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Research paper

Structure-activity study of quinazoline derivatives leading to the discovery of potent EGFR-T790M inhibitors

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ABSTRACT

We have developed a series of 6, 7-disubstituted-4-(arylamino) quinazoline derivatives that functioned as irreversible EGFR inhibitors, and these compounds exhibited excellent enzyme inhibition potency. As compared with afatinib, some of them showed significantly enhanced activities towards H1975 cells (EGFR-T790M). Furthermore, the optimized compounds **7q** and **8f** also demonstrated good pharmacokinetic profiles, oral bioavailability as well as excellent *in vivo* efficacy in H1975 and HCC827 xenografts at a non-toxic dose. Based on the improved safety and efficacy against EGFR-T790M resistance, **7q** and **8f** are promising candidates for further studies.

1. Introduction

EGFR inhibitors, such as gefitinib and erlotinib, are effective clinical treatments for NSCLC patients whose tumors harbor activating mutations in EGFR [1–3]. However, all patients will ultimately manifest disease progression due to acquired resistance which in part is explained by a second-site T790M mutation in EGFR kinase domain. Although the second-generation irreversible EGFR inhibitors including dacomitinib [4], neratinib [5] and afatinib [6] have demonstrated activity in preclinical studies against T790M mutations, clinical trial data did not demonstrate distinctly improved efficacy. This was partially attributed to the dosage limitation imposed by the toxicity, which led to insufficient exposure level in plasma and remarkably decreased efficacy when used in patients with advanced lung tumor harboring the T790M acquired mutation [7–10]. Two kinds of compounds may be used to solve the above problem. The first class of compounds has less activity against EGFR-wt but keeping the high efficacy against EGFR-T790M. The third-generation irreversible EGFR inhibitors, such as AZD-9291 [11,12] and CO-1686 [13], are characterized by potently inhibiting EGFR phosphorylation in EGFRm+/T790M, whilst demonstrating much less activity against EGFR-wt. Avoiding the toxicity induced by the inhibition of EGFR-wt, AZD-9291 and CO-1686 are currently in human phase 2 clinical trials. The second class of compounds has comparable efficacy against EGFR-wt, but with greatly increased efficacy against EGFR-T790M in comparison with afatinib. Without needing the high dosage, these compounds can achieve safe and effective inhibiting concentration in *vivo* against EGFR-T790M resistance tumor. The designing of the second type of compounds has been proved to be quite challenging, and few reports exists.

Despite the rapid advances in EGFR oncology therapeutics over the past decade, substantial room for improvement remains. Most cancer patients do not respond to EGFR inhibitors therapy, which implied intrinsic resistance (e.g., over-expressing EGFR-wt or 'oncogenic shift') [14,15]. Although many papers or patents have been presented for quinazoline-based EGFR inhibitors [16–19], and afatinib has been discovered, it is still in high demand to develop safer and more effective irreversible EGFR inhibitors. As part of our

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Abbreviations: EGFR, Epidermal growth factor receptor; NSCLC, Non-small cell lung cancer; SAR, Structure-activity relationship; DMF, Dimethylformamide; TLC, Thin layer chromatography; THF, Tetrahydrofuran; NMP, N-methyl-2-pyrrolidone; Rf, Retention factor; DMSO, Dimethyl sulphoxide; RPMI, Roswell Park Memorial Institute; GI_{50}, The concentration that causes 50% growth inhibition; PO, Oral administration; QD, One a day (from the Latin quaque die).

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ongoing research program in designing new irreversible inhibitors that overcome EGFR-over-expressing or EGFR-T790M resistance, a series of 6, 7-disubstituted-4-(arylamino) quinazoline derivatives were synthesized. We discovered that compounds with a primary amine-substituted center at the end of the Michael acceptor caused a significant improvement in cellular potency against T790M in comparison with afatinib. These efforts resulted in the identification of the novel quinazoline-based compounds **7q** and **8f** with greatly increased efficacy against H1975 (EGFR-T790M) tumors at a non-toxic dose in comparison with afatinib.

2. Results and discussion

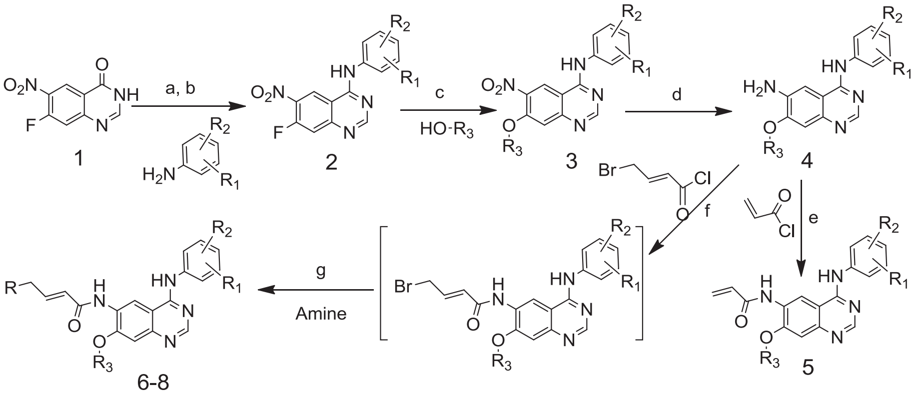
The aniline-substituted quinazoline motif (Intermediate **4**) was prepared in the following way: 7-fluoro-6-nitro-3*H*-quinazolin-4-one was firstly treated with thionyl chloride, and then reacted with an aromatic amine to give the intermediate **2**, which was further reacted with an alcohol of formula R_3OH in the presence of NaH to provide the intermediate **3**. Reduction of **3** gave the aniline-substituted quinazoline motif **4**. The Michael acceptor at the 6-position was constructed by reacting intermediate **4** with acryloyl chloride or (*E*)-4-bromobut-2-enoyl chloride which further reacted with various secondary amines or primary amines (Scheme 1).

The optimization of aromatic amine groups at the 4-position was firstly investigated, and the results are shown in Table 1. These data indicated that 3-chloro-4-fluoroaniline, 3-ethynylaniline, 4-(pyridin-2-ylmethoxy)aniline or 3-chloro-4-(pyridin-2-ylmethoxy)aniline group gratifyingly afforded a number of analogs (e.g., **5b**, **5n**, **6b**) with high activities against EGFR. 3-Chloro-4-(3-fluorobenzyloxy)aniline, 4-chloro-3-(trifluoromethyl) aniline, 5-amino-2-fluorobenzonitrile and *N*-(4-amino-2-(trifluoromethyl)phenyl)acrylamide were not ideal pharmacophore groups, and compounds containing those groups (e.g., **6a**, **6e**, **6p**) couldn't effectively inhibit EGFR kinase. The presence of linear chain or heterocyclic groups at the 7-position of the quinazoline scaffold was well tolerated and often had little effect on its' *in vitro* activities. The introduction of a dimethylamine group at the end of the Michael acceptor led to a modest increase in potency, most compounds of series 6 in Table 1 were more active in comparison with the corresponding compounds of series 5. Although with excellent *in vitro* activities, compounds containing the 4-(pyridin-2-ylmethoxy)aniline or 3-chloro-4-(pyridin-2-ylmethoxy)aniline group (e.g., **6g**, **6m** and **6n**) exhibited weak activities against A431 (human epidermoid carcinoma) xenografts in nude mice, which might be attributed to their large molecular weight and low permeability. Hence, the ideal groups at the 4-position of the quinazoline were 3-chloro-4-fluoroaniline and 3-ethynylaniline.

Considering that the terminal dialkylamino group of the crotonamide Michael acceptor affected the compound's physicochemical properties, water-solubility as well as the activity in both kinase and cell proliferation assays [20], further optimizing the Michael acceptor side chains were done. Tables 2 and 3 show compounds where the terminal alkylamino group of the crotonamide Michael acceptor was varied. It was evident that *N*-piperidinyl, cyclopropanamine, *N*-methylcyclopropanamine and propan-2-amine groups were very well tolerated, and for most of these analogs, the kinase and cellular activities were minimally affected by the choice of these alkylamino groups. One exception was the dicyclopropylamine group that greatly reduced potency of compounds **7k**–**7n**, which implied that incorporation of some steric bulk at the end of the Michael acceptor might be unfavorable and hinder the intramolecular base catalysis of the Michael addition to form a covalent adduct. Compound **7g**, where the Michael acceptor was terminated with a 3, 3-difluoroazetidine group, showed reduced activity in the kinase assay, and this loss of activity was likely attributed to the reduced basicity [21]. However, the diminished activity of piperidin-4-one-*N*-substituted analog **7c** or thiomorpholine-1-oxide-*N*-substituted analogs **7h**–**7j** may be due to the acyl group which interrupted the intramolecular base-catalyzed Michael addition. As expected, when the Michael acceptor side chains containing piperidinyl, cyclopropanamine, *N*-methylcyclopropanamine or propan-2-amine group were introduced into 4-(3-ethynylaniline)-substituted quinazoline analogs, compounds **8a**–**8i** also showed high *in vitro* efficacy. There was no major difference in activities between the 3-chloro-4-fluoroaniline-substituted derivatives and the 3-ethynylaniline -substituted derivatives (Tables 2 and 3).

In addition, H1975 cell growth inhibition assay was used to demonstrate the superior cell-based efficacy of those analogs against the resistant EGFR mutants (EGFR-T790M). The primary amine-substituted analogs **7o**–**7q** showed the highest potency and were at least 5-fold more effective than afatinib in abolishing survival of H1975 cells (Table 2). Similar results were also observed in the 3-ethynylaniline-substituted derivatives **8f**–**8i** (Table 3).

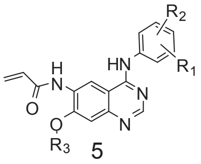
After the promising *in vitro* results were observed, further *in vivo* antitumor activities of the primary amine-substituted analogs **7o**–**7q**, **7r**, **7u** and **8e**–**8i** were evaluated first using a H1975 xenograft model (Supplementary information). Because the afatinib free base was difficult to dissolve at a high dose, and resulted in uneven dispersion, afatinib dimaleate was prepared for *in vivo* evaluation. Except for **7u** and **8i**, reductions of tumor size were observed versus controls in H1975 xenograft (Fig. 1). Intriguingly, although with high potency *in vitro*, compound **7u** or **8i** at 50 mg/kg/day dose level didn't show any activities in H1975 xenograft.

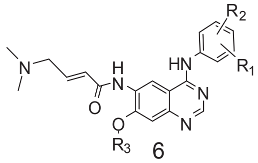


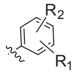
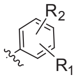
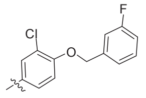
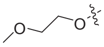
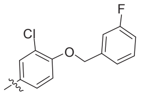
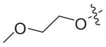
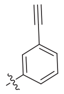
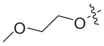
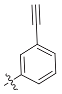
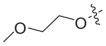
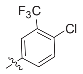
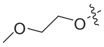
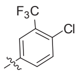
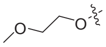
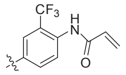
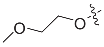
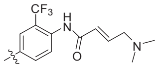
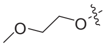
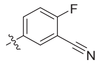
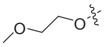
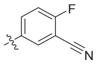
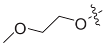
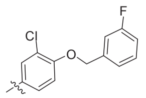
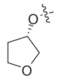
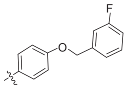
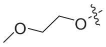
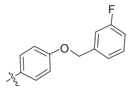
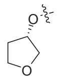
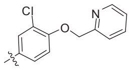
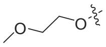
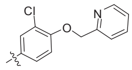
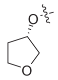
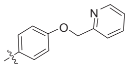
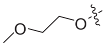
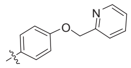
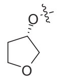
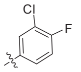
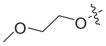
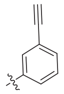
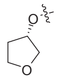
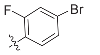
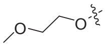
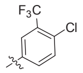
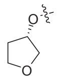
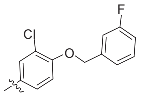
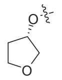
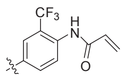
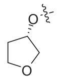
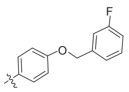
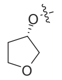
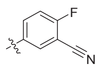
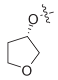
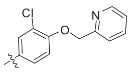
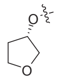
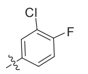
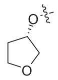
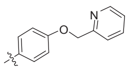
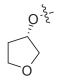
Scheme 1. Synthesis of 6, 7-disubstituted-4-anilino quinazoline derivatives (series **5**–**8**). Reaction and conditions: (a) thionyl chloride, DMF, reflux; (b) CH_3CN, reflux; (c) NaH, anhydrous THF, 0 °C to rt; (d) Fe, NH_4Cl, ethanol/water, 60 °C; (e) CH_3CN, NMP, −5 °C; (f) anhydrous THF, triethylamine, 0 °C; (g) K_2CO_3, KI, DMF, 40 °C.

Table 1

EGFR kinase inhibition (IC_{50}) by 6, 7-disubstituted-4-anilino quinazoline derivatives **5** and **6**.

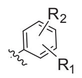
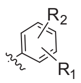
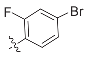
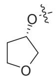
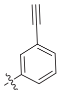
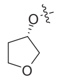
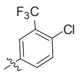
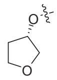
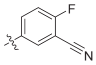
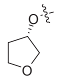
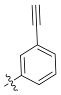
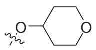
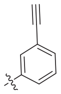
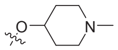




Comp.		R_3O-	EGFR (IC_{50}, nM)	Comp.		R_3O-	EGFR (IC_{50}, nM)
5a			102.2	**6a**			>1000
5b			1.8	**6b**			1.2
5c			>1000	**6c**			573.6
5d			115.1	**6d**			102.3
5e			195.8	**6e**			>1000
5f			560.4	**6f**			91.0
5g			72.2	**6g**			5.4
5h			134.9	**6h**			10.0
5i			100.1	**6i**			1.2
5j			32.2	**6j**			3.0
5k			104.7	**6k**			510.2
5l			>1000	**6l**			133.9
5m			167.3	**6m**			8.1
5n			5.8	**6n**			9.0

(*continued on next page*)

Table 1 (*continued*)

Comp.		R_3O-	EGFR (IC_{50}, nM)	Comp.		R_3O-	EGFR (IC_{50}, nM)
5o			121.1	**6o**			1.2
				6p			>1000
				6q			147.4
				6r			6.0
				6s			8.1

Even at a dose of 100 mg/kg/day from day 7, **8i** still couldn't achieve effective inhibition (Fig. 1a). Further PK study indicated that the low *in vivo* activities of **7u** and **8i** might be attributed to their low oral bioavailability and fast clearance (Table 4). Afatinib dimaleate at 20 mg/kg/day were tolerated, but couldn't effectively inhibit the growth of H1975 tumor (TGI < 50%) (Fig. 1a), and when 30 mg/kg/day dose was given, high potency as well as severe toxicity were observed and mice began to die from day 10 (Fig. 1c). Compounds **7o**, **7p**, **8e** and **8h** exhibited better *in vivo* activities, but also higher toxicity in comparison with afatinib dimaleate. In case of **7o** and **7p**, severe weight-loss was observed, the experimental athymic mice became weak or lethargic, further developed eye diseases and exfoliative skin disorder, and nine days later, more than half of the mice had died. These two groups' animals were sacrificed. A similar observation was noted in mice treated with **8e** and **8h**, and more than half of the mice had died at day 7. For observation, we sacrificed the mice of **8e** group and kept **8h**. The rest of the mice in the **8h** group were gradually recovering after stopping the administration of compound **8h** at day 7 (Fig. 1d). Compound **7q**, **8f** and **8g** exhibited improved safety profiles in comparison with afatinib dimaleate, and the animals treated with these compounds appeared healthy and active throughout the study duration. Although no significant effect on the body weight of the mice in **8g** group was noticed, a slightly skin toxicity was observed. While providing higher *in vivo* activities (*vs* afatinib), **7q** and **8f** were well tolerated, and no overt toxicity (e.g., eye diseases and exfoliative skin disorder) or weight-loss was observed in mice. These data indicated the (*S*)-tetrahydrofuran-3-ol substitution at the 7-position improved the safety profiles in comparison with alkyl groups. Hence **7q** and **8f** were selected for further *in vivo* studies.

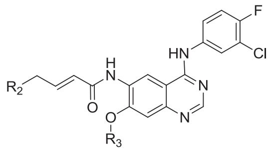
Compounds **7q** and **8f** showed high selectivity for HCC827 xenograft (EGFR-delE746-A750 represents EGFRm+) over A431 xenograft (EGFR-wt) (Fig. 2). In A431 xenograft, **7q** and **8f** couldn't achieve effective inhibition at 5 mg/kg/day dose level (Fig. 2a). However, in HCC827 xenograft, **7q** and **8f** at 5 mg/kg/day dose level significantly inhibited the growth of tumor, and tumor regressions were observed in all mice after being treated with **7q** and **8f** (Fig. 2c and table in Supplementary information). Afatinib dimaleate at 5 mg/kg/day dose level effectively inhibited the growth of A431 tumor and HCC827 tumor (Fig. 2a and c). As compared with afatinib dimaleate (5 mg/kg/day dose), **7q** was more active and **8f** was as active against HCC827 xenograft at 5 mg/kg/day dose level. Both compounds when administrated at a dose of 10 mg/kg/day exhibited higher potency against A431 xenograft (Fig. 2a and 2c). Besides, no overt toxicity (e.g., eye diseases and exfoliative skin disorder) or weight-loss was observed in all mice at those dose levels (Fig. 2b and 2d). Because patients with advanced lung tumor harboring the T790M acquired mutation usually have a high EGFR-wt/EGFRm+ expression ratio, **7q** and **8f** might have special advantages, and more patients would be benefit from them.

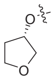
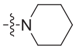
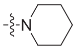
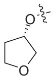
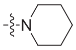
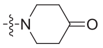
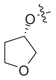
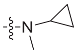
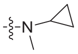
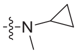
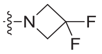
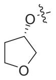
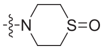
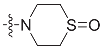
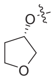
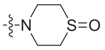
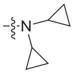
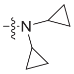
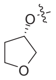
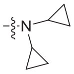
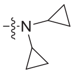
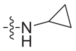
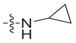
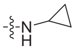
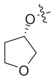
The cyclopropylamine moiety has been widely used in the structures of fluoroquinolone antimicrobials (e.g., moxifloxacin [22], gemifloxacin [23], ciprofloxacin [24], sitafloxacin [25] and trovafloxacin [26]). Except for trovafloxacin, these cyclopropylamine-containing drugs were tolerated, and no sever hepatotoxicity was observed [22–27]. The cyclopropylamine group of trovafloxacin is considered to be the most suspected substructure responsible for its hepatotoxicity [28]. The unique chemistry of cyclopropylamine moiety was illustrated by their tendency to produce a nitrogen radical cation when oxidized by P450 enzymes, which followed by rapid ring opening to form a highly reactive carbon-centered radical [28,29]. In the present investigation, the cyclopropylamine group was introduced into the structures of anticancer compounds, and **7q** and **8f** were discovered. Although **7q** and **8f** at present dose level were well tolerated, and no overt toxicity was observed, more studies (e.g., metabolite identification and toxicity) should be done to investigate whether the sever hepatotoxicity would be observed at higher dose level as well as the potential metabolic reactive intermediates and the metabolism. Because of the existence of a, ß-unsaturated Michael acceptor, the toxicological mechanism of compounds **7q** and **8f** will be expected to be very complex.

3. Conclusions

In summary, we have described the SARs of a series of 6, 7-disubstituted-4-anilino quinazoline derivatives and confirmed that the ideal groups at the 4-position of the quinazoline are 3-

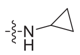
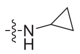
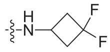
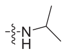
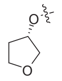
Table 2
EGFR inhibition (IC_{50}) and H1975 cancer cell proliferation inhibition (GI_{50}) by **7a**–**7u**.



Comp.	R_2	R_3O-	EGFR (IC_{50}, nM)	H1975 (GI_{50}, nM)
Afatinib			1.0	107.1
Dacomitinib		$-OCH_3$	1.8	123.3
7a			5.3	168.0
7b		$-OCH_2CH_2OCH_3$	2.1	92.3
7c			520.2	ND
7d		$-OCH_3$	26.9	32.2
7e		$-OCH_2CH_2OCH_3$	8.9	87.1
7f		$-OCH_2CH_3$	5.5	160.2
7g			>1000	ND
7h		$-OCH_3$	>1000	ND
7i			109.4	ND
7j		$-OCH_2CH_2OCH_3$	356.6	ND
7k		$-OCH_3$	>1000	ND
7l			>1000	ND
7m		$-OCH_2CH_2OCH_3$	>1000	ND
7n		$-OCH_2CH_3$	>1000	ND
7o		$-OCH_2CH_3$	0.9	11.6
7p		$-OCH_3$	2.1	11.2
7q			6.5	10.2

(*continued on next page*)

Table 2 (*continued*)

Comp.	R_2	R_3O-	EGFR (IC_{50}, nM)	H1975 (GI_{50}, nM)
7r		$-OCHF_2$	9.6	34.6
7s		$-OCH_2CF_3$	6.9	20.3
7t		$-OCH_3$	141.0	98.7
7u			7.0	22.4

chloro-4-fluoroaniline and 3-ethynylaniline for EGFR inhibition. Most importantly, we found that a primary amine-substituted center at the end of the Michael acceptor resulted in a significant improvement in T790M cellular potency relative to afatinib. These findings led to the discovery of some promising compounds (e.g., **7o**–**7q**, **8f**–**8i**) which manifested higher activities against H1975 cells (EGFR-T790M) and kept certain potency against A431 cells (EGFR-wt) in comparison with afatinib. Further studies showed that the optimized compounds **7q** and **8f** demonstrated good pharmacokinetic profiles, oral bioavailability as well as excellent *in vivo* efficacy in H1975 and HCC827 xenografts at a non-toxic dose.

4. Experimental protocols

4.1. Chemistry

The reagents were all analytically grade. Yields refer to purified products and are not optimized. ^1H NMR and ^{13}C NMR spectra were recorded on a on a Varian-600 or Bruck-400 spectrometer in DMSO-d_6 with TMS as the internal reference. The values of chemical shifts are expressed in ppm. MS spectra were determined using either an Agilent 1100 LC/MSD or a Thermo Fisher Scientific LCQFleet LC/MS^n, and the signals were given in m/z. The elemental carbon, hydrogen, and nitrogen content were measured using a ThermoFisher FLASH 2000 Organic Elemental Analyzer. The exact amount of residue solvent in products was determined by Agilent 7890A using external standard calibration.

In a similar manner to that described in paper, the following compounds of formula 5 were prepared.

4.1.1. N-(4-(3-Chloro-4-(3-fluorobenzyloxy)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)acrylamide (*5a*)

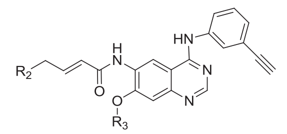
To a suspension of 7-fluoro-6-nitroquinazolin-4-ol (41.8 g, 0.2 mol) in thionyl chloride (350 ml) was added DMF (5 ml) dropwise under stirring at room temperature, and then the mixture was raised to reflux for 4 h until to be a clear solution. After removing thionyl chloride under vacuum, the residue was diluted with CH_2Cl_2 and concentrated to provide 4-chloro-7-fluoro-6-nitroquinazoline 49 g (216 mmol, 108%).

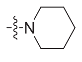
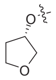
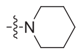
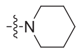
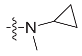
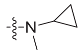
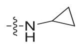
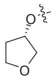
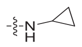
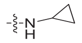
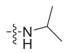
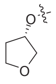
To a solution of 4-chloro-7-fluoro-6-nitroquinazoline (4.58 g, 20 mmol) in acetonitrile (500 ml) was added 3-chloro-4-(3-fluorobenzyloxy)aniline (4.77 g, 19 mmol), and then the mixture was raised to reflux. Once the reaction was completed as indicated by TLC, The precipitate was collected by filtration, and washed with acetonitrile to give *N*-(3-chloro-4-(3-fluorobenzyloxy)phenyl)-7-fluoro-6-nitroquinazolin-4-amine 7.5 g (16.9 mmol, 85%).

To a suspension of NaH (800 mg) in anhydrous THF (240 ml) were added the solution of 2-methoxyethanol (1.5 g, 20 mmol) in anhydrous THF (10 ml) dropwise at 0 °C. After the addition, the mixture was warmed to room temperature and stirred for 0.5 h. Then, the mixture was cooled to 0 °C, the suspension of *N*-(3-chloro-4-(3-fluorobenzyloxy)phenyl)-7-fluoro-6-nitroquinazolin-4-amine (4.4 g, 10 mmol) in anhydrous THF (50 ml) were added into dropwise. The mixture was warmed to room temperature and reacted for 2 h. Once the reaction was completed as indicated by TLC, the mixture was concentrated under vacuum at 30 °C to remove THF, and diluted with ice water (400 ml). The precipitate was collected by filtration, washed with water and dried to provided *N*-(3-chloro-4-(3-fluorobenzyloxy)phenyl)-7-(2-methoxyethoxy)-6-nitroquinazolin-4-amine 3.5 g (7 mmol, 71%).

To a suspension of *N*-(3-chloro-4-(3-fluorobenzyloxy)phenyl)-7-(2-methoxyethoxy)-6-nitroquinazolin-4-amine (2.5 g, 5 mmol) in alcohol (25 ml) and water (25 ml), were added Fe powder (1.1 g,

Table 3
EGFR inhibition (IC_{50}) and H1975 cancer cell proliferation inhibition (GI_{50}) by **8a**–**8i**.



Comp.	R_2	R_3O-	EGFR (IC_{50}, nM)	H1975 (GI_{50}, nM)
8a			5.3	40.1
8b		$-OCH_3$	2.7	48.9
8c		$-OCH_2CH_3$	6.1	30.4
8d		$-OCH_3$	3.3	70.5
8e		$-OCH_2CH_3$	2.4	41.0
8f			5.6	16.1
8g		$-OCH_3$	7.9	18.9
8h		$-OCH_2CH_3$	4.2	16.5
8i			6.4	19.8

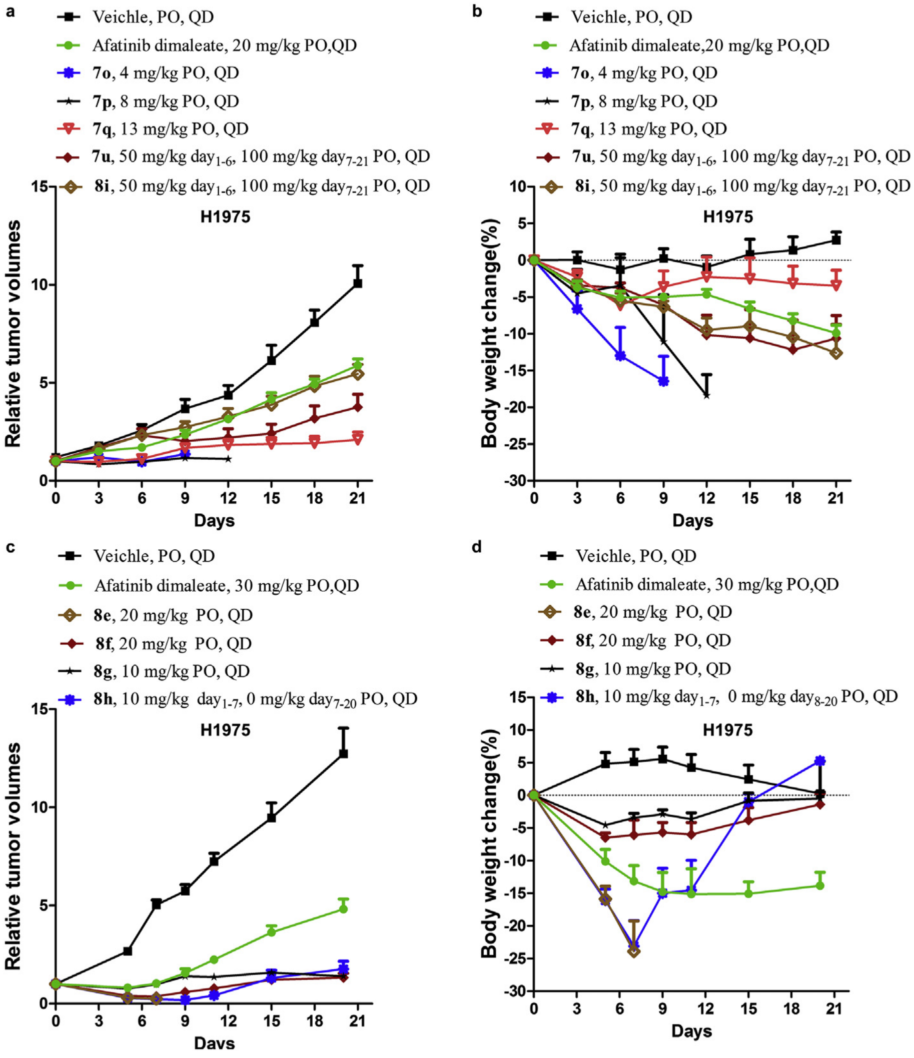


Fig. 1. Antitumor activities of **7o**–**7u** and **8e**–**8i** in H1975 xenograft model. (a) and (c) Relative tumor volumes *vs* time; (b) and (d) Body weight change *vs* time.

Table 4
Pharmacokinetic study of **7q**, **7u**, **8f** and **8i** in rats (IV, 1.00 mg/kg, n = 3).

Parameters	7u	8i	7q	8f	Afatinib
AUC_{0-24} (ng h/ml)[a]	166.3	92.6	659.6	471.4	276.8
$AUC_{0-\infty}$ (ng h/ml)[b]	196.7	105.3	662.4	480.2	324.5
MRT (h)[c]	8.8	2.6	3.88	1.7	10.57
$T_{1/2}$ (h)[d]	9.9	1.5	3.15	2.3	9.6
CL(L/h/kg)[e]	5.4	10.2	1.54	3.0	3.25
Vd(L/kg)[f]	6.5	7.4	3.82	2.2	10.77
F[g]	<5%	<5%	83.47%	37.9%	62.3%

[a] AUC_{0-24} (ng h/ml), Area under the plasma concentration-time curve (0–24 h).
[b] $AUC_{0-\infty}$ (ng h/ml), Area under the plasma concentration-time curve (0–∞ h).
[c] MRT, Mean retention time.
[d] $T_{1/2}$, Elimination half life.
[e] Vd, Apparent volume of distribution.
[f] CL, Clearance.
[g] F, Bioavailability.

19.6 mmol) and NH_4Cl (1.1 g, 20.6 mmol) respectively, and then the temperature was raised to 60 °C and the mixture was stirred for 6 h. Once the reaction was completed, the mixture was diluted with water (50 ml), and extracted with CH_2Cl_2 (3 × 100 ml). The combined organic phase was washed with water, dried over anhydrous Na_2SO_4, and concentrated to provide N^4-(3-chloro-4-(3-fluorobenzyloxy)phenyl)-7-(2-methoxyethoxy)quinazoline-4,6-diamine 2.1 g (4.5 mmol, 90%).

N^4-(3-chloro-4-(3-fluorobenzyloxy)phenyl)-7-(2-methoxyethoxy)quinazoline-4,6-diamine (0.94 g, 2 mmol) was dissolved in acetonitrile (50 ml) and NMP (3 ml) and stirred at −5 °C, to which a solution of acryloyl chloride (0.5 ml) in acetonitrile (3 ml) was added dropwise. Once the reaction was completed as indicated by TLC, water (2 ml) was added, and the mixture was concentrated under vacuum at 35 °C. The residue was diluted with 10% sodium bicarbonate solution (160 ml), and the precipitate was collected by filtration, washed with 10% sodium bicarbonate solution, and dried to give a crude product, which was purified by column chromatograph on silica gel (Solvent system: ethyl acetate/methanol, gradient elution (volume-to-volume ratios) from 50:1 to 20:1; Rf = 0.31 at 20:1 solvent system) to obtain the title compound 489 mg (0.94 mmol, 47%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.69 (s, 1H), 9.62 (s, 1H), 8.87 (s, 1H), 8.49 (s, 1H), 7.98 (d, 1H, *J* = 2.4 Hz, arylamine-2-=C*H*), 7.69–7.71 (dd, 1H, *J* = 8.4 Hz, *J* = 2.4 Hz, arylamine-6-=C*H*), 7.45–7.49 (dd, 1H, *J* = 7.8 Hz, *J* = 7.2 Hz, 3-fluorobenzyloxy-5-=C*H*), 7.33–7.34 (m, 2H, 3-fluorobenzyloxy-2,6-=C*H*), 7.31 (s, 1H), 7.24 (d, 1H, *J* = 8.4 Hz, arylamine-5-=C*H*), 7.17–7.20 (dd, 1H, $^3J_{F-H}$ = 8.4 Hz, *J* = 7.8 Hz, 3-fluorobenzyloxy-4-=C*H*), 6.70–6.74 (dd, 1H,

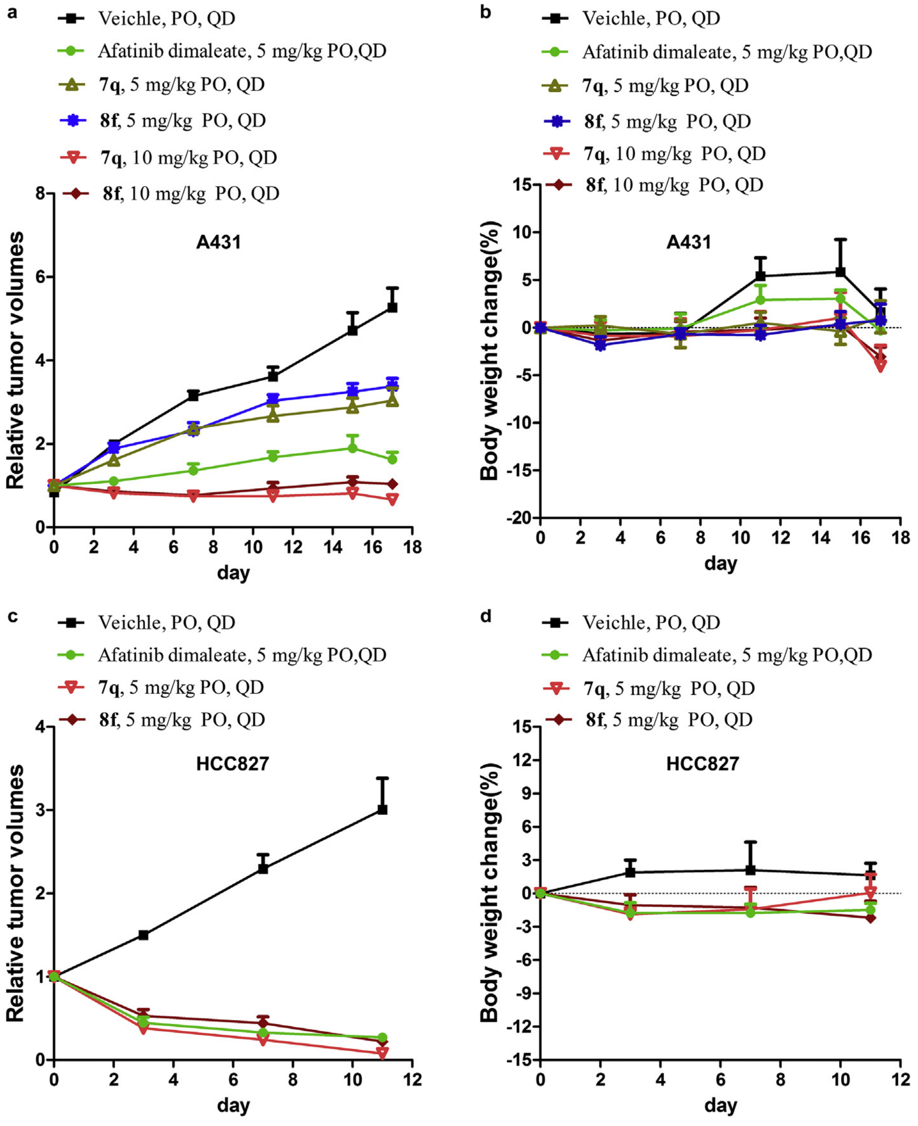


Fig. 2. Antitumor activities of **7q** and **8f** in A431 and HCC827 xenograft models. (a) and (c) Relative tumor volumes *vs* time; (b) and (d) Body weight change *vs* time.

$J = 17.4$ Hz, $J = 10.2$ Hz, $-CH{=}CH_2$), 6.32 (d, 1H, $J = 17.4$ Hz, $-CH{=}CH_2$), 5.82 (d, 1H, $J = 10.2$ Hz, $-CH{=}CH_2$), 5.25 (s, 2H, 3-fluorobenzyloxy-CH_2O-), 4.36–4.37 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O-$), 3.79–3.81 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O-$), 3.35 (s, 3H, CH_3O-). ESI-MS (m/z): $[M-H]^-$ 521.3, $[M+H]^+$ 523.2.

*4.1.2. N-(4-(3-Ethynylphenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)acrylamide (**5b**)*

The title compound was prepared in a manner similar to that described for **5a** yielding 136 mg (0.35 mmol, 72%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.76 (s, 1H), 9.64 (s, 1H), 8.91 (s, 1H), 8.54 (s, 1H), 8.01 (s, 1H), 7.87–7.89 (dd, 1H, $J = 8.4$ Hz, $J = 1.2$ Hz, arylamine-6-$=CH$), 7.37–7.40 (ap. t., 1H, $J = 8.4$ Hz, $J = 7.8$ Hz, arylamine-5-$=CH$), 7.33 (s, 1H), 7.20 (d, 1H, $J = 7.8$ Hz, arylamine-4-$=CH$), 6.70–6.75 (dd, 1H, $J = 16.8$ Hz, $J = 9.6$ Hz, $-CH{=}CH_2$), 6.31–6.34 (dd, 1H, $J = 16.8$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 5.82–5.83 (dd, 1H, $J = 9.6$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 4.37–4.38 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O-$), 4.19 (s, 1H, alkyne-H), 3.80–3.81 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O-$), 3.36 (s, 3H, CH_3O-). ESI-MS (m/z): $[M+H]^+$ 389.2.

*4.1.3. N-(4-(4-Chloro-3-(trifluoromethyl)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)acrylamide (**5c**)*

The title compound was prepared in a manner similar to that described for **5a** yielding 152 mg (0.33 mmol, 60%).

^{1}H-NMR (600 MHz, DMSO-d_6, δ_{ppm}): 10.0 (s, 1H), 9.69 (s, 1H), 8.95 (s, 1H), 8.59 (s, 1H), 8.42 (d, 1H, $J = 2.4$ Hz, arylamine-2-$=CH$), 8.29–8.31 (dd, 1H, $J = 8.4$ Hz, $J = 2.4$ Hz, arylamine-6-$=CH$), 7.73 (d, 1H, $J = 8.4$ Hz, arylamine-5-$=CH$), 7.37 (s, 1H), 6.75–6.78 (dd, 1H, $J = 16.8$ Hz, $J = 10.8$ Hz, $-CH{=}CH_2$), 6.32–35 (dd, 1H, $J = 16.8$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 5.83–5.85 (ap. t., 1H, $J = 10.8$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 4.39–4.40 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O-$), 3.80–3.82 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O-$), 3.35 (s, 3H, CH_3O-). ESI-MS (m/z): $[M+H]^+$ 467.3.

*4.1.4. N-(4-(4-Acrylamido-3-(trifluoromethyl)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)acrylamide (**5d**)*

The title compound was prepared in a manner similar to that described for **5a** yielding 174 mg (0.35 mmol, 69%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.97 (s, 1H), 9.74 (s, 1H), 9.67 (s, 1H), 8.94 (s, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.22 (d, 1H,

J = 8.4 Hz, arylamine-5-=C*H*), 7.51 (d, 1H, J = 8.4 Hz, arylamine-6-=C*H*), 7.35 (s, 1H), 6.73–6.75 (dd, 1H, J = 17.4 Hz, J = 10.2 Hz, −C*H*=CH$_2$), 6.52–6.54 (dd, 1H, J = 17.4 Hz, J = 10.2 Hz, −C*H*=CH$_2$), 6.34 (d, 1H, J = 17.4 Hz, −CH=C*H*$_2$), 6.25 (d, 1H, J = 17.4 Hz, −CH=C*H*$_2$), 5.83 (d, 1H, J = 10.2 Hz, −CH=C*H*$_2$), 5.78 (d, 1H, J = 10.2 Hz, −CH=C*H*$_2$), 4.39–4.40 (ap. t., 2H, J = 4.8 Hz, J = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O−), 3.80–3.82 (ap. t., 2H, J = 4.8 Hz, J = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O−), 3.35 (s, 3H, C*H*$_3$O−). ESI-MS (m/z): [M+H]$^+$ 502.4, [M−H]$^-$ 500.3.

4.1.5. *N-(4-(3-Cyano-4-fluorophenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)acrylamide (**5e**)*

The title compound was prepared in a manner similar to that described for **5a** yielding 102 mg (0.25 mmol, 59%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.96 (s, 1H), 9.65 (s, 1H), 8.92 (s, 1H), 8.56 (s, 1H), 8.38–8.39 (dd, 1H, $^4J_{\mathrm{F\text{-}H}}$ = 5.4 Hz, J = 2.4 Hz, arylamine-2-=C*H*), 8.14–8.17 (m, 1H, arylamine-6-=C*H*), 7.56 (t, 1H, J = 9.0 Hz, arylamine-5-=C*H*), 7.34 (s, 1H), 6.72–6.76 (dd, 1H, J = 17.4 Hz, J = 10.8 Hz, −C*H*=CH$_2$), 6.31–6.34 (dd, 1H, J = 17.4 Hz, J = 1.8 Hz, −CH=C*H*$_2$), 5.82–5.84 (dd, 1H, J = 10.8 Hz, J = 1.8 Hz, −CH=C*H*$_2$), 4.38–4.39 (ap. t., 2H, J = 4.8 Hz, J = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O−), 3.80–3.81 (ap. t., 2H, J = 4.8 Hz, J = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O−), 3.33 (s, 3H, C*H*$_3$O−). ESI-MS (m/z): [M+H]$^+$ 408.2.

4.1.6. *(S)-N-(4-(3-Chloro-4-(3-fluorobenzyloxy)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5f**)*

The title compound was prepared in a manner similar to that described for **5a** yielding 198 mg (0.37 mmol, 37%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.70 (s, 1H), 9.45 (s, 1H), 8.90 (s, 1H), 8.49 (s, 1H), 7.97 (d, 1H, J = 2.4 Hz, arylamine-2-=C*H*), 7.68–7.70 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, arylamine-6-=C*H*), 7.45–7.49 (m, 1H, 3-fluorobenzyloxy-5-=C*H*), 7.31–7.34 (ap. t., 2H, $J_{\mathrm{F\text{-}H}}$ = 11.4 Hz, J = 7.8 Hz, 3-fluorobenzyloxy-2,6-=C*H*), 7.25 (d, 1H, J = 8.4 Hz, arylamine-5-=C*H*), 7.23 (s, 1H), 7.17–7.20 (m, 1H, 3-fluorobenzyloxy-4-=C*H*), 6.74–6.76 (dd, 1H, J = 17.4 Hz, J = 10.2 Hz, −C*H*=CH$_2$), 6.31–6.34 (dd, 1H, J = 17.4 Hz, J = 2.4 Hz, −CH=C*H*$_2$), 5.83 (d, 1H, J = 10.2 Hz, −CH=C*H*$_2$), 5.29 (broad s, 1H, tetrahydrofuran-3-C*H*), 5.25 (s, 2H, 3-fluorobenzyloxy-C*H*$_2$O−), 3.97–4.02 (m, 2H, tetrahydrofuran-2-C*H*$_2$), 3.91–3.95 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.77–3.80 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 2.32–2.38 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 2.12–2.16 (m, 1H, tetrahydrofuran-4-C*H*$_2$). ESI-MS (m/z): [M+H]$^+$ 535.4.

4.1.7. *(S)-N-(4-(4-(3-Fluorobenzyloxy)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5g**)*

The title compound was prepared in a manner similar to that described for **5a** yielding 200 mg (0.40 mmol, 50%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.62 (s, 1H), 9.53 (s, 1H), 8.89 (s, 1H), 8.42 (s, 1H), 7.65 (d, 2H, J = 8.4 Hz, arylamine-2,6-=C*H*), 7.44–7.47 (m, 1H, 3-fluorobenzyloxy-5-=C*H*), 7.29–7.32 (ap. t., 2H, $^3J_{\mathrm{F\text{-}H}}$ = 9.6 Hz, J = 7.8 Hz, 3-fluorobenzyloxy-2,6-=C*H*), 7.20 (s, 1H), 7.17–7.18 (m, 1H, 3-fluorobenzyloxy-4-=C*H*), 7.03 (d, 2H, J = 8.4 Hz, arylamine-3,5-=C*H*), 6.71–6.75 (dd, 1H, J = 17.4 Hz, J = 10.2 Hz, −C*H*=CH$_2$), 6.31 (d, 1H, J = 17.4 Hz, −CH=C*H*$_2$), 5.82 (d, 1H, J = 10.2 Hz, −CH=C*H*$_2$), 5.28 (broad s, 1H, tetrahydrofuran-3-C*H*), 5.15 (s, 2H, 3-fluorobenzyloxy-C*H*$_2$O−), 3.97–4.02 (m, 2H, tetrahydrofuran-2-C*H*$_2$), 3.91–3.95 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.76–3.80 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 2.31–2.36 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 2.12–2.15 (m, 1H, tetrahydrofuran-4-C*H*$_2$). ESI-MS (m/z): [M+H]$^+$ 501.3.

4.1.8. *(S)-N-(4-(3-Chloro-4-(pyridin-2-ylmethoxy)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5h**)*

The title compound was prepared in a manner similar to that described for **5a** yielding 238 mg (0.46 mmol, 46%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.71 (s, 1H), 9.55 (s, 1H), 8.91 (s, 1H), 8.60 (d, 1H, J = 3.6 Hz, pyridin-6-=C*H*), 8.49 (s, 1H), 7.99 (s, 1H), 7.88–7.90 (ap. t., 1H, J = 7.8 Hz, J = 7.2 Hz, pyridin-4-=C*H*), 7.69 (d, 1H, J = 8.4 Hz, arylamine-6-=C*H*), 7.59 (d, 1H, J = 7.8 Hz, pyridin-3-=C*H*), 7.36–7.38 (ap. t., 1H, J = 6.6 Hz, J = 5.4 Hz, pyridin-5-=C*H*), 7.25 (d, 1H, J = 8.4 Hz, arylamine-5-=C*H*), 7.23 (s, 1H), 6.72–6.77 (dd, 1H, J = 17.4 Hz, J = 10.2 Hz, −C*H*=CH$_2$), 6.33 (d, 1H, J = 16.2 Hz, −CH=C*H*$_2$), 5.83 (d, 1H, J = 10.2 Hz, −CH=C*H*$_2$), 5.29 (broad s, 3H, pyridin-2-yl-C*H*$_2$O− and tetrahydrofuran-3-C*H*), 3.98–4.02 (m, 2H, tetrahydrofuran-2-C*H*$_2$), 3.91–3.95 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.77–3.80 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 2.32–2.38 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 2.13–2.15 (m, 1H, tetrahydrofuran-4-C*H*$_2$). ESI-MS (m/z): [M+H]$^+$ 518.4.

4.1.9. *(S)-N-(4-(4-(Pyridin-2-ylmethoxy)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5i**)*

The title compound was prepared in a manner similar to that described for **5a** giving 174 mg (0.36 mmol, 46%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.63 (s, 1H), 9.53 (s, 1H), 8.89 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H, pyridin-6-=C*H*), 8.41 (d, 1H), 7.84–7.87 (m, 1H, pyridin-4-=C*H*), 7.64 (d, 2H, J = 9.0 Hz, arylamine-2,6-=C*H*), 7.55 (d, 1H, J = 8.4 Hz, pyridin-3-=C*H*), 7.35–7.38 (m, 1H, pyridin-5-=C*H*), 7.20 (s, 1H), 7.04 (d, 2H, J = 9.0 Hz, arylamine-3,5-=C*H*), 6.71–6.74 (dd, 1H, J = 16.8 Hz, J = 10.2 Hz, −C*H*=CH$_2$), 6.30–6.33 (dd, 1H, J = 16.8 Hz, J = 1.2 Hz, −CH=C*H*$_2$), 5.81–5.83 (ap. t., 1H, J = 10.2 Hz, J = 1.2 Hz, −CH=C*H*$_2$), 5.28 (broad s, 1H, tetrahydrofuran-3-C*H*), 5.19 (s, 2H, pyridin-2-yl-C*H*$_2$O−), 3.97–4.02 (m, 2H, tetrahydrofuran-2-C*H*$_2$), 3.91–3.95 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.76–3.80 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 2.31–2.36 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 2.11–2.15 (m, 1H, tetrahydrofuran-4-C*H*$_2$). ESI-MS (m/z): [M+H]$^+$ 484.4.

4.1.10. *(S)-N-(4-(3-Ethynylphenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5j**)*

The title compound was prepared in a manner similar to that described for **5a** giving 168 mg (0.41 mmol, 42%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.78 (s, 1H), 9.56 (s, 1H), 8.95 (s, 1H), 8.54 (s, 1H), 8.01 (s, 1H), 7.87 (d, 1H, J = 7.8 Hz, arylamine-6-=C*H*), 7.37–7.40 (ap. t., 1H, J = 8.4 Hz, J = 7.8 Hz, arylamine-5-=C*H*), 7.25 (s, 1H), 7.20 (d, 1H, J = 8.4 Hz, arylamine-4-=C*H*), 6.72–6.77 (dd, 1H, J = 16.8 Hz, J = 12.0 Hz, −C*H*=CH$_2$), 6.31–6.34 (dd, 1H, J = 16.8 Hz, J = 1.8 Hz, −CH=C*H*$_2$), 5.82–5.84 (dd, 1H, J = 12.0 Hz, J = 1.8 Hz, −CH=C*H*$_2$), 5.30 (broad s, 1H, tetrahydrofuran-3-C*H*), 4.20 (s, 1H, alkyne-*H*), 3.97–4.02 (m, 2H, tetrahydrofuran-2-C*H*$_2$), 3.91–3.94 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.78–3.80 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 2.33–2.36 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 2.12–2.16 (m, 1H, tetrahydrofuran-4-C*H*$_2$). ESI-MS (m/z): [M+H]$^+$ 401.3.

4.1.11. *(S)-N-(4-(4-Chloro-3-(trifluoromethyl)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5k**)*

The title compound was prepared in a manner similar to that described for 5a giving 167 mg (0. 35 mmol, 49%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.58 (s, 1H), 8.99 (s, 1H), 8.59 (s, 1H), 8.41 (d, 1H, J = 2.4 Hz, arylamine-2-=C*H*), 8.28–8.30 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, arylamine-6-=C*H*), 7.73 (d, 1H, J = 8.4 Hz, arylamine-5-=C*H*), 7.28 (s, 1H), 6.74–6.79 (dd, 1H, J = 16.8 Hz, J = 12.0 Hz, −C*H*=CH$_2$), 6.32–6.35 (ap. t., 1H, J = 16.8 Hz, J = 1.8 Hz, −CH=C*H*$_2$), 5.84 (d, 1H, J = 11.4 Hz, −CH=C*H*$_2$), 5.31 (broad s, 1H, tetrahydrofuran-3-C*H*), 3.97–4.03 (m, 2H, tetrahydrofuran-2-C*H*$_2$), 3.92–3.95 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.77–3.81 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 2.33–2.39 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 2.14–2.18 (m, 1H, tetrahydrofuran-4-C*H*$_2$). ESI-MS (m/z): [M+H]$^+$ 479.2.

4.1.12. *(S)-N-(4-(4-Acrylamido-3-(trifluoromethyl)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5l**)*

The title compound was prepared in a manner similar to that described for **5a** giving 159 mg (0.31 mmol, 62%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.97 (s, 1H), 9.74 (s, 1H), 9.58 (s, 1H), 8.98 (s, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.21 (d, 1H, $J = 8.4$ Hz, arylamine-6-=C*H*), 7.50 (d, 1H, $J = 8.4$ Hz, arylamine-5-=C*H*), 7.27 (s, 1H), 6.74–6.78 (dd, 1H, $J = 16.8$ Hz, $J = 10.2$ Hz, $-CH{=}CH_2$), 6.51–6.56 (dd, 1H, $J = 16.8$ Hz, $J = 10.8$ Hz, $-CH{=}CH_2$), 6.32–6.35 (dd, 1H, $J = 16.8$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 6.24–6.27 (dd, 1H, $J = 16.8$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 5.84 (d, 1H, $J = 10.2$ Hz, $-CH{=}CH_2$), 5.78 (d, 1H, $J = 10.8$ Hz, $-CH{=}CH_2$), 5.31 (broad s, 1H, tetrahydrofuran-3-C*H*), 3.99–4.03 (m, 2H, tetrahydrofuran-CH_2), 3.92–3.96 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.81 (m, 1H, tetrahydrofuran-5-CH_2), 2.33–2.39 (m, 1H, tetrahydrofuran-4-CH_2), 2.14–2.18 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 514.3, $[M-H]^-$ 512.3.

4.1.13. *(S)-N-(4-(3-Cyano-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5m**)*

The title compound was prepared in a manner similar to that described for **5a** giving 168 mg (0.40 mmol, 35%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.97 (s, 1H), 9.57 (s, 1H), 8.96 (s, 1H), 8.56 (s, 1H), 8.37–8.39 (dd, 1H, $^4J_{F\text{-}H} = 5.4$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 8.14–8.17 (m, 1H, arylamine-6=C*H*), 7.54–7.57 (ap. t., 1H, $^3J_{F\text{-}H} = 9.6$ Hz, $J = 9.0$ Hz, arylamine-5-=C*H*), 7.27 (s, 1H), 6.74–6.79 (dd, 1H, $J = 16.8$ Hz, $J = 10.2$ Hz, $-CH{=}CH_2$), 6.32–6.35 (dd, 1H, $J = 16.8$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 5.83–5.85 (dd, 1H, $J = 10.2$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 5.31 (broad s, 1H, tetrahydrofuran-3-C*H*), 3.99–4.04 (m, 2H, tetrahydrofuran-2-CH_2), 3.92–3.96 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.81 (m, 1H, tetrahydrofuran-5-CH_2), 2.33–2.39 (m, 1H, tetrahydrofuran-4-CH_2), 2.13–2.17 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 420.3.

4.1.14. *(S)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5n**)*

The title compound was prepared in a manner similar to that described for **5a** giving 184 mg (0.43 mmol, 55%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.83 (s, 1H), 9.56 (s, 1H), 8.95 (s, 1H), 8.54 (d, 1H), 8.13–8.15 (dd, 1H, $^4J_{F\text{-}H} = 6.6$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.79–7.82 (m, 1H, arylamine-6-=C*H*), 7.41–7.44 (ap. t., $^3J_{F\text{-}H} = 9.6$ Hz, 1H, $J = 8.4$ Hz, arylamine-5-=C*H*), 7.26 (s, 1H), 6.73–6.78 (dd, 1H, $J = 16.8$ Hz, $J = 10.2$ Hz, $-CH{=}CH_2$), 6.32–6.35 (dd, 1H, $J = 16.8$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 5.83–5.85 (dd, 1H, $J = 10.2$ Hz, $J = 1.8$ Hz, $-CH{=}CH_2$), 5.31 (broad s, 1H, tetrahydrofuran-3-C*H*), 3.99–4.03 (m, 2H, tetrahydrofuran-2-CH_2), 3.92–3.96 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.81 (m, 1H, tetrahydrofuran-5-CH_2), 2.32–2.38 (m, 1H, tetrahydrofuran-4-CH_2), 2.13–2.17 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 429.3.

4.1.15. *(S)-N-(4-(4-Bromo-2-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)acrylamide (**5o**)*

The title compound was prepared in a manner similar to that described for **5a** giving 280 mg (0.59 mmol, 49%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.78 (s, 1H), 9.53 (s, 1H), 8.95 (s, 1H), 8.40 (s, H), 7.64 (d, 1H, $^3J_{F\text{-}H} = 9.6$ Hz, arylamine-3-=C*H*), 7.44–7.50 (m, 2H, arylamine-5,6-=C*H*), 7.25 (s, 1H), 6.74–6.79 (dd, 1H, $J = 17.4$ Hz, $J = 10.2$ Hz, $-CH{=}CH_2$), 6.32 (d, 1H, $J = 17.4$ Hz, $-CH{=}CH_2$), 5.83 (d, 1H, $J = 10.2$ Hz, $-CH{=}CH_2$), 5.30 (broad s, 1H, tetrahydrofuran-3-C*H*-), 4.00–4.04 (m, 2H, tetrahydrofuran-5-CH_2), 3.92–3.96 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.80 (m, 1H, tetrahydrofuran-5-CH_2), 2.32–2.37 (m, 1H, tetrahydrofuran-4-CH_2), 2.14–2.18 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 475.1.

4.1.16. *(E)-N-(4-(3-Chloro-4-(3-fluorobenzyloxy)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide (**6a**)*

To a solution of *N*^{4}-(3-chloro-4-(3-fluorobenzyloxy)phenyl)-7-(2-methoxyethoxy)quinazoline-4,6-diamine (0.94 g, 2 mmol) in anhydrous THF (10 ml) and triethylamine (0.4 ml) was added a solution of 4-bromo-but-2-enoyl chloride (0.46 g, 2.5 mmol) in anhydrous THF (5 ml) dropwise at 0 °C, and the mixture was stirred for 1 h. Once the reaction was completed as indicated by TLC, water (0.5 ml) was added into the mixture. After the solvent was removed under vacuum at 35 °C, the residue was diluted with water (20 ml), and extracted with CH_2Cl_2 (3 × 30 ml). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by column chromatograph to provide (*E*)-4-bromo-*N*-(4-(3-chloro-4-(3-fluorobenzyloxy)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)but-2-enamide 497 mg (0.98 mmol, 49%).

To a solution of (*E*)-4-bromo-*N*-(4-(3-chloro-4-(3-fluorobenzyloxy)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)but-2-enamide (470 mg, 0.93 mmol) in DMF (5 ml) were added dimethylamine hydrochloride (300 mg, 3.68 mmol), potassium carbonate (300 mg, 2.17 mmol) and potassium iodide (270 mg, 1.63 mmol) at 0 °C. The mixture was raised to 40 °C and stirred for 3 h under N_2 atmosphere. Once the reaction was completed as indicated by TLC, the mixture was diluted with water (60 ml) and extracted with CH_2Cl_2 (3 × 30 ml). The combined extracts were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatograph on silica gel (Solvent system: ethyl acetate/methanol from 20:1 to 5:1 and 0.5% triethylamine (volume-to-volume ratios), gradient elution; Rf = 0.15 at 5:1 solvent system and 0.5% triethylamine) to obtain the title compound 108 mg (0.19 mmol, 24%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.68 (s, 1H), 9.52 (s, 1H), 8.88 (s, 1H), 8.48 (s, 1H), 7.97 (d, 1H, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.69–7.71 (dd, 1H, $J = 9.0$ Hz, $J = 2.4$ Hz, arylamine-6-=C*H*), 7.46–7.49 (m, 1H, 3-fluorobenzyloxy-5-=C*H*), 7.31–7.34 (m, 2H, 3-fluorobenzyloxy-2,6-=C*H*), 7.29 (s, 1H), 7.24 (d, 1H, $J = 9.0$ Hz, arylamine-5-=C*H*), 7.17–7.20 (m, 1H, 3-fluorobenzyloxy-4-=C*H*), 6.78–6.82 (m, 1H, $-CH{=}CH-CH_2-$), 6.56 (d, 1H, $J = 15.0$ Hz, $-CH{=}CH-CH_2-$), 5.25 (s, 2H, 3-fluorobenzyloxy-CH_2O–), 4.35–4.36 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O-$), 3.79–3.81 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O-$), 3.35 (s, 3H, CH_3O-), 3.10 (d, 2H, $J = 5.4$ Hz, -–$CH_2-N(CH_3)_2$), 2.19 (s, 6H, $-N(CH_3)_2$). ESI-MS(m/z): $[M+H]^+$ 580.5.

4.1.17. *(E)-4-(Dimethylamino)-N-(4-(3-ethynylphenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)but-2-enamide (**6b**)*

The title compound was prepared in a manner similar to that described for **6a** giving 276 mg (0.62 mmol, 15%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.75 (s, 1H), 9.54 (s, 1H), 8.92 (s, 1H), 8.53 (s, 1H), 8.00 (s, 1H), 7.80 (d, 1H, $J = 7.8$ Hz, arylamine-6-=C*H*), 7.37–7.40 (ap. t., 1H, $J = 7.8$ Hz, $J = 7.2$ Hz, arylamine-5-=C*H*), 7.30 (s, 1H), 7.20 (d, 1H, $J = 7.2$ Hz, arylamine-4-=C*H*), 6.78–6.83 (m, 1H, $-CH{=}CH-CH_2-$), 6.57 (d, 1H, $J = 15.0$ Hz, -–$CH{=}CH-CH_2$-), 4.36–4.37 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O-$), 4.20 (s, 1H, alkyne-*H*), 3.80–3.81 (ap. t., 2H, $J = 4.8$ Hz, $J = 4.2$ Hz, $CH_3OCH_2CH_2O$-), 3.35 (s, 3H, CH_3O-), 3.09 (d, 2H, $J = 6.0$ Hz, $-CH_2-N(CH_3)_2$), 2.19 (s, 6H, $-N(CH_3)_2$). ESI-MS(m/z): $[M+H]^+$ 446.4.

4.1.18. *(E)-N-(4-(4-Chloro-3-(trifluoromethyl)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide (**6c**)*

The title compound was prepared in a manner similar to that described for **6a** giving 283 mg (0.54 mmol, 21%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 10.00 (s, 1H), 9.56 (s, 1H), 8.96 (s, 1H), 8.58 (s, 1H), 8.40 (d, 1H, *J* = 2.4 Hz, arylamine-2-=C*H*), 8.28–8.30 (dd, 1H, *J* = 8.4 Hz, *J* = 2.4 Hz, arylamine-6-=C*H*), 7.72 (d, 1H, *J* = 8.4 Hz, arylamine-5-=C*H*), 7.35 (s, 1H), 6.79–6.84 (m, 1H, –CH=C*H*–CH$_2$–), 6.58 (d, 1H, *J* = 15.6 Hz, –C*H*=CH–CH$_2$–), 4.37–4.39 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O–), 3.80–3.82 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O–), 3.35 (s, 3H, C*H*$_3$O–), 3.09 (d, 2H, *J* = 6.0 Hz, –C*H*$_2$–N(CH$_3$)$_2$), 2.19 (s, 6H, –N(C*H*$_3$)$_2$). ESI-MS(m/z): [M+H]$^+$524.40.

*4.1.19. (E)-4-(Dimethylamino)-N-(4-(4-((E)-4-(dimethylamino)but-2-enamido)-3-(trifluoromethyl)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)but-2-enamide (**6d**)*

The title compound was prepared in a manner similar to that described for **6a** giving 277 mg (0.45 mmol, 12%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.95 (s, 1H), 9.64 (s, 1H), 9.56 (s, 1H), 8.95 (s, 1H), 8.55 (s, 1H), 8.23 (s, 1H), 8.20 (d, 1H, *J* = 7.8 Hz, arylamine-5-=C*H*), 7.50 (d, 1H, *J* = 7.8 Hz, arylamine-6-=C*H*), 7.34 (s, 1H), 6.79–6.84 (m, 1H, –CH=C*H*–CH$_2$–), 6.70–6.75 (m, 1H, –CH=C*H*–CH$_2$–), 6.58 (d, 1H, *J* = 15.0 Hz, –C*H*=CH–CH$_2$–), 6.36 (d, 1H, *J* = 15.0 Hz, –C*H*=CH–CH$_2$–), 4.37–4.38 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O–), 3.81–3.82 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O–), 3.35 (s, 3H, C*H*$_3$O–), 3.09 (d, 2H, *J* = 5.4 Hz, –C*H*$_2$–N(CH$_3$)$_2$), 3.06 (d, 2H, *J* = 5.4 Hz, –C*H*$_2$–N(CH$_3$)$_2$), 2.19 (s, 6H, –N(C*H*$_3$)$_2$), 2.18 (s, 6H, –N(C*H*$_3$)$_2$). ESI-MS(m/z): [M+H]$^+$ 616.5, [M–H]$^-$ 614.4.

*4.1.20. (E)-N-(4-(3-Cyano-4-fluorophenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide (**6e**)*

The title compound was prepared in a manner similar to that described for **6a** giving 172 mg (0.37 mmol, 17%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.95 (s, 1H), 9.55 (s, 1H), 8.93 (s, 1H), 8.55 (s, 1H), 8.37–8.38 (m, 1H, $^4J_{F\text{-}H}$ = 5.4 Hz, *J* = 2.4 Hz, arylamine-2-=C*H*), 8.14–8.16 (m, 1H, arylamine-6-=C*H*), 7.55 (t, 1H, *J* = 9.0 Hz, arylamine-5-=C*H*), 7.34 (s, 1H), 6.78–6.83 (m, 1H, –CH=C*H*–CH$_2$–), 6.58 (d, 1H, *J* = 15.6 Hz, –C*H*=CH–CH$_2$–), 4.37–4.38 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O–), 3.80–3.82 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O–), 3.33 (s, 3H, C*H*$_3$O–), 3.09 (d, 2H, *J* = 6.0 Hz, –C*H*$_2$–N(CH$_3$)$_2$), 2.19 (s, 6H, –N(C*H*$_3$)$_2$). ESI-MS (m/z): [M+H]$^+$ 465.4.

*4.1.21. (E)-4-(Dimethylamino)-N-(4-(4-(3-fluorobenzyloxy)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)but-2-enamide (**6f**)*

The title compound was prepared in a manner similar to that described for **6a** giving 190 mg (0.35 mmol, 20%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.62 (s, 2H), 8.85 (s, 1H), 8.42 (s, 1H), 7.65 (d, 2H, *J* = 8.4 Hz, arylamine-2,6-=C*H*), 7.44–7.47 (m, 1H, 3-fluorobenzyloxy-5-=C*H*), 7.29–7.32 (ap. t., 2H, $^3J_{F\text{-}H}$ = 9.6 Hz, *J* = 7.8 Hz, 3-fluorobenzyloxy-2,6-=C*H*), 7.27 (s, 1H), 7.15–7.18 (m, 1H, 3-fluorobenzyloxy-4-=C*H*), 7.03 (d, 2H, *J* = 8.4 Hz, arylamine-3,5-=C*H*), 6.77–6.82 (m, 1H, –CH=C*H*–CH$_2$–), 6.54 (d, 1H, *J* = 15.0 Hz, –C*H*=CH–CH$_2$–), 5.15 (s, 2H, 3-fluorobenzyloxy-C*H*$_2$O–), 4.34–4.37 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O–), 3.80–3.81 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O–), 3.34 (s, 3H, C*H*$_3$O–), 3.09 (d, 2H, *J* = 5.4 Hz, –C*H*$_2$–N(CH$_3$)$_2$), 2.19 (s, 6H, –N(C*H*$_3$)$_2$). ESI-MS (m/z): [M+H]$^+$ 546.5, [M–H]$^-$ 544.4.

*4.1.22. (E)-N-(4-(3-Chloro-4-(pyridin-2-ylmethoxy)phenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide (**6g**)*

The title compound was prepared in a manner similar to that described for **6a** giving 219 mg (0.39 mmol, 38%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.69 (s, 1H), 9.54 (s, 1H), 8.88 (s, 1H), 8.60 (d, 1H, *J* = 4.2 Hz, pyridin-6-=C*H*), 8.48 (s, 1H), 7.98 (d, 1H, *J* = 2.4 Hz, arylamine-2-=C*H*), 7.88–7.90 (m, 1H, pyridin-4-=C*H*), 7.68–7.70 (dd, 1H, *J* = 8.4 Hz, *J* = 2.4 Hz, arylamine-6-=C*H*), 7.59 (d, 1H, *J* = 7.8 Hz, pyridin-3-=C*H*), 7.37 (t, 1H, pyridin-5-=C*H*), 7.29 (s, 1H), 7.25 (d, 1H, *J* = 8.4 Hz, arylamine-5-=C*H*), 6.78–6.81 (m, 1H, –CH=C*H*–CH$_2$–), 6.57 (d, 1H, *J* = 15.6 Hz, –C*H*=CH–CH$_2$–), 5.29 (s, 2H, pyridin-2-yl-C*H*$_2$O-), 4.35–4.36 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O–), 3.79–3.81 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O–), 3.35 (s, 3H, C*H*$_3$O–), 3.14 (broad s, 2H, –C*H*$_2$–N(CH$_3$)$_2$), 2.22 (s, 6H, –N(C*H*$_3$)$_2$). ESI-MS (m/z): [M+H]$^+$563.5.

*4.1.23. (E)-4-(Dimethylamino)-N-(7-(2-methoxyethoxy)-4-(4-(pyridin-2-ylmethoxy)phenylamino)quinazolin-6-yl)but-2-enamide (**6h**)*

The title compound was prepared in a manner similar to that described for **6a** giving 185 mg (0.35 mmol, 35%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 8.86 (s, 1H), 8.59 (d, 1H *J* = 4.8 Hz, pyridin-6-=C*H*), 8.41 (s, 1H), 7.84–7.87 (m, 1H, pyridin-4-=C*H*), 7.65 (d, 2H, *J* = 9.0 Hz, arylamine-2,6-=C*H*), 7.54 (d, 1H, *J* = 8.4 Hz, pyridin-3-=C*H*), 7.35–7.37 (m, 1H, pyridin-5-=C*H*), 7.27 (s, 1H), 7.04 (d, 2H, *J* = 9.0 Hz, arylamine-3,5-=C*H*), 6.77–6.81 (m, 1H, –CH=C*H*–CH$_2$–), 6.55 (d, 1H, *J* = 15.0 Hz, –C*H*=CH–CH$_2$–), 4.34–4.35 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O–), 3.79–3.80 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O–), 3.35 (s, 3H, C*H*$_3$OCH$_2$CH$_2$O–), 3.10 (d, 2H, *J* = 5.4 Hz, –C*H*$_2$–N(CH$_3$)$_2$), 2.19 (s, 6H, –N(C*H*$_3$)$_2$). ESI-MS (m/z): [M+H]$^+$ 529.5.

*4.1.24. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide (**6i**)*

The title compound was prepared in a manner similar to that described for **6a** giving 142 mg (0.30 mmol, 55%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.75 (s, 1H), 9.53 (s, 1H), 8.93 (s, 1H), 8.53 (s, 1H), 8.13–8.15 (dd, 1H, $^4J_{F\text{-}H}$ = 6.6 Hz, *J* = 2.4 Hz, arylamine-2-=C*H*), 7.80–7.82 (m, 1H, arylamine-6-=C*H*), 7.41–7.44 (ap. t., 1H, $^3J_{F\text{-}H}$ = 9.6 Hz, *J* = 8.4 Hz, arylamine-5-=C*H*), 7.26 (s, 1H), 6.80 (m, 1H, –CH=C*H*–CH$_2$–), 6.57 (d, 1H, *J* = 15.0 Hz, –C*H*=CH–CH$_2$–), 4.35–4.37 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O–), 3.80–3.82 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O–), 3.35 (s, 3H, C*H*$_3$O–), 3.09 (d, 2H, *J* = 5.4 Hz, –C*H*$_2$–N(CH$_3$)$_2$), 2.19 (s, 6H, –N(C*H*$_3$)$_2$). ESI-MS (m/z): [M+H]$^+$ 474.3.

*4.1.25. (E)-N-(4-(4-Bromo-2-fluorophenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide (**6j**)*

The title compound was prepared in a manner similar to that described for **6a** giving 129 mg (0.25 mmol, 49%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.75 (s, 1H), 9.51 (s, 1H), 8.92 (s, 1H), 8.39 (s, 1H), 7.63–7.65 (m, 1H, arylamine-3-=C*H*), 7.44–7.50 (m, 2H, arylamine-5,6-=C*H*), 7.31 (s, 1H), 6.78–6.82 (m, 1H, –CH=C*H*–CH$_2$–), 6.59 (d, 1H, *J* = 15.0 Hz, –C*H*=CH–CH$_2$–), 4.36–4.38 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OCH$_2$C*H*$_2$O–), 3.80–3.82 (ap. t., 2H, *J* = 4.8 Hz, *J* = 4.2 Hz, CH$_3$OC*H*$_2$CH$_2$O–), 3.35 (s, 3H, C*H*$_3$O–), 3.09 (d, 2H, *J* = 5.4 Hz, –C*H*$_2$–N(CH$_3$)$_2$), 2.19 (s, 6H, –N(C*H*$_3$)$_2$). ESI-MS (m/z): [M+H]$^+$ 518.2.

*4.1.26. (S,E)-N-(4-(3-Chloro-4-(3-fluorobenzyloxy)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide (**6k**)*

The title compound was prepared in a manner similar to that described for **6a** giving 248 mg (0.42 mmol, 28%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.70 (s, 1H), 9.45 (s, 1H), 8.93 (s, 1H), 8.55 (s, 1H), 7.97 (d, 1H, J = 2.4 Hz, arylamine-2-=C*H*), 7.70 (d, 1H, J = 7.2 Hz, arylamine-6-=C*H*), 7.45–7.49 (m, 1H, 3-fluorobenzyloxy-5-=C*H*), 7.31–7.34 (m, 2H, $^3J_{F\text{-}H}$ = 11.4 Hz, J = 7.8 Hz, 3-fluorobenzyloxy-2,6-=C*H*), 7.24 (d, 1H, J = 7.2 Hz, arylamine-5-=C*H*), 7.21 (s, 1H), 7.17–7.20 (m, 1H, 3-fluorobenzyloxy-5-=C*H*), 6.78–6.83 (m, 1H, −CH=C*H*−CH_2−), 6.60 (d, 1H, J = 15.0 Hz, −C*H*=CH−CH_2−), 5.29 (broad s, 1H, tetrahydrofuran-3-C*H*), 5.25 (s, 2H, 3-fluorobenzyloxy-CH_2O−), 4.00 (d, 2H, J = 2.4 Hz, tetrahydrofuran-2-CH_2), 3.91–3.95 (m, 1H, tetrahydrofuran-5-CH_2), 3.78–3.80 (m, 1H, tetrahydrofuran-5-CH_2), 3.09 (d, 2H, J = 5.4 Hz, −CH_2−N$(CH_3)_2$), 2.32–2.37 (m, 1H, tetrahydrofuran-4-CH_2), 2.19 (s, 6H, −N$(CH_3)_2$), 2.14–2.17 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 592.5.

4.1.27. (S,E)-4-(Dimethylamino)-N-(4-(4-(3-fluorobenzyloxy)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)but-2-enamide (*6l*)

The title compound was prepared in a manner similar to that described for **6a** giving 173 mg (0.31 mmol, 41%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.63 (d, 1H), 9.44 (s, 1H), 8.89 (d, 1H), 8.42 (s, 1H), 7.65 (d, 2H, J = 8.4 Hz, arylamine-2,6-=C*H*), 7.43–7.46 (m, 1H, 3-fluorobenzyloxy-5-=C*H*), 7.29–7.32 (m, 2H, $^3J_{F\text{-}H}$ = 9.6 Hz, J = 7.8 Hz, 3-fluorobenzyloxy-2,6-=C*H*), 7.16–7.21 (m, 1H, 3-fluorobenzyloxy-4-=C*H*), 7.03 (d, 2H, J = 8.4 Hz, arylamine-3,5-=C*H*), 6.77–6.81 (m, 1H, −CH=C*H*−CH_2−), 6.59 (d, 1H, J = 15.0 Hz, −C*H*=CH−CH_2−), 5.27 (broad s, 1H, tetrahydrofuran-3-C*H*), 5.15 (s, 2H, 3-fluorobenzyloxy-CH_2O−), 3.99 (broad s, 2H, tetrahydrofuran-2-CH_2), 3.92–3.97 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.79 (m, 1H, tetrahydrofuran-5-CH_2), 3.10 (d, 2H, J = 5.4 Hz, −CH_2−N$(CH_3)_2$), 2.32–2.35 (m, 1H, tetrahydrofuran-4-CH_2), 2.19 (s, 6H, −N$(CH_3)_2$), 2.12–2.16 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): [M+H]+ 558.5.

4.1.28. (S,E)-N-(4-(3-Chloro-4-(pyridin-2-ylmethoxy)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide (*6m*)

The title compound was prepared in a manner similar to that described for **6a** giving 195 mg (0.34 mmol, 38%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.69 (s, 1H), 9.44 (s, 1H), 8.93 (s, 1H), 8.60 (d, 1H, J = 4.8 Hz, pyridin-6-=C*H*), 8.48 (s, 1H), 7.98 (d, 1H, J = 2.4 Hz, arylamine-2-=C*H*), 7.87–7.90 (m, 1H, pyridin-4-=C*H*), 7.68–7.70 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, arylamine-6-=C*H*), 7.59 (d, 1H, J = 7.8 Hz, pyridin-3-=C*H*), 7.36–7.38 (m, 1H, pyridin-5-=C*H*), 7.24 (d, 1H, J = 8.4 Hz, arylamine-5-=C*H*), 7.19 (s, 1H), 6.78–6.83 (m, 1H, −CH=C*H*−CH_2−), 6.59 (d, 1H, J = 15.0 Hz, −C*H*=CH−CH_2−), 5.29 (s, 3H, pyridin-2-yl-CH_2O− and tetrahydrofuran-3-C*H*), 4.00 (d, 2H, J = 2.4 Hz, tetrahydrofuran-2-CH_2), 3.91–3.95 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.80 (m, 1H, tetrahydrofuran-5-CH_2), 3.09 (d, 2H, J = 5.4 Hz, -CH_2-N$(CH_3)_2$), 2.31–2.37 (m, 1H, tetrahydrofuran-4-CH_2), 2.20 (s, 6H, −N$(CH_3)_2$), 2.14–2.16 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 575.4.

4.1.29. (S,E)-4-(Dimethylamino)-N-(4-(4-(pyridin-2-ylmethoxy)phenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)but-2-enamide (*6n*)

The title compound was prepared in a manner similar to that described for **6a** giving 189 mg (0.35 mmol, 45%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.65 (d, 1H, J = 18.6 Hz), 9.48 (s, 1H), 8.90 (s, 1H), 8.59 (d, 1H, J = 4.2 Hz, 1H, pyridin-6-=C*H*), 8.41 (s, 1H), 7.85 (t, 1H, J = 7.8 Hz, pyridin-4-=C*H*), 7.65 (d, 2H, J = 8.4 Hz, arylamine-2,6-=C*H*), 7.55 (d, 1H, J = 7.8 Hz, pyridin-3-=C*H*), 7.35–7.37 (ap. t., 1H, J = 7.2 Hz, J = 4.8 Hz, pyridin-5-=C*H*), 7.19 (s, 1H), 7.04 (d, 2H, J = 8.4 Hz, arylamine-3,5-=C*H*), 6.77–6.82 (m, 1H, −CH=C*H*−CH_2−), 6.56–6.61 (ap. t., 1H, J = 15.0 Hz, J = 8.4 Hz, −C*H*=CH−CH_2−), 5.27 (broad s, 1H, tetrahydrofuran-3-C*H*), 5.19 (s, 2H, pyridin-2-yl-CH_2O−), 3.99 (broad s, 2H, tetrahydrofuran-2-CH_2), 3.91–3.95 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.79 (m, 1H, tetrahydrofuran-5-CH_2), 3.10 (d, 2H, J = 3.0 Hz, −CH_2−N$(CH_3)_2$), 2.31–2.36 (m, 1H, tetrahydrofuran-4-CH_2), 2.20 (s, 6H, −N$(CH_3)_2$), 2.13–2.16 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 541.4.

4.1.30. (S,E)-4-(Dimethylamino)-N-(4-(3-ethynylphenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)but-2-enamide (*6o*)

The title compound was prepared in a manner similar to that described for **6a** giving 210 mg (0.46 mmol, 39%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.75 (s, 1H), 9.45 (s, 1H), 8.97 (s, 1H), 8.53 (s, 1H), 8.00 (s, 1H), 7.87 (d, 1H, J = 7.8 Hz, arylamine-6-=C*H*), 7.37–7.40 (ap. t., 1H, J = 7.8 Hz, J = 7.2 Hz, arylamine-5-=C*H*), 7.24 (s, 1H), 7.20 (d, 1H, J = 7.2 Hz, arylamine-4-=C*H*), 6.79–6.83 (m, 1H, −CH=C*H*−CH_2−), 6.60 (d, 1H, J = 15.6 Hz, −C*H*=CH−CH_2-−), 5.30 (s, 1H, tetrahydrofuran-3-C*H*), 4.20 (s, 1H, alkyne-*H*), 4.00 (d, 2H, J = 3.0 Hz, tetrahydrofuran-2-CH_2), 3.91–3.95 (m, 1H, tetrahydrofuran-5-CH_2), 3.78–3.81 (m, 1H, tetrahydrofuran-5-CH_2), 3.09 (d, 2H, J = 3.0 Hz, −CH_2−N$(CH_3)_2$), 2.33–2.36 (m, 1H, tetrahydrofuran-4-CH_2), 2.19 (s, 6H, −N$(CH_3)_2$), 2.13–2.17 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 458.4.

4.1.31. (S,E)-4-(Dimethylamino)-N-(4-(4-chloro-3-(trifluoromethyl)phenylamino) -7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)but-2-enamide (*6p*)

The title compound was prepared in a manner similar to that described for **6a** giving 214 mg (0.40 mmol, 33%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 10.0 (s, 1H), 9.48 (s, 1H), 9.01 (s, 1H), 8.58 (s, 1H), 8.40 (d, 1H, J = 2.4 Hz, arylamine-2-=C*H*), 8.28–8.30 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz, arylamine-6-=C*H*), 7.72 (d, 1H, J = 8.4 Hz, arylamine-5-=C*H*), 7.27 (s, 1H), 6.80–6.85 (m, 1H, −CH=C*H*−CH_2−), 6.61 (d, 1H, J = 15.6 Hz, −C*H*=CH−CH_2−), 5.31 (broad s, 1H, tetrahydrofuran-3-C*H*), 4.00 (broad s, 2H, tetrahydrofuran-2-CH_2), 3.92–3.96 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.81 (m,1H, tetrahydrofuran-5-CH_2), 3.09 (d, 2H, J = 3.0 Hz, −CH_2-−N$(CH_3)_2$), 2.34–2.37 (m, 1H, tetrahydrofuran-4-CH_2), 2.19 (s, 6H, −N$(CH_3)_2$), 2.13–2.17 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 536.4.

4.1.32. (S,E)-N-(4-(3-Cyano-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide (*6q*)

The title compound was prepared in a manner similar to that described for **6a** giving 261 mg (0.55 mmol, 25%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.96 (s, 1H), 9.46 (s, 1H), 8.98 (s, 1H), 8.55 (s, 1H), 8.38 (d, 1H, J = 2.4 Hz, arylamine-2-=C*H*), 8.15–8.16 (ap. t., 1H, $^4J_{F\text{-}H}$ = 4.2 Hz, J = 3.6 Hz, arylamine-6-=C*H*), 7.55 (t, 1H, J = 9.0 Hz, arylamine-5-=C*H*), 7.26 (s, 1H), 6.79–6.84 (m, 1H, −CH=C*H*−CH_2−), 6.61 (d, 1H, J = 15.6 Hz, −C*H*=CH−CH_2−), 5.31 (broad s, 1H, tetrahydrofuran-3-C*H*), 4.00 (d, 2H, J = 2.4 Hz, tetrahydrofuran-2-CH_2), 3.92–3.96 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.81 (m, 1H, tetrahydrofuran-5-CH_2), 3.10 (d, 2H, J = 3.0 Hz, −CH_2−N$(CH_3)_2$), 2.31–2.38 (m, 1H, tetrahydrofuran-4-CH_2), 2.19 (s, 6H, -N$(CH_3)_2$), 2.15–2.17 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 477.4, $[M-H]^-$ 475.3.

4.1.33. (E)-4-(Dimethylamino)-N-(4-(3-ethynylphenylamino)-7-(tetrahydro-2H-pyran-4-yloxy)quinazolin-6-yl)but-2-enamide (*6r*)

The title compound was prepared in a manner similar to that described for **6a** giving 151 mg (0.32 mmol, 32%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.78 (s, 1H), 8.93 (s, 1H), 8.60 (s, 1H), 7.97 (s, 1H), 7.85 (d, 1H, J = 7.8 Hz, arylamine-6-=C*H*), 7.41 (s, 1H), 7.41 (t, 1H, $J = 7.8$ Hz, arylamine-5-=C*H*), 7.24 (d, 1H, $J = 7.8$ Hz, arylamine-4-=C*H*), 6.76–6.83 (m, 2H, $-CH=CH-CH_2-$), 4.94–4.97 (m, 1H, tetrahydro-2H-pyran-4-C*H*), 4.22 (s, 1H, alkyne-*H*), 3.99 (d, 2H, $J = 5.4$ Hz, $-CH_2-N(CH_3)_2$), 3.89–3.92 (m, 2H, tetrahydro-2H-pyran-2-CH_2), 3.54–3.58 (m, 2H, tetrahydro-2H-pyran-2-CH_2), 2.83 (s, 6H, $-N(CH_3)_2$), 2.06–2.09 (m, 2H, tetrahydro-2H-pyran-3-CH_2), 1.73–1.78 (m, 2H, tetrahydro-2H-pyran-3-CH_2). ESI-MS (m/z): $[M+H]^+$ 472.3.

*4.1.34. (E)-4-(Dimethylamino)-N-(4-(3-ethynylphenylamino)-7-(1-methylpiperidin-4-yloxy)quinazolin-6-yl)but-2-enamide (**6s**)*

The title compound was prepared in a manner similar to that described for **6a** giving 223 mg (0.46 mmol, 30%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.73 (s, 1H), 9.44 (s, 1H), 8.89 (s, 1H), 8.52 (s, 1H), 8.01 (s, 1H), 7.88–7.89 (dd, 1H, $J = 7.8$ Hz, $J = 1.2$ Hz, arylamine-6-=C*H*), 7.38 (t, 1H, $J = 7.8$ Hz, arylamine-5-=C*H*), 7.32 (s, 1H), 7.19 (d, 1H, $J = 7.2$ Hz, arylamine-4-=C*H*), 6.78–6.83 (m, 1H, $-CH=CH-CH_2-$), 6.56 (d, 1H, $J = 15.6$ Hz, $-CH=CH-CH_2-$), 4.71–4.72 (m, 1H, 1-methylpiperidin-4-C*H*-), 4.20 (s, 1H, alkyne-*H*), 3.09 (d, 2H, J = 5.4 Hz, $-CH_2-N(CH_3)_2$), 2.62–2.65 (m, 2H, 1-methylpiperidin-2-CH_2), 2.23–2.26 (m, 2H, 1-methylpiperidin-2-CH_2), 2.19 (broad s, 9H, $-N(CH_3)_2$ and 1-methylpiperidin-1-CH_3), 1.92–2.01 (m, 2H, 1-methylpiperidin-3-CH_2), 1.79–1.85 (m, 2H, 1-methylpiperidin-3-CH_2). ESI-MS (m/z): $[M+H]^+$ 485.3.

*4.1.35. (S,E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(piperidin-1-yl)but-2-enamide (**7a**)*

The title compound was prepared in a manner similar to that described for **6a** giving 457 mg (0.87 mmol, 47%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.82 (s, 1H), 9.47 (s, 1H), 8.95 (s, 1H), 8.53 (s, H), 8.12–8.14 (dd, 1H, $^4J_{F\text{-}H} = 6.6$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.79–7.82 (m, 1H, arylamine-6-=C*H*), 7.41–7.44 (ap. t., 1H, $^3J_{F\text{-}H} = 9.6$ Hz, $J = 8.4$ Hz, arylamine-5-=C*H*), 7.24 (s, 1H), 6.79–6.84 (m, 1H, $-CH_2-CH=CH$-), 6.58 (d, 1H, $J = 15.0$ Hz, $-CH_2-CH=CH-$), 5.30 (s, 1H, tetrahydrofuran-3-C*H*), 4.01–4.05 (m, 2H, tetrahydrofuran-2-CH_2), 3.92–3.95 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.80 (m, 1H, tetrahydrofuran-5-CH_2), 3.13 (broad s, 2H, $-CH_2-CH=CH-$), 2.32–2.38 (m, 5H, one hydrogen of tetrahydrofuran-4-CH_2 and 2 × piperidin-2-CH_2), 2.14–2.16 (m, 1H, tetrahydrofuran-4-CH_2), 1.54 (broad s, 4H, 2 × piperidin-3-CH_2), 1.39–1.44 (m, 2H, piperidin-4-CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.0, 157.2, 154.3, 153.6 (d, $^1J_{F\text{-}C} = 242$ Hz), 153.7, 149.2, 142.0, 137.3 (d, $^3J_{F\text{-}C} = 3$ Hz), 128.0, 126.7, 124.0, 122.9, 122.8, 119.2 (d, $^2J_{F\text{-}C} = 18$ Hz), 116.9 (d, $^2J_{F\text{-}C} = 21$ Hz), 109.4, 108.5, 79.3, 72.5, 67.1, 59.6, 54.5, 32.9, 25.8, 24.2. ESI-MS (m/z): $[M+H]^+$ 526.2.

*4.1.36. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(piperidin-1-yl)but-2-enamide (**7b**)*

The title compound was prepared in a manner similar to that described for **6a** giving 385 mg (0.75 mmol, 50%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.81 (s, 1H), 9.54 (s, 1H), 8.89 (s, 1H), 8.53 (s, H), 8.13–8.14 (dd, 1H, $^4J_{F\text{-}H} = 6.0$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.80–7.81 (m, 1H, arylamine-6-=C*H*), 7.41–7.44 (ap. t., 1H, $^3J_{F\text{-}H} = 9.6$ Hz, $J = 8.4$ Hz, arylamine-5-=C*H*), 7.32 (s, 1H), 6.78–6.83 (m, 1H, $-CH_2-CH=CH-$), 6.54 (d, 1H, $J = 15.6$ Hz, $-CH_2-CH=CH-$), 4.37 (broad s, 2H, $CH_3OCH_2CH_2O-$), 3.80 (broad s, 2H, $CH_3OCH_2CH_2O-$), 3.35 (s, 3H, CH_3O-), 3.13 (broad s, 2H, $-CH_2-CH=CH-$), 2.37 (broad s, 4H, 2 × piperidin-2-CH_2), 1.53 (broad s, 4H, 2 × piperidin-3-CH_2), 1.39 (broad s, 2H, piperidin-4-CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.1, 157.2, 155.2, 154.3, 153.6 (d, $^1J_{F\text{-}C} = 241$ Hz), 149.4, 142.5, 137.3, 127.8, 126.3, 124.0, 122.9, 122.8, 119.1 (d, $^2J_{F\text{-}C} = 15$ Hz), 116.9 (d, $^2J_{F\text{-}C} = 22$ Hz), 109.4, 108.2, 70.5, 68.9, 59.8, 58.8, 54.6, 26.0, 24.4. ESI-MS (m/z): $[M+H]^+$ 514.2.

*4.1.37. (S,E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(4-oxopiperidin-1-yl)but-2-enamide (**7c**)*

The title compound was prepared in a manner similar to that described for **6a** giving 232 mg (0.43 mmol, 43%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.82 (s, 1H), 9.49 (s, 1H), 8.95 (s, 1H), 8.54 (s, H), 8.12–8.14 (dd, 1H, $^4J_{F\text{-}H} = 6.0$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.79–7.81 (m, 1H, arylamine-6-=C*H*), 7.43 (t, 1H, $J = 9.0$ Hz, arylamine-5-=C*H*), 7.25 (s, 1H), 6.83–6.89 (m, 1H, $-CH_2-CH=CH--$), 6.61–6.63 (m, 1H, $-CH_2-CH-CH-$), 5.30 (d, 1H, $J = 3.0$ Hz, tetrahydrofuran-3-C*H*), 4.00–4.02 (m, 2H, tetrahydrofuran-2-CH_2), 3.92–3.95 (m, 1H, tetrahydrofuran-5-CH_2), 3.78–3.80 (m, 1H, tetrahydrofuran-5-CH_2), 3.09–3.10 (m, 2H, $-CH_2-CH=CH-$), 2.72–2.76 (m, 4H, 2 × 4-oxopiperidin-3-CH_2), 2.35–2.39 (m, 5H, one hydrogen of tetrahydrofuran-4-CH_2 and 2 × 4-oxopiperidin-2-CH_2), 2.14–2.16 (m, 1H, tetrahydrofuran-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 540.3.

*4.1.38. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl)-4-(cyclopropyl(methyl)amino)but-2-enamide (**7d**)*

The title compound was prepared in a manner similar to that described for **6a** giving 273 mg (0.6 mmol, 40%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.83 (s, 1H), 9.70 (s, 1H), 8.94 (s, 1H), 8.54 (s, H), 8.12–8.14 (dd, 1H, $^4J_{F\text{-}H} = 6.6$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.79–7.81 (m, 1H, arylamine-6-=C*H*), 7.41–7.44 (ap. t., 1H, $^3J_{F\text{-}H} = 9.6$ Hz, $J = 8.4$ Hz, arylamine-5-=C*H*), 7.29 (s, 1H), 6.81–6.86 (m, 1H, $-CH_2-CH=CH-$), 6.57–6.59 (m, 1H, $-CH_2-CH=CH-$), 4.02 (s, 3H, CH_3O), 3.34–3.35 (m, 2H, $-CH_2-CH=CH-$), 2.29 (s, 3H, $N-CH_3$), 1.77–1.82 (m, 1H, cyclopropyl-1-C*H*), 0.36–0.47 (m, 4H, 2 × cyclopropyl-2-CH_2). ESI-MS (m/z): $[M+H]^+$ 456.2.

*4.1.39. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(cyclopropyl(methyl)amino)but-2-enamide (**7e**)*

The title compound was prepared in a manner similar to that described for **6a** giving 524 mg (1.05 mmol, 38%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.82 (s, 1H), 9.52 (s, 1H), 8.91 (s, 1H), 8.53 (s, H), 8.13–8.14 (dd, 1H, $^4J_{F\text{-}H} = 6.6$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.79–7.82 (m, 1H, arylamine-6-=C*H*), 7.43 (t, 1H, $J = 8.4$ Hz, arylamine-5-=C*H*), 7.32 (s, 1H), 6.82–6.87 (m, 1H, $-CH_2-CH=CH-$), 6.54 (d, 1H, $J = 15.6$ Hz, $-CH_2-CH=CH-$), 4.36–4.38 (m, 2H, $CH_3OCH_2CH_2O-$), 3.80–3.81 (m, 2H, $CH_3OCH_2CH_2O-$), 3.35 (s, 3H, CH_3O-), 3.17–3.18 (m, 2H, $-CH_2-CH=CH-$), 2.29 (s, 3H, $N-CH_3$), 1.75–1.76 (m, 1H, cyclopropyl-1-C*H*), 0.36–0.47 (m, 4H, 2 × cyclopropyl-2-CH_2). ^{13}C NMR (150 MHz, DMSO-d_6, δ_{ppm}): 164.0, 157.2, 155.0, 154.3, 153.6 (d, $^1J_{F\text{-}C} = 242$ Hz), 149.3, 142.3, 137.2 (d, $^3J_{F\text{-}C} = 3.5$ Hz), 127.7, 126.2, 123.9, 122.8, 122.7, 119.1 (d, $^2J_{F\text{-}C} = 18$ Hz), 116.9 (d, $^2J_{F\text{-}C} = 22$ Hz), 116.5, 109.4, 108.0, 70.4, 68.8, 58.7, 58.5, 42.6, 38.7, 7.2. ESI-MS (m/z): $[M+H]^+$ 500.2.

*4.1.40. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-ethoxyquinazolin-6-yl)-4-(cyclopropyl(methyl)amino)but-2-enamide (**7f**)*

The title compound was prepared in a manner similar to that described for **6a** giving 423 mg (0.90 mmol, 45%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.80 (s, 1H), 9.52 (s, 1H), 8.93 (s, 1H), 8.52 (s, H), 8.12–8.14 (dd, 1H, $^4J_{F\text{-}H} = 6.6$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.78–7.81 (m, 1H, arylamine-6-=C*H*), 7.41–7.44 (ap. t., 1H, $^3J_{\text{F-H}}$ = 9.6 Hz, J = 9.0 Hz, arylamine-5-=C*H*), 7.27 (s, 1H), 6.82–6.86 (m, 1H, –CH$_2$–C*H*=CH–), 6.55 (d, 1H, J = 16.2 Hz, –CH$_2$–CH=C*H*–), 4.29–4.31 (m, 2H, CH$_3$C*H*$_2$O–), 3.32–3.34 (m, 2H, –C*H*$_2$–CH=CH–), 2.28 (s, 3H, N–C*H*$_3$), 1.75–1.76 (m, 1H, cyclopropyl-1-C*H*), 1.45–1.47 (m, 3H, C*H*$_3$CH$_2$O-), 0.36–0.47 (m, 4H, 2 × cyclopropyl-2-C*H*$_2$). ^{13}C NMR (150 MHz, DMSO-d_6, δ_{ppm}): 164.0, 157.2, 154.9, 154.3, 153.6 (d, $^1J_{\text{F-C}}$ = 241 Hz), 149.4, 142.3, 137.3 (d, $^3J_{\text{F-C}}$ = 3 Hz), 127.8, 126.2, 124.0, 122.9, 122.8, 119.1 (d, $^2J_{\text{F-C}}$ = 18 Hz), 116.9 (d, $^2J_{\text{F-C}}$ = 22 Hz), 116.3, 109.2, 107.6, 65.0, 58.6, 42.7, 38.7, 14.7, 7.2. ESI-MS (*m/z*): [M+H]$^+$ 470.3.

4.1.41. *(S,E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(3,3-difluoroazetidin-1-yl)but-2-enamide (**7g**)*

The title compound was prepared in a manner similar to that described for **6a** giving 192 mg (0.36 mmol, 31%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.90 (s, 1H), 9.59 (s, 1H), 8.93 (s, 1H), 8.53 (s, H), 8.12–8.14 (dd, 1H, $^4J_{\text{F-H}}$ = 6.0 Hz, J = 2.4 Hz, arylamine-2-=C*H*), 7.78–7.80 (m, 1H, arylamine-6-=C*H*), 7.42 (t, 1H, J = 9.0 Hz, arylamine-5-=C*H*), 7.33 (s, 1H), 6.82–6.87 (m, 1H, –CH$_2$–C*H*=CH–), 6.55 (d, 1H, J = 15.0 Hz, –CH$_2$–CH=C*H*–), 4.47–4.50 (m, 1H, tetrahydrofuran-3-C*H*), 4.00–4.02 (m, 2H, tetrahydrofuran-2-C*H*$_2$), 3.91–3.95 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.78–3.80 (m, 2H, tetrahydrofuran-5-C*H*$_2$), 3.50–3.53 (m, 4H, 2 × 3,3-difluoroazetidin-2-C*H*$_2$), 3.43–3.44 (m, 2H, –C*H*$_2$–CH=CH–), 2.42–2.44 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 2.15–2.17 (m, 1H, tetrahydrofuran-4-C*H*$_2$). ESI-MS (m/z): [M+H]$^+$ 534.2.

4.1.42. *(E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl)-4-(thiomorpholine-1-oxide-4-yl)but-2-enamide (**7h**)*

The title compound was prepared in a manner similar to that described for **6a** giving 136 mg (0.27 mmol, 32%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.87 (s, 1H), 9.77 (s, 1H), 8.94 (s, 1H), 8.56 (s, H), 8.12–8.14 (dd, 1H, $^4J_{\text{F-H}}$ = 6.0 Hz, J = 3.0 Hz, arylamine-2-=C*H*), 7.78–7.80 (m, 1H, arylamine-6-=C*H*), 7.42–7.45 (m, 1H, $^3J_{\text{F-H}}$ = 9.6 Hz, J = 9.0 Hz, arylamine-5-=C*H*), 7.30 (s, 1H), 6.81–6.83 (m, 1H, –CH$_2$–C*H*=CH–), 6.65 (d, 1H, J = 15.0 Hz, –CH$_2$–CH=C*H*–), 4.02 (s, 3H, C*H*$_3$O–), 3.26–3.27 (m, 2H, –C*H*$_2$–CH=CH–), 2.88–2.93 (m, 4H, 2 × thiomorpholine-1-oxide-3-C*H*$_2$), 2.76–2.80 (m, 2H, thiomorpholine-1-oxide-2-C*H*$_2$), 2.66–2.69 (m, 2H, thiomorpholine-1-oxide-2-C*H*$_2$). ESI-MS (m/z): [M+H]$^+$ 504.1.

4.1.43. *(S,E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(thiomorpholine-1-oxide-4-y)but-2-enamide (**7i**)*

The title compound was prepared in a manner similar to that described for **6a** giving 168 mg (0.30 mmol, 49%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.82 (s, 1H), 9.50 (s, 1H), 8.95 (s, 1H), 8.54 (s, H), 8.13–8.14 (dd, 1H, $^4J_{\text{F-H}}$ = 7.2 Hz, J = 2.4 Hz, arylamine-2-=C*H*), 7.79–7.82 (m, 1H, arylamine-6-=C*H*), 7.41–7.44 (ap. t., 1H, $^3J_{\text{F-H}}$ = 9.6 Hz, J = 9.0 Hz, arylamine-5-=C*H*), 7.25 (s, 1H), 6.79–6.84 (m, 1H, –CH$_2$–C*H*=CH–), 6.61 (d, 1H, J = 15.0 Hz, –CH$_2$–CH=C*H*–), 5.30 (d, 1H, J = 2.4 Hz, tetrahydrofuran-3-C*H*), 4.00 (d, 2H, J = 3.0 Hz, tetrahydrofuran-2-C*H*$_2$), 3.92–3.96 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.77–3.80 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.26–3.27 (m, 2H, –C*H*$_2$–CH=CH–), 2.88–2.94 (m, 4H, 2 × thiomorpholine-1-oxide-3-C*H*$_2$), 2.76–2.79 (m, 2H, thiomorpholine-1-oxide-2-C*H*$_2$), 2.66–2.69 (m, 2H, thiomorpholine-1-oxide-2-C*H*$_2$), 2.34–2.37 (m, 1H, tetrahydrofuran-3-yloxy-4-C*H*$_2$), 2.14–2.17 (m, 1H, tetrahydrofuran-4-C*H*$_2$). ESI-MS (m/z): [M+H]$^+$ 560.3. Anal. Calc'd for C$_{26}$H$_{27}$ClFN$_5$O$_4$S-1.5H$_2$O: C, 53.19; H, 5.15; N, 11.93. Found; C, 53.26; H, 5.24; N, 11.75.

4.1.44. *(E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(thiomorpholine-1-oxide-4-y)but-2-enamide (**7j**)*

The title compound was prepared in a manner similar to that described for **6a** giving 384 mg (0.70 mmol, 46%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.82 (s, 1H), 9.58 (s, 1H), 8.90 (s, 1H), 8.54 (s, H), 8.13 (d, 1H, $^4J_{\text{F-H}}$ = 5.4 Hz, arylamine-2-=C*H*), 7.79–7.81 (m, 1H, arylamine-6-=C*H*), 7.42 (t, 1H, J = 9.0 Hz, arylamine-5-=C*H*), 7.33 (s, 1H), 6.79–6.83 (m, 1H, –CH$_2$–C*H*=CH–), 6.60 (d, 1H, J = 15.6 Hz, –CH$_2$–CH=C*H*–), 4.37 (broad s, 2H, CH$_3$OCH$_2$C*H*$_2$O-), 3.80 (broad s, 2H, CH$_3$OC*H*$_2$CH$_2$O–), 3.35 (s, 3H, C*H*$_3$O-), 3.27–3.30 (m, 2H, –C*H*$_2$–CH=CH–), 2.90–2.93 (m, 4H, 2 × thiomorpholine-1-oxide-3-C*H*$_2$), 2.77–2.81 (m, 2H, thiomorpholine-1-oxide-2-C*H*$_2$), 2.65–2.70 (m, 2H, thiomorpholine-1-oxide-2-C*H*$_2$). ^{13}C NMR (150 MHz, DMSO-d_6, δ_{ppm}): 163.8, 157.2, 155.2, 154.3, 153.6 (d, $^1J_{\text{F-C}}$ = 242 Hz), 149.1, 137.2, 127.6, 124.0, 122.9, 119.1 (d, $^2J_{\text{F-C}}$ = 18 Hz), 116.9 (d, $^2J_{\text{F-C}}$ = 21 Hz), 109.3, 107.9, 70.4, 68.9, 58.8, 58.4, 45.7, 44.0. ESI-MS (m/z): [M+H]$^+$ 548.2. Anal. Calc'd for C$_{25}$H$_{27}$ClFN$_5$O$_4$S-1.1H$_2$O: C, 52.88; H, 5.18; N, 12.33. Found; C, 52.91; H, 5.26; N, 12.29.

4.1.45. *(E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl)-4-(dicyclopropylamino)but-2-enamide (**7k**)*

The title compound was prepared in a manner similar to that described for **6a** giving 151 mg (0.26 mmol, 28%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.82 (s, 1H), 9.67 (s, 1H), 8.95 (s, 1H), 8.54 (s, H), 8.13 (d, 1H, $^4J_{\text{F-H}}$ = 4.8 Hz, arylamine-2-=C*H*), 7.79–7.81 (m, 1H, arylamine-6-=C*H*), 7.41–7.44 (ap. t., 1H, $^3J_{\text{F-H}}$ = 9.6 Hz, J = 9.0 Hz, arylamine-5-=C*H*), 7.29 (s, 1H), 6.96–7.01 (m, 1H, –CH$_2$–C*H*=CH–), 6.58 (d, 1H, J = 15.0 Hz, –CH$_2$–CH=C*H*–), 4.01 (s, 3H, C*H*$_3$O–), 3.45 (d, 2H, J = 6.6 Hz, –C*H*$_2$–CH=CH–), 2.00 (broad s, 2H, 2 × dicyclopropylamino-1-C*H*), 0.43–0.44 (m, 4H, 2 × dicyclopropylamino-2-C*H*$_2$), 0.34–0.36 (m, 4H, 2 × dicyclopropylamino-2-C*H*$_2$). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.1, 157.3, 155.7, 154.3, 153.6 (d, $^1J_{\text{F-C}}$ = 242 Hz), 149.4, 142.3, 137.3 (d, $^3J_{\text{F-C}}$ = 2 Hz), 127.8, 126.3, 124.0, 122.9, 122.8, 119.1 (d, $^2J_{\text{F-C}}$ = 18 Hz), 116.9 (d, $^2J_{\text{F-C}}$ = 22 Hz), 116.1109.4, 107.1, 57.5, 56.7, 36.6, 6.3. ESI-MS (m/z): [M+H]$^+$ 582.4. Anal. Calc'd for C$_{25}$H$_{25}$ClFN$_5$O$_2$-1.5H$_2$O: C, 58.99; H, 5.54; N, 13.76. Found; C, 58.97; H, 5.60; N, 13.75.

4.1.46. *(S,E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(dicyclopropylamino)but-2-enamide (**7l**)*

The title compound was prepared in a manner similar to that described for **6a** giving 349 mg (0.65 mmol, 28%).

^{1}H-NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.83 (s, 1H), 9.42 (s, 1H), 8.97 (s, 1H), 8.53 (s, H), 8.12–8.14 (dd, 1H, $^4J_{\text{F-H}}$ = 6.6 Hz, J = 2.4 Hz, arylamine-2-=C*H*), 7.79–7.81 (m, 1H, arylamine-6-=C*H*), 7.43 (t, 1H, J = 9.0 Hz, arylamine-5-=C*H*), 7.24 (s, 1H), 6.98–7.03 (m, 1H, –CH$_2$–C*H*=CH–), 6.58 (d, 1H, J = 15.0 Hz, –CH$_2$–CH=C*H*–), 5.30 (d, 1H, J = 3.0 Hz, tetrahydrofuran-3-C*H*), 4.01 (d, 2H, J = 3.0 Hz, tetrahydrofuran-2-C*H*$_2$), 3.92–3.95 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.77–3.81 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.47 (d, 2H, J = 6.6 Hz, –C*H*$_2$-CH=CH–), 2.33–2.36 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 2.14–2.18 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 1.98–2.02 (m, 2H, 2 × dicyclopropylamino-1-C*H*), 0.42–0.48 (m, 4H, 2 × dicyclopropylamino-2-C*H*$_2$), 0.34–0.37 (m, 4H, 2 × dicyclopropylamino-2-C*H*$_2$). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.0, 157.3, 154.3, 153.7, 153.6 (d, $^1J_{\text{F-C}}$ = 242 Hz), 149.2, 142.4, 137.3 (d, $^3J_{\text{F-C}}$ = 3 Hz), 128.1, 126.3, 124.0, 122.9, 122.8, 119.1 (d, $^2J_{\text{F-C}}$ = 18 Hz), 116.9 (d, $^2J_{\text{F-C}}$ = 22 Hz), 116.5109.4, 108.5, 79.3, 72.5, 67.1, 57.6, 36.6, 32.9, 6.3. ESI-MS (m/z): [M+H]$^+$ 538.3. Anal. Calc'd for C$_{28}$H$_{29}$ClFN$_5$O$_3$-0.8H$_2$O: C, 60.88; H, 5.58; N, 12.68. Found; C, 60.91; H, 5.66; N, 12.60.

*4.1.47. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(2-methoxyethoxy)quinazolin-6-yl)-4-(dicyclopropylamino)but-2-enamide (**7m**)*

The title compound was prepared in a manner similar to that described for **6a** giving 268 mg (0.51 mmol, 32%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.82 (s, 1H), 9.51 (s, 1H), 8.93 (s, 1H), 8.53 (s, H), 8.12–8.14 (dd, 1H, $^4J_{F\text{-}H} = 7.2$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.79–7.82 (m, 1H, arylamine-6-=C*H*), 7.42 (t, 1H, $J = 9.0$ Hz, arylamine-5-=C*H*), 7.32 (s, 1H), 6.97–7.02 (m, 1H, −CH$_2$−C*H*=CH−), 6.55 (d, 1H, $J = 15.6$ Hz, −CH$_2$−CH=C*H*−), 4.36–4.38 (m, 2H, CH$_3$OCH$_2$C*H*$_2$O−), 3.80–3.81 (m, 2H, CH$_3$OC*H*$_2$CH$_2$O−), 3.47 (d, 2H, $J = 6.6$ Hz, −C*H*$_2$−CH=CH−), 3.35 (s, 3H, C*H*$_3$O−), 1.99–2.02 (m, 2H, 2 × dicyclopropylamino-1-C*H*), 0.40–0.45 (m, 4H, 2 × dicyclopropylamino-2-C*H*$_2$), 0.35–0.39 (m, 4H, 2 × dicyclopropylamino-2-C*H*$_2$). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.1, 157.3, 155.0, 154.3, 153.6 (d, $^1J_{F\text{-}C} = 241$ Hz), 149.3, 142.3, 137.3 (d, 1C, $^3J_{F\text{-}C} = 3$ Hz), 127.8, 126.3, 124.0, 122.9, 122.8, 119.1 (d, $^2J_{F\text{-}C} = 19$ Hz), 116.8 (d, $^2J_{F\text{-}C} = 21$ Hz), 116.5, 109.5, 108.1, 70.5, 68.9, 58.8, 57.5, 36.6, 6.3. ESI-MS (m/z): [M+H]$^+$ 526.2. Anal. Calc'd for $C_{27}H_{29}ClFN_5O_3$-0.3CH$_3$CH$_2$OOCCH$_3$-0.5H$_2$O: C, 60.33; H, 5.82; N, 12.47. Found; C, 60.34; H, 5.90; N, 12.41.

*4.1.48. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-ethoxyquinazolin-6-yl)-4-(dicyclopropylamino)but-2-enamide (**7n**)*

The title compound was prepared in a manner similar to that described for **6a** giving 198 mg (0.4 mmol, 40%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.81 (s, 1H), 9.50 (s, 1H), 8.94 (s, 1H), 8.52 (s, H), 8.12–8.13 (dd, 1H, $^4J_{F\text{-}H} = 6.6$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.79–7.81 (m, 1H, arylamine-6-=C*H*), 7.42 (t, 1H, $J = 9.0$ Hz, arylamine-5-=C*H*), 7.26 (s, 1H), 6.97–7.02 (m, 1H, −CH$_2$−C*H*=CH−), 6.57 (d, 1H, $J = 15.0$ Hz, −CH$_2$−CH=C*H*−), 4.28–4.31 (m, 2H, CH$_3$C*H*$_2$O−), 3.47 (d, 2H, $J = 6.6$ Hz, −C*H*$_2$−CH=CH−), 1.98–2.01 (m, 2H, 2 × dicyclopropylamino-1-C*H*), 1.45–1.47 (m, 3H, C*H*$_3$CH$_2$O−), 0.43–0.45 (m, 4H, 2 × dicyclopropylamino-2-C*H*$_2$), 0.35–0.36 (m, 4H, 2 × dicyclopropylamino-2-C*H*$_2$). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.0, 157.2, 154.9, 154.2, 153.6 (d, $^1J_{F\text{-}C} = 241$ Hz), 149.4, 142.3, 137.3 (d, $^3J_{F\text{-}C} = 3$ Hz), 127.8, 126.3, 124.0, 122.9, 122.8, 119.1 (d, $^2J_{F\text{-}C} = 18$ Hz), 116.8 (d, $^2J_{F\text{-}C} = 21$ Hz), 116.20, 109.3, 107.6, 65.0, 57.6, 36.6, 14.7, 6.3. ESI-MS (m/z): [M+H]$^+$ 496.1. Anal. Calc'd for $C_{26}H_{27}ClFN_5O_2$: C, 62.96; H, 5.49; N, 14.12. Found; C, 62.94; H, 5.50; N, 14.12.

*4.1.49. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-ethoxyquinazolin-6-yl)-4-(cyclopropylamino)but-2-enamide (**7o**)*

The title compound was prepared in a manner similar to that described for **6a** giving 1.912 g (4.2 mmol, 21%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.80 (s, 1H), 9.47 (s, 1H), 8.92 (s, 1H), 8.52 (s, H), 8.12–8.14 (dd, 1H, $^4J_{F\text{-}H} = 6.6$ Hz, $J = 1.8$ Hz, arylamine-2-=C*H*), 7.80–7.81 (m, 1H, arylamine-6-=C*H*), 7.42 (t, 1H, $J = 9.0$ Hz, arylamine-5-=C*H*), 7.26 (s, 1H), 6.87–6.91 (m, 1H, −CH$_2$−C*H*=CH−), 6.55 (d, 1H, $J = 15.6$ Hz, -−CH$_2$−CH=C*H*−), 4.27–4.31 (m, 2H, CH$_3$C*H*$_2$O−), 3.42 (d, 2H, $J = 4.8$ Hz, −C*H*$_2$−CH=CH−), 2.12–2.14 (m, 1H, cyclopropylamino-1-C*H*), 1.45–1.47 (m, 3H, C*H*$_3$CH$_2$O-), 0.39–0.40 (m, 2H, cyclopropylamino-2-C*H*$_2$), 0.26–0.28 (m, 2H, cyclopropylamino-2-C*H*$_2$). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.3, 157.2, 154.9, 154.2, 153.6 (d, $^1J_{F\text{-}C} = 241$ Hz), 149.3, 144.5, 137.4, 127.9, 124.5, 123.9, 122.8, 122.76, 119.1 (d, $^2J_{F\text{-}C} = 19$ Hz), 116.8 (d, $^2J_{F\text{-}C} = 21$ Hz), 116.2, 109.2, 107.6, 65.0, 50.2, 30.6, 14.7, 6.5. ESI-MS (m/z): [M+H]$^+$ 456.2. Anal. Calc'd for $C_{23}H_{23}ClFN_5O_2$-0.1CH$_3$CH$_2$OOCCH$_3$-1.0H$_2$O: C, 58.22; H, 5.39; N, 14.51. Found; C, 58.31; H, 5.45; N, 14.44.

*4.1.50. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl)-4-(cyclopropylamino)but-2-enamide (**7p**)*

The title compound was prepared in a manner similar to that described for **6a** giving 2.426 g (5.5 mmol, 19%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.82 (s, 1H), 9.64 (s, 1H), 8.93 (s, 1H), 8.53 (s, H), 8.12–8.14 (dd, 1H, $^4J_{F\text{-}H} = 7.2$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.79–7.82 (m, 1H, arylamine-6-=C*H*), 7.42 (t, 1H, $J = 9.0$ Hz, arylamine-5-=C*H*), 7.29 (s, 1H), 6.86–6.90 (m, 1H, −CH$_2$−C*H*=CH−), 6.55 (d, 1H, $J = 15.6$ Hz, −CH$_2$−CH=C*H*−), 4.14 (s, 3H, C*H*$_3$O-), 3.43 (d, 2H, $J = 4.8$ Hz, −C*H*$_2$−CH=CH−), 2.16–2.18 (m, 1H, cyclopropylamino-1-C*H*), 0.40–0.43 (m, 2H, cyclopropylamino-2-C*H*$_2$), 0.29–0.30 (m, 2H, cyclopropylamino-2-C*H*$_2$). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.4, 157.2, 155.7, 154.2, 153.6 (d, $^1J_{F\text{-}C} = 241$ Hz), 149.3, 144.6, 137.3, 127.8, 124.5, 124.0, 122.9, 122.8, 119.1 (d, $^2J_{F\text{-}C} = 18$ Hz), 116.8 (d, $^2J_{F\text{-}C} = 21$ Hz), 116.1, 109.4, 107.1, 56.7, 50.2, 30.5, 6.6. ESI-MS (m/z): [M+H]$^+$ 442.1. Anal. Calc'd for $C_{22}H_{21}ClFN_5O_2$-0.3CH$_3$CH$_2$OOCCH$_3$-0.5H$_2$O: C, 58.38; H, 5.15; N, 14.67. Found; C, 58.50; H, 5.17; N, 14.61.

*4.1.51. (S,E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(cyclopropylamino)but-2-enamide (**7q**)*

The title compound was prepared in a manner similar to that described for **6a** giving 2.287 g (4.6 mmol, 23%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.83 (s, 1H), 9.41 (s, 1H), 8.95 (s, 1H), 8.53 (s, H), 8.12–8.14 (dd, 1H, $^4J_{F\text{-}H} = 7.2$ Hz, $J = 2.4$ Hz, arylamine-2-=C*H*), 7.79–7.82 (m, 1H, arylamine-6-=C*H*), 7.41–7.44 (ap. t., 1H, $J = 9.0$ Hz, $^3J_{F\text{-}H} = 9.6$ Hz, arylamine-5-=C*H*), 7.24 (s, 1H), 6.88–6.92 (m, 1H, −CH$_2$−C*H*=CH−), 6.55 (d, 1H, $J = 15.6$ Hz, −CH$_2$−CH=C*H*−), 5.30 (d, 1H, $J = 3.6$ Hz, tetrahydrofuran-3-C*H*), 4.00 (d, 2H, $J = 2.4$ Hz, tetrahydrofuran-2-C*H*$_2$), 3.91–3.95 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.77–3.81 (m, 1H, tetrahydrofuran-5-C*H*$_2$), 3.43 (d, 2H, $J = 4.8$ Hz, −C*H*$_2$−CH=CH−), 2.33–2.36 (m, 1H, tetrahydrofuran-4-C*H*$_2$), 2.13–2.17 (m, 2H, tetrahydrofuran-4-C*H*$_2$ and cyclopropylamino-1-C*H*), 0.39–0.42 (m, 2H, cyclopropylamino-2-C*H*$_2$), 0.27–0.29 (m, 2H, cyclopropylamino-2-C*H*$_2$). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.3, 157.2, 154.3, 153.6 (d, $^1J_{F\text{-}C} = 242$ Hz), 153.6, 149.1, 144.7, 137.3 (d, $^3J_{F\text{-}C} = 3$ Hz), 128.1, 124.4, 124.0, 122.9, 122.8, 119.1 (d, $^2J_{F\text{-}C} = 18$ Hz), 116.8 (d, $^2J_{F\text{-}C} = 22$ Hz), 116.4, 109.4, 108.4, 79.2, 72.5, 67.1, 50.3, 32.9, 30.6, 6.6. ESI-MS (m/z): [M+H]$^+$ 498.1. Anal. Calc'd for $C_{25}H_{25}ClFN_5O_3$-1.1H$_2$O: C, 57.99; H, 5.30; N, 13.53. Found; C, 58.01; H, 5.40; N, 13.49.

*4.1.52. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(difluoromethoxy)quinazolin-6-yl)-4-(cyclopropylamino)but-2-enamide (**7r**)*

To a suspension of p-toluenesulfonic acid (13 g, 76 mmol) in DMSO (120 ml) was added NaH (7.4 g) under stirred at 0 °C. After the addition, the mixture was warmed to room temperature and stirred for 0.5 h. Then, *N*-(3-chloro-4-fluorophenyl)-7-fluoro-6-nitroquinazolin-4-amine (prepared in a manner similar to that described in 5a) (20 g, 60 mmol) was added into, and the mixture was raised to 90 °C and stirred for 3 h. Once the reaction was completed as indicated by TLC, the mixture was diluted with water (800 ml). After adjusting the pH to 3–4 with 4 N hydrochloric acid solution, the precipitate was collected by filtration, washed with water and dried under vacuum to provide 4-((3-chloro-4-fluorophenyl)amino)-6-nitroquinazolin-7-ol 18.8 g (56.3 mmol, 94.6%).

The mixture of 4-((3-chloro-4-fluorophenyl)amino)-6-nitroquinazolin-7-ol (6.68 g, 20 mmol), sodium chlorodifluoroacetate (4.6 g, 30 mmol) and Cs$_2$CO$_3$ (16.3 g, 50 mmol) in DMSO (200 ml) and water (50 ml) was raised to 110 °C and stirred for 48 h under N$_2$ atmosphere. Once the reaction was completed as indicated by TLC, the mixture was diluted with water (1 L). After adjusting the pH to 7 with 4 N hydrochloric acid solution, the precipitate was collected by filtration, washed with water and dried under vacuum to provide N-(3-chloro-4-fluorophenyl)-7-(difluoromethoxy)-6-nitroquinazolin-4-amine 2.15 g (5.6 mmol, 28%).

(*E*)-*N*-(4-(3-chloro-4-fluorophenylamino)-7-(difluoromethoxy) quinazolin-6-yl)-4-(cyclopropylamino)but-2-enamide (**7r**) was prepared in a manner similar to that described for **6a** giving 115 mg (0.24 mmol, 24%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 10.0 (s, 1H), 9.89 (s, 1H), 8.94 (s, 1H), 8.61 (s, 1H), 8.14–8.16 (dd, 1H, $^4J_{F\text{-}H} = 6.6$ Hz, $J = 2.4$ Hz, arylamine-2-═C*H*), 7.80–7.83 (m, 1H, arylamine-6-═C*H*), 7.56 (s, 1H), 7.43–7.47 (ap. t., 1H, $^3J_{F\text{-}H} = 9.6$ Hz, $J = 9.0$ Hz, arylamine-5-═C*H*), 6.90–6.93 (m, 1H, $-CH_2-CH{=}CH-$), 6.51 (d, 1H, $J = 15.0$ Hz, $-CH_2-CH{=}CH-$), 3.42 (d, 2H, $J = 4.8$ Hz, $-CH_2-CH{=}CH-$), 2.12–2.14 (m, 1H, cyclopropylamino-1-C*H*), 0.38–0.40 (m, 2H, cyclopropylamino-2-CH_2), 0.26–0.28 (m, 2H, cyclopropylamino-2-CH_2). ESI-MS (m/z): $[M+H]^+$ 478.2. ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.6, 157.4, 155.0, 153.6 (d, $^1J_{F\text{-}C} = 241$ Hz), 152.7, 148.5, 145.0, 136.9, 128.1, 124.4, 123.9, 123.2, 123.15, 119.3 (d, $^2J_{F\text{-}C} = 18$ Hz), 117.1, 116.7 (d, $^2J_{F\text{-}C} = 29$ Hz), 114.0, 112.2, 50.2, 30.6, 6.6. Anal. Calc'd for $C_{22}H_{19}ClF_3N_5O_2$-0.3$CH_3CH_2OOCCH_3$-0.3H_2O: C, 54.67; H, 4.35; N, 13.74. Found; C, 54.67; H, 4.40; N, 13.72.

*4.1.53. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(2,2,2-trifluoroethoxy)quinazolin-6-yl)-4-(cyclopropylamino)but-2-enamide (**7s**)*

The title compound was prepared in a manner similar to that described for **6a** giving 1.884 g (3.7 mmol, 22%).

^{1}H NMR (400 MHz, DMSO-d_6, δ_{ppm}): 9.86 (s, 1H), 9.58 (s, 1H), 8.81 (s, 1H), 8.56 (s, 1H), 8.12–8.15 (dd, 1H, $^4J_{F\text{-}H} = 6.8$ Hz, $J = 2.8$ Hz, arylamine-2-═C*H*), 7.78–7.82 (m, 1H, arylamine-6-═C*H*), 7.48 (s, 1H), 7.42 (t, 1H, $J = 9.2$ Hz, arylamine-5-═C*H*), 6.84–6.91 (m, 1H, $-CH_2-CH{=}CH-$), 6.45 (d, 1H, $J = 15.6$ Hz, $-CH_2-CH{=}CH-$), 5.00–5.07 (m, 2H, CF_3CH_2O-), 3.38 (d, 2H, $J = 4.4$ Hz, $-CH_2-CH{=}CH-$), 2.08–2.13 (m, 1H, cyclopropylamino-1-C*H*), 0.35–0.39 (m, 2H, cyclopropylamino-2-CH_2), 0.23–0.26 (m, 2H, cyclopropylamino-2-CH_2). ^{13}C NMR (150 MHz, DMSO-d_6, δ_{ppm}): 164.5, 157.2, 154.7, 154.1, 153.7 (d, $^1J_{F\text{-}C} = 242$ Hz), 149.3, 144.7, 137.1 (d, $^3J_{F\text{-}C} = 2$ Hz), 121.3–127.3 (q, CF_3CH_2O-), 124.1, 122.923, 122.877, 119.2 (d, $^2J_{F\text{-}C} = 17$ Hz), 118.8, 117.0, 116.9, 110.2, 109.2, 65.8–65.4 (q, CF_3CH_2O-), 50.2, 30.5, 6.5. ESI-MS (m/z): $[M+H]^+$ 510.2. Anal. Calc'd for $C_{23}H_{20}ClF_4N_5O_2$-0.1$CH_3CH_2OOCCH_3$: C, 54.18; H, 4.04; N, 13.50. Found; C, 54.20; H, 4.14; N, 13.45.

*4.1.54. (E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl)-4-(3, 3-difluorocyclobutylamino)but-2-enamide (**7t**)*

The title compound was prepared in a manner similar to that described for **6a** giving 2.113 g (4.3 mmol, 20%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.81 (s, 1H), 9.65 (s, 1H), 8.92 (s, 1H), 8.34 (s, 1H), 8.12–8.14 (dd, 1H, $^4J_{F\text{-}H} = 7.2$ Hz, $J = 2.4$ Hz, arylamine-2-═C*H*), 7.79–7.81 (m, 1H, arylamine-6-═C*H*), 7.43 (t, 1H, $J = 9.0$ Hz, arylamine-5-═C*H*), 7.29 (s, 1H), 6.82–6.87 (m, 1H, $-CH_2-CH{=}CH-$), 6.56 (d, 1H, $J = 15.0$ Hz, $-CH_2-CH{=}CH-$), 4.04 (s, 3H, CH_3O-), 3.30 (d, 2H, $J = 4.2$ Hz, $-CH_2-CH{=}CH-$), 2.73–2.76 (m, 2H, 3,3-difluorocyclobutylamino-2-CH_2), 2.33–2.36 (m, 2H, 3,3-difluorocyclobutylamino-2-CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.3, 157.3, 155.8, 154.3, 153.6 (d, $^1J_{F\text{-}C} = 241$ Hz), 149.4, 143.9, 137.3 (d, $^3J_{F\text{-}C} = 3$ Hz), 127.8, 124.7124.0, 117.4–123.3 (q, 3,3-difluorocyclobutylamino-3-CF_2), 119.1 (d, $^2J_{F\text{-}C} = 18$ Hz), 117.0, 116.8, 116.2, 109.4, 107.1, 56.7, 48.0, 42.4–42.9 (t, 2C, 3,3-difluorocyclobutylamino-2-CH_2). ESI-MS (m/z): $[M+H]^+$ 492.4. Anal. Calc'd for $C_{23}H_{21}ClF_3N_5O_2$-0.1$CH_3CH_2OOCCH_3$-0.5H_2O: C, 55.14; H, 4.51; N, 13.74. Found; C, 55.15; H, 4.55; N, 13.72.

*4.1.55. (S,E)-N-(4-(3-Chloro-4-fluorophenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(isopropylamino)but-2-enamide (**7u**)*

The title compound was prepared in a manner similar to that described for **6a** giving 1.447 g (2.9 mmol, 30%).

^{1}H NMR (400 MHz, DMSO-d_6, δ_{ppm}): 9.80 (s, 1H), 9.42 (s, 1H), 8.92 (s, 1H), 8.52 (s, 1H), 8.10–8.13 (dd, 1H, $^4J_{F\text{-}H} = 6.8$ Hz, $J = 2.4$ Hz, arylamine-2-═C*H*), 7.77–7.81 (m, 1H, arylamine-6-═C*H*), 7.42 (t, 1H, $J = 9.2$ Hz, arylamine-5-═C*H*), 7.23 (s, 1H), 6.85–6.90 (m, 1H, $-CH_2-CH{=}CH-$), 6.56 (d, 1H, J = 15.2 Hz, $-CH_2-CH{=}CH-$), 5.28 (d, 1H, J = 3.2 Hz, tetrahydrofuran-3-C*H*), 3.98–3.99 (m, 2H, tetrahydrofuran-2-CH_2), 3.89–3.95 (m, 1H, tetrahydrofuran-5-CH_2), 3.75–3.80 (m, 1H, tetrahydrofuran-5-CH_2), 3.39 (d, 2H, $J = 4.4$ Hz, $-CH_2-CH{=}CH-$), 2.76–2.80 (m, 1H, isopropylamino-C*H*), 2.31–2.34 (m, 1H, tetrahydrofuran-4-CH_2), 2.12–2.15 (m, 1H, tetrahydrofuran-4-CH_2), 1.01 (d, 6H, $J = 6.0$ Hz, 2 × isopropylamino-CH_3). ^{13}C NMR (150 MHz, DMSO-d_6, δ_{ppm}): 164.3, 157.2, 154.3, 153.6 (d, $^1J_{F\text{-}C} = 241$ Hz), 149.1, 144.5, 137.2, 128.0, 124.5, 123.9, 122.8, 119.1 (d, $^2J_{F\text{-}C} = 18$ Hz), 116.9, 116.8, 116.5, 109.3, 108.4, 79.2, 72.4, 67.0, 48.3, 47.8, 32.8, 22.9. ESI-MS (m/z): $[M+H]^+$ 500.1. Anal. Calc'd for $C_{25}H_{27}ClFN_5O_3$-0.8H_2O: C, 58.37; H, 5.60; N, 13.62. Found; C, 58.35; H, 5.67; N, 13.61.

*4.1.56. (S,E)-N-(4-(3-Ethynylphenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(piperidin-1-yl)but-2-enamide (**8a**)*

The title compound was prepared in a manner similar to that described for **6a** giving 547 mg (1.1 mmol, 42%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.74 (s, 1H), 9.45 (s, 1H), 8.95 (s, 1H), 8.53 (s, 1H), 8.00 (s, 1H), 7.87 (d, 1H, $J = 8.4$ Hz, arylamine-6-═C*H*), 7.38 (t, 1H, $J = 7.8$ Hz, arylamine-5-═C*H*), 7.24 (s, 1H), 7.20 (d, 1H, $J = 7.8$ Hz, arylamine-4-═C*H*), 6.79–6.83 (m, 1H, $-CH_2-CH{=}CH-$), 6.57 (d, 1H, $J = 15.6$ Hz, $-CH_2-CH{=}CH-$), 5.30 (d, 1H, $J = 1.8$ Hz, tetrahydrofuran-3-C*H*), 4.19 (s, 1H, alkyne-*H*), 3.99–4.01 (m, 2H, tetrahydrofuran-2-CH_2), 3.91–3.95 (m, 1H, tetrahydrofuran-5-CH_2), 3.77–3.80 (m, 1H, tetrahydrofuran-5-CH_2), 3.12 (broad s, 2H, $-CH_2-CH{=}CH-$), 2.32–2.38 (m, 5H, one hydrogen of tetrahydrofuran-4-CH_2 and 2 × piperidin-2-CH_2), 2.13–2.16 (m,1H, tetrahydrofuran-4-CH_2), 1.53 (broad s, 4H, 2 × piperidin-3-CH_2), 1.40 (broad s, 2H, piperidin-4-CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.0, 157.4, 154.4, 153.7, 149.3, 142.4, 140.3, 129.2, 127.9, 126.8, 125.3, 123.1, 123.0, 122.1, 116.9, 109.5, 108.5, 84.1, 80.9, 79.2, 72.5, 67.1, 59.7, 54.5, 32.9, 26.0, 24.3, 14.5. ESI-MS (m/z): $[M+H]^+$ 498.4. Anal. Calc'd for $C_{29}H_{31}N_5O_3$-0.2$CH_3CH_2OOCCH_3$-1.5H_2O: C, 66.01; H, 6.62; N, 12.92. Found; C, 66.05; H, 6.70; N, 12.90.

*4.1.57. (E)-N-(4-(3-Ethynylphenylamino)-7-methoxyquinazolin-6-yl)-4-(piperidin-1-yl)but-2-enamide (**8b**)*

The title compound was prepared in a manner similar to that described for **6a** giving 119 mg (0.27 mmol, 40%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.76 (s, 1H), 9.71 (s, 1H), 8.94 (s, 1H), 8.55 (s, 1H), 8.02 (s, 1H), 7.88 (d, 1H, $J = 8.4$ Hz, arylamine-6-═C*H*), 7.38 (t, 1H, $J = 7.8$ Hz, arylamine-5-═C*H*), 7.29 (s, 1H), 7.20 (d, 1H, $J = 7.8$ Hz, arylamine-4-═C*H*), 6.79–6.83 (m, 1H, $-CH_2-CH{=}CH-$), 6.59 (d, 1H, $J = 15.0$ Hz, $-CH_2-CH{=}CH-$), 4.20 (s, 1H, alkyne-*H*), 4.02 (s, 3H, CH_3O-), 3.14 (broad s, 2H, $-CH_2-CH{=}CH-$), 2.40 (broad s, 4H, 2 × piperidin-2-CH_2), 1.54 (broad s, 4H, 2 × piperidin-3-CH_2), 1.40 (broad s, 2H, piperidin-4-CH_2). ESI-MS (m/z): $[M+H]^+$ 442.3. Anal. Calc'd for $C_{26}H_{27}N_5O_2$: C, 70.73; H, 6.16; N, 15.86. Found; C, 70.71; H, 6.21; N, 15.85.

*4.1.58. (E)-N-(7-Ethoxy-4-(3-ethynylphenylamino)quinazolin-6-yl)-4-(piperidin-1-yl)but-2-enamide (**8c**)*

The title compound was prepared in a manner similar to that described for **6a** giving 291 mg (0.64 mmol, 41%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.74 (s, 1H), 9.54 (s, 1H), 8.93 (s, 1H), 8.53 (s, 1H), 8.00 (s, 1H), 7.88 (d, 1H, J = 8.4 Hz, arylamine-6-=CH), 7.39 (t, 1H, J = 7.8 Hz, arylamine-5-=CH), 7.27 (s, 1H), 7.20 (d, 1H, J = 7.8 Hz, arylamine-4-=CH), 6.79–6.83 (m, 1H, $-CH_2-CH{=}CH-$), 6.56 (d, 1H, J = 15.0 Hz, $-CH_2-CH{=}CH-$), 4.28–4.31 (m, 2H, CH_3CH_2O-), 4.20 (s, 1H, alkyne-H), 3.12 (broad s, 2H, $-CH_2-CH{=}CH-$), 2.37 (broad s, 4H, 2 × piperidin-2-CH_2), 1.54 (broad s, 4H, 2 × piperidin-3-CH_2), 1.46 (t, 3H, J = 6.6 Hz, CH_3CH_2O-), 1.40 (broad s, 2H, piperidin-4-CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.0, 157.3, 155.0, 154.4, 149.5, 142.4, 140.3, 129.3, 127.6, 126.8, 126.4, 125.3, 123.1, 122.1, 116.7, 109.4, 107.6, 84.1, 80.9, 64.9, 59.8, 54.5, 26.0, 24.3, 14.5. ESI-MS (m/z): $[M+H]^+$ 456.4.

*4.1.59. (E)-4-(Cyclopropyl(methyl)amino)-N-(4-(3-ethynylphenylamino)-7-methoxyquinazolin-6-yl)but-2-enamide (**8d**)*

The title compound was prepared in a manner similar to that described for **6a** giving 154 mg (0.36 mmol, 36%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.76 (s, 1H), 9.68 (s, 1H), 8.95 (s, 1H), 8.54 (s, 1H), 8.01 (s, 1H), 7.88 (d, 1H, J = 8.4 Hz, arylamine-6-=CH), 7.39 (t, 1H, J = 7.8 Hz, arylamine-5-=CH), 7.29 (s, 1H), 7.20 (d, 1H, J = 7.8 Hz, arylamine-4-=CH), 6.81–6.86 (m, 1H, $-CH_2-CH{=}CH-$), 6.56 (d, 1H, J = 15.6 Hz, $-CH_2-CH{=}CH-$), 4.20 (s, 1H, alkyne-H), 4.02 (s, 3H, CH_3O-), 3.32 (d, 2H, J = 6.0 Hz, $-CH_2-CH{=}CH-$), 2.28 (s, 3H, N–CH_3), 1.74–1.76 (m, 1H, cyclopropyl-1-CH), 0.45–0.46 (m, 2H, cyclopropyl-2-CH_2), 0.35–0.36 (m, 2H, cyclopropyl-2-CH_2). ESI-MS (m/z): $[M+H]^+$ 428.3.

*4.1.60. (E)-4-(Cyclopropyl(methyl)amino)-N-(7-ethoxy-4-(3-ethynylphenylamino)quinazolin-6-yl)but-2-enamide (**8e**)*

The title compound was prepared in a manner similar to that described for **6a** giving 1.765 g (4.0 mmol, 40%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.75 (s, 1H), 9.54 (s, 1H), 8.94 (s, 1H), 8.54 (s, 1H), 8.01 (s, 1H), 7.88 (d, 1H, J = 8.4 Hz, arylamine-6-=CH), 7.39 (t, 1H, J = 7.8 Hz, arylamine-5-=CH), 7.29 (s, 1H), 7.20 (d, 1H, J = 7.8 Hz, arylamine-4-=CH), 6.82–6.86 (m, 1H, $-CH_2-CH{=}CH-$), 6.54–6.57 (m, 1H, J = 15.6 Hz, $-CH_2-CH{=}CH-$), 4.27–4.31 (m, 2H, CH_3CH_2O-), 4.20 (s, 1H, alkyne-H), 3.32–3.33 (m, 2H, $-CH_2-CH{=}CH-$), 2.28 (s, 3H, N–CH_3), 1.74–1.75 (m, 1H, cyclopropyl-1-CH), 1.44–1.47 (t, 3H, J = 7.2 Hz, CH_3CH_2O-), 0.45–0.47 (m, 2H, cyclopropyl-2-CH_2), 0.35–0.36 (m, 2H, cyclopropyl-2-CH_2). ESI-MS (m/z): $[M+H]^+$ 442.3.

*4.1.61. (S,E)-4-(Cyclopropylamino)-N-(4-(3-ethynylphenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)but-2-enamide (**8f**)*

The title compound was prepared in a manner similar to that described for **6a** giving 1.783 g (3.8 mmol, 19%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.77 (s, 1H), 9.41 (s, 1H), 8.96 (s, 1H), 8.53 (s, 1H), 8.01 (s, 1H), 7.87 (d, 1H, J = 8.4 Hz, arylamine-6-=CH), 7.38 (t, 1H, J = 7.8 Hz, arylamine-5-=CH), 7.23 (s, 1H), 7.20 (d, 1H, J = 7.8 Hz, arylamine-4-=CH), 6.88–6.92 (m, 1H, -$-CH_2-CH{=}CH-$), 6.54 (d, 1H, J = 15.6 Hz, $-CH_2-CH{=}CH-$), 5.29 (d, 1H, J = 3.6 Hz, tetrahydrofuran-3-CH), 4.19 (s, 1H, alkyne-H), 4.01 (d, 2H, J = 2.4 Hz, tetrahydrofuran-2-CH_2), 3.91–3.95 (m, 1H, tetrahydrofuran-5-CH_2), 3.78–3.80 (m, 1H, tetrahydrofuran-5-CH_2), 3.42 (d, 2H, J = 4.8 Hz, $-CH_2-CH{=}CH-$), 2.31–2.36 (m, 1H, tetrahydrofuran-4-CH_2), 2.11–2.17 (m, 2H, tetrahydrofuran-4-CH_2 and cyclopropylamino-1-CH), 0.38–0.41 (m, 2H, cyclopropylamino-2-CH_2), 0.27–0.28 (m, 2H, cyclopropylamino-2-CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.3, 157.4, 154.4, 153.7, 149.2, 144.7, 140.3, 129.2, 128.0, 126.8, 125.4, 124.4, 123.2, 122.1, 116.6, 109.6, 108.4, 84.1, 80.8, 79.2, 72.5, 67.1, 65.4, 50.3, 32.9, 30.6, 6.6. ESI-MS (m/z): $[M+H]^+$ 470.2. Anal. Calc'd for $C_{27}H_{27}N_5O_3$-$0.8H_2O$: C, 68.28; H, 5.86; N, 14.75. Found; C, 68.30; H, 5.87; N, 14.74.

*4.1.62. (E)-4-(Cyclopropylamino)-N-(4-(3-ethynylphenylamino)-7-methoxyquinazolin-6-yl)but-2-enamide (**8g**)*

The title compound was prepared in a manner similar to that described for **6a** giving 1.859 g (4.5 mmol, 20%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.75 (s, 1H), 9.62 (s, 1H), 8.94 (s, 1H), 8.53 (s, 1H), 8.01 (s, 1H), 7.87 (d, 1H, J = 8.4 Hz, arylamine-6-=CH), 7.38 (t, 1H, J = 7.8 Hz, arylamine-5-=CH), 7.28 (s, 1H), 7.20 (d, 1H, J = 7.8 Hz, arylamine-4-=CH), 6.86–6.90 (m, 1H, $-CH_2-CH{=}CH-$), 6.53 (d, 1H, J = 15.0 Hz, $-CH_2-CH{=}CH-$), 4.19 (s, 1H, alkyne-H), 3.98 (s, 3H, CH_3O-), 3.39 (d, 2H, J = 4.2 Hz, $-CH_2-CH{=}CH-$), 2.53 (s, 1H), 2.12–2.13 (m, 1H, cyclopropylamino-1-CH), 0.38–0.39 (m, 2H, cyclopropylamino-2-CH_2), 0.26 (broad s, 2H, cyclopropylamino-2-CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.4, 157.4, 155.8, 154.4, 149.4, 144.5, 140.3, 129.2, 127.8, 126.8, 125.3, 124.5, 123.2, 122.1, 116.4, 109.5, 107.1, 84.1, 80.8, 56.7, 50.2, 30.5, 6.6. ESI-MS (m/z): $[M+H]^+$ 414.2. Anal. Calc'd for $C_{24}H_{23}N_5O_2$-$1.0H_2O$: C, 66.81; H, 5.84; N, 16.23. Found; C, 68.82; H, 5.87; N, 16.22.

*4.1.63. (E)-4-(Cyclopropylamino)-N-(7-ethoxy-4-(3-ethynylphenylamino)quinazolin-6-yl)but-2-enamide (**8h**)*

The title compound was prepared in a manner similar to that described for **6a** giving 2.051 g (0.48 mmol, 24%).

^{1}H NMR (600 MHz, DMSO-d_6, δ_{ppm}): 9.75 (s, 1H), 9.46 (s, 1H), 8.94 (s, 1H), 8.53 (s, 1H), 8.01 (s, 1H), 7.88 (d, 1H, J = 8.4 Hz, arylamine-6-=CH), 7.37–7.40 (ap. t., 1H, J = 8.4 Hz, J = 7.8 Hz, arylamine-5-=CH), 7.26 (s, 1H), 7.20 (d, 1H, J = 7.8 Hz, arylamine-4-=CH), 6.87–6.92 (m, 1H, $-CH_2-CH{=}CH-$), 6.54 (d, 1H, J = 15.0 Hz, $-CH_2-CH{=}CH-$), 4.28–4.31 (m, 2H, CH_3CH_2O-), 4.20 (s, 1H, alkyne-H), 3.42 (d, 2H, J = 4.2 Hz, $-CH_2-CH{=}CH-$), 2.12–2.15 (m, 1H, cyclopropylamino-1-CH), 1.47 (ap. t., 3H, J = 7.2 Hz, J = 6.6 Hz, CH_3CH_2O-), 0.38–0.42 (m, 2H, cyclopropylamino-2-CH_2), 0.27–0.28 (m, 2H, cyclopropylamino-2-CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.3, 157.4, 154.9, 154.3, 149.4, 144.3, 140.3, 129.2, 127.8, 126.8, 125.3, 124.6, 123.1, 122.1, 116.4, 109.4, 107.5, 84.1, 80.8, 64.9, 50.2, 30.5, 14.7, 6.5. ESI-MS (m/z): $[M+H]^+$ 428.3. Anal. Calc'd for $C_{25}H_{25}N_5O_2$-$0.06CH_3CH_2OOCCH_3$-$0.5H_2O$: C, 68.62; H, 6.04; N, 15.85. Found; C, 68.68; H, 6.15; N, 15.79.

*4.1.64. (S,E)-N-(4-(3-Ethynylphenylamino)-7-(tetrahydrofuran-3-yloxy)quinazolin-6-yl)-4-(isopropylamino)but-2-enamide (**8i**)*

The title compound was prepared in a manner similar to that described for **6a** giving 1.32 g (2.8 mmol, 22%).

^{1}H NMR (400 MHz, DMSO-d_6, δ_{ppm}): 9.74 (s, 1H), 9.41 (s, 1H), 8.93 (s, 1H), 8.51 (s, 1H), 7.99 (s, 1H), 7.85–7.87 (ap. t., 1H, J = 8.4 Hz, J = 1.2 Hz, arylamine-6-=CH), 7.37 (t, 1H, J = 8.0 Hz, arylamine-5-=CH), 7.22 (s, 1H), 7.18 (d, 1H, J = 7.6 Hz, arylamine-4-=CH), 6.85–6.90 (m, 1H, -$-CH_2-CH{=}CH-$), 6.55 (d, 1H, J = 15.6 Hz, $-CH_2-CH{=}CH-$), 5.28 (d, 1H, J = 3.2 Hz, tetrahydrofuran-3-CH), 4.18 (s, 1H), 3.99-3.40 (m, 2H, tetrahydrofuran-2-CH_2), 3.91–3.93 (m, 1H, tetrahydrofuran-5-CH_2), 3.76–3.80 (m, 1H, tetrahydrofuran-5-CH_2), 3.36–3.39 (m, 2H, $-CH_2-CH{=}CH-$), 2.74–2.78 (m, 1H, isopropylamino-CH), 2.30–2.34 (m, 1H, tetrahydrofuran-4-CH_2), 2.13–2.15 (m, 1H, tetrahydrofuran-4-CH_2), 1.01 (d, 6H, J = 6.4 Hz, 2 × isopropylamino-CH_3).^{13}C NMR (100 MHz, DMSO-d_6, δ_{ppm}): 164.3, 157.1, 154.4, 149.2, 140.2, 129.2, 127.9, 126.8, 125.3, 123.1, 122.1, 109.5, 108.4, 84.0, 80.9, 79.1, 72.5, 67.0, 48.3, 47.8, 32.8, 23.0. ESI-MS (m/z): $[M+H]^+$ 472.3. Anal. Calc'd for $C_{27}H_{29}N_5O_3$: C, 68.77; H, 6.20; N, 14.85. Found; C, 68.78; H, 6.25; N, 14.82.

4.2. Biological evaluation

4.2.1. EGFR tyrosine kinase enzyme inhibition assay

EGFR tyrosine kinase activity was determined by an enzyme-linked-immuno-sorbent assay (ELISA) as described in our previous report [30].

4.2.2. *Cancer cell proliferation inhibition assay*

NCI-H1975 cells were purchased from the American Type Culture Collection (ATCC, Manassas/VA), and were cultured in RPMI medium containing 1 mM sodium pyruvate. The RPMI medium was supplemented with 1% penicillin–streptomycin and 10% fetal bovine serum (FBS). Cells were incubated in a humidified atmosphere under 5% CO_2 at 37 °C. Cell growth inhibition assays and GI_{50} determinations were performed as previously described [4].

4.2.3. *In vivo efficacy study*

Pathogen-free, 6-8 week-old, female BALB/c nude mice (Vital River Laboratory Animal Technology Co. Ltd) were maintained under clean-room conditions in sterile filter-top cages with Aspen Chip bedding. A431, HCC-827 or NCI-H1975 xenograft model was established by inoculated 2×10^6 cancer cells subcutaneous in the right flanks of athymic mice. When the tumor reached a volume of 100–300 mm^3, the mice were randomly assigned into control and treatment groups ($n = 6$ per group). Control groups were given vehicle alone, and treatment groups received different drugs. Health conditions of mice were observed daily. The size of tumor and body weight was measured on the indicated days during the treatment. Tumor volume (V) was calculated as $V = (\text{length} \times \text{width}^2)/2$. The individual relative tumor volume (RTV) was calculated as follows: $RTV = V_t/V_0$, where V_t represented the tumor size measured on the indicated days and V_0 represented the predosing tumor size (in case where tumor regression occurred, $RTV < 1$). The body weight change (%) was calculated as follows: body weight change (%) $= (W_t/W_0 - 1) \times 100$, where W_t represented the body weight measured on the indicated days and W_0 represented the predosing body weight. Results are presented as mean for each group. Error bars represent the standard error of the mean (SEM). Therapeutic effect of each compound was expressed in terms of Tumor Growth Inhibition (TGI) and the calculation formula was: $TGI = (1 - T/C) \times 100\%$, where T was mean RTV of the treated group and C was mean RTV of the control group.

4.3. *Pharmacokinetics (PK) analysis*

PK studies were conducted in rats, and compound **7q**, **7u**, **8f**, **8i** or afatinib was formulated as a clear solution of 1 mg/ml in 5%DMSO/30%PEG400/65%H_2O, respectively. By use of the same formulation of each compound, male Sprague–Dawley rats were administered intravenously via the tail vein at a single 1 mg/kg dose ($n = 3$) or orally via gavage at a single 5 mg/kg dose ($n = 3$). Serial blood samples were collected from each rat over a 24 h period after dosing. Plasma samples were analyzed for the corresponding compound concentrations by LC/MS/MS (Column: Angilent Zorbax Rx-C18 150 × 2.1 mm; Mobil phase: 10 mM ammonium formate-0.1% formic acid water/methanol = 10/90; Ionization: electrospray positive ion mode; Data acquisition: Analyst®, Version 1.5). Pharmacokinetic parameters for all compounds were determined from the plasma concentration-time data using noncompartmental methods.

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Appendix A. Supplementary information

Supplementary information associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2015.08.026. These data include MOL files and InChiKeys of the most important compounds described in this article.

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