Accepted Manuscript

Synthesis and biological evaluation of 4-(2-fluorophenoxy)-3,3′-bipyridine derivatives as potential c-met inhibitors

Sijia Zhao, Yu Zhang, Hongyang Zhou, Shuancheng Xi, Bin Zou, Guanglong Bao, Limei Wang, Jiao Wang, Tianfang Zeng, Ping Gong, Xin Zhai

PII: S0223-5234(16)30355-5

DOI: 10.1016/j.ejmech.2016.04.062

Reference: EJMECH 8577

To appear in: *European Journal of Medicinal Chemistry*

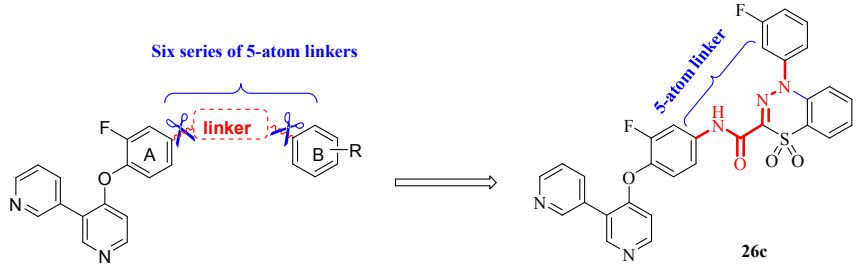
Received Date: 10 January 2016

Revised Date: 20 April 2016

Accepted Date: 23 April 2016

Please cite this article as: S. Zhao, Y. Zhang, H. Zhou, S. Xi, B. Zou, G. Bao, L. Wang, J. Wang, T. Zeng, P. Gong, X. Zhai, Synthesis and biological evaluation of 4-(2-fluorophenoxy)-3,3′-bipyridine derivatives as potential c-met inhibitors, *European Journal of Medicinal Chemistry* (2016), doi: 10.1016/j.ejmech.2016.04.062.

Graphical Abstract



Compd.	IC_{50} (nM)				
	A549	HT-29	MKN-45	MDA-MB-231	c-Met
26c	430	900	3	10	8.2

Six series of novel 4-(2-fluorophenoxy)-3,3'-bipyridine derivatives conjugated with aza-aryl formamide/amine scaffords were synthesized and evaluated for their cytotoxicity and c-Met kinase activity *in vitro*. Compound **26c** was identified as a lead compound for further structural optimization and antitumor activity screening purpose.

Synthesis and biological evaluation of 4-(2-fluorophenoxy)-3,3'-bipyridine derivatives as potential c-met inhibitors

Sijia Zhao, Yu Zhang, Hongyang Zhou, Shuancheng Xi, Bin Zou, Guanglong Bao, Limei Wang, Jiao Wang, Tianfang Zeng, Ping Gong, Xin Zhai*

Key Laboratory of Structure-Based Drug Design and Discovery, Ministry of Education, Shenyang Pharmaceutical University, Shenyang 110016, PR China

Abstract

Six series of novel 4-(2-fluorophenoxy)-3,3'-bipyridine derivatives conjugated with aza-aryl formamide/amine scaffords were designed and synthesized through a structure-based molecular hybridization approach. The target compounds were evaluated for c-Met kinase inhibitory activities and cytotoxicity against four cancer cell lines (HT-29, A549, MKN-45 and MDA-MB-231) *in vitro*. Most compounds exhibited moderate to excellent potency, and the most promising candidate **26c** (c-Met kinase IC_{50} = 8.2 nM) showed a 4.7-fold increase in cytotoxicity against c-Met-addicted MKN-45 cell line *in vitro* (IC_{50} = 3 nM), superior to that of Foretinib (IC_{50} = 23 nM). The preliminary structure–activity relationship indicated that a 1*H*-benzo[e][1,3,4]thiadiazine-3-carboxamide-4,4-dioxide moiety as linker contributed to the antitumor potency.

Keywords: Synthesis; Bipyridine derivatives; Aza-aryl formamides; c-Met; Cytotoxicity

1. Introduction

The c-mesenchymal-epithelia transition factor (c-Met), known as a hepatocyte growth factor receptor (HGFR), belongs to a prototype member of the receptor tyrosine kinases (RTKs) subfamily [1, 2]. c-Met plays a key role in several cellular processes [3], while abnormal c-Met stimulates signaling pathways responsible for proliferation, invasion, migration, angiogenesis, survival, metastasis, and drug resistance [4-6]. Therefore, deregulation of the c-Met/HGF signaling axis has been identified as a key contributing factor for cancer treatment [7]. To date, significant progress has been made on the development of c-Met inhibitors, resulting in the marketing of Foretinib (GSK1363089) [6], Cabozantinib (XL-184) [8], and more than ten candidates currently under clinical trials, such as MGCD265 [9], BMS-777607 [10] and E-7050 [11] (Fig.1). Besides that, varieties of hit-like molecules are reported recently [12-14].

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

BMS-777607, a pyridine-based selective ATP-competitive c-Met kinase inhibitor which primarily targets c-Met (IC_{50} = 3.9 nM) and several Met family members, including Axl (IC_{50} = 1.1 nM), Ron (IC_{50} = 1.8 nM), and Tyro3 (IC_{50} = 4.3 nM), is currently undergoing phase I clinical trials for various cancers [15, 16]. Due to its excellent efficacy *in vivo*, favorable pharmacokinetic and preclinical safety profiles, our attention was drown to the optimization of BMS-777607 as an extension of our work on the development of novel potent c-Met inhibitors. Application of bioisosterism theory, the aminopyridine moiety in BMS-777607 was replaced with 3, 3'-bipyridine

* Corresponding author. Tel. / fax: +86 24 2398 6429.
E-mail address:zhaixin_syphu@126.com (X. Zhai).

ring to give a new parent structure, which led to the design of the target compounds in this paper. Further modification mainly focused on the linkers between moiety A and moiety B (Fig. 2**)**, which was characterized important for gaining favorable enzyme activities and cellular potencies. According to our previous work, two structural characteristics of the linkers were interpreted [17-21]. One is "**five-atom regulation**", which demonstrates a distance of six chemical bonds should be existed between moiety A and moiety B, and the other characteristic is that the linkers should have "**both hydrogen-bond donor and acceptor**" as well. Thus, in order to explore more varieties of linkers according to the "**five-atom regulation**"**,** we designed six different cyclic moieties. Differ from other aza-aryl formamide linkers, a pyrimidine-4, 6-diamine framework was introduced to further enrich the "**five-atom regulation**". Additionally, on the molecular design level, various substituents were introduced to the terminal phenyl ring (moiety B) aiming at exploring the influence of substituents on anticancer activity by regulating the electronic and steric effects. Accordingly, six series of novel 4-(2-fluorophenoxy)-3, 3'-bipyridine derivatives conjugated with aza-aryl formamide/amine scaffords (**23a-f**, **24a-d**, **25a-e**, **26a-f**, **27a-b** and **28a-b**) were designed and synthesized (Fig. 2).

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

In this paper, all target compounds were evaluated for their cytotoxic activity against four cell lines (HT-29, A549, MKN-45 and MDA-MB-231) *in vitro*. Moreover, the enzymatic assays against c-Met of most compounds were also performed.

2. Chemistry

A series of 4-phenoxy-3,3'-pyridine derivatives and their intermediates were synthesized according to the pathways described in Scheme 1-6.

As shown in Scheme 1, the general synthesis of compounds **23a-g** involved six steps. Compound **1** was obtained from bromination reaction of commercially available 4-aminopyridine with *N*-bromosuccinimide (NBS) [22]. Treatment of **1** with sodium nitrite in sulfuric acid aqueous solution afforded the diazotization intermediate, which was subsequently hydrolysis with sodium hydroxide, without further purification, gave rise to 3-bromopyridin-4-ol **2** [23]. **2** was *O*-arylated with 3, 4-difluoronitrobenzene in the presence of potassium carbonate in *N*, *N*-dimethylformamide (DMF) to provide 4-phenoxypyridine intermediate **3**. Suzuki coupling reaction of intermediate **3** with 3-pyridinylborate, which was afforded by treatment of 3-bromopyridine with bis(pinacolato)diboron using *trans*-dichlorobis(triphenyl-phosphine)Palladium(II) and potassium carbonate as catalyst, to furnish compound **4** [24]. The key intermediates **5** were obtained *via* reduction of compound **4** with iron powder and catalytic amounts of ammonium chloride in ethanol at reflux [25]. Finally, the target compounds **23a-g** were successfully obtained by the nucleophilic displacement of **5** with **6a-g** in the presence of *N*, *N*-diisopropylethylamine (DIPEA) in ethanol for 15h at reflux. Herein, intermediates **6a-g** were available *via* the *N*-arylation of 4, 6-dichloropyrimidine with substituted anilines under alkaline conditions in an acceptable yield (30.0% - 45.1%).

(**Scheme 1** should be listed here)

The target compounds **24a-f** were synthesized according to the method summarized in Scheme 2. With one-pot strategy, treatment of commercially available substituted anilines with sodium nitrite in concentrated hydrochloric acid provided corresponding substituted phenylhydrazine intermediates, which then underwent an electrophilic substitution reaction with

ethyl(2-cyanoacetyl)carbamate to generate compounds **7a-f**. Intramolecular cyclization of **7a-f** with glyoxal in the presence of sodium acetate furnished **8a-f**, which were methylated with iodomethane and sodium hydride afforded **9a-f**. Subsequently, the cyano group of **9a-f** was hydrolyzed with glyoxal and hydrochloric acid gave rise to carboxylic acid derivatives **10a-f** [26, 27]. *N*-acylation reaction of **10a-f** with thionyl chloride produced the corresponding acyl chlorides, which were further treatment with intermediate **5** in the presence of DIPEA in dichloromethane to obtain target compounds **24a-f**.

(**Scheme 2** should be listed here)

Scheme 3 depicts the sequence of reactions that led to the preparation of compounds **25a–e**. Acylation of substituted phenylhydrazine **12a-e** with *O*-formyl carboxylic acid **11** gave access to dihydrophthalazinecarboxylic acid **13a-e** [28]. Herein, intermediate **11** was prepared by oxidation of naphthalene with potassium permanganate under basic condition. Meanwhile, treatment of substituted anilines with sodium nitrite in sulfuric acid aqueous solution to give the corresponding diazotization intermediates, which were subjected to reduction reaction with sodium sulfite to obtain substituted phenylhydrazine **12a-e** [29]. Subsequently, the resultant carboxylates **13a-e** were converted to the desired acyl chlorides on exposure to thionyl chloride in toluene, which underwent a *N*-acylation reaction with intermediate **5** to provide target compounds **25a-e**.

(**Scheme 3** should be listed here)

The general strategy to synthesize compounds **26a-c** were outlined in Scheme 4. According to this approach，the side chains **17a–c** were prepared from 2-fluorobenzenethiol by a four-step procedure. 2-Fluorobenzenethiol was substituted by ethyl chloroacetate led to **14** [30]. Oxidation reaction of **14** with 30% hydrogen peroxide aqueous in glacial acetic acid to obtain the sulfone **15** successfully [31], which was further treated with various substituted phenylhydrazines to generate compounds **16a-c**. An intramolecular *N*-arylation reaction of **16a-c** with potassium carbonate catalyst gave a good yield of benzothiadiazine intermediate，which were hydrolyzed in the presence of sodium hydroxide to give the key intermediates **17a-c**. Finally, the target compounds **26a-c** were synthesized as previously described reactions shown in Scheme 2.

(**Scheme 4** should be listed here)

The synthesis of compounds **27a-b** was illustrated in Scheme 5. Treatment of intermediates **12d-e** with glyoxal in 40% acetic acid aqueous solution provided Schiff base **18a-b**, respectively. Knoevenagel reaction of **18a-b** with meldrum's acid on exposure to pyridine in toluene furnished methylene condensation compounds **19a-b**, which underwent an intramolecular nucleophilic substitution reaction with sodium methoxide to afford pyridazinone acids **20a-b** [32]. Ultimately, the synthesis of **27a-b** was progressed as previously described *N*-acylation reaction in Scheme 2.

(**Scheme 5** should be listed here)

The target compounds **28a-b** were prepared according to the method as depicted in Scheme 6. Treatment of substituted phenylacetic acid with phosphorus oxychloride in DMF led to the formation of Vinamidinium salt (1,5-diazapentadiene salt) **21a-b**, which were widely used in the synthesis of the aromatic ring and a variety of aza-aromatic scaffolds by virtue of the constructing of three carbon atoms skeleton [33]. Compounds **21a-b** were treated with diethyl malonate in the presence of potassium *t*-butoxide in tetrahydrofuran gave the quatemary ammonium intermediates, which were passed into methylamine gas, without separation, to obtain pyridonecarboxylic acids **22a-b**. Similarly, the desired compounds **28a-b** were accomplished using the same method as preparing **24a-f**.

(**Scheme 6** should be listed here)

3. Result and discussion

The prepared twenty-five target compounds (**23a-g**, **24a-f**, **25a-e**, **26a-c**, **27a-b** and **28a-b**) were evaluated for their cytotoxicity *in vitro* against c-Met-addicted cancer cell lines including HT-29 (human colon cancer), A549 (human lung adenocarcinoma), MKN-45 (human gastric cancer) and a c-Met less sensitive MDA-MB-231 (human breast cancer) by the 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay, taking Foretinib as positive control. The results 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 in Table 1, most target compounds showed moderate to significant cytotoxic activities against one or more tested cancer cells with potencies in the single digit micromole range, which suggested that the introduction of six new moiety as "five-atom linker" to 4-(2-fluorophenoxy)-3, 3'-bipyridine framework maintained the potent cytotoxic activity. Four compounds (**23e**, **25b**, **26a** and **26c**) exhibited promising cytotoxicity with IC_{50} values ranging from 0.003 to 1.75 μM, which was comparable to that of Foretinib. Notably, the most prominent candidate **26c** displayed prominent activity with IC_{50} value of 0.43 μM, 0.9 μM, 0.003 μM and 0.01 μM against HT-29, A549, MKN-45 and MDA-MB-231 cells, which was 4.7- and 54-fold more active than that of Foretinib against c-Met-addicted MKN-45 cell (0.003 μM *vs.* 0.023 μM) and c-Met less sensitive MDA-MB-231 cell (0.01 μM *vs.* 0.54 μM). Moreover, three compounds (**23c**, **25c** and **26b**) showed antitumor potency either, whose IC_{50} value less than 0.1 μM. As a general trend, the target compounds were more potent on MKN-45 cell than on other three cells, suggesting the higher selectivity for gastric cancer.

Fourteen new compounds were further determined for c-Met kinase activity using homogenous time-resolved fluorescence (HTRF) assays. As shown in Table 1, the tested compounds exhibited moderate c-Met enzymatic potency with IC_{50} values ranging from 8.2 to 106.4 nM, suggesting that the inhibition of c-Met may be a main mechanism for the antitumor activity of the prepared compounds. Though compound **26c** demonstrated the best c-Met enzymatic potency (IC_{50} = 8.2 nM) superior to others, whose biological activity was slightly lower than that of the positive control Foretinib (8.2 nM *vs.* 1.1 nM).

The structure-activity relationship (SAR) was commenced by the introduction of "**five-atom linker**" that contains different kinds of nitrogen aromatic heterocyclic between moiety A and moiety B. The pharmacological activity data indicated that the different linker affected the activity dramatically. A clear preference for activity in compounds **25a-e** and **26a-c** whose linker bears 4-oxo-3,4-dihydrophthalazine-1-carboxamide and 1*H*-benzo[e][1,3,4]thiadiazine-3-carboxamide-4, 4-dioxide fragment respectively, indicating that a benzoheterocyle moiety of the linkers contributed positively to the antitumor potency. Compounds **24a-f**, **27a-b** and **28a-b** containing 4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide, 3-oxo-2,3-dihydropyridazine-4-carboxamide and 1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide linkers respectively, by contrast, revealed a weak antitumor activity. Furthermore, **26a-c** displayed higher potency than that of **25a-e**, which probably due to the existence of sulfonyl group that was favor of hydrogen-bond interaction between molecules with target proteins. Interestingly, compounds **23a-g** bearing pyrimidine-4,6-diamine skeleton showed moderate activity as well, disclosing that the acylamino

group was not essential for antitumor potency, as very meaningful for extending the structural categories of traditional aza-aryl formamide or aliphatic acylamino moiety as linkers.

Further investigations were performed to study the effect of different substituents on the phenyl ring (moiety B) on the cytotoxic activity. Introduction of mono-electron-withdrawing groups (mono-EWGs) on the phenyl ring led to an obvious improvement in activity, such as compounds **26c** (R = 3-fluoro, IC_{50} = 3.0 nM) and **26a** (R = 3-trifluoromethyl, IC_{50} = 27.0 nM). However, the introduction of double-electron-withdrawing groups (double-EWGs) caused negative effect against MKN-45 cells, such as **26b** (R = 3, 4-difluoro, IC_{50} = 90.0 nM). Another case in point is that **24e** with double-EWGs (R = 3-chloro-4-flourophenyl) nearly vanished the cytotoxicity on all tested cell lines compared to **24a** (R = 2-flouro) and **24b** (R = 4-chloro) with mono-EWGs. However, **23b** (R = 4-trimethoxy) and **23g** (R = 3, 5-dimethoxy) is an exception.

The data shown in Table 1 indicated that the introduction of halogen group (F, Cl or CF_3) at the phenyl ring B made a good contribution to potency. Compounds with electron-donating groups, by contrast, lost activity significantly. Compared 4-trimethoxy analog **25a** with 3-fluoro analog **25b**, a 4.7-fold drop in c-Met inhibition and approximate 3- to 145-fold decrease against tested cells were observed. It suggested that fluoro group at meta-position of phenyl ring B is a preference for enhanced activity.

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

4. Conclusions

In summary, twenty-five novel bipyridine derivatives bearing aza-aryl formamide/amine skeleton as potential c-Met kinase inhibitors were designed and synthesized. Our preliminary cytotoxic investigation showed that most compounds displayed moderate to excellent activity against MKN-45, MDA-MB-231 and A549 cancer cell lines. The exploration of preliminary SAR led to the identification of c-Met inhibitor **26c** as a valuable leading molecule, which possessed excellent c-Met kinase inhibition on a single-digital nanomolar level (IC_{50} = 8.2 nM). Moreover, it displayed better cytotoxicity against MKN-45 (IC_{50} = 3.0 nM) and MDA-MB-231 (IC_{50} = 10.0 nM nM) than against HT-29 (IC_{50} = 430 nM) and A549 cells (IC_{50} = 900 nM). The initial SARs discovered a novel 1*H*-benzo[e][1,3,4]thiadiazine-3-carboxamide-4,4-dioxide scaffold as the preferred linker for enhanced potency. Moreover, fluoro group at meta-position on the phenyl ring (moiety B) was a best option, and compounds with mono-EWGs were more active than those with double-EDGs or without substituents on moiety B. Further studies on structural optimization and the mechanism of kinase selectivity are in progress and will be reported in the future.

5. Experimental protocols

5.1. Chemistry

All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, 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 spectra was performed using Bruker 300 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Column chromatography was run on silica gel (200-300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China). Unless otherwise noted, all materials were obtained from commercially available sources and were used without further purification.

5.1.2. Preparation of 3-bromo-4-aminopyridine (**1**)

To the mixture of 4-aminopyridine (20.0 g, 0.21 mol) and acetonitrile (300.0 mL), NBS (39.8 g, 0.22 mol) was added in batches at 0°C avoiding light. Subsequently, the reaction mixture was stirred at room temperature for 24 h. After completion of reaction as indicated by thin layer chromatography (TLC), the mixture was then cooled and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica, dichloromethane/methanol, 20:1) to afford the desired compound **1** as a light yellow solid (33.2 g, 91.4%). MS (ESI) m/z: 172.9 $[M+H]^+$.

5.1.3. Preparation of 3-bromo-4-hydroxypyridine (**2**)

Concentrated sulfuric acid (85.0 mL) and the 3-bromo-4-aminopyridine (113.0 g, 0.65 mol) were added successively to the distilled water (550.0 mL) at 0°C, and then $NaNO_2$ (63.1 g, 0.91 mol) aqueous solution (130.0 mL) was added drop-wise to maintain the temperature between 0-5°C. After stirring at r.t. for 1 h, the reaction mixture was heated at 95°C for a further 0.5 h. Upon cooling to below 0°C, the mixture was alkalized to pH 6 with saturated sodium hydroxide solution, washed with ethyl acetate (200mL×3) and brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to yield the title compound **2** as a yellow solid (75.1 g, 66.2%). MS (ESI) m/z: 173.9 $[M+H]^+$.

5.1.4. Preparation of 3-bromo-4-(2-fluoro-4-nitrohenoxyl)pyridine (**3**)

To a stirred solution of 3-bromo-4-hydroxypyridine (**2**) (17.0 g, 98.0 mmol) in DMF (80.0 mL) was added 3, 4-difluoronitrobenzene (13.0 mL, 0.12 mol) and anhydrous K_2CO_3 (34.0 g, 0.25 mol). Upon the completion of addition, the reaction mixture was heated at 80°C for 2 h. The mixture was cooled and poured into ice-water. The mixture was filtrated and washed with water, and then dried to give **3** as a yellow solid (20.1 g, 66.1%). MS (ESI) m/z: 312.9 $[M+H]^+$.

5.1.5. Preparation of 4-(2-fluoro-4-nitrophenoxyl)-3,3'-bipyridine (**4**)

A mixture of 3-bromopyridine (5.5 mL, 57.0 mmol), bis(pinacolato)diboron (18.3 g, 72.0 mmol), potassium acetate (19.9 g, 0.14 mol), bis(triphenylphosphine)palladium dichloride (1.7 g, 2.4 mmol) in dioxane (300.0 mL) was heated at 90°C for 4h under nitrogen atmosphere. Upon cooling to room temperature, 3-bromo-4-(2-fluoro-4-nitrohenoxyl)pyridine (**3**) (15.0 g, 48.0 mmol), sodium carbonate (15.3 g, 0.14 mol) and H_2O (30.0 mL) were added, the reaction mixture was stirred for another 4.5 h. The solid was removed by filtration, and the filtrate was concentrated to dryness in vacuum. The residue was purified by column chromatography (silica, dichloromethane/methanol, 30: 1) to furnish the compound **4** as a yellow solid (8.2 g, 55.4%). MS (ESI) m/z: 312.1$[M+H]^+$.

5.1.6. Preparation of 4-(2-fluoro-4-aminophenoxyl)-3,3'-bipyridine (**5**)

To the mixture of 4-(2-fluoro-4-nitrophenoxyl)-3,3'-bipyridine (**4**) (22.0 g, 71.0 mmol), 2.2 mL glacial acetic acid and 60% ethanol (150.0 mL), iron powder (11.9 g, 0.21 mol) and catalytic amount ammonium chloride were added. Upon the completion of addition, the reaction mixture was heated at reflux for 5 h, and then filtered immediately. Subsequently, the filtrate was concentrated and anhydrous ether (200.0 mL) was added to the residue, stirred for 0.5h and then

filtrated to give the compound **5** as a yellow solid (15.0 g, 73.2%). MS (ESI) m/z: 282.1$[M+H]^+$.

5.1.7. Preparation of 6-chloro-*N*-(substituted phenyl)pyrimidin-4-amine (**6a-g**)

A mixture of 4, 6-dichloropyrimidine (3.0 g, 23.6 mmol), substituted aniline (23.6 mmol), DIPEA (4.1 mL, 25.0 mmol) in ethanol (30.0 mL) was heated at reflux for 12 h. Upon cooling to room temperature, the mixture was filtered and the filtrate was concentrated to give the oil, column chromatography (CH_2Cl_2: MeOH = 25: 1) to give compounds (**6a-g**).

5.1.7.1. 6-Chloro-*N*-phenylpyrimidin-4-amine (**6a**).

Yield: 45.1%; MS (ESI) m/z: 206.1 $[M+H]^+$.

5.1.7.2. 6-Chloro-*N*-(4-methoxyphenyl)pyrimidin-4-amine (**6b**).

Yield: 30.0%; MS (ESI) m/z: 236.1 $[M+H]^+$.

5.1.7.3. 6-Chloro-*N*-(3, 4-difluorophenyl)pyrimidin-4-amine (**6c**).

Yield: 34.7%; MS (ESI) m/z: 242.0 $[M+H]^+$.

5.1.7.4. 6-Chloro-*N*-(4-chlorophenyl)pyrimidin-4-amine (**6d**).

Yield: 42.2%; MS (ESI) m/z: 240.0 $[M+H]^+$.

5.1.7.5. 6-Chloro-*N*-(3-chlorophenyl)pyrimidin-4-amine (**6e**).

Yield: 45.0%; MS (ESI) m/z: 240.0 $[M+H]^+$.

5.1.7.6. 6-Chloro-*N*-(4-fluorophenyl)pyrimidin-4-amine (**6f**).

Yield: 36.9%; MS (ESI) m/z: 224.1 $[M+H]^+$.

5.1.7.7. 6-Chloro-*N*-(3,5-dimethoxyphenyl)pyrimidin-4-amine (**6g**).

Yield: 38.4%; MS (ESI) m/z: 266.1 $[M+H]^+$.

5.1.8. Preparation of ethyl (*Z*)-(2-cyano-2-(substituted phenyl)hydrazono)acetyl) carbamate (**7a-f)**

To the mixture of substituted anilines (0.08 mol), concentrated hydrochloric acid (45.0 mL) and water (120.0 mL), aqueous solution of $NaNO_2$ (60.0 mL, 0.11 mol) was added drop-wise under stir at a rate that the temperature below 0 °C, and the reaction mixture was stirred for 0.5 h. A mixture of ethyl (2-cyanoacetyl)carbamate (13.7 g, 0.09 mol) and sodium acetate (24.0 g, 0.27 mol) in ethanol (400.0 mL) was added drop-wise to the resulting diazonium salt solution below 0 °C and stirred for a further 2 h. The precipitate was collected by filtration and washed with water (40.0 mL×2), dried to give compounds **7a-f**.

5.1.8.1. Ethyl (*Z*)-(2-cyano-2-(2-(2-fluorophenyl)hydrazono)acetyl)carbamate (**7a**)

Orange solid; yield: 88.07%; MS (ESI) m/z: 279.1 $[M+H]^+$.

5.1.8.2. Ethyl (*Z*)-(2-cyano-2-(2-(4-chlorophenyl)hydrazono)-2-cyanoacetyl)carbamate (**7b**)

Orange solid; yield: 89.34%; MS (ESI) m/z: 295.1 $[M+H]^+$.

5.1.8.3. Ethyl (*Z*)-(2-cyano-2-(2-(3-(trifluoromethyl)phenyl)hydrazono)acetyl)carbamate (**7c**)
Orange solid; yield: 84.27%; MS (ESI) m/z: 329.1 $[M+H]^+$.

5.1.8.4. Ethyl (*Z*)-(2-cyano-2-(2-(2, 5-dichlorophenyl)hydrazono)acetyl)carbamate (**7d**)
Orange solid; yield: 85.07%; MS (ESI) m/z: 329.0 $[M+H]^+$.

5.1.8.5. Ethyl (*Z*)-(2-(2-(3-chloro-4-fluorophenyl)hydrazono)-2-cyanoacetyl)carbamate (**7e**)
Orange solid; yield: 90.02%; MS (ESI) m/z: 313.1 $[M+H]^+$.

5.1.8.6. Ethyl (*Z*)-(2-cyano-2-(2-(2, 4-dimethoxyphenyl)hydrazono)acetyl)carbamate (**7f**)
Orange solid; yield: 90.02%; MS (ESI) m/z: 321.2 $[M+H]^+$.

5.1.9. Preparation of 2-(substituted phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2, 4-triazine-6-carbonitrile (**8a-f**)

A mixture of compounds **7a-f (**0.07 mol), sodium acetate (29.0 g, 0.35 mol) and glacial acetic acid (400.0 ml) was stirred at reflux for 2 h. Subsequently, upon cooling to room temperature, the mixture was poured into water (1.2 L), and then stirred for 0.5 h .The precipitate was collected by filtration and washed with water (60.0 mL×2) and petroleum ether (40.0 mL×2), dried to give compounds **8a-f**.

5.1.9.1. 2-(2-Fluorophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**8a**)
Orange solid; yield: 65.21%; MS (ESI) m/z: 233.2 $[M+H]^+$.

5.1.9.2. 2-(4-Chlorophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**8b**)
Orange solid; yield: 67.21%; MS (ESI) m/z: 249.0 $[M+H]^+$.

5.1.9.3. 3,5-Dioxo-2-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**8c**)
Orange solid; yield: 63.01%; MS (ESI) m/z: 283.1 $[M+H]^+$.

5.1.9.4. 2-(2,5-Dichlorophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**8d**)
Orange solid; yield: 66.15%; MS (ESI) m/z: 282.9 $[M+H]^+$.

5.1.9.5. 2-(3-Chloro-4-fluorophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**8e**)
Orange solid; yield: 68.20%; MS (ESI) m/z: 267.0 $[M+H]^+$.

5.1.9.6. 2-(2,4-Dimethoxyphenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**8f**)
Orange solid; yield: 61.89%; MS (ESI) m/z: 275.1 $[M+H]^+$.

5.1.10. Preparation of 2-(substituted phenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6- carbonitrile (**9a-f**).

To the solution of compounds **8a-f** (36 mmol) in DMF (60.0 mL), sodium hydride was added in portions after stirred for 0.5h in an ice bath, then the solution of iodomethane (2.35 mL, 38

mmol) in DMF (10.0 mL) was added drop-wise to the reaction mixture stirred for 2 h. The reaction mixture was poured into water (200.0 mL), the precepitate was collected by filtration and washed with water (30.0 mL×2) and petroleum ether(20.0 mL×2), dried to give compounds **9a-f**.

5.1.10.1. 2-(2-Fluorophenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**9a**)

Orange solid; yield: 78.89%; MS (ESI) m/z: 247.06 $[M+H]^+$.

5.1.10.2. 2-(4-Chlorophenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**9b**)

Orange solid; yield: 75.04%; MS (ESI) m/z: 263.03 $[M+H]^+$.

5.1.10.3. 4-methyl-3,5-dioxo-2-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**9c**)

Orange solid; yield: 79.34%; MS (ESI) m/z: 297.06 $[M+H]^+$.

5.1.10.4. 2-(2,5-Dimethoxyphenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**9d**)

Orange solid; yield: 75.78%; MS (ESI) m/z: 289.10 $[M+H]^+$.

5.1.10.5. 2-(3-Chloro-4-fluorophenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**9e**)

Orange solid; yield: 80.08%; MS (ESI) m/z: 281.03 $[M+H]^+$.

5.1.10.6. 2-(2,4-Dimethoxyphenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**9f**)

Orange solid; yield: 79.03%; MS (ESI) m/z: 289.10 $[M+H]^+$.

5.1.11. Preparation of 2-(substituted phenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6- carboxylic acid (**10a-f**).

A mixture of compounds **9a-f (**0.03 mol), concentrated hydrochloric acid (72.0 mL) and glacial acetic acid (150.0 mL) was stirred at reflux for 4 h. The solvent was evaporated in vacuo, then water (50.0 mL) was added, the precepitate was collected by filtration. Subsequently, the precepitate was stirred for 10min in anhydrous ether (30.0 mL), dried to give compounds **10a-f.**

5.1.11.1. 2-(2-Fluorophenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (**10a**)

Pale white solid; yield: 39.03%; MS (ESI) m/z: 266.1 $[M+H]^+$.

5.1.11.2. 2-(4-Chlorophenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (**10b**)

Pale white solid; yield: 45.05%; MS (ESI) m/z: 282.0 $[M+H]^+$.

5.1.11.3. 4-Methyl-3,5-dioxo-2-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-6-

carboxylic acid (**10c**）

Pale white solid; yield: 41.76%; MS (ESI) m/z: 316.1 $[M+H]^+$.

5.1.11.4. 2-(2,5-Dichlorophenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (**10d**)

Pale white solid; yield: 45.66%; MS (ESI) m/z: 315.9 $[M+H]^+$.

5.1.11.5. 2-(3-Chloro-4-fluorophenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (**10e**)

Pale white solid; yield: 43.15%; MS (ESI) m/z: 300.0 $[M+H]^+$.

5.1.11.6. 2-(2,6-Dimethoxyphenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (**10f**)

Pale white solid; yield: 44.05%; MS (ESI) m/z: 308.1 $[M+H]^+$.

5.1.12. Preparation of 2-carboxyethl formyl benzoic acid (**11**)

Potassium permanganate (132.5 g, 0.84 mol) in H_2O (937.0 mL) was added drop-wise to the vigorously stirred liquated solution of naphthalene (20.0 g, 0.16 mol) in sodium hydroxide solution (312.0 mL, 0.5 mol). After completion of reaction as indicated by TLC, ethanol (30.0 mL) was added and stirred for another 15 min. The mixture was then cooled and filtered, and the filtrate was acidified by concentrated hydrochloric acid (93.8 mL) and evaporated to dryness to give the compound **11** as a white solid (14.2 g, 45.3%). MS (ESI) m/z: 195.1 $[M+H]^+$.

5.1.13. General procedure for the preparation of substituted phenyl hydrazine hydrochoride (**12a-e**)

Substituted aniline (0.17 mol) and aqueous solution of $NaNO_2$ (71.0 mL, 1.24 mol) were successively added to aqueous hydrochloric acid (115mL) maintaining the temperature between 0-5°C. The reaction mixture was stirred for 2 h, alkalized to pH 6-7 with 12% w/v sodium carbonate solution, and the resulting diazonium salt solution was added drop-wise to sodium sulfite solution (443.0 mL, 1.9 mol) below 0°C. And then the mixture was stirred at room temperature for a future 1 h, concentrated hydrochloric acid (277.0 mL) was added slowly, and heated to 100°C for 3h. The mixture was then cooled and filtered, and dried to give compounds **12a-e**.

5.1.13.1. (4-Methoxyphenyl)hydrazine (**12a**)

White solid; yield: 70.05%; MS (ESI) m/z: 138.08 $[M+H]^+$.

5.1.13.2. (3-Fluorophenyl)hydrazine (**12b**)

Yellow solid; yield: 74.81%; MS (ESI) m/z: 127.06 $[M+H]^+$.

5.1.13.3. Phenylhydrazine (**12c**)

Red solid; yield: 78.74%; MS (ESI) m/z: 109.07 $[M+H]^+$.

5.1.13.4. (4-Fluorophenyl)hydrazine (**12d**)

Yellow solid; yield: 78.15%; MS (ESI) m/z: 127.06 $[M+H]^+$.

5.1.13.5. (4-Chlorophenyl)hydrazine (**12e**)

Yellow solid; yield: 70.67%; MS (ESI) m/z: 143.03 $[M+H]^+$.

5.1.14. General procedure for the preparation of 3-substituted phenyl-4-oxo-3,4-dihydrophthalazine- 1-carboxylic acid (**13a-e**)

A mixture of compounds **11** (15.7 g, 81 mmol) and **12a-e** (88 mmol) in ethanol (25.5 mL) and water (62.7 mL) was stirred at room temperature for 12 h. The precipitate was collected by filtration, and then dissolved in 5% potassium hydroxide solution, stirred for 1h. The reaction mixture was filtrated, washed with dichloromethane, and then acidified to pH 3-4 by concentrated hydrochloric acid. The target compounds **13a-e** was collected by filtration.

5.1.14.1. 3-(4-Methoxyphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (**13a**)

White solid; yield: 36.20%; MS (ESI) m/z: 297.1 $[M+H]^+$.

5.1.14.2. 3-(3-Fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (**13b**)

Yellow solid; yield: 29.00%; MS (ESI) m/z: 285.2 $[M+H]^+$.

5.1.14.3. 4-Oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxylic acid (**13c**)

Red solid; yield: 39.81%; MS (ESI) m/z: 267.1 $[M+H]^+$.

5.1.14.4. 3-(4-Fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (**13d**)

Yellow solid; yield: 45.10%; MS (ESI) m/z: 285.1 $[M+H]^+$.

5.1.14.5. 3-(4-Chlorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid(**13e**)

Yellow solid; yield: 30.62%; MS (ESI) m/z: 301.0 $[M+H]^+$.

5.1.15. Preparation of 2-(2-fluorobenzenethio)ethyl acetate (**14**)

To the stirred mixture of 2-fluorobenzeneththiol (17.0 mL, 0.16 mol), anhydrous potassium carbonate (43.0 g, 0.31 mol) and acetone (120.0 mL), ethyl chloroacetate (18 mL, 0.168 mol) was added drop-wise below 25°C. After completion of reaction as indicated by TLC, the reaction mixture was filtrated, and the filtrate was concentrated to give the compound **14** as a pale yellow oil (28.11 g, 82.1%), MS (ESI) m/z: 215.1 $[M+H]^+$.

5.1.16. Preparation of 2-(2-fluorobenzenesulfonyl)ethyl acetate (**15**)

To the mixture of compound **14** (30.0 g, 0.14 mol) and glacial acetic acid (120.0 mL), 30% aqueous hydrogen peroxide (50.0 mL, 0.5 mol) was added drop-wise. After completion of reaction as indicated by TLC, the mixture was cooled and poured into 300.0 mL water, then extracted with dichloromethane (60.0 mL×3) and the organic phase was washed with 10% aqueous sodium bicarbonate (40.0 mL×2), then washed to neutral by water. The organic phase was dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated to yield the title compound **15**

as a white solid (25.9 g, 74.9%), MS (ESI) m/z: 247.0 $[M+H]^+$.

5.1.17. General procedure for the preparation of (*E*)-2-(2-fluorobenzenesulfonyl)-2-(2-substituted phenyl hydrazone) ethyl acetate (**16a-c**)

To the mixture of substituted aniline (0.04 mol), concentrated hydrochloric acid (13.0 mL) and water (20.0 mL), aqueous solution of $NaNO_2$ (40.0 mL, 0.08 mol) was added drop-wise at a rate that the temperature below $0^{\circ}C$, and the reaction mixture was stirred for 0.5 h. A mixture of **15** (5.0 g, 0.02 mol) and sodium acetate (6.6 g, 0.08 mol) in methanol (150.0 mL) was added drop-wise to the resulting diazonium salt solution and stirred for a further 2 h. The precipitate was collected by filtration and washed with water (30.0 mL×2), dried to give the compounds**16a-c**.

5.1.17.1.
(*E*)-ethyl-2-((2-fluorophenyl)sulfonyl)-2-(2-(2-(trifluoromethyl)phenyl)hydrazono)acetate (**16a**)
White solid; yield 42.21%; MS (ESI) m/z: 419.1 $[M+H]^+$.

5.1.17.3. (*E*)-ethyl-2-(2-(3,4-difluorophenyl)hydrazono)-2-((2-fluorophenyl)sulfonyl)acetate (**16b**)
White solid; yield 47.10%; MS (ESI) m/z: 369.2 $[M+H]^+$.

5.1.17.2. (*E*)-ethyl-2-(2-(3-fluorophenyl)hydrazono)-2-((2-fluorophenyl)sulfonyl)acetate (**16c**)
White solid; yield 49.80%; MS (ESI) m/z: 387.2 $[M+H]^+$.

5.1.18. General procedure for the preparation of 1-substituted phenyl-1*H*-4,1,2-benzothiadiazine-3- carboxylic acid-4,4-dioxide (**17a-c**)

A mixture of **16a-c** (2.0 mmol), anhydrous potassium carbonate (0.33 g, 2.4 mmol) in DMF (10.0 mL) was stirred at room temperature for 4h, then the reaction mixture was poured into water (50.0 mL) and stirred for another 0.5 h. The solids was collected by filtration and washed with water (30.0 mL×2), dried to give compounds **17a-c**.

5.1.18.1.
(*E*)-ethyl-2-((2-fluorophenyl)sulfonyl)-2-(2-(2-(trifluoromethyl)phenyl)hydrazono)acetate (**17a**)
Off-white solid; yield 80.10%; MS (ESI) m/z: 419.1 $[M+H]^+$.

5.1.18.2. (*E*)-ethyl-2-(2-(3,4-difluorophenyl)hydrazono)-2-((2-fluorophenyl)sulfonyl)acetate (**17b**)
Off-white solid; yield 76.20%; MS (ESI) m/z: 387.4 $[M+H]^+$.

5.1.18.3. (*E*)-ethyl-2-(2-(3-fluorophenyl)hydrazono)-2-((2-fluorophenyl)sulfonyl)acetate (**17c**)
Off-white solid; yield 85.10%; MS (ESI) m/z: 369.3 $[M+H]^+$.

5.1.19. Preparation of (*E*)-2-(2-substituted phenylhydrazono)acetaldehyde (**18a-b**)

To the mixture of water (25mL) and glacial acetic acid (25mL), substituted phenylhydrazine (8g, 0.049mol) and 40% aqueous glyoxal solution (23mL, 0.2mol) were added drop-wise successively. Upon the completion of addition, the reaction mixture was stirred at room temperature for 4h, then the precipitate was collected by filtration and washed with water (30mL×2), dried to give compounds **18a-b**.

5.1.19.1. (*E*)-2-(2-(4-chlorophenyl)hydrazono)acetaldehyde (**18a**)

White solid; yield 80.20%; MS (ESI) m/z: 183.0 $[M+H]^+$.

5.1.19.2. (*E*)-2-(2-(4-fluorophenyl)hydrazono)acetaldehyde (**18b**)

White solid; yield 77.68%; MS (ESI) m/z: 167.3 $[M+H]^+$.

5.1.20. Preparation of (*E*)-5-(2-Substituted phenyl hydrazono)ethylidene)-2,2-dimethyl-1,3-dioxane- 4,6-dione (**19a-b**)

A mixture of **18a** or **18b** (35 mmol), meldrum's acid (5.0 g, 35 mmol), glacial acetic acid (0.5 mL) and piperidine (0.5 mL) intoluene (50.0 mL) was stirred at r.t. for 24 h. The solid was obtained by filtration and washed with petroleum ether, dried to give compounds **19a** or **19b.**

5.1.20.1. (*Z*)-5-((*E*)-2-(2-(4-chlorophenyl)hydrazono)ethylidene)-2,2-dimethyl-1,3-dioxan-4-one (**19a**)

White solid; yield 75.32%; MS (ESI) m/z: 295.1 $[M+H]^+$.

5.1.20.2. (*Z*)-5-((*E*)-2-(2-(4-fluorophenyl)hydrazono)ethylidene)-2,2-dimethyl-1,3-dioxan-4-one (**19b**)

White solid; yield 74.80%; MS (ESI) m/z: 279.1 $[M+H]^+$.

5.1.21. Preparation of 2-substituted phenyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (**20a-b**)

To the solution of sodium methoxide (0.65 g, 12 mmol) in methanol (30.0 mL), compound **19a** or **19b** (0.01 mol) was added, and heated at reflux for 12 h. Subsequently, the mixture was poured into ice-water (150.0 mL) slowly, acidified to pH 1 by aqueous 10% HCl solution, then extracted with dichloromethane (60.0 mL×3), dried over Na_2SO_4, filtered and concentrated to yield compounds **20a** or **20b**.

5.1.21.1. 2-(4-Chlorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (**20a**)

White solid; yield 57.98%; MS (ESI) m/z: 251.0 $[M+H]^+$.

5.1.21.2. 2-(4-Fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (**20b**)

White solid; yield 58.37%; MS (ESI) m/z: 235.1 $[M+H]^+$.

5.1.22. Preparation of *N*-(3-(dimethylamino)-2-substituted phenylallylidene)-*N*-methyl ammonium hexafluorophosphate (**21a-b**)

A solution of substituted phenylacetic acid (5.0 g, 32 mmol) in DMF (30.0 mL) was heated at 70°C for 20 min under nitrogen atmosphere. Then, phosphorus oxychloride (6.1 mL) was added drop-wise to the mixture, and stirred at 75°C for another 1 h. Upon cooling to room temperature, a brown solution was obtained. During this process, hexafluorophosphoric acid (3.1 mL, 35 mmol) and aqueous sodium hydroxide solution (9.7 mL, 48 mmol) were added to water (20.0 mL) and stirred for 0.5 h. Subsequently, the former brown solution and aqueous sodium hydroxide solution (13.1 mL, 65 mmol) were added drop-wise to maintaining the temperature below 10°C and stirred

for 1 h. The precipitate was collected by filtration and washed with water (30.0 mL×2), dried to give compounds **21a** or **21b**.

5.1.22.1. *N*-(3-(dimethylamino)phenyl-allylidene)-*N*-methyl ammonium hexafluorophosphate (**21a**)

White solid; yield 54.81%; MS (ESI) m/z: 349.1 $[M+H]^+$.

5.1.22.2. (*E*)-*N*-(3-(dimethylamino)-2-(4-fluorophenyl)allylidene)-*N*-methylmethanaminium hexafluorophosphate (**21b**)

White solid; yield 50.21%; MS (ESI) m/z: 367.3 $[M+H]^+$.

5.1.23. Preparation of 1-methyl-2-oxo-5-substituted phenyl-1,2-dihydropyridine-3-carboxylic acid (**22a-b**)

To the solution of diethyl malonate (1.5 g, 9.4 mmol) in tetrahydrofuran (40.0 mL), potassium *t*-butoxide (1.27 g, 11.3 mmol) was added in batches, keeping the temperature below 0^{o}C, and then the reaction mixture was stirred at room temperature for 50 min. Subsequently, compounds **21a** or **22b** (11.3 mmol) was added to the mixture and heated at 45°C for a further 3h. The reaction mixture was concentrated to dryness to give a yellow solid, which was dissolved in DMF (30.0 mL), heated at 70°C for 1.5 h under methylamine atmosphere. Upon cooling to .t., water (100.0 mL) was added and then extracted with dichloromethane (30.0 mL×3), evaporated the organic phase to dryness and dissolved in ethanol (30.0 mL). Subsequently, aqueous sodium hydroxide solution (30.0 mL, 18.0 mmol) was added drop-wise to the solution and stirred at room temperature for 4 h. The reaction mixture was washed with ethyl acetate (30.0 mL×3), and then acidified to pH 3 by concentrated hydrochloric acid. The precipitate was collected by filtration and dried to give compounds **22a** or **22b**.

5.1.23.1. 1-methyl-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxylic acid (**22a**)

White solid; yield 41.20%; MS (ESI) m/z: 230.2 $[M+H]^+$.

5.1.23.2. 5-(4-fluorophenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**22b**)

White solid; yield: 38.23%; MS (ESI) m/z: 248.1 $[M+H]^+$.

5.1.24. General procedure for the preparation of compounds (**23a-g**)

A mixture of **5** (0.1 g, 0.3 mmol), *N*-substitutedphenyl-6-chloropyrimidine-4-amine (0.3 mmol) and DIPEA (0.1 mL) in ethanol (10.0 mL) was heated at reflux for 15 h. Upon cooling to room temperature, the reaction mixture was filtrated and washed with ethanol (10.0 mL×2), dried to obtain compounds **23a-g**.

5.1.24.1. N^4-(4-(3,3'-bipyridin-4-yloxy)-3-fluorophenyl)-N^6-phenylpyrimidine-4,6-diamine (**23a**).

White solid; yield:71.6%; m.p.: 172-175°C; MS (ESI) *m/z*: 451.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.98 (s, 1H), 9.47 (s, 1H), 8.86 (s, 1H), 8.50 (dd, *J* = 4.4, 1.3 Hz,1H), 8.37 (s, 1H), 8.18 (s, 1H), 8.13–8.02 (m, 2H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.61 (m, 3H), 7.52 (dd, *J* = 9.0, 1.9Hz, 1H), 7.41 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 2H), 6.99 (t, *J*=7.4 Hz, 1H), 6.39 (d, *J* = 7.6 Hz, 1H), 6.34 (s, 1H); Anal. calcd. for $C_{26}H_{19}FN_6O$ (%): C, 69.32; H, 4.25; N, 18.66.

Found (%): C, 69.23; H, 4.21; N, 18.57.

5.1.24.2.

N^4-(4-(3,3'-bipyridin-4-yloxy)-3-fluorophenyl)-N^6-(4-methoxyphenyl)pyrimidine-4,6-diamine (**23b**).

Gray solid; yield: 70.2%; m.p.: 142-144°C; MS (ESI) *m/z*: 481.5 $[M+H]^+$, 503.5 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.61 (s, 1H), 9.05 (s, 1H), 8.85 (s, 1H), 8.50 (dd, *J*=3.3, 1.2 Hz, 1H), 8.30 (s, 1H), 8.15 (s, 1H), 8.10 (m, 1H), 8.02 (dd, *J* = 13.7, 2.1 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.61 (t, 1H), 7.47–7.35 (m, 4H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.38 (d, *J* = 7.7 Hz, 1H), 6.09 (s, 1H), 3.74(s, 3H); Anal. calcd. for $C_{27}H_{21}FN_6O$ (%): C, 67.49; H, 4.41; N, 17.49. Found (%): C, 67.41; H, 4.45; N, 17.47.

5.1.24.3.

N^4-(4-(3,3'-bipyridin-4-yloxy)-3-fluorophenyl)-N^6-(3,4-difluorophenyl)pyrimidine-4,6-diamine (**23c**).

White solid; yield:68.2%; m.p.: 242-244°C; MS (ESI) *m/z*: 487.5 $[M+H]^+$, 509.5 $[M+Na]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 10.01(s, 1H), 9.76(s, 1H), 8.91(s, 1H), 8.54(d, *J* = 4.1 Hz, 1H), 8.42(s, 1H), 8.22(dd, *J* = 10.0, 4.6 Hz, 2H), 8.07(dd, *J* = 13.8, 2.0 Hz, 1H), 7.97-7.87(m, 2H), 7.65(t, *J* = 8.9 Hz, 1H), 7.54-7.47(m, 2H), 7.41-7.32(m, 2H), 6.41(d, *J* = 7.6 Hz, 1H), 6.32(s, 1H); Anal. calcd. for $C_{26}H_{17}F_3N_6O$ (%): C, 64.20; H, 3.52; N, 17.28. Found (%): C, 64.12; H, 3.56; N, 17.24.

5.1.24.4.

N^4-(4-(3,3'-bipyridin-4-yloxy)-3-fluorophenyl)-N^6-(4-chlorophenyl)pyrimidine-4,6-diamine (**23d**).

White solid; yield: 75.0%; m.p.: 178-180°C; MS (ESI) *m/z*: 485.6 $[M+H]^+$, 507.5 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.91 (s, 1H), 9.58 (s, 1H),8.86 (s, 1H), 8.50 (dd, *J* = 4.4, 1.7 Hz ,1H), 8.39 (s, 1H), 8.16 (s, 1H), 8.10 (m, 1H), 8.04 (dd, *J* = 13.9, 1.8 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.67 (d,*J* = 8.8 Hz, 2H), 7.62 (t, 1H), 7.50 (dd, *J* = 9.6, 1.8Hz, 1H), 7.40 (dd, *J* = 8.1, 4.5 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 6.39 (d, *J* = 7.6 Hz, 1H), 6.31 (s, 1H); Anal. calcd. for $C_{26}H_{18}ClFN_6O$ (%): C, 64.40; H, 3.74; N, 17.33. Found (%): C, 64.42; H, 3.76; N, 17.29.

5.1.24.5.

N^4-(4-(3,3'-bipyridin-4-yloxy)-3-fluorophenyl)-N^6-(3-chlorophenyl)pyrimidine-4,6-diamine (**23e**).

White solid; yield: 75.7%; m.p.: 180-182°C; MS (ESI) *m/z*: 485.5 $[M+H]^+$, 507.4 $[M+Na]^+$. IR (KBr, cm^{-1}): 3325.5, 3183.4, 3046.2, 3019.3, 1663.1, 1644.9, 1546.8, 1324.2, 1260.8, 1220.6, 1151.4, 1131.5, 1031.5, 977.1, 884.7, 758.1, 697.2, 651.3; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.98 (s, 1H), 9.70 (s, 1H), 8.85 (s, 1H), 8.50 (dd, *J* = 4.0, 1.1Hz, 1H), 8.43 (s, 1H), 8.16 (s, 1H), 8.10 (m, 1H), 8.05 (dd, *J* = 13.7, 2.2 Hz, 1H), 7.92 (t, 1H), 7.87 (d, *J*=7.6 Hz, 1H), 7.64 (t, 1H), 7.52 (m, 2H), 7.40 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.31 (t, 1H), 7.00 (m, 1H), 6.39 (d, *J* = 7.6 Hz,1H), 6.36 (s, 1H); Anal. calcd. for $C_{26}H_{18}ClFN_6O$ (%): C, 64.40; H, 3.74; N, 17.33. Found (%): C, 64.37; H, 3.71; N, 17.26.

5.1.24.6.

N^4-(4-(3,3'-bipyridin-4-yloxy)-3-fluorophenyl)-N^6-(4-fluorophenyl)pyrimidine-4,6-diamine (**23f**).

White solid; yield: 75.4%; m.p.: 162-164°C; MS (ESI) *m/z*: 469.1 $[M+H]^+$, 491.1 $[M+Na]^+$.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.79 (s, 1H), 9.37 (s, 1H), 8.85 (d, J = 1.9 Hz, 1H), 8.50 (dd, J = 4.8, 1.4Hz, 1H), 8.36 (s, 1H), 8.16 (s, 1H), 8.10 (m, 1H), 8.03 (dd, J = 13.8, 2.1 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.64–7.56 (m, 3H), 7.47 (dd, J = 8.9, 2.0 Hz, 1H), 7.40 (dd, J = 7.8, 4.8 Hz, 1H), 7.15 (t, J = 8.9, 2H), 6.39 (d, J = 7.6Hz, 1H), 6.22 (s, 1H); Anal. calcd. for $C_{26}H_{18}F_2N_6O$ (%): C, 66.66; H, 3.87; N, 17.94. Found (%): C, 66.57; H, 3.76; N, 17.92.

5.1.24.7.

N^4-(4-([3,3'-bipyridin]-4-yloxy)-3-fluorophenyl)-N^6-(3,5-dimethoxyphenyl)pyrimidine-4,6-diamin e (**23g**).

Gray solid; yield: 72.5%; m.p.: 148-150°C; MS (ESI) *m/z*: 511.5 $[M+H]^+$, 533.6 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.61 (s, 1H), 9.05 (s, 1H), 8.85 (s, 1H), 8.50 (dd, J = 3.3, 1.2 Hz, 1H), 8.31 (s, 1H), 8.15 (s, 1H), 8.10 (m, 1H), 8.04 (dd, J = 13.7, 2.1 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.61 (t, 1H), 7.51–7.36 (m, 4H), 6.73 (s, 1H), 6.38 (d, J = 7.7 Hz, 1H), 6.09 (s, 1H), 3.74 (s, 6H); Anal. calcd. for $C_{28}H_{23}FN_6O_3$ (%): C, 65.87; H, 4.54; N, 16.46. Found (%): C, 65.82; H, 4.52; N, 16.41.

5.1.25. General procedure for the preparation of compounds (**24a-f**, **25a-d**, **26a-c**, **27a-b**, **28a-b**)

To the solution of **10a-f** (or **13a-d**, **17a-c**, **20a-b**, **22a-b**) (6.0 mmol) in toluene (20.0 mL), thionyl chloride (10.0 mL) was added drop-wise, and then heated at reflux for 5 h. Upon cooling to room temperature, the reaction mixture was concentrated to dryness to obtain the corresponding acyl chloride as a powdered solid. Subsequently, the freshly prepared acyl chloride (0.75 mmol) was added to the mixture of **5** (0.5 mmol) and DIPEA (2.5 mmol) in dichloromethane (50.0 mL) in batches, keeping the temperature below 0°C. Then, the reaction mixture was stirred at .t. for 10 h. Upon the completion of reaction as indicated by TLC, the mixture was washed successively with 10% aqueous potassium carbonate solution (20.0 mL×3) and brine (20.0 mL×2), the organic phase was dried over anhydrous sodium sulfate. The solid was removed by filtration, and the filtrate was concentrated to yield the title compounds **24a-f**, **25a-d**, **26a-c**, **27a-b**, **28a-b**.

5.1.25.1.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-4-methyl-3,5-dioxo-2-phenyl-2,3,4,5-tetrahydro-1 ,2,4-triazine-6-carboxamide (**24a**).

Yellow solid; yield: 41.2%; m.p.: 174-176°C; MS (ESI) *m/z*: 510.5 $[M+H]^+$, 532.4 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 11.13(s, 1H), 8.90(s, 1H), 8.56(d, J = 4.4 Hz, 1H), 8.27(s, 1H), 8.16(d, J = 7.9 Hz, 1H), 7.98(dd, J = 9.3, 4.6 Hz, 2H), 7.83(t, J = 8.8 Hz, 1H), 7.67(dd, J = 11.9, 7.7 Hz, 3H), 7.50(dt, J = 13.4, 8.4 Hz, 3H), 6.46(d, J = 7.6 Hz, 1H), 3.36(s, 3H); Anal. calcd. for $C_{27}H_{18}F_2N_6O_4$ (%): C, 61.36; H, 3.43; N, 15.90. Found (%): C, 61.32; H, 3.40; N, 15.87.

5.1.25.2.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-2-(2-fluorophenyl)-4-methyl-3,5-dioxo-2,3,4,5-tet rahydro-1,2,4-triazine-6-carboxamide (**24b**).

Yellow solid; yield: 43.5%; m.p.: 192-195°C; MS (ESI) *m/z*: 529.5 $[M+H]^+$, 561.4 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 11.06(s, 1H), 8.86(s, 1H), 8.52(d, J = 3.9 Hz, 1H), 8.23(d, J = 1.0 Hz, 1H), 8.13(dt, J = 8.0, 1.8 Hz, 1H), 7.93(ddd, J = 6.7, 5.8, 2.1 Hz, 2H), 7.79(t, J = 8.8 Hz, 1H), 7.63(s, 5H), 7.44(dd, J = 7.9, 4.8 Hz, 1H), 6.41(d, J = 7.6 Hz, 1H), 3.30(s, 3H); Anal. calcd. for

$C_{27}H_{18}ClFN_6O_4$ (%): C, 59.51; H, 3.33; N, 15.42. Found (%): C, 59.54; H, 3.36; N, 15.38.

5.1.25.3.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-4-methyl-5-oxo-2-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (**24c**).

Yellow solid; yield: 39.6%; m.p.: 193-195°C; MS (ESI) *m*/*z*: 529.5 $[M+H]^+$, 561.4 $[M+Na]^+$. IR (KBr, cm^{-1}): 3432.1, 3034.5, 2963.2, 2874.5, 1678.2, 1661.2, 1654.8, 1521.9, 1446.2, 1376.4, 1264.8, 1253.9, 1231.1, 1140.2, 1095.9, 881.3, 826.5, 755.8, 651.8; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 11.32(s, 1H), 8.86(s, 1H), 8.51(d, *J* = 2.8 Hz, 1H), 8.23(s, 1H), 8.11(d, *J* = 7.9 Hz, 1H), 8.04-7.91(m, 4H), 7.82(dt, *J* = 24.6, 8.3 Hz, 3H), 7.67(d, *J* = 9.0 Hz, 1H), 7.42(dd, *J* = 7.7, 4.8 Hz, 1H), 6.42(d, *J* = 7.6 Hz, 1H), 3.31(s, 3H); Anal. calcd. for $C_{28}H_{18}F_4N_6O_4$ (%): C, 58.14; H, 3.14; N, 14.53. Found (%): C, 58.11; H, 3.16; N, 14.50.

5.1.25.4.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-2-(2,5-dichlorophenyl)-4-methyl-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (**24d**).

Yellow solid; yield: 39.6%; m.p.: 183-185°C; MS (ESI) *m*/*z*: 529.5$[M+H]^+$, 561.4 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 11.13(s, 1H), 8.85(s, 1H), 8.51(d, *J* = 3.7 Hz, 1H), 8.23(s, 1H), 8.11(d, *J* = 7.9 Hz, 1H), 7.91(dd, *J* = 14.4, 3.7 Hz, 2H), 7.82-7.75(m, 3H), 7.70-7.64(m, 1H), 7.59(d, *J* = 8.6 Hz, 1H), 7.42(dd, *J* = 7.8, 4.8 Hz, 1H), 6.41(d, *J* = 7.6 Hz, 1H), 3.37(s, 3H); Anal. calcd. for $C_{27}H_{17}Cl_2FN_6O_4$ (%): C, 55.97; H, 2.96; N, 14.51. Found (%): C, 55.95; H, 2.94; N, 14.54.

5.1.25.5.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-2-(3-chloro-4-fluorophenyl)-4-methyl-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (**24e**).

Yellow solid; yield: 39.6%; m.p.: 208-211°C; MS (ESI) *m*/*z*: 529.5 $[M+H]^+$, 561.4 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 11.03(s, 1H), 8.85(s, 1H), 8.51(d, *J* = 3.8 Hz, 1H), 8.22(s, 1H), 8.10(dt, *J* = 7.9, 1.7 Hz, 1H), 7.98-7.86(m, 3H), 7.79(t, *J* = 8.8 Hz, 1H), 7.67-7.60(m, 3H), 7.42(dd, *J* = 7.8, 4.8 Hz, 1H), 6.41(d, *J* = 7.6 Hz, 1H), 3.30(s, 3H); Anal. calcd. for $C_{27}H_{17}ClF_2N_6O_4$ (%): C, 57.61; H, 3.04; N, 14.93. Found (%): C, 57.60; H, 3.06; N, 14.94.

5.1.25.6.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-2-(2,4-dimethoxyphenyl)-4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxamide (**24f**).

Yellow solid; yield: 43.5%; m.p.: 187-189°C; MS (ESI) *m*/*z*: 529.5$[M+H]^+$, 561.4 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 11.19(s, 1H), 8.85(s, 1H), 8.51(d, *J* = 3.7 Hz, 1H), 8.22(s, 1H), 8.11(d, *J* = 7.9 Hz, 1H), 7.93(dd, *J* = 14.4, 3.7 Hz, 2H), 7.82-7.79(m, 3H), 7.70-7.62(m, 1H), 7.56(d, *J* = 8.6 Hz, 1H), 7.40(dd, *J* = 7.8, 4.8 Hz, 1H), 6.41(d, *J* = 7.6 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.37(s, 3H); Anal. calcd. for $C_{29}H_{23}FN_6O_6$ (%): C, 61.05; H, 4.06; N, 14.73. Found (%): C, 61.02; H, 4.08; N, 14.74.

5.1.25.7.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-3-(4-methoxyphenyl)-4-oxo-3,4-dihydrophth

alazine-1-carboxamide (**25a**).

Pale yellow solid; yield: 42.1%; m.p.: 162-164°C; MS (ESI) *m/z*: 582.5 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 11.08(d, *J* = 6.5 Hz, 1H), 8.85(d, *J* = 1.1 Hz, 1H), 8.52-8.41(m, 3H), 8.23(s, 1H), 8.13-7.91(m, 6H), 7.85-7.64(m, 4H), 7.42(dd, *J* = 7.8, 4.8 Hz, 1H), 7.10(d, *J* = 9.0 Hz, 1H), 6.42(d, *J* = 7.6 Hz, 1H), 3.95-3.83(m, 3H); Anal. calcd. for $C_{32}H_{22}FN_5O_4$ (%): C, 68.69; H, 3.96; N, 12.52. Found (%): C, 68.65; H, 3.98; N, 12.56.

5.1.25.8.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-3-(3-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (**25b**).

Gray solid; yield: 36.2%; m.p.: 193-195°C; MS (ESI) *m/z*: 548.1 $[M+H)^+$, 570.1$(M+Na]^+$. IR (KBr, cm^{-1}): 3412.5, 3322.5, 3183.4, 3019.3, 1670.5, 1660.9, 1644.9, 1529.9, 1262.8, 1234.6, 1145.2, 1136.2, 1095.3, 1034.7, 884.7, 798.1, 756.2, 697.4, 631.5; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.85(d, *J* = 1.4 Hz, 1H), 8.52–8.43 (m, 3H), 8.20 (s, 1H), 8.11 (m, 1H), 8.07–7.97 (m, 3H), 7.91 (d, *J*=7.5 Hz, 1H), 7.78–7.69 (m, 4H), 7.60 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.2, 4.6 Hz, 1H),7.33 (m, 1H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.41 (d, *J* = 7.5 Hz, 1H); Anal. calcd. for $C_{33}H_{25}F_2N_5O_3$ (%): C, 68.62; H, 4.36; N, 12.13. Found (%): C, 68.65; H, 4.32; N, 12.16.

5.1.25.9.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-4-oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxamide (**25c**).

Gray solid; yield: 37.6%; m.p.: 202-204°C; MS (ESI) *m/z*: 530.6 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 11.11(s, 1H), 8.86(d, *J* = 1.7 Hz, 1H), 8.51(dd, *J* = 4.8, 1.5 Hz, 1H), 8.50-8.41(m, 2H), 8.23(d, *J* = 0.6 Hz, 1H), 8.13-8.10(m, 1H), 8.09-7.98(m, 3H), 7.94(d, *J* = 7.6 Hz, 1H), 7.89-7.76(m, 3H), 7.72(dd, *J* = 8.8, 1.7 Hz, 1H), 7.66-7.55(m, 2H), 7.52-7.38(m, 2H), 6.42(dd, *J* = 7.6, 2.8 Hz, 1H); Anal. calcd. for $C_{31}H_{20}FN_5O_3$ (%): C, 70.32; H, 3.81; N, 13.23. Found (%): C, 70.35; H, 3.84; N, 13.26.

5.1.25.10.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (**25d**).

Gray solid; yield: 35.5%; m.p.: 168-170°C; MS (ESI) *m/z*: 548.1 $[M+H]^+$, 570.1 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 9.34 (s, 1H), 9.25 (d, *J* = 7.7 Hz, 1H), 8.72 (s, 1H), 8.56 (m, 2H), 8.15 (m, 1H), 8.03–7.89 (m, 3H), 7.67–7.53 (m, 3H), 7.52–7.44 (m, 2H), 7.40 (t, 1H), 7.34 (dd, *J* = 7.9, 5.2 Hz, 1H), 7.25 (t, 2H), 6.60 (d, *J* =7.7 Hz, 1H); Anal. calcd. for $C_{31}H_{19}F_2N_5O_3$ (%): C, 68.00; H, 3.50; N, 12.79. Found (%): C, 68.03; H, 3.54; N, 12.72.

5.1.25.11.

N-(4-([3,3'-bipyridin]-4-yloxy)-3-fluorophenyl)-3-(4-chlorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (**25e**).

Gray solid; yield: 34.21%; m.p.: 178-180°C; MS (ESI) *m/z*: 565.0 $[M+H]^+$, 587.1 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 9.34 (s, 1H), 9.25 (d, *J* = 7.7 Hz, 1H), 8.72 (s, 1H), 8.56 (m, 2H), 8.15 (m, 1H), 8.04–7.90 (m, 3H), 7.67–7.64 (m, 3H), 7.48–7.39 (m, 2H), 7.40 (t, 1H), 7.34 (dd, *J* = 7.9, 5.2 Hz, 1H), 7.13 (t, 2H), 6.62 (d, *J* = 7.7 Hz, 1H); Anal. calcd. for $C_{31}H_{19}ClFN_5O_3$

(%): C, 66.02; H, 3.40; N, 12.42. Found (%): C, 68.06; H, 3.36; N, 12.38.

5.1.25.12.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-1-(2-trifluoromethylphenyl)-1*H*-4,1,2-benzothiadiazine-3-carboxamide-4,4-dioxide (**26a**).

Pale yellow solid; yield: 31.4%; m.p.: 186-188°C; MS (ESI) *m*/*z*: 634.0$(M+H)^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 10.53(s, 1H), 8.85(d, *J* = 1.4 Hz, 1H), 8.50(dd, *J* = 4.6, 1.2 Hz, 1H), 8.24-8.15(m, 2H), 8.08(dd, *J* = 16.1, 8.0 Hz, 4H), 7.92(ddd, *J* = 14.9, 11.7, 5.3 Hz, 3H), 7.80-7.58(m, 4H), 7.41(dd, *J* = 7.9, 4.8 Hz, 1H), 6.67(d, *J* = 8.6 Hz, 1H), 6.40(d, *J* = 7.6 Hz, 1 H); Anal. calcd. for $C_{31}H_{19}F_4N_5O_4S$ (%): C, 58.77; H, 3.02; N, 11.05. Found (%): C, 58.72; H, 3.06; N, 11.02.

5.1.25.13.

N-(4-(3,3'-bipyridin-4-yloxy)-3-fluorophenyl)-1-(3,4-difluorophenyl)-1*H*-4,1,2-benzothiadiazine-3-carboxamide-4,4-dioxide (**26b**).

Gray solid; yield: 36.1%; m.p.: 175-177°C; MS (ESI) *m*/*z*: 602.0 $[M+H]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 9.08 (s, 1H), 8.70 (s, 1H), 8.52 (d, *J* = 3.9 Hz, 1H), 8.16 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.10 (m, 1H), 7.88 (dd, *J* = 11.7, 1.1 Hz, 1H), 7.63 (s, 1H), 7.59–7.50 (m, 2H), 7.50–7.42 (m, 3H), 7.38 (m, 2H), 7.34–7.30 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.56 (d, *J* = 7.6 Hz, 1H); Anal. calcd. for $C_{30}H_{18}F_3N_5O_4S$ (%): C, 59.90; H, 3.02; N, 11.64. Found (%): C, 59.86; H, 3.01; N, 11.62.

5.1.25.14.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-1-(3-fluorophenyl)-1*H*-4,1,2-benzothiadiazine-3-carboxamide-4,4-dioxide (**26c**).

Gray solid; yield: 38.2%; m.p.: 216-218°C; MS (ESI) *m*/*z*: 584.5 $[M+H]^+$, 606.6 $[M+Na]^+$. IR (KBr, cm^{-1}): 3423.3, 3331.9, 3182.4, 3032.5, 1678.9, 1662.1, 1653.2, 1528.4, 1479.9, 1263.4, 1252.8, 1234.6, 1152.2, 1139.4, 1136.2, 1038.3, 874.4, 758.1, 631.5;^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.85 (s, 1H), 8.70 (s, 1H), 8.54 (d, *J* = 3.7 Hz, 1H), 8.19 (dd, *J* = 7.3, 2.3 Hz, 1H), 8.11 (m, 1H), 7.90 (dd, *J* = 12.2, 2.0 Hz, 1H), 7.62 (m, 2H), 7.55 (m, 2H), 7.47 (m, 2H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.33 (m, 4H), 6.90 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.57 (d, *J* = 7.7 Hz, 1H); Anal. calcd. for $C_{30}H_{19}F_2N_5O_4S$ (%): C, 61.75; H, 3.28; N, 12.00. Found (%): C, 61.72; H, 3.23; N, 11.95.

5.1.25.15.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-2-(4-chlorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide (**27a**).

Gray solid; yield: 41.2%; m.p.: 175-179°C; MS (ESI) *m*/*z*: 564.1 $[M+H]^+$, 586.2 $[M+Na]^+$. IR (KBr, cm^{-1}): 3436.2, 3312.4, 3179.2, 3029.3, 1680.9, 1663.1, 1651.9, 1525.8, 1265.1, 1254.8, 1231.1, 1156.2, 1132.7, 1097.1, 1036.7, 881.9, 798.1, 697.9, 651.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.85 (s, 1H), 8.50 (d, *J* = 4.6, 1H), 8.38 (d, *J* = 4.0 Hz), 8.27 (d, *J* = 4.0 Hz), 8.21 (s, 1H), 8.11–8.02 (m, 2H), 7.91 (d, *J* = 7.5Hz, 1H), 7.76 (t, 1H), 7.61–7.52 (m, 3H), 7.34–7.28 (m, 3H), 6.40 (d, *J* = 7.6 Hz, 1H); Anal. calcd. for $C_{27}H_{17}ClFN_5O_3$ (%): C, 63.10; H, 3.33; N, 13.63. Found (%): C, 63.12; H, 3.28; N, 13.66.

5.1.25.16.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-

4-carboxamide (**27b**).

Gray solid; yield: 37.3%; m.p.: 204-206°C; MS (ESI) *m/z*: 548.2 $[M+H]^+$, 560.2 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.85(s, 1H), 8.50 (d, J = 4.6, 1H), 8.38 (d, J = 4.0 Hz, 1H), 8.27(d, J = 4.0 Hz, 1H), 8.21 (s, 1H), 8.12–8.03 (m, 2H), 7.92 (d, J = 7.6 Hz, 1H), 7.78 (t, 1H), 7.71–7.62 (m, 3H), 7.45–7.39 (m, 3H), 6.40 (d, J = 7.6 Hz, 1H); Anal. calcd. for $C_{27}H_{17}F_2N_5O_3$ (%): C, 65.19; H, 3.44; N, 14.08. Found (%): C, 65.15; H, 3.48; N, 14.06.

5.1.25.17.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-5-phenyl-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (**28a**).

Pale yellow solid; yield: 48.6%; m.p.: 203-206°C; MS (ESI) *m/z*: 493.2 $[M+H]^+$. IR (KBr, cm^{-1}): 3431.7, 3031.5, 2963.6, 2882.3, 1680.8, 1665.1, 1653.0, 1529.2, 1445.1, 1377.1, 1261.6, 1252.9, 1233.1, 1151.7, 1135.6, 1098.1, 876.2, 821.3, 659.1; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 12.53(s, 1H), 8.87(s, 1H), 8.76(d, J = 2.8 Hz, 1H), 8.67(d, J = 2.6 Hz, 1H), 8.51(d, J = 3.8 Hz, 1H), 8.23(d, J = 2.0 Hz, 1H), 8.16-8.07(m, 2H), 7.99-7.89(m, 1H), 7.78(t, J = 8.7 Hz, 1H), 7.69(d, J = 7.3 Hz, 2H), 7.61(dd, J = 7.6, 1.9 Hz, 1H), 7.51(t, J = 7.7 Hz, 2H), 7.45-7.38(m, 2H), 6.41(d, J = 7.6 Hz, 1H), 3.76(s, 3H); Anal. calcd. for $C_{29}H_{20}ClFN_4O_3$ (%): C, 66.10; H, 3.83; N, 10.63. Found (%): C, 66.08; H, 3.77; N, 10.61.

5.1.25.18.

N-(4-((3,3'-bipyridin)-4-yloxy)-3-fluorophenyl)-5-(4-fluorophenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (**28b**).

Pale yellow solid; yield: 41.3%; m.p.: 193-195°C; MS (ESI) *m/z*: 511.2 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 12.52(s, 1H), 8.97(s, 1H), 8.72(d, J = 2.8 Hz, 1H), 8.65(d, J = 2.8 Hz, 1H), 8.58(s, 1H), 8.29(d, J = 9.8 Hz, 2H), 8.11(dd, J = 13.0, 2.1 Hz, 1H), 7.99-7.93(m, 1H), 7.78(t, J = 8.8 Hz, 1H), 7.75-7.69(m, 2H), 7.59(ddd, J = 12.5, 7.8, 3.1 Hz, 2H), 7.38-7.30(m, 2H), 6.44(d, J = 7.6 Hz, 1H), 3.74(s, 3H); Anal. calcd. for $C_{29}H_{20}F_2N_4O_3$ (%): C, 68.23; H, 3.95; N, 10.98. Found (%): C, 68.21; H, 3.92; N, 10.94.

5.2. Pharmacology

5.2.1. MTT assay *in vitro*

The cytotoxic activity of compounds (**23a-f**, **24a-d**, **25a-e**, **26a-f**, **27a-b** and **28a-b**) was evaluated with HT-29, MKN-45, A549 and MDA-MB-231 cells by the MTT assay *in vitro*, with Foretinib as references. The cancer cells were cultured in minimum essential medium (MEM) supplemented with 10% fetal bovine serum (FBS). Approximately 4×10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37°C for 24 h. The test compounds were added to the culture medium at the indicated final concentrations and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a final concentration of 5.0 μg/mL and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100.0 μL DMSO per each well, and the absorbency at 492 nm (for the absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with the ELISA reader. All of the compounds were tested three times in each of the cell lines. The results expressed as

IC_{50} (inhibitory concentration of 50%) were the mean ± SD and were calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

5.2.2. c-Met Kinase assays

The c-Met kinase activity was determined using homogenous time-resolved fluorescence (HTRF) assays following the manufacture's instruction, with Foretinib as positive control. Briefly, 20.0 mg/mL poly (Glu, Tyr) 4:1 (Sigma) was precoated as a substrate in 384-well plates. Then 50.0 mL of 10.0 mM ATP (Invitrogen) solution diluted in kinase reaction buffer (50.0 mM HEPES, pH 7.0, 1.0 M DTT, 1.0 M $MgCl_2$, 1.0 M $MnCl_2$, 0.1% NaN_3) was added to each well. Various concentrations of compounds diluted in 10.0 mL of 1% DMSO v/v were used as the negative control. The kinase reaction was initiated by the addition of purified tyrosine kinase proteins duluted in 39.0 mL of kinase reaction buffer solution. Reactions were incubated for 30 min at 25°C and stopped by the addition of 5.0 mL Streptavidin-XL665 and 5.0 mL Tk Antibody Cryptate working solution to all of wells. The plate was read using Envision (PerkinElmer) at 320 nm and 615 nm. The inhibition rate (%) was calculated using the following equation: % inhibition = 100 - [(activity of enzyme with tested compounds - min)/(max - min)]×100 (max: the observed enzyme activity measured in the presence of enzyme, substrates, and cofactors; min: the observed enzyme activity in the presence of substrates, cofactors and in the absence of enzyme). IC_{50} values were calculated from the inhibition curves.

Acknowledgments

The work was supported by Program for Liaoning Excellent Talents in University (LR2014030 and 2013921042) and National Natural Science Foundation of China (21002065).

References

[1] E. Gherardi, M. Stoker, *Nature* 346 (1990) 228.

[2] M. Trovato, M. Grosso, E. Vitarelli, S. Benvenga, F. Trimarchi, G. Barresi, *Cell. Mol. Biol*. 17 (2002) 691-698.

[3] N. D. D'Angelo, S. F. Bellon, S. K. Booker, Y. Cheng, *J. Med. Chem.* 51 (2008) 5766-5779.

[4] C. Birchmeier, W. Birchmeier, E. Gherardi, G. F. V. Woude, *Nat. Rev. Mol. Cell Biol.* 4 (2003) 915-925.

[5] K. Okuda, H. Sasaki, H. Yukiue, M. Yano, Y. Fujii, *Cancer Sci.* 99 (2008) 2280-2285.

[6] T. L. Underiner, T. Herbertz, S. J. Miknyoczki, *Anti-cancer Agents Med. Chem.* 10 (2010) 7-27.

[7] K. H. Jung, B. H. Park, S. S. Hong, *Arch. Pharmacol. Res*. 35 (2012) 595-604.

[8] R. Kurzrock, S. I. Sherman, D. W. Ball, A. A. Forastiere, R. B. Cohen, R. Mehra, D. G. Pfister, E. E.W. Cohen, L. Janisch, F. Nauling, D. S. Hong, C. S. Ng, L. Ye, R. F. Gagel, J. Frye, T. Müller, M. J. Ratain, R. Salgia, *J. Clin. Oncol*. 29 (2011) 2660-2666.

[9] C. K. Kollmannsberger, H. Hurwitz, G. Vlahovic, C. Maroun, J. Dumouchel, G. Reid, R. Martell, G. Shapiro, *The ASCO Annual Meeting*. Abstract (2009) e14525

[10] G. M. Schroeder, Y. M. An, Z. W. Cai, X. T. Chen, C. Clark, L. A. M. Cornelius, J. Dai, J. Gullo-Brown, A. Gupta, B. Henley, J. T. Hunt, R. Jeyaseelan, A. Kamath, K. Kim, J. Lippy, L. J. Lombardo, V. Manne, S. Oppenheimer, J. S. Sack, R. J. Schmidt, G. X. Shen, K. Stefanski, J. S. Tokarski, G. L. Trainor, B. S. Wautlet, D. Wei, D. K. Williams, Y. R. Zhang, Y. P. Zhang, J. Fargnoli, R. M. Borzilleri, *J. Med. Chem.* 52 (2009) 1251-1254.

[11] *https://integrity.thomson-pharma.com/integrity/xmlxsl*.

[12] W. Q. Xing, J. Ai, S. Y. Jin, Z. X. Shi, X. Peng, L. Wang, Y. C. Ji, D. Lu, Y. Liu, M. Y. Geng, Y. H. Hu, *Eur. J. Med. Chem*. 95 (2015) 302-312.

[13] W. K. Liao, C. Xu, X. H. Ji, G. Hu, L. X. Ren, Y. J. Liu, R. J. Li, P. Gong, T. M. Sun, *Eur. J. Med. Chem.* 87 (2014) 508-518.

[14] W. Zhang, J. Ai, D. K. Shi, X. Peng, Y. C. Ji, J. Liu, M. Y. Geng, Y. X. Li, *Eur. J. Med. Chem*. 80 (2014) 254-266.

[15] Y. Dai, D. W. Siemann, *Mol Cancer Ther*. 9 (2010) 1554-1561.

[16] S. Sharma, J. Y. Zeng, C. M. Zhuang, Y. Q. Zhou, H. P. Yao, X. Hu, R. Zhang, M. H. Wang, *Mol. Cancer Ther*. 12 (2013) 725-736.

[17] B. H. Qi, B. Mi, X. Zhai, Z. Y. Xu, X. L. Zhang, Z. R. Tian, P. Gong, *Bioorg. Med. Chem.* 21(2013) 5246-5260.

[18] S. Li, Q. Huang, Y. J. Liu, X. L. Zhang, S. Liu, C. He, P. Gong, *Eur. J. Med. Chem.* 64 (2013) 62-73.

[19] Q. D. Tang, Y. F. Zhao, X. M. Du, L. E. Chong, P. Gong, C. Guo, *Eur. J. Med. Chem.* 69 (2013) 77-89.

[20] S. Li, R. Jiang, M. Z. Qin, H. C. Liu, G. Y. Zhang, P. Gong, *Arch. Pharm. Chem. Life Sci*. 346 (2013) 521-533.

[21] Q. D. Tang, G. G. Zhang, X. M. Du, W. F. Zhu, R. J. Li, H. F. Lin, P. H. Li, M. S. Cheng, P. Gong, Y. F. Zhao, *Bioorg. Med. Chem.* 22 (2014) 1236-1249.

[22] V. Canibano, J. F. Rodriguez, M. Santos, M. A. Sanz-Tejedor, M. C. Carreno, G. Gonzalez, J. L. Garcia-Ruano, *Synthesis* 14 (2001) 2175-2179.

[23] R. C. F. Jones, A. K. Choudhury, J. N. Iley, G. Loizou, C. Lumley, V. McKee, *Synlett.* 4 (2010) 654-658.

[24] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* 60 (1995) 7508-7510.

[25] Y. T. Pratt, N. L. Drake, *J. Am. Chem. Soc. 82* (1960) 1155-1161.

[26] R. D. Carroll, M. W. Miller, B. L. Mylari, L.R. Chappel, H. L. Howes Jr, M. J. Lynch, J. E. Lynch, S. K. Gupta, J. J. Rash, R.C. Koch, *J. Med. Chem*. 26 (1983) 96-100.

[27] P. Bilek, J. Slouka, *Heterocycl. Commun*. 4 (1998) 325-331.

[28] A. Sugimoto, K. Sakamoto, Y. Fujino, Y. Takashima, M. Ishikawa, *Chem. Pharm. Bull.* 33 (1985) 2809-2820.

[29] R. C. Elderfield, S. L. Wythe, *J. Org. Chem.* 19 (1995) 683-692.

[30] R. K. Mahajan, V. P. Patial, *P Natl A Sci India A*. 72 (2002) 287-300.

[31] S. P. McManus, M. R. Smith, F. T. Herrmann, R. A. Abramovitch, *J. Org. Chem.* 43 (1978) 647-649.

[32] H. McNab, I. Stobie, *J. Chem. Soc. Perkin Trans. Ⅰ*. (1982) 1845-1853.

[33] J. Marcoux, F. Marcotte, J. Wu, P. G. Dormer, I. W. Davies, D. Hughes, P. J. Reider, *J. Org. Chem*. 66 (2001) 4194-4199.

Legends

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

Fig. 2. Design and structures of the target compounds.

Scheme 1. Reagents and conditions: (i) NBS, CH_3CN, r.t.; (ii) $NaNO_2$, H_2SO_4/H_2O, NaOH 0°C to 95°C; (iii) 3,4-difluoronitrobenzene, DMF, K_2CO_3, 80°C; (iv) 3-bromopyridine, bis(pinacolato)diboron, KOAc, $PdCl_2(PPh_3)_2$, dioxane, 90°C to r.t.; Na_2CO_3, H_2O, 90°C; (v) Fe, 95% EtOH, NH_4Cl (cat), AcOH, reflux; (vi) DIPEA, EtOH, reflux; (vii) DIPEA, EtOH, substituted anilines, reflux to r.t..

Scheme 2. Reagents and conditions: (i) HCl, $NaNO_2$, AcONa, EtOH, 0°C; (ii) glyoxal, AcONa, reflux; (iii) NaH, CH_3I, DMF, 0°C (iv) glyoxal, HCl, H_2O, reflux; (v) $SOCl_2$, Tol, reflux; DIPEA, CH_2Cl_2, 0°C to r.t..

Scheme 3. Reagents and conditions: (i) $KMnO_4$, NaOH, H_2O, 100°C (ii) EtOH, H_2O, r.t.; (iii) $SOCl_2$, Tol, reflux; DIPEA, CH_2Cl_2, 0°C to r.t.; (iv) $NaNO_2$, HCl, H_2O, 0°C to r.t.; Na_2SO_3, r.t..

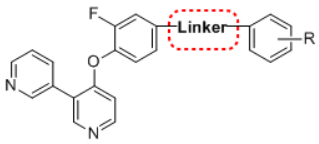
Scheme 4. Reagents and conditions: (i) ethyl chloroacetate, K_2CO_3, acetone, r.t.; (ii) 30% H_2O_2, AcOH, 100°C; (iii) AcONa, MeOH, 0°C; (iv) K_2CO_3, DMF, r.t., $NaOH/H_2O$, r.t.;(v) $SOCl_2$, Tol, reflux; DIPEA, CH_2Cl_2, 0°C to r.t..

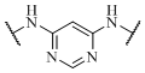
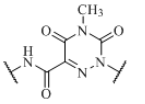
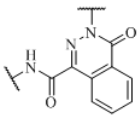
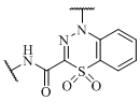
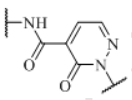
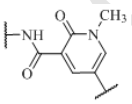
Scheme 5. Reagents and conditions: (i) 40% glyoxal, $AcOH/H_2O$ (1:1), r.t.; (ii) meldrum's acid, piperidine, Tol, r.t.; (iii) MeONa, MeOH, reflux.; (v) $SOCl_2$, Tol, reflux; DIPEA, CH_2Cl_2, 0°C to r.t..

Scheme 6. Reagents and conditions: (i) $POCl_3$, DMF, HPF_6, NaOH, H_2O, 10°C; (ii) diethyl malonate, *t*-BuOK, THF, 45°C; CH_3NH_2, DMF, 70°C; (iii) $SOCl_2$, Tol, reflux; DIPEA, CH_2Cl_2, 0°C to r.t..

Table 1. Cytotoxicity of target compounds against A549, HT-29, MKN-45 and MDA-MB-231 cells and c-Met kinase inhibition *in vitro*.

Table 1. Cytotoxicity of target compounds against A549, HT-29, MKN-45 and MDA-MB-231 cells and c-Met kinase inhibition *in vitro*.



Compd.	Linker	R	IC_{50}(μM) [a]				c-Met
			HT-29	A549	MKN-45	MDA-MB-231	IC_{50}(nM)
23a		H	0.88±0.07	0.41±0.04	6.3±0.58	2.74±0.29	53.1
23b		4-OCH_3	4.11±0.39	2.14±0.02	1.01±0.11	ND [b]	ND
23c		3,4-di-F	2.32±0.15	7.63±0.07	0.08±0.008	6.77±0.68	37.5
23d		4-Cl	0.98±0.10	1.61±0.16	0.24±0.03	ND	ND
23e		3-Cl	0.69±0.06	0.18±0.02	0.03±0.003	0.09±0.009	24
23f		4-F	0.33±0.03	0.71±0.07	0.16±0.02	14.10±1.42	ND
23g		3,5-OCH_3	1.13±0.12	0.56±0.06	1.75±0.16	4.24±0.42	ND
24a		2-F	2.10±0.18	0.61±0.06	4.78±0.05	6.76±0.66	84.6
24b		4-Cl	0.44±0.04	0.93±0.09	1.6±0.15	3.22±0.32	47.5
24c		3-CF_3	0.51±0.055	0.46±0.044	1.95±0.19	3.98±0.38	ND
24d		2,6-di-Cl	0.78±0.082	0.72±0.078	3.93±0.38	9.69±0.94	56.3
24e		3-Cl,4-F	4.78±0.49	12.50±1.21	10.10±1.03	11.3±1.15	103.2
24f		2,4-di-OCH_3	0.89±0.092	0.89±0.091	2.82±0.28	3.27±0.33	ND
25a		4-OCH_3	ND	6.8±0.70	0.74±0.07	10.4±1.02	89.3
25b		3-F	0.41±0.04	1.75±0.18	0.027±0.003	0.072±0.007	19.0
25c		H	1.24±0.14	7.9±0.81	0.09±0.009	8.2±0.81	ND
25d		4-F	0.99±0.09	0.82±0.08	0.32±0.03	ND	51.6
25e		4-Cl	0.71±0.07	1.02±0.11	0.43±0.04	ND	ND
26a		2-CF_3	0.19±0.02	0.12±0.01	0.027±0.003	0.046±0.005	17.3
26b		3,4-di-F	1.55±0.14	1.3±0.01	0.09±0.009	0.034±0.003	46.5
26c		3-F	0.43±0.04	0.9±0.09	0.003±0.0003	0.01±0.001	8.2
27a		4-Cl	4.56±0.48	6.56±0.68	4.23±0.43	4.84±0.49	89.8
27b		4-F	4.77±0.43	2.88±0.28	3.12±0.34	5.2±0.54	ND
28a		H	7.42±0.79	7.6±0.75	5.4±0.53	9.5±0.98	ND
28b		4-F	11.23±1.09	8.3±0.81	7.1±0.68	11.9±0.18	106.4
Foretinib			0.17±0.019 [c]	0.26 ± 0.026 [d]	0.023 ± 0.0015 [e]	0.54± 0.06	1.1 [f]

[a] Data presented is the mean ± SD value of three independent determinations.

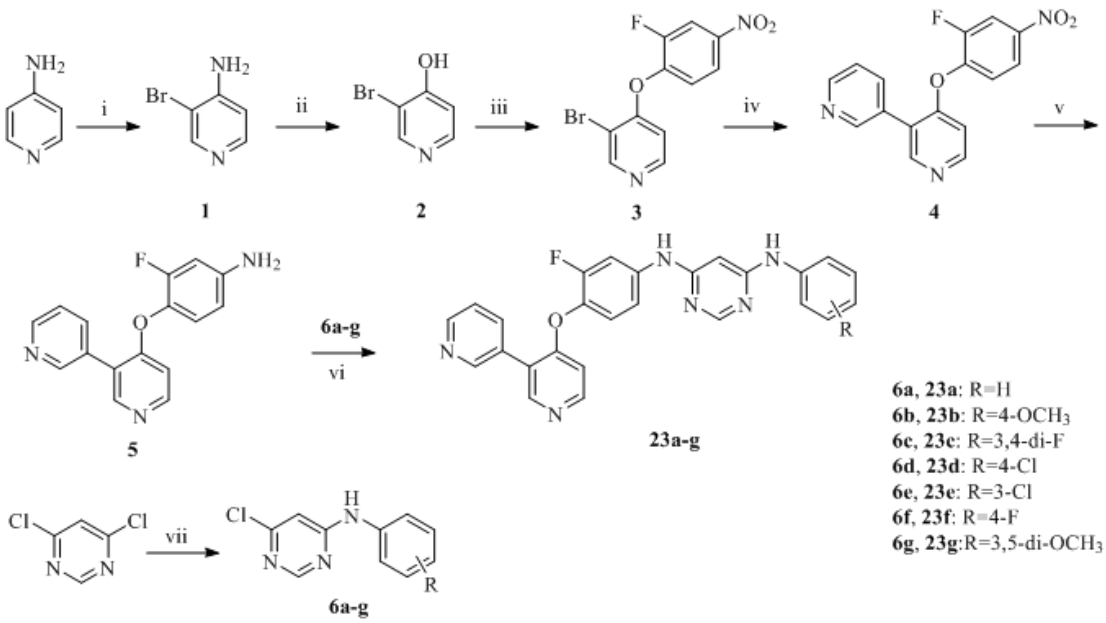
[6] ND = not determined

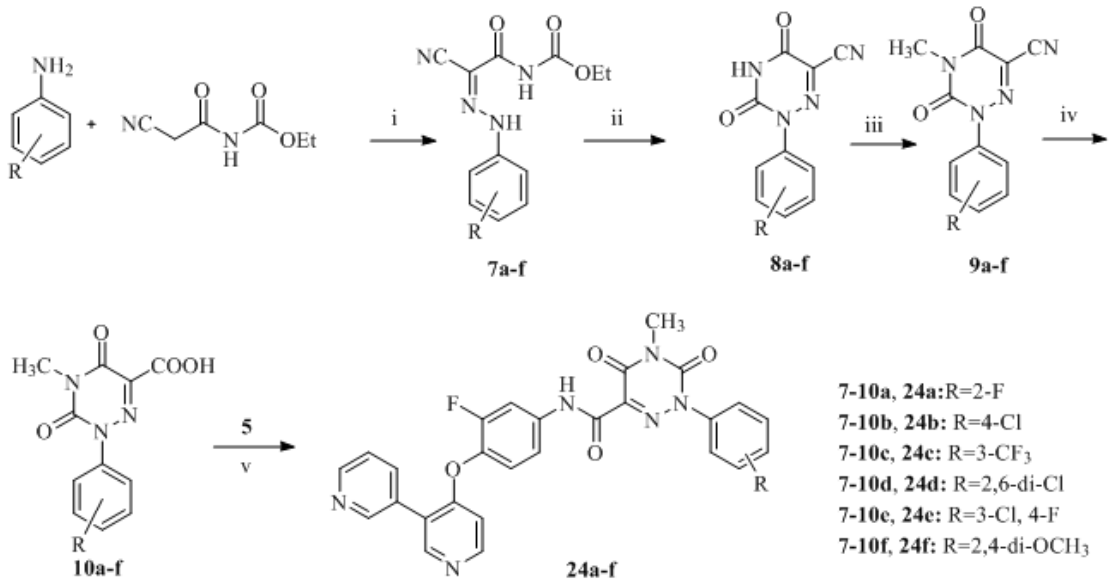
[c] Reported IC_{50} = 29 nM.[31]

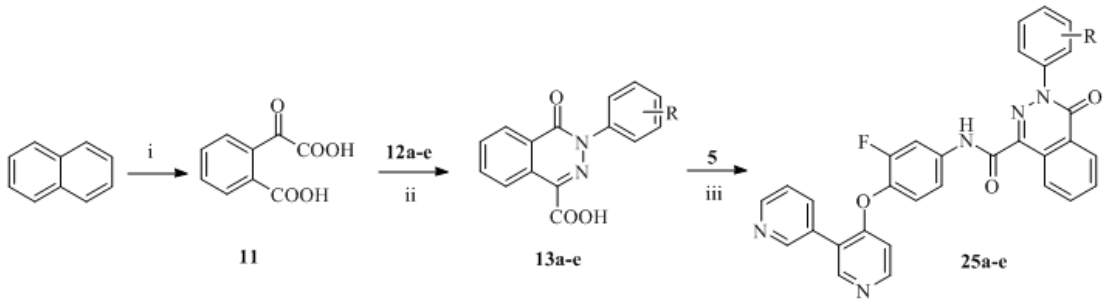
[d] Reported IC_{50} = 165 nM.[31]

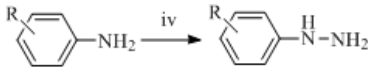
[e] Reported IC_{50} = 8 nM.[32]

[f] Reported IC_{50} = 4 nM.[31]



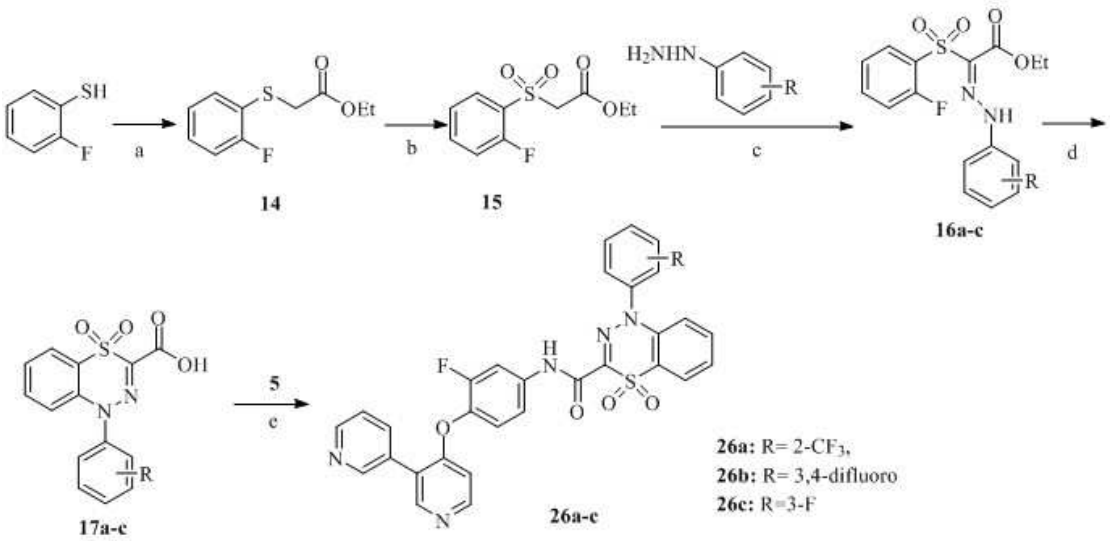


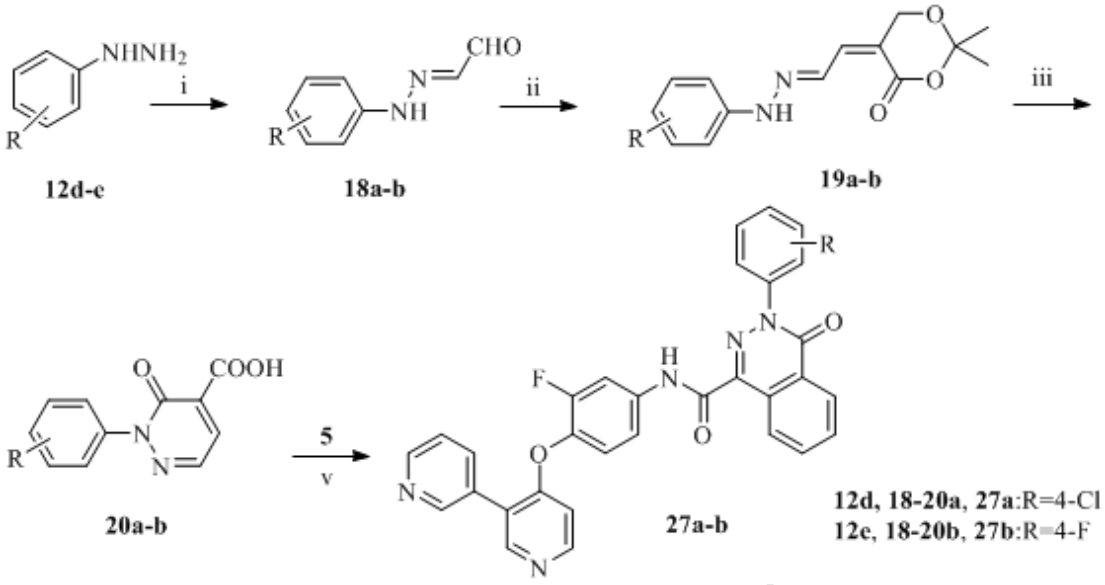


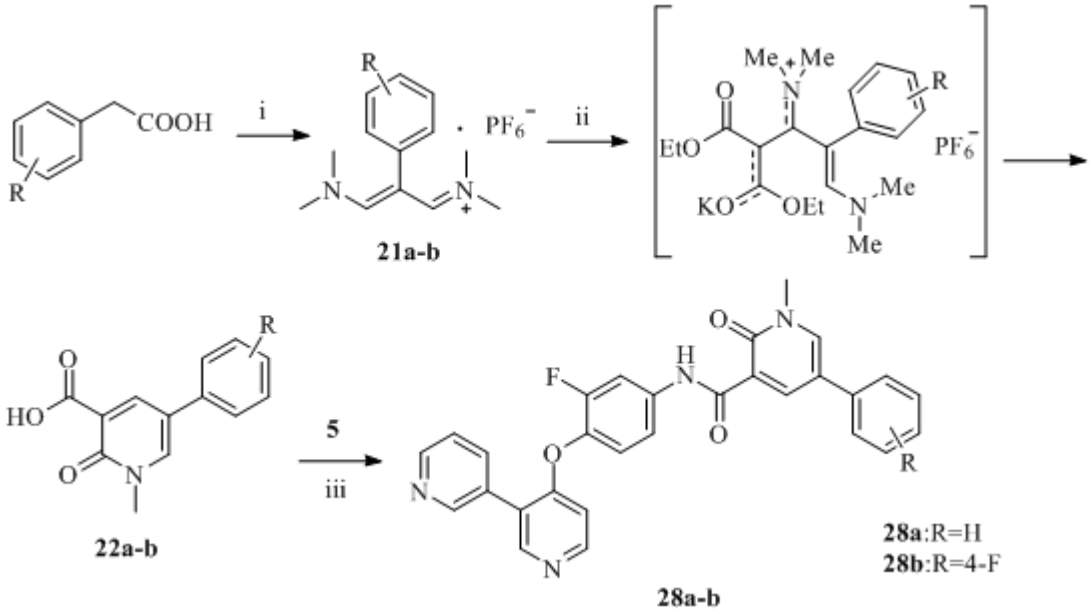


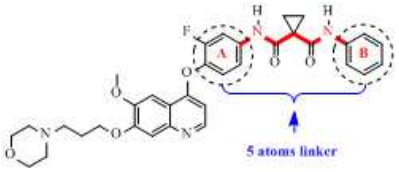
12a-e

12-13a, **25a**: R=4-OCH_3
12-13b, **25b**: R=3-F
12-13c, **25c**: R=H
12-13d, **25d**: R=4-F
12-13e, **25e**: R=4-Cl

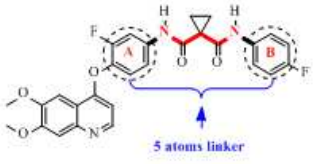




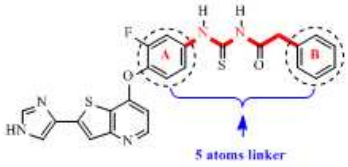




Foretinib

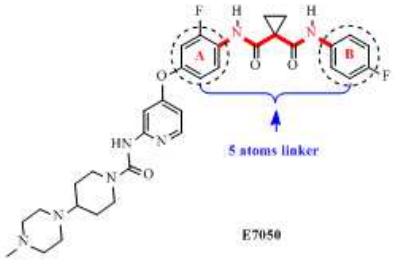


Cabozantinib

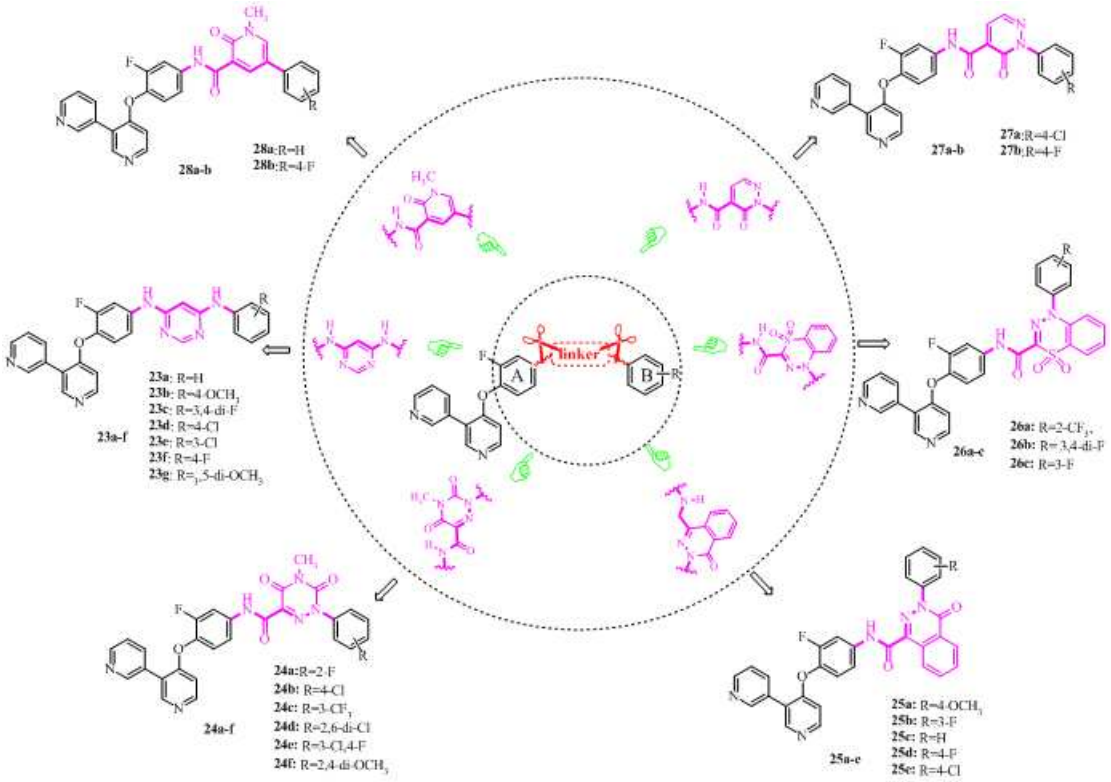


MGCD-265

BMS-777607



E7050



- Twenty-five novel 4-(2-fluorophenoxy)-3, 3'-bipyridine derivatives were designed and synthesized.
- Six series of aza-aryl formamide/amine scaffolds as linker were designed to identify the "**five-atom regulation**"
- The cytotoxicity of **26c** was more potent against MKN-45 and MDA-MB-231 cell lines than Foretinib.
- Compound **23n** displayed preferable activity for c-Met kinase (IC_{50} =8.2 nM).