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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis and biological evaluation of phenylpicolinamide sorafenib derivatives as antitumor agents

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Abstract Two series of phenylpicolinamide sorafenib derivatives (**14a–k**, **15a–k**) were designed and synthesized. They were evaluated for IC_{50} values against three cancer cell lines (A549, Hela, and MCF-7) and VEGFR2/KDR, BRAF, and CRAF kinases. Fourteen target compounds showed moderate to excellent cytotoxicity activity against the different cancer cells with potency from the single-digit μM to nanomole range. What's more, six of them were equal to more potent than sorafenib against one or more cell lines. Most of the compounds showed bad activity against VEGFR2/KDR, BRAF, or CRAF kinases. The most promising compound **15f** showed strong antitumor activities against A549 and MCF-7 cell lines with IC_{50} values of 5.43 ± 0.74 and 0.62 ± 0.21 μM, which were 1.29–6.79-fold more active than sorafenib (6.53 ± 0.82, 4.21 ± 0.62 μM), respectively and it exhibited moderate IC_{50} (7.1 μM) than **14f** (IC50 = 3.1 μM). Structure–activity relationships (SARs) and docking studies indicated that replacement of diarylurea of sorafenib with phenylpicolinamide moiety benefits to the activity. The position of aryl group and the substitutions of aryl group have a great influence on antitumor activity and selectivity. Small volume groups of aryl group such as (substituted) alkyl groups (–CH_3, –CF_3), halogen atoms (–F) were favorable to the cytotoxicity. Exact action mechanism of target compounds is not quite clear and further study will be carried out to identify the target in near future.

Keywords Synthesis · Anticancer activity · Breast cancer MCF-7 · Inhibitors

Introduction

Cancer, which endangers human life, is still one of the most common and serious diseases in the world. The development of molecular oncology and pharmacology accelerates the development of new anticancer drugs. However, it remains desirable to find new antitumor agents with improved tumor selectivity, efficiency, and safety.

In the past 15 years, many small molecules antitumor agents targeting in different kinases were developed and approved. vascular endothelial growth factor receptor kinase inhibitors such as sorafenib (Strumberg 2005), sunitinib (Motzer et al. 2006), and pazopanib (Harris et al. 2008) are one important group of tyrosine kinase inhibitors. As the first diaryl urea multikinase inhibitor, sorafenib was approved by FDA for the treatment of patients with advanced renal cell carcinoma (Strumberg 2005; Wilhelm et al. 2006) and unresectable hepatocellular carcinoma (Keating and Santoro 2009) in December 2005 and November 2007, respectively. It can inhibit cancer cell growth by interrupting the RAS/RAF/MEK/ERK and VEGFR2 signaling pathway (Wilhelm et al. 2004, 2008; Wan et al. 2004; Lyons et al. 2001).

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In recent years, a number of new sorafenib analogs have been reported (Fig. 1). Among those alalogs, BMS-794833 is a potent ATP competitive inhibitor of Met/VEGFR2 with IC_{50} of 1.7/15 nM. The main modification of BMS-794833 focused on diarylurea and nucleus of sorafenib. The structure–activity relationships (SARs) of BMS-794833 and its derivatives showed that as part of 4-oxo-5-phenyl-1, 4-dihydropyridine-3-carboxamide played an important role in the antitumor activity. Inspired by BMS-794833, we proposed phenylpicolinamide fragments instead of diarylurea to afford several series of compounds, which showed excellent potency as c-met inhibitor in our previous study (Fig. 1) (Tang et al. 2013). In the same way, we replaced diarylurea of sorafenib with phenylpicolinamide obtaining compounds **14a–k** and **15a–k** in this study. Further investigations were also carried out in detail to study the effect of different aryl ring substitutions on antitumor activity. The design strategy for target compounds is shown in Fig. 2.

Herein, we disclosed the synthesis and activity against A549, Hela, and MCF-7 cancer cell lines, VEGFR2/KDR, BRAF, and CRAF kinases of phenylpicolinamide sorafenib derivatives. Moreover, docking studies were presented in this paper as well.

Results and discussion

Chemistry

The preparation of target compounds **14a–k** and **15a–k** were described in Scheme 1.

The key intermediate 4-(4-aminophenoxy)-*N*-methylpicolinamide **4** was achieved from picolinic acid **1** as shown in Scheme 1, which has been illustrated in detail in our previous study (Zhu et al. 2014).

4-Bromo-pyridine-carboxylic acid **5** or 5-bromo-pyridine-carboxylic acid **6** was reacted with substituted phenylboronic acid **7a–k** through Suzuki-coupling reaction with bis (triphenylphosphine) palladium(II) dichloride as catalyst to get **8a–k** and **9a–k**, which were then chlorinated with oxalyl chloride to obtain **10a–k** and **11a–k**, respectively. Finally, reaction of amides **4** with acyl chlorides **10a–k** or **11a–k** promoted by DIPEA in dichloromethane at room temperature yielded the target compounds **14a–k** and **15a–k**.

Biological evaluation

Taking sorafenib as reference compound, the target compounds (**14a–k** and **15a–k**) were evaluated by the cytotoxicity against three cancer cell lines A549 (human lung cancer), Hela (human cervical cancer), and MCF-7(human breast cancer) by 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide (MTT) cell proliferation assay. In addition, these compounds were evaluated for IC_{50} values against VEGFR2/KDR, B-Raf, and C-Raf kinases in vitro by the Mobility shift assay or Lanthascreen assay together with reference compounds sorafenib and Staurosporine. The results expressed as inhibition rates or IC_{50} values were summarized in Tables 1, 2 and the values are the average of at least two independent experiments.

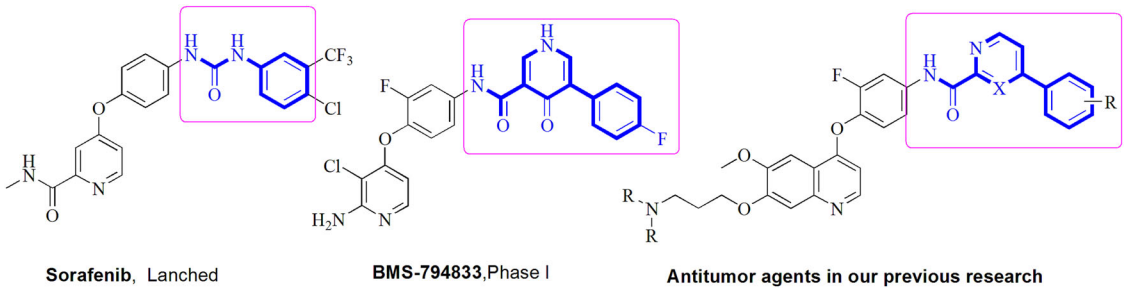


Fig. 1 Structures of small-molecule antitumor agents

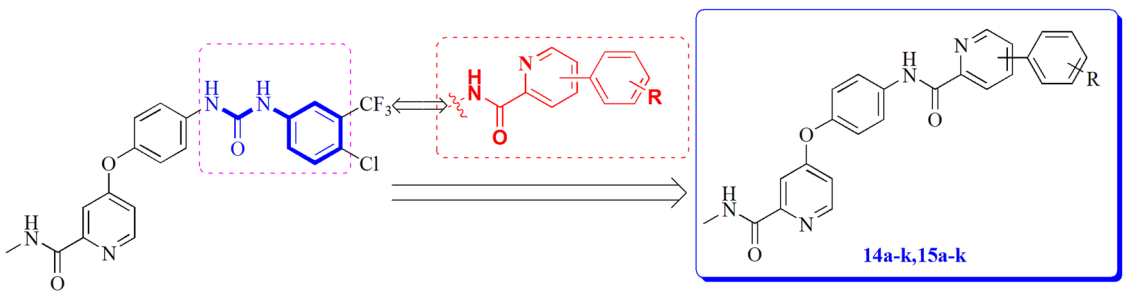
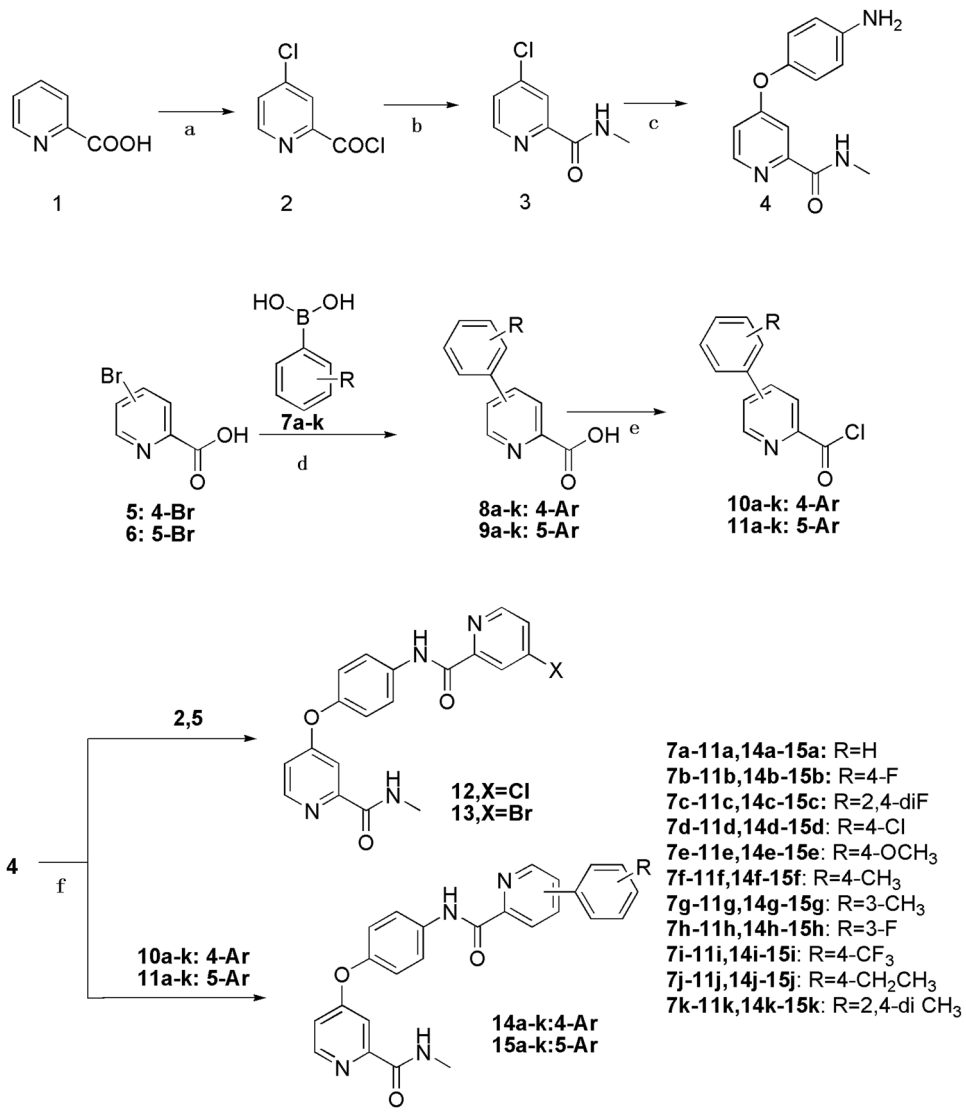


Fig. 2 Design strategies for 4-phenylpicolinamide sorafenib derivatives

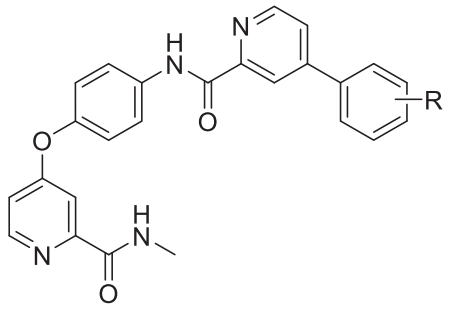


Scheme 1 Synthetic route of target compounds. Reagents and conditions: **a**$SOCl_2$,NaBr, chlorobenzene, 85 °C, 20 h; **b** 30% $MeNH_2$, toluene, 20, 6 h; **c** t-BuOK, NaI, DMF, 6 h; **d** $[(C_6H_5)_3P]_2PdCl_2$, Na_2CO_3, H_2O, 1,4-dioxane, 5–8 h; **e** $(COCl)_2$, DMF, CH_2Cl_2, 0.5 h; **f** DIPEA, CH_2Cl_2, 0.5 h

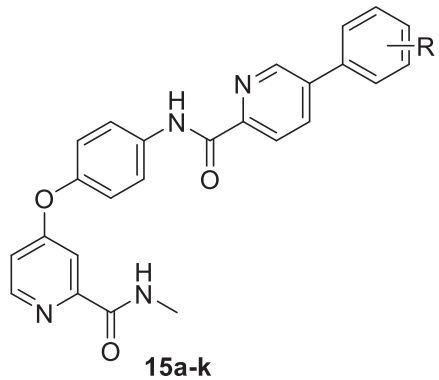
As illustrated in Tables 1 and 2, fourteen target compounds showed moderate to excellent cytotoxicity activity against different cancer cells with potency from the single-digit μM to nanomole range. In general, the first series of the target compounds (**14a–k**) were less active than the second series (**15a–k**) against the three tested cancer cell lines. The cytotoxicity activity against MCF-7cancer cell line was well while it's bad against Hela cell line. What's more, the two series of synthesized compounds exhibited well selectivity against MCF-7 to the other two cell lines, with the selectivity index (SI1 and SI2) from 0.9 to 20.5, which was higher than reference compound sorafenib (SI from 1.6 to 1.9). It's indicated that the position of substituted benzene ring has a strong influence on antitumor activity and selectivity.

Among fourteen active compounds, six of them (compounds **14k**, **15c**, and **15f–i**) were equal to more potent than sorafenib against one or more cell lines. Compounds **14k**, and **15f–i** exhibit excellent activity with the IC_{50} values in single-digit μM to nanomole range. Especially, compound **15f** showed superior activity against A549 and MCF-7 cancer cell lines to sorafenib, with the IC_{50} values of 5.43 and 0.62 μM against A549 and MCF-7 cell lines, which are 1.29 and 6.79 times more active than sorafenib (IC_{50} values: 6.53 and 4.21 μM), respectively. The results suggested that replacement of sorafenib diarylurea with phenylpicolinamide moiety maintained even improved the potent cytotoxic activity. Furthermore, substitutions of aryl group affected the cytotoxicity of target compounds. But, no obvious regularity can be found about these two series of compounds. It seems that small volume aryl groups such as substitutions alkyl groups (–CH_3, –CF_3), halogen atoms (–F) may be favored by the cytotoxicity. For the first series, small volume group in 2-position is very important and that's why compounds **14c** (2, 4-di F), **14k** (2,4-di CH_3) are more active than **14a** (H), **14b** (4-F) and **14f** (4-CH_3). For

Table 1 Structures and cytotoxicity activity of compounds **12–13**, **14a–k**, **15a–k**



14a-k



15a-k

Comp. no.	R	$IC_{50}(\mu M)$[a]			Selective index	
		A549	Hela	MCF-7	SI1[c]	SI2[d]
12	–	ND	ND	ND	–	–
13	–	ND	ND	ND	–	–
14a	H	NA	NA	NA	–	–
14b	4-F	NA	NA	NA	–	–
14c	2,4-di F	**17.14 ± 1.23**[e]	NA	**11.64 ± 1.07**	1.5	–
14d	4-Cl	NA	NA	NA	–	–
14e	4-OCH_3	NA	NA	NA	–	–
14f	4-CH_3	**45.66 ± 1.66**	NA	50.95 ± **1.71**	0.9	–
14g	3-CH_3	NA	NA	26.28 ± 1.42	–	–
14h	3-F	NA	NA	NA	–	–
14i	4-CF_3	NA	NA	NA	–	–
14j	4-CH_2CH_3	NA	NA	NA	–	–
14k	2,4-di CH_3	**13.34 ± 1.13**	**50.01 ± 1.70**	**4.49 ± 0.65**	3.0	11.1
15a	H	**29.72 ± 1.47**	**49.61 ± 1.69**	**10.37 ± 1.02**	2.9	4.8
15b	4-F	27.70 ± 1.44	NA	14.89 ± 1.17	1.9	–
15c	2,4-di F	**9.72 ± 0.99**	NA	NA	–	–
15d	4-Cl	NA	NA	36.73 ± 1.56	–	–
15e	4-OCH_3	NA	NA	21.33 ± 1.33	–	–
15f	4-CH_3	**5.43 ± 0.74**	NA	**0.62 ± 0.21**	8.8	–
15g	3-CH_3	**14.69 ± 1.17**	**19.93 ± 1.30**	**3.41 ± 0.53**	4.3	5.8
15h	3-F	**55.26 ± 1.74**	NA	**2.69 ± 0.43**	20.5	–
15i	4-CF_3	NA	NA	**6.06 ± 0.78**	–	–
15j	4-CH_2CH_3	**18.48 ± 1.27**	**36.00 ± 1.56**	**14.38 ± 1.16**	1.3	2.5
15k	2,4-di CH_3	**23.99 ± 1.38**	**14.13 ± 1.15**	NA	–	–
Sorafenib[b]	–	6.53 ± 0.82	8.08 ± 0.91	4.21 ± 0.62	1.6	1.9

NA not active (IC50 > 50 μM), *ND* not determined

[a] The values are an average of two separate determinations

[b] Used as a positive controls

[c] SI1 = IC_{50}(A549)/ IC_{50}(MCF-7)

[d] SI2 = IC_{50}(Hela)/ IC_{50}(MCF-7)

[e] Bold values means the IC_{50}s<50μM

Table 2 Activity against VEGFR2/KDR, BRAF, and CRAF kinases of compounds **12–13**, **14a–k**, and **15a–k**

Comp. no.	$IC_{50}(\mu M)$[a]		
	VEGFR2/KDR	BRAF	CRAF
12	>10	>10	>10
13	>10	>10	>10
14a	>10	>10	>10
14b	>10	>10	>10
14c	>10	>10	>10
14d	>10	>10	>10
14e	>10	>10	>10
14f	3.1	>10	>10
14g	>10	>10	>10
14h	>10	>10	>10
14i	>10	>10	>10
14j	6.6	>10	>10
14k	>10	>10	>10
15a	>10	>10	>10
15b	>10	>10	>10
15c	>10	>10	>10
15d	>10	>10	>10
15e	>10	>10	>10
15f	7.1	>10	>10
15g	>10	>10	>10
15h	>10	>10	>10
15i	>10	>10	>10
15j	>10	>10	>10
15k	>10	>10	>10
Sorafenib[b]	$94.9 \pm 1.1\%$ @10 μM	0.31 ± 0.62	ND
Staurosporine[b]	$97.3 \pm 2.8\%$	ND	ND

ND not determined

[a] The values are an average of two separate determinations

[b] Used as a positive controls

the second series, substitute in 2-position is not beneficial to the activity (**15f** vs. **15k**, **15b** vs. **15c**, with **15c** against A549 as an exception). Small volume aryl groups such as substitutions alkyl groups ($-CH_3$, $-CF_3$), halogen atoms (–F) substituted in 3-position or 4-position of aryl group remarkably improved the activity against MCF-7 cell line (**15f–i** vs. **15d**, **15e**, **15j**).

Activity against VEGFR2/KDR, BRAF, and CRAF kinases of target compounds were further carried out in this paper to investigate the target of these compounds. To our disappointment, nearly all of the compounds showed no activity against all those three kinases. Only three (**14f**, **14j**, and **15f**) of the compounds showed IC_{50} less than 10 μM. The results suggested that this series of target compounds may target in none of VEGFR2/KDR, BRAF, and CRAF kinases.

Shortly, the target compounds especially the second series (**15a–k**) showed high cytotoxicity and selectivity toward MCF-7 to other cancer cell lines. It is suggested that phenylpicolinamide moiety benefits to the activity and selectivity of target compounds. Nevertheless, almost all of the compounds showed bad activity against VEGFR2/KDR, BRAF, and CRAF kinases. Therefore, exact action mechanism is not quite clear right now. Further study will be carried out to identify the target in near future.

Molecular docking study

To explain why compound **15f** was most active and to explore the binding modes of target compounds with the active site of VEGFR2/KDR, molecular docking simulation studies were carried out by using SURFLEX-DOCK module of SYBYL package. Based on the in vitro results, we selected compound **15f** in this study as the ligand examples, and the structure of VEGFR2/KDR was selected as the docking model (PDB ID code: 4ASD (Wang et al. 2014)).

The binding modes of compound **15f** and lead compounds were shown in Fig. 3. As depicted in Fig. 3, compound **15f** and Sorafenib mostly overlap in the binding model and amide group, phenylpicolinamide group, form three hydrogen bonds with residues ASP1046, CYS919, respectively. According to compound **15f**'s binding mode in the active binding site, it demonstrate that the docking mode of the **15f** is similar to the lead compound sorafenib and the three hydrogen bonds play an important role in the increasement of the inhibitory potency of phenylpicolinamide derivatives against VEGFR2/KDR kinase. Furthermore, the docking results also give us a new direction to design new VEGFR2 inhibitors. Those SAR analysis results and molecular docking study reveal the possibility of rational design of more potent VEGFR2 inhibitors

Conclusion

In summary, two series of phenylpicolinamide sorafenib derivatives were designed and synthesized. All the target compounds were evaluated against three cancer cell lines, VEGFR2/KDR, BRAF, and CRAF kinases. Fourteen synthesized compounds showed moderate to excellent cytotoxicity activity against different cancer cells with potencies from the single-digit μM to nanomole range and six of them were equal to more potent than sorafenib against one or more cell lines. The cytotoxicity and activity against MCF-7 cancer cell line was attractive and two series compounds exhibited well selectivity against MCF-7 to the other two cell lines. Compound **15f** showed best activity against A549 and MCF-7 cancer cell lines with the IC_{50} values of 5.43 and 0.62 μM against A549 and MCF-7 cell lines, which are

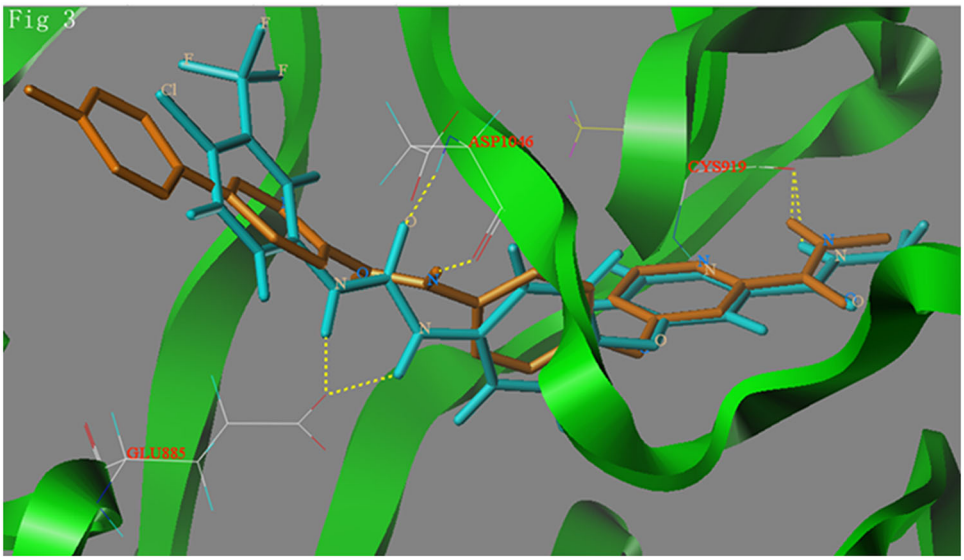


Fig. 3 Binding poses of compound **15f** with VEGFR2. The proteins were denoted by green ribbon. Compound **15f** and lead compound were denoted by orange and cyan sticks, respectively. H-bonding interactions between the **15f**, lead compound and VEGFR2 were denoted by dashed lines in yellow (color figure online)

1.29 and 6.79 times more active than sorafenib. The aryl group position and aryl group substitutions have a strong influence on antitumor activity and selectivity. Small aryl group volume groups such as substitutions alkyl groups (–CH_3, –CF_3), halogen atoms (–F) were favorable to the cytotoxicity. Three compounds show moderate activity against VEGFR2/KDR kinases and the most promising compound **15f** exhibited moderate IC_{50} (7.1 μM) than **14f** (IC50 = 3.1 μM). Although all the target compounds showed less activity against VEGFR2/KDR kinases than the positive compounds sorafenib and staurosporine, it still showed that replacement of urea with phenylpicolinamide unit is important to the activity of this series of compounds. More compounds of sorafenib analogs bearing a phenylpicolinamide may be screened by replacing the aryl groups with heterocyclic rings in future study.

Experimental

Chemistry

All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were unchanged. Nuclear magnetic resonance (NMR) spectra were performed by using Bruker 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with tetramethylsilane as an internal standard. Mass spectra (MS) were taken into ESI mode on Agilent 1100 LCMS (Agilent, Palo Alto, CA, USA). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specification. Yields were not optimized. Thin layer chromatography (TLC) analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specification. Numbering for ^{13}C NMR spectra was shown in Fig. 4.

General procedure for the key intermediate of 4-(4-aminophenoxy)-*N*-methylpicolinamide 4

Compound **4** was synthesized from compound **1** based on the procedures in our previous research Wilhelm et al. (2008).

General procedure for the preparation of compounds 8a–k and 9a–k

To the mixture of an appropriate amount of 4-bromo-pyridine-carboxylic acid **5** (0.9 mmol) or 5-bromo-pyridine-carboxylic acid **6**, substituted phenylboronic acid **7a–k** (0.18 mmol), anhydrous sodium carbonate (0.29 g, 2.7 mmol), 1,4-dioxane (30 mL), H_2O (10 mL), and bis (triphenylphosphine) palladium (II) dichloride (0.09 g, 0.135 mmol) were added under an atmosphere of nitrogen at room temperature. The reaction mixture was then stirred at 100 °C for 5–8 h and monitored by TLC. The reaction mixture was cooled to room temperature and the resulting precipitate was isolated by filtration to furnish the acid intermediate as the sodium salt, and then the solution was acidified to pH 5 to furnish the desired target compounds **8a–k** and **9a–k**.

Preparation of phenylpyridine chloride 10a–k and 11a–k

Oxalyl chloride (0.4 mmol) was added drop-wise into a stirred mixture of compounds **8a–k** or **9a–k** (0.2 mmol) and DMF(0.01 mmol) in dichloromethane (10 mL) under room

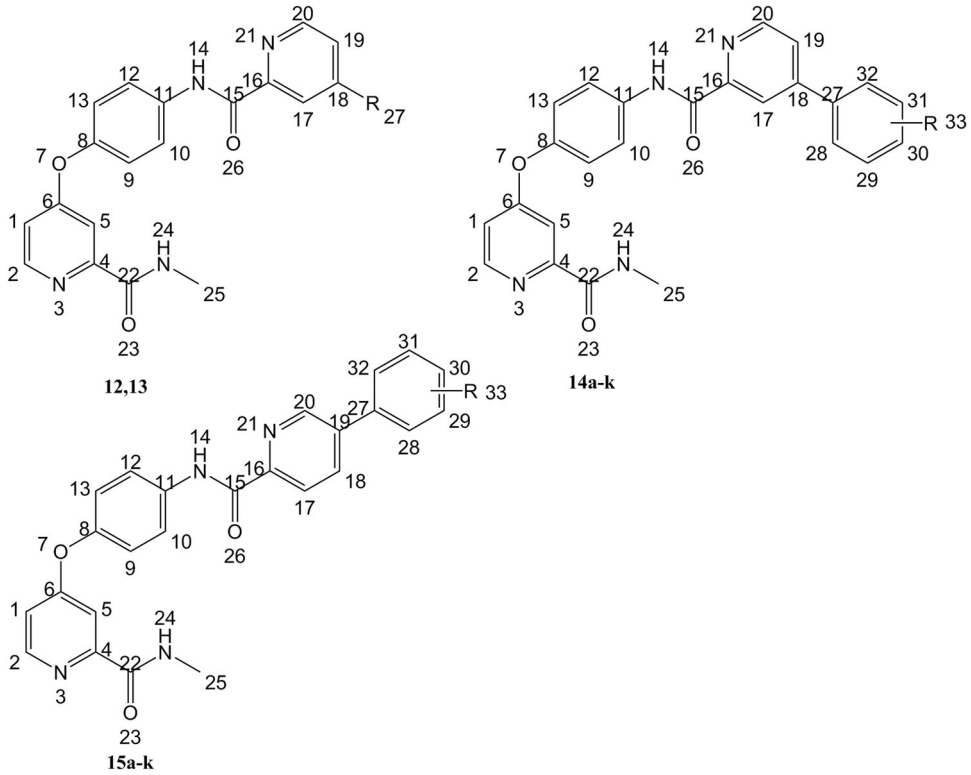


Fig. 4 Numbering for **13C** NMR spectra

temperature for 10 min, and the mixture was used in the coming step immediately without further purification.

General procedure for the preparation of compounds 12, 13, 14a–k, and 15a–k

A solution of an appropriate aniline **4** (0.41 mmol) and diisopropylethylamine (0.49 mmol) in dichloromethane (10 mL) was added drop-wise into a solution of phenylpyridine chloride (0.82 mmol, obtained in the previous step) in dichloromethane (10 mL) in an ice bath. With the above addition, the reaction mixture was removed from the ice bath and placed under room temperature for 30 min and monitored by TLC. The mixture was washed with 10% K_2CO_3 (50 mL × 3) followed by brine (50 mL × 1), and the organic phase was separated, dried, and evaporated to yield **12**, **13**, **14a–k**, and **15a–k** which was purified by isopropanol.

4-Chloro-N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl) picolinamide (**12**)*

Yield: 72.01%; m.p. 169.7–171.1 °C; MS (ESI) *m/z* (%): 383.2 $[M + H]^+$; ^{1}H NMR (400 MHz, dimethyl sulfoxide (DMSO)) δ 10.92 (s, 1H), 8.80 (d, $J = 4.6$ Hz, 1H), 8.73 (d, $J = 5.3$ Hz, 1H), 8.51 (d, $J = 5.6$ Hz, 1H), 8.17 (s, 1H), 8.04 (d, $J = 8.7$ Hz, 2H), 7.85 (d, $J = 5.2$ Hz, 1H), 7.39 (s, 1H), 7.25 (d, $J = 8.7$ Hz, 2H), 7.18–7.14 (m, 1H), 2.78 (d, $J = 4.7$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.63 (C, C-15), 164.31 (C, C-22), 161.94 (C, C-16), 152.88 (C, C-6), 150.92 (C, C-4), 149.72 (C, C-8), 145.37 (CH, C-20), 136.34 (C, C-11), 131.01 (C, C-18), 129.23 (CH, C-19), 128.53 (CH, C-2), 122.30 (CH, C-17), 121.31 (CH, C-10, C-12), 120.67 (CH, C-9, C-13), 115.45 (CH, C-1), 114.77 (CH, C-5), 26.32 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by ultraviolet (UV) absorption at 325 nm, revealed 98.2% purity.

4-Bromo-N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) pheny l) picolinamide (**13**)*

Yield: 65.52%; m.p. 172.7–173.9 °C; MS (ESI) *m/z* (%): 427.3 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.89 (d, $J = 4.8$ Hz, 1H), 8.74 (d, $J = 5.2$ Hz, 1H), 8.53 (d, $J = 5.7$ Hz, 1H), 8.17 (d, $J = 1.5$ Hz, 1H), 8.05 (d, $J = 8.9$ Hz, 2H), 7.85 (dd, $J = 5.3$, 2.0 Hz, 1H), 7.47 (d, $J = 2.3$ Hz, 1H), 7.26 (d, $J = 8.9$ Hz, 2H), 7.20 (dd, $J = 5.7$, 2.5 Hz, 1H), 2.79 (d, $J = 4.8$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.63 (C, C-15), 164.73 (C, C-22), 160.94 (C, C-16), 151.98 (C, C-6), 150.72 (C, C-4), 149.51 (C, C-8), 144.85 (CH, C-20), 136.25 (C, C-11), 131.31 (C, C-18), 128.93 (CH, C-19), 128.43 (CH, C-2), 122.82 (CH, C-17),

121.51 (CH, C-10, C-12), 119.97 (CH, C-9, C-13), 115.73 (CH, C-1), 114.51 (CH, C-5), 26.43 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.6% purity.

N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) pheny l)-4-phenylpicolinamide (**14a**)*

Yield: 45.25%; m.p. 190.7–192.9 °C; MS (ESI) *m/z* (%): 425.3 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.91 (s, 1H), 8.82 (t, $J = 4.5$ Hz, 1H), 8.79 (d, $J = 4.8$ Hz, 1H), 8.52 (d, $J = 5.6$ Hz, 1H), 8.43 (d, $J = 1.3$ Hz, 1H), 8.09 (d, $J = 9.0$ Hz, 2H), 8.02 (dd, $J = 5.1$, 1.8 Hz, 1H), 7.94–7.88 (m, 2H), 7.56 (ddd, $J = 10.8$, 9.8, 5.4 Hz, 3H), 7.42 (d, $J = 2.5$ Hz, 1H), 7.26 (d, $J = 9.0$ Hz, 2H), 7.18 (dd, $J = 5.6$, 2.6 Hz, 1H), 2.79 (d, $J = 4.8$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.91 (C, C-6), 162.76 (C, C-15), 160.92 (C, C-22), 151.73 (C, C-16), 151.14 (C, C-18), 150.76 (C, C-4), 149.51 (C, C-8), 146.53 (CH, C-2), 144.73 (CH, C-20), 143.35 (C, C-27), 31.31 (C, C-11), 129.23 (CH, C-30), 129.10 (CH, C-31), 128.83 (CH, C-29), 128.43 (CH, C-32), 126.42 (CH, C-28), 122.82 (CH, C-10, C-12), 121.01 (CH, C-19), 119.99 (CH, C-9, C-13), 114.82 (CH, C-17), 114.56 (CH, C-1), 109.85 (CH, C-5), 26.71 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 97.9% purity.

4-(4-fluorophenyl)-N-*(4-(2-(methylcarbamoy l) pyridin-4-yloxy) phenyl) picolinamide (**14b**)*

Yield: 58.09%; m.p. 213.6–214.2 °C; MS (ESI) *m/z* (%): 481.1 $[M + k]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.81 (d, $J = 4.6$ Hz, 2H), 8.52 (d, $J = 5.2$ Hz, 1H), 8.41 (s, 1H), 8.16–8.05 (m, 2H), 8.00 (d, $J = 8.5$ Hz, 2H), 7.42 (d, $J = 9.2$ Hz, 3H), 7.26 (d, $J = 8.6$ Hz, 2H), 7.18 (s, 1H), 2.79 (d, $J = 4.3$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.83 (C, C-6), 165.81 (C, C-30), 163.17 (C, C-15), 160.98 (C, C-22), 151.88 (C, C-16), 151.28 (C, C-18), 150.86 (C, C-4), 148.34 (C, C-8), 146.32 (CH, C-2), 144.62 (CH, C-20), 136.89 (C, C-27), 133.57 (C, C-11), 130.23 (CH, C-28, C-32), 122.51 (CH, C-10, C-12), 120.76 (CH, C-19), 120.12 (CH, C-9, C-13), 115.41 (CH, C-29, C-31), 114.83 (CH, C-17), 114.23 (CH, C-1), 109.56 (CH, C-5), 26.85 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.2% purity.

4-(2,4-Difluorophenyl)-N-*(4-(2-(methylcarbamoy l) pyridin-4-yloxy) phenyl) picolinamide (**14c**)*

Yield: 45.81%; m.p. 162.8–163.6 °C; MS (ESI) *m/z* (%): 499.1 $[M + k]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.94 (d, $J = 4.4$ Hz, 1H), 8.87 (d, $J = 5.0$ Hz, 1H), 8.56 (d, $J = 5.7$ Hz, 1H), 8.33 (s, 1H), 8.10 (d, $J = 8.9$ Hz, 2H), 7.90 (d, $J = 4.9$ Hz, 1H), 7.88–7.82 (m, 1H), 7.54 (s, 1H), 7.31 (dd, $J = 19.0$, 8.1 Hz, 3H), 7.25–7.20 (m, 1H), 2.81 (d, $J = 4.6$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.53 (C, C-6), 164.68 (C, C-15), 161.67 (C, C-30), 161.45 (C, C-22), 158.02 (C, C-28), 151.72 (C, C-16), 151.17 (C, C-18), 151.00 (C, C-4), 148.01 (C, C-8), 146.47 (CH, C-2), 144.60 (CH, C-20), 133.81 (C, C-11), 130.67 (CH, C-32), 126.45 (C, C-27), 122.37 (CH, C-10, C-12), 120.93 (CH, C-19), 119.25 (CH, C-9, C-13), 114.63 (CH, C-17), 113.92 (CH, C-1), 111.10 (CH, C-31), 109.67 (CH, C-5), 102.59 (CH, C-29), 26.74 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 99.1% purity.

4-(4-Chlorophenyl)-N-*(4-(2-(methylcarbamoy l) pyridin-4-yloxy) pheny l) picolinamide (**14d**)*

Yield: 51.6%; m.p. 217.1–217.9 °C; MS (ESI) *m/z* (%): 481.1 $[M+Na]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.83 (s, 1H), 8.79 (s, 1H), 8.52 (d, $J = 4.9$ Hz, 1H), 8.42 (s, 1H), 8.09 (d, $J = 6.9$ Hz, 2H), 8.03 (s, 1H), 7.95 (d, $J = 6.7$ Hz, 2H), 7.63 (d, $J = 6.7$ Hz, 2H), 7.42 (s, 1H), 7.26 (d, $J = 6.9$ Hz, 2H), 7.17 (s, 1H), 2.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.83 (C, C-6), 163.51 (C, C-15), 161.78 (C, C-22), 151.83 (C, C-16), 151.22 (C, C-18), 150.87 (C, C-4), 148.74 (C, C-8), 146.62 (CH, C-2), 143.45 (CH, C-20), 140.71 (C, C-27), 134.93 (C, C-30), 132.84 (C, C-11), 129.45 (CH, C-29, C-31), 128.10 (CH, C-28, C-32), 122.65 (CH, C-10, C-12), 120.83 (CH, C-19), 119.65 (CH, C-9, C-13), 114.36 (CH, C-17), 113.73 (CH, C-1), 109.46 (CH, C-5), 26.82 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.7% purity.

4-(4-Methoxyphenyl)-N-*(4-(2-(methylcarbamoy l) pyridin-4-yloxy) phenyl) picolinamide (**14e**)*

Yield: 44.69%; m.p. 168.9–171.1 °C; MS (ESI) *m/z* (%): 477.3 $[M + Na]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 8.79 (d, $J = 4.7$ Hz, 1H), 8.76 (d, $J = 5.2$ Hz, 1H), 8.52 (d, $J = 5.5$ Hz, 1H), 8.39 (s, 1H), 8.09 (d, $J = 8.7$ Hz, 2H), 7.97 (d, $J = 5.0$ Hz, 1H), 7.89 (d, $J = 8.6$ Hz, 2H), 7.42 (d, $J = 2.0$ Hz, 1H), 7.26 (d, $J = 8.7$ Hz, 2H), 7.20–7.16 (m,

1H), 7.13 (d, $J = 8.6$ Hz, 2H), 3.85 (s, 3H), 2.80 (d, $J = 4.7$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.92 (C, C-6), 162.57 (C, C-15), 161.32 (C, C-22), 151.58 (C, C-16), 151.13 (C, C-18), 151.07 (C, C-4), 148.09 (C, C-8), 146.74 (CH, C-2), 144.63 (CH, C-20), 139.42 (C, C-27), 133.94 (C, C-11), 132.17 (C, C-30), 129.54 (CH, C-29, C-31), 127.31 (CH, C-28, C-32), 122.47 (CH, C-10, C-12), 121.11 (CH, C-19), 119.45 (CH, C-9, C-13), 114.72 (CH, C-17), 114.02 (CH, C-1), 109.58 (CH, C-5), 55.79 (OCH_3, C-33), 26.83 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.8% purity.

N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl)-4-p-tolylpicolinamide (**14f**)*

Yield: 57.83%; m.p. 195.0–195.8 °C; MS (ESI) *m/z* (%): 461.3 $[M + Na]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.80 (d, $J = 4.9$ Hz, 2H), 8.53 (d, $J = 5.5$ Hz, 1H), 8.42 (s, 1H), 8.10 (d, $J = 8.7$ Hz, 2H), 8.01 (s, 1H), 7.82 (d, $J = 7.8$ Hz, 2H), 7.43 (s, 1H), 7.40 (d, $J = 7.6$ Hz, 2H), 7.27 (d, $J = 8.6$ Hz, 2H), 7.20 (s, 1H), 2.80 (d, $J = 4.5$ Hz, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.56 (C, C-6), 162.78 (C, C-15), 161.53 (C-22), 151.62 (C, C-16), 151.17 (C, C-18), 151.00 (C, C-4), 148.01 (C, C-8), 146.47 (CH, C-2), 144.60 (CH, C-20), 139.31 (C, C-27), 133.67 (C, C-11), 132.08 (C, C-30), 129.37 (CH, C-29, C-31), 127.43 (CH, C-28, C-32), 122.67 (CH, C-10, C-12), 120.91 (CH, C-19), 119.25(CH, C-9, C-13), 114.63 (CH, C-17), 113.92 (CH, C-1), 109.67 (CH, C-5), 26.75 (CH_3, C-25), 21.68 (CH_3, C-33). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 97.5% purity.

N-*(4-(2-(methylcarbamoy l) pyridin-4-yloxy) phenyl)-4-m-tolylpicolinamide (**14g**)*

Yield: 54.97%; m.p. 181.5–182.4 °C; MS (ESI) *m/z* (%): 477.1 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.81 (d, $J = 4.8$ Hz, 2H), 8.53 (d, $J = 5.6$ Hz, 1H), 8.42 (s, 1H), 8.10 (d, $J = 8.9$ Hz, 2H), 8.04–7.98 (m, 1H), 7.74 (s, 1H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.47 (t, $J = 7.7$ Hz, 1H), 7.43–7.39 (m, 1H), 7.36 (d, $J = 7.4$ Hz, 1H), 7.27 (d, $J = 9.0$ Hz, 2H), 7.18 (dt, $J = 8.3$, 4.1 Hz, 1H), 2.80 (d, $J = 4.8$ Hz, 3H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 168.96 (C, C-6), 162.97 (C, C-15), 160.16 (C, C-22), 151.72 (C, C-16), 157.32 (C, C-18), 151.11 (C, C-4), 149.00 (C, C-8), 146.32 (CH, C-2), 144.61 (CH, C-20), 143.17 (C, C-27), 138.60 (C, C-29), 131.54 (C, C-11), 129.57 (CH, C-30), 129.13 (CH, C-31), 128.87 (CH, C-28), 124.41 (CH, C-32), 122.34 (CH, C-10, C-12), 120.62 (CH, C-19), 119.61 (CH, C-9, C-13), 114.52 (CH, C-17), 113.43 (CH, C-1), 109.46 (CH, C-5), 26.88 (CH_3, C-25), 21.43 (CH_3,C-33). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.9% purity.

*4-(3-Fluorophenyl)-*N*-(4-(2-(methylcarbamoyl) pyridin-4-yloxy)phenyl) picolinamide (**14h**)*

Yield: 45.31%; m.p. 198.5–199.5 °C; MS (ESI) *m/z* (%): 481.1 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 8.85 (d, $J = 5.0$ Hz, 1H), 8.81 (d, $J = 4.4$ Hz, 1H), 8.53 (d, $J = 5.6$ Hz, 1H), 8.45 (s, 1H), 8.08 (dd, $J = 12.6$, 6.9 Hz, 3H), 7.85–7.75 (m, 2H), 7.63 (dd, $J = 14.3$, 7.8 Hz, 1H), 7.42 (d, $J = 2.0$ Hz, 2H), 7.27 (d, $J = 8.8$ Hz, 2H), 7.21–7.16 (m, 1H), 2.80 (d, $J = 4.7$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.87 (C, C-6), 162.44 (C, C-15), 161.99 (C, C-29), 159.61 (C, C-22), 152.37 (C, C-16), 149.97 (C, C-18), 149.71 (C, C-4), 149.06 (C, C-8), 146.72 (CH, C-2), 144.99 (CH, C-20), 143.67 (C, C-27), 133.91 (C, C-11), 124.36 (CH, C-31), 123.65 (CH, C-32), 122.85 (CH, C-10, C-12), 120.34 (CH, C-19), 119.70 (CH, C-9, C-13), 116.01 (CH, C-30), 114.25 (CH, C-28), 114.02 (CH, C-17), 113.23 (CH, C-1), 109.39 (CH, C-5), 26.14 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 97.9% purity.

N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl)-4-(4-(trifluoromethyl) phenyl) picolinamide (**14i**)*

Yield: 46.96%; m.p. 239.9–241.2 °C; MS (ESI) *m/z* (%): 531.2 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 8.90 (s, 1H), 8.82 (s, 1H), 8.54 (d, $J = 5.6$ Hz, 1H), 8.50 (s, 1H), 8.16 (d, $J = 8.0$ Hz, 2H), 8.11 (d, $J = 7.7$ Hz, 2H), 7.95 (d, $J = 7.8$ Hz, 2H), 7.42 (s, 1H), 7.28 (d, $J = 8.6$ Hz, 2H), 7.20 (s, 1H), 2.80 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.75 (C, C-6), 163.51 (C, C-15), 161.79 (C, C-22), 151.53 (C, C-16), 151.02 (C, C-18), 149.74 (C, C-4), 148.79 (C, C-8), 146.36 (CH, C-2), 145.67 (C, C-27), 144.60 (CH, C-20), 133.43 (C, C-11), 129.37 (C, C-30), 127.61 (CH, C-28, C-32), 125.93 (CH, C-29, C-31), 124.34 (C, C-33), 121.55 (CH, C-10, C-12), 120.88 (CH, C-19), 119.19 (CH, C-9, C-13), 114.04 (CH, C-17), 113.92 (CH, C-1), 109.67 (CH, C-5), 26.17 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.6% purity.

4-(4-Ethylphenyl)-N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl) picolinamide (**14j**)*

Yield: 43.23%; m.p. 199.1–200.5 °C; MS (ESI) *m/z* (%): 475.1 $[M + Na]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.81 (s, 2H), 8.53 (d, $J = 5.5$ Hz, 1H), 8.42 (s, 1H), 8.10 (d, $J = 8.6$ Hz, 2 H), 8.02 (s, 1H), 7.85 (d, $J = 7.8$ Hz, 2H), 7.43 (d, $J = 7.2$ Hz, 3H), 7.27 (d, $J = 8.6$ Hz, 2H), 7.20 (s, 1H), 2.80 (d, $J = 4.5$ Hz, 3H), 2.71 (dd, $J = 15.1$, 7.3 Hz, 2H), 1.24 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.73 (C, C-6), 163.95 (C, C-15), 161.13 (C, C-22), 151.73 (C, C-16), 150.92 (C, C-18), 150.31 (C, C-4), 148.25 (C, C-8), 146.69 (CH, C-2), 144.75 (C, C-30), 144.34 (CH, C-20), 140.11 (C, C-27), 133.59 (C, C-11), 129.43 (CH, C-29, C-31), 127.75 (CH, C-28, C-32), 122.91 (CH, C-10, C-12), 120.91 (CH, C-19), 119.25 (CH, C-9, C-13), 114.82 (CH, C-17), 113.53 (CH, C-1), 109.79 (CH, C-5), 28.79 ($\underline{C}H_2CH_3$, C-33), 25.73 (CH_3, C-25), 15.27 ($CH_2\underline{C}H_3$, C-33). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.9% purity.

4-(2, 4-dimethylphenyl)-N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl) picolinamide (**14k**)*

Yield: 43.48%; m.p. 108.7–110.2 °C; MS (ESI) *m/z* (%): 491.2 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 8.78 (s, 2H), 8.51 (d, $J = 5.4$ Hz, 1H), 8.07 (d, $J = 7.7$ Hz, 3H), 7.68 (s, 1H), 7.41 (s, 1H), 7.24 (d, $J = 7.5$ Hz, 3H), 7.18 (d, $J = 11.5$ Hz, 3H), 2.79 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.18 (C, C-6), 164.68 (C, C-15), 161.33 (C, C-22), 151.92 (C, C-16), 151.62 (C, C-18), 151.23 (C, C-4), 148.15 (C, C-8), 146.41 (CH, C-2), 144.55 (CH, C-20), 138.80 (C, C-30), 133.81 (C, C-11), 132.97 (CH, C-32), 132.45 (C, C-27), 131.37 (CH, C-31), 130.53 (C, C-28), 125.95 (CH, C-29), 122.63 (CH, C-10, C-11), 120.54 (CH, C-19), 119.92 (CH, C-9, C-13), 114.10 (CH, C-17), 113.67 (CH, C-1), 109.59 (CH, C-5), 26.79 (CH_3, C-25), 21.79 (4-CH_3, C-33), 19.25 (2-CH_3, C-33). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.0% purity.

N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl)-5-phenylpicolinamide (**15a**)*

Yield: 42.34%; m.p. 176.4–177.6 °C; MS (ESI) *m/z* (%): 425.1 $[M + H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 9.04 (s, 1H), 8.77 (d, $J = 4.6$ Hz, 1H), 8.51 (d, $J = 5.4$ Hz, 1H), 8.36 (d, $J = 8.1$ Hz, 1H), 8.25 (d, $J = 8.3$ Hz, 1H), 8.08 (d, $J = 8.8$ Hz, 2H), 7.84 (d, $J = 7.4$ Hz, 2H), 7.56 (t, $J = 7.3$ Hz, 2H), 7.52–7.47 (m, 1H), 7.41 (s, 1H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.17 (d, $J = 2.8$ Hz, 1H), 2.79 (d, $J = 4.5$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.79 (C, C-6), 162.68 (C, C-15), 161.42 (C, C-22), 151.02 (C, C-16), 149.87 (C, C-4), 148.00 (C, C-8), 146.21 (CH, C-2), 141.97 (CH, C-20), 139.60 (C, C-19), 136.71 (C, C-27), 134.53 (CH, C-18), 133.80 (C, C-11), 129.27 (CH, C-29, C-31), 128.73 (CH, C-30), 127.65 (CH, C-28, C-32), 124.83 (CH, C-17), 122.82 (CH, C-10, C-12), 119.10 (CH, C-9, C-13), 113.67 (CH, C-1), 109.59 (CH, C-5), 26.92 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.2% purity.

5-(4-Fluorophenyl)-N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl) picolinamide (**15b**)*

Yield: 46.01%; m.p. 222.5–224.4 °C; MS (ESI) *m/z* (%): 481.1 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 9.02 (s, 1H), 8.77 (s, 1H), 8.51 (d, $J = 5.5$ Hz, 1H), 8.34 (d, $J = 8.1$ Hz, 1H), 8.24 (d, $J = 8.1$ Hz, 1H), 8.08 (d, $J = 8.7$ Hz, 2H), 7.93–7.87 (m, 2H), 7.43–7.39 (m, 2H), 7.37 (s, 1H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.18–7.12 (m, 1H), 2.79 (d, $J = 4.5$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.12 (C, C-6), 163.74 (C, C-15), 162.61 (C, C-30), 162.14 (C, C-22), 149.72 (C, C-16), 149.17 (C, C-4), 148.30 (C, C-8), 146.32 (CH, C-2), 141.65 (CH, C-20), 139.73 (C, C-19), 134.19 (CH, C-18), 133.81 (C, C-11), 132.21 (C, C-27), 130.08 (CH, C-28, C-32), 124.17 (CH, C-17), 122.63 (CH, C-10, C-12), 119.57 (CH, C-9, C-13), 116.25 (CH, C-29, C-31), 113.63 (CH, C-1), 109.92 (CH, C-5), 26.68 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 97.9% purity.

5-(2, 4-Difluoropheny l)-N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl) picolinamide (**15c**)*

Yield: 57.16%; m.p. 230.9–232.2 °C; MS (ESI) *m/z* (%): 499.1 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.91 (s, 1H), 8.91 (s, 1H), 8.77 (d, $J = 3.8$ Hz, 1H), 8.52 (d, $J = 5.5$ Hz, 1H), 8.30–8.23 (m, 2H), 8.08 (d, $J = 8.6$ Hz, 2H), 7.79 (dd, $J = 15.5$, 8.4 Hz, 1H), 7.49 (t, $J = 10.0$ Hz, 1H), 7.41 (s, 1H), 7.31 (t, $J = 8.8$ Hz, 1H), 7.25 (d, $J = 8.6$ Hz, 2H), 7.17 (d, $J = 2.9$ Hz, 1H), 2.79 (d, $J = 4.4$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.89 (C, C-6), 164.34 (C, C-15), 161.78 (C, C-30), 161.22 (C, C-22), 158.47 (C, C-28), 151.43 (C, C-4), 149.01 (C, C-16), 148.47 (C, C-8), 146.95 (CH, C-2), 141.31 (CH, C-20), 139.37 (C, C-19), 134.06 (CH, C-18), 133.95 (C, C-11), 130.75 (CH, C-32), 126.83 (C, C-27), 124.07 (CH, C-17), 122.38 (CH, C-10, C-12),

119.43 (CH, C-9, C-13), 113.82 (CH, C-1), 111.62 (CH, C-31), 109.79 (CH, C-5), 102.76 (CH,C-29), 26.83 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.3% purity.

5-(4-Chlorophenyl)-N-*(4-(2-(methylcarbamoy l) pyridin-4-yloxy) phenyl) picolinamide (**15d**)*

Yield: 64.68%; m.p. 213.2–214.7 °C; MS (ESI) *m/z* (%): 491.1 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 9.04 (s, 1H), 8.77 (s, 1H), 8.51 (d, $J = 5.5$ Hz, 1H), 8.37 (d, $J = 8.1$ Hz, 1H), 8.25 (d, $J = 8.2$ Hz, 1H), 8.07 (d, $J = 8.8$ Hz, 2H), 7.88 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.41 (s, 1H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.17 (d, $J = 3.0$ Hz, 1H), 2.79 (d, $J = 4.5$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.83 (C, C-6), 163.76 (C, C-15), 162.23 (C, C-22), 150.85 (C, C-4), 149.62 (C, C-16), 148.74 (C, C-8), 146.32 (CH, C-2), 141.43 (CH, C-20), 139.89 (C, C-19), 134.65 (C, C-27), 134.54 (C, C-30), 133.94 (CH, C-18), 133.64 (C, C-11), 130.43 (CH, C-29, C-31), 128.56 (CH, C-28, C-32), 124.59 (CH, C-17), 122.81 (CH, C-10, C-12), 119.57 (CH, C-9, C-13), 113.51 (CH, C-1), 109.81 (CH, C-5), 26.46 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.6% purity.

5-(4-Methoxyphenyl)-N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy)phenyl) picolinamide (**15e**)*

Yield: 46.67%; m.p. 199.2–200.6 °C; MS (ESI) *m/z* (%): 493.3 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.00 (s, 1H), 8.77 (s, 1H), 8.51 (d, $J = 5.5$ Hz, 1H), 8.31 (d, $J = 8.2$ Hz, 1H), 8.21 (d, $J = 8.1$ Hz, 1H), 8.07 (d, $J = 8.6$ Hz, 2H), 7.80 (d, $J = 8.5$ Hz, 2H), 7.41 (s, 1H), 7.25 (d, $J = 8.6$ Hz, 2H), 7.17 (d, $J = 3.1$ Hz, 1H), 7.11 (d, $J = 8.5$ Hz, 2H), 3.83 (s, 3H), 2.79 (d, $J = 4.2$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 168.03 (C, C-6), 163.19 (C, C-15), 161.94 (C, C-22), 161.22 (C, C-30), 151.03 (C, C-4), 149.08 (C, C-16), 147.02 (C, C-8), 146.79 (CH, C-2), 141.82 (CH, C-20), 140.08 (C, C-19), 134.21 (CH, C-18), 133.79 (C, C-11), 129.35 (CH, C-28, C-32), 128.34 (C, C-27), 124.86 (CH, C-17), 122.91 (CH, C-10, C-12), 119.35 (CH, C-9, C-13), 114.28 (CH, C-29, C-31), 113.79 (CH, C-1), 109.47 (CH, C-5), 55.34 (OCH_3, C-33), 26.68 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.9% purity.

N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl)-5-p-tolylpicolinamide (**15f**)*

Yield: 57.48%; m.p. 189.5–190.7 °C; MS (ESI) *m/z* (%): 477.3 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.01 (s, 1H), 8.77 (s, 1H), 8.51 (d, $J = 5.5$ Hz, 1H), 8.31 (s, 1H), 8.22 (d, $J = 8.1$ Hz, 1H), 8.08 (d, $J = 8.7$ Hz, 2H), 7.73 (d, $J = 7.8$Hz, 2H), 7.42 (s, 1H), 7.36 (d, $J = 7.8$ Hz, 2H), 7.24 (d, $J = 8.7$ Hz, 2H), 7.16 (d, $J = 3.0$ Hz, 1H), 2.79 (d, $J = 4.5$ Hz, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.74 (C, C-6), 164.68 (C, C-15), 161.43 (C, C-22), 151.30 (C, C-4), 151.17 (C, C-16), 148.32 (C, C-8), 146.65 (CH, C-2), 141.63 (CH, C-20), 139.43 (C, C-19), 134.64 (CH, C-18), 133.82 (C, C-11), 133.67 (C, C-27), 131.21 (C, C-30), 129.42 (CH, C-29, C-31), 127.53(CH, C-28, C-32), 124.71 (CH, C-17), 122.57 (CH, C-10, C-12), 119.25 (CH, C-9, C-13), 113.92 (CH, C-1), 109.10 (CH, C-5), 26.85 (CH_3, C-25), 21.68 (CH_3, C-33). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.1% purity.

N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl)-5-m-tolylpicolinamide (**15g**)*

Yield: 46.50%; m.p. 142.0–143.4 °C; MS (ESI) *m/z* (%): 477.1 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 9.02 (s, 1H), 8.78 (d, $J = 4.2$ Hz, 1H), 8.52 (d, $J = 5.4$ Hz, 1H), 8.34 (d, $J = 8.1$ Hz, 1H), 8.24 (d, $J = 8.1$ Hz, 1H), 8.08 (d, $J = 8.7$ Hz, 2H), 7.68–7.60 (m, 2H), 7.44 (dd, $J = 15.3$, 7.5 Hz, 2H), 7.31 (d, $J = 7.2$ Hz, 1H), 7.25 (d, $J = 8.7$ Hz, 2H), 7.20–7.15 (m, 1H), 2.79 (d, $J = 4.4$ Hz, 3H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.65 (C, C-6), 163.93 (C, C-15), 161.36 (C, C-22), 151.72 (C, C-4), 149.01 (C, C-16), 148.87 (C, C-8), 146.57 (CH, C-2), 141.31 (CH, C-20), 139.87 (C, C-19), 138.96 (C, C-29), 136.37 (C, C-27), 134.35 (CH, C-18), 133.83 (C, C-11), 129.54 (CH, C-31), 129.07 (CH, C-30), 128.25 (CH, C-28), 124.92 (CH, C-32), 124.63 (CH, C-17), 122.10 (CH, C-10, C-12), 119.67 (CH, C-9, C-13), 113.53 (CH, C-1), 109.64 (CH, C-5), 26.87 (CH_3, C-25), 21.79 (CH_3, C-33). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 97.5% purity.

5-(3-Fluorophenyl)-N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl) picolinamide (**15h**)*

Yield: 54.99%; m.p. 191.8–192.5 °C; MS (ESI) *m/z* (%): 481.3 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 9.07 (s, 1H), 8.78 (s, 1H), 8.52 (d, $J = 5.2$ Hz, 1H),

8.40 (d, $J = 6.8$ Hz, 1H), 8.25 (d, $J = 8.0$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 2H), 7.73 (dd, $J = 17.1$, 9.0 Hz, 2H), 7.61 (dd, $J = 14.0$, 7.4 Hz, 1H), 7.41 (s, 1H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.25 (d, $J = 8.5$ Hz, 2H), 7.17 (d, $J = 2.6$ Hz, 1H), 2.79 (d, $J = 3.9$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.27 (C, C-6), 163.14 (C, C-15), 162.68 (C, C-29), 161.10 (C, C-22), 151.72 (C, C-4), 149.17 (C, C-16), 148.07 (C, C-8), 146.31 (CH, C-2), 141.87 (CH, C-20), 139.60 (C, C-19), 138.31 (C, C-27), 134.07 (CH, C-18), 133.87 (C, C-11), 127.43 (CH, C-31), 124.47 (CH, C-17), 123.11 (CH, C-32), 122.65 (CH, C-10, C-12), 119.63 (CH, C-9, C-13), 115.92 (CH, C-28), 115.64 (CH, C-30), 113.67 (CH, C-1), 109.86 (CH, C-5), 26.88 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.2% purity.

N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl)-5-(4-(trifluoromethyl) phenyl)picolinamide* (***15i***)

Yield: 51.57%; m.p. 240.5–241.7 °C; MS (ESI) *m/z* (%): 531.2 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.91 (s, 1H), 9.10 (s, 1H), 8.77 (d, $J = 4.2$ Hz, 1H), 8.52 (d, $J = 5.4$ Hz, 1H), 8.44 (d, $J = 8.0$ Hz, 1H), 8.29 (d, $J = 8.1$ Hz, 1H), 8.05 (t, $J = 17.1$ Hz, 4H), 7.92 (d, $J = 7.9$ Hz, 2H), 7.41 (s, 1H), 7.25 (d, $J = 8.6$ Hz, 2H), 7.17 (d, $J = 2.9$ Hz, 1H), 2.79 (d, $J = 4.3$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.37 (C, C-6), 164.58 (C, C-15), 161.10 (C, C-22), 151.00 (C, C-4), 149.62 (C, C-16), 148.15 (C, C-8), 146.38 (CH, C-2), 141.56 (CH, C-20), 139.72 (C, C-27), 139.35 (C, C-19), 134.05 (CH, C-18), 133.97 (C, C-11), 131.21 (C, C-30), 127.43 (CH, C-28, C-32), 125.67 (CH, C-29, C-31), 124.52 (CH, C-17), 124.11 (C, C-33), 122.67 (CH, C-10, C-12), 119.25 (CH, C-9, C-13), 113.75 (CH, C-1), 109.10 (CH, C-5), 26.78 (CH_3, C-25). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.6% purity.

5-(4-Ethylphenyl)-N-*(4-(2-(methylcarbamoy l) pyridin-4-yloxy) pheny l) picolinamide* (***15j***)

Yield: 45.67%; m.p. 164.5–165.6 °C; MS (ESI) *m/z* (%): 491.1 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 9.02 (s, 1H), 8.76 (s, 1H), 8.51 (d, $J = 5.6$ Hz, 1H), 8.33 (d, $J = 8.3$ Hz, 1H), 8.23 (d, $J = 8.1$ Hz, 1H), 8.07 (d, $J = 8.8$ Hz, 2H), 7.76 (d, $J = 7.9$ Hz, 2H), 7.41 (s, 2H), 7.39 (s, 1H), 7.25 (d, $J = 8.6$ Hz, 2H), 7.17 (d, $J = 2.9$ Hz, 1H), 2.79 (s, 3H), 2.68 (q, $J = 7.5$ Hz, 2H), 1.22 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.74 (C, C-6), 163.85 (C, C-15), 162.91 (C, C-22), 151.43 (C, C-4), 149.72 (C, C-16), 148.79 (C, C-8), 146.58 (CH, C-2), 144.28 (C, C-30), 140.04 (CH, C-20), 139.96 (C, C-19), 134.71 (CH, C-18), 133.84 (C, C-11), 133.69 (C, C-27), 129.34 (CH, C-29, C-31), 127.69 (CH, C-28, C-32), 124.11 (CH, C-17), 122.83 (CH, C-10, C-12), 119.38 (CH, C-9, C-13), 113.85 (CH, C-1), 109.09 (CH, C-5), 28.79 ($\underline{C}H_2CH_3$, C-33), 26.84 (CH_3, C-25), 14.62 ($CH_2\underline{C}H_3$, C-33). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.4% purity.

5-(2, 4-Dimethylphenyl)-N-*(4-(2-(methylcarbamoyl) pyridin-4-yloxy) phenyl) picolinamide* (***15k***)

Yield: 45.81%; m.p. 172.1–173.4 °C; MS (ESI) *m/z* (%): 491.2 $[M + K]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 8.77 (d, $J = 4.3$ Hz, 1H), 8.70 (s, 1H), 8.52 (d, $J = 5.4$ Hz, 1H), 8.23 (d, $J = 8.0$ Hz, 1H), 8.07 (t, $J = 8.1$ Hz, 3H), 7.41 (s, 1H), 7.20 (m, 6H), 2.79 (d, $J = 4.4$ Hz, 3H), 2.34 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 167.78 (C, C-6), 164.82 (C, C-15), 161.08 (C, C-22), 151.83 (C, C-4), 149.61 (C, C-16), 148.47 (C, C-8), 146.26 (CH, C-2), 141.81 (CH, C-20), 139.56 (C, C-19), 138.37 (C, C-30), 134.07 (CH, C-18), 133.95 (C, C-11), 133.03 (CH, C-32), 131.56 (CH, C-31), 130.59 (C, C-27), 130.47 (C, C-28), 125.95 (CH, C-29), 124.63 (CH, C-17), 122.75 (CH, C-10, C-12), 119.54 (CH, C-9, C-13), 113.93 (CH, C-1), 109.73 (CH, C-5), 26.76 (CH_3, C-25), 21.79 (4-CH_3, C-33), 19.27 (2-CH_3, C-33). Analytical HPLC on an Agilent (1100) using a 250 × 4.6 mm SD-C18 analytical column, H_2O/MeOH (15%H_2O) eluent at 1 mL/min flow, monitored by UV absorption at 325 nm, revealed 98.6% purity.

VEGFR2/KDR kinase assay

The inhibitory activity against VEGFR2/KDR at 10 μM level in vitro was evaluated through the mobility shift assay together with reference compounds sorafenib and Staurosporine (Roper et al. 2011). All kinase assays were performed on 384-well plates in a 50 μL reaction volume. The kinase base buffer contains 50 mM HEPES, pH 7.5, 10 mM $MgCl_2$, 0.0015% Brij-35 and 2 mM DTT. The stop buffer contains 100 mM HEPES, pH 7.5, 0.015% Brij-35, 0.2% Coating Reagent #3 and 50 mM EDTA. Dilute the compounds to 500 μM by 100% DMSO, then transfer 10 μL of compound to a new 96-well plate as the intermediate plate, add 90 μL kinase buffer to each well. Transfer 5 μL of each well of the intermediate plate to 384-well plates. The following amounts of enzyme and substrate were used per well: kinase base buffer, FAM-labeled peptide, ATP and enzyme solution. Wells containing the substrate, enzyme, DMSO without compound were used as DMSO control. Wells containing substrate without enzyme were used as low control. Incubate at room temper-ature for 10 min. Add

10 µL peptide solution to each well. Incubate at 28 °C for specified period of time and stop reaction by 25 µL stop buffer. At last, collect data on Caliper program and convert conversion values to inhibition values. Percent inhibition = (max-conversion)/ (max-min)*100. "max" denoted DMSO control; "min" denoted low control.

BRAF and CRAF kinases assay

The kinase activity of BRAF and CRAF was measured by Lanthascreen assay (Roper et al. 2011). All kinase assays were performed on 384-well plates in a 100 µL reaction volume. The kinase base buffer contains 50 mM HEPES, pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA and 0.01% Brij-35. The stop buffer contains 2-fold of final concentration in Antibody Dilution Buffer. The final concentration: Antibody 2 nM and EDTA 10 mM. Dilute the compound to 100× of the final desired highest inhibitor concentration in reaction by 100%DMSO. Then transfer 4 µl of compound from source plate to a new 96-well plate as the intermediate plate. Add 96 µL of 1x kinase buffer to each well of the intermediate plate. Transfer 2.5 µL of each well from the 96-well intermediate plate to a 384-well plate in duplicates. The following amounts of enzyme and substrate were used per well: kinase base buffer, FAM-labeled peptide, ATP and enzyme solution. Wells containing the substrate, enzyme, DMSO without compound and enzyme were used as DMSO control. Add 2.5 µL of substrate solution to each well of the assay plate to start reaction. Cover the assay plate and incubate under room temperature for 1 h. Add 10 µL of detection solution to each well of the assay plate to stop the reaction. At last, collect data on Caliper program and convert conversion values to inhibition values. Percent inhibition = (max-conversion)/(max-min)*100. "max" denoted DMSO control; "min" denoted low control.

Cytotoxicity assay in vitro

The cytotoxic activities of compounds were evaluated by A549, Hela and MCF-7 cell lines by the standard MTT assay in vitro, with compounds VEGFR2 inhibitors Sorafenib as positive control. The cancer cell lines were cultured in minimum essential medium (MEM) supplement with 10% fetal bovine serum. Approximately 4 × 103 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 at indicated final concentrations were added into the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 µg/mL and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 µL DMSO each well, and the absorbency at 492 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured by the ELISA reader. All the compounds were tested three times in each of the cell lines. The results expressed as inhibition rates or IC_{50} (half-maximal inhibitory concentration) were the averages of two determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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