Full Paper

Design and Synthesis of 2-Iminothiazolidin-4-one Moiety-Containing Compounds as Potent Antiproliferative Agents

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A new series of 2,5-diaryliminothiazolidin-4-ones were designed and synthesized as potent antiproliferative agents. The antiproliferative activities of the 25 target compounds were evaluated against three cancer cell lines (A549, H460 and HT29) by MTT assay. Pharmacological data indicated that most of the compounds possessed moderate activity, some showed remarkable activity against one or more cell lines. As the most promising compound, **8s** (with IC_{50} values of 1.1, 0.01 and 1.3 μM against the A549, H460 and HT29 cell lines) was 1.1- to 270-fold more potent than the reference drug sorafenib. Furthermore, preliminary structure–activity relationships (SARs) were summarized to provide guidance for further design and discovery of 2-iminothiazolidin-4-one-based antiproliferative agents.

Keywords: 2-Iminothiazolidin-4-one moiety / Antiproliferative evaluation / Design / Synthesis

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Introduction

The leading cause of death remains mainly cardiovascular disease and cancer worldwide, while a recent report disclosed that cancer mortality presented an increasing tendency despite the great success of many chemotherapeutics [1]. Therefore it is urgent to develop novel antiproliferative agents with high efficiency and low toxicity.

Drug discovery paradigm suggested that hybridizing privileged scaffolds or merging different pharmacophore fragments into one single structure could lead to innovative chemicals bearing interesting biological activity. 2-Iminothiazolidin-4-one derivative, a special derivative of 4-thiazolidinone, has been proved to be intermediate between amino and imino tautomeric forms [2, 3]; furthermore, a pharmacophore derived from active molecules suggested that two hydrogen bond acceptors and three hydrophobic regions were common features of 5-benzylidene-2-(phenylimino)thiazolidin-4-one derivatives [4]. Special structural characteristics, hydrogen bond accepting ability and inherent hydrophobic nature make 2-iminothiazolidin-4-one moiety a versatile scaffold in drug discovery. Considerable studies revealed that structures based on 2-iminothiazolidin-4-one-containing moiety have been endowed with antiproliferative, antimicrobial, and anti-inflammatory activity [4, 5]. Interestingly, darbufelone, a non-steroidal anti-inflammatory drug (NSAID), was reported with encouraging activity inducing growth inhibition of lung cancer cells both *in vitro* and *in vivo* [6].

Sorafenib, a synthetic compound targeting multiple kinases of tumor proliferation and angiogenesis [7–8], was approved by the FDA for the treatment of primary renal cell carcinoma and advanced primary hepatocellular carcinoma. In addition, it could induce complete tumor stasis in human colon tumor xenograft model (HT-29) at doses of 30 mg per kg and inhibited the growth of NSCLC xenograft model (A549) [9]. Currently, efforts for developing potent analogs of sorafenib have been the focus of many studies [10–15]. In most modification researches including our previous work [13], it was found that derivatives bearing a diaryl urea framework constituted various compounds with superior antitumor activity. Recent researches focusing on optimizations of the diaryl urea framework of

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sorafenib led to the discovery of an interesting class of compounds containing the *N*-methyl-4-phenoxypicolinamide motif [14, 15].

Chemical and biological properties of 2-iminothiazolidin-4-ones prompted us to design a series of 4-(4-((5-benzylidene-4-oxothiazolidin-2-ylidene)amino)phenoxy)-*N*-methylpicolinamides (Figure 1) in continuation of our interest in optimizations of sorafenib. Herein, the *N*-methyl-4-phenoxypicolinamide motif of sorafenib was preserved, the 2-iminothiazolidin-4-one motif was hybridized with the C-4′ position of the *N*-methyl-4-phenoxypicolinamide scaffold, furthermore, arylidene group was incorporated into the C-5″ position of the 2-iminothiazolidin-4-one motif to construct a bioisoster of the aryl urea. 23 benzylidenes (substituted by −F, −Cl, −Br, −OH, −OMe) and 2 heterocyclidenes (pyridin-4-ylmethylene, thiophen-2-ylmethylene) were incorporated to study the influence of the substitution position and the electronic effect of the arylidene motif. Further studies focusing on modifications of the *N*-methyl-4-phenoxypicolinamide scaffold and introduction of other thiazole-based heterocyclic nucleus are in progress in our laboratories and will be reported upon soon.

Results and discussion

Chemistry

The synthetic route was illustrated as outlined in Scheme 1. The synthesis was initiated by chloration of the commercially available picolinic acid in thionyl chloride to afford **2**, which was subsequently reacted with 2.0 M methyl amine in tetrahydrofuran to give compound **3** as pale-yellow crystals. Intermediate **4** was obtained by etherification of **3** with 4-aminophenol, and compound **5** was prepared by reacting intermediate **4** with thiophosgen in chloroform and sodium bicarbonate. Treating **5** with ammonium hydroxide in dioxane at 0°C yielded the primary thiourea **6**. Subsequently, heterocyclization of **6** with ethyl chloroacetate furnished the key intermediate **7** in the presence of sodium acetate. Knoevenagal condensation of **7** and different substituted aromatic aldehydes was accelerated employing sodium acetate as catalyst in acetic acid under microwave irradiation, which led to the formation of the target compounds **8a–8y** with a yield of ∼40 to ∼80%.

First screening for biological activities

Antiproliferative activities of compound **7** and target compounds **8a–8y** were evaluated by MTT assay employing three human cancer cell lines (human lung carcinoma cells A549, human lung carcinoma cells H460 and human colon carcinoma cells HT29). Some of the compounds exhibited remarkable antiproliferative activity against one or more cell lines in low micromolar range as shown in Table 1. Especially, the most promising compound **8s** (with IC_{50} values of 1.1, 0.01 and 1.3 μM against the A549, H460 and HT29 cell lines, respectively) is 1.1, 270 and 2.8 fold more

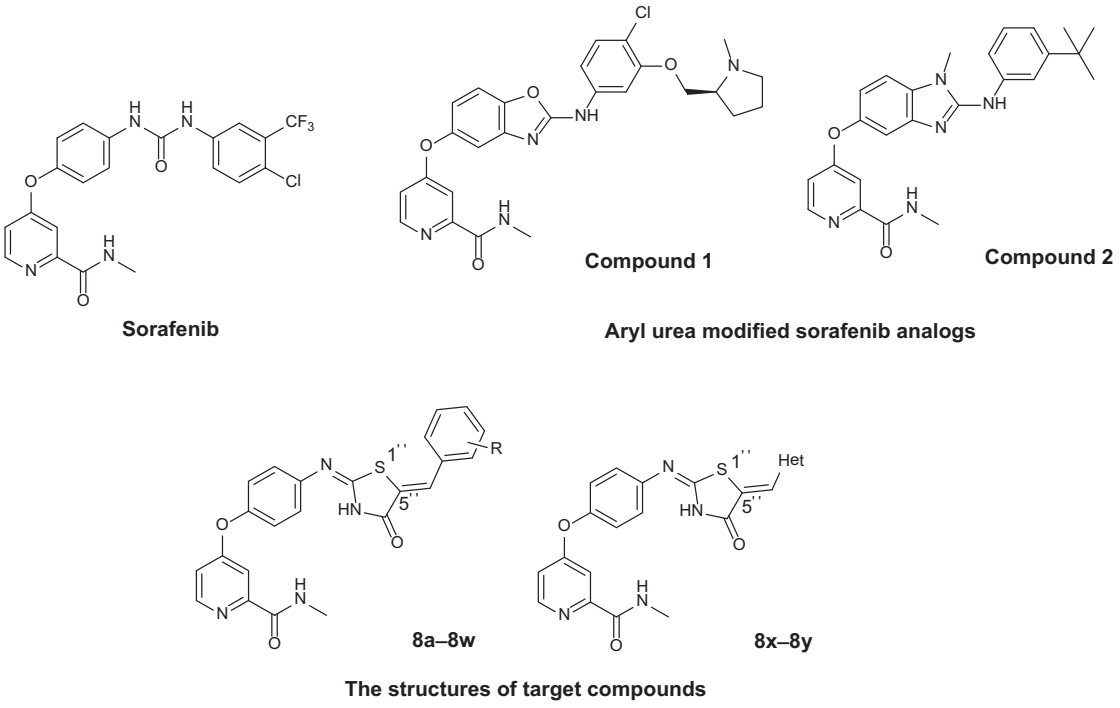
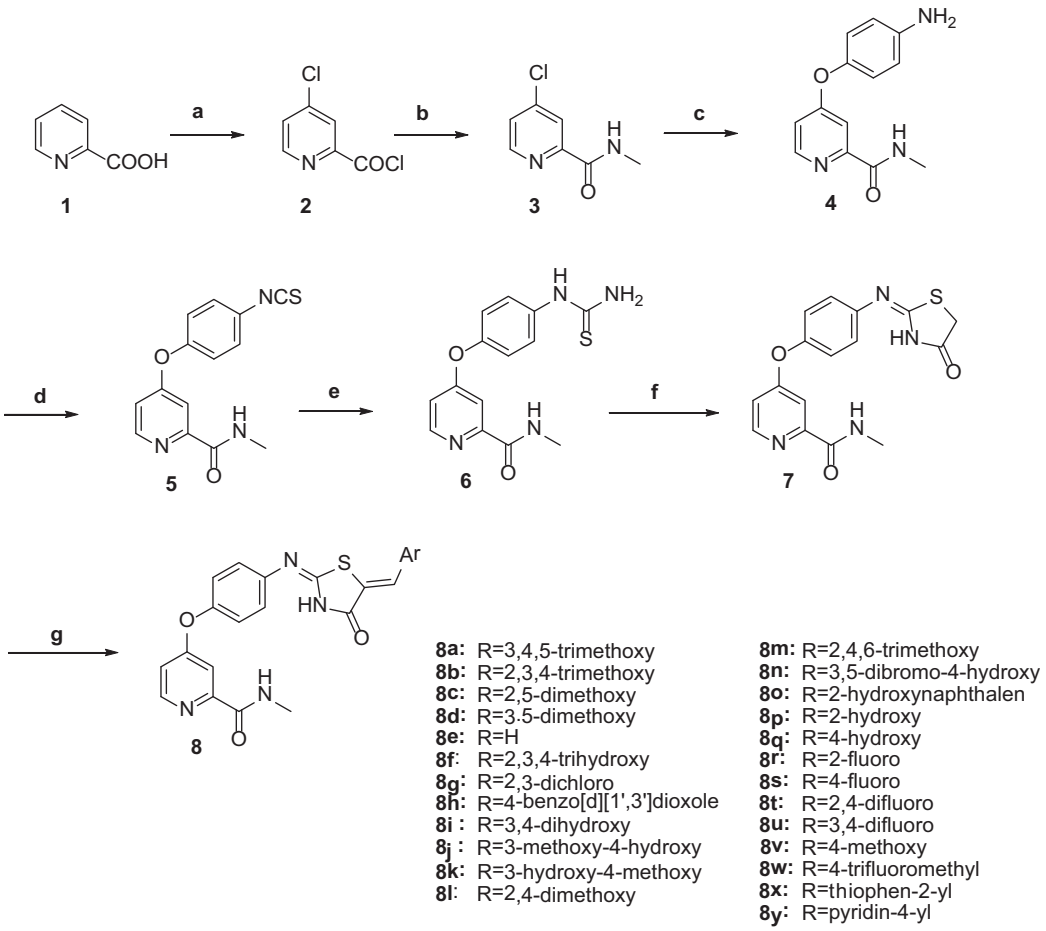


Figure 1. The structures of sorafenib, aryl urea modified sorafenib analogs and the target compounds.

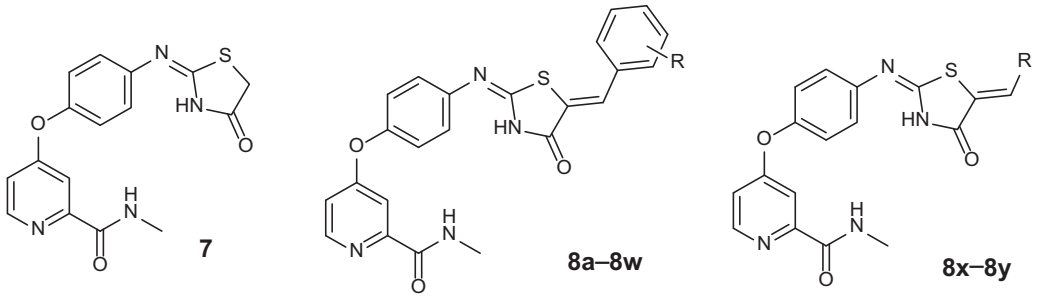


Scheme 1. Reagents and conditions: a) $SOCl_2$/DMF, 50°C 10 min, r.f. 17 h; b) CH_3NH_2/THF/MeOH, 0°C, then ambient temperature 2 h; c) 4-aminophenol/*t*-BuOK/DMF, 80°C, 6 h; d) 6% $NaHCO_3$/CH_2Cl_2/thiophosgene, 0°C, then r.t. 5 h; e) NH_4OH/dioxane, 0°C, 1 h; f) ethyl chloroacetate/AcONa/EtOH, 60°C, 6 h; g) AcONa/AcOH, microwave, 12 min.

potent than the reference drug sorafenib. In addition, compound **8r** exhibited optimal activity against the HT29 and A549 cell lines with IC_{50} values of 1.1 and 0.9 μM among the tested compounds.

The preliminary structure-activity relationships (SARs) suggested that substituted arylidene on C-5'' position of 2-iminothiazolidin-4-one ring is essential for the antiproliferative activity. A case in point is that compound **7** without substitution of arylidene moiety exhibited less antitumor activity than the target compounds. Introduction of heterocyclidene (e.g. **8x** and **8y**) led to weakened antitumor activity, while it was opposite in that the introduction of benzylidene showed enhanced antitumor activity in most compounds. Pharmacological data indicated that the substitution position of the substituents on the benzylidene influences the antitumor activities of the target compounds dramatically. As shown in Table 1, it was obvious that the introduction of substituents on the *meta*-position of the benzylidene weakened or even abolished antitumor activity against the three cell lines. It is noteworthy that the nature of the substituents on the benzylidene affects the antitumor activity at different degrees. Among the tested compounds, fluorine atom is the most preferable substitution group (e.g. **8r**, **8t** and the most promising compound **8s** showed more potent antitumor activity among the tested compounds in one or more cell lines), while other electron withdrawing groups showed no evident influence on potency. Some electron donating group including hydroxyl group and methoxy group exhibited moderate to significant influence on the antitumor activity. In conclusion, the SARs summarized may provide guidance for further design and discovery of 2-iminothiazolidin-4-one based antiproliferative agents.

Table 1. IC_{50} for tested compounds **8a–y** (in μM) against A549, H460 and HT29 cancer cell lines



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Compd.	R	IC_{50} (μM)		
		A549	H460	HT29
7	–	38.6	83.2	39.5
8a	3,4,5-trimethoxy	27.1	4.1	13.0
8b	2,3,4-trimethoxy	97.0	47.2	5.6
8c	2,5-dimethoxy	7.6	37.0	25.2
8d	3,5-dimethoxy	NA[a]	NA	NA
8e	–	3.8	3.0	2.8
8f	2,3,4-trihydroxy	25.9	39.7	NA
8g	2,3-dichloro	NA	NA	NA
8h	4-benzo[d][1',3']dioxole	NA	88.3	NA
8i	3,4-dihydroxy	17.1	19.6	27.9
8j	3-methoxy-4-hydroxy	NA	48.5	4.4
8k	3-hydroxy-4-methoxy	NA	NA	NA
8l	2,4-dimethoxy	5.6	4.2	1.3
8m	2,4,6-trimethoxy	11.4	1.8	5.0
8n	3,5-dibromo-4-hydroxy	72.2	16.8	5.2
8o	2-hydroxynaphthalene	9.1	8.1	1.9
8p	2-hydroxy	1.7	0.3	3.1
8q	4-hydroxy	3.2	4.7	14.6
8r	2-fluoro	0.9	1.2	1.1
8s	4-fluoro	1.1	0.01	1.3
8t	2,4-difluoro	8.9	0.3	2.2
8u	3,4-difluoro	NA	NA	3.7
8v	4-methoxy	3.3	4.1	NA
8w	4-trifluoromethyl	NA	NA	NA
8x	thiophen-2-yl	40.4	22.8	19.3
8y	pyridin-4-yl	20.9	46.5	29.1
Sorafenib	–	1.3	2.7	3.7

[a] NA means not active, the IC_{50} of which is more than 100 μM

Experimental protocols

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). Proton (^{1}H) nuclear magnetic resonance spectroscopy was performed using Bruker ARX-300, 300MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as internal standard. Reactions under microwaves were performed in a CEM Discover1 monomode microwave reactor. Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China). Unless otherwise noted, all the materials were obtained from commercially available sources and were used without further purification.

*4-Chloropicolinoyl chloride (**2**)*

Anhydrous *N*,*N*-dimethylformamide (0.1 mL) was added to thionyl chloride (90 mL) at 50°C under nitrogen. The solution was stirred at 50°C for 10 min prior to portionwise addition of picolinic acid **1** (30 g, 0.244 mol) over 30 min. The initial green color went to orange and then to purple. The solution was heated to reflux, and vigorous SO_2 evolution was observed. A yellow

solid precipitated after 17 h. The mixture was then cooled to room temperature, diluted with toluene (200 mL), and concentrated under reduced pressure to 70 mL. This process was repeated two additional times to give **2** as a brown oil which was used in the next step without further purification.

*4-Chloro-N-methylpicolinamide (**3**)*

4-Chloropicolinoyl chloride **2** (20.0 g, 113.7 mmol) was added portionwise to 2.0 M methylamine in tetrahydrofuran (350 mL) and methanol (70 mL) at 0°C. The mixture was stirred at ambient temperature for 2 h, concentrated to near dryness, and dissolved in ethyl acetate (350 mL). The organics were washed with brine (350 mL), dried over sodium sulfate, and concentrated to provide **3** (16.0 g, 94.3 mmol, 83%) as a yellow, crystalline solid. m.p.: 41–42°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.87–8.85 (m, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.75–7.73 (q, J = 2.4 Hz, J = 5.7 Hz, 1H), 2.82 (d, J = 5.1 Hz, 3H); ESI-MS *m/z*: 171.3 $(M+H)^+$.

*4-(4-Aminophenoxy)-N-methylpicolinamide (**4**)*

A solution of 4-aminophenol (9.6 g, 88.0 mmol) in dry *N*,*N*-dimethylformamide (150 mL) was treated with potassium *tert*-butoxide (10.29 g, 91.69 mmol), and the reddish-brown mixture was stirred at room temperature for 2 h. The contents were treated with 4-chloro-*N*-methylpicolinamide **3** (15.0 g, 87.9 mmol) and potassium carbonate (6.5 g, 47.0 mmol) and then heated to 80°C under nitrogen for 6 h. The mixture was cooled to room temperature and poured into the mixture of ethyl acetate (500 mL) and brine (500 mL). The layers were separated, and the aqueous phase was back-extracted with ethyl acetate (300 mL). The combined organics were washed with brine (4 × 300 mL), dried over sodium sulfate, and concentrated to afford **4** (17.1 g, 70.3 mmol, 80%) as a purple solid. ^{1}H-NMR (300 MHz, DMSO) δ: 8.74–8.72 (m, 1H), 8.45 (d, J = 5.4 Hz, 1H), 7.34 (d, J = 3 Hz, 1H), 7.07–7.05 (q, J = 3 Hz, J = 5.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.7 Hz, 2H), 2.78 (d, J = 4.8 Hz, 3H); ESI-MS *m/z*: 244.0 $(M+H)^+$.

*4-(4-Isothiocyanatophenoxy)-N-methylpicolinamide (**5**)*

To a stirred solution of 4-(4-aminophenoxy)-*N*-methylpicolinamide **4** (17.1 g, 70.3 mmol) in 1300 mL of 6% $NaHCO_3$ solution was added 600 mL CH_2Cl_2. After 20 min of vigorous stirring at 0°C, thiophosgene (4.1 mL, 70.3 mmol) was added dropwise. The reaction mixture was left under stirring for 5 h at room temperature, and the organic solvent was removed under reduced pressure and the crude residue was washed with cold ethanol to afford **5** (15.4 g, 54.1 mmol, 77%) as a brown powder. ^{1}H-NMR (300 MHz, DMSO) δ: 8.79–8.78 (m, 1H), 8.54 (d, J = 6 Hz, 1H), 7.59 (d, J = 9.3 Hz, 2H), 7.43 (d, J = 3 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.20–7.17 (q, J = 3 Hz, J = 6 Hz, 1H), 2.80 (d, J = 4.5 Hz, 3H); ESI-MS *m/z*: 286.2 $(M+H)^+$.

*N-Methyl-4-(4-thioureidophenoxy)picolinamide (**6**)*

To a mixture of ammonium hydroxide (10 mL) and dioxane (60 mL) was added **5** (15.4 g, 54.1 mmol), and the temperature was kept at 0°C for a period of 1 h until most participated from the reaction mixture. Crude product was obtained after filtration. The solid obtained was recrystallized in ethanol to yield an off white solid **6** (13.1 g, 43.2 mmol, 80%) after filtration. m.p.: 72–73°C. ^{1}H-NMR (300 MHz, DMSO) δ: 9.77 (br, 1H), 8.79–8.78 (m, 1H), 8.52 (d, J = 6.0 Hz, 1H), 7.54 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 2.7 Hz, 1H), 7.20–7.14 (m, 3H), 2.79 (d, J = 4.8 Hz, 3H); ESI-MS *m/z*: 303.1 $(M+H)^+$.

*N-Methyl-4-(4-(4-oxo-4,5-dihydrothiazol-2-ylamino)-phenoxy)picolinamide (**7**)*

To a stirred suspension of thiourea **6** (1.81g, 6.0 mmol) and anhydrous sodium acetate (2.48 g, 30.0 mmol) in 20 mL of absolute ethanol was added 1.42 mL (12.0 mmol) of ethyl chloroacetate. The mixture was heated at 60°C for 6 h. After being cooled to room temperature, the solvent was evaporated under reduced pressure, 10 mL water was added to form precipitates. The precipitates were filtered and washed with ethanol to produce the crude product. The crude product was recrystallized from ethanol to produce 2-arylimino-thiazolidin-4-one **7** (1.58 g, 4.62 mmol, 77%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.43–8.41 (m, 1H), 8.07 (d, J = 4.8 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 7.15 (q, J = 8.7 Hz, 2H), 7.02 (q, J = 2.4 Hz, J = 4.8 Hz, 1H), 3.92 (s, 1H), 3.03 (d, J = 5.1 Hz, 3H); ESI-MS *m/z*: 342.3 $(M+H)^+$; Anal. Calcd. for $C_{16}H_{14}N_4O_3S$ (%): C 56.13, H 4.12, N 16.36, O 14.02, S 9.37; found C 56.20, H 4.24, N 16.49, S 9.45.

*General procedure for preparation of compound (**8a–8y**)*

A mixture of the aromatic aldehyde (1.0 mmol), 2-imino-4-thiazolidinone (1.0 mmol), sodium acetic (0.12 g, 1.5 mmol), and acetic acid (5 mL) was placed in a flask sealed with a cap containing a septum. The flask was then placed into the cavity of the microwave reactor and heated at 150 W, 160°C for 6 min twice. After cooling to ambient temperature, 20 mL water was added and the mixture was allowed to being stirred for 10 mins. The participate formed was filtered, some crude product was recrystallized from ethanol, other crude product was purified by chromatography on silica gel using $MeOH/CH_2Cl_2$ to afford the solids **8a–8y**.

*(E)-N-Methyl-4-(4-(4-oxo-5-(3,4,5-trimethoxybenzylidene)-4,5-dihydrothiazol-2-ylamino)phenoxy)picolinamide (**8a**)*

Yield: 61%. m.p.: 233–234°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.79–8.77 (m, 1H), 8.54 (d, J = 6.0 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.71 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.34–7.25 (m, 2H), 7.21–7.17 (m, 2H), 6.99 (s, 1H), 6.88 (s, 1H), 3.79 (s, 6H), 3.80 (s, 3H), 2.80 (d, J = 4.5 Hz, 3H); ESI-MS *m/z*: 521.5 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{24}N_4O_6S$ (%): C 59.99, H 4.65, N 10.76, O 18.44, S 6.16; found C 60.08, H 4.66, N 11.03, S 6.22.

*(E)-N-Methyl-4-(4-(4-oxo-5-(2,3,4-trimethoxybenzylidene)-4,5-dihydrothiazol-2-ylamino)phenoxy)picolinamide (**8b**)*

Yield: 63%. m.p.: 267–268°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.44–8.42 (m, 1H), 8.15–8.04 (br, 2H), 7.80 (d, J = 2.7 Hz, 1H), 7.27–7.20 (m, 3H), 7.17–7.13 (m, 2H), 7.04–7.01 (q, J = 3.0 Hz, J = 2.7 Hz, 1 H), 6.79 (d, J = 8.7 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.04 (d, J = 5.4 Hz, 3H); ESI-MS *m/z*: 521.8 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{24}N_4O_6S_2$ (%): C 59.99, H 4.65, N 10.76, O 18.44, S 6.16; found C 59.85, H 4.71, N 10.65, S 6.00.

*(E)-4-(4-(5-(2,5-Dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8c**)*

Yield: 66%. m.p.: 233–234°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.44–8.42 (m, 1H), 8.59 (br, 2H), 7.82 (d, J = 2.4 Hz, 1H), 7.22–7.12

(m, 4H), 7.04–7.01 (q, J = 2.4 Hz, J = 4.8 Hz, 1H), 6.95 (s, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 3.8 (s, 3H), 3.79 (s, 3H), 3.05 (d, J = 5.1 Hz, 3H); ESI-MS *m/z*: 491.2 $(M+H)^+$; Anal. Calcd. for $C_{25}H_{22}N_4O_5S$ (%): C 61.21, H 4.52, N 11.42, O 16.31, S 6.54; found C 61.30, H 4.70, N 11.40, S 6.66.

*(E)-4-(4-(5-(3,5-Dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8d**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 52%. m.p.: 231–232°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44–8.42 (m, 1H), 8.09 (d, J = 6.0 Hz, 1H), 7.81 (s, 1H), 7.70 (s, 1H), 7.22 (d, J = 9.0 Hz, 2H), 7.16 (d, J = 9.0 Hz, 2H), 7.04–7.01 (q, J = 3.0 Hz, J = 6.0 Hz, 1H), 6.62 (s, 2H), 6.51 (s, 1H), 3.82 (s, 6H), 3.05 (d, J = 5.1 Hz, 3H); ESI-MS *m/z*: 491.3 $(M+H)^+$; Anal. Calcd. for $C_{25}H_{22}N_4O_5S$ (%): C 61.21, H 4.52, N 11.42, O 16.31, S 6.54; found C 61.30, H 4.60, N 11.55, S 6.55.

*(E)-4-(4-(5-Benzylidene-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8e**)*

Flash chromatography (silica gel, methylene chloride/methanol (25:1)). Yield: 76%. m.p.: 249–250°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.79–8.78 (m, 1H), 8.54 (d, J = 5.1 Hz, 1H), 7.93 (d, J = 6.3 Hz, 1H), 7.75 (s, 2H), 7.66 (d, J = 9.0 Hz, 1H), 7.58–7.43 (m, 5H), 7.34 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.20–7.10 (m, 2H), 2.81 (d, J = 4.2 Hz, 3H); ESI-MS *m/z*: 431.7 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{18}N_4O_3S$ (%): C 64.17, H 4.21, N 13.01, O 11.15, S 7.45; found C 63.88, H 4.17, N 12.99, S 7.27.

*(E)-N-Methyl-4-(4-(4-oxo-5-(2,3,4-trihydroxybenzylidene)-4,5-dihydrothiazol-2-ylamino)phenoxy)picolinamide (**8f**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 68%. m.p.: 255–257°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.78–8.77 (m, 1H), 8.59 (d, J = 5.7 Hz, 1H), 8.53 (d, J = 5.1 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.83 (s, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.65–7.49 (m, 2H), 7.41–7.38 (q, J = 2.4 Hz, J = 6.0 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 7.21–7.15 (m, 2H), 2.80 (d, J = 5.7 Hz, 3H); ESI-MS *m/z*: 479.1 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{18}N_4O_6S$ (%): C 57.73, H 3.79, N 11.71, O 20.06, S 6.70; found C 58.01, H 3.85, N 11.73, S 6.77.

*(E)-4-(4-(5-(2,3-Dichlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8g**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 41%. m.p.: 252–253°C. ^{1}H-NMR (300 MHz, DMSO) δ: 10.1 (br, 1H), 8.78–8.76 (m, 1H), 8.53 (d, J = 5.4 Hz, 1H), 7.88 (d, J = 5.7 Hz, 1H), 7.70–7.53 (m, 4H), 7.42 (s, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 7.17–7.15 (m, 2H), 2.80 (d, J = 3.0 Hz, 3H); ESI-MS *m/z*: 500.2 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{16}N_4O_3S$ (%): C 55.32, H 3.23, N 11.22, O 9.61, S 6.42; found C 55.51, H 3.37, N 11.19, S 6.48.

*(E)-4-(4-(5-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8h**)*

Yield: 73%. m.p.: 244–245°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44–8.42 (m, 1H), 8.08 (d, J = 4.8 Hz, 1 H), 7.81 (s, 1 H), 7.68 (s, 1 H), 7.23 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 9.0 Hz, 2H), 7.06–7.01 (m, 2 H), 6.97 (s, 1 H), 6.92 (d, J = 9.0 Hz, 1 H), 6.04 (s, 2H), 3.05 (d, J = 5.1 Hz, 2 H); ESI-MS *m/z*: 475.2 $(M+H)^+$; Anal. Calcd. for $C_{24}H_{18}N_4O_5S$ (%): C, 60.75; H, 3.82; N, 11.81; O, 16.86; S, 6.76; found C 60.80, H 3.87, N 11.84, S 6.69.

*(E)-4-(4-(5-(3,4-Dihydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8i**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 78%. m.p.: 261–262°C. ^{1}H-NMR (300 MHz, DMSO) δ: 9.67 (br, 1H), 9.41 (br, 1H), 8.80–8.79 (m, 1H), 8.54 (d, J = 5.7 Hz, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.56 (s, 1H), 7.47 (d, J = 4.2 Hz, 1H), 7.29 (d, J = 9.3 Hz, 2H), 7.19–7.17 (m, 2H), 7.03–6.82 (m, 3H), 2.80 (d, J = 4.2 Hz, 3H); ESI-MS *m/z*: 463.2 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{18}N_4O_5S$ (%): C 59.73, H 3.92, N 12.11, O 17.30, S 6.93; found C 59.91, H 3.97, N 12.24, S 7.01.

*(E)-4-(4-(5-(4-Hydroxy-3-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8j**)*

Flash chromatography (silica gel, methylene chloride/methanol (25:1)). Yield: 55%. m.p.: 237–238°C. ^{1}H-NMR (300 MHz, DMSO) δ: 9.85–9.80 (br, 1H), 8.79–8.77 (m, 1H), 8.54 (d, J = 5.7 Hz, 1H), 7.93 (d, J = 9.6 Hz, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 7.33–7.26 (m, 2H), 7.20–7.10 (m, 3H), 7.00–6.90 (m, 2H), 3.85 (s, 3H), 2.81 (d, J = 5.1 Hz, 3H); ESI-MS *m/z*: 572.7 $(M+H)^+$; Anal. Calcd. for $C_{24}H_{20}N_4O_5S$ (%): C 60.49, H 4.23, N 11.76, O 16.79, S 6.73; found C 60.60, H 4.21, N 11.76, S 6.82.

*(E)-4-(4-(5-(3-Hydroxy-4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8k**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 67%. m.p.: 243–244°C. ^{1}H-NMR (300 MHz, DMSO) δ: 9.47–9.45 (br, 1H), 8.81–8.79 (m, 1H), 8.54 (d, J = 5.7 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 9.0 Hz, 2H), 7.20–7.19 (m, 2H), 7.09–6.97 (m, 2H), 3.84 (s, 3H), 2.80 (d, J = 4.2 Hz, 3H); ESI-MS *m/z*: 477.5 $(M+H)^+$; Anal. Calcd. for $C_{24}H_{20}N_4O_5S$ (%): C 60.49, H 4.23, N 11.76, O 16.79, S 6.73; found C 60.41, H 4.28, N 11.82, S 6.81.

*(E)-4-(4-(5-(2,4-Dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8l**)*

Yield: 48%. m.p.: 229–230°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.43–8.41 (m, 1H), 8.12 (br, 2H), 7.82 (d, J = 2.7 Hz, 1H), 7.17–7.12 (m, 4H), 7.03–7.00 (q, J = 3.0 Hz, J = 6.0 Hz, 2H), 6.95 (d, J = 7.8 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.05 (d, J = 5.4 Hz, 3H); ESI-MS *m/z*: 491.7 $(M+H)^+$; Anal. Calcd. for $C_{25}H_{22}N_4O_5S$ (%): C 61.21, H 4.52, N 11.42, O 16.31, S 6.54; found C 61.30, H 4.65, N 11.47, S 6.60.

*(E)-N-Methyl-4-(4-(4-oxo-5-(2,4,6-trimethoxybenzylidene)-4,5-dihydrothiazol-2-ylamino)phenoxy)picolinamide (**8m**)*

Flash chromatography (silica gel, methylene chloride/methanol (25:1)). Yield: 76%. m.p.: 251–252°C. ^{1}H-NMR (300 MHz, $CDCl_3$)

δ: 8.41–8.39 (m, 1H), 8.06 (br, 2H), 7.77 (d, J = 2.4 Hz,1H), 7.20–7.11 (m, 4H), 7.00–6.97 (q, J = 4.2 Hz, J = 7.5 Hz, 1H), 6.10 (s, 2H), 3.86 (s, 6H), 3.82 (s, 3H), 3.04 (d, J = 5.4 Hz, 3H); ESI-MS *m/z*: 521.9 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{24}N_4O_6S$ (%): C 59.99, H 4.65, N 10.76, O 18.44, S 6.16; found C 60.11, H 4.71, N 10.82, S 6.21.

*(E)-4-(4-(5-(3,5-Dibromo-4-hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8n**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 72%. m.p.: 236–237°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.79–8.77 (m, 1H), 8.53 (d, J = 5.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.83 (s, 1H), 7.70 (s, 1H), 7.64 (s, 1H), 7.46–7.41 (q, J = 2.1 Hz, J = 6.0 Hz, 1H), 7.43–7.28 (m, 2H), 7.21–7.16 (m, 2H), 2.80 (d, J = 4.8 Hz, 3H); ESI-MS *m/z*: 604.1 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{16}Br_2N_4O_4S$ (%): C 45.72, H 2.67, N 9.27, O 10.59, S 5.31; found C 45.70, H 2.71, N 9.23, S 3.36.

*(E)-4-(4-(5-((2-Hydroxynaphthalen-1-yl)methylene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8o**)*

Yield: 47%. m.p.: 261–262°C. ^{1}H-NMR (300 MHz, DMSO) δ: 10.67 (br, 1H), 8.77–8.76 (m, 1H), 8.59 (d, J = 5.7 Hz, 1H), 8.09 (s, 1H), 7.91–7.82 (m, 3H), 7.78–7.69 (q, J = 6.0 Hz, J = 9.0 Hz, 1H), 7.78–7.69 (m, 1H), 7.41–7.24 (m, 3H), 7.19 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 2.79 (d, J = 4.2 Hz, 3H); ESI-MS *m/z*: 497.3 $(M+H)^+$; Anal. Calcd. for $C_{27}H_{20}N_4O_4S$ (%): C 65.31, H 4.06, N 11.28, O 12.89, S 6.46; found C 65.22, H 4.11, N 11.31, S 6.51.

*(E)-4-(4-(5-(2-Hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8p**)*

Flash chromatography (silica gel, methylene chloride/methanol (25:1)). Yield: 59%. m.p.: 247–248°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.50–8.48 (m, 1H), 8.32 (d, J = 4.2 Hz, 1H), 8.09 (s, 1H), 7.60 (d, J = 2.7 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.29–7.20 (m, 4H), 7.14–7.12 (q, J = 3.0 Hz, J = 4.2 Hz, 2H), 7.04 (d, J = 3.6 Hz, 1H), 7.01 (d, J = 3.6 Hz, 1H), 2.97 (d, J = 4.8 Hz, 3H); ESI-MS *m/z*: 447.8 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{18}N_4O_4S$ (%): C 61.87, H 4.06, N 12.55, O 14.33, S 7.18; found C 62.01, H 4.14, N 12.71, S 7.22.

*(E)-4-(4-(5-(4-Hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8q**)*

Yield: 63%. m.p.: 227–228°C. ^{1}H-NMR (300 MHz, DMSO) δ: 10.21 (br, 1H), 8.80–8.78 (m, 1H), 8.54 (d, J = 5.4 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.56–7.34 (m, 3H), 7.29 (d, J = 9.0 Hz, 2 H), 7.19 (d, J = 9.0 Hz, 2H), 6.96–6.88 (m, 2 H), 2.79 (d, J = 4.8 Hz, 3H); ESI-MS *m/z*: 447.8 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{18}N_4O_4S$ (%): C 61.87, H 4.06, N 12.55, O 14.33, S 7.18; found C 62.85, H 4.22, N 12.63, S 7.09.

*(E)-4-(4-(5-(2-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8r**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 42%. m.p.: 221–211°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.79–8.78 (m, 1H), 8.54 (d, J = 5.4 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.78 (s, 1H), 7.51 (d, J = 5.7 Hz, 1H), 7.42–7.28 (m, 5H), 7.19 (br, 2H), 2.79 (d, J = 4.2 Hz, 3H); ESI-MS *m/z*: 449.2 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{17}FN_4O_3S$ (%): C 61.60, H 3.82, N 12.49, O 10.70, S 7.15; found C 61.71, H 3.99, N 12.63, S 7.32.

*(E)-4-(4-(5-(4-Fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8s**)*

Yield: 65%. m.p.: 237–238°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.13–8.12 (m, 1H), 7.79 (d, J = 2.7 Hz, 1 H), 7.74 (s, 1 H), 7.52–7.47 (m, 2H), 7.21–7.15 (m, 6 H), 7.08–7.05 (q, J = 2.7 Hz, J = 5.7 Hz, 1 H), 2.81 (d, J = 4.8 Hz, 3 H); ESI-MS *m/z*: 449.2 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{17}FN_4O_3S$ (%): C 61.60, H 3.82, N 12.49, O 10.70, S 7.15; found C 61.75, H 4.03, N 12.50, S 10.74.

*(E)-4-(4-(5-(2,4-Difluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8t**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 68%. m.p.: 228–229°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.79–8.78 (m, 1H), 8.54 (d, J = 5.7Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.69–7.39 (m, 4H), 7.32–7.26 (q, J = 8.7 Hz, J = 12.0 Hz, 3H), 7.19 (d, J = 8.4 Hz, 2H), 2.79 (d, J = 5.1 Hz, 3H); ESI-MS *m/z*: 467.0 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{16}F_2N_4O_3S$ (%): C 59.22, H 3.46, N 12.01, O 10.29, S 6.87; found C 59.17, H 3.51, N 12.00, S 6.81.

*(E)-4-(4-(5-(3,4-Difluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8u**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 45%. m.p.: 242–243°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.80–8.78 (m, 1H), 8.54 (d, J = 5.7 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.72–7.57 (m, 3H), 7.51–7.39 (m, 2H), 7.33–7.26 (q, J = 9.0 Hz, J = 11.4 Hz, 2H), 7.20–7.17 (ms, 2H), 2.80 (d, J = 4.2 Hz, 3H); ESI-MS *m/z*: 467.0 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{16}F_2N_4O_3S$ (%): C 59.22, H 3.46, N 12.01, O 10.29, S 6.87; found C 59.30, H 3.55, N 12.03, S 6.85.

*(E)-4-(4-(5-(4-Methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)phenoxy)-N-methylpicolinamide (**8v**)*

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 73%. m.p.: 225–226°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.80–8.78 (m, 1H), 8.54 (d, J = 5.4 Hz, 1H), 7.92 (d, J = 87. Hz, 1H), 7.71 (s, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.43–7.42 (m, 2H), 7.37–7.26 (m, 4H), 7.17–7.17 (m, 2H), 2.80 (s, 3H), 2.23 (d, J = 4.2 Hz, 3H); ESI-MS *m/z*: 461.7 $(M+H)^+$; Anal. Calcd. for $C_{24}H_{20}N_4O_4S$ (%): C 62.60, H 4.38, N 12.17, O 13.90, S 6.96; found C 62.72, H 4.50, N 12.31, S 7.01.

*(E)-N-Methyl-4-(4-(4-oxo-5-(4-(trifluoromethyl)-benzylidene)-4,5-dihydrothiazol-2-ylamino)phenoxy)-picolinamide (**8w**)*

Yield: 53%. m.p.: 243–244°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.46–8.44 (m, 1H), 8.11 (d, J = 4.5 Hz, 1H), 7.78 (d, J = 2.4 Hz, 2H), 7.75 (s, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 7.08–7.05 (q, J = 2.7 Hz, J = 6.0 Hz, 1H), 3.05 (d, J = 5.1 Hz, 3H); ESI-MS *m/z*: 499.7 $(M+H)^+$; Anal. Calcd.

for $C_{24}H_{17}F_3N_4O_3S$ (%): C 57.83, H 3.44, F 11.43, N 11.24, O 9.63, S 6.43; found C 57.99, H 3.52, N 11.26, S 6.45.

*(E)-N-Methyl-4-(4-(4-oxo-5-(thiophen-2-ylmethylene)-4,5-dihydrothiazol-2-ylamino)phenoxy)picolinamide (**8x**)*

Flash chromatography (silica gel, methylene chloride/methanol (25:1)). Yield: 73%. m.p.: 225–226°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.79–8.78 (m, 1H), 8.55 (d, J = 5.1 Hz, 1H), 7.98–7.88 (m, 3H), 7.65–7.59 (m, 1H), 7.43–7.42 (m, 1H), 7.33–7.19 (m, 5H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS *m/z*: 437.5 $(M+H)^+$; Anal. Calcd. for $C_{21}H_{16}N_4O_3S_2$ (%): C 57.78, H 3.69, N 12.84, O 11.00 S 14.69; found C 57.83, H 3.77, N 12.91, S 14.81.

*(E)-N-Methyl-4-(4-(4-oxo-5-(pyridin-4-ylmethylene)-4,5-dihydrothiazol-2-ylamino)phenoxy)picolinamide (**8y**)*

Yield: 57%. m.p.: 232–233°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.80–8.78 (m, 1H), 8.75 (d, J = 6.0 Hz, 1H), 8.69 (d, J = 6.0 Hz, 1H), 8.57–8.52 (q, J = 3.0 Hz, J = 6.0 Hz, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.70 (s, 1H), 7.58 (d, J = 5.7 Hz, 1H), 7.49 (d, J = 5.7 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 9.0 Hz, 1H), 7.21–7.18 (m, 2H), 2.81 (d, J = 5.1 Hz, 3H); ESI-MS *m/z*: 432.3 $(M+H)^+$; Anal. Calcd. for $C_{22}H_{17}N_5O_3S$ (%): C 61.24, H 3.97, N 16.23, O 11.12, S 7.43; found C 61.33, H 4.05, N 16.44, S 7.27.

Biological activity

The cytotoxic activities of compounds **8a–8y** were evaluated with human lung carcinoma cells A549 (ATCC), human lung carcinoma cells H460 (ATCC) and human colon carcinoma cells HT29 (ATCC) by the standard MTT assay *in vitro*, with sorafenib as the positive control. The cancer cell lines were cultured in minimum essential medium (MEM) supplemented with 10% fetal bovine serum (FBS). The cells were maintained at 37°C in a moisture-saturated atmosphere containing 5% CO_2.

Approximately 4×10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and plates were incubated in 5% CO_2 at 37°C for 24 h before treatment with the compounds to allow attachment to the wall of the plate. The test compounds **8a–8y** at the indicated final concentrations were added to 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 with an ELISA reader. All of the compounds were tested at six concentrations in each cell line and the optical density (OD) values were measured. Furthermore, the inhibition rate of cell survival was caculated and the results expressed as IC_{50} values were calculated by regression analysis by means of SPSS.

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