.84 - 1.65 (m, 8H); ^{13}C NMR (101 MHz, DMSO) δ 166.90, 165.69, 164.56 (d, *J* = 250.0 Hz), 164.01, 159.67, 153.77 (d, *J* = 246.4 Hz), 152.39, 150.04, 149.31, 146.86, 137.93 (d, *J* = 9.2 Hz), 136.60 (d, *J* = 12.3 Hz), 129.77 (d, *J* = 9.1 Hz), 124.43, 120.73 (d, *J* = 3.2 Hz), 117.52, 117.16 (d, *J* = 22.5 Hz), 114.94, 109.60 (d, *J* = 23.8 Hz), 109.01, 102.57, 99.48, 67.12, 56.27, 54.06, 52.61, 28.19, 23.55, 23.16, 17.28; Anal. calcd. For $C_{35}H_{33}F_2N_5O_5$ (%): C, 65.51; H, 5.18; F, 5.92; N, 10.91; O, 12.47. Found (%): C, 65.52; H, 5.16; N, 10.90.

4.7.29

N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)cyclopropane-1-carboxamide (**47e**)

Yield: 63%; m.p. 150 - 151°C; MS (ESI) m/z (%): 656.2 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.37 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.19 - 8.05 (m, 2H), 7.86 (dd, *J* = 13.0, 2.2 Hz, 1H), 7.55 - 7.37 (m, 6H), 6.45 (d, *J* = 5.2 Hz, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.95 (s, 3H), 2.44 (dd, *J* = 22.3, 15.4 Hz, 6H), 2.04 - 1.92 (m, 2H), 1.83 - 1.68 (m, 4H), 1.51 (dd, *J* = 10.7, 5.3 Hz, 4H), 1.39 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ 166.89, 165.69, 164.55 (d, *J* = 250.2 Hz), 164.01, 159.67, 153.78 (d, *J* = 245.6 Hz), 152.43, 150.06, 149.29, 146.87, 137.93 (d, *J* = 9.9 Hz), 136.60 (d, *J* = 12.5 Hz), 129.77 (d, *J* = 9.1 Hz), 124.43, 120.74, 117.54, 117.15 (d, *J* = 22.4 Hz), 114.92, 109.59 (d, *J* = 23.0 Hz), 109.00, 102.53, 99.48, 67.27, 56.25, 55.52, 54.53, 40.62, 40.41, 40.20, 39.99, 39.79, 39.58, 39.37, 26.49, 25.99, 24.53, 23.15, 17.28; Anal. calcd. For $C_{36}H_{35}F_2N_5O_5$ (%): C, 66.36; H, 5.57; F, 5.67; N, 10.46; O, 11.94. Found (%): C, 66.33; H, 5.55; N, 10.45.

4.8. In vitro cell assays

The cytotoxic activity of all target compounds were evaluate with A549, HT-29, PC-3 and MCF-7 by the MTT method *in vitro*, with Foretinib or Cabozantinib as references. The cancer cells were cultured in minimum essential medium (MEM) supplemented with 10% fetal bovine serum (FBS).

Approximately 4×10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37 °C for 24 h. The test compounds were added to the culture medium at the indicated final concentrations and the cell cultures were continued for 72 h. Fresh MTT was added to each

well at a final concentration of 5μg/mL and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 μL DMSO per each well, and the absorbency at 492 nm (for the absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with the ELISA reader. All of the compounds were tested three times in each of the cell lines. The results expressed as IC_{50} (inhibitory concentration of 50%) were the mean ± SD and were calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

4.9. In vitro kinase assays

IC_{50} measurements versus c-Met (Cat: 08-151, Carna), VEGFR-2 (Cat: 08-191, Carna), c-kit (Cat: 14-559M, Eurofins), Flt-3 (Cat: 08-154, Carna), PDGFRβ (PR4465B, Invitrogen) and Axl (Cat: 08-170, Carna) kinases were determined using Mobility shift assay. The solution of peptide substrates, ATP, appropriate kinase, and various concentrations of compounds were mixed with the kinase reaction buffer (50m MHEPES, pH 7.5, 0.0015% Brij-35, 10 mM $MgCl_2$, 2 mM DTT), with blank DMSO solution as the negative control. The kinase reaction was initiated by the addition of tyrosine kinase proteins diluted in 39 mL of kinase reaction buffer solution and incubated at 28^{o}C for 1 h. And then add 25 mL of stop buffer (100 mM HEPES, pH 7.5, 0.015% Brij-35, 0.2% Coating Reagent#3, 50mMEDTA) to stop reaction. The data were collected on Caliper at 320 nm and 615 nm and converted to inhibition values. IC_{50} was presented in MS Excel and the curves fitted by XLfit exceladd-in version 4.3.1. Compound **47e** was profiled against a panel of 30 kinases at 200 nM using Eurofins's SelectScreen kinase profiling service. https://www.eurofinsdiscoveryservices.com/

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Highlights

- Seven novel series of 4-benzyloxyquinoline derivatives were designed and synthesized.
- Most of the target compounds showed potent antitumor activity.
- Compound **47e** (Axl IC_{50} = 10 nM) showed remarkable cytotoxicity.
- **47e** exhibits prominent inhibition against EGFR-TKI resistant NSCLC cell line H1975/gefitinib.
- A novel type of linker for Axl kinase inhibitors was provided.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: