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Structure-guided design and development of novel *N*-phenylpyrimidin-2-amine derivatives as potential c-Met inhibitors

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ABSTRACT

The HGF/Met signaling pathway is over-expressed in many types of cancers and closely related to oncogenesis and metastasis. Thus, we developed novel *N*-phenylpyrimidin-2-amine derivatives to test their inhibitory activities towards c-Met kinase, and most of the compounds (**15a-i**, **15o-r**, **20** and **34a-c)** could inhibit the target with IC_{50} values from 550.8 nM to 15.0 nM. Subsequently, compound **15b**, **15d**, **15f**, **15i**, **15o**, **15r**, **20**, **34a** and **34b** also showed high antiproliferative activities in c-Met sensitive tumor cell lines (PC-3, Panc-1, HepG2, HCT116 and Caki-1) with IC_{50} values from 0.53 to 1.37 μM. The lead compound **34a** displayed outstanding c-Met inhibitory activity (IC_{50}: 15.0 nM) and antiproliferative activities. Furthermore, **34a** also performed favorable pharmacokinetic properties in mice (F%: 59.3) and an acceptable safety profile in preclinical studies. Further docking studies showed a common interaction of **34a** with c-Met at the ATP-binding site, which indicated that **34a** could be a potential candidate for c-Met inhibitors.

1. Introduction

c-Mesenchymal epithelial transition factor (c-Met) is a receptor tyrosine kinase (RTK) and also known as hepatocyte growth factor receptor (HGFR) [1,2], which is critical in the progression of malignancy and essential for embryogenesis [3], wound healing [4] and organ regeneration [5]. However, abnormally high levels of c-Met kinase have been found to be implicated in a variety of solid tumors (gastric cancer, thyroid cancer and lung cancer) [6] and they are frequently associated with metastatic phenotypes and poor prognosis [7]. Also, c-Met mutations might be one of the causes of poor prognosis and drug-resistance in targeted therapies at clinical studies [8]. Therefore, c-Met kinase and its ligand have become desirable targets for cancer treatment.

Small-molecule inhibitors are the main approach to inhibit c-Met kinase activity, besides antibodies and antagonists. Several pipelines of small-molecule c-Met inhibitors with different binding modes and selectivity profiles have been launched or in clinical trials. Type-I inhibitors, such as Crizotinib [9], JNJ-38877605 [10], INC-280 [11] and MK-2461 [12], bind to c-Met in a U shape conformation competed with ATP, and type-II inhibitors, such as Cabozantinib [13], Foretinib [14], MGCD265 [15], Tepotinib [16], S-49076 [17] and Golvatinib [18], exhibit an extended binding mode with c-Met other than the way of Type-I inhibitors does (Fig. 1). Crizotinib (Xalkori) was approved by FDA for the treatment of non-small cell lung cancer (NSCLC) in 2011, and Cabozantinib (Cometriq) was first approved in 2012 for the treatment of progressive metastatic medullary thyroid cancer, and then in 2017 was approved in the USA for the treatment of advanced renal cell carcinoma (RCC) in the patients who had received prior antiangiogenic therapy. In 2020, Tepotinib developed by Merck was approved in Japan for the treatment of unresectable non-small cell lung cancer with MET exon 14-skipping mutations [19], which is the first oral c-Met inhibitor launched in the world. Furthermore, new variations based on these molecules have also been reported [20–26].

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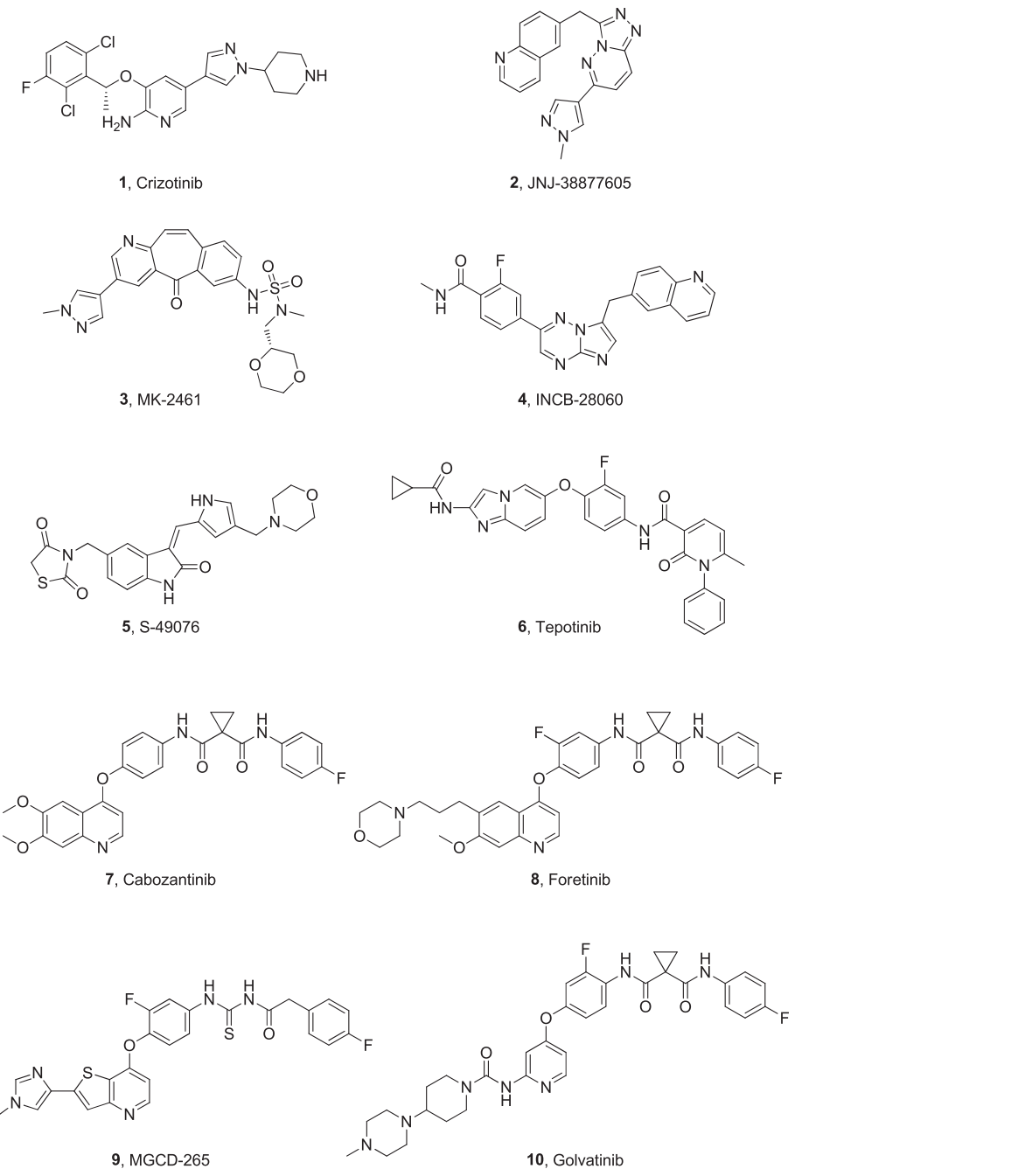


Fig. 1. The representative small-molecule c-Met kinase inhibitors.

Generally, Type-II inhibitors show multi-target activities with effective kinases inhibition, low toxicity and anti-drug resistance. Cabozantinib is the first launched Type-II inhibitor and well inhibits c-Met, VEGFR-2, c-Kit, Mer and other targets. The molecular structure of Cabozantinib contains moiety A, moiety B, and moiety C as three major moieties (Fig. 2). Binding mode (Fig. 3) indicates that the quinoline group is competitively hydrogen-bonded to Met1160, which results in the displacement of ATP at the binding pocket to inhibit the kinase activity. Similarly, the two carbonyl oxygens from moiety B form two hydrogen bonds with Lys1110 and Asp1222, respectively, and moiety C is engaged in a π-π interaction with Phe1223 to further improve c-Met inhibitory activity [27,28]. The reported structure-activity relationship may provide guidance

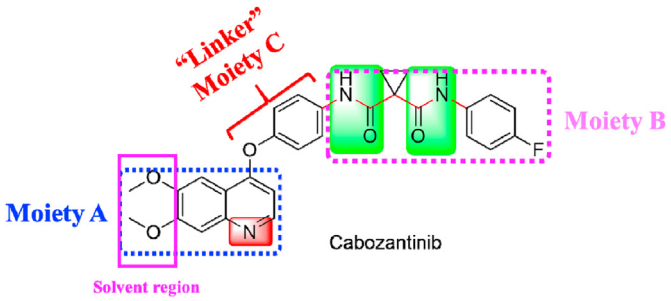


Fig. 2. The structure features of type II inhibitor Cabozantinib.

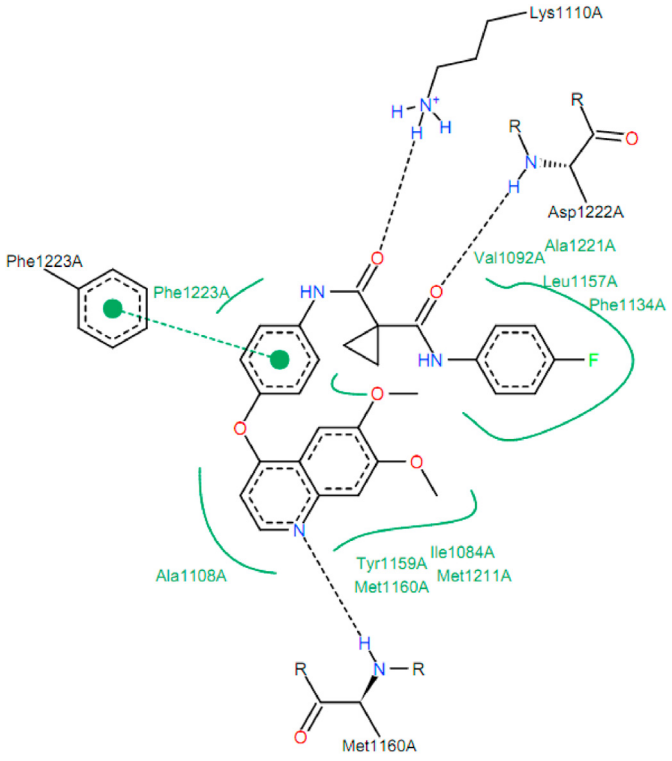


Fig. 3. The docking mode of Cabozantinib with c-Met protein (PDB: 3LQ8).

for designing Type-II inhibitors. Moiety B is commonly a linear or cyclic group under "five-atom rule" [29–32], which contains at least one amide bond. Many heterocycle scaffolds, such as substituted quinolones [33], thienopyridines [34], pyrrolopyridines [35], and pyrimidodiazepines [36,37] can be introduced to moiety A, as their nitrogen atoms can facilitate the inhibitors to bind to the target.

The *N*-phenylpyrimidin-2-amine fragment has been widely used as a building block in the design of anticancer agents, which contains a pyrimidine nitrogen that is capable of binding to the ATP binding pocket [38,39]. In this work, the *N*-phenylpyrimidin-2-amine fragment and different structures based on the "five-atom rule" were introduced to moiety A and moiety B to achieve the inhibitory potency on c-Met kinase (Fig. 4). Twenty-seven new compounds were designed, synthesized and evaluated by the structure-activity relationship (SAR) studies to develop novel c-Met inhibitors with high activity, low toxicity and favorable pharmacokinetic properties.

The binding model of the target compounds (Fig. 5) is similar to that of Cabozantinib, which indicates that the *N*-phenylpyrimidin-2-amine scaffold would be an important core structure for developing c-Met inhibitors. Compounds **15a-i**, **15o-r**, **20** and **34a-c** possess great inhibitory activities, and compound **15b**, **15d**, **15f**, **15i**, **15o**, **15r**, **20**, **34a** and **34b** also perform great anti-proliferative activities against five types of cancer cells (PC-3, Panc-1, HepG2, HCT116 and Caki-1). In particular, compound **34a** exhibits favorable properties in pharmacokinetic study, and acceptable safety profiles in MTD and hERG test, making it a promising compound for future development.

2. Chemistry

A series of *N*-phenylpyrimidin-2-amine analogs and the related intermediates were synthesized according to the pathways shown in Schemes 1–5. These compounds were confirmed by MS, HRMS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Intermediates **13a-b** were synthesized via peptide coupling between 1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxylic acid (**11**) and substituted 4-aminophenols (**12**) with EDCI, which were then reacted with substituted 2,4-dichloropyrimidines or 2,4-dichloropyridines to yield **14a** through S_NAr reactions. The products **15a-r** were synthesized by nucleophilic substitution of **14a** and substituted anilines [40] in the catalyst of *p*-Toluenesulfonic acid (PTSA). The method was shown in Scheme 1.

Intermediate **18** was obtained by S_NAr substitution of 2,4-dichloropyridine (**16**) by 4-aminophenol (**17**) in the presence of potassium *tert*-butoxide as the base, which was found to enhance the reactivity of 4-Cl. Then peptide coupling between intermediate **18** and 1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxylic acid yielded the key intermediate **19**. Finally, **19** reacted with 3-morpholinoaniline to give the desired compound **20** via Buchwald coupling. Noted that attempts failed to get compound **20** by common S_NAr conditions with either acid or base catalysis. The method was shown in Scheme 2.

2-Bromobenzoic acid (**21**) was coupled with 4-fluoroaniline (**22**) by Cu/Cu_2O to yield the intermediate **23**, which then reacted with

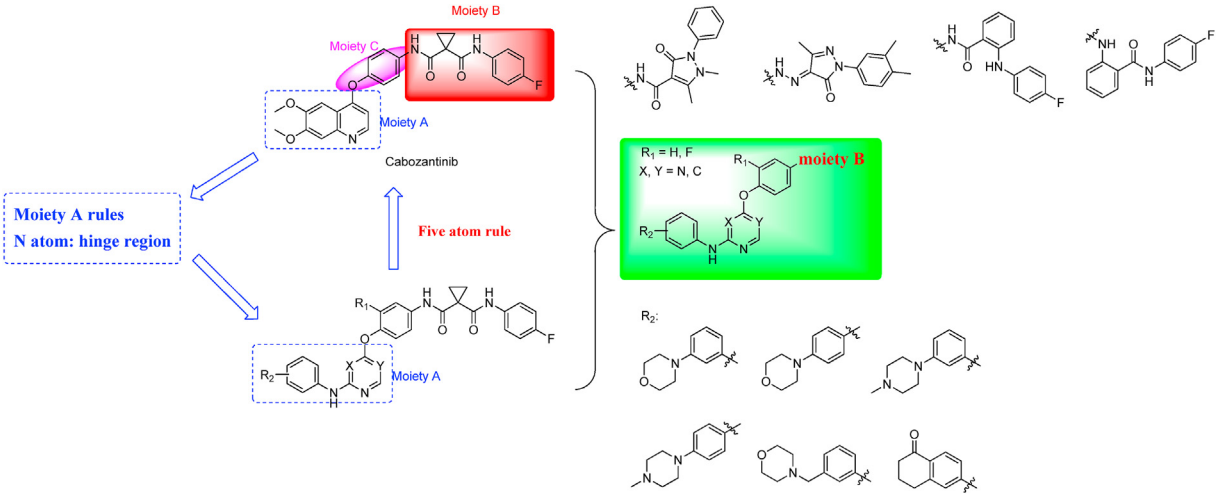


Fig. 4. Design strategy of the target compounds.

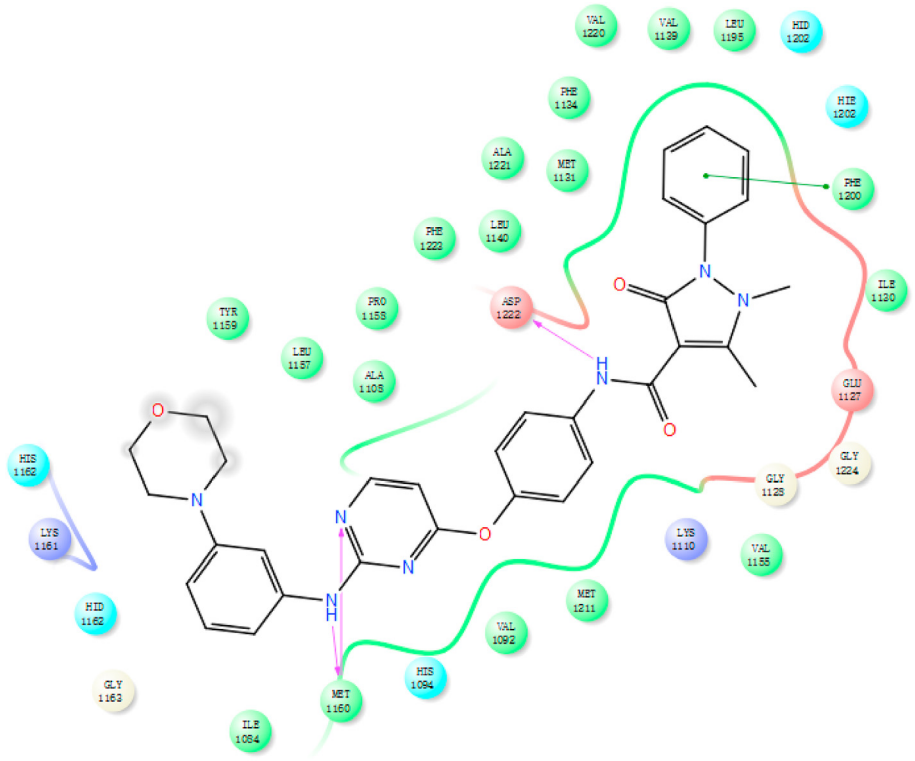
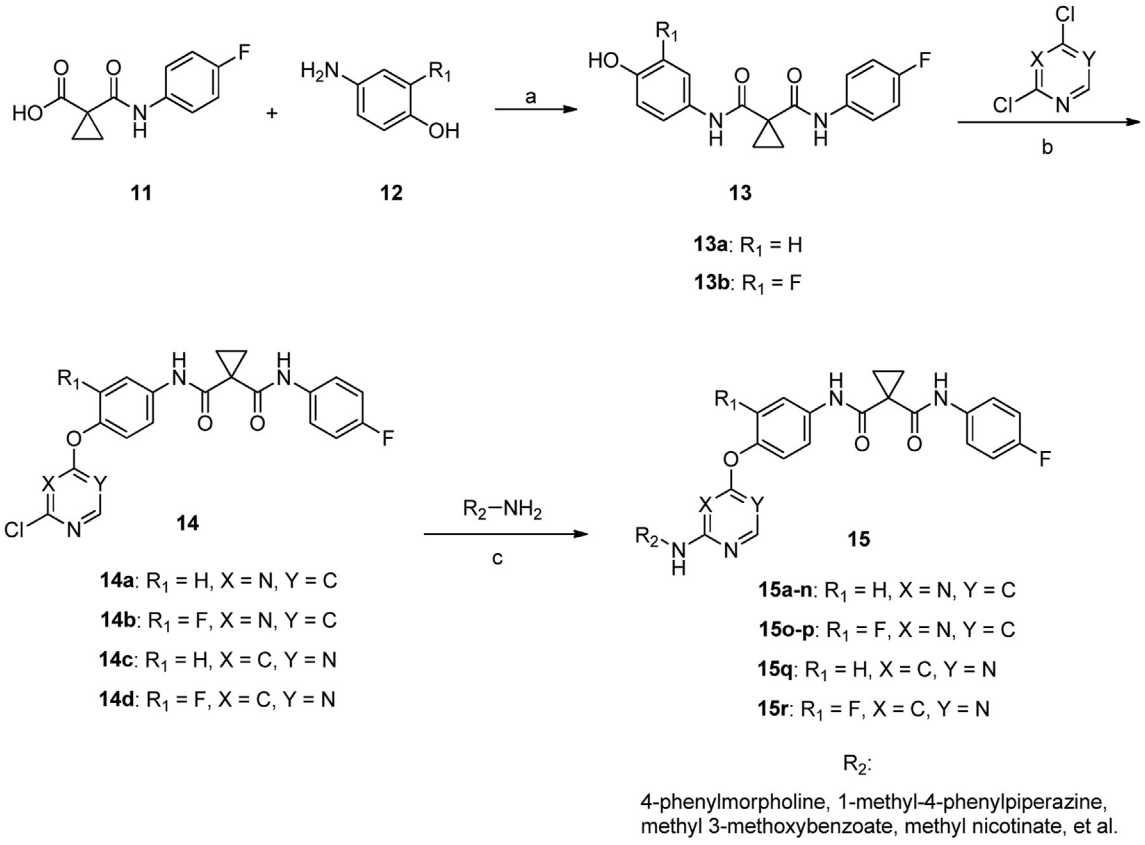
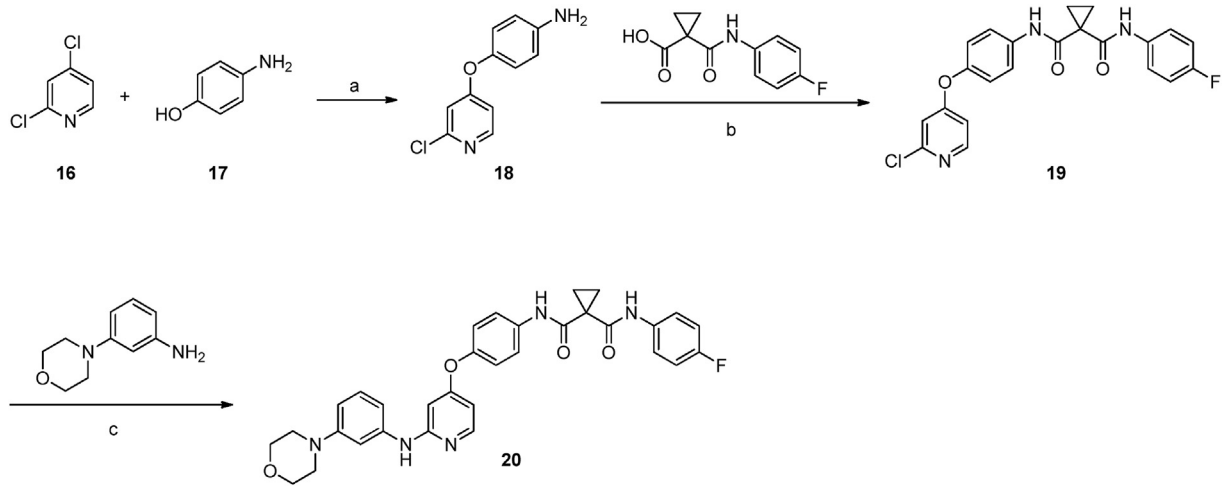


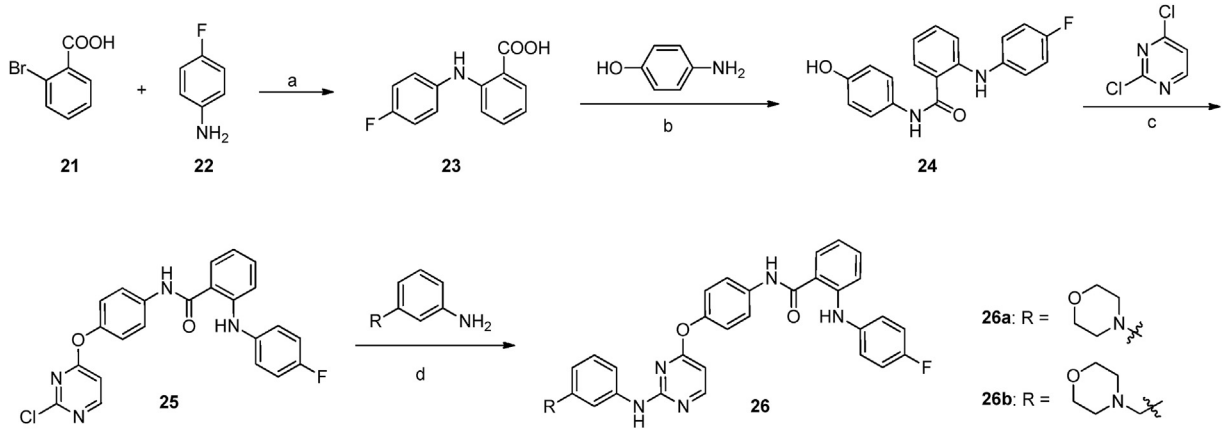
Fig. 5. The docking mode of **34a** with c-Met protein (PDB: 3LQ8).



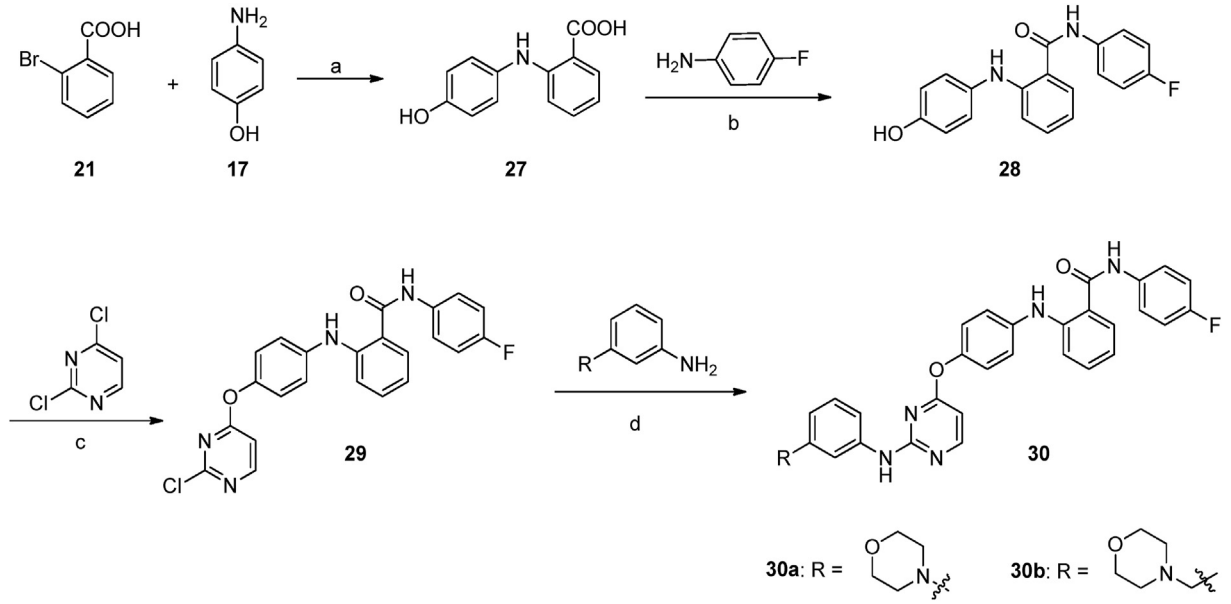
Scheme 1. Reagents and conditions: (a) EDCI/DMF, rt, 4 h; (b) K_2CO_3/DMF, 80 °C, 5 h; (c) PTSA/DMF, 90 °C, 10 h.



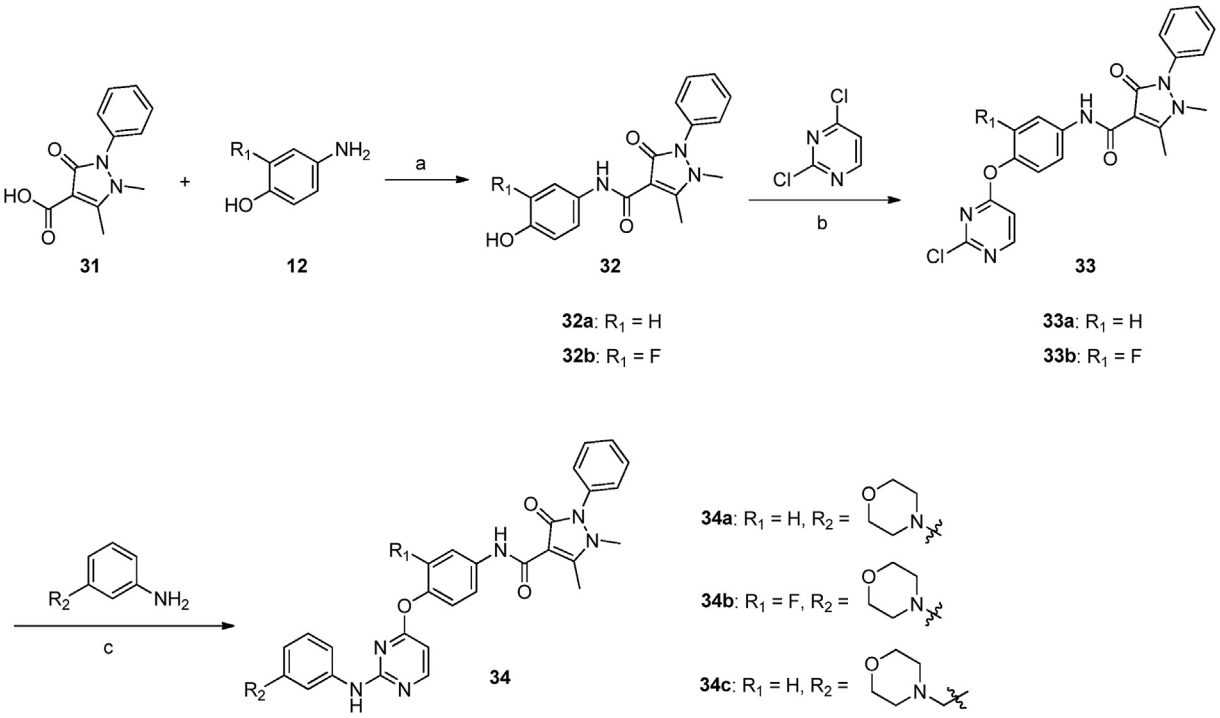
Scheme 2. Reagents and conditions: (a) Potassium tert-butylate/DMF, 100 °C, 10 h; (b) EDCI/DMF, rt, 4 h; (c) $Pd(OAc)_2$/BINAP/Cs_2CO_3/1,4-dioxane, reflux, 2 h.



Scheme 3. Reagents and conditions: (a) Cu/Cu_2O/K_2CO_3/2-ethoxyethanol, 130 °C, 24 h; (b) EDCI/DMF, rt, 4 h; (c) K_2CO_3/DMF, 80 °C, 2 h; (d) PTSA/DMF, 90 °C, 10 h.



Scheme 4. Reagents and conditions: (a) Cu/Cu_2O/K_2CO_3/2-ethoxyethanol, 130 °C, 24 h; (b) EDCI/DMF, rt, 4 h; (c) K_2CO_3/DMF, 80 °C, 2 h; (d) PTSA/DMF, 90 °C, 10 h.



Scheme 5. Reagents and conditions: (a) EDCI/DMF, rt, 4 h; (b) K_2CO_3/DMF, 80 °C, 5 h; (c) PTSA/DMF, 90 °C, 10 h.

4-aminophenol to obtain intermediate **24**. Intermediate **25** was prepared from 2,4-dichloropyrimidine and intermediate **24** with a similar method to intermediate **14**. Compounds **26a-b** were prepared by nucleophilic substitution with substituted anilines [41]. The method was shown in Scheme 3.

Compounds **30a-b** were prepared from 2-bromobenzoic acid (**21**) and 4-aminophenol (**17**) with a similar method to Scheme 3, which was shown in Scheme 4.

The general method to synthesize compounds **34a-c** is shown in Scheme 5 [42]. Intermediates **32a-b** were prepared by peptide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (**31**) and substituted 4-aminophenols (**12**) followed by S_NAr reactions with 2,4-dichloropyrimidine to yield **33a-b**. The final products **34a-c** were prepared from **33a-b** and substituted anilines with a similar method to compound **30**.

3. Results and discussion

3.1. In vitro activities and structure–activity relationships

All the prepared compounds were treated by c-Met kinase-based assay, then the lead compounds were selected to determine their antiproliferative activities against PC-3, Panc-1, HepG2, HCT116 and Caki-1 cell lines. The assay procedures were the same as reported in our previous work [36]. Cabozantinib was applied as the reference compound. The IC_{50} values were summarized in Table 1, as the mean values of experiments performed in triplicate.

Based on the results reported in Table 1 and Table 2, most compounds (**15a-i**, **15o-r**, **20** and **34a-c**) have shown great inhibitory activities against c-Met kinase (IC_{50}: 550.8 nM ~ 15.0 nM). Particularly, the activity of **34a** (IC_{50}: 15.0 nM) is better than that of Cabozantinib (34.0 nM), and the activity of **15o** (IC_{50}: 34.9 nM) was comparable to Cabozantinib, which further indicated that the designed compounds are potent inhibitors of c-Met kinase.

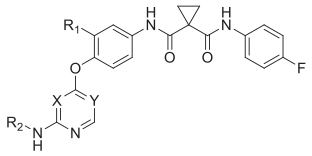
Nine preferred compounds (**15b**, **15d**, **15f**, **15i**, **15o**, **15r**, **20** and **34a-b**) were selected to be further assayed for antiproliferative activities in cancer cells (Table 3). All nine compounds have shown significant antiproliferative activities with IC_{50} values ranging from 0.53 to 1.37 μM, which is comparable to Cabozantinib. More specially, compound **34a** displayed three to five-fold greater activity than Cabozantinib. The results indicate the efficacy to apply *N*-phenylpyrimidin-2-amine group in the development of novel c-Met inhibitors.

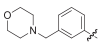
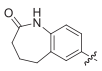
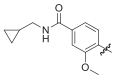
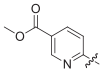
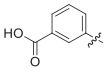
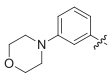
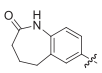
The pharmacological activities indicate that the number and position of substituents play critical roles in c-Met inhibitory activities. For instance, the replacement of hydrogen with fluorine in R^1 position increased the c-Met activity (**15o** > **15f**, **15r** > **15q**). The presence of nitrogen in position "X" does not increase the inhibitory activity, while affords the improved antiproliferative activity (**15f** < **20**), probably due to the better cell permeability. However, the inhibitory activity decreases with nitrogen in position "Y" (**15q** < **20**), because this results in the change of molecular orientation that breaks the hydrogen bonding.

When R^2 position is functionalized by aniline with an electron-donating substitution, the activities of meta-substituted analogs are better than the para-substituted analogs (**15f** > **15g**, **15d** > **15c**, **15b** > **15a**), which could be attributed to different binding mode. In addition, when R^2 is a substituted aniline with carboxyl acid display the superior activities compared to ester and amide (**15n** > **15k** > **15j** > **15l** > **15m**).

According to Table 2, the lack of c-Met inhibitory activity in compound **26a-b** and **30a-b** indicate that 2-((4-fluorophenyl) amino)-*N*-phenylbenzamide and *N*-(4-fluorophenyl)-2-(phenylamino)benzamide can't bind to c-Met kinase, so these two motifs do not fit Moiety B. The better activities of **34a** and **34b** suggest the corresponding moiety B form hydrogen bonds with the residues at the binding pocket of c-Met kinase protein. Furthermore, the replacement of hydrogen by fluorine would decrease the activity

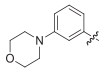
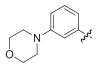
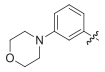
Table 1
Structures and inhibitory activities against c-Met kinase of compound **15a-r**, **20** and Cabozantinib *in vitro*.



Compd.	X	Y	R1	R2	IC50 (nM)①
15a	N	C	H		137.0 ± 20.1
15b	N	C	H		58.9 ± 9.4
15c	N	C	H		120.3 ± 14.5
15d	N	C	H		63.8 ± 10.1
15e	N	C	H		255.7 ± 27.4
15f	N	C	H		64.2 ± 9.2
15g	N	C	H		143.89 ± 19.5
15h	N	C	H		528.5 ± 58.3
15i	N	C	H		112.9 ± 11.7
15j	N	C	H		>2000
15k	N	C	H		2182.7 ± 149.6
15l	N	C	H		>2000
15m	N	C	H		>2000
15n	N	C	H		1202.3 ± 84.2
15o	N	C	F		34.9 ± 6.5
15p	N	C	F		550.8 ± 60.1

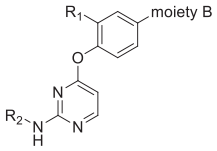
(*continued on next page*)

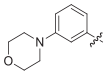
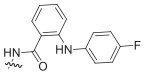
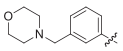
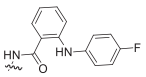
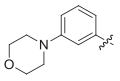
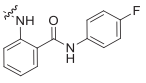
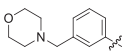
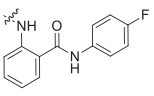
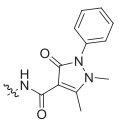
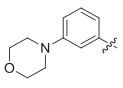
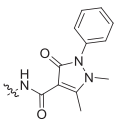
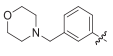
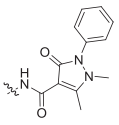
Table 1 (*continued*)

Compd.	X	Y	R1	R2	IC50 (nM)①
15q	C	N	H		312.61 ± 33.8
15r	C	N	F		110.2 ± 8.4
20	C	C	H		59.4 ± 6.9
Cabozantinib					34.0 ± 2.4

①Data are expressed as means ± SD of three experiments, confidence limits 95% (CL 95%).

Table 2
Structures and inhibitory activities against c-Met kinase of compound **26a-b**, **30a-b**, **34a-c** and Cabozantinib *in vitro*.



Compd.	R_1	R_2	moiety B	IC_{50} (nM)①
26a	H			>1000
26b	H			>1000
30a	H			>1000
30b	H			>1000
34a	H			15.0 ± 1.6
34b	F			67.3 ± 3.5
34c	H			119.2 ± 8.7
Cabozantinib				34.0 ± 2.4

①Data are expressed as means ± SD of three experiments, confidence limits 95% (CL 95%).

(**34b** < **34a**), which shows a different trend as compound **15f** and **15o**. However, the rationale for these results needs to be investigated in further studies.

Table 3
Cytotoxic activities of compounds cell lines *in vitro*.

Cpds	$IC_{50}(\mu M)$① of 5 cell lines				
	Panc-1	HepG2	PC-3	Caki-1	HCT116
15b	2.85 ± 0.021	7.01 ± 0.056	1.93 ± 0.016	3.31 ± 0.032	3.56 ± 0.027
15d	3.16 ± 0.027	1.73 ± 0.012	2.25 ± 0.020	1.63 ± 0.015	2.02 ± 0.015
15f	6.67 ± 0.054	3.57 ± 0.033	2.65 ± 0.022	3.90 ± 0.034	4.20 ± 0.035
15i	3.28 ± 0.029	3.24 ± 0.028	2.60 ± 0.019	1.47 ± 0.008	3.14 ± 0.028
15o	3.40 ± 0.031	2.21 ± 0.019	2.34 ± 0.018	2.92 ± 0.022	3.15 ± 0.029
15r	5.53 ± 0.048	5.97 ± 0.052	4.71 ± 0.038	2.69 ± 0.024	7.99 ± 0.057
20	4.01 ± 0.036	4.86 ± 0.039	3.30 ± 0.029	2.59 ± 0.021	4.79 ± 0.041
34a	1.01 ± 0.008	1.34 ± 0.007	1.34 ± 0.011	0.53 ± 0.002	1.37 ± 0.012
34b	2.00 ± 0.017	2.10 ± 0.015	1.80 ± 0.012	1.88 ± 0.014	2.34 ± 0.020
Cabozantinib	5.13 ± 0.034	3.05 ± 0.026	3.68 ± 0.031	1.66 ± 0.012	3.78 ± 0.032

①Data are expressed as means ± SD of three experiments, confidence limits 95% (CL 95%).

3.2. Binding model analysis

To elucidate the binding mode of the compounds, a detailed docking analysis was performed. In our study, the co-crystal structure of Cabozantinib with c-Met was selected as the docking mode. The inhibitor was docked using the GLIDE docking algorithm in XP (extra-precision) mode [43]. Compound **34a** shows great inhibitory potency, which indicates that the *N*-phenylpyrimidin-2-amine in moiety A and 1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one in moiety B are effectively pharmacophores to inhibit the activity of c-Met kinase. The potency of compound **34a** may come from the two hydrogen bonds by *N*-phenylpyrimidin-2-amine in moiety A with MET (Fig. 5). In addition, the amide group forms a hydrogen-bonding interaction with ASP1222, and the benzene group forms π-π interaction with residues. Further modification of **34a** is currently in progress.

3.3. Acute toxicity test

The acute toxicity of compound **34a** was tested to build up the safety profile of this series of compounds with *N*-phenylpyrimidin-2-amine and 1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one scaffolds (Table 4). The ICR mice were treated with **34a** orally at a single dose of 600, 800, 1000, 1200, 1500 and 2000 mg/kg or vehicle control ($n = 10$), and then monitored for 14 days. The results showed that the dosage of 1500 mg/kg killed 30% of the mice. On the other hand, no abnormalities were observed in the dosage of 600−1200 mg/kg, which suggests that the maximum safety dosage of **34a** in mice should be 1500 mg/kg (PO).

3.4. Evaluation of activity on hERG potassium currents

The activation of hERG channels is related to cardiotoxicity, so it is necessary to evaluate the activity on hERG potassium currents (Table 5). The detailed procedures are the same as our previous work [36]. The corresponding IC_{50} values (>40 μM) indicate the inactivated status of hERG channels while c-Met kinase is inhibited, so compound **34a** has no risk of cardiotoxicity.

Table 4
Acute toxicity of compound **34a**.

Dose (mg/Kg)	Mice (N)	Deaths (N)	Survival on day 14 (%)
2000	10	10	0
1500	10	3	70
1200	10	0	100
1000	10	0	100
800	10	0	100
600	10	0	100
Vehicle	10	0	100

Table 5
Activity on hERG potassium currents of compound **34a**.

Compound	IC_{50} (μM)
34a	>40
Cabozantinib	>30

3.5. Pharmacokinetics study

The pharmacokinetics (PK) studies of **34a** were conducted in male SD rats at 20 mg/kg (PO). A C_{max} of 3050.2 ng/mL was achieved at 6.0 h. Compound **34a** also was well cleared ($CL_{z/F} = 0.66$ L/h/kg) in rats. The elimination half-life after administration was 9.04 h and the oral bioavailability was 59.3%. In summary, compound **34a** displays favorable pharmacokinetics properties (Table 6).

4. Conclusions

In this study, a series of novel *N*-phenylpyrimidin-2-amine derivatives were designed, synthesized and evaluated as c-Met kinase inhibitors. SAR exploration led to the identification of a highly potent c-Met inhibitor **34a** with excellent activity (IC_{50}: 15.0 nM). In addition, its antiproliferative activities in multiple cancer cell lines were three to five times better than Cabozantinib. Notably, as a candidate, **34a** has also shown good pharmacokinetic properties, low body toxicity by acute toxicity tests, and negative cardiotoxicity by hERG potassium channel tests. Further docking studies identified two hydron-bonding interactions between **34a** and c-Met kinase as the key structural rationale for the inhibitory activity. In conclusion, our studies suggest that compound **34a** is a promising c-Met inhibitor worthy of further investigation.

5. Experimental

5.1. Chemistry

All melting points were obtained on a BüchiMelting Point B-540 apparatus (BüchiLabortechnik) and were uncorrected. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, USA). ^{1}H NMR and ^{13}C NMR spectra were generated on Bruker AM-400 spectrometers (Bruker Bioscience, USA) with TMS as the internal standard. All activities were tested at Shanghai Sudia

Table 6
Pharmacokinetic Parameters of compound **34a**.

Dose (mg/Kg)	$AUC_{(0-t)}$ (ngh/mL)	$CL_{Z/F}$ (L/h/Kg)	$T_{1/2Z}$ (h)	T_{max} (h)	C_{max} (ng/mL)	*F* (%)
20 (po)	18999.37	0.66	9.04	6.0	3050.2	59.3
4 (iv)	8224.8	0.41	8.9		2469.0	

Co., Ltd. All other chemicals were analytical grade and used without further purification.

5.2. Preparation of N-(4-fluorophenyl)-N-(3-substitued-4-hydroxyphenyl) cyclopropane-1,1-dicarboxamide (**13a-b**)

To a solution of 1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxylic acid (1.0 g, 4.48 mmol) and 4-aminophenol or 4-amino-2-fluorophenol (5.38 mmol) in DMF (15 mL) was added EDCI.HCl (1.03 g, 5.38 mmol). The reaction solution was stirred at room temperature for 2 h and monitored by thin-layer chromatograph (TLC). Water (30 mL) was added and adjusting pH 5.0 by 1 M HCl, and the precipitate was filtered off, washed, dried in vacuum to yield **13** as a white solid. The production was used for the next step without further purification.

5.2.1. N-(4-fluorophenyl)-N-(4-hydroxyphenyl)cyclopropane-1,1-dicarboxamide (**13a**)

White solid; Yield: 87.9%; MS (ESI) *m/z*: 315.15 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.53–7.49 (m, 2H), 7.03–6.96 (m, 2H), 6.85–6.81 (m, 2H), 6.71–6.66 (m, 2H), 1.97–1.92 (m, 4H).

5.2.2. N-(3-fluoro-4-hydroxyphenyl)-N-(4-fluorophenyl) cyclopropane-1,1-dicarbox- amide (**13b**)

White solid; Yield: 81.4%; MS (ESI) *m/z*: 333.12 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H, CONH), 9.64 (s, 1H, CONH), 9.13 (s, 1H, OH), 6.61–7.82 (m, 7H, Ar-H), 1.44 (s, 4H, CH_2CH_2).

5.3. General procedure for preparation of intermediate **14**

To a solution of the intermediate **13** (10.0 mmol) and 2,4-dichloropyrimidine or 4,6-dichloropyrimidine (5.38 mmol) in DMF (15 mL) was added K_2CO_3 (1.52 g, 11.0 mmol). The mixture was stirred at 80 °C for 5 h. Then water (50 mL) was added to precipitate white solid, which was filtered off, washed and dried in vacuum to afford intermediate **14**.

5.3.1. N-(4-((2-chloropyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1 dicarboxamide (**14a**)

White solid; Yield: 87.4%; MS (ESI) *m/z*: 427.19 $[M+H]^+$.

5.3.2. N-(4-((2-chloropyrimidin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (**14b**)

White solid; Yield: 81.3%; MS (ESI) *m/z*: 445.12 $[M+H]^+$.

5.3.3. N-(4-((6-chloropyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane- 1,1-dicarboxamide (**14c**)

White solid; Yield: 82.4%; MS (ESI) *m/z*: 427.11 $[M+H]^+$.

5.3.4. N-(4-((6-chloropyrimidin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (**14d**)

White solid; Yield: 84.6%; MS (ESI) *m/z*: 445.09 $[M+H]^+$.

5.4. General procedure for preparation of compound **15**

To a solution of the intermediate **14** (11.0 mmol) and R_2-substituedaniline (10.0 mmol) in DMF (20 mL) was added *p*-Toluenesulfonic acid monohydrate (7.60 g, 40.0 mmol). The mixture was stirred at 90 °C for 10 h. Then water (50 mL) was added to precipitate white solid, which was filtered off, and recrystallized from ethanol to afford **15**.

5.4.1. N-(4-fluorophenyl)-N-(4-((2-((4-(methylcarbamoyl)phenyl) amino)pyrimidin-4- yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**15a**)

White solid; Yield: 70.0%. ^1H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H, CONH), 10.10 (s, 1H, CONH), 9.84 (s, 1H, CONH), 8.39 (d, $J = 5.6$ Hz, 1H, ArH), 8.15 (d, $J = 4.4$ Hz, 1H, ArH), 7.73–7.58 (m, 8H, ArH), 7.22–7.13 (m, 4H, ArH), 6.48 (d, $J = 5.6$ Hz, 1H, NH), 2.73 (d, $J = 4.4$ Hz, 3H, CH_3), 1.53–1.47 (m, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.74, 168.49, 167.45, 167.02, 164.18, 162.73, 155.82, 147.31, 138.49, 136.13, 131.22, 127.28, 123.64, 121.54, 119.82, 117.74, 113.49, 96.42, 34.05, 29.76, 24.08. HRMS (ESI) *m/z* calcd. for $C_{29}H_{25}FN_6O_4$ $[M+H]^+$ 541.2214, found 541.2219. Purity: > 95% (HPLC).

5.4.2. N-(4-fluorophenyl)-N-(4-((2-((3-(methylcarbamoyl)phenyl) amino)pyrimidin-4- yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**15b**)

White solid; Yield: 71.4%. ^1H NMR (400 MHz, DMSO-d_6) δ 10.12 (d, $J = 28.0$ Hz, 2H, CONH), 9.68 (s, 1H, CONH), 8.36 (d, $J = 5.6$ Hz, 1H, ArH), 8.27 (d, $J = 4.4$ Hz, 1H, ArH), 7.96 (s, 1H, ArH), 7.64–7.23 (m, 5H, ArH), 7.29 (d, $J = 7.2$ Hz, 1H, ArH), 7.20–7.14 (m, 5H, ArH), 6.41 (d, $J = 5.6$ Hz, 1H, NH), 2.76 (d, $J = 4.4$ Hz, 3H, CH_3), 1.48 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.02, 180.67, 168.48, 167.23, 165.12, 162.41, 151.83, 145.96, 139.16, 136.42, 135.33, 134.51, 127.64, 126.65, 121.82, 119.74, 117.41, 115.68, 114.14, 96.45, 37.05, 29.31, 23.76. HRMS (ESI) *m/z* calcd. for $C_{29}H_{25}FN_6O_4$ $[M+H]^+$ 541.5203, found 541.5217. Purity: > 95% (HPLC).

5.4.3. N-(4-fluorophenyl)-N-(4-((2-((4-(4-methylpiperazin-1-yl) phenyl)amino)pyrimidin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**15c**)

White solid; Yield: 74.2%. ^1H NMR (400 MHz, DMSO-d_6) δ 10.13 (d, $J = 22.4$ Hz, 2H, CONH), 9.32 (s, 1H, NH), 8.27 (d, $J = 5.6$ Hz, 1H, ArH), 7.70–7.64 (m, 4H, ArH), 7.29 (s, 2H, ArH), 7.16 (t, $J = 8.8$ Hz, 4H, ArH), 6.70 (d, $J = 8.0$ Hz, 2H, ArH), 6.33 (d, $J = 5.6$ Hz, 1H, ArH), 2.99 (s, 4H, CH_2), 2.41 (s, 4H, CH_2), 2.19 (s, 4H, CH_2), 1.49 (m, $J = 6.8$ Hz, 3H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.73, 168.42, 167.46, 164.88, 162.61, 154.56, 141.65, 137.42, 135.11, 126.48, 124.61, 121.65, 119.76, 118.34, 116.16, 114.62, 94.37, 58.72, 54.03, 47.68, 32.01, 21.05. HRMS (ESI) *m/z* calcd. for $C_{32}H_{32}FN_7O_3$ $[M+H]^+$ 582.5422, found 582.5431. Purity: > 95% (HPLC).

5.4.4. N-(4-fluorophenyl)-N-(4-((2-((3-(4-methylpiperazin-1-yl) phenyl)amino)pyrimidin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**15d**)

White solid; Yield: 75.3%. ^1H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H, CONH), 10.07 (s, 1H, CONH), 9.36 (s, 1H, NH), 8.33 (d, $J = 5.6$ Hz, 1H, ArH), 7.71–7.63 (m, 4H, ArH), 7.18–7.14 (m, 5H, ArH), 7.03 (d, $J = 7.6$ Hz, 1H, ArH), 6.93 (t, $J = 8.0$ Hz, 1H, ArH), 6.44–6.38 (m, 2H, ArH), 2.94 (s, 4H, CH_2), 2.40 (s, 4H, CH_2), 2.20 (s, 3H, CH_3), 1.48 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.75, 169.67, 164.84, 163.15, 162.16, 154.82, 149.37, 144.35, 137.41, 133.14, 130.92,

127.63, 121.67, 118.44, 115.84, 109.32, 106.31, 102.76, 94.32, 58.29, 54.02, 46.61, 34.11, 21.73. HRMS (ESI) *m/z* calcd. for $C_{32}H_{32}FN_7O_3$ $[M+H]^+$ 582.5414, found 582.5423. Purity: > 95% (HPLC).

*5.4.5. N-(4-fluorophenyl)-N-(4-((2-((3-(morpholinomethyl)phenyl) amino)pyrimidin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**15e**)*

White solid; Yield: 75.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H, CONH), 10.04 (s, 1H, CONH), 9.62 (s, 1H, NH), 8.35 (d, J = 6.8 Hz, 1H, ArH), 7.75–7.64 (m, 5H, ArH), 7.47 (d, J = 8.4 Hz, 1H, ArH), 7.33–7.26 (m, 4H, ArH), 7.12–7.07 (m, 2H, ArH), 6.49 (d, J = 5.8 Hz, 1H, ArH), 5.13 (s, 2H, CH_2), 3.67 (t, J = 4.6 Hz, 4H, CH_2), 2.95 (s, 4H, CH_2), 1.46 (d, J = 2.4 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.73, 169.65, 165.19, 163.46, 162.82, 154.81, 146.13, 138.36, 136.42, 134.17, 127.27, 124.64, 121.52, 119.59, 117.81, 116.73, 115.86, 115.26, 91.44, 68.78, 62.71, 58.74, 34.05, 23.72. HRMS (ESI) *m/z* calcd. for $C_{32}H_{31}FN_6O_4$ $[M+H]^+$ 583.2637, found 583.2654. Purity: > 95% (HPLC).

*5.4.6. N-(4-fluorophenyl)-N-(4-((2-((3-morpholinophenyl)amino) pyrimidin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamideCompound (**15f**)*

White solid; Yield: 77.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H, CONH), 10.07 (s, 1H, CONH), 9.67 (s, 1H, NH), 8.34 (d, J = 6.0 Hz, 1H, ArH), 7.72–7.61 (m, 5H, ArH), 7.48 (d, J = 8.0 Hz, 1H, ArH), 7.31–7.21 (m, 4H, ArH), 7.09–7.01 (m, 2H, ArH), 6.47 (d, J = 5.6 Hz, 1H, ArH), 3.69 (t, J = 4.0 Hz, 4H, CH_2), 2.97 (s, 4H, CH_2), 1.47 (d, J = 2.4 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.78, 169.51, 166.17, 164.12, 162.34, 156.83, 150.18, 143.25, 137.43, 134.17, 128.46, 124.61, 121.64, 119.46, 116.78, 109.32, 105.38, 102.71, 96.42, 66.34, 57.39, 32.05, 27.72. HRMS (ESI) *m/z* calcd. for $C_{31}H_{29}FN_6O_4$ $[M+H]^+$ 569.2744, found 569.2761. Purity: > 95% (HPLC).

*5.4.7. N-(4-fluorophenyl)-N-(4-((2-((4-morpholinophenyl)amino) pyrimidin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**15g**)*

White solid; Yield: 73.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H, CONH), 10.09 (s, 1H, CONH), 9.34 (s, 1H, NH), 8.28 (d, J = 4.8 Hz, 1H, ArH), 7.70–7.65 (m, 4H, ArH), 7.32 (s, 2H, ArH), 7.16 (t, J = 8.4 Hz, 4H, ArH), 6.71 (d, J = 7.2 Hz, 2H, ArH), 6.34 (d, J = 5.2 Hz, 1H, ArH), 3.68 (s, 4H, CH_2), 2.96 (s, 4H, CH_2), 1.49 (d, J = 8.4 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.24, 170.41, 167.43, 163.57, 162.93, 156.81, 138.65, 136.42, 135.17, 129.43, 124.65, 121.66, 119.78, 118.31, 116.74, 113.67, 97.41, 65.32, 54.31, 33.05, 24.74. HRMS (ESI) *m/z* calcd. for $C_{31}H_{29}FN_6O_4$ $[M+H]^+$ 569.4674, found 569.4692. Purity: > 95% (HPLC).

*5.4.8. N-(4-fluorophenyl)-N-(4-((2-((5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)amino)pyrimidin-4-yl)oxy)phenyl) cyclopropane-1,1-dicarboxamide (**15h**)*

White solid; Yield: 67.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H, NH), 10.04 (s, 1H, CONH), 10.00 (s, 1H, CONH), 8.42 (d, J = 4.8 Hz, 1H, ArH), 7.76 (d, J = 8.0 Hz, 2H, ArH), 7.65–7.63 (m, 3H, ArH), 7.51 (s, 1H, ArH), 7.31 (d, J = 8.0 Hz, 1H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH), 7.16 (t, J = 4.0 Hz, 2H, ArH), 6.57 (d, J = 4.0 Hz, 1H, ArH), 2.59 (t, J = 4.0 Hz, 2H, CH_2), 2.40 (t, J = 4.0 Hz, 2H, CH_2), 1.90–1.86 (m, 2H, CH_2), 1.50–1.46 (m, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 205.41, 180.63, 168.57, 167.85, 164.34, 162.18, 152.83, 147.71, 140.39, 137.42, 134.56, 129.72, 127.83, 124.79, 122.68, 119.49, 116.91, 115.62, 107.22, 95.47, 38.74, 34.02, 27.71, 17.62, 8.44. HRMS (ESI) *m/z* calcd. for $C_{31}H_{26}FN_5O_4$ $[M+H]^+$ 552.2021, found 552.2033. Purity: > 95% (HPLC).

*5.4.9. N-(4-fluorophenyl)-N-(4-((2-((2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl)amino)pyrimidin-4-yl)oxy)phenyl) cyclopropane-1,1-dicarboxamide (**15i**)*

White solid; Yield: 64.5%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H, NH), 10.01 (s, 1H, CONH), 9.80 (s, 1H, CONH), 9.28 (s, 1H, CONH), 8.34 (d, J = 4.0 Hz, 1H, ArH), 7.75 (d, J = 8.0 Hz, 2H, ArH), 7.65–7.63 (m, 2H, ArH), 7.48 (s, 1H, ArH), 7.41 (s, 1H, ArH), 7.20 (d, J = 4.0 Hz, 2H, ArH), 7.17–7.11 (m, 3H, ArH), 6.51 (d, J = 4.0 Hz, 1H, ArH), 2.29 (s, 2H, CH_2), 2.04 (t, J = 4.0 Hz, 2H, CH_2), 1.95 (t, J = 4.0 Hz, 2H, CH_2), 1.46–1.52 (m, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.72, 174.92, 169.57, 168.32, 164.12, 162.78, 154.81, 139.18, 134.67, 134.22, 131.19, 126.56, 124.63, 122.61, 120.87, 119.73, 117.72, 115.86, 115.67, 93.57, 37.57, 35.61, 32.08, 23.24, 21.77. HRMS (ESI) *m/z* calcd. for $C_{31}H_{27}FN_6O_4$ $[M+H]^+$ 567.1749, found 566.1756. Purity: > 95% (HPLC).

*5.4.10. Methyl 4-((4-(4-(1-((4-fluorophenyl)carbamoyl) cyclopropanecarboxamido)phenoxy)pyrimidin-2-yl)amino)-3-methoxybenzoate (**15j**)*

White solid; Yield: 69.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H, CONH), 10.14 (s, 1H, CONH), 8.43 (s, 1H, NH), 8.11 (s, 1H, ArH), 8.02 (d, J = 7.6 Hz, 1H, ArH), 7.76–7.66 (m, 4H, ArH), 7.46–7.38 (m, 2H, ArH), 7.23–7.16 (m, 4H, ArH), 6.58 (s, 1H, ArH), 3.90 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 1.53 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.12, 169.45, 167.62, 165.56, 163.33, 162.71, 154.86, 149.32, 137.93, 134.28, 125.07, 123.68, 121.14, 120.92, 119.57, 117.74, 115.85, 114.93, 94.87, 56.81, 54.52, 34.02, 22.74. HRMS (ESI) *m/z* calcd. for $C_{30}H_{26}FN_5O_6$ $[M+H]^+$ 567.3907, found 572.3916. Purity: > 95% (HPLC).

*5.4.11. 4-((4-(4-(1-((4-fluorophenyl)carbamoyl) cyclopropanecarboxamido)phenoxy)pyrimidin-2-yl)amino)-3-methoxybenzoic acid (**15k**)*

White solid; Yield: 62.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H, CONH), 10.61 (s, 1H, CONH), 8.33 (d, J = 5.6 Hz, 1H, NH), 7.83 (s, 1H, ArH), 7.77–7.67 (m, 5H, ArH), 7.47 (d, J = 0.8 Hz, 1H, ArH), 7.27 (t, J = 8.4 Hz, 1H, ArH), 7.17–7.09 (m, 4H, ArH), 6.42 (d, J = 5.6 Hz, 1H, ArH), 3.81 (s, 3H, CH_3), 1.34 (s, 4H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.04, 169.56, 169.17, 167.72, 164.18, 162.64, 154.82, 147.43, 138.83, 135.49, 134.54, 123.18, 122.79, 121.35, 120.71, 119.47, 117.83, 115.92, 115.63, 94.41, 56.82, 53.36, 19.46, 9.75. HRMS (ESI) *m/z* calcd. for $C_{29}H_{24}FN_5O_6$ $[M+H]^+$ 558.1962, found 558.1976. Purity: > 95% (HPLC).

*5.4.12. N-(4-((2-((4-((cyclopropylmethyl)carbamoyl)-2-methoxyphenyl)amino)pyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**15l**)*

White solid; Yield: 59.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H, CONH), 10.09 (s, 1H, CONH), 8.39 (d, J = 5.6 Hz, 1H, NH), 8.01 (s, 1H, ArH), 7.96 (s, 1H, ArH), 7.73–7.62 (m, 4H, ArH), 7.46 (d, J = 1.6 Hz, 1H, ArH), 7.22–7.13 (m, 5H, ArH), 6.50 (d, J = 5.6 Hz, 1H, ArH), 3.89 (s, 3H, CH_3), 3.11 (t, J = 6.0 Hz, 2H, CH_2), 1.48 (t, J = 5.6 Hz, 4H, CH_2), 1.35 (s, 2H, CH_2), 1.23 (s, 2H, CH_2), 1.04 (m, 1H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.46, 169.52, 167.63, 167.09, 164.18, 162.83, 154.81, 149.57, 137.05, 134.81, 134.14, 127.39, 122.54, 122.02, 120.41, 119.79, 117.73, 115.83, 112.94, 94.46, 56.24, 47.56, 33.05, 21.74, 4.47. HRMS (ESI) *m/z* calcd. for $C_{33}H_{31}FN_6O_5$ $[M+H]^+$ 611.12541, found 611.2569. Purity: > 95% (HPLC).

*5.4.13. Methyl 6-((4-(4-(1-((4-fluorophenyl)carbamoyl) cyclopropanecarboxamido)phenoxy)pyrimidin-2-yl)amino) nicotinate (**15m**)*

White solid; Yield: 34.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H, CONH), 10.07 (s, 1H, CONH), 8.24 (d, J = 6.4 Hz, 1H, NH), 8.07 (s, 1H, ArH), 7.81 (s, 1H, ArH), 7.74–7.65 (m, 4H, ArH), 7.45 (d,

J = 2.4 Hz, 1H, ArH), 7.26–7.11 (m, 5H, ArH), 6.74 (d, J = 6.4 Hz, 1H, ArH), 3.88 (s, 3H, CH_3), 1.48 (t, J = 5.6 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.12, 169.32, 167.67, 165.01, 163.45, 162.61, 157.32, 152.83, 149.65, 139.77, 134.75, 134.34, 122.56, 121.43, 119.52, 116.79, 115.62, 109.23, 93.67, 57.52, 34.02, 24.74. HRMS (ESI) m/z calcd. for $C_{28}H_{23}FN_6O_5$ $[M+H]^+$ 543.2043, found 543.2059. Purity: > 95% (HPLC).

5.4.14. 3-((4-(4-(1-((4-fluorophenyl)carbamoyl) cyclopropanecarboxamido)phenoxy)pyrimidin-2-yl)amino)benzoic acid (**15n**)

White solid; Yield: 69.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H, COOH), 10.17 (s, 1H, CONH), 10.10 (s, 1H, CONH), 9.76 (s, 1H, NH), 8.38 (d, J = 5.6 Hz, 1H, ArH), 8.17 (s, 1H, ArH), 7.87 (d, J = 8.4 Hz, 1H, ArH), 7.72–7.65 (m, 4H, ArH), 7.46 (d, J = 7.6 Hz, 1H, ArH), 7.26–7.14 (m, 5H, ArH), 6.43 (d, J = 5.6 Hz, 1H, ArH), 1.49 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.19, 169.73, 167.92, 166.58, 164.17, 162.43, 152.81, 146.32, 135.42, 134.15, 133.22, 129.06, 124.18 122.63, 121.92, 120.77, 119.79, 117.71, 112.68, 94.43, 33.09, 23.83. HRMS (ESI) m/z calcd. for $C_{28}H_{22}FN_6O_5$ $[M+H]^+$ 528.1703, found 528.1729. Purity: > 95% (HPLC).

5.4.15. N-(3-fluoro-4-((2-((3-morpholinophenyl)amino)pyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**15o**)

White solid; Yield: 51.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H, CONH), 10.05 (d, J = 7.6 Hz, 1H, CONH), 9.43 (s, 1H, NH), 8.28 (d, J = 4.8 Hz, 1H, ArH), 7.70–7.65 (m, 3H, ArH), 7.32 (s, 2H, ArH), 7.16 (t, J = 8.4 Hz, 4H, ArH), 6.71 (d, J = 7.2 Hz, 2H, ArH), 6.34 (d, J = 5.2 Hz, 1H, ArH), 3.68 (s, 4H, CH_2), 2.96 (s, 4H, CH_2), 1.49 (d, J = 8.4 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.52, 169.62, 167.74, 164.17, 162.79, 159.76, 152.18, 143.86, 138.91, 137.19, 134.55, 132.46, 125.14, 121.63, 119.28, 116.74, 112.17, 107.3, 104.71, 102.03, 96.49, 68.32, 54.39, 32.05, 21.74. HRMS (ESI) m/z calcd. for $C_{31}H_{28}F_2N_6O_4$ $[M+H]^+$ 587.1713, found 587.1721. Purity: > 95% (HPLC).

5.4.16. N-(3-fluoro-4-((2-((2-oxo-2,3,4,5-tetrahydro-1H-benzo[b] azepin-7-yl)amino)pyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (**15p**)

White solid; Yield: 70.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H, CONH), 10.07 (s, 1H, CONH), 9.91 (s, 1H, CONH), 9.74 (s, 1H, NH), 8.37 (s, 1H, ArH), 6.74 (d, J = 16.0 Hz, 2H, ArH), 7.41 (d, J = 8.0 Hz, 2H, ArH), 7.27 (t, J = 8.0 Hz, 1H, CH_2), 7.17–7.11 (m, 3H, ArH), 7.05 (d, J = 8.0 Hz, 1H, ArH), 6.61 (t, J = 8.0 Hz, 1H, ArH), 6.21 (s, 1H, ArH), 3.23 (t, J = 4.0 Hz, 2H, CH_2), 3.17 (t, J = 4.6 Hz, 2H, CH_2), 2.74–2.56 (m, 2H, CH_2), 1.46 (d, J = 4.0 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.78, 174.41, 169.57, 167.83, 164.19, 162.85, 160.33, 138.64, 136.89, 136.34, 134.75, 131.39, 128.47, 124.12, 122.61, 120.94, 118.73, 116.49, 115.13, 115.09, 111.12, 94.41, 38.59, 35.72, 33.01, 23.24, 21.75. HRMS (ESI) m/z calcd. for $C_{31}H_{26}F_2N_6O_4$ $[M+H]^+$ 585.1249, found 585.1261. Purity: > 95% (HPLC).

5.4.17. N-(4-fluorophenyl)-N-(4-((6-((3-morpholinophenyl)amino) pyrimidin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**15q**)

White solid; Yield: 71.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H, CONH), 10.06 (s, 1H, CONH), 9.45 (s, 1H, NH), 8.34 (s, 1H, ArH), 7.62–7.69 (m, 5H, ArH), 7.17–7.13 (m, 5H, ArH), 7.02 (d, J = 8.0 Hz, 1H, ArH), 6.62 (dd, J = 8.0 Hz, 1.6 Hz, 1H, ArH), 6.04 (s, 1H, ArH), 2.73 (t, J = 4.0 Hz, 4H, CH_2), 3.05 (t, J = 4.0 Hz, 4H, CH_2), 1.46 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.42, 172.59, 171.46, 162.77, 161.81, 154.81, 147.12, 144.37, 135.46, 134.32, 130.93, 124.67, 121.64, 119.75, 116.71, 108.63, 104.87, 102.76, 91.82, 66.72, 54.31, 31.73, 22.47. HRMS (ESI) m/z calcd. for $C_{31}H_{29}FN_6O_4$ $[M+H]^+$ 569.1775, found 569.1782. Purity: > 95% (HPLC).

5.4.18. N-(3-fluoro-4-((6-((3-morpholinophenyl)amino)pyrimidin-4-yl)oxy)phenyl)-N- (4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**15r**)

White solid; Yield: 72.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H, CONH), 10.02 (s, 1H, CONH), 9.53 (s, 1H, NH), 8.30 (s, 1H, ArH), 6.79 (dd, 1H, J = 16.0 Hz, 4.0 Hz, ArH), 7.66–7.62 (m, 2H, ArH), 7.42 (d, J = 8.0 Hz, 1H, ArH), 7.29 (t, J = 8.0 Hz, 1H, CH_2), 7.19–7.13 (m, 4H, ArH), 7.04 (d, J = 8.0 Hz, 1H, ArH), 6.64 (dd, 1H, J = 8.0 Hz, 4.0 Hz, ArH), 6.20 (s, 1H, ArH), 3.74 (t, J = 4.0 Hz, 4H, CH_2), 3.07 (t, J = 4.0 Hz, 4H, CH_2), 1.46 (d, J = 4.0 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.92, 172.41, 171.67, 164.92, 162.57, 159.75, 147.13, 144.39, 137.92, 136.67, 134.24, 131.45, 127.16, 120.62, 118.84, 116.71, 114.19, 108.37, 104.74, 101.77, 90.36, 66.72, 54.21, 31.57, 21.74. HRMS (ESI) m/z calcd. for $C_{31}H_{28}F_2N_6O_4$ $[M+H]^+$ 586.2159, found 586.2167. Purity: > 95% (HPLC).

5.5. Preparation of intermediate 4-((2-chloropyridin-4-yl)oxy) aniline (**18**)

To a solution of 2,4-dichloropyridine (1.47 g, 0.01 mol) and KOBu-t (1.34 g, 12.0 mmol) in DMF (10 mL) was added 4-aminophenol (1.09 g, 0.01 mol). The mixture then was stirred at 100 °C for 10 h. The reaction solution was cooled to room temperature and ice water was added, then viscous solid was precipitated, filtered off to obtain crude product which was purified by silica gel chromatography using a mixture of PE/EA (5:1) to afford the intermediate **18** as a white solid (1.57 g, 71%). ESI-MS(m/z): 221.07 $[M+H]^+$.

5.6. Preparation of N-(4-((2-chloropyridin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**19**)

Intermediate **18** (1.0 g, 4.54 mmol), 1-((4-fluorophenyl)carbamoyl)cyclopro panecarboxylic acid (1.01 g, 4.54 mmol) and EDCI (3.48 g, 18.16 mmol) in DMF (15 mL). The solution was stirred at room temperature for 4 h. Then water (20 mL) was added, extracted with ethyl acetate (10 mL × 3), washed by saturated brine (10 mL × 3), and then dried by anhydrous Na_2SO_4, filtered and concentrated to yield the crude product, which was purified by stirring it with ethanol (40 mL) for 30 min to yield the intermediate **19** as a white solid (1.60 g, 83%). ESI-MS(m/z): 426.10 $[M+H]^+$.

5.7. Preparation of N-(4-fluorophenyl)-N-(4-((2-((3-morpholinophenyl)amino)pyridine-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**20**)

To a solution of intermediate **19** (0.50 mmol, 1.18 mmol), 3-morpholinoaniline (0.23 g, 1.29 mmol) and BINAP (37 mg, 0.06 mmol) in 1,4-dioxane (15 mL) was added Cs_2CO_3 (0.57 g, 1.76 mmol). The mixture then was stirred at reflux for 2 h. The reaction solution was cooled to room temperature and filtered through celite, then concentrated to obtain crude product which was purified by silica gel chromatography using a mixture of DCM/MeOH (40:1) to afford the title compounds **20**.

White solid; Yield: 67.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H, CONH), 10.04 (s, 1H, CONH), 8.85 (s, 1H, NH), 8.03 (d, J = 4.0 Hz, 1H, ArH), 7.72 (d, J = 8.0 Hz, 2H, ArH), 7.65–7.62 (m, 2H, ArH), 7.19–7.13 (m, 5H, ArH), 7.04 (d, J = 8.0 Hz, 2H, ArH), 6.49–6.46 (m, 1H, ArH), 6.39 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H, ArH), 6.16 (d, J = 4.0 Hz, 1H, ArH), 3.72 (t, J = 4.0 Hz, 4H, CH_2), 3.02 (t, J = 4.0 Hz, 4H, CH_2), 1.46 (d, J = 4.0 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.42, 166.61, 163.63, 155.27, 149.82, 148.55, 146.01, 143.74, 134.25, 134.64, 131.48, 126.61, 122.69, 119.93, 117.78, 109.33, 105.32, 101.87, 100.46, 95.17, 68.38, 54.35, 39.02, 23.74. HRMS (ESI) m/z calcd. for $C_{32}H_{30}FN_5O_4$ $[M+H]^+$ 568.1419, found 568.1426. Purity: > 95% (HPLC).

*5.8. Preparation of the intermediate 2-((4-fluorophenyl)amino) benzoic acid (**23**)*

A mixture of 2-bromobenzoic acid (2.0 g,0.01 mol), 4-fluoroaniline (1.17 g,10.5 mmol), Cu (power, 0.06 g,0.9 mmol), Cu_2O (64 mg, 0.45 mmol) and K_2CO_3 (1.38 g,0.01 mmol) in 2-ethoxyethanol (10 mL) was heated at 130 °C for 24 h under nitrogen atmosphere. Upon cooling to room temperature, H_2O (20 mL) was added to, and filtered through celite. The filtrate was adjusted to pH 7.0 to precipitate solid, and then filtered and dried to yield the intermediate **23** (1.51 g, 65.3%). MS (ESI) *m/z*: 232.08 $[M+H]^+$

*5.9. Preparation of 2-((4-fluorophenyl)amino)-N-(4-hydroxyphenyl)benzamide (**24**)*

A solution of **23** (2.31 g, 0.01 mol), 4-aminophenol (1.09 g, 0.01 mmol) and EDCI (5.75 g, 0.03 mmol) in DMF (20 mL) was stirred at room temperature for 4 h. Then water (40 mL) was added, extracted with ethyl acetate (15 mL × 3), washed by saturated brine (10 mL × 3), and then dried by anhydrous Na_2SO_4, filtered and concentrated to yield the crude product, which was purified by silica gel chromatography using a mixture of petroleum ether/ethyl acetate (40:1) to yield the intermediate **24** as a white solid (2.89 g, 89.6%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.10 (s, 1H), 9.27 (s, 1H), 9.17 (s, 1H), 7.78−7.68 (m, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.38−7.29 (m, 1H), 7.21−7.09 (m, 5H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.79−6.68 (m, 2H). ESI-MS(*m/z*): 323.13$[M+H]^+$.

*5.10. Preparation of the intermediate N-(4-((2-chloropyrimidin-4-yl)oxy)phenyl)-2- ((4-fluorophenyl)amino)benzamide (**25**)*

To a solution of intermediate **24** (3.22 g, 0.01 mol) and 2,4-dichloropyrimidine (1.48 g, 0.01 mmol) in DMF (15 mL) was added K_2CO_3 (1.09 g, 0.01 mol). The mixture then was stirred at 80 °C for 2 h. The reaction mixture was cooled to room temperature and ice water was added, then viscous solid was precipitated, filtered off to obtain intermediate **25** as a pale white solid (3.45 g, 79.4%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.04 (s, 1H), 8.62 (d, *J* = 5.7 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.77 (d, *J* = 7.1 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.23−7.17 (m, 3H), 7.17−7.11 (m, 3H), 6.92 (t, *J* = 7.5 Hz, 1H). ESI-MS(*m/z*): 435.11 $[M+H]^+$.

*5.11. Preparation of the title compounds **26a-b***

To a solution of the intermediate **25** (4.77 g, 11.0 mmol) and R_2-substituedaniline (10.0 mmol) in DMF (20 mL) was added *p*-Toluenesulfonic acid monohydrate (7.60 g, 40.0 mmol). The solution was stirred at 90 °C for 10 h. Then water (50 mL) was added to precipitate white solid. The white solid was filtered and recrystallized from ethanol to afford **26**.

*5.11.1. 2-((4-fluorophenyl)amino)-N-(4-((2-((3-morpholinophenyl) amino)pyridine-4-yl)oxy)phenyl)benzamide (**26a**)*

White solid, Yield: 62.8%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H, CONH), 9.67 (s, 1H, NH), 9.15 (s, 1H, NH), 8.34 (d, *J* = 4.4 Hz, 1H, ArH), 7.87−7.82 (m, 3H, ArH), 7.41 (s, 1H, ArH), 7.39−7.33 (m, 2H, ArH), 7.24−7.12 (m, 7H, ArH), 7.03 (t, *J* = 8.6 Hz, 1H, ArH), 6.98 (t, *J* = 6.8 Hz, 1H, ArH), 6.77 (d, *J* = 8.4 Hz, 1H, ArH), 6.34 (t, *J* = 8.0 Hz, 1H, ArH), 3.46 (s, 4H, CH_2), 2.27 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.56, 167.43, 167.09, 164.25, 157.72, 152.73, 150.36, 148.61, 145.72, 138.88, 134.51, 134.63, 131.73, 129.93, 127.43, 124.61, 121.69, 119.21, 119.33, 118.25, 117.38, 109.33, 107.28, 103.71, 94.42, 65.39, 54.34. HRMS (ESI) *m/z* calcd. for $C_{33}H_{29}FN_6O_3$ $[M+H]^+$ 577.2457; found 577.2462. Purity: > 95% (HPLC).

*5.11.2. 2-((4-fluorophenyl)amino)-N-(4-((2-((3-(morpholinomethyl)phenyl)amino)pyridin-4-yl)oxy)phenyl) benzamide (**26b**)*

White solid, Yield: 79.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H, CONH), 9.59 (s, 1H, NH), 9.11 (s, 1H, NH), 8.35 (d, 1H, *J* = 4.0 Hz, ArH), 7.80−7.86 (m, 3H, ArH), 7.46 (s, 1H, ArH), 7.33−7.41 (m, 2H, ArH), 7.14−7.25 (m, 7H, ArH), 7.07 (t, 1H, *J* = 8.0 Hz, ArH), 6.94 (t, 1H, *J* = 8.0 Hz, ArH), 6.79 (d, 1H, *J* = 8.0 Hz, ArH), 6.45 (t, 1H, *J* = 8.0 Hz, ArH), 3.48 (s, 4H, CH_2), 3.19 (s, 2H, CH_2), 2.24 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.31, 167.47, 167.21, 163.67, 158.81, 152.33, 149.42, 143.11, 138.32, 136.89, 133.87, 133.36, 130.28, 128.27, 126.41, 123.87, 121.29, 119.73, 119.54, 118.71, 118.13, 116.77, 116.62, 115.52, 94.41, 67.12, 65.92, 56.37. HRMS (ESI) *m/z* calcd. for $C_{34}H_{31}FN_6O_3$ $[M+H]^+$ 591.4007, found 591.4022. Purity: > 95% (HPLC).

*5.12. Preparation of the intermediate 2-((4-hydroxyphenyl)amino) benzoic acid (**27**)*

A mixture of 2-bromobenzoic acid (2.0 g,0.01 mol), 4-aminophenol (1.15 g,10.5 mmol), Cu (power, 0.06 g,0.9 mmol), Cu_2O (64 mg, 0.45 mmol) and K_2CO_3 (1.38 g,0.01 mmol) in 2-ethoxyethanol (10 mL) was stirred at 130 °C for 24 h under nitrogen atmosphere. Upon cooling to room temperature, H_2O (20 mL) was added and filtered through celite. The filtrate was adjusted to pH 7.0 to precipitate solid, and then filtered and dried to yield the intermediate **27** (1.53 g, 67.0%). MS (ESI) *m/z*: 230.09 $[M+H]^+$

*5.13. Preparation of N-(4-fluorophenyl)-2-((4-hydroxyphenyl) amino)benzamide (**28**)*

A solution of **27** (2.29 g, 0.01 mol), 4-fluoroaniline (1.11 g, 0.01 mmol) and EDCI (5.75 g, 0.03 mmol) in DMF (20 mL) was stirred at room temperature for 4 h. Then water (40 mL) was added, extracted with ethyl acetate (15 mL × 3), washed by saturated brine (10 mL × 3), and then dried by anhydrous Na_2SO_4, filtered and concentrated to yield the crude product, which was purified by silica gel chromatography using a mixture of petroleum ether/ethyl acetate (20:1) to yield the intermediate **28** as a white solid (3.05 g, 94.6%). ESI-MS(*m/z*): 323.12$[M+H]^+$.

*5.14. Preparation of the intermediate 2-((4-((2-chloropyrimidin-4-yl)oxy)phenyl) amino)-N-(4-fluorophenyl)benzamide (**29**)*

To a solution of intermediate **28** (3.22 g, 0.01 mol) and 2,4-dichloropyrimidine (1.48 g, 0.01 mmol) in DMF (15 mL) was added K_2CO_3 (1.52 g, 0.01 mol). The mixture then was stirred at 80 °C for 2 h. The reaction solution was cooled to room temperature and ice water was added, then viscous solid was precipitated, filtered off to obtain intermediate **29** as a pale white solid (3.70 g, 85.2%). ESI-MS(*m/z*): 435.11$[M+H]^+$.

*5.15. Preparation of the title compounds **30a-b***

To a solution of the intermediate **29** (4.77 g, 11.0 mmol) and R_2-substituedaniline (10.0 mmol) in DMF (20 mL) was added *p*-Toluenesulfonic acid monohydrate (7.60 g, 40.0 mmol). The solution was stirred at 90 °C for 10 h. Then water (50 mL) was added to precipitate white solid. The white solid was filtered and recrystallized from ethanol to afford **30**.

*5.15.1. N-(4-fluorophenyl)-2-((4-((2-((3-morpholinophenyl)amino) pyridin-4-yl)oxy)phenyl)amino)benzamide (**30a**)*

White solid, Yield: 63.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H, CONH), 9.62 (s, 1H, NH), 9.15 (s, 1H, NH), 8.34 (d, 1H,

J = 4.4 Hz, ArH), 7.87–7.82 (m, 3H, ArH), 7.41 (s, 1H, ArH), 7.39–7.33 (m, 2H, ArH), 7.24–7.12 (m, 7H, ArH), 7.03 (t, 1H, J = 8.6 Hz, ArH), 6.98 (t, 1H, J = 6.8 Hz, ArH), 6.77 (d, 1H, J = 8.4 Hz, ArH), 6.34 (t, 1H, J = 8.0 Hz, ArH), 3.46 (s, 4H, CH_2), 2.27 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.51, 167.68, 167.27, 164.85, 162.76, 149.47, 148.15, 144.74, 143.84, 139.31, 135.13, 133.62, 130.79, 129.43, 126.38, 125.67, 122.56, 122.84, 119.76, 118.55, 116.13, 109.34, 105.63, 101.45, 94.02, 64.28, 54.43. HRMS (ESI) m/z calcd. for $C_{33}H_{29}FN_6O_3$ $[M+H]^+$ 577.2527, found 577.2542; Purity: > 95% (HPLC).

*5.15.2. N-(4-fluorophenyl)-2-((4-((2-((3-(morpholinomethyl) phenyl)amino)pyridin-4-yl)oxy)phenyl)amino)benzamide (**30b**)*

White solid, Yield: 59.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δppm: 10.47 (s, 1H, CONH), 9.64 (s, 1H, NH), 9.17 (s, 1H, NH), 8.35 (d, J = 4.0 Hz, 1H, ArH), 7.86–7.80 (m, 3H, ArH), 7.46 (s, 1H, ArH), 7.41–7.33 (m, 2H, ArH), 7.25–7.14 (m, 7H, ArH), 7.01 (t, J = 8.0 Hz, 1H, ArH), 6.91 (t, J = 8.0 Hz, 1H, ArH), 6.76 (d, J = 8.0 Hz, 1H, ArH), 6.42 (t, J = 8.6 Hz, 1H, ArH), 3.46 (s, 4H, CH_2), 3.22 (s, 2H, CH_2), 2.15 (s, 4H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.54, 167.61, 167.02, 163.95, 162.85, 150.32, 145.31, 142.71, 140.23, 138.12, 134.42, 133.21, 130.25, 128.74, 126.89, 124.72, 121.55, 121.67, 119.36, 118.81, 118.45, 117.92, 116.54, 115.62, 94.41, 67.54, 65.37, 53.65. HRMS (ESI) m/z calcd. for $C_{33}H_{29}FN_6O_3$ $[M+H]^+$ 591.2657, found 591.2672; Purity: > 95% (HPLC).

*5.16. Preparation of N-(3-substituted-4-hydroxyphenyl)-1,5-dimethyl-3-oxo-2-phenyl- 2,3-dihydro-1H-pyrazole-4-carboxamide (**32a-b**)*

A mixture of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4- carboxylic acid (2.32 g, 0.01 mol), 2-substituted-4-aminophenol (0.01 mmol) and EDCI (5.75 g, 0.03 mmol) in DMF (15 mL) was heated at room temperature for 4 h. Then water (40 mL) was added, extracted with ethyl acetate (15 mL × 3), washed by saturated brine (10 mL × 3), and then dried by anhydrous Na_2SO_4, filtered and concentrated to yield the intermediate **32** as a white solid.

*5.16.1. Intermediate N-(4-hydroxyphenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**32a**)*

White solid, Yield: 94.0%, ESI-MS(m/z): 324.14 $[M+H]^+$.

*5.16.2. Intermediate N-(3-fluoro-4-hydroxyphenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**32b**)*

White solid, Yield: 92.4%, ESI-MS(m/z): 342.13 $[M+H]^+$.

*5.17. Preparation of the intermediate **33***

To a solution of intermediate **32** (0.01 mol) and 2,4-dichloropyrimidine (1.48 g, 0.01 mmol) in DMF (15 mL) was added K_2CO_3 (1.52 g, 0.01 mol). The mixture then was stirred at 80 °C for 2 h. The reaction mixture was cooled to room temperature and ice water was added, then viscous solid was precipitated, filtered off to obtain intermediate **33** as a pale white solid.

*5.17.1. N-(4-((2-chloropyrimidin-4-yl)oxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**33a**)*

Pale white solid, Yield: 86.4%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.40 (d, J = 5.7 Hz, 1H), 7.75–7.72 (m, 2H), 7.55 (t, J = 7.8 Hz, 2H), 7.49–7.44 (m, 1H), 7.39–7.34 (m, 2H), 7.10–7.07 (m, 2H), 6.74 (d, J = 5.6 Hz, 1H), 3.35 (s, 3H), 2.78 (s, 3H). ESI-MS(m/z): 436.12 $[M+H]^+$.

*5.17.2. N-(4-((2-chloropyrimidin-4-yl)oxy)-3-fluorophenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**33b**)*

Pale white solid, Yield: 84.27%, ESI-MS(m/z): 454.11 $[M+H]^+$.

*5.18. Preparation of the title compounds **34a-c***

To a solution of the intermediate **33** (11.0 mmol) and R_2-substituedaniline (10.0 mmol) in DMF (20 mL) was added *p*-toluenesulfonic acid monohydrate (7.60 g, 40.0 mmol). The solution was stirred at 90 °C for 10 h. Then water (50 mL) was added to precipitate white solid. The white solid was filtered and recrystallized from ethanol to afford **34**.

*5.18.1. 1,5-dimethyl-N-(4-((2-((3-morpholinophenyl)amino) pyrimidin-4-yl)oxy)phenyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**34a**)*

White solid, Yield: 63.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H, CONH), 9.35 (s, 1H, NH), 8.33 (d, J = 5.6 Hz, 1H, ArH), 7.66 (d, J = 8.9 Hz, 2H, ArH), 7.59 (t, J = 7.6 Hz, 2H, ArH), 7.51 (t, J = 7.4 Hz, 1H, ArH), 7.44 (d, J = 7.1 Hz, 2H, ArH), 7.20–7.15 (m, 3H, ArH), 7.08 (d, J = 8.3 Hz, 1H, ArH), 6.95 (t, J = 8.1 Hz, 1H, ArH), 6.48 (dd, J = 8.2, 2.3 Hz, 1H, ArH), 6.39 (d, J = 5.5 Hz, 1H, ArH), 3.67 (t, J = 4.0 Hz, 4H, CH_2), 3.36 (s, 3H, CH_3), 2.92 (t, J = 4.7 Hz, 4H, CH_2), 2.71 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.81, 163.56, 161.62, 160.32, 154.33, 151.84, 148.11, 141.31, 136.59, 133.55, 129.93, 129.29, 129.08, 127.58, 122.50, 120.59, 110.91, 109.42, 106.36, 98.73, 97.62, 66.53, 49.04, 33.79, 11.94. HRMS Calcd for $C_{32}H_{31}N_7O_4$ $[M+H]^+$, 578.2524; found, 578.2523. Purity: > 95%.

*5.18.2. N-(3-fluoro-4-((2-((3-morpholinophenyl)amino)pyrimidin-4-yl)oxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**34b**)*

White solid, Yield: 71.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H, CONH), 9.23 (s, 1H, NH), 8.13 (d, J = 5.6 Hz, 1H, ArH), 7.59 (d, J = 8.0 Hz, 2H, ArH), 7.47 (t, J = 8.0 Hz, 2H, ArH), 7.24 (t, J = 8.0 Hz, 1H, ArH), 7.37 (d, J = 8.0 Hz, 2H, ArH), 7.18 (d, J = 8.0 Hz, 2H, ArH), 7.07 (d, J = 8.0 Hz, 1H, ArH), 6.67 (t, J = 8.0 Hz, 1H, ArH), 6.38 (d, J = 8.0 Hz, 1H, ArH), 6.27 (d, J = 8.0 Hz, 1H, ArH), 3.47 (t, J = 4.0 Hz, 4H, CH_2), 2.75 (t, J = 4.0 Hz, 4H, CH_2), 2.64 (s, 3H, CH_3), 1.27 (d, J = 4.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.72, 166.54, 164.16, 163.76, 162.53, 160.37, 158.48, 147.79, 145.51, 137.01, 134.14, 133.96, 131.18, 129.42, 125.19, 123.58, 122.41, 117.24, 111.37, 108.32, 106.36, 103.95, 101.71, 94.48, 67.39, 55.30, 34.23, 12.06. HRMS (ESI) m/z calcd. for $C_{32}H_{30}FN_7O_4$ $[M+H]^+$ 596.2759, found 596.2771; Purity: > 95% (HPLC).

*5.18.3. 1,5-dimethyl-N-(4-((2-((3-(morpholinomethyl)phenyl) amino)pyrimidin-4-yl)oxy)phenyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**34c**)*

White solid, Yield: 67.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H, CONH), 9.58 (s, 1H, NH), 8.34 (d, J = 8.0 Hz, 1H, ArH), 7.70 (d, J = 8.0 Hz, 2H, ArH), 7.60 (t, J = 8.0 Hz, 2H, ArH), 7.51 (t, J = 8.0 Hz, 1H, ArH), 7.44 (d, J = 4.0 Hz, 3H, ArH), 7.30 (d, J = 4.0 Hz, 1H, ArH), 7.20 (d, J = 8.0 Hz, 2H, ArH), 7.04 (t, J = 8.0 Hz, 1H, ArH), 6.83 (d, J = 8.0 Hz, 1H, ArH), 6.44 (d, J = 4.0 Hz, 1H, ArH), 3.49 (s, 4H, CH_2), 3.36 (s, 3H, CH_3), 3.17 (s, 2H, CH_2), 2.72 (s, 3H, CH_3), 2.24 (s, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.49, 166.13, 164.41, 163.15, 162.37, 158.26, 151.83, 147.35, 137.74, 134.59, 134.18, 130.42, 126.63, 124.76, 124.44, 119.14, 118.27, 116.81, 115.23, 104.91, 94.44, 67.79, 64.25, 55.70, 34.64, 12.09. HRMS (ESI) m/z calcd. for $C_{33}H_{33}N_7O_4$ $[M+H]^+$ 592.4143, found 592.4168; Purity: > 95% (HPLC).

5.19. c-Met kinase assay

The inhibitory activities on c-Met kinase were determined using enzyme-linked immunosorbent (ELISAs) with purified recombinant proteins. The detailed procedures were described in our previous work [36]. The IC_{50} values were calculated from the inhibition curves in two separate experiments.

5.20. Antiproliferation assay

The antiproliferative activities were tested by using MTT method, which was detailed described in our previous work [36]. The IC_{50} values were calculated by concentration-response curve fitting using the four-parameter method.

5.21. Pharmacokinetic study

Male SD rats (SLRC laboratory Animal Inc., Shanghai, China) were used, and the detailed procedures were described in our previous work [36]. The concentrations of compounds in plasma were determined by LC/MS/MS (Shimadzu LC-30AD).

5.22. Acute toxicity test

Male and female KM mice (18–22 g) were purchased from SLRC Laboratory Animal Inc., Shanghai, China. Mice were randomly divided into six groups according to our previous method [36]. Mice were orally given **34a** with a single dose 600, 800, 1000, 1200, 1500 and 2000 mg/kg, or vehicle conrol. The mice were monitored and recorded for 14 days. Finally, all the experimental animals were euthanized and necropsied to exam the status of the heart, liver, and kidneys.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2021.113648.

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