Supporting Information

Discovery of potent and noncovalent reversible EGFR kinase inhibitors of $EGFR^{L858R/T790M/C797S}$

Qiannan Li[1,‡], Tao Zhang[2,‡], Shiliang Li[1,‡], Linjiang Tong[2], Junyu Li[1], Zhicheng Su[1], Fang Feng[2], Deheng Sun[1], Yi Tong[1], Xia Wang[1], Zhenjiang Zhao[1], Lili Zhu[1], Jian Ding[2], Honglin Li[1,*], Hua Xie[2,*], Yufang Xu[1,*]

1 Shanghai Key Laboratory of New Drug Design, State Key Laboratory of Bioreactor Engineering, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China.

2 Division of Anti-tumor Pharmacology, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China.

‡ Authors contributed equally to this work

* To whom correspondence should be addressed. Email: yfxu@ecust.edu.cn, hxie@jding.dhs.org, hlli@ecust.edu.cn

Content

Structures of representative EGFR inhibitors

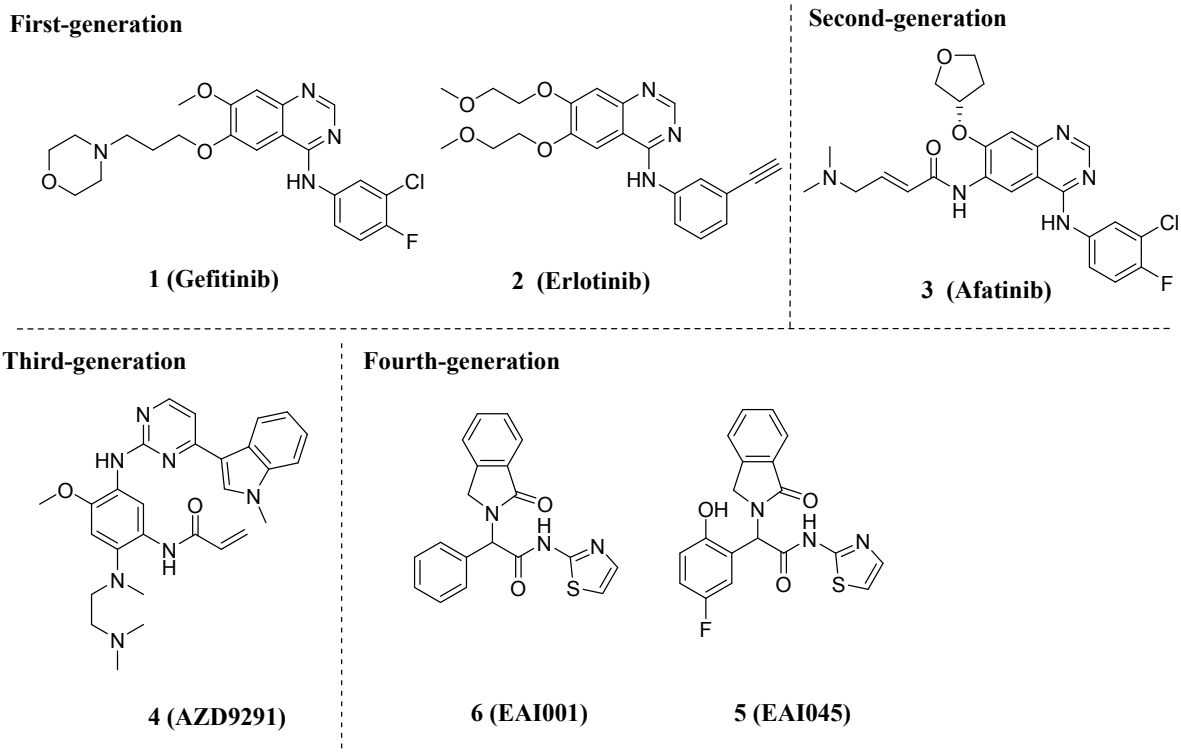
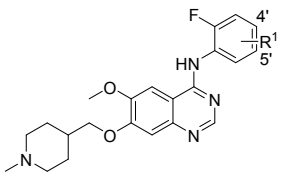


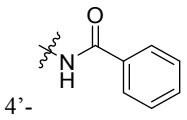
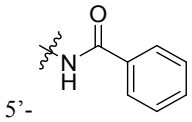
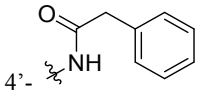
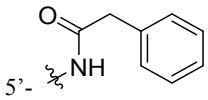
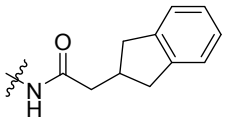
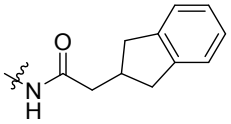
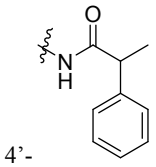
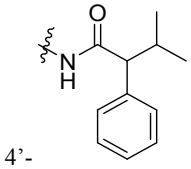
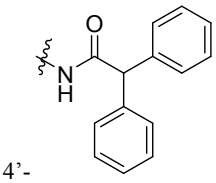
Figure S1. Structures of representative first-, second-, third- and fourth-generation EGFR inhibitors.

Results of kinase activities

Table S1. In vitro EGFR kinase inhibition of compounds **18a-18i** and **2**[a]



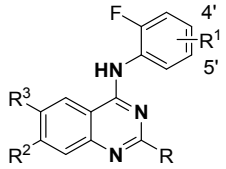
Compd.	R^1	EGFR Kinase IC_{50} (nM)		
		WT	LR/TM[b]	LR/TM/CS[c]

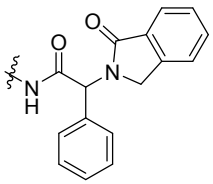
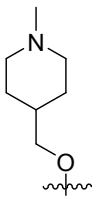
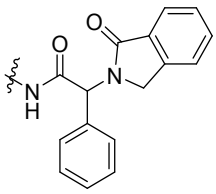
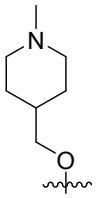
18a	 4’-	59.9 ± 1.8	6631.5 ± 657.5	>10000
18b	 5’-	53.7 ± 13.8	>10000	>10000
18c	 4’-	3.7 ± 1.6	7555.2 ± 1200.0	>10000
18d	 5’-	1346.3 ± 312.4	>10000	>10000
18e	4’- 	68.3 ± 13.0	1381.4 ± 234.6	>10000
18f	5’- 	1095.0 ± 180.3	3033.4 ± 688.9	>10000
18g	 4’-	7.7 ± 1.8	2555.2 ± 800.0	4808.5 ± 2924.2
18h	 4’-	23.1 ± 8.3	2032.2 ± 755.3	3186.0 ± 2502.1
18i	 4’-	5.6 ± 3.3	1001.2 ± 435.0	1295.9 ±308.2

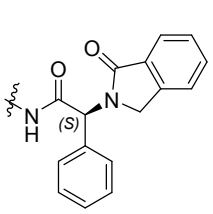
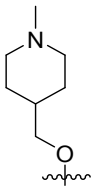
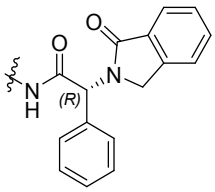
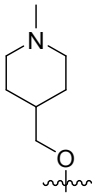
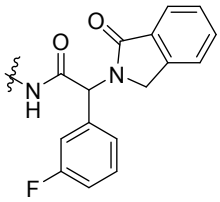
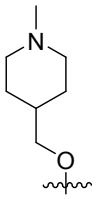
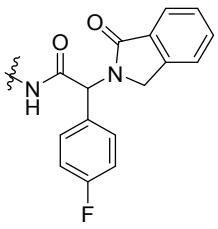
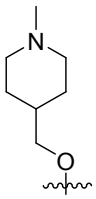
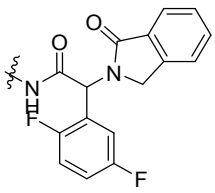
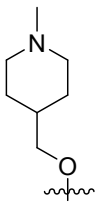
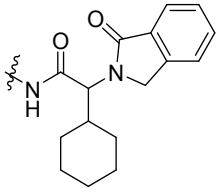
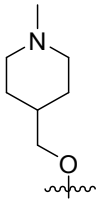
2	4'-Br	242.3 ± 82.5	4724.1 ± 1062.9	369.2 ± 58.3
AZD9291	-	216.2±109.4	2.8±2.0	461.7±234.0
Staurosporine	-	390.5±176.3	41.8±17.2	3.6±1.7

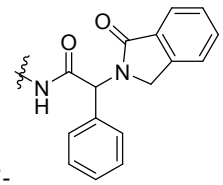
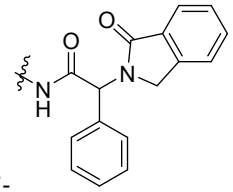
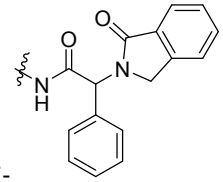
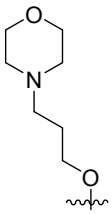
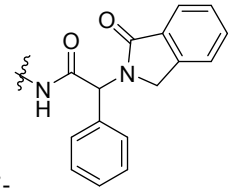
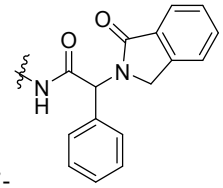
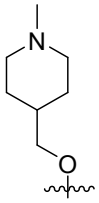
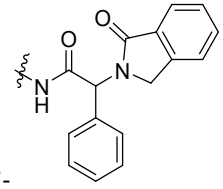
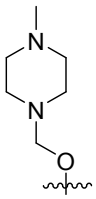
[a]Kinase activity assays were examined by using the ELISA-based EGFR-TK assay. Date are averages of at least two independent determinations and reported as the mean ± SD (standard deviations). [b]Dual-mutant ($EGFR^{L858R/T790M}$). [c]Triple-mutant ($EGFR^{L858R/T790M/C797S}$).

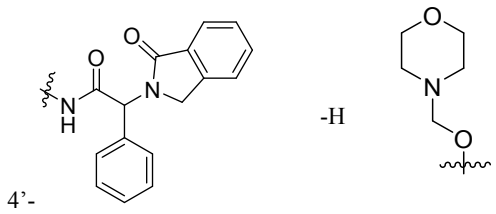
Table S2. In vitro EGFR kinase inhibition of compounds **25a-25o**[a]



Compd.	R1	R	R3	R2	EGFR Kinase IC_{50} (nM)		
					WT	LR/TM[b]	LR/TM/CS[c]
25a	 4'-	-H	$-OCH_3$		1.3 ± 0.6	3.2 ± 1.3	9.3 ± 2.7
25b	 5'-	-H	$-OCH_3$		16.1 ± 4.8	8.5 ± 0.7	37.1 ± 18.8

25c	4'- 	-H	-OCH_3		4.6 ± 2.8	8.6 ± 2.1	7.9 ± 2.0
25d	4'- 	-H	-OCH_3		3.5 ± 1.0	6.4 ± 1.6	19.2 ± 3.2
25e	4'- 	-H	-OCH_3		2.0 ± 0.5	6.7 ± 2.2	13.4 ± 2.7
25f	4'- 	-H	-OCH_3		1.5 ± 0.5	39.7 ± 14.0	43.0 ± 19.1
25g	4'- 	-H	OCH_3		2.5 ± 0.8	35.3 ± 12.1	2.2 ± 1.1
25h	4'- 	-H	-OCH_3		27.1 ± 12.0	179.6 ± 94.9	361.3 ± 123.4

25i	 4’-	-H	$-OCH_3$	$-OCH_3$	0.6 ± 0.1	1.9 ± 0.2	36.7 ± 27.0
25j	 4’-	$-NH_2$	$-OCH_3$	$-OCH_3$	388.3 ± 55.3	>10000	>10000
25k	 4’-	-H		$-OCH_3$	1.6 ± 0.3	7.3 ± 1.3	97.5 ± 12.9
25l	 4’-	-H			0.7 ± 0.1	1.5 ± 0.2	21.1 ± 9.8
25m	 4’-	-H		$-OCH_3$	0.8 ± 0.3	2.4 ± 0.5	18.0 ± 8.6
25n	 4’-	-H		$-OCH_3$	1.0 ± 0.2	4.8 ± 0.7	19.1 ± 4.6

25o	 4'-	-H		$-OCH_3$	8.9 ± 5.3	37.2 ± 11.1	174.3 ± 38.5
AZD9291	-	-	-	-	216.2±109.4	2.8±2.0	461.7±234.0
EAI045					>1000	4.6±0.2	55.7±18.2
Staurosporine	-	-	-	-	390.5±176.3	41.8±17.2	3.6±1.7
Brigatinib					35.9±2.8	4.0±0.1	1.6±0.1

[a]Kinase activity assays were examined by using the ELISA-based EGFR-TK assay. Date are averages of at least two independent determinations and reported as the mean ± SD (standard deviations). [b]Dual-mutant ($EGFR^{L858R/T790M}$). [c]Triple-mutant ($EGFR^{L858R/T790M/C797S}$). **Brigatinib**, a known ALK inhibitor[2], was found to have activity to overcome EGFR C797S resistant mutation.[3]

Table S3. $EGFR^{T790M/19Del/C797S}$ kinase inhibition of compound **25g**[a]

Kinase inhibition IC_{50} (nM) against $EGFR^{T790M/19Del/C797S}$	
25g	331.3±25.3
EAI045	>1000
Brigatinib	6.1±1.8

[a]Kinase activity assays were examined by using the ELISA-based EGFR-TK assay. Date are averages of at least three independent determinations and reported as the mean ± SD (standard deviations).

Results of in vitro EGFR anti-proliferation activities

Table S4. Anti-proliferation activity against BaF3-$EGFR^{T790M/19Del/C797S}$ cells of compound **25g**[a]

Anti-proliferation IC_{50} (μM)	
25g	3.54±0.21

AZD9291	5.32±0.46
EAI045	>10
Brigatinib	0.27±0.02

[a]Anti-proliferation activity assays were examined by using the Resazurin assay. Date are averages of at least three independent determinations and reported as the mean ± SD (standard deviations).

Table S5. In vitro anti-proliferation activities of **EAI045** [a]

Anti-proliferation IC_{50} (μM)	
Cells	**EAI045** (IC_{50}, μM)
BaF3	>10
BaF3-EGFR$^{L858R/T790M/C797S}$	>10

[a]Anti-proliferation activities assays were examined by using the Resazurin assay or SRB assay. Date are averages of at least two independent determinations and reported as the mean ± SD (standard deviations).

Results of preliminary pharmacokinetic properties

Table S6. Pharmacokinetic parameters for compound **25g** in rats

Dose (route)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng·h/mL)	$AUC_{(0-\infty)}$ (ng·h/mL)	V_z (mL/kg)	CL (mL/h/kg)	F (%)
1 mg/kg (IV)	18.9	0.1	2512.8	933.6	1041.3	26146.4	960.8	-
10 mg/kg (PO)	15.1	3.3	7.0	41.8	56.9	-	-	0.55%

Results of druglikeness properties

Table S7. Predicted druglikeness properties of **18a**-**18i**, and **25a**-**25o**[a]

Compd.	**QPlogP**[b]	**QPlogS**[c]	**QPPCaco**[d]	**QPPMDCK**[e]	**QPlogKhsa**[f]
18a	4.942	-6.384	260.533	218.055	0.86
18b	4.886	-6.19	301.729	255.714	0.826
18c	5.36	-7.081	281.232	236.837	0.983
18d	5.266	-6.948	262.394	174.28	0.974
18e	5.939	-7.412	305.252	204.489	1.253

18f	6.052	-8.164	266.786	177.442	1.308
18g	4.762	-4.138	386.997	334.979	0.781
18h	6.374	-7.855	406.281	352.424	1.331
18i	6.955	-8.356	360.612	309.871	1.509
25a	6.244	-8.809	142.14	113.272	1.234
25b	6.1	-8.513	127.131	79.719	1.218
25c	6.248	-8.811	142.17	113.298	1.235
25d	6.111	-8.338	149.838	119.914	1.187
25e	5.503	-5.452	210.2	313.212	0.901
25f	6.355	-8.662	146.594	212.181	1.235
25g	6.633	-9.159	161.839	352.507	1.289
25h	6.123	-8.118	184.389	150.08	1.256
25i	5.649	-8.063	909.67	655.493	0.853
25j	4.936	-8.029	275.444	178.24	0.706
25k	5.026	-5.712	162.094	130.714	0.645
25l	6.127	-8.823	937.132	677.321	0.678
25m	5.61	-5.89	365.516	315.062	0.908
25n	4.09	-3.75	95.344	60.749	0.466
25o	4.312	-5.129	176.177	143.14	0.408

[a] The properties were predicted using Maestro software package.

[b] QPlogP: Predicted octanol/water partition coefficient (–2.0 – 6.5).

[c] Predicted aqueous solubility, log S (‐ 6.5 ‐ 0.5).

[d] QPPCaco2: Predicted apparent Caco-2 cell permeability in nm/sec (<25 poor, >500 great).

[e] QPPMDCK: Predicted apparent MDCK cell permeability in nm/sec (<25 poor, >500 great).

[f] QPlogKhsa: Prediction of binding to human serum albumin (-1.5~1.5).

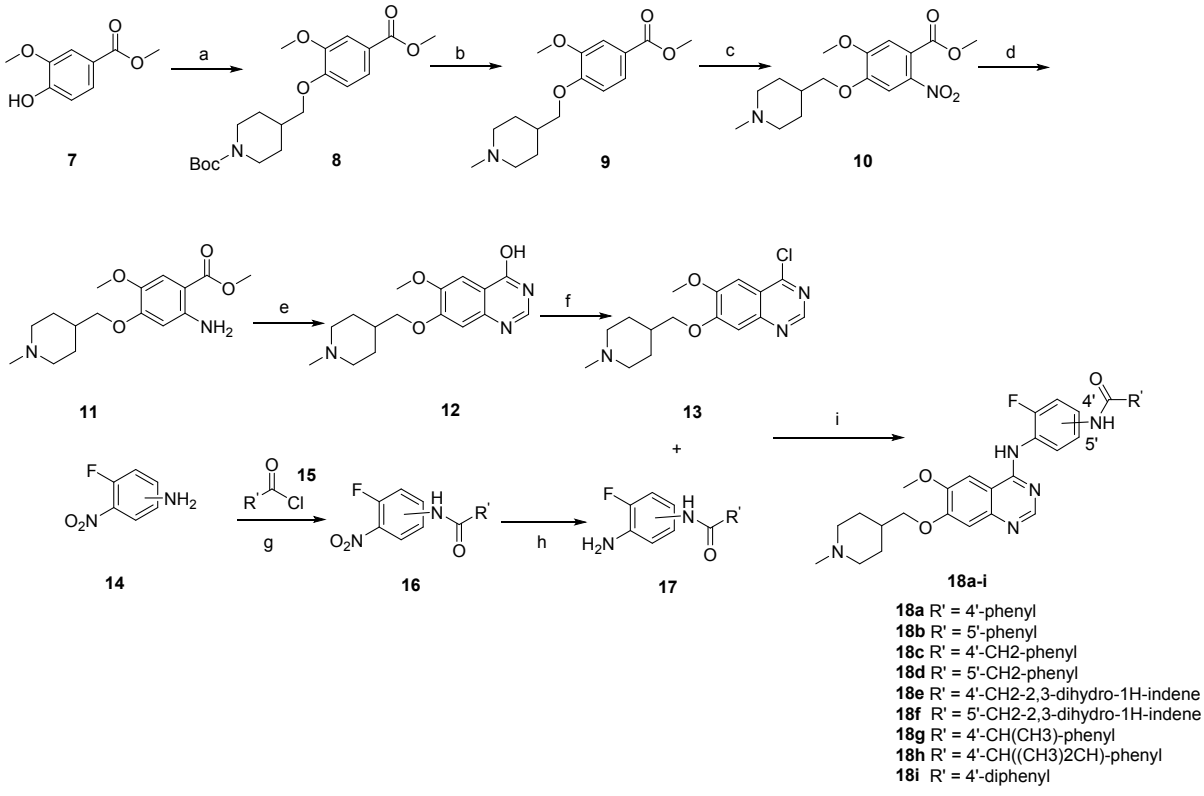
Table S8. The solubility of **25a, 25g, 25i, 25l** [a]

Compd.	**Solubility (μg/mL) @PBS (pH 6.8)**
25a	10.3
25g	19.5
25i	＜10.0
25l	＜10.0

[a] Aqueous solubility of these derivatives was examined by using UV-visible spectrophotometer in PBS buffer (0.1 M, pH 6.8).

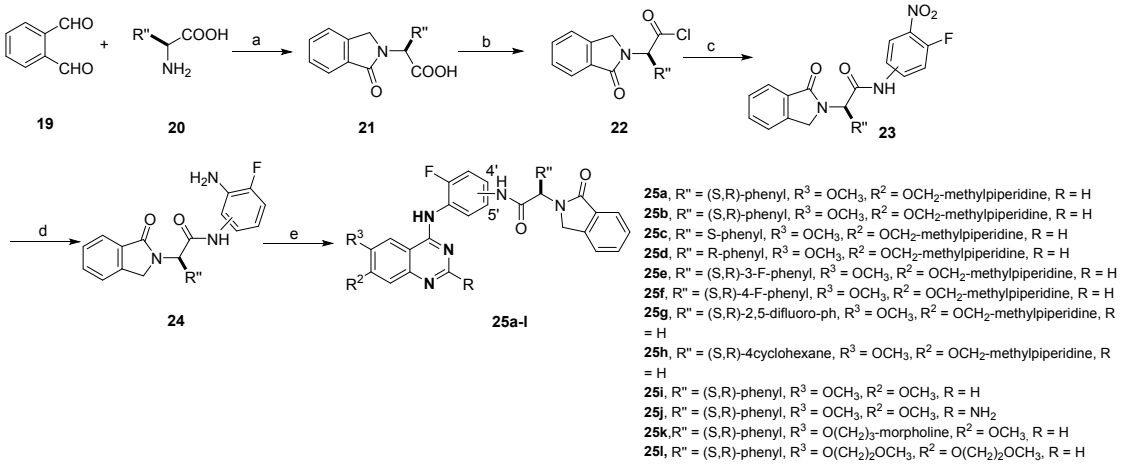
Synthetic procedures

As shown in Scheme S1, compounds **18a-18i** were synthesized starting from a substituted reaction of methyl vanillate with tert-butyl-4-((tosyloxy)methyl)piperidine-1-carboxylate in DMF to give Boc-protected ester (**8**). Then, compound (**8**) was deprotected and methylation in the formic acid and formaldehyde solvent to generate methyl 3-methoxy-4-((1-methylpiperidin-4-yl)methoxy)benzoate (**9**) in a good yield. The fuming nitric acid was as the nitrating agent to obtain compound (**10**), and then 10% Pd/C was used as reduction catalys, reducing the nitro group to generate amine (**11**). Cyclization with formamidine acetate and chlorination in thionyl chloride to give pyrimidine chloride (**13**). N-(4-amino-3-fluorophenyl)-benzamide derivatives (**17**) and (**13**) above were substituted in isopropanol solvent to produce the target products **18a-18i**.



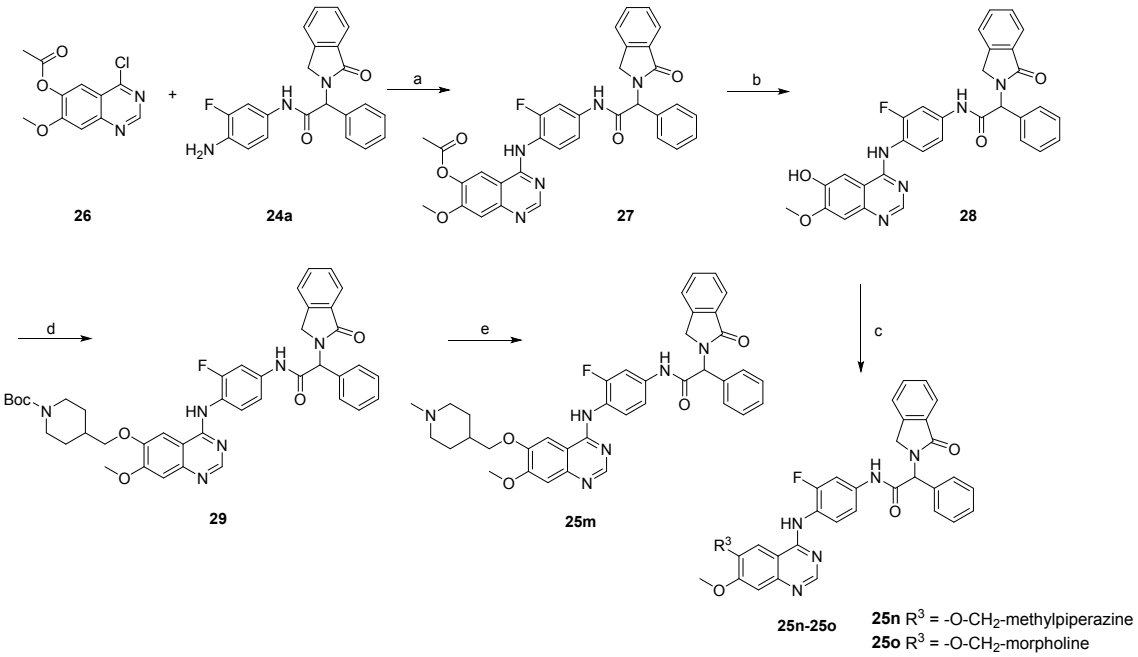
Scheme S1. Synthetic route of target compounds **18a-18i**[a]. [a]Reagents and conditions: (a) tert-butyl 4-((tosyloxy)methyl)piperidine-1-carboxylate, DMF, K_2CO_3, 120 °C, 5 h, 86%; (b) HCHO, HCOOH, 120 °C, 8 h, 80%; (c) Fuming nitric acid, DCM, 25 °C, overnight, 78%; (d) Pd/C, MeOH, H_2, 25 °C, 4 h, 95%; (e) Formamidine acetate, $CH_3OCH_2CH_2OH$, 120 °C, 8 h, 30%; (f) $SOCl_2$, DMF, 80 °C, 3 h, 70%; (g) THF, Et_3N, 60 °C, 5 h, 50-75%; (h) Pd/C, H_2, MeOH, 25 °C, 5 h, 73-85%; (i) $(CH_3)_2CHOH$, HCl, 80 °C, 8 h, 35-55%.

In order to study the structure-activity relationship and to obtain compounds with better inhibitory activity, we synthesized the target products **25a-25o-**. The synthesis route of target compounds **25a-l** is as shown in Scheme S2. Using phthalaldehyde as a starting material to react with glycine derivatives (**20**) to form a 2-(1-oxoisoindolin-2-yl)acetic acid derivatives (**21**), (**21**) was chlorinated with thionyl chloride and amidated with 3-fluoro-4-nitroaniline to give derivatives (**23**). The nitro group of derivatives (**23**) was then reduced to amino with 10% Pd/C in methanol solvent. Then, amine derivatives (**24**) reacted with quinazoline derivatives to give the final compounds **25a-25l**. The synthesis route of target compounds **25m-25o** is as shown in Scheme S3. Pyrimidine chloride (**26**) was reacted with aniline (**24a**) in isopropanol solvent to give compound (**27**). Hydrolysis of the methyl ester by 20% NaOH to afford bare hydroxyl compound (**28**). Compound (**28**) was reacted with (1-methylpiperidin-4-yl)methyl 4-methylbenzenesulfonate in DMF solvent to give compound (**29**). Boc-deprotected and N-methylation of (**29**) to obtain target compound **25m**. Reaction of compound (**28**) with a morpholine ring/piperazine ring with the addition of paraformaldehyde gave final compounds **25n-25o**.



25a, R'' = (S,R)-phenyl, R^3 = OCH_3, R^2 = OCH_2-methylpiperidine, R = H
25b, R'' = (S,R)-phenyl, R^3 = OCH_3, R^2 = OCH_2-methylpiperidine, R = H
25c, R'' = S-phenyl, R^3 = OCH_3, R^2 = OCH_2-methylpiperidine, R = H
25d, R'' = R-phenyl, R^3 = OCH_3, R^2 = OCH_2-methylpiperidine, R = H
25e, R'' = (S,R)-3-F-phenyl, R^3 = OCH_3, R^2 = OCH_2-methylpiperidine, R = H
25f, R'' = (S,R)-4-F-phenyl, R^3 = OCH_3, R^2 = OCH_2-methylpiperidine, R = H
25g, R'' = (S,R)-2,5-difluoro-ph, R^3 = OCH_3, R^2 = OCH_2-methylpiperidine, R = H
25h, R'' = (S,R)-4cyclohexane, R^3 = OCH_3, R^2 = OCH_2-methylpiperidine, R = H
25i, R'' = (S,R)-phenyl, R^3 = OCH_3, R^2 = OCH_3, R = H
25j, R'' = (S,R)-phenyl, R^3 = OCH_3, R^2 = OCH_3, R = NH_2
25k,R'' = (S,R)-phenyl, R^3 = $O(CH_2)_3$-morpholine, R^2 = OCH_3, R = H
25l, R'' = (S,R)-phenyl, R^3 = $O(CH_2)_2OCH_3$, R^2 = $O(CH_2)_2OCH_3$, R = H

Scheme S2. Synthetic route of target compound **25a-k**[a]. [a]Reagents and conditions: (a) CH_3COOH, THF, 80 °C, 5h, 65-75%; (b) $SOCl_2$, 80 °C, 3 h, 50-70%; (c)3-fluoro-4-nitroaniline/4-fluoro-3-nitroaniline, THF, Et_3N, 60 °C, 5 h, 50-75%; (d) Pd/C, MeOH, H_2, 25 °C, 4 h, 85-95%; (e)compound **13** /4-chloro-6,7-dimethoxyquinazolin-2-amine/4-chloro-6,7-bis(2-methoxyethoxy)quinazoline/4-chloro-6,7-dimethoxyquinazoline/4-(3-((4-chloro-7-methoxyquinazolin-6-yl)oxy)propyl)morpholine, $(CH_3)_2CHOH$, HCl, 80 °C, 8 h, 45-55%.



Scheme S3. Synthetic route of target compound **25m-o**[a]. [a]Reagents and conditions: (a) $(CH_3)_2CHOH$, HCl, 80 °C, 5 h, 65%; (b) EtOH, 20% NaOH, 25 °C, 5 h, 65%; (c) 1-methylpiperazine/morpholine, NaOEt, EtOH, HCl, HCHO, 90 °C, 5 h, 45-55%; (d) (1-methylpiperidin-4-yl)methyl-4-methylbenzenesulfonate, K_2CO_3, DMF, 95 °C, 2 h, 80%; (e) HCOOH, HCHO, 95 °C, 5 h, 28%.

Materials and methods

Molecular Docking

The X-ray structure (PDB code: 5d41) was downloaded from the Protein Data Bank. The EGFR structure was prepared using the Protein Preparation Wizard in Maestro (Schrodinger, Inc., version 10.2). Energy was minimized with Root Mean Square Deviation (RMSD) value of 0.3 Å using OPLS-2005 force field. Compounds were prepared using the LigPrep module with pH of 7.0±2.0 for Epik. The prepared compounds were docked into the pocket including both the ATP-binding site and the allosteric site of EGFR using Glide with default settings. The docked poses were ranked by Gscore, and the one with the lowest binding energy was selected for binding mode analysis.

Cell culture and reagents

H1975 and A431 cell lines were purchased from the American Type Culture Collection (ATCC). Mouse original B cell line, BaF3 cell line was purchased from the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ). Cell lines were cultured according to the suppliers' instructions. $EGFR^{L858R/T790M/C797S}$-BaF3 and $EGFR^{19D/T790M/C797S}$-BaF3 cell lines were constructed by our group. BaF3-$EGFR^{L858R/T790M/C797S}$ and BaF3-$EGFR^{19D/T790M/C797S}$ cells were subsequently cultured in the absences of interleukin-3 (IL-3). **AZD9291**, **Brigatinib**, and **Staurosporine** were purchased from Selleck.

In vitro enzymatic activity assay

Enzyme-Linked Immunosorbent Assay (ELISA) was used to determine the ability of kinases to phosphorylate substrates. The $EGFR^{L858R/T790M/C797S}$ kinase protein and $EGFR^{19D/T790M/C797S}$ kinase protein were purchased from BPS Bioscience, and the $EGFR^{L858R/T790M}$ and $EGFR^{WT}$ kinase proteins were purchased from Eurofins Scientific. The enzyme reaction substrate Poly $(Glu, Tyr)_{4:1}$ was diluted to 2.5 μg/well with potassium-free PBS. Active kinases were incubated with indicated drugs in a 1× reaction buffer (50 mmol/L HEPES, pH 7.4, 20 mmol/L $MgCl_2$, 0.1 mmol/L $MnCl_2$, 0.2 mmol/L Na_3VO_4, and 1 mmol/L DTT) containing 5 μmol L^{-1} ATP at 37 °C for 1 hour. After incubation, the plates were washed three times with PBST. Next, 100 μL of anti-phosphotyrosine (PY99; 1:500 dilution) antibody was added. After 0.5 h incubation at 37 °C, the plate was washed three times. The plate was reincubated at 37 °C for 0.5 h and washed as before. Finally, 100 μL of color development solution (0.03% H_2O_2 and 2 mg/mL o-phenylenediamine in 0.1 mol/L citrate buffer, pH 5.4) was added and the plate was incubated at room temperature until color emerged. And the absorbance was read using a multi-well spectrophotometer (SpectraMax Plus384, Molecular Devices) at 490nm.

Cell proliferation inhibition assay

BaF3 cells proliferation was evaluated using the Resazurin (7-hydroxy-3H-phenoxazin-3-one 10-oxide) Assay. Cells were seeded in 96-well plates (10^4 cells per well) and grown overnight. The cells were treated with various concentrations of the compounds. After 72 h, 10 μL of resazurin solution (500 μM resazurin solution in DPBS, Sigma) was

added to each well, and the cells were incubated for 2 h at 37 °C. The Fluorescence signals were measured at an excitation wavelength at 540 nm and an emission wavelength at 590 nm using a microplate reader (Synergy2, BioTek). The percent inhibition rate for cell proliferation was calculated as [1 − (A540/590treated/ A540/590control)] × 100%.

H1975 and A431 cells proliferation were evaluated using the Sulforhodamine B (SRB) Assay. Cells were seeded in 96-well plates (3000 cells per well) and grown overnight. The cells were treated with various concentrations of the compounds for 72 h, and the cells were then fixed with 10% precooled trichloroacetic acid (TCA) for 2 h at 4 °C and stained for 15 min at room temperature with 100 μL of 4 mg/mL sulforhodamine B (SRB, Sigma) solution in 1% acetic acid. After washing the plates three times, the SRB solution was dissolved in 150 μL of 10 mmol/L Tris base for 5 min and measured at 515 nm using a multiwell spectrophotometer (VERSAmax, Molecular Devices). The percent inhibition rate for cell proliferation was calculated as [1 − (A515 treated/A515 control)] × 100. The IC_{50} value was obtained using the Logit method.

Western blot analysis

Cells were collected and suspended in lysis buffer (100 mmol/L Tris-HCl, pH 6.8, 200 mmol/L DTT, 4% SDS, 0.2% bromophenol blue, 20% glycerol). Equivalent amounts of proteins were loaded and separated by 10% SDS-PAGE and transferred to nitrocellulose membranes. Western blot analysis was subsequently performed using standard procedures. Antibodies used for immune detection of proteins were p-EGFR (Y1068; #3777S), EGFR (#4267S), and GAPDH (#5174S; Cell Signaling).

EGFR mutant constructs and retroviral infection. The $EGFR^{L858R/T790M}$ construct has been previously described， and the $EGFR^{C797S}$ mutation was introduced to $EGFR^{L858R/T790M}$ construct via site-directed mutagenesis using the Fast Mutagenesis System （TransGen Biotech）） according to the manufacturer's instructions. All constructs were confirmed by DNA sequencing. EGFR mutant constructs were introduced into BaF3 cells by retroviral infection, and stable clones were obtained by selection in puromycin (2 μg ml^{-1}). BaF3-$EGFR^{L858R/T790M}$ and BaF3-$EGFR^{L858R/T790M/C797S}$ subsequently cultured in the absences of interleukin-3 (IL-3).

Measurements of aqueous solubility.

Determination of the aqueous solubility was performed according to the published literature.[4]

In vivo pharmacokinetics study in rats.

The in vivo pharmacokinetic study in rats was conducted by Shanghai Medicilon, Inc. Rats were separately administered to some groups (three rats /group) for oral (10 mg/kg) or intravenous (1 mg/kg) administration. At time points 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 h after dosing, the blood sample was collected from each animal and stored in 2−8 ^{o}C, then separated by centrifugation (6800 r/min for 6 min). All samples were analyzed using LC−MS/MS (SIMADZU LC system; Applied Biosystems mass spectrometer), and the acquired data were analyzed by using the WinNonlin (v5.2).

Chemistry

Reagents and general methods.

All chemical reagents used in the experiment (such as 3-fluoro-4-nitroaniline, o-phthalaldehyde, etc.) and solvents (such as methanol, dichloromethane, etc.) are commercial products. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data were provided by Super Conducting Fourier NMR Spectrometer (AV-400). The high-resolution mass spectrometry test (HRMS, Waters LCT Premier XE TOF) was completed by the Institute of Fine Chemicals of ECUST. The apparatus for testing the melting point is the WRS-1B Digital Melting Point apparatus (WRS-1B). The purity of the target compounds was analyzed by high-performance liquid chromatography (HPLC, Hewlett-Packard 1100), with the purity of all compounds being over than 95%.

Chemistry

Synthesis of compound **18a**.

***Methyl 4-(N-Boc-4-piperidinylmethoxy)-3-methoxybenzoate* (8).** Methyl trioxalate (1 g, 5.49 mmol), anhydrous potassium carbonate (1.52 g, 10.98 mmol) in DMF (50mL) was stirred at room temperature for 15 min. Tert-Butyl tert-butyl-4-((tosyloxy)methyl)piperidine-1-carboxylate (2.75 g, 7.41 mmol) was added and

the reaction mixture was heated at 120 °C for 5 h. After cooling to room temperature, the reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 8:1) to obtain the product **8** (2.00 g, 86%)..^{1}H NMR（400 MHz, DMSO-d_6）: δ 7.57 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 3.97 (d, J = 12 Hz, 2H), 3.9 (d, J = 6.4 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 2.74 (s, 2H), 1.95-1.85 (m, 1H), 1.75 (d, J = 8.4 Hz, 2H), 1.4 (s, 9H), 1.15-1.10 (m, 2H)。

***Methyl 4-(N-methyl-4-piperidinylmethoxy)-3-methoxybenzoate* (9).** Compound **8** (1.02 g, 2.64 mmol) in formic acid (12mL) was stirred at room temperature for 30 min. The formaldehyde solution (4 mL, 47.44 mmol, 37%) was slowly added and the reaction mixture was heated at 120 °C with argon for 8 h. After cooling to room temperature, the reaction solution was concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 30:1) to give the product **9** (0.43 g, 94%). ^{1}H NMR（400 MHz, DMSO-d_6): δ 7.57 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 3.94 (d, J = 6 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.25 (d, J = 12 Hz, 2H), 2.70 (dd, J_1 = 11.2 Hz, J_2 = 22.8 Hz, 2H), 2.6 (s, 3H), 1.97-1.80 (m, 1H), 1.88 (d, J = 21.6 Hz, 2H), 1.49-1.40 (m, 2H)。

***Methyl 6-nitro-4-(N-methyl-4-piperidinylmethoxy)-3-methoxybenzoate* (10)**. Compound **3** (0.50 g, 1.7 mmol) in dichloromethane (20mL) was slowly added trifluoroacetic acid (2mL) ,24 M fuming nitric acid (400 μL, 8.52 mmol). The reaction mixture was stirred at room temperature overnight. Then neutralizing with saturated aqueous sodium bicarbonate. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 30:1) to give product **10** (0.45 g, 78%). ^{1}H NMR（400MHz, DMSO-d_6): δ 7.62 (s, 1H), 7.31 (s, 1H), 3.97 (d, J = 6 Hz), 3.92 (s, 3H), 3.83 (s, 3H), 2.77 (d, J = 11.2 Hz, 2H), 2.15 (s, 3H), 1.86 (t, J = 11.2 Hz, 2H), 1.76-1.74 (m, 1H), 1.72 (d, J = 10.4 Hz, 2H), 1.30-1.25 (m, 2H)。

***6-methoxy-7-(N-methyl-4-piperidinylmethoxy)-3,4-dihydroquinazolin-4-one* (12).** Compound **10** (0.40 g, 1.36 mmol), Pd/C (0.04 g, 10%) in methanol (100mL) was stirred at room temperature for 4 h with hydrogen. Pd/C was removed by filtration, and the solution

was concentrated in vacuo to obtain compound 11, an oily liquid (0.35 g, 95%), which was used in the next reaction without further purification.

To a solution of compound **11** (0.35 g, 1.13 mmol) in $CH_3OCH_2CH_2OH$ (100mL) was added formamidine acetate (0.35 g, 3.4 mmol). The reaction solution was heated with reflux at 120 ^oC for 8 h. Then the solution was concentrated in vacuo. The reaction solution was neutralized with saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 10:1) to give the product **12** (0.10 g, 30%). ^1H NMR（400MHz, DMSO-d_6): δ 7.98 (s, 1H), 7.45 (s, 1H), 7.13 (s, 1H), 3.98 (d, J = 6.0 Hz, 2H), 3.87 (s, 3H), 2.92 (d, J = 10.8 Hz, 2H), 2.29 (s, 3H), 2.13 (t, J = 10.4 Hz, 2H), 1.85-1.81 (m, 1H), 1.79 (d, J = 12 Hz, 2H), 1.39-1.32 (m, 2H)。

4-Chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline **(13)**. N, N-dimethylformamide (50 μl) in thionyl chloride (5mL) was stirred for 30 min at 0 ^oC. Then product **12** (0.10 g, 0.35 mmol) was added. The mixture solution was stirred at 120 ^oC for 3 h, and then concentrated in vacuo. The reaction solution was neutralized with saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 10:1) to give the product **13** as light yellow solid (0.08 mg, 70%). ^1H NMR（400MHz, DMSO-d_6): δ 8.87 (s, 1H), 7.45 (s, 1H), 7.40 (s, 1H), 4.00 (d, J = 6.4 Hz, 2H), 4.00 (s, 3H), 2.78 (d, J = 11.2 Hz, 2H), 2.16 (s, 3H), 1.90 (t, J=13.2 Hz, 2H),1.79 (d, J = 12 Hz, 3H), 1.35-1.32 (m, 2H)。

N-(3-Fluoro-4-nitrophenyl)-4-methoxybenzamide **(16)**. A mixture of 3-Fluoro-4-nitroaniline 14 (2.01g, 12.55 mmol), benzenesulfonyl chloride (2 mL, 15.07 mmol), triethylamine (2.2 mL, 15.07 mmol) in ethyl acetate (50mL) was stirred at room temperature for 1 h. Then the mixture was heated at 60 ^oC for 5 h. After cooling to room temperature, the reaction solution was concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/petroleum ether=3:1) to give the product **16** as pale yellow solid (2.78 g, 75%). ^1H NMR（400MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.22 (t, J = 9.2 Hz, 1H), 8.10 (d, J = 14.4 Hz, 1H), 8.00 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H)。

N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)benzamide **(18a).** Compound **16** (0.50 g, 1.92 mmol) in methanol (50mL) was added Pd/C (0.05 g, 10%). The mixture was stirred at room temperature for 5 hours with hydrogen atmosphere. Pd/C was removed by filtration. And the reaction solution was concentrated in vacuo to give the product **17** (0.43 g, 85%), which was used in the next reaction without further purification.

Compound **17**(0.18 g, 0.56 mmol) and product **13** (0.20 g, 0.75 mmol) in isopropanol (15mL) was stirred for 1 h at room temperature. 2N hydrochloric acid (2 drop) was added and the mixture was heated with reflux at 80 ^{o}C for 8 hours. The resulting solid was collected by filtration and dissolved in methylene chloride. The solution was neutralized with saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 10:1) to give the target compound **18a** as white solid (0.18 g, 52%), mp: 201.5-201.7 ^{o}C. ^{1}H NMR（400MHz, DMSO-d_6): δ 10.49 (s, 1H), 9.48 (s, 1H), 8.34 (s, 1H), 7.98 (d, J = 7.2 Hz, 2H), 7.89 (dd, J_1 = 2 Hz, J_2 =12.8 Hz, 1H), 7.83 (s, 1H), 7.60 (m, 5H), 7.17 (s, 1H), 4.00 (d, J = 6 Hz, 2H), 3.99 (s, 3H), 2.79 (d, J = 11.2 Hz, 2H), 2.17 (s, 3H), 1.89 (t, J = 11.2 Hz, 2H), 1.77(d, J = 9.2 Hz, 3H), 1.32-1.40 (m, 2H).^{13}C NMR (100 MHz, DMSO-d_6): δ 165.69, 157.37, 153.60, 153.10, 148.94, 148.77, 138.04, 137.94, 134.64, 131.75, 128.43, 127.67, 121.81, 121.68, 115.86, 108.45, 107.61, 102.01, 72.70, 56.12, 54.83, 46.16, 34.57, 28.45. HRMS (ESI) (*m/z*): $[M + H]^+$calcd for $C_{29}H_{31}FN_5O_3$, 516.2411; found, 516.2410. HPLC purity: 96.92%, retention time = 11.06 min.

The following compounds **18b-18i** were prepared by a similar method to that of compound **18a**.

N-(4-fluoro-3-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)benzamide **(18b).** Yellow solid (yield 43%). mp 201.5-201.7 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6)：δ 10.38 (s, 1H), 9.58 (s, 1H), 8.36 (s, 1H), 8.05 (d, J = 7.2 Hz, 1H), 7.87 (d, J = 7.2 Hz, 2H), 7.84 (s, 1H), 7.67-7.53 (m, 4H), 7.31 (t, J =12 Hz, 1H), 7.18 (s, 1H), 4.01(d, J = 6 Hz, 2H), 3.95 (s, 3H), 2.83 (d, J = 11.2 Hz, 2H), 2.21 (s, 3H), 1.96 (t, J = 12 Hz, 3H), 1.78(d, J = 10.4 Hz, 2H), 1.30-1.58 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.74, 157.40, 153.54, 153.10, 148.90, 146.73, 142.50, 128.62, 126.13, 124.39, 114.60, 108.43, 107.62, 102.02, 72.58, 56.12, 54.65, 48.55, 45.86, 42.02, 38.30, 36.20, 34.37, 28.22. HRMS

(ESI) (*m/z*): [M + H]$^+$calcd for $C_{29}H_{31}FN_5O_3$, 516.2411; found, 516.2410. HPLC purity: 95.36%, retention time = 10.78 min.

N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-phenylacetamide **(18c)**. White solid (yield 35%). mp 161.6-161.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6)： δ 10.42 (s, 1H), 9.41(s, 1H), 8.30 (s, 1H), 7.80 (s, 1H), 7.73(dd, J_1 = 12.4Hz, J_2 = 2 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.37-7.32 (m, 5H), 7.28-7.26 (m, 1H), 7.16 (s, 1H), 4.00(d, J = 6 Hz, 2H), 3.94 (s, 3H), 3.68 (s, 2H), 2.80 (d, J = 12 Hz, 2H), 2.17 (s, 3H), 1.89 (t, J = 11.2 Hz, 2H), 1.78-1.76 (m, 3H), 1.38-1.34 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.32, 157.36, 153.58, 153.08, 148.92 146.75, 135.73, 129.10, 128.31, 126.57, 114.67, 108.42, 107.61, 106.75, 102.00, 72.67, 56.11, 54.81, 48.56, 46.11, 43.26, 34.54, 28.42. HRMS (ESI) (*m/z*): [M + H]$^+$calcd for $C_{30}H_{33}FN_5O_3$, 530.2567; found, 530.2543. HPLC purity: 95.00%, retention time = 11.20 min.

N-(4-fluoro-3-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-phenylacetamide (**18d**). White solid (yield 43%). mp 211.4-211.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6)： δ 10.29 (s, 1H), 9.50 (s, 1H), 8.35 (s, 1H), 7.87 (dd, J_1 = 7.2 Hz, J_2 =2.8 Hz, 1H), 7.80 (s, 1H), 7.44-7.45 (m, 1H), 7.34-7.24 (m, 6H), 7.17 (s, 1H), 4.00 (d, J = 6 Hz, 2H), 3.94 (s, 3H), 3.65 (s, 2H), 2.80 (d, J = 12 Hz, 2H), 2.17 (s, 3H), 1.89 (t, J = 11.2 Hz, 2H), 1.78-1.76 (m, 3H), 1.37-1.33 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.06, 157.03, 153.67, 153.00, 149.00 146.85, 135.90, 129.00, 128.29, 126.52, 118.55, 115.90, 108.51, 107.60, 102.00, 72.71, 56.10, 54.83, 46.16, 43.26, 34.56, 26.44. HRMS (ESI) (*m/z*): [M + H]$^+$calcd for $C_{30}H_{33}FN_5O_3$, 530.2567; found, 530.2573. HPLC purity: 97.22%, retention time = 11.05 min.

2-(2,3-dihydro-1H-inden-2-yl)-N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)acetamide(**18e**). White solid (yield 38%). mp 210.9-211.1 °C. ^{1}H NMR（400MHz, DMSO-d_6): δ 10.20 (s, 1H), 9.44 (s, 1H), 8.31 (s, 1H), 7.82 (s, 1H), 7.73 (d, J = 13.2 Hz, 1H), 7.43 (t, J = 8.8 Hz 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 3.2 Hz, 1H), 7.22 (d, J = 3.2 Hz, 1H), 7.16 (s, 1H), 7.14-7.11 (m, 2H), 4.00 (d, J = 6 Hz, 2H), 3.94 (s, 3H), 3.17 (s, 2H), 3.11 (d, J = 8.0 Hz, 1H), 3.09-3.05 (m, 2H), 2.87-2.83 (m, 2H), 2.67 (d, J = 6.8 Hz, 1H), 2.63 (d, J = 6.8 Hz, 1H), 2.21 (s, 3H), 1.98-1.95 (m, 2H), 1.78-1.77 (m, 3H), 1.43-1.34 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.74, 157.40, 153.54, 153.10, 148.89, 146.73, 142.50, 128.62, 126.13, 124.39, 114.60, 108.43, 107.62, 106.46, 102.02, 72.58, 56.12, 54.65, 48.55, 45.86, 42.02, 38.30, 36.20, 34.37, 28.22. HRMS

(ESI) (*m/z*): [M + H]$^+$calcd for $C_{33}H_{37}FN_5O_3$, 570.2880; found, 570.2889. HPLC purity: 99.64%, retention time = 12.4 min.

2-(2,3-dihydro-1H-inden-2-yl)-N-(4-fluoro-3-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)acetamide **(18f)**. White solid (yield 40%). mp 157.2-157.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 9.67 (s, 1H), 7.90 (s, 2H), 7.50-7.48 (m, 1H), 7.25-7.20 (m, 4H), 7.12-7.10 (m, 2H), 4.03 (d, J = 6 Hz, 2H), 3.96 (s, 3H), 3.08-3.02 (m, 4H), 2.89-2.82 (m, 1H), 2.64 (dd, J_1 = 15.2 Hz, J_2 =6.8 Hz, 2H), 2.42 (s, 5H), 2.02-1.86 (m, 4H), 1.79-1.77 (m, 3H), 1.55-1.47 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.48, 157.08, 153.62, 153.03, 148.98, 146.80, 142.50, 126.12, 124.37, 118.52, 115.86, 108.52, 107.60, 102.05, 56.11, 54.60, 45.80, 41.95, 38.28, 36.28, 34.31. HRMS (ESI) (*m/z*): [M + H]$^+$calcd for $C_{33}H_{37}FN_5O_3$, 570.2880; found, 570.2879. HPLC purity: 95.33%, retention time = 12.20 min.

N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-phenylpropanamide (**18g**). White solid (yield 35%). mp 199.6-199.8 °C. ^{1}H NMR (400MHz, DMSO-d_6): δ 10.67 (s, 1H), 9.58 (s, 1H), 8.31 (s, 1H), 7.91 (s, 1H), 7.77 (d, J = 8.8 Hz,1H), 7.46-7.42 (m, 4H), 7.34 (t, J = 7.6 Hz, 2H), 7.27-7.20 (m, 2H), 4.17-4.15 (m, 1H), 4.05 (d, J = 6.0 Hz, 2H), 3.95 (s, 3H), 3.28 (d, J = 10.4 Hz, 2H), 2.85-2.83 (m, 2H), 2.62 (s, 3H), 2.07-1.98 (m, 3H), 1.67-1.64 (m, 2H), 1.45-1.43 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.04, 157.91, 155.86, 153.77, 153.63, 149.29, 147.16, 142.23, 138.74, 129.00, 128.84, 127.81, 127.20, 115.17, 109.10, 108.29, 107.25, 107.00, 102.85, 72.16, 58.73, 53.22, 49.04, 46.23, 33.03, 26.42, 18.97. HRMS (ESI) (*m/z*): [M + H]$^+$calcd for $C_{31}H_{35}FN_5O_3$, 544.2724; found, 544.2709. HPLC purity: 98.56%, retention time = 12.02 min.

N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-3-methyl-2-phenylbutanamide (**18h**). White solid (yield 37%). mp 196.0-196.2 °C。 ^{1}H NMR (400MHz, DMSO-d_6): δ 10.52 (s, 1H), 9.49 (s, 1H), 8.30 (s, 1H), 7.85 (s, 1H), 7.75 (dd, J_1 = 2.0 Hz, J_2 = 13.2 Hz, 1H), 7.45-7.38 (m, 4H), 7.33 (t, J = 7.6 Hz, 2H), 7.24-7.20 (m, 1H), 7.18 (s, 1H), 4.01 (d, J = 6.4 Hz , 2H), 3.94 (s, 3H), 3.33 (d, J = 10.4 Hz, 1H), 3.03 (d, J = 11.6 Hz, 2H), 2.37 (s, 3H), 2.34-2.24 (m, 3H), 1.91-1.84 (m, 3H), 1.50-1.45 (m, 2H), 1.04 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.48, 157.89, 155.86, 153.93, 153.59, 149.35, 147.21, 140.04, 128.77, 128.68, 127.37, 115.19, 108.99, 108.17, 107.26, 107.00, 102.63, 72.70, 60.98, 56.65, 54.43, 45.27, 34.14, 31.47,

27.65, 21.70, 20.68. HRMS (ESI) (*m/z*): $[M + H]^+$ calcd for $C_{33}H_{39}FN_5O_3$, 572.3037; found, 572.3047. HPLC purity: 97.51%, retention time = 13.00 min.

N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2,2-diphenylacetamide (*18i*). White solid (yield 37%). mp 257.0-257.2 °C。^{1}H NMR (400MHz, DMSO-d_6): δ 10.83 (s, 1H), 9.50 (s, 1H), 8.31 (s, 1H), 7.85 (s, 1H), 7.78 (d, *J* = 12.8 Hz, 1H), 7.47-7.34 (m, 10H), 7.29-7.26 (m, 2H), 7.18 (s, 1H), 5.27 (s, 1H), 4.01(d, *J* = 5.6 Hz, 2H), 3.94 (s, 3H), 3.02 (d, *J* = 10.8 Hz, 2H), 2.38 (s, 3H), 2.33-2.25 (m, 2H), 1.90-1.84 (m, 3H), 1.50-1.42 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.64, 157.86, 155.86, 153.94, 153.60, 149.37, 147.22, 140.26, 129.04, 128.89, 127.38, 115.33, 109.00, 108.19, 107.41, 102.62, 72.69, 57.74, 56.65, 54.43, 45.25, 34.12, 27.84. HRMS (ESI) (*m/z*): $[M + H]^+$ calcd for $C_{36}H_{37}FN_5O_3$, 606.2880; found, 606.2888. HPLC purity: 98.61%, retention time = 13.25 min.

Synthesis of compound **25a**

2-(1-oxoisoindolin-2-yl)-2-phenylacetic acid (**21**). A mixture of o-phthalaldehyde (1.00 g, 7.46 mmol), D, L-phenylglycine (1.13 g, 7.46 mmol), acetic acid (2 mL) in dry THF was heated at 80 °C for 5 h. The resulting solid was collected by filtration, washed with THF to give the product **21** as brown solid (1.00 g, 50%).. ^{1}H NMR（400MHz, DMSO-d_6): δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 6.8 Hz, 1H), 7.56-7.50 (m, 2H), 7.46-7.39 (m, 5H), 5.99 (s, 1H), 4.83 (d, *J* = 17.6 Hz, 1H), 3.92 (d, *J* = 17.6 Hz, 1H).

N-(3-Fluoro-4-nitrophenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide (**23**). Compound **21** (1.03 g, 3.74 mmol) in $SOCl_2$ (10 mL) was stirred for 5 hours at room temperature. The reaction solution was concentrated in vacuo to give the product **22** (0.80 g, 74%), which was used in the next reaction without further purification.

A mixture of compound **22** (0.80 g, 2.80 mmol), 3-fluoro-4-nitroaniline (0.44 g, 2.8 mmol), triethylamine (1.2 mL) in dry THF was heated at 60 °C for 5 h. The solution was concentrated in vacuo. And the residue was purified by silica gel chromatography to give the product **23** as yellow solid (0.60 g, 50%). ^{1}H NMR（400MHz, DMSO-d_6): *δ* 11.29 (s, 1H), 8.20 (t, *J* = 8.8 Hz, 1H), 7.92 (d, *J* = 14.0 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.64-7.57 (m, 2H), 7.54-7.43 (m, 7H), 6.23 (s, 1H), 4.75 (d, *J* = 17.6 Hz, 1H), 3.95 (d, *J* = 17.6 Hz, 1H).

N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide (**25a**). Compound **23** (0.60 g, 1.48 mmol)

and Pd/C (0.06 g, 10%) in MeOH (50 mL) was stired at room temperature for 4 h. Pd/C was removed by filtration, and the solution was concentrated in vacuo to give the product **24** (0.43 g, 85%), without further purification.

A mixture of compound **13** (0.10 g, 0.32 mmol) was added, compound **24** (0.12 g, 0.32 mmol), 6N hydrochloric acid (2 drop) in isopropanol (15 mL) was heated with reflux at 80 ^{o}C for 8 h. The resulting solid was collected by filtration and dissolved in methylene chloride. The reaction solution was neutralized with saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 10:1) to give the product **25a** (0.09 g, 45%), mp 270.3-270.5 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H), 9.45 (s, 1H), 8.32 (s, 1H), 7.82 (s, 1H), 7.78 (s, 1H), 7.75 (d, *J* = 4.4Hz 1H), 7.64-7.57 (m, 2H), 7.54-7.43 (m, 7H), 7.39 (d, *J* = 8.4Hz, 1H), 7.17 (s, 1H), 7.26 (s, 1H), 4.85 (d, *J* = 18 Hz, 1H), 4.02-3.87 (m, 3H), 3.96 (s, 3H), 2.82 (d, *J* = 12.0 Hz, 2H), 2.18 (s, 3H), 2.03 (t, *J* = 11.2 Hz, 2H), 1.81-1.78 (m, 3H), 1.38-1.35 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.34, 167.73, 157.33, 153.60, 153.06, 148.95, 146.77, 142.38, 135.18, 131.70, 131.42, 129.09, 128.54, 127.95, 123.64, 122.94, 108.45, 107.63, 102.02, 72.66, 58.54, 56.13, 54.76, 48.35, 46.05, 34.50, 28.37. HRMS (ESI) (*m/z*): $[M + H]^+$ calcd for $C_{38}H_{38}FN_6O_4$, 661.2939; found, 661.2929. HPLC purity: 95.64%, retention time = 12.42 min.

The following compounds **25b-15l** were prepared by a similar method to that of compound **25a**.

N-(4-fluoro-3-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide (**25b**). White solid (yield 38%). mp: 156.7-156.9 ^{o}C. ^{1}H NMR（400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 9.70 (s, 1H), 8.36 (s, 1H), 7.90 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.64-7.62 (m, 2H), 7.53-7.49 (m, 3H), 7.47-7.41 (m, 5H), 7.28 (t, *J* = 10.0 Hz, 1H), 7.21 (s, 1H), 6.26 (s, 1H), 4.82 (d, *J* = 17.6 Hz, 1H), 4.03 (d, *J* = 17.6 Hz, 1H), 4.00 (d, *J* = 6.0 Hz, 2H), 3.96 (s, 3H), 3.12 (d, *J* = 11.6 Hz, 2H), 2.48 (s, 3H), 2.02-1.95 (m, 1H), 1.94-1.91 (m, 4H), 1.56-1.49 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.64, 168.19, 157.70, 153.89, 149.45, 142.86, 135.81, 135.28, 132.17, 131.92, 129.53 129.02, 128.43, 124.12, 123.41, 119.39, 109.15, 108.11, 105.63, 103.00, 62.07, 58.96, 56.81,

56.28, 53.27, 48.89, 46.99. HRMS (ESI) (*m/z*): $[M + H]^+$ calcd for $C_{38}H_{38}FN_6O_4$, 661.2939; found, 661.2943. HPLC purity: 95.85%, retention time = 12.42 min.

(S)-N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino) phenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide (25c). White solid (yield 43%). mp 229.4-230.2 °C。^{1}H NMR（400 MHz, DMSO-d_6): δ 10.37 (s, 1H), 9.54 (s, 1H), 8.33 (s, 1H), 7.85 (s, 1H), 7.80 (dd, J_1 = 2 Hz, J_2 = 5.6 Hz, 1H), 7.77 (s, 1H), 7.62-7.58 (m, 2H), 7.54-7.44 (m, 7H), 7.39 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 2H), 7.18 (s, 1H), 6.27 (s, 1H), 4.85 (d, J = 17.6 Hz, 1H), 4.02 (d, J = 5.6 Hz, 2H), 4.00 (d, J = 17.6 Hz, 2H), 3.96 (s, 3H), 2.93 (d, J = 11.2 Hz, 2H), 2.29 (s, 3H), 2.13 (t, J = 11.2 Hz, 2H). 1.82-1.80 (m, 3H), 1.48-1.38 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.86, 168.23, 157.83, 155.87, 154.01, 153.57, 149.39, 147.24, 142.88, 135.86, 132.21, 129.59, 129.19, 128.45, 124.15, 123.44, 115.45, 108.98, 108.12, 107.59, 102.57, 72.89, 59.03, 58.48, 56.64, 54.79, 49.07, 48.88, 45.82, 34.50, 28.28. HRMS (ESI) (*m/z*): $[M + H]^+$ calcd for $C_{38}H_{38}FN_6O_4$, 661.2939; found, 661.2938. HPLC purity: 97.68%, retention time = 12.48 min.

(R)-N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino) phenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide (**25d**). White solid (yield 38%). mp 282.1-282.3 °C. ^{1}H NMR（400 MHz, DMSO-d_6): δ 10.96 (s, 1H), 9.73 (s, 1H), 8.32 (s, 1H), 7.96 (s, 1H), 7.79-7.78 (m, 1H), 7.77 (s, 1H), 7.64-7.58 (m, 2H), 7.52 (t, J = 14 Hz, 1H), 7.49 (s, 1H), 7.47-7.43 (m, 5H), 7.39 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 7.22 (s, 1H), 6.28 (s, 1H), 4.84 (d, J = 17.6 Hz, 1H), 4.02 (d, J = 5.6 Hz, 2H), 4.00 (d, J = 17.6 Hz, 1H), 3.96 (s, 3H), 3.22 (d, J = 11.2 Hz, 2H), 2.74 (t, J = 9.6 Hz, 2H), 2.57 (s, 3H), 1.96-1.92 (m, 3H), 1.86-1.80 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.92, 168.19, 158.14, 154.06, 149.49, 142.87, 135.71, 132.20, 131.93, 129.55, 129.09, 128.99, 124.45, 123.42, 115.45, 108.12, 107.59, 102.57, 72.90, 60.42, 59.05, 58.48, 56.98, 53.14, 49.94, 43.05, 33.00, 26.31. HRMS (ESI) (*m/z*): $[M + H]^+$ calcd for $C_{38}H_{38}FN_6O_4$, 661.2939; found, 661.2935. HPLC purity: 97.35%, retention time = 11.35 min.

N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phe nyl)-2-(3-fluorophenyl)-2-(1-oxoisoindolin-2-yl)acetamide (**25e**). White solid (yield 41%). mp 234.2-234.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H), 9.63 (s, 1H), 8.32 (s, 1H), 7.90 (s, 1H), 7.78 (s, 1H), 7.76 (d, J = 4.8 Hz, 1H), 7.65-7.59 (m, 2H), 7.57-7.50 (m, 2H), 7.46 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.31-7.26 (m, 3H), 7.22 (s, 1H), 6.26

(s, 1H), 4.82 (d, *J* = 17.6 Hz, 1H), 4.02 (d, *J* = 5.6 Hz, 2H), 4.00 (d, *J* = 17.6 Hz, 1H), 3.95 (s, 3H), 3.31 (d, *J* = 11.2 Hz, 2H), 2.84 (t, *J* = 9.6 Hz, 2H), 2.64 (s, 3H), 1.96-1.92 (m, 3H), 1.66-1.58 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.25, 163.96, 161.52, 157.81, 155.84, 154.00, 153.57, 149.39, 147.24, 142.92, 132.28, 131.79, 129.16, 128.48, 125.18, 124.18, 123.47, 108.98, 108.12, 102.58, 74.35, 72.87, 60.47, 58.48, 56.64, 54.76, 48.92, 45.77, 34.54, 28.25. HRMS (ESI) (*m/z*): $[M + H]^+$calcd for $C_{38}H_{37}F_2N_6O_4$, 679.2844; found, 679.2845. HPLC purity: 97.51%, retention time = 12.72 min.

***N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-(4-fluorophenyl)-2-(1-oxoisoindolin-2-yl)acetamide* (25f).** White solid (yield 39%). mp 218.4-218.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 9.55 (s, 1H), 8.32 (s, 1H), 7.79 (s, 1H), 7.86 (s, 1H), 7.78-7.76 (m, 2H), 7.64-7.58 (m, 2H), 7.52-7.46 (m, 4H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 8.8 Hz, 2H), 7.18 (s, 1H), 6.25 (s, 1H), 4.82 (d, *J* = 17.6 Hz, 1H), 4.03 (d, *J* = 17.6 Hz, 1H), 4.00 (d, *J* = 6.0 Hz, 2H), 3.95 (s, 3H), 2.92 (d, *J* = 10.4 Hz, 2H), 2.29 (s, 3H), 2.13 (t, *J* = 11.2 Hz, 2H), 1.83-1.80 (m, 3H), 1.49-1.38 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.72, 168.20, 161.29, 157.83, 154.01, 153.56, 149.40, 147.23, 142.86, 132.23, 131.90, 131.36, 129.18, 128.46, 124.15, 123.44, 116.54, 116.32, 115.47, 108.97, 108.12, 102.62, 72.90, 58.38, 56.65, 54.73, 48.85, 45.78, 34.50, 28.26, 21.87. HRMS (ESI) (*m/z*): $[M + H]^+$calcd for $C_{38}H_{37}F_2N_6O_4$, 679.2844; found, 679.2841. HPLC purity: 98.46%, retention time = 12.87 min.

***2-(2,5-difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-(1-oxoisoindolin-2-yl)acetamide* (25g)**. White solid (yield 37%). mp 202.2-202.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 9.53 (s, 1H), 8.33 (s, 1H), 7.85 (s, 1H), 7.79-7.73 (m, 2H), 7.66-7.29 (m, 9H), 7.18 (s, 1H), 6.42 (s, 1H), 4.82 (d, *J* = 17.6 Hz, 1H), 4.14 (d, *J* = 17.6 Hz, 1H), 4.01 (d, *J* = 6.0 Hz, 2H), 3.95 (s, 3H), 2.96 (d, *J* = 10.4 Hz, 2H), 2.32 (s, 3H), 2.19 (t, *J* = 11.2 Hz, 2H), 1.85-1.75 (m, 3H), 1.48-1.36 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.00, 167.40, 157.82, 155.92, 154.01, 153.57, 149.40, 147.25, 142.82, 132.38, 131.63, 129.14, 128.53, 124.23, 123.53, 115.73, 108.99, 108.15, 102.59, 72.84, 56.65, 56.68, 53.35, 48.77, 45.64, 34.38, 28.14. HRMS (ESI) (*m/z*): $[M + H]^+$calcd for $C_{38}H_{36}F_3N_6O_4$, 697.2750; found, 679.2759. HPLC purity: 98.02%, retention time = 8.75 min.

***2-cyclohexyl-N-(3-fluoro-4-((6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-(1-oxoisoindolin-2-yl)acetamide* (25h)**. Yellow solid (yield 42%). mp

269.7-269.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 9.51 (s, 1H), 8.32 (s, 1H), 7.84 (s, 1H), 7.77 (d, *J* = 6.8 Hz , 1H), 7.75 (s, 1H), 7.67-7.63 (m, 2H), 7.53-7.41 (m, 3H), 7.18 (s, 1H), 4.87 (d, *J* = 18.4 Hz, 1H), 4.83 (s, 1H), 4.61 (d, *J* = 18.4 Hz, 1H), 4.00 (d, *J* = 6 Hz, 2H), 3.95 (s, 3H), 2.91 (d, *J* = 11.2 Hz, 2H), 2.26 (s, 3H), 2.11 (t, *J* = 10.8 Hz, 3H), 1.83-1.76 (m, 4H), 1.62-1.64 (m, 3H), 1.48-1.37 (m, 3H), 1.26-1.22 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.29, 168.32, 158.23, 157.83, 155.79, 154.00, 153.56, 149.38, 147.23, 142.79, 137.68, 137.57, 129.08, 128.36, 124.04, 123.43, 122.43, 122.31, 115.85, 108.96, 108.11, 107.72, 107.47, 102.54, 72.91, 60.24, 56.63, 54.84, 47.70, 45.90, 37.54, 34.55, 29.67, 29.58, 28.35, 26.27, 25.56, 25.41. HRMS (ESI) (m/z): $[M + H]^+$calcd for $C_{38}H_{44}FN_6O_4$, 667.3408; found, 667.3406. HPLC purity: 96.75%, retention time = 13.09 min.

N-(4-((6,7-dimethoxyquinazolin-4-yl)amino)-3-fluorophenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide (**25i**). White solid (yield 34%). mp 233.6-233.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H), 9.45 (s, 1H), 8.33 (s, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.75 (d, *J* = 4.4 Hz 1H), 7.64-7.57 (m, 2H), 7.54-7.43 (m, 7H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.17 (s, 1H), 6.26 (s, 1H), 4.85 (d, *J* = 18Hz, 1H), 4.00 (d, *J* = 18Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.35, 157.36, 154.22, 153.07, 148.81, 146.81, 142.39, 137.28, 135.17, 131.71, 131.42, 129.09, 128.54, 127.95, 123.65, 122.93, 108.53, 107.01, 101.90, 58.54, 56.04, 55.76, 48.57. HRMS (ESI) (*m/z*): $[M + H]^+$calcd for $C_{32}H_{27}FN_5O_4$, 564.2047; found, 564.2045. HPLC purity: 96.86%, retention time = 14.16 min.

N-(4-((2-amino-6,7-dimethoxyquinazolin-4-yl)amino)-3-fluorophenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide (**25j**). White solid (yield 39%). mp 142.7-142.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.18 (t, *J* = 8.8 Hz, 1H), 7.79 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 12.8 Hz, 1H), 7.62-7.56 (m, 2H), 7.52-7.44 (m, 5H), 7.27-7.25 (m, 3H), 6.80 (s, 1H), 6.24 (s, 1H), 4.85 (d, *J* = 17.6 Hz, 1H), 4.97 (d, *J* = 17.6 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.38 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.70, 168.20, 162.05, 155.24, 146.58, 142.88, 135.72, 132.19, 131.93, 129.55, 129.05, 128.45, 124.15, 123.41, 115.47, 107.34, 107.09, 104.74, 103.88, 107.08, 59.03, 56.53, 56.22, 48.91. HRMS (ESI) (*m/z*): $[M + H]^+$calcd for $C_{32}H_{28}FN_6O_4$, 579.2156; found, 579.2155. HPLC purity: 98.12%, retention time = 14.71 min.

N-(3-fluoro-4-((7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-yl)amino)phenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide **(25k)**. White solid (yield 55%). mp 229.6-229.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 9.55 (s, 1H), 8.33 (s, 1H), 7.85 (s, 1H), 7.77 (d,

J = 8.4 Hz , 2H), 7.64-7.58 (m, 2H), 7.54-7.44 (m, 7H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.19 (s, 1H), 6.27 (s, 1H), 4.84 (d, *J* = 18.0 Hz, 1H), 4.17 (t, *J* = 6.4 Hz, 2H), 4.00 (d, *J* = 18.0 Hz , 1H), 3.94 (s, 3H), 3.79-3.74 (m, 4H), 2.47-2.44 (m, 2H), 2.42-2.41 (m, 4H), 2.02-1.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.32, 168.03, 157.16, 156.97, 154.62, 152.71, 148.42, 142.36, 136.46, 134.68, 131.45, 131.39, 128.70, 128.67, 128.37, 127.59, 127.27, 123.06, 122.76, 114.96, 108.58, 107.31, 107.06, 106.86, 101.59, 66.86, 66.98, 59.25, 55.36, 54.83, 53.12, 48.24, 25.48. HRMS (ESI) (*m/z*): [M + H]$^+$calcd for $C_{38}H_{38}FN_6O_5$, 677.2888; found, 677.2892. HPLC purity: 95.91%, retention time = 12.25 min.

N-(4-((6,7-bis(2-methoxyethoxy)quinazolin-4-yl)amino)-3-fluorophenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide (**25l**). White solid (yield 42%). mp 277.8-280.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 9.47 (s, 1H), 8.33 (s, 1H), 7.85 (s, 1H), 7.77 (d, *J* = 8.0 Hz , 2H), 7.62-7.58 (m, 2H), 7.54-7.44 (m, 7H), 7.38 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 3H), 7.22 (s, 1H), 6.26 (s, 1H), 4.84 (d, *J* = 18.4 Hz, 1H), 4.27 (m, 4H), 4.99 (d, *J* = 18.4 Hz, 1H), 3.79-3.74 (m, 4H), 3.37 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.86, 168.24, 157.82, 155.83, 154.02, 153.63, 148.44, 147.18, 142.88, 135.64, 132.22, 131.90, 129.00, 129.05, 128.46, 124.16, 123.44, 115.43, 109.04, 108.45, 103.58, 70.52, 68.63, 68.43, 59.03, 58.84, 58.80, 48.87. HRMS (ESI) (*m/z*): [M + H]$^+$calcd for $C_{36}H_{35}FN_5O_6$, 652.2571; found, 642.2567. HPLC purity: 97.77%, retention time = 14.36 min.

Synthesis of compound **25m**

4-((2-fluoro-4-(2-(1-oxoisoindolin-2-yl)-2-phenylacetamido)phenyl)amino)-7-methoxyquinazolin-6-yl acetate **(27)**. A mixture of 4-Chloro-7-methoxyquinazolin-6-yl acetate (1.00 g, 3.96 mmol), compound **24a** (1.49 g, 3.96 mmol), 6N hydrochloric acid (2 drop) in isopropanol (15 mL) was heated with reflux at 80 °C for 5 h. The resulting solid was collected by filtration and dissolved in methylene chloride. The reaction solution was neutralized with saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 10:1) to give the product **27** (1.51 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6)： δ 10.85 (s, 1H), 8.49 (s, 1H), 8.29 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.64-7.57 (m, 2H), 7.54-7.43 (m, 7H), 7.39-7.36 (m, 2H), 6.25 (s, 1H), 4.82 (d, *J* = 18 Hz, 1H), 3.98 (d, *J* = 18Hz , 1H), 3.96 (s, 3H), 2.37 (s, 3H).

N-(3-fluoro-4-((6-hydroxy-7-methoxyquinazolin-4-yl)amino)phenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide **(28)**. Compound **27** (1.50 g, 2.54 mmol) and 20% sodium hydroxide (5 mL) in ethanol (20 mL) was stirred at room temperature for 6 h. The solution was acidified with 6N HCl and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 10:1) to give the product **28** (0.80 g, 65%) without purification.

Tert-butyl 4-(((4-((2-fluoro-4-(2-(1-oxoisoindolin-2-yl)-2-phenylacetamido)phenyl)amino)-7-methoxyquinazolin-6-yl)oxy)methyl)piperidine-1-carboxylate **(29)**. Compound **28** (0.80 g, 1.46 mmol) and anhydrous potassium carbonate (0.61 g, 4.37 mmol) in DMF (50 mL) was stirred at room temperature for 15 min. Tert-Butyl tert-butyl-4-((tosyloxy) methyl)piperidine-1-carboxylate (1.08 g, 2.91 mmol) was added and the reaction solution was heated at 95 ^{o}C for 3 h. After cooling to room temperature, the reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na2SO4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 10:1) to give the product **29** (0.60 g, 55%).^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 9.50 (s, 1H), 8.32 (s, 1H), 7.82 (s, 1H), 7.78 (s, 1H), 7.75 (d, *J* = 4.8 Hz, 1H), 7.64-7.57 (m, 2H), 7.54-7.44 (m, 7H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.18 (s, 1H), 6.25 (s, 1H), 4.83 (d, *J* = 17.6 Hz, 1H), 4.00-3.99 (m, 4H), 3.98 (d, *J* = 17.6 Hz , 1H), 3.93 (s, 3H), 2.83-2.73 (m, 2H), 2.56-2.42 (m, 2H), 2.07-1.98 (m, 1H), 1.82 (d, *J* = 11.2 Hz, 2H), 1.41 (s, 9H).

N-(3-fluoro-4-((7-methoxy-6-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide **(25m)**. Compound **29** (0.60 g, 0.80 mmol) in formic acid (12 mL) was stirred at room temperature for 30 min. Formaldehyde solution (4 mL, 47.44 mmol, 37%) was slowly added dropwise, and the mixture was heated at 95 °C for 5 h. The reaction solution was concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol = 10:1) to give the product **25m** (0.12 g, 28%) as a white solid, mp 175.3-175.5 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 9.59 (s, 1H), 8.31 (s, 1H), 7.91 (s, 1H), 7.77 (s, 1H), 7.75 (d, *J* = 3.2 Hz, 1H), 7.64-7.57 (m, 2H), 7.54-7.43 (m, 7H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.19 (s, 1H), 6.25 (s, 1H), 4.82 (s, 1H), 4.24 (d, *J* = 17.6 Hz, 1H), 4.04-4.03 (m, 2H), 3.98 (d, *J* = 17.6 Hz , 1H), 3.94 (s, 3H), 3.01-2.90 (m, 2H), 2.69 (s, 3H), 2.16-2.08 (m, 1H), 2.03-1.96 (m, 3H), 1.67-1.64 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.87, 168.23, 158.36, 157.88, 155.92, 154.79, 153.60, 148.52, 147.22,

142.88, 135.65, 132.21, 131.91, 129.59, 129.29, 129.05, 128.46, 124.15, 123.43, 115.48, 109.01, 107.59, 107.34, 103.29, 73.09, 59.05, 56.33, 54.03, 49.06, 44.57, 33.94, 27.52. HRMS (ESI) (*m/z*): $[M + H]^+$calcd for $C_{38}H_{38}FN_6O_4$, 661.2939; found, 661.2932. HPLC purity: 95.95%, retention time = 12.32 min.

N-(3-fluoro-4-((7-methoxy-6-((4-methylpiperazin-1-yl)methoxy)quinazolin-4-yl)amino)phenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide (25n). A mixture of compound **28** (0.30 g, 0.54 mmol), N-methylpiperazine (0.14 g, 1.36 mmol), sodium ethoxide (0.10 g, 1.36 mmol), paraformaldehyde (0.05 g, 1.09 mmol), concentrated HCl (3 drops) in ethanol (40 mL) was heated at 90 ^oC for 5h. After cooling to room temperature, the solution was concentrated with a rotary evaporator. The residue was purified by silica gel chromatography (dichloromethane/methanol = 10:1) to give the product **25n** as white solid (0.12 g, 45%), mp 151.5-151.7 ^oC. ^1H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 9.49 (s, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.78-7.72 (m, 2H), 7.63-7.56 (m, 3H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.48-7.43 (m, 5H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.15 (s, 1H), 6.25 (s, 1H), 4.23 (d, *J* = 17.6 Hz, 1H), 3.98 (d, *J* = 17.6 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 2H), 2.89 (s, 2H), 2.73 (s, 2H), 2.67-2.58 (m, 4H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.75, 168.19, 158.66, 153.08, 147.81, 146.35, 142.88, 135.77, 132.18, 131.93, 129.55, 129.03, 128.44, 124.13, 123.43, 114.77, 111.46, 107.56, 107.31, 107.08, 59.98, 56.52, 54.48, 51.67, 48.87, 45.90, 45.70, 43.14. HRMS (ESI) (*m/z*): $[M + H]^+$calcd for $C_{37}H_{37}FN_7O_4$, 662.2891; found, 662.2885. HPLC purity: 98.81%, retention time = 12.00 min.

The following compound **25o** was prepared by a similar method to that of compound **25n**.

***N-(3-fluoro-4-((7-methoxy-6-(morpholinomethoxy)quinazolin-4-yl)amino)phenyl)-2-(1-oxoisoindolin-2-yl)-2-phenylacetamide* (25o)**. White solid (yield 42%). mp 224.5-224.7 ^oC. ^1H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 9.50 (s, 1H), 8.26 (s, 1H), 7.79 (s, 1H), 7.76 (d, *J* = 5.6 Hz,1H), 7.66-7.59 (m, 3H), 7.54 (s, 1H), 7.50-7.41 (m, 6H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.18 (s, 1H), 6.26 (s, 1H), 4.85 (d, *J* = 17.6 Hz, 1H), 4.00 (s, 3H), 3.99 (d, *J* = 17.6 Hz, 1H), 3.95 (s, 2H), 3.63-3.61 (m, 4H), 2.58-2.55 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.71, 168.20, 158.53, 153.09, 154.43, 147.87, 146.47, 142.88, 135.77, 132.18, 131.92, 129.56, 129.00, 128.43, 127.65, 124.13, 123.43, 115.43, 114.33, 111.51, 107.53, 107.15, 81.30, 66.60, 66.28, 58.95, 56.52, 52.02. HRMS (ESI) (*m/z*): $[M + H]^+$calcd for $C_{36}H_{34}FN_6O_5$, 649.2575; found, 649.2584. HPLC purity: 96.88%, retention time = 11.08 min.

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