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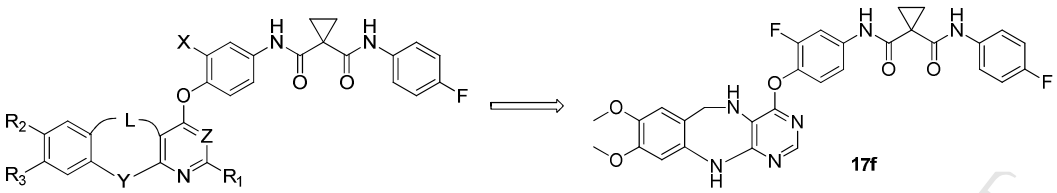
Graphical Abstract



A series of novel 6,11-dihydro-5*H*-benzo[e]pyrimido[5,4-*b*][1,4]diazepine derivatives were designed, synthesised and evaluated for their c-Met kinase inhibition. The promising compound **17f** displayed favourable pharmacokinetic properties, an acceptable safety profile, and significant anti-tumour activity in the Caki-1 tumour xenograft model.

Synthesis and biological evaluation of novel 6,11-dihydro-5*H*-benzo[e]pyrimido-[5,4-*b*][1,4]diazepine derivatives as potential c-Met inhibitors

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Abstract Over expression of c-Met tyrosine kinase is known to promote tumorigenesis and metastasis, as well as to cause therapeutic resistance. Herein a series of novel 6,11-dihydro-5*H*-benzo[e]pyrimido[5,4-*b*][1,4]diazepine derivatives were designed, synthesised and evaluated for their c-Met kinase inhibition. Compounds **17e**, **17f**, **18a**, and **18b** were further examined for their anti-proliferative activities against four typical cancer cell lines (PC-3, Panc-1, HepG2, and Caki-1). The promising compound **17f** was identified as a multi-target receptor tyrosine kinase inhibitor, which also displayed favourable pharmacokinetic properties in rats, had an acceptable safety profile in preclinical studies, and significant anti-tumour activity in the Caki-1 tumour xenograft model.

1. Introduction

Mesenchymal epithelial transition factor (c-Met), known as a hepatocyte growth factor receptor, was discovered in 1984 as an oncogenic fusion protein, translocation promoter region (TPR-MET) [1]. Physiologically, c-Met mediates a diverse array of biological processes that lead to cell proliferation, migration, and invasion [2-5]. As such, normal c-Met signalling plays an important role during embryogenesis, wound healing, and liver regeneration in adulthood, however, the dysregulation of c-Met has been associated with a wide range of solid tumours, including thyroid cancer, lung cancer, gastric cancer, colorectal cancer, pancreatic cancer, prostate cancers, renal cancer, *etc.* [6-7]. Accordingly, compelling evidence has linked c-Met over-activation

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to mediating intrinsic, or acquired, resistance to targeted therapies, and to the poor prognosis in clinical studies [8]. As a result, c-Met has become an attractive target for cancer therapy.

A variety of approaches have been used to target the c-Met signaling pathway including antibodies [9,10], antagonists [11,12], and small-molecule kinase inhibitors [13-17]. All reported small-molecule inhibitors have basically been categorised into two classes based on their structures and binding modes in the c-Met kinase domain. Type-I inhibitors (Crizotinib, JNJ-38877605, INCB-28060, MK-2461) bind in a U-shaped conformation to the ATP-binding site at the entrance of the kinase pocket and wrap around Met1211, while type-□ inhibitors (Cabozantinib, Foretinib, MGCD-265, Golvatinib) bind to c-Met with an extended conformation that stretches from the ATP-binding site (hinge region) to the deep hydrophobic Ile1145 pocket near the C-helix region. Among those representative compounds, shown in Figure 1, Crizotinib and Cabozantinib were approved by the FDA in August, 2011 for the treatment of non-small cell lung cancer (NSCLC) patients and in November, 2012 for the treatment of patients with progressive metastatic medullary thyroid cancer, respectively [18-19]. Furthermore, varieties of analogues have been reported recently [20-29].

(**Fig. 1.** should be inserted here)

In general, type-I inhibitors showed high selectivity to c-Met kinase, however, many projects involving these inhibitors in discovery, development or clinical were stopped due to toxicity or unknown reasons. While type-□ inhibitors can inhibit other kinases, display high potency and low toxicity, and endure drug-resistance. Structurally, type-□ inhibitors are composed of three moieties (Figure 2): a pharmacophore quinolone group (moiety A), a cyclopropyl-malonamide group (moiety B), and a linking phenoxy group (moiety C). An early discovery found that nitrogen in moiety A could form hydrogen bond with Met1160, so compounds could bind to the kinase to inhibit its activity. In addition, the carbonyl oxygens in moiety B engaged in hydrogen bonding with Lys1110 and Asp1222, respectively. The moiety C is capable of participating in π-π interaction with Phe1223 to increase the affinity with the c-Met kinase [30,31]. The binding mode of Cabozantinib with c-Met kinase is shown in Figure 3. Generally, the modification of Cabozantinib mainly focused on moiety A and moiety B, where moiety B was designed as a linear, or cyclic, five-atom

chain bearing at least one amide bond between the two benzene groups, which is known as “five-atom regulation” [32-35]. Additionally, the replacement of moiety A by various *N*-containing heterocycles, such as substituted quinolone, thienopyridine, pyrrolopyridine, aminopyridine, *etc*. has been investigated [36-39].

(**Fig. 2.** should be inserted here)

(**Fig. 3.** should be inserted here)

As shown in Figure 3, the ATP binding pocket is spacious enough to bind larger groups, however, moiety A is reported as being limited to monocyclic, or bicyclic, ring groups, and there are still no examples of the use of polycyclic ring to explore the binding mode to the pocket residues. It is worth mentioning that several 6,11-dihydro-5*H*-benzo[e]pyrimido-[5,4-*b*][1,4]diazepine compounds, which have pyridine nitrogen with potential to bind to the ATP binding pocket, have been reported to exhibit excellent anti-tumour activities [40]. This inspired us to introduce tricyclic groups, such as 6,11-dihydro-5*H*-benzo[e]pyrimido-[5,4-*b*][1,4]diazepine and its derivatives, as a moiety A scaffold to investigate the requirements of the ATP binding pocket. Therefore, twenty-two new compounds have been designed, synthesised and evaluated (with regard to their biological activities) to study the structure-activity relationships, and to develop novel c-Met inhibitors with good potential for use as drug with low toxicity. The design strategy is shown in Figure 4.

(**Fig. 4.** should be inserted here)

The target compounds synthesised were evaluated for c-Met kinase inhibition, and compounds **17e**, **17f**, **18a**, and **18b** were further tested for anti-proliferative activities against four cancer cell lines (PC-3, Panc-1, HepG2, and Caki-1). Furthermore, later research indicated that compound **17f** exhibited favourable pharmacokinetic properties, an acceptable safety profile in preliminary safety studies (MTD and hERG), and potent activity in a c-Met-amplified (Caki-1) subcutaneous tumour xenograft model.

2. Chemistry

A series of diazepine derivatives and their intermediates were synthesised according to the pathways described in Schemes 1 to 6.

As depicted in Scheme 1, intermediate **9**, obtained from the condensation of commercially available cyclopropane-1,1-dicarboxylic acid with 4-fluoroaniline, was

treated with (un) substituted 4-aminophenol to yield the key intermediate **10a-b**. Then, the substituted 5-nitro-4,6-dichloropyrimidine was reduced to yield **11a-c**, which reacted with **10a** to give the desired intermediates **12a-c**.

The target compounds **13a-c** were synthesised by reaction of **12a-c** with substituted salicylic acid [41].

(**Scheme 1.** should be inserted here)

As shown in Scheme 2, the substituted 5-nitro-4,6-dichloropyrimidine, or pyridine, reacted with substituted aniline, or phenol, to yield the intermediate **14a-i**, which reacted with **10a-b** and was then reduced to yield **16a-i**. Finally, the target compounds **17a-i** were prepared by cyclisation of **16a-i** [42].

(**Scheme 2.** should be inserted here)

The target compounds **18a-d** were prepared from starting material **17e-f** and **17h-i** under microwave conditions as outlined in Scheme 3.

(**Scheme 3.** should be inserted here)

Scheme 4 depicts the preparation of compounds **21a-b**. Treatment of commercially available 4,6-dichloro-5-nitropyrimidine with methyl 6-amino-2,3-dimethoxybenzoate provided corresponding intermediate **19**, which then reacted with **10a-b** to generate intermediates **20a-b**. Intramolecular cyclisation of **20a-b** furnished the target compounds **21a-b**.

(**Scheme 4.** should be inserted here)

The general strategy to synthesise compounds **24a-b** is outlined in Scheme 5 using the same method as was used to prepare **21a-b** in Scheme 4, albeit modified so that the inorganic base $KF.2H_2O$ was used instead of K_2CO_3 [43].

(**Scheme 5.** should be inserted here)

As shown in Scheme 6, compounds **25a-b** were synthesised from **17e-f** via methylation.

(**Scheme 6.** should be inserted here)

The chemical structures of the target compounds were confirmed by MS, HRMS, ^{1}H-NMR, and ^{13}C-NMR spectroscopy.

3. Results and discussion

3.1. *In vitro cytotoxicity and structure–activity relationships*

The 22 prepared target compounds (**13a-c**, **17a-i**, **18a-d**, **21a-b**, **24a-b**, and

25a-b) were evaluated for their *in vitro* inhibitory activity against c-Met kinase using homogenous time-resolved fluorescence (HTRF) assay, and then the compounds with potent c-Met enzyme activities were further tested against 4 c-Met-addicted cancer cell lines including PC-3, Panc-1, HepG2, and Caki-1 by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cabozantinib was taken as a positive control. The results were expressed as half-maximal inhibitory concentration (IC_{50}) values and are presented in Table 1, as mean values of experiments performed in triplicate.

As illustrated from Tables 1 to 4, six compounds (**17d-g**, and **18a-b**) exhibited promising activity against c-Met kinase with IC_{50} values ranging from 2322 nM to 24.4 nM, which suggested that the inhibition of c-Met kinase may be a main mechanism underpinning the anti-tumour activity of the prepared compounds. However, other compounds showed weak inhibitory activity with their values of IC_{50} being above 10 μM. Notably, compound **17f** demonstrated the best activity with an IC_{50} value of 24.4 nM, which is approximately equal to that of Cabozantinib (24.4 nM *versus* 5.3 nM).

(**Table 1.** should be inserted here)

(**Table 2.** should be inserted here)

(**Table 3.** should be inserted here)

(**Table 4.** should be inserted here)

Four preferred compounds (**17e-f**, and **18a-b**), mentioned above, were further assayed for cancer cell activity (Table 5): all four compounds showed moderate, to significant, anti-proliferative activities with IC_{50} values ranging from 0.748 to 7.125 μM, which is superior to Cabozantinib against all four tested cancer cells, which suggested that the introduction of 6,11-dihydro-5*H*-benzo[e]pyrimido[5,4-b][1,4]diazepine group, as moiety A, maintained the potent cytotoxic activity. In particular, the most prominent compound (**17f**) displayed three to seven times more activity than that of Cabozantinib.

(**Table 5.** should be inserted here)

The biological activity data indicated that the tricyclic scaffold affected the activity to a significant extent. For example, the introduction of an NH group into position “Y” could make a better contribution to the inhibitory activity than an oxygen (O) group (**18a-b** > **13c**, **17e** > **17g**) (Table 1, 2), when “Z” was substituted by

nitrogen, the activity increased (**18a** *versus* **18c**, **18b** *versus* **18d**, **17e** *versus* **17h**, **17f** *versus* **17i**) (Table 1, 2). The activities of compounds **17d** (R_1 = H) were significantly higher than that of compounds **17b** (R_1 = CH_3) (Table 1, 2). Besides, the inhibitory activity increased significantly when groups R_2 and R_3 were substituted with a methoxy group (**17g** > **17c**, **17e** > **17d**) (Table 2), and this could be validated by the subsequent binding mode analysis.

Compounds **17e-f** with their CH_2-NH group exhibited strong inhibitory activity against c-Met kinase with IC_{50} values of 29.3 nM and 24.4 nM, respectively; however, the activity declined in compounds **18a-b** due to conformational restriction with the CH=N group that affected the affinity to the kinase (Table 1, 2). In addition, the inhibition against c-Met kinase vanished when NCH_3 and CONH groups were incorporated in **25a-b** and **21a-b** (Table 3, 4). In the end, modifications at position "X" (whether fluorine substituted or not) could not affect the potency to any significant extent, such as in compound **18a** *versus* **18b**, and **17e** *versus* **17f** (Table 1, 2).

3.2. *Enzymatic selectivity assays*

To examine whether, or not, **17f** is a selective c-Met inhibitor, this compound was screened against five other tyrosine kinases. Compared with its high potency against c-Met, **17f** also exhibited high inhibitory effects against VEGFR-2, EGFR, RET, c-Kit and FLT-3. These results suggested that compound **17f** is a promising multi-target inhibitor of tyrosine kinase. The results are given in Table 6.

(**Table 6.** should be inserted here)

3.3. *Acute toxicity test*

To explore the safety profile of these 6,11-dihydro-5H-benzo[e]pyrimido-[5,4-b][1,4]diazepine derivatives, the acute toxicity of **17f** was measured in ICR mice at a single dose of 420, 520, 620, 720, 820 and 920 mg/kg or vehicle control (n = 10) by oral administration. Animals were monitored for 14 days. Treatment with **17f** at 720 mg/kg killed 20 % of the mice, whereas the lower doses (420, 520, and 620 mg/kg) caused no abnormalities or animal deaths throughout the experiment. These results suggest that administration of **17f** at, or below, 620 mg/kg (PO) may be safe for mice. The results are given in Table 7.

(**Table 7.** should be inserted here)

3.4. T*est of activity on hERG potassium currents*

The activity of **17f** on hERG potassium currents was evaluated, since activation of hERG channels may induce cardiotoxicity. A compound solution was administrated, from low- to high-concentrations, and each concentration was tested on at least three cells. The IC_{50} value of **17f** was greater than 40 μM, which demonstrated that compound **17f** did not activate hERG channels and had no cardiotoxicity. The results are given in Table 8.

(**Table 8.** should be inserted here)

3.5. *Pharmacokinetics study*

The pharmacokinetics (PK) of **17f** were measured in male SD rats. After administration of 20 mg/kg (PO) **17f** to SD rats, a C_{max} of 1934.2 ng/mL was obtained at 1.67 h. Compound **17f** was well cleared ($CL_{z/F}$ = 2.93 L/h/kg) in rats. The elimination half-life of **17f** after administration was 2.36 h. Compound **17f** was also well distributed ($V_{z/F}$ = 4.52 L/kg) and had a moderate oral bioavailability (*F* = 39 %) in rats. The results are given in Table 9.

(**Table 9.** should be inserted here)

3.6. *In vivo pharmacology*

The *in vivo* activity of **17f** was evaluated in a c-Met amplified (Caki-1) subcutaneous tumour xenograft. Observations were made following oral administration of **17f** to the mouse model once daily for 21d: these demonstrated that **17f** strongly inhibited tumour growth with inhibitory levels of 51.1 %, 58.87 %, and 64.54 % compared to untreated controls at respective dosages of 20, 40, and 80 mg/kg. Moreover, **17f**, at all dosage levels, was well tolerated by mice. The results are given in Figure 6.

(**Fig.5.** should be inserted here)

4. Conclusions

In summary, 22 novel diazepine, oxazepines and pyridodiazepine derivatives possessing 6,11-dihydro-5*H*-benzo[e]pyrimido-[5,4-*b*][1,4] diazepine derivatives as

moiety A were designed, synthesised and evaluated to elucidate their c-Met kinase inhibitory activities. Among these compounds, **17f** exhibited excellent activity with an IC_{50} value of 24 nM. Moreover, it displayed better anti-proliferative activities against PC-3, HepG2, Caki-1, and Panc-1, and was five, to seven, times more active than Cabozantinib. Preliminary SARs revealed that the C=N, N-CH_3, and CONH groups had a negative effect on c-Met kinase inhibitory activity compared with that of C-N group, and the activity increased significantly when X, R_2, and R_3 were substituted with fluorine and a methoxy group, respectively. Binding model analysis of **17f** suggested that the diazepine group could form two hydrogen-bonding interactions in the ATP-binding site and another hydrogen-bonding interaction in moiety C, which could be the reason for the aforementioned activity.

In addition, the primary PK profiles showed that compound **17f**, with its diazepine group, had favourable physico-chemical properties. There was no toxicity observed in acute toxicity tests following administration in mice and in hERG potassium channel testing. Meanwhile, **17f** displayed significant anti-tumour activity in a c-Met-amplified (Caki-1) subcutaneous tumor xenograft model. The additional biological evaluation of **17f** is currently in progress, and the novel scaffold that binds to the ATP pocket in **17f** provided a new starting point for further optimisation studies.

5. Experimental

5.1. Chemistry

Unless otherwise noted, all reagents and solvents employed were purchased commercially and used as received. All reactions were conducted in microwave vials or flasks containing Tefloncoated magnetic stirrer. Microwave irradiation experiments were performed in a CEM-Discover$^{@}$LabMate mono-mode microwave apparatus.

Reactions' time and purity of the products were monitored by TLC on FLUKA silica gel aluminum cards (0.2 mm thickness) with fluorescent indicator 254 nm. Column chromatography was run on silica gel (200-300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China). All melting points were obtained on a BüchiMelting Point B-540 apparatus (BüchiLabortechnik, Flawil, Switzerland) 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, Billerica, MA, USA)

with TMS as an internal standard. All reagents were analytical reagent (AR) and chemical pure (CP). Biological activities evaluation were performed at the Shanghai Sudia Co., Ltd.

*5.2. Preparation of 1-((4-fluorophenyl)carbamoyl)cyclopropane carboxylic acid (**9**)*

To a solution of cyclopropane-1,1-dicarboxylic acid (13.01 g, 0.10 mol) in THF (120 mL), trimethylamine (10.12 g, 0.10 mol) was added drop-wise under nitrogen atmosphere at 0 □. Then, $SOCl_2$ (9.95 g, 0.10 mol) and a solution of 4-fluoroaniline (12.22 g, 0.11 mol) in THF (60 mL) were added drop-wise at 0 □, respectively. The reaction solution was stirred in an ice bath for 2 h and monitored by thin-layer chromatograph (TLC). After adjusting pH to 9.0 by 1 M NaOH, the solution was acidified by 1 M HCl to pH 5.0, and the precipitate was filtered off, washed, dried in vacuum, yielding **9** (14.71 g) as a white solid in 65.9% yield [44]. The production was used for the next step without further purification. MS (ESI) m/z: 224.5 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δ: 13.05 (s, 1H, COOH), 10.58 (s, 1H, CONH), 7.67~7.12 (m, 4H, Ar-H), 1.47 (s, 4H, CH_2CH_2).

*5.3. General procedure for Preparation of N-(4-fluorophenyl)-N-(4-hydroxy-3-substitutedphenyl)cyclopropane-1,1-dicarboxamide (**10a-b**)*

To a solution of the intermediate **9** (1.0 g, 4.48 mmol) and substituted aminophenol (5.38 mmol) in DMF (15 mL) was added EDCI (1.03 g, 5.38 mmol). The solution was stirred at room temperature for 3 h. Then water (50 mL) was added to precipitate white solid, adjusting pH to 4.0~5.0 by 1 M HCl. The white solid was filtered off, washed and dried in vacuum to afford **10a-b** [45].

*5.3.1. N-(4-fluorophenyl)-N-(4-hydroxyphenyl)cyclopropane-1,1-dicarboxamide (**10a**)*

Yield: 87.9%; MS (ESI) m/z: 315.4 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δ: 10.17 (s, 1H, CONH), 9.73 (s, 1H, CONH), 9.23 (s, 1H, OH), 7.83~6.68 (m, 8H, Ar-H), 1.48 (s, 4H, CH_2CH_2).

*5.3.2. N-(3-fluoro-4-hydroxyphenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**10b**)*

Yield: 86.5%; MS (ESI) m/z: 332.9 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δ: 10.21 (s, 1H, CONH), 9.84 (s, 1H, CONH), 9.32 (s, 1H, OH), 7.74~6.47 (m, 7H, Ar-H), 1.42 (s, 4H, CH_2CH_2).

*5.4. General procedure for Preparation of 4,6-dichloro-2-substituted-5-nitropyrimidine (**11a,b**)*

10% Pd/C（0.05 g）was added to the solution of substituted pyrimidine (4.48 mmol) in ethyl acetate (EA, 20 mL) in Parr hydrogenater. Then, replace the air with nitrogen three times, and react for 4 h at room temperature in normal pressure. Filter the solution to remove Pd/C through Celite filter agent, the filtrate was concentrated to yield the intermediates **11a,b** [46].

*5.4.1. 4,6-dichloro-2-methyl-5-nitropyrimidine (**11a**)*

Pale solid; Yield: 84.0%; MS (ESI) m/z: 177.94 $[M+H]^+$.

*5.4.2. 4,6-dichloro-2-methyl-5-nitropyrimidine (**11b**)*

Pale solid; Yield: 86.0%; MS (ESI) m/z: 163.87 $[M+H]^+$.

*5.5. General procedure for Preparation of N-(4-((5-amino-6-chloro-2-substitutedpyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide (**12a,b**)*

To a solution of intermediates **11a,b** (0.02 mol) and **10a** (6.28 g, 0.02 mol) in DMF (15 mL) was added K_2CO_3 (3.04 g, 0.022 mol). The mixture then was stirred at 60 ℃ for overnight. The reaction mixture 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 stirring it with petroleum ether (40 mL) for 30 min to yield the title compound **12a,b** as a light white solid.

*5.5.1. N-(4-((5-amino-6-chloro-2-methylpyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**12a**)*

Pale white solid; Yield: 87.0%; MS (ESI) m/z: 456.08 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δppm: 10.24 (s, 1H, CONH), 10.12 (s, 1H, CONH), 8.11~7.07 (m, 8H, Ar-H), 5.74 (br, 2H, NH_2), 1.43 (s, 4H, CH_2CH_2).

*5.5.2. N-(4-((5-amino-6-chloropyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (**12b**)*

Pale white solid; Yield: 85.0%; MS (ESI) m/z: 442.13 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δppm: 10.20 (s, 1H, CONH), 10.14 (s, 1H, CONH), 8.06 (s, 1H, pyrimidine-H), 8.01~7.13 (m, 8H, Ar-H), 5.81 (br, 2H, NH_2), 2.21 (s, 3H, CH_3), 1.46 (s, 4H, CH_2CH_2).

*5.6. General procedure for Preparation of Compounds **13a-c***

To a mixture of intermediates **12a-c** (0.50 mmol), substituted salicylaldehyde (0.50 mmol) and $MgSO_4$ (0.18 g, 1.5 mmol) in DMF (15 mL) was added one drop concentrated hydrochloric acid. The mixture then was stirred at 95 ℃ for overnight.

The reaction solution was cooled to room temperature and ice water was added, solid was precipitated, filtered off to obtain crude product which was purified by silica gel chromatography using PE/EA (3:1) to afford the title compounds **13a-c**.

*5.6.1. N-(4-fluorophenyl)-N-(4-((2-methylbenzo[f]pyrimido[4,5-b][1,4]oxazepin-4-yl) oxyphenyl)cyclopropane-1,1-dicarboxamide (**13a**)*

Yellow solid; Yield: 38.2%; m.p.: 183-185 □; MS (ESI) m/z: 524.18 $[M+H]^+$, ^{1}H-NMR (400MHz, DMSO-d_6) δppm: 10.11 (s, 1H, CONH), 10.07 (s, 1H, CONH), 8.72 (s, 1H, CH=N), 7.86~7.13 (m, 12H, Ar-H), 2.41 (s, 3H, CH_3), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.39, 25.12, 30.29, 115.76, 117.11, 121.22, 121.58, 122.32, 125.29, 131.04, 133.67, 134.47, 136.33, 146.21, 154.79, 158.16, 160.05, 162.42, 163.67, 166.13, 168.18. HRMS Calcd for $C_{29}H_{22}FN_5O_4$ $[M+H]^+$, 523.1716; found, 524.1825. Purity: > 95%.

*5.6.2. N-(4-(benzo[f]pyrimido[4,5-b][1,4]oxazepin-4-yloxy)phenyl)-N-(4-fluorophen-yl)cyclopropane-1,1-dicarboxamide (**13b**)*

Yellow solid; Yield: 38.4%; m.p.: 170-172 ℃; MS (ESI) m/z: 510.16 $[M+H]^+$, ^{1}H-NMR (400MHz, DMSO-d_6) δppm: 10.17 (s, 1H, CONH), 10.03 (s, 1H, CONH), 8.79 (s, 1H, CH=N), 8.36 (s, 1H, pyrimidine-H), 7.91~7.10 (m, 12H, Ar-H), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.42, 31.43, 114.99, 119.67, 121.29, 121.63, 122.40, 126.43, 131.05, 134.76, 135.14, 136.31, 148.25, 155.73, 157.11, 159.45, 162.85, 163.60, 165.90, 168.10. HRMS Calcd for $C_{28}H_{20}FN_5O_4$ $[M+H]^+$, 509.1499; found, 510.1578. Purity: > 95%.

*5.6.3. N-(4-((8,9-dimethoxybenzo[f]pyrimido[4,5-b][1,4]oxazepin-4-yl)oxy)phenyl)-N -(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**13c**)*

Yellow solid; Yield: 39.1%; m.p.: 196-199 ℃; MS (ESI) m/z: 570.15 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.22 (s, 1H, CONH), 10.18 (s, 1H, CONH), 8.64 (s, 1H, CH=N), 8.46 (s, 1H, pyrimidine-H), 7.87~7.25 (m, 10H, Ar-H), 3.67 (s, 6H, 2×CH_3), 1.43 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.28, 30.69, 53.14, 113.97, 116.07, 121.19, 121.46, 123.08, 128.47, 130.61, 134.77, 135.82, 136.17, 144.49, 156.70, 157.72, 159.48, 160.59, 162.45, 165.96, 167.14. HRMS Calcd for $C_{30}H_{24}FN_5O_6$ $[M+H]^+$, 569.1728; found, 570.1532. Purity: > 95%.

*5.7. General procedure for Preparation of the intermediates **14a-i***

A mixture of substituted pyrimidine, or pyridine (1.0 mmol), substituted phenol, or aniline (1.2 mmol) and K_2CO_3 (0.42 g，3.0 mmol) in DMF (3 mL) was heated at

60 ℃ for 8 h. Upon cooling to room temperature, the reaction mixture was diluted with EA (15 mL), washed by 10% NaOH solution (5 mL×2) and saturated bine (5 mL×3), and then dried by anhydrous Na_2SO_4, filtered and concentrated to yield the intermediates **14a-i**.

*5.7.1. 4-chloro-2-methyl-5-nitro-6-phenoxypyrimidine (**14a**)*

Light orange solid; Yield: 97.0%; MS (ESI) m/z: 266.01 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 7.01~6.79 (m, 5H), 2.41 (s, 3H).

*5.7.2. 6-chloro-N-(4-methoxyphenyl)-2-methyl-5-nitropyrimidin-4-amine (**14b**)*

Light orange solid; Yield: 98.0%; MS (ESI) m/z: 295.07 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 9.13 (s, 1H), 7.07~6.83 (m, 4H), 3.71 (d, J = 6.8 Hz, 3H), 2.44 (s, 3H).

*5.7.3. 4-chloro-5-nitro-6-phenoxypyrimidine (**14c**)*

Light orange solid; Yield: 96.5%; MS (ESI) m/z: 252.03 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 8.01 (s, 1H), 7.01~6.79 (m, 5H).

*5.7.4. 6-chloro-N-(4-methoxyphenyl)-5-nitropyrimidin-4-amine (**14d**)*

Light orange solid; Yield: 97.6%; MS (ESI) m/z: 281.05 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 9.17 (s, 1H), 8.04 (s, 1H), 7.11~6.78 (m, 4H), 3.65 (d, J = 6.4 Hz, 3H).

*5.7.5. 6-chloro-N-(3,4-dimethoxyphenyl)-5-nitropyrimidin-4-amine (**14e,f**)*

Light orange solid; Yield: 98.2%; MS (ESI) m/z: 311.07 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 9.14 (s, 1H), 7.97 (s, 1H), 7.15~6.83 (m, 3H), 3.74 (d, J = 8.6 Hz, 6H).

*5.7.6. 4-chloro-6-(3,4-dimethoxyphenoxy)-5-nitropyrimidine (**14g**)*

Light orange solid; Yield: 95.4%; MS (ESI) m/z: 312.04 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 9.06 (s, 1H), 7.22~6.91 (m, 3H), 3.57 (d, J = 8.0 Hz, 6H).

*5.7.7.4-chloro-N-(3,4-dimethoxyphenyl)-3-nitropyridin-2-amine (**14h-i**)*

Light orange solid; Yield: 95.4%; MS (ESI) m/z: 310.06 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 9.11 (s, 1H), 7.99 (d, J = 4.0 Hz, 1H), 7.21 (d, J = 4.6 Hz, 1H), 7.14~6.87 (m, 3H), 3.76 (d, J = 8.4 Hz, 6H).

*5.8. General procedure for Preparation of the intermediates **15a-i***

A mixture of **14a-i** (7.55 mmol), **10a-b** (6.25 mmol) and K_2CO_3 (2.59 g, 18.75 mmol) in DMF (30 mL) was heated at 50 ℃ for 13 h. Upon cooling to room

temperature, the reaction mixture was added water (100 mL), extracted by EA (15 mL×3). The organic phase was combined and concentrated to get the crude product, which was purified by silica gel chromatography using a mixture of PE/EA (2:1~1:1) to afford the intermediates **15a-i**.

*5.8.1. N-(4-fluorophenyl)-N-(4-((2-methyl-5-nitro-6-phenoxypyrimidin-4-yl)oxy) phenyl)cyclopropane-1,1-dicarboxamide (**15a**)*

Orange yellow solid; Yield: 72.8%; MS (ESI) m/z: 544.17 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.15 (t, *J* = 12.0 Hz, 2H), 7.86~7.64 (m, 4H), 7.17~7.11 (m, 4H), 7.04~6.93 (m, 5H), 2.42 (s, 3H), 1.46 (s, 4H, CH_2CH_2).

*5.8.2. N-(4-fluorophenyl)-N-(4-((6-((4-methoxyphenyl)amino)-2-methyl-5-nitropyrimidin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**15b**)*

Orange yellow solid; Yield: 73.4%; MS (ESI) m/z: 573.20 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.11 (t, *J* = 8.6 Hz, 2H), 7.94 (s, 1H), 7.76~7.68 (m, 4H), 7.25~7.17 (m, 4H), 7.01~6.89 (m, 4H), 2.43 (s, 3H), 1.46 (s, 4H, CH_2CH_2).

*5.8.3. N-(4-fluorophenyl)-N-(4-((5-nitro-6-phenoxypyrimidin-4-yl)oxy)phenyl) cyclopsropane-1,1-dicarboxamide (**15c**)*

Orange yellow solid; Yield: 74.6%; MS (ESI) m/z: 530.16 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.14 (t, *J* = 8.8 Hz, 2H), 8.03 (s, 1H), 7.79~7.64 (m, 4H), 7.27~7.14 (m, 4H), 7.01~6.89 (m, 5H), 1.46 (s, 4H, CH_2CH_2).

*5.8.4. N-(4-fluorophenyl)-N-(4-((6-((4-methoxyphenyl)amino)-5-nitropyrimidin-4-yl) oxy)phenyl)cyclopropane-1,1-dicarboxamide (**15d**)*

Orange yellow solid; Yield: 72.5%; MS (ESI) m/z: 559.19 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.12 (t, *J* = 6.8 Hz, 2H), 9.04 (s, 1H), 8.12 (s, 1H), 7.71~7.62 (m, 4H), 7.24~7.11 (m, 4H), 7.01~6.84 (m, 4H), 2.41 (s, 3H), 1.46 (s, 4H, CH_2CH_2).

*5.8.5. N-(4-((6-((3,4-dimethoxyphenyl)amino)-5-nitropyrimidin-4-yl)oxy)phenyl)-N-(4 -fluorophenyl)cyclopropane-1,1-dicarboxamide (**15e**)*

Orange yellow solid; Yield: 75.1%; MS (ESI) m/z: 589.17 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.14 (t, *J* = 8.4 Hz, 2H), 9.01 (s, 1H), 8.07 (s, 1H), 7.75~7.61 (m, 4H), 7.27~7.13 (m, 4H), 7.02~6.93 (m, 3H), 2.44 (s, 6H), 1.47 (s, 4H, CH_2CH_2).

*5.8.6. N-(4-((6-((3,4-dimethoxyphenyl)amino)-5-nitropyrimidin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**15f**)*

Orange yellow solid; Yield: 70.8%; MS (ESI) m/z: 607.14 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.13 (t, *J* = 8.6 Hz, 2H), 9.02 (s, 1H), 8.04 (s, 1H), 7.72~7.67 (m, 3H), 7.25~7.18 (m, 4H), 7.08~6.97 (m, 3H), 2.41 (s, 6H), 1.44 (s, 4H, CH_2CH_2).

*5.8.7. N-(4-((6-(3,4-dimethoxyphenoxy)-5-nitropyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**15g**)*

Orange yellow solid; Yield: 79.2%; MS (ESI) m/z: 590.11 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.14 (t, *J* = 8.4 Hz, 2H), 9.04 (s, 1H), 7.78~7.66 (m, 3H), 7.27~7.13 (m, 4H), 7.01~6.84 (m, 3H), 2.43 (s, 6H), 1.46 (s, 4H, CH_2CH_2).

*5.8.8. N-(4-((2-((3,4-dimethoxyphenyl)amino)-3-nitropyridin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**15h**)*

Orange yellow solid; Yield: 61.4%; MS (ESI) m/z: 588.22 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.14 (t, *J* = 8.0 Hz, 2H), 9.14 (s, 1H), 7.95 (d, *J* = 4.6 Hz, 1H), 7.74~7.62 (m, 4H), 7.42 (d, *J* = 4.4 Hz, 1H), 7.29~7.15 (m, 4H), 7.03~6.81 (m, 3H), 2.46 (s, 6H), 1.44 (s, 4H, CH_2CH_2).

*5.8.9. N-(4-((2-((3,4-dimethoxyphenyl)amino)-3-nitropyridin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**15i**)*

Orange yellow solid; Yield: 62.5%; MS (ESI) m/z: 606.17 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.15 (t, *J* = 8.2 Hz, 2H), 9.05 (s, 1H), 7.88 (d, *J* = 5.6 Hz, 1H), 7.71~7.57 (m, 3H), 7.40 (d, *J* = 4.8 Hz, 1H), 7.27~7.14 (m, 4H), 7.01~6.89 (m, 3H), 2.44 (s, 6H), 1.46 (s, 4H, CH_2CH_2).

*5.9. General procedure for Preparation of the intermediates **16a-i***

10% Pd/C (0.05 g) was added to the solution of **15a-i** (1.84 mmol) in EA (20 mL) in Parr hydrogenater. Then, replace the air with nitrogen three times, and react for overnight at room temperature in normal pressure. Filter the solution to remove Pd/C through Celite filter agent, the filtrate was concentrated to yield the intermediates **16a-i**.

*5.9.1. N-(4-((5-amino-2-methyl-6-phenoxypyrimidin-4-yl)oxy)phenyl)-N-(4-fluoroph enyl)cyclopropane-1,1-dicarboxamide (**16a**)*

Pale solid; Yield: 84.2%; MS (ESI) m/z: 514.19 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.17 (t, *J* = 8.6 Hz, 2H), 7.82~7.69 (m, 4H), 7.34~7.21 (m, 4H), 7.08~6.97 (m, 5H), 5.83 (s, 2H), 2.41 (s, 3H), 1.44 (s, 4H, CH_2CH_2).

5.9.2. N-(4-((5-amino-6-((4-methoxyphenyl)amino)-2-methylpyrimidin-4-yl)oxy)

*phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**16b**)*

Pale solid; Yield: 86.7%; MS (ESI) m/z: 543.24 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.12 (t, *J* = 8.0 Hz, 2H), 7.95 (s, 1H), 7.77~7.64 (m, 4H), 7.26~7.14 (m, 4H), 7.04~6.84 (m, 4H), 5.81 (s, 2H), 2.41 (s, 3H), 1.43 (s, 4H, CH_2CH_2).

*5.9.3. N-(4-((5-amino-6-phenoxypyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (**16c**)*

Pale solid; Yield: 81.4%; MS (ESI) m/z: 500.14 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.11 (t, *J* = 8.6 Hz, 2H), 8.01 (s, 1H), 7.74~7.61 (m, 4H), 7.23~7.17 (m, 4H), 7.02~6.81 (m, 5H), 5.86 (s, 2H), 1.44 (s, 4H, CH_2CH_2).

*5.9.4. N-(4-((5-amino-6-((4-methoxyphenyl)amino)pyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**16d**)*

Pale solid; Yield: 88.2%; MS (ESI) m/z: 529.20 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.17 (t, *J* = 6.4 Hz, 2H), 9.07 (s, 1H), 8.19 (s, 1H), 7.78~7.69 (m, 4H), 7.23~7.15 (m, 4H), 7.02~6.87 (m, 4H), 5.80 (s, 2H), 2.43 (s, 3H), 1.44 (s, 4H, CH_2CH_2).

*5.9.5. N-(4-((5-amino-6-((3,4-dimethoxyphenyl)amino)pyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**16e**)*

Pale solid; Yield: 87.5%; MS (ESI) m/z: 559.20 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.12 (t, *J* = 8.6 Hz, 2H), 9.03 (s, 1H), 8.05 (s, 1H), 7.74~7.62 (m, 4H), 7.28~7.19 (m, 4H), 7.06~6.87 (m, 3H), 5.74 (s, 2H), 2.46 (s, 6H), 1.43 (s, 4H, CH_2CH_2).

*5.9.6. N-(4-((5-amino-6-((3,4-dimethoxyphenyl)amino)pyrimidin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**16f**)*

Pale solid; Yield: 87.9%; MS (ESI) m/z: 577.18 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.11 (t, *J* = 8.4 Hz, 2H), 8.95 (s, 1H), 8.12 (s, 1H), 7.75~7.69 (m, 3H), 7.21~7.12 (m, 4H), 7.01~6.74 (m, 3H), 5.80 (s, 2H), 2.44 (s, 6H), 1.46 (s, 4H, CH_2CH_2).

*5.9.7. N-(4-((5-amino-6-(3,4-dimethoxyphenoxy)pyrimidin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**16g**)*

Pale solid; Yield: 81.4%; MS (ESI) m/z: 560.17 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.17 (t, *J* = 8.6 Hz, 2H), 9.01 (s, 1H), 7.71~7.67 (m, 3H), 7.29~7.15 (m, 4H), 7.07~6.86 (m, 3H), 5.86 (s, 2H), 2.47 (s, 6H), 1.42 (s, 4H,

CH_2CH_2).

*5.9.8. N-(4-((3-amino-2-(3,4-dimethoxyphenoxy)pyridin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**16h**)*

Pale solid; Yield: 81.4%; MS (ESI) m/z: 558.23 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.12 (t, *J* = 7.6 Hz, 2H), 9.17 (s, 1H), 7.96 (d, *J* = 4.8 Hz, 1H), 7.71~7.67 (m, 4H), 7.46 (d, *J* = 4.8 Hz, 1H), 7.27~7.14 (m, 4H), 7.01~6.89 (m, 3H), 5.72 (s, 2H), 2.47 (s, 6H), 1.46 (s, 4H, CH_2CH_2).

*5.9.9. N-(4-((3-amino-2-(3,4-dimethoxyphenoxy)pyridin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**16i**)*

Pale solid; Yield: 78.6%; MS (ESI) m/z: 576.14 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.14 (t, *J* = 8.8 Hz, 2H), 9.11 (s, 1H), 7.90 (d, *J* = 5.6 Hz, 1H), 7.74~7.59 (m, 3H), 7.41 (d, *J* = 4.8 Hz, 1H), 7.26~7.17 (m, 4H), 7.04~6.81 (m, 3H), 5.77 (s, 2H), 2.46 (s, 6H), 1.44 (s, 4H, CH_2CH_2).

*5.10. General procedure for Preparation of the title compounds **17a-i***

A mixture of **16a-i** (7.79 mmol), $(HCHO)_n$ (0.35 g, 11.69mmol), CF_3COOH (TFA, 0.80 g, 7.01 mmol) and $MgSO_4$ (1.88 g, 15.58 mmol) in DCM (30 mL) was heated at 40 ℃ for 12 h. Upon cooling to room temperature, the reaction mixture was filtered off to remove $MgSO_4$. The filtrate was concentrated to obtain crude product which was purified by stirred with ethanol (20 mL) at 60 ℃for 1 h to give the title compounds **17a-i**.

*5.10.1. N-(4-fluorophenyl)-N-(4-((2-methyl-5,6-dihydrobenzo[f]pyrimido[4,5-b][1,4]-oxazepin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**17a**)*

Yield: 81.4%; m.p.: 121-123 ℃; MS (ESI) m/z: 526.19 $[M+H]^+$, ^1H NMR (400MHz, DMSO-d_6) δppm: 10.09 (s, 1H, CONH), 10.07 (s, 1H, CONH), 7.71~7.09 (m, 12H, Ar-H), 5.88 (br, 1H, $CH_2N\underline{H}$), 4.43 (s, 2H, $C\underline{H}_2NH$), 2.20 (s, 3H, CH_3), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.71, 25.14, 32.06, 44.37, 113.70, 116.42, 117.68, 121.65, 122.54, 124.41, 126.89, 134.11, 146.95, 149.81, 151.94, 157.79, 161.62, 162.93, 165.84, 168.71. HRMS Calcd for $C_{29}H_{24}FN_5O_4$ $[M+H]^+$, 525.1807; found, 526.1905. Purity: > 95%.

*5.10.2. N-(4-fluorophenyl)-N-(4-((8-methoxy-2-methyl-6,11-dihydro-5H-benzo[e] pyrimido[5,4-b][1,4]diazepin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**17b**)*

Yield: 77.2%; m.p.: 120-122 ℃; MS (ESI) m/z: 555.20 $[M+H]^+$,^1H NMR (400MHz, DMSO-d_6) δppm: 10.11 (s, 1H, CONH), 10.07 (s, 1H, CONH), 9.22 (s, 1H,

Ar-NH), 7.71~6.69 (m, 11H, Ar-H), 5.36 (br, 1H, $CH_2N\underline{H}$), 4.19 (s, 2H, Ar-CH_2), 3.71 (s, 3H, OCH_3), 2.22 (s, 3H, pyrimidine-CH_3), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.84, 24.81, 31.09, 47.73, 55.84, 109.76, 112.06, 113.12, 116.72, 117.18, 119.46, 120.37, 122.59, 130.47, 131.23, 134.11, 134.44, 149.85, 152.97, 155.74, 157.36, 160.12, 162.34, 165.86, 168.47. HRMS Calcd for $C_{30}H_{27}FN_6O_4$ $[M+H]^+$, 554.2102; found, 555.2024. Purity: > 95%.

*5.10.3. N-(4-((5,6-dihydrobenzo[f]pyrimido[4,5-b][1,4]oxazepin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**17c**)*

Yield: 72.6%; m.p.: 117-119 □; MS (ESI) m/z: 512.16 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.12 (s, 1H, CONH), 10.04 (s, 1H, CONH), 7.79 (s, 1H, pyrimidine-H), 7.68~7.11 (m, 12H, Ar-H), 5.74 (br, 1H, $CH_2N\underline{H}$), 4.32 (s, 2H, $C\underline{H}_2NH$), 1.41 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.63, 31.01, 45.26, 114.28, 117.58, 119.02, 119.31, 120.62, 122.69, 125.07, 127.96, 134.41, 148.89, 150.84, 151.94, 158.27, 162.04, 164.25, 168.44. HRMS Calcd for $C_{28}H_{22}FN_5O_4$ $[M+H]^+$, 511.1767; found, 512.1683. Purity: > 95%.

*5.10.4. N-(4-fluorophenyl)-N-(4-((8-methoxy-6,11-dihydro-5H-benzo[e]pyrimido[5,4-b][1,4]diazepin-4-yl)oxy)phenyl)cyclopropane-1,1-dicarboxamide (**17d**)*

Yield: 84.7%; m.p.: 116-118 □; MS (ESI) m/z: 541.21 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.09 (s, 1H, CONH), 10.07 (s, 1H, CONH), 9.22 (s, 1H, Ar-NH), 7.87~6.71 (m, 12H, Ar-H), 5.52 (s, 1H, $CH_2N\underline{H}$), 4.20 (s, 2H, $C\underline{H}_2NH$), 3.71 (s, 3H, OCH_3), 1.47 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.14, 30.19, 46.33, 54.67, 107.54, 110.86, 113.42, 115.93, 117.78, 119.05, 120.49, 122.72, 130.39, 131.08, 133.01, 134.47, 149.18, 151.37, 153.14, 155.66, 160.32, 161.44, 165.46, 168.41. HRMS Calcd for $C_{29}H_{25}FN_6O_4$ $[M+H]^+$, 540.1936; found, 541.2109. Purity: > 95%.

*5.10.5. N-(4-((8,9-dimethoxy-6,11-dihydro-5H-benzo[e]pyrimido[5,4-b][1,4]diazepin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**17e**)*

Yield: 88.2%; m.p.: 127-130 □; MS (ESI) m/z: 571.10 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.08 (s, 1H, CONH), 10.07 (s, 1H, CONH), 9.11 (s, 1H, NH), 7.69 (s, 1H, pyrimidine-H), 7.66~6.54 (m, 10H, Ar-H), 5.50 (s, 1H, $CH_2N\underline{H}$), 4.17 (s, 2H, $C\underline{H}_2NH$), 3.97 (s, 6H, 2×CH_3), 1.47 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.46, 31.32, 49.73, 55.52, 56.02, 104.19, 113.08, 115.01, 117.61, 119.82, 121.49, 122.40, 134.94, 135.28, 142.51, 146.48, 148.14, 149.12,

150.52, 156.63, 157.08, 159.46, 168.15. HRMS Calcd for $C_{30}H_{27}FN_6O_5$ $[M+H]^+$, 570.2064; found, 571.1055. Purity: > 95%.

*5.10.6. N-(4-((8,9-dimethoxy-6,11-dihydro-5H-benzo[e]pyrimido[5,4-b][1,4]diazepin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**17f**)*

Yield: 86.3%; m.p.: 132-135 □; MS (ESI) m/z: 589.20 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.27 (s, 1H, CONH), 10.03 (s, 1H, CONH), 9.14 (s, 1H, NH), 7.87 (s, 1H, pyrimidine-H), 7.77~6.55 (m, 9H, Ar-H), 5.57 (s, 1H, $CH_2N\underline{H}$), 4.17 (s, 2H, $C\underline{H}_2NH$), 3.71 (s, 6H, 2×CH_3), 1.41 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.33, 31.69, 49.67, 55.52, 56.01, 104.22, 108.54, 113.05, 114.99, 116.30, 116.81, 119.86, 122.42, 123.95, 134.68, 135.17, 135.51, 142.54, 146.31, 148.13, 150.55, 152.21, 154.63, 156.12, 157.07, 159.46, 168.05. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 588.1924; found, 589.2036. Purity: > 95%.

*5.10.7. N-(4-((8,9-dimethoxy-5,6-dihydrobenzo[f]pyrimido[4,5-b][1,4]oxazepin-4-yl) oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**17g**)*

Yield: 77.2%; m.p.: 114-117 □; MS (ESI) m/z: 572.11 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.10 (s, 1H, CONH), 10.07 (s, 1H, CONH), 7.70 (s, 1H, pyrimidine-H), 7.65~6.87 (m, 10H, Ar-H), 6.10 (s, 1H, $CH_2N\underline{H}$), 4.42 (s, 2H, $C\underline{H}_2NH$), 3.78 (s, 6H, 2×CH_3), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.03, 30.12, 45.13, 52.64, 59.46, 102.15, 113.07, 114.87, 116.92, 119.87, 120.54, 122.47, 132.19, 137.23, 144.58, 146.02, 148.39, 149.82, 150.07, 154.43, 157.28, 159.67, 168.74. HRMS Calcd for $C_{30}H_{26}FN_5O_6$ $[M+H]^+$, 571.1906; found, 572.1163. Purity: > 95%.

*5.10.8. N-(4-((8,9-dimethoxy-6,11-dihydro-5H-benzo[e]pyrido[3,2-b][1,4]diazepin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**17h**)*

Yield: 79.4%; m.p.: 129-131 □; MS (ESI) m/z: 570.21 $[M+H]^+$,^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.11 (s, 1H, CONH), 10.02 (s, 1H, CONH), 8.54 (s, 1H, NH), 7.66~6.56 (m, 12H, Ar-H), 5.36 (s, 1H, $CH_2N\underline{H}$), 4.16 (s, 2H, $C\underline{H}_2NH$), 3.71 (d, J = 12.0 Hz, 6H, 2×CH_3), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.27, 31.83, 49.24, 55.61, 58.94, 101.47, 106.67, 113.22, 115.36, 117.69, 120.80, 121.41, 126.49, 134.96, 137.25, 144.51, 146.48, 148.38, 149.95, 153.57, 156.03, 157.48, 159.21, 168.15. HRMS Calcd for $C_{31}H_{28}FN_5O_5$ $[M+H]^+$, 569.2116; found, 570.2139. Purity: > 95%.

5.10.9. N-(4-((8,9-dimethoxy-6,11-dihydro-5H-benzo[e]pyrido[3,2-b][1,4]diazepin-4-

*yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**17i**)*

Yield: 75.8%; m.p.: 131-134 □; MS (ESI) m/z: 588.14 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.22 (s, 1H, CONH), 10.05 (s, 1H, CONH), 8.53 (s, 1H, NH), 7.72~6.51 (m, 11H, Ar-H), 5.41 (s, 1H, $CH_2N\underline{H}$), 4.16 (d, *J* = 4.0 Hz, 2H, $C\underline{H_2}NH$), 3.71 (d, *J* = 8.0 Hz, 6H, 2×CH_3), 1.45 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.12, 31.49, 47.62, 54.53, 56.06, 101.36, 103.27, 107.55, 113.26, 114.79, 116.08, 116.64, 119.81, 122.72, 126.91, 134.61, 135.52, 138.17, 143.76, 146.39, 148.03, 150.51, 152.40, 154.93, 156.72, 157.77, 163.14, 168.43. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 587.2067; found, 588.1493. Purity: > 95%.

*5.11. General procedure for Preparation of the title compounds **18a-b***

A dried vial was charged with compounds **17e-f** (3.51 mmol) and Cs_2CO_3 (3.43 g, 10.53 mmol) in DMF (15 mL). The resulting suspension was irradiated at 100 □ for 1 h. Upon cooling to room temperature, the mixture was concentrated, and the residue was purified by silica gel chromatography using PE/EA (1:1) to afford the compounds **18a-b**.

*5.11.1. N-(4-((8,9-dimethoxy-11H-benzo[e]pyrimido[5,4-b][1,4]diazepin-4-yl)oxy) phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**18a**)*

White solid; Yield: 34.0%; m.p.: 127-129 □; MS (ESI) m/z: 569.12 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.17 (s, 1H, CONH), 10.11 (s, 1H, CONH), 7.75 (s, 1H), 7.62 (t, *J* = 6.8 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 7.12 (t, *J* = 12.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 6.03 (t, *J* = 4.0 Hz, 2H), 3.73 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.24, 31.66, 54.60, 102.27, 110.58, 114.72, 115.47, 118.33, 121.69, 122.15, 122.97, 134.25, 143.78, 145.26, 146.69, 148.42, 150.43, 154.82, 157.64, 161.76, 166.04. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 568.1933; found, 569.1241. Purity: > 95%.

*5.11.2. N-(4-((8,9-dimethoxy-11H-benzo[e]pyrimido[5,4-b][1,4]diazepin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**18b**)*

White solid; Yield: 32.7%; m.p.: 136-138 □; MS (ESI) m/z: 587.22 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.28 (s, 1H, CONH), 10.02 (s, 1H, CONH), 8.17 (s, 1H), 7.76 (t, *J* = 8.0 Hz, 2H), 7.63 (dd, *J* = 8.0 Hz, 12.0 Hz, 2H), 7.54 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.23~7.12 (m, 4H), 6.70 (s, 1H), 6.44 (s, 1H), 6.70 (s, 1H), 3.69 (d, *J* = 8.0 Hz, 6H, OCH_3), 1.45 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ

15.62, 33.21, 55.25, 102.71, 104.56, 110.71, 112.30, 114.75, 115.02, 118.22, 120.36, 121.47, 122.39, 122.90, 133.55, 134.51, 137.93, 143.73, 145.02, 149.14, 150.39, 152.57, 156.41, 159.62, 162.47, 168.17. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 586.1820; found, 587.2216. Purity: > 95%.

*5.12. General procedure for Preparation of the title compounds **18c-d***

A dried vial was charged with compounds **17h-i** (3.51 mmol) and Cs_2CO_3 (3.43 g, 10.53 mmol) in DMF (15 mL). The resulting suspension was irradiated at 100 □ for 1 h. Upon cooling to room temperature, the mixture was concentrated, then the residue was purified by silica gel chromatography using PE/EA (3:1) to afford the compounds **18c-d**.

*5.12.1. N-(4-((8,9-dimethoxy-11H-benzo[e]pyrido[3,2-b][1,4]diazepin-4-yl)oxy) phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**18c**)*

Brown solid; Yield: 27.0%; m.p.: 134-137 □; MS (ESI) m/z: 567.98 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.11 (s, 1H, CONH), 10.01 (s, 1H, CONH), 7.73 (s, 1H), 7.64 (t, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 7.15 (t, *J* = 12.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.70 (s, 1H), 6.26 (t, *J* = 4.0 Hz, 2H), 3.72 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 1.45 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.41, 31.28, 55.64, 103.22, 110.72, 114.99, 115.41, 118.02, 120.77, 121.62, 122.31, 122.95, 134.88, 143.90, 145.07, 146.11, 150.44, 152.69, 154.43, 159.66, 163.71, 168.07. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 587.2067; found, 568.1989. Purity: > 95%.

*5.12.2. N-(4-((8,9-dimethoxy-11H-benzo[e]pyrido[3,2-b][1,4]diazepin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**18d**)*

Brown solid; Yield: 24.7%; m.p.: 139-142 □; MS (ESI) m/z: 585.94 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.29 (s, 1H, CONH), 10.04 (s, 1H, CONH), 7.76 (s, 1H), 7.63 (t, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.41 (s, 1H), 7.18 (t, *J* = 10.0 Hz, 2H), 6.94 (s, 1H), 6.74 (s, 1H), 6.52 (d, *J* = 4.0 Hz, 2H), 3.76 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.37, 31.22, 54.63, 101.29, 103.20, 104.55, 105.32, 107.81, 111.76, 114.39, 115.26, 119.01, 120.31, 121.68, 122.39, 122.62, 134.82, 140.62, 143.91, 145.24, 146.17, 150.43, 153.67, 155.02, 159.61, 165.78, 167.22. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 585.1861; found, 585.9426. Purity: > 95%.

5.13. Preparation of methyl

*6-((6-chloro-5-nitropyrimidin-4-yl)amino)-2,3-dimethoxybenzoate (**19**)*

A mixture of 4,6-dichloro-5-nitropyrimidine (3.0 g, 15.55 mmol), methyl 6-amino-2,3-dimethoxybenzoate (3.94 g, 18.66 mmol) and K_2CO_3 (6.44 g, 46.65 mmol) in DMF (20 mL) was heated at 60 □ for 8 h. Upon cooling to room temperature, the reaction mixture was added water (100 mL), and filtered off to get the crude product, which was purified by silica gel chromatography using PE/EA (10:1) to afford the intermediate **19** as a yellow solid (4.98 g, 87%). MS (ESI) m/z: 368.94 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.91 (s, 1H), 8.57 (s, 1H), 7.72 (s, 1H), 7.43 (s, 1H), 3.82 (t, J = 8.0 Hz, 9H).

*5.14. General procedure for Preparation of the intermediates **20a-b***

A mixture of **19** (2.0 g, 5.43 mmol), **10a-b** (4.53 mmol) and K_2CO_3 (1.88 g, 13.59 mmol) in DMF (15 mL) was heated at 50 □ for 13 h. Upon cooling to room temperature, the reaction mixture was added water (100 mL), and extracted by EA (15 mL×3). The organic phase was combined and concentrated to get the crude product, which was purified by silica gel chromatography using PE/EA (5:1) to afford the intermediates **20a-b** as a pale-yellow solid.

*5.14.1. Methyl6-((6-(4-(1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxamido) phenoxy)-5-nitropyrimidin-4-yl)amino)-2,3-dimethoxybenzoate (**20a**)*

Pale-yellow solid; Yield: 84.0%; MS (ESI) m/z: 647.11 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.92 (s, 1H), 10.17 (t, J = 8.6 Hz, 2H), 8.59 (s, 1H), 7.77 (s, 1H), 7.44 (s, 1H), 7.29~7.12 (m, 4H), 7.02~6.84 (m, 4H), 3.88 (t, J = 8.6 Hz, 9H), 1.45 (s, 4H).

*5.14.2. Methyl6-((6-(2-fluoro-4-(1-((4-fluorophenyl)carbamoyl)cyclopropane carboxamido)phenoxy)-5-nitropyrimidin-4-yl)amino)-2,3-dimethoxybenzoate (**20b**)*

Pale-yellow solid; Yield: 82.7%; MS (ESI) m/z: 665.19 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.90 (s, 1H), 10.16 (t, J = 6.8 Hz, 2H), 8.54 (s, 1H), 7.71 (s, 1H), 7.42 (s, 1H), 7.19~7.11 (m, 4H), 6.97~6.81 (m, 4H), 3.83 (t, J = 6.8 Hz, 9H), 1.44 (s, 4H).

*5.15. General procedure for Preparation of the title compounds (**21a-b**)*

A mixture of **20a-b** (4.64 mmol) and iron dust (1.30 g, 23.20 mmol) in AcOH (40 mL) was heated at 110 □ for 12 h. Upon cooling to room temperature, the reaction mixture was filtered off and the filtrate was concentrated to obtain the crude product, which was purified by stirred with ethanol (20 mL) at 80 □ for 1 h giving the

title compounds **21a-b**.

*5.15.1. N-(4-((8,9-dimethoxy-6-oxo-6,11-dihydro-5H-benzo[e]pyrimido[5,4-b][1,4] diazepin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**21a**)*

Pale-white solid; Yield: 64.0%; m.p.: 252-254 □; MS (ESI) m/z: 585.19 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.10 (s, 1H, CONH), 10.04 (s, 1H, CONH), 8.85 (s, 1H, CONH), 7.65~7.55 (m, 5H), 7.20~7.05 (m, 5H), 5.65 (s, 2H), 3.97 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 1.45 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.21, 30.34, 55.87, 56.73, 102.61, 106.09, 108.34, 114.03, 117.47, 124.41, 129.02, 133.07, 136.11, 142.75, 144.93, 149.24, 151.82, 154.48, 156.26, 157.47, 162.63, 168.72. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 584.1867; found, 585.1936. Purity: > 95%.

*5.15.2. N-(4-((8,9-dimethoxy-6-oxo-6,11-dihydro-5H-benzo[e]pyrimido[5,4-b][1,4] diazepin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**21b**)*

Pale-white solid; Yield: 61.0%; m.p.: 257-259 □; MS (ESI) m/z: 602.98 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.24 (s, 1H, CONH), 10.02 (s, 1H, CONH), 8.80 (s, 1H, CONH), 7.77 (dd, *J* = 2.4 Hz, 13.2 Hz, 1H), 7.65~7.62 (m, 2H), 7.50 (s, 1H), 7.38 (dd, *J* = 1.2 Hz, 9.2 Hz, 1H), 7.22 (t, *J* = 8.8 Hz, 1H), 7.17~7.12 (m, 3H), 5.67 (s, 2H), 3.96 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.37, 31.66, 55.93, 56.06, 105.01, 106.70, 108.63, 108.89, 115.01, 116.41, 120.33, 122.43, 122.58, 127.86, 135.17, 136.39, 136.71, 141.02, 141.72, 144.89, 147.88, 151.83, 154.26, 156.35, 157.01, 159.48, 168.08. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 602.1743; found, 602.9826. Purity: > 95%.

*5.16. Preparation of methyl 6-((4-chloro-3-nitropyridin-2-yl)amino)-2,3-dimethoxybenzoate (**22**)*

A solution of 4,6-dichloro-5-nitropyridine (4.0 g, 0.02 mol), methyl 6-amino-2,3-dimethoxybenzoate (5.07 g, 0.024 mol) and KF.2H_2O (5.65 g，0.06 mol) in DMF (25 mL) was heated at 130 ℃ for 9 h. Upon cooling to room temperature, the reaction solution was added water (100 mL), and filtered off to get the crude product, which was purified by silica gel chromatography using PE/EA (5:1) to afford the intermediate **22** as a yellow solid (2.94 g, 40%). MS (ESI) m/z: 367.95 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.91 (s, 1H), 8.57 (d, *J* = 6.4 Hz, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.85 (s, 1H), 7.47 (s, 1H), 3.86 (t, *J* = 8.8 Hz, 9H).

*5.17. General procedure for Preparation of the intermediates **23a-b***

A solution of **22** (3.0 g, 8.17 mmol), **10a-b** (9.80 mmol) and KF.2H_2O (2.31 g, 24.51 mmol) in DMF (20 mL) was heated at 140 ℃ for 15 h. Upon cooling to room temperature, water (100 mL) was added to the reaction solution. The precipitate was collected by filtration, stirred with ethanol (20 mL) at 80 ℃for 1 h, and filtered to get the crude product, which was purified by silica gel chromatography using PE/EA (3:2) to afford the intermediates **23a-b** as yellow solids.

*5.17.1. Methyl6-((4-(4-(1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxamido) phenoxy)-3-nitropyridin-2-yl)amino)-2,3-dimethoxybenzoate (**23a**)*

Yellow solid; Yield: 76.0%; MS (ESI) m/z: 646.20 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.94 (s, 1H), 10.12 (t, *J* = 8.6 Hz, 2H), 8.56 (d, *J* = 6.8 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.82 (s, 1H), 7.62 (s, 1H), 7.27~7.14 (m, 4H), 7.07~6.82 (m, 4H), 3.84 (t, *J* = 8.8 Hz, 9H), 1.44 (s, 4H).

*5.17.2. Methyl6-((4-(2-fluoro-4-(1-((4-fluorophenyl)carbamoyl)cyclopropanecarbox amido)phenoxy)-3-nitropyridin-2-yl)amino)-2,3-dimethoxybenzoate (**23b**)*

Yellow solid; Yield: 74.8%; MS (ESI) m/z: 664.14 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.92 (s, 1H), 10.14 (t, *J* = 8.0 Hz, 2H), 8.51 (d, *J* = 6.4 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.79 (s, 1H), 7.67 (s, 1H), 7.21~7.12 (m, 3H), 7.06~6.87 (m, 4H), 3.85 (t, *J* = 6.8 Hz, 9H), 1.44 (s, 4H).

*5.18. General procedure for Preparation of the title compounds (**24a-b**)*

A mixture of **23a-b** (3.10 mmol) and iron dust (0.87 g, 15.50 mmol) in AcOH (35 mL) was heated at 110 ℃ for 12 h. Upon cooling to room temperature, the reaction mixture was filtered off and the filtrate was concentrated to obtain the crude product, which was purified by stirred with ethanol (20 mL) at 80 ℃ for 1 h giving the title compounds **24a-b** as white solids.

*5.18.1. N-(4-((8,9-dimethoxy-6-oxo-6,11-dihydro-5H-benzo[e]pyrido[3,2-b][1,4] diazepin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**24a**)*

Yellow solid; Yield: 60.0%; m.p.: 241-244 ℃; MS (ESI) m/z: 583.91 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.11 (s, 1H, CONH), 10.08 (s, 1H, CONH), 8.95 (s, 1H, CONH), 8.32 (s, 1H, NH), 7.64~7.55 (m, 5H, Ar-H), 7.22~6.88 (m, 5H, Ar-H), 6.67~6.62 (m, 2H, Ar-H), 3.80 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.61, 32.17, 53.66, 58.06, 102.33, 104.58, 106.27, 108.64, 115.06, 120.40, 123.12, 126.55, 134.16, 136.19, 142.55, 146.39, 148.21,

151.25, 155.47, 156.19, 160.22, 162.37, 167.53. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 583.1975; found, 583.9168. Purity: > 95%.

*5.18.2. N-(4-((8,9-dimethoxy-6-oxo-6,11-dihydro-5H-benzo[e]pyrido[3,2-b][1,4] diazepin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**24b**)*

Yellow solid; Yield: 64.0%; m.p.: 243-245 □; MS (ESI) m/z: 602.19 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.16 (s, 1H, CONH), 10.02 (s, 1H, CONH), 8.91 (s, 1H, CONH), 8.54 (s, 1H, NH), 7.63~7.49 (m, 4H, Ar-H), 7.20~6.78 (m, 5H, Ar-H), 6.62~6.57 (m, 2H, Ar-H), 3.86 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 1.45 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.22, 30.63, 54.91, 56.74, 102.61, 104.16, 106.73, 108.66, 109.34, 112.07, 116.48, 120.19, 122.52, 124.35, 127.82, 133.11, 136.26, 136.88, 141.01, 142.79, 144.89, 147.52, 150.82, 154.64, 156.40, 157.36, 159.42, 167.04. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 601.1821; found, 602.1907. Purity: > 95%.

*5.19. General procedure for Preparation of the title compounds (**25a-b**)*

17e-f (1.0 mmol) was added drop-wise to HCOOH (2.5 mL) at 10-15 □, and then 37% aq. HCHO (0.25 mL) was added. The solution was heated at 90 □ for 2 h. Upon cooling to room temperature, the reaction solution was added to 20 mL saturated aq. $NaHCO_3$, and extracted by EA (15 mL×3). The organic phase was combined and concentrated to get the crude product, which was purified by silica gel chromatography using PE/EA (1:1 to 2:3, to 1:2) to afford the target compounds **25a-b** as white solids.

*5.19.1. N-(4-((8,9-dimethoxy-5-methyl-6,11-dihydro-5H-benzo[e]pyrimido[5,4-b]-[1, 4]diazepin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**25a**)*

White solid; Yield: 40.0%; m.p.: 247-249 □; MS (ESI) m/z: 585.13 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.09 (s, 1H, CONH), 10.07 (s, 1H, CONH), 9.29 (s, 1H, NH), 7.87~6.83 (m, 11H, Ar-H), 3.98 (s, 2H, CH_2), 3.72 (d, J = 4.8 Hz, 6H, CH_3), 2.55 (s, 3H, NCH_3),1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.72, 31.39, 54.48, 55.11, 56.83, 104.09, 112.01, 114.32, 116.17, 119.82, 121.40, 123.34, 131.07, 135.33, 137.29, 147.31, 151.44, 153.45, 157.36, 159.13, 164.07, 167.01. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 584.2214; found, 585.1316. Purity: > 95%.

*5.19.2. N-(4-((8,9-dimethoxy-5-methyl-6,11-dihydro-5H-benzo[e]pyrimido[5,4-b]-[1, 4]diazepin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**25b**)*

White solid; Yield: 44.0%; m.p.: 251-253 □; MS (ESI) m/z: 603.21 $[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δppm: 10.27 (s, 1H, CONH), 10.04 (s, 1H, CONH), 9.36 (s, 1H, NH), 7.86~6.84 (m, 10H, Ar-H), 4.00 (s, 2H, CH_2), 3.72 (d, J = 6.0 Hz, 6H, CH_3), 2.56 (s, 3H, NCH_3),1.46 (s, 4H, CH_2CH_2). ^{13}C NMR (100MHz, DMSO-d_6): δ 15.35, 31.68, 55.50, 55.89, 56.35, 104.45, 108.51, 113.94, 114.99, 116.27, 116.30, 119.93, 122.43, 123.85, 134.57, 135.17, 135.61, 137.08, 148.35, 151.42, 152.13, 154.55, 157.08, 158.57, 159.47, 162.91, 168.04. HRMS Calcd for $C_{30}H_{26}F_2N_6O_5$ $[M+H]^+$, 602.2089; found, 603.2164. Purity: > 95%.

5.20. c-Met kinase assay

The effects of indicated compounds on the activities of c-Met kinase determined using enzyme-linked immunosorbent (ELISAs) with purified recombinant proteins [47]. Briefly, 20 μg/mL poly $(Glu, Tyr)_{4:1}$ (Sigma, St. Louis, MO, USA) was pre-coated in 96-well plates as a substrate. A 50-μL aliquot of 10 μg/mL ATP solution diluted in kinase reaction buffer (50 mmol/L HEPES [pH 7.4], 50 mmol/L $MgCl_2$, 0.5 mmol/L $MnCl_2$, 0.2 mmol/L Na_3VO_4, and 1 mmol/L DTT) was added to each well; 1 μL of various concentrations of indicated compound diluted in 1% DMSO (*v/v*) (sigma) were then added to each reaction well. DMSO (1%, *v/v*) was used as the negative control. The kinase reaction was initiated by the addition of purified c-Met tyrosine kinase proteins diluted in 49 μL of kinase reaction buffer. After incubation for 60 min at 37 □, the plate was washed three times with phosphate-buffered saline (PBS) containing 0.1% Tween 20 (T-PBS). Anti-phosphotyrosine (PY99) antibody (100μL; 1:500, diluted in 5 mg/mL BSA T-PBS) was then added. After a 30-min incubation at 37 □, the plate was washed three times, and 100 μL horseradish peroxidase-conjugated goat anti-mouse IgG (1:2000, diluted in 5 mg/mL BSA T-PBS) was added. The plate was then incubated at 37 ℃ for 30 min and washed 3 times. A 100-μL aliquot of a solution containing 0.03% H_2O_2 and 2 mg/mL *o*-phenylenediamine in 0.1 mol/L citrate buffer (pH 5.5) was added. The reaction was terminated by the addition of 50 μL of 2 mol/L H_2SO_4 as the color changed, and the plate was analyzed using a multi-well spectrophotometer (SpectraMA 190, Molecular Devices, Sunnyvale, CA, USA) at 490 nm. The inhibition rate (%) was calculated

using the following equation: [1-(A490/A490 control)] × 100%. The IC50 values were calculated from the inhibition curves in two separate experiments.

5.21. Cell Proliferation Assay

Cells were essded in 96-well tissue culture plates. On the next day, the cells were exposed to various concentrations of compounds and further cultured for 72 h. Cell proliferation was then determined using sulforhodamine B (SRB, Sigma, St. Louis, MO, USA). The IC_{50} values were calculated by concentration-response curve fitting using the four-parameter method [47].

5.22. Pharmacokinetic study

Male SD rats (SLRC laboratory Animal Inc., Shanghai, China) were used. For intravenous administration, prepared dosing solution was injected via the femoral vein. The rats were fasted overnight before drug administration and until 6 h after dosing. For the PO experiment, rats (24 in each group) were given a single dose of 20 mg/kg, and heparinized samples of blood were collected at 5, 15, 30 min, 1, 2, 4, 8, and 24 h postdose. For the *iv* experiment, rats (24 in each group) were given a single 4 mg/kg dose, and blood samples were collected at 5, 15, 30 min, 1, 2, and 4 h postdose. Plasma was harvested after centrifugation and stored frozen at -40 □ until analyzed. The concentrations of compounds in plasma were determined by LC/MS/MS (Shimadzu LC-30AD). The results are shown as the maximum plasma concentration (C_{max}), the time to reach peak plasma concentration (T_{max}), terminal half-life ($T_{1/2}$), and the area under the plasma concentration-time curve from zero to time infinity ($AUC_{0\text{-}inf}$) [48].

5.23. 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 with ten mice each (five males, five females). Mice were orally given **17f** with a single dose 420, 520, 620, 720, 820 and 920 mg/kg, or vehicle conrol, respectively. The mouse death was monitored daily, and recored up to 14 days after treatment. All animals were euthanized and necropsied for gross lesion examination for possible damage to the heart, liver, and kidneys [49].

5.24. Compound activity on hERG

Whole-cell recordings were performed using automated Qpatch (Sophion). Cells were voltage clamped at a holding potential of -80 mV. The hERG current was

activated by depolarizing at +20 mV for 5 sec, after which the voltage was taken back to -50 mV for 5 sec to remove the inactivation and observe the deactivating hERG tail current. The voltage stimulation was applied per 15 sec. Compounds solutions were administrated from low to high concentration, 2 min for each concentration and 10 μM cisapride was applied at the end of perfusion of compound solution. Each concentration was tested [50].

on at least 3 cells.

5.25. In vivo antitumor activity assay

Female nude mice (4-6 weeks old) were housed and maintained under specific-pathogen free conditions. Animal procedures were performed according to institutional ethical guidelines of animal care [51]. The Caki-1 cells at a density of 5×10^6 in 200 μL were injected s.c. into the right flank of nude mice and then allowed to grow to 700-800 mm^3, defined as a well-developed tumor. After that, the well-developed tumors were cut into 1 mm^3 fragments and transplanted s.c. into the right flank of nude mice using a trocar. When the mean tumour volume reached 120-130 mm^3, the mice were randomly assigned into vehicle and treatment groups (n = 6 in treated group, n = 12 in vehicle group). Vehicle groups were given vehicle alone, and treatment groups received **17f** as indicated doses via intraperitoneal injection once daily for 3 weeks in Caki-1 model. The sizes of the tumours were measured twice per week using microcaliper. The tumour volume (V) was calculated as follows: V = [length (mm) × $width^2$ (mm^2)]/2. Percent (%) inhibition values (TGI) were measured on the final day of study for drugtreated compared with vehicle-treated mice and were calculated as 100% × (1- (($treated^{final\ day}$ – $treated^{day\ 0}$)/$control^{final\ day}$ – $control^{day\ 0}$))).

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SUPPLEMENTARY MATERIAL

MS spectra, ^1H NMR, ^{13}C NMR and HRMS spectra of compounds **17e**, **17f** and

25b; Means of tumor weight during experiment; Means of body weight of rats during experiment.

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Legends:

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

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

Fig.3. The docking mode of Cabozantinib with c-Met protein.

Fig.4. Design strategy of the target compounds.

Fig.5. Inhibitory activity of compound **17f** on tumor growth in Caki-1 xenograft.

Scheme 1. Reagents and conditions: (a) $SOCl_2$, TEA/THF, N_2, 0 □, 2 h; (b) EDC.HCl/DMF, r.t., 3 h; (c) 10%Pd/C/H_2, EA, r.t., 4 h; (d) DMF/K_2CO_3, 60 □, overnight; (e) DMF/$MgSO_4$/Conc.HCl, 95 □, overnight.

Scheme 2. Reagents and conditions: (a) DMF/K_2CO_3, 60 □, 8 h; (b) DMF/K_2CO_3, 50 □, 13 h; (c) 10%Pd/C/H_2, EA, r.t., overnight; (d) $(HCHO)_n$/TFA/$MgSO_4$/DCM, 40 □, 12 h.

Scheme 3. Reagents and conditions: Cs_2CO_3/DMF, M.W., 60 w, 100 □, 1 h.

Scheme 4. Reagents and conditions: (a) DMF/K_2CO_3, 60 □, 8 h; (b) DMF/K_2CO_3, 50 □, 13 h; (c) Fe/AcOH, 110 □, 12 h.

Scheme 5. Reagents and conditions: (a) DMF/KF.$2H_2O$, 130 □, 9 h; (b) DMF/ KF.$2H_2O$, 140 □, 15 h; (c) Fe/AcOH, 110 □, 12 h.

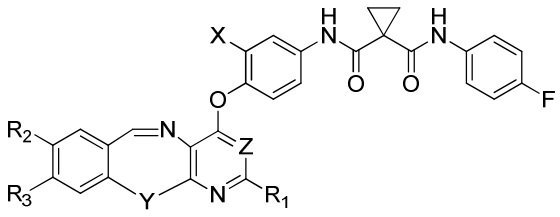
Scheme 6. Reagents and conditions: 37%HCHO, HCOOH, 90 □, 2 h.

Table 1. Structures and inhibitory activities against c-Met kinase of compound **13a-c**, **18a-d**, and Cabozantinib *in vitro*.

Table 2. Structures and inhibitory activities against c-Met kinase of compound **17a-i**, and Cabozantinib *in vitro*.

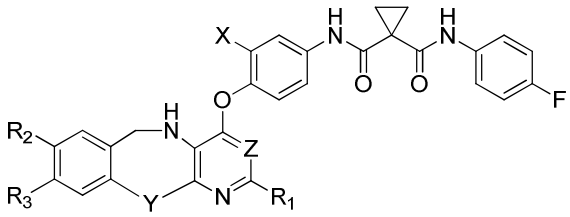
Table 3. Structures and inhibitory activities against c-Met kinase of compound **21a-b**, **24a-b**, and Cabozantinib *in vitro*.

Table 1. Structures and inhibitory activities against c-Met kinase of compound **13a-c**, **18a-d**, and Cabozantinib *in vitro*.



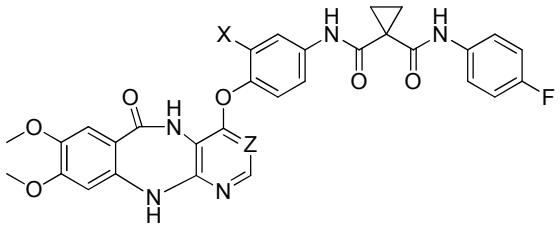
Compd.	R_1	R_2	R_3	X	Y	Z	c-Met IC_{50} (nM) Mean±SD
13a	Me	H	H	H	O	N	>1000
13b	H	H	H	H	O	N	>1000
13c	H	OMe	OMe	H	O	N	>1000
18a	H	OMe	OMe	H	NH	N	136±21.4
18b	H	OMe	OMe	F	NH	N	49.7±10.3
18c	H	OMe	OMe	H	NH	C	>1000
18d	H	OMe	OMe	F	NH	C	>1000
Cabozantinib							5.3±0.3

Table 2. Structures and inhibitory activities against c-Met kinase of compound **17a-i**, and Cabozantinib *in vitro*.



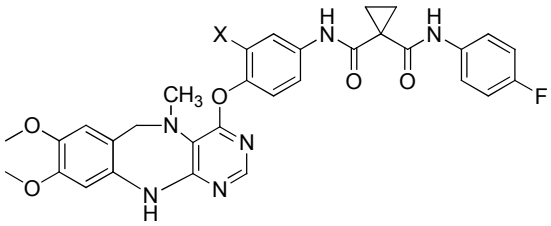
Compd.	R_1	R_2	R_3	X	Y	Z	c-Met IC_{50} (nM)
17a	Me	H	H	H	O	N	>1000
17b	Me	OMe	H	H	NH	N	>1000
17c	H	H	H	H	O	N	>1000
17d	H	OMe	H	H	NH	N	168.7±24.7
17e	H	OMe	OMe	H	NH	N	29.3±4.7
17f	H	OMe	OMe	F	NH	N	24.4±2.9
17g	H	OMe	OMe	H	O	N	2322±136.1
17h	H	OMe	OMe	H	NH	C	>1000
17i	H	OMe	OMe	F	NH	C	>1000
Cabozantinib							5.3±0.3

Table 3. Structures and inhibitory activities against c-Met kinase of compound **21a-b**, **24a-b**, and Cabozantinib *in vitro*.



Compd.	X	Z	c-Met IC_{50} (nM)
21a	H	N	>1000
21b	F	N	>1000
24a	H	C	>1000
24b	F	C	>1000
Cabozantinib			5.3±0.3

Table 4. Structures and inhibitory activities against c-Met kinase of compound **25a-b** and Cabozantinib *in vitro*.



Compd.	X	c-Met IC_{50} (nM)
25a	H	>1000
25b	F	>1000
Cabozantinib		5.3±0.3

Table 5. Cytotoxic activities of compounds **17e-f**, **18a-b** against PC-3, Panc-1, Capan-1 and Caki-1 cell lines *in vitro*.

Compd.	IC_{50} (nM) Mean±SD			
	PC-3	Panc-1	HepG2	Caki-1
17e	7125±76	5343±466	4914±141	1471±125
17f	4098±488	1858±123	2946±107	748±27
18a	1424±161	2719±114	2071±108	1482±47
18b	1609±88	1655±31	1342±11	864±7
Cabozantinib	11840±1415	12658±994	8483±147	4318±122

Table 6. Inhibition of other tyrosine kinases by compound **17f**.

Kinase	IC_{50} (nM) Mean±SD
VEGFR-2	62.5±1.5
EGFR	267.6±60.7
RET	162.8±71.5
c-kit	258.7±88.2
Flt-3	851.8±188.3

Table 7. Acute toxicity of compound **17f**

Dose (mg/Kg)	Mice (N)	Deaths (N)	Survival on day 14 (%)
920	10	6	40
820	10	4	60
720	10	2	80
620	10	0	100
520	10	0	100
420	10	0	100
vechicle	10	0	100

Table 8. Activity on hERG potassium currents of compound **17f**

Compound	IC_{50} (μM)
17f	>40
Cabozantinib	>40

Table 9. Pharmacokinetic parameters of compound **17f**.

Dose (mg/Kg)	$AUC_{(0-t)}$ (ngh/mL)	$AUC_{(0-\infty)}$ (ngh/mL)	$MRT_{(0-t)}$ (h)	$V_{Z/F}$ (L/Kg)	$CL_{Z/F}$ (L/h/Kg)	$T_{1/2Z}$ (h)	T_{max} (h)	C_{max} (ng/mL)	*F* (%)
20 (po)	6991.6	7079.5	2.36	4.52	2.93	1.09	1.67	1934.2	39
4 (iv)	3585.5	3592.3	1.00	1.48	1.14	0.91		4656.0	

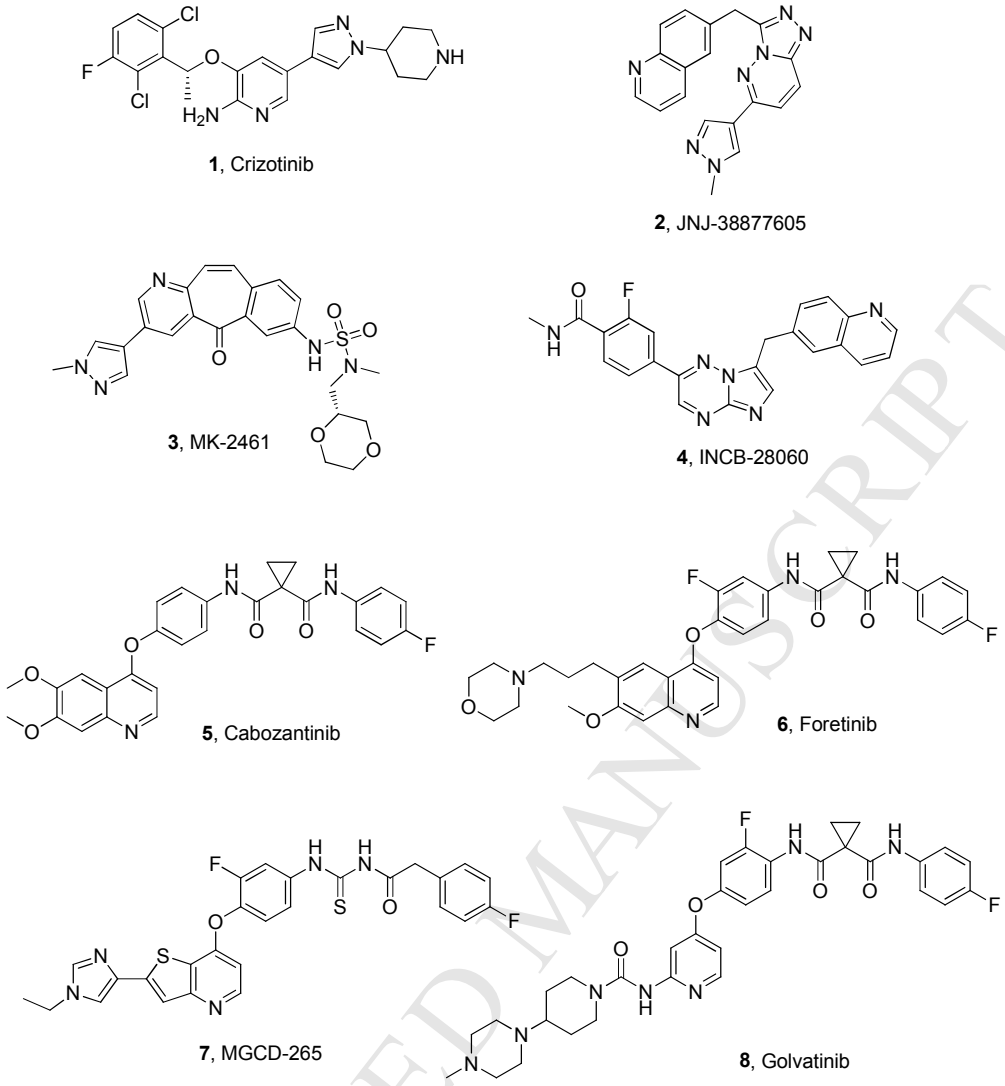


Fig.1. The representative small-molecule c-Met kinase inhibitors.

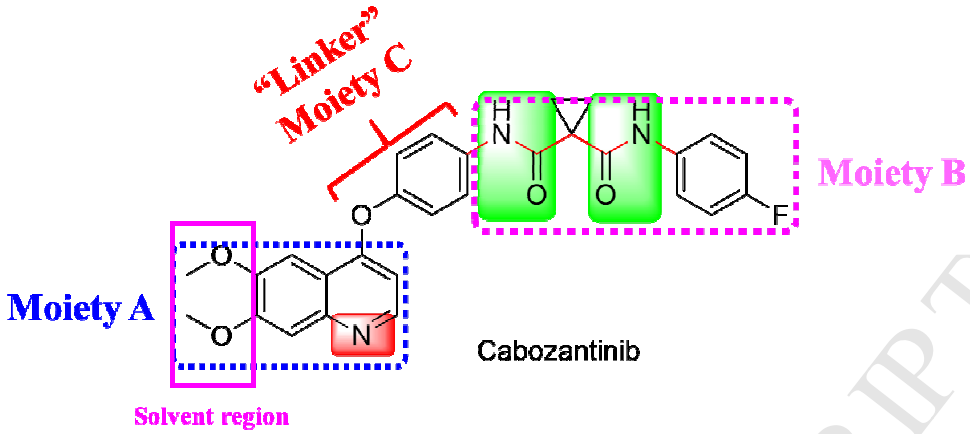


Fig.2. The structure features of type □ inhibitor Cabozantinib.

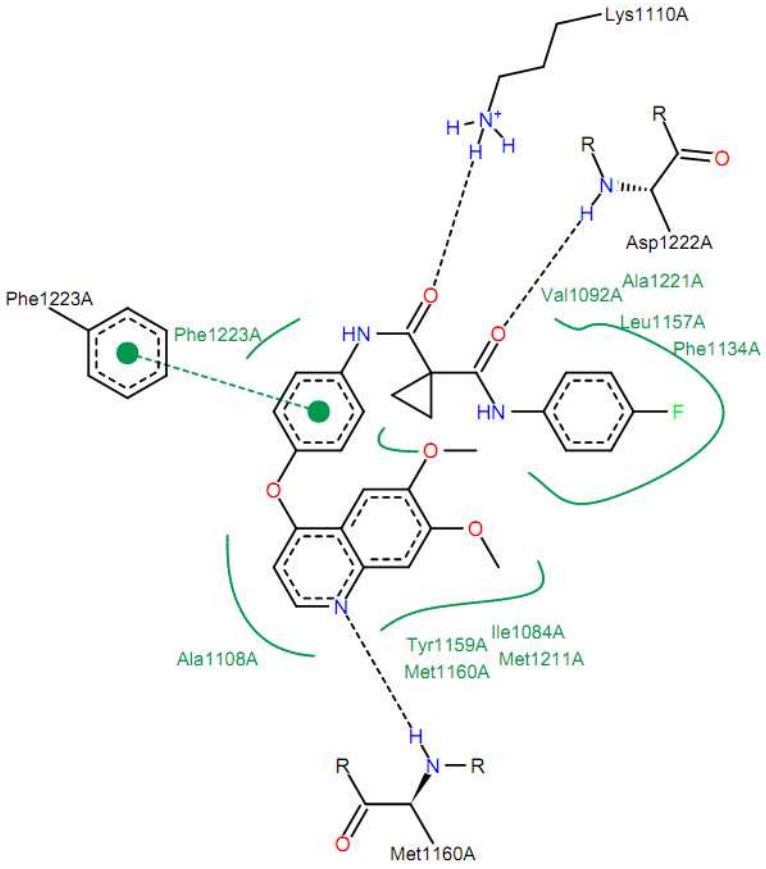


Fig.3. The docking mode of Cabozantinib with c-Met protein.

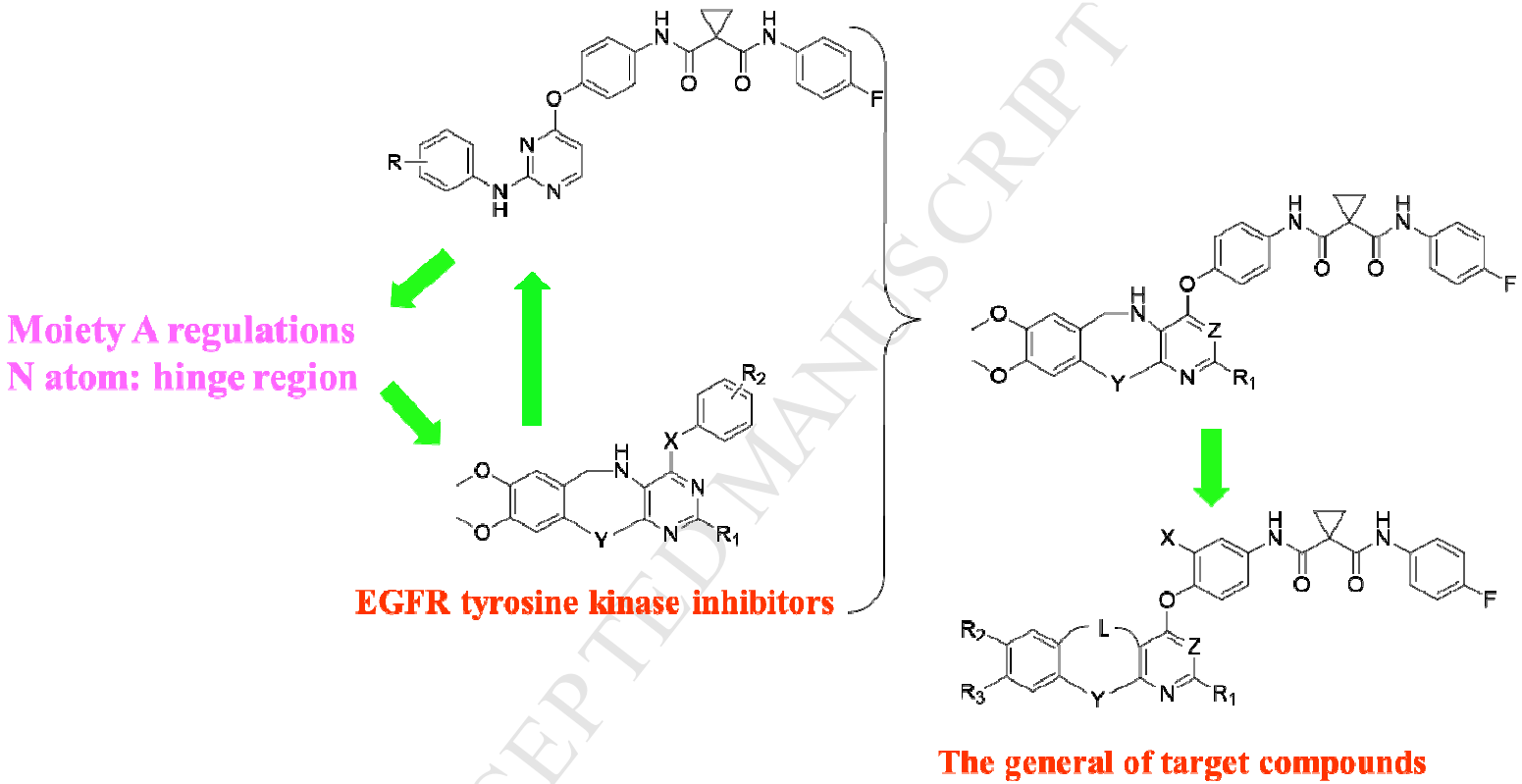


Fig.4. Design strategy of the target compounds.

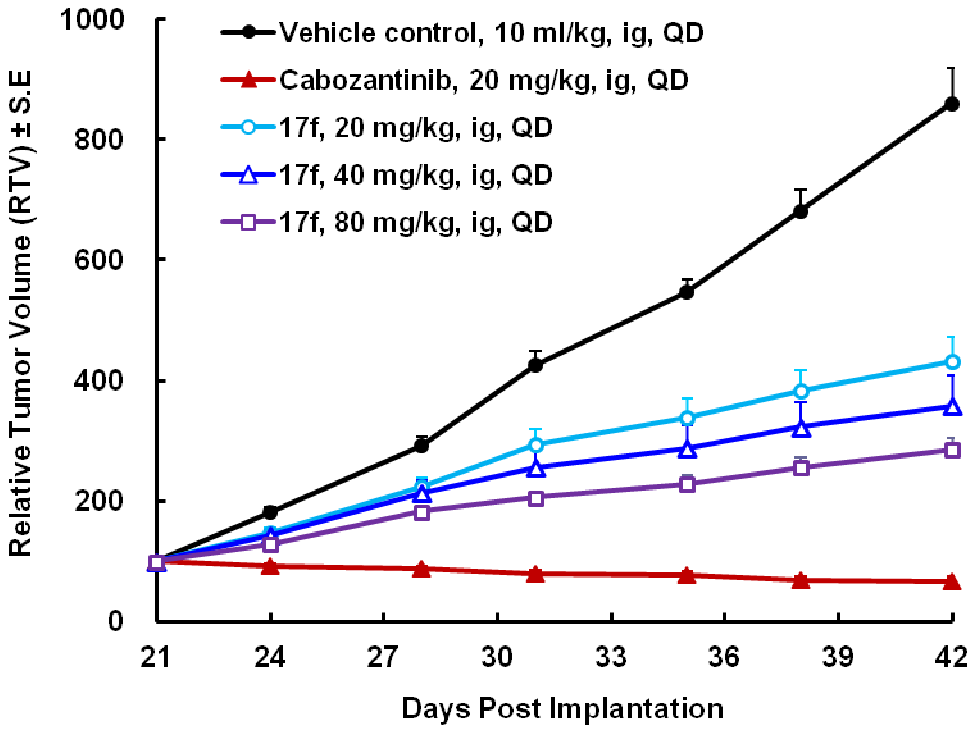
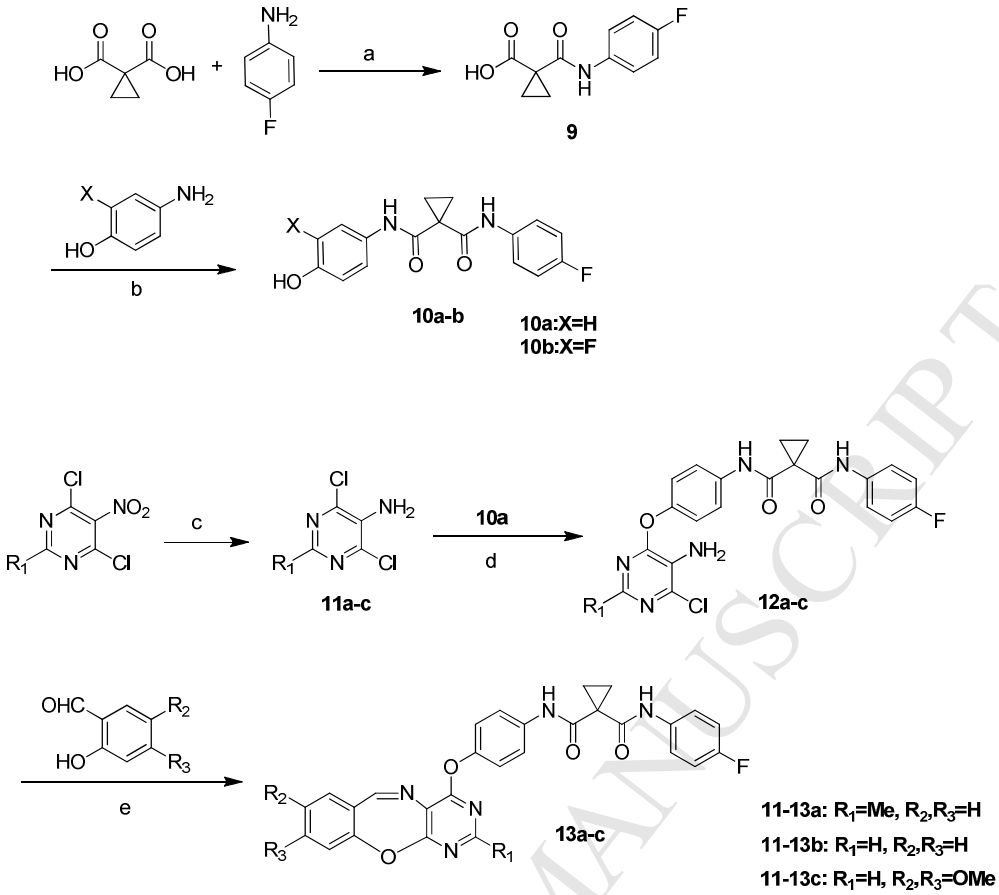
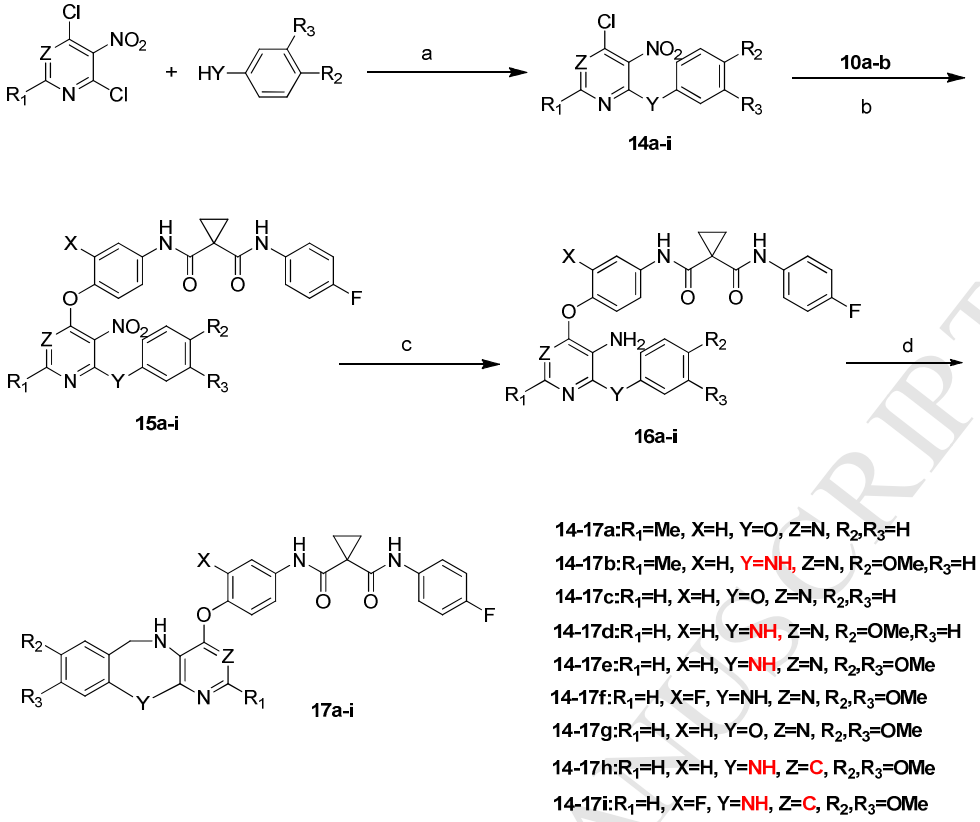


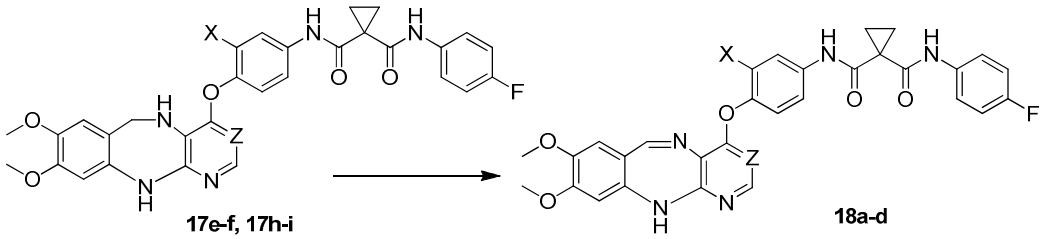
Fig.5. Inhibitory activity of compound **17f** on tumor growth in Caki-1 xenograft. **17f** was administrated to tumour-bearing mice once daily for 21d. Mean relative tumor volume ± SD are shown (n = 6 in treated group, n = 12 in vehicle group). *p < 0.01, ***p < 0.001 vs vehicle group, determined using Student's t test.



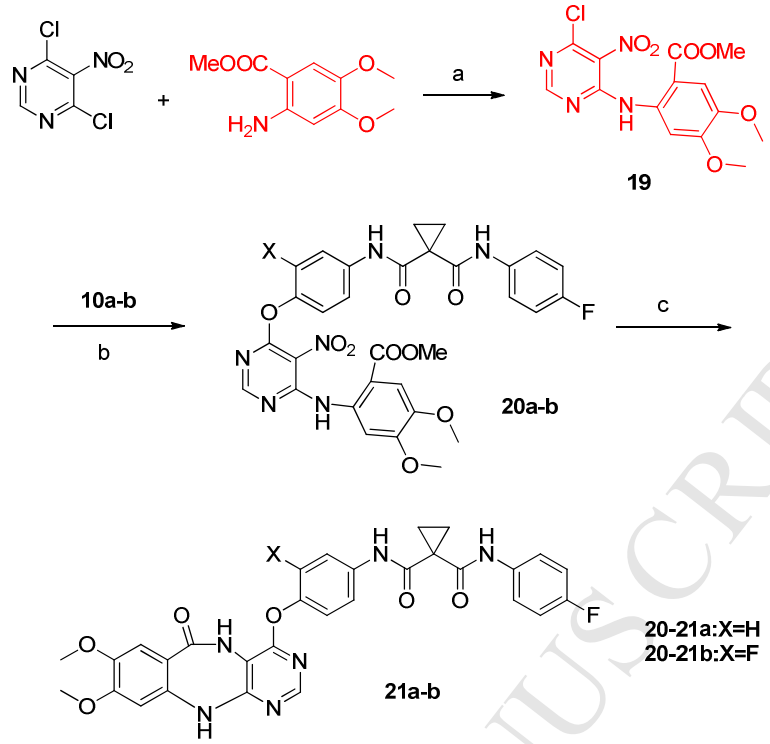
Scheme 1. Reagents and conditions: (a) $SOCl_2$, TEA/THF, N_2, 0 □, 2 h; (b) EDC.HCl/DMF, r.t., 3 h; (c) 10%Pd/C/H_2, EA, r.t., 4 h; (d) DMF/K_2CO_3, 60 □, overnight; (e) DMF/ $MgSO_4$/Conc.HCl, 95 □, overnight.



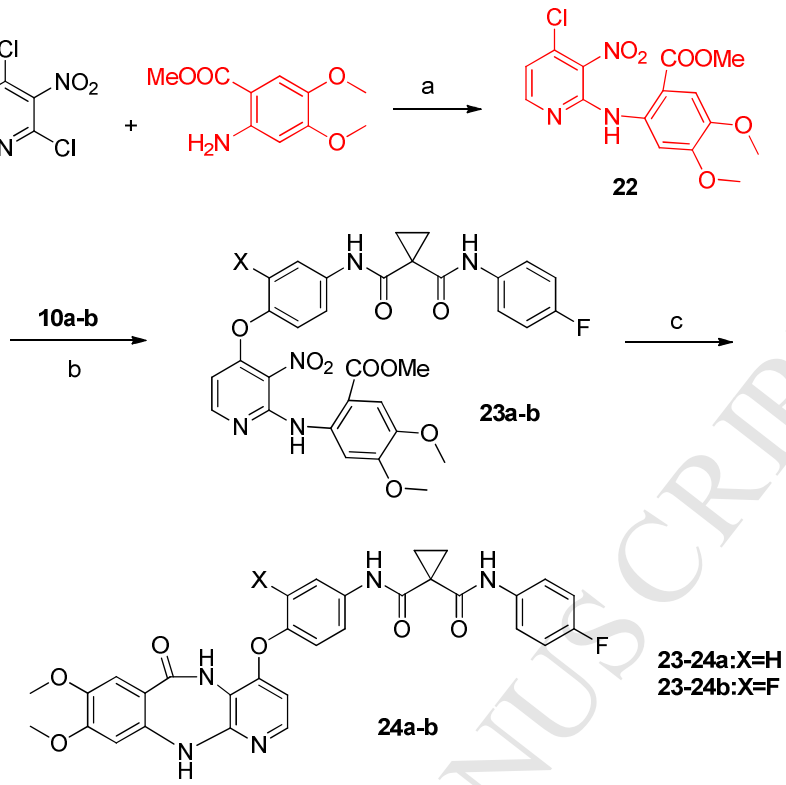
Scheme 2. Reagents and conditions: (a) DMF/K_2CO_3, 60 □, 8 h; (b) DMF/K_2CO_3, 50 □, 13 h; (c) 10%Pd/C/H_2, EA, r.t., overnight; (d) $(HCHO)_n$/TFA/$MgSO_4$/DCM, 40 □, 12 h.



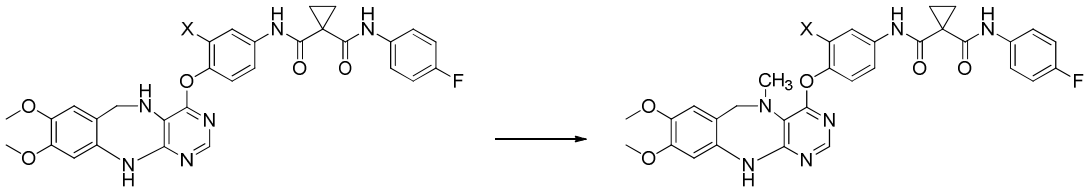
Scheme 3. Reagents and conditions: Cs_2CO_3/DMF, M.W., 60 w, 100 □, 1 h.



Scheme 4. Reagents and conditions: (a) DMF/K_2CO_3, 60 □, 8 h; (b) DMF/K_2CO_3, 50 □, 13 h; (c) Fe/AcOH, 110 □, 12 h.



Scheme 5. Reagents and conditions: (a) DMF/KF.2H_2O, 130 □, 9 h; (b) DMF/ KF.2H_2O, 140 □, 15 h; (c) Fe/AcOH, 110 □, 12 h.



Scheme 6. Reagents and conditions: 37%HCHO, HCOOH, 90 □, 2 h.

Highlights

- A series of diazepine derivatives were designed and synthesized.
- Target compounds were tested for *in vitro* activities.
- **17f** displayed desirable pharmacokinetic properties, and acceptable safety profile.
- **17f** showed *in vivo* activities in a Caki-1 xenograft.