Full Paper

Design, Synthesis and Evaluation of Novel Rhodanine-containing Sorafenib Analogs as Potential Antitumor Agents

Wei Li[1], Xin Zhai[1], Zheng Zhong[2], Guangyue Li[1], Yongxiao Pu[1], and Ping Gong[1]

[1] Key Laboratary of Original New Drugs Design and Discovery of Ministry of Education, School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, P.R. China
[2] 146 Depot, State Food and Drug Administration, Shijiazhuang, P.R. China

A series of rhodanine-containing sorafenib analogs was designed, synthesized and evaluated for their *in-vitro* antitumor activity against three cancer cell lines (A549, H460 and HT29). Pharmacological data indicated that some of the target compounds possessed marked antiproliferative activity superior to the reference drug sorafenib, especially the most promising compound **7r** (with the IC_{50} value of 0.8, 1.3 and 2.8 μM against A549, H460 and HT29 cell lines, respectively). The activity was found to strongly depend on the substitution pattern of the rhodanine motif at C-5″ position. Results suggested that this series of compounds could serve as the bases for the development of novel antitumor agents.

Keywords: Antitumor activity / Design / Rhodanine-containing sorafenib analogs / Structure–activity relationship

Received: November 1, 2010; Revised: December 13, 2010; Accepted: December 15, 2010

DOI 10.1002/ardp.201000326

Introduction

Chemotherapy is considered to be the mainstay of cancer treatments, while traditional cytotoxic chemotherapeutics are far from satisfactory due to diverse toxic side effects. It is urgent to develop novel antitumor chemotherapeutics with high efficiency and low toxicity. Recent advances and applications on multiple targeted agents may afford effective chemotherapeutics with low side effect profile.

Sorafenib, a novel oral multiple-targeted antitumor agent, was proved to inhibit kinases involved both in tumor proliferation and angiogenesis including Raf, VEGFR, PDGFR and KIT [1–3]. In December 2005 and November 2007, sorafenib was approved by the FDA for the treatment of primary renal cell carcinoma and advanced primary hepatocellular carcinoma respectively [4]. Due to the virtue of dual mechanisms, broad-spectrum anticancer potency, and well-tolerated results in combination trials, researchers drew attentions to the optimization of sorafenib [5–10]. In most studies including our previous work, it was found that sorafenib analogs bearing a diaryl urea framework constituted various compounds with superior antitumor activity [8]. Recently, optimizations of diaryl urea framework of sorafenib led to the discovery of an interesting class of compounds with *N*-methyl-4-phenoxypicolinamide motif preserved [9, 10].

Considerable studies suggest that the rhodanine scaffold is versatile and privileged in drug discovery [11, 12]. It is known, that the thioxo group in the rhodanine motif is a carboxylic acid bioisoster by size with low electronegativity and possesses the ability to build hydrogen bonds [13, 14]. So far, rhodanine-containing compounds have been developed as promising antitumor, antimicrobial, anti-inflammatory, antidiabetic agents, etc. [11, 12].

Inspired by the recent modifications on the diaryl urea framework of sorafenib (compound **1** and compound **2**) and the remarkable antitumor activity of rhodanine-containing compounds, we designed and synthesized 29 4-(4-(5-arylidene-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-*N*-methylpicolinamides (Fig. 1) in an attempt to develop novel antitumor chemotherapeutics. Herein, the *N*-methyl-4-phenoxypicolinamide motif of the sorafenib was preserved, the rhodanine ring was hybrided into the C-4′ position of the *N*-methyl-4-phenoxypicolinamide scaffold. Furthermore, the arylidene group was incorporated into the C-5″ position of the rhodanine motif to construct a bioisoster of the arylurea. 24 benzylidenes (substituted by: Fluorine atom, chlorine atom, bromine atom, hydroxyl group, methoxy group) and 5 heterocyclidenes (pyridin-4-ylmethylene, thiophen-2-ylmethylene, (5-hydroxythiophen-2-yl)methylene and 1*H*-indol-3-yl)methylene) were

Correspondence: Ping Gong, 103 Wenhua Road, Shenhe District, 110016 Shenyang, Liaoning, P. R. China.
E-mail: gongpinggp@126.com
Fax: +86 24 2398-6429

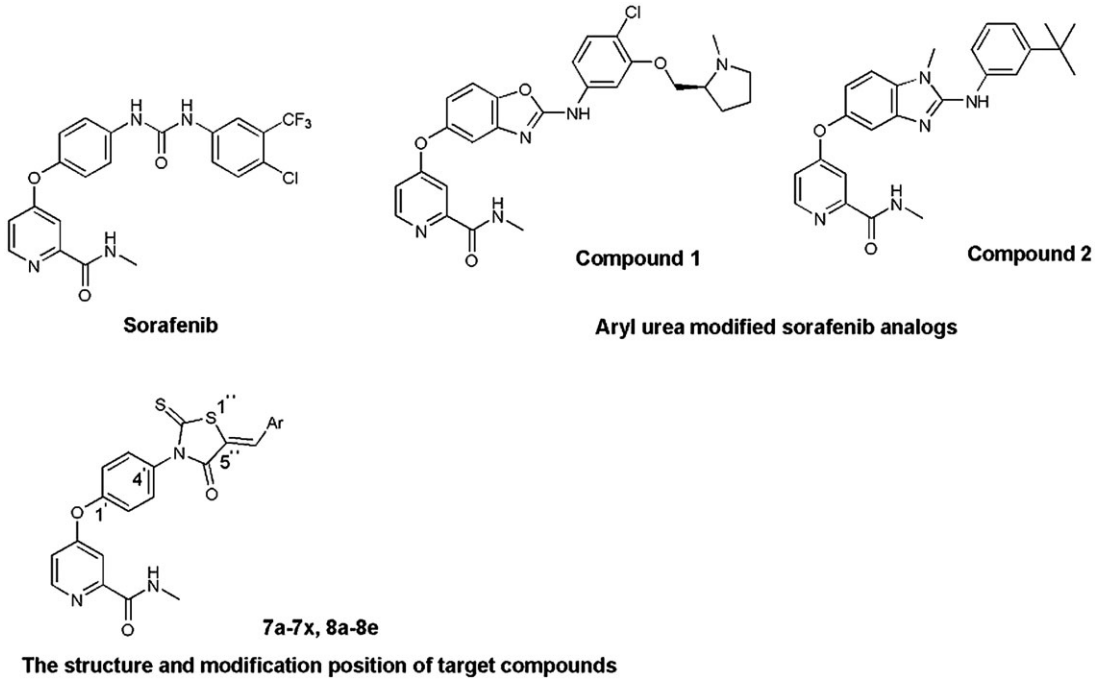


Figure 1. The structures of sorafenib, aryl urea modified sorafenib analogs and the target compounds.

introduced to investigate the influence of the substitution position and electrical effect of the arylidene motif.

Results and discussion

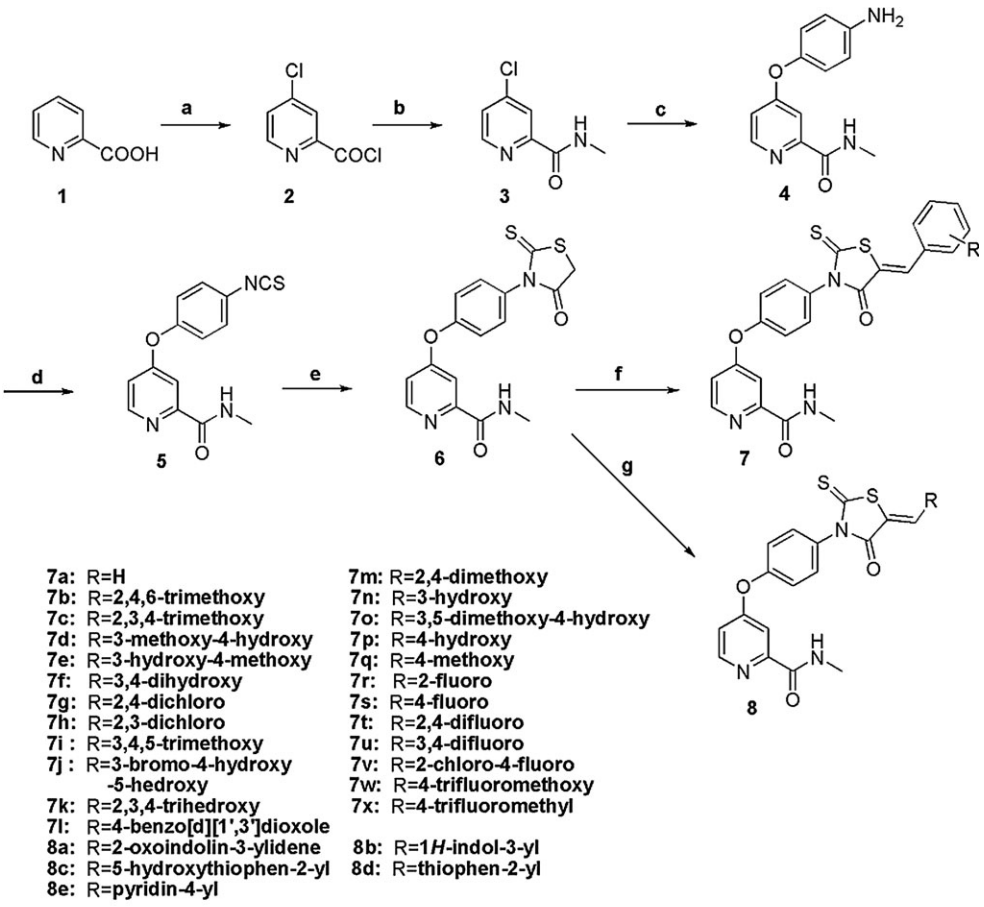
Chemistry

The synthetic route was illustrated as outlined in Scheme 1. Chloration of the commercial available picolinic acid in thionyl chloride afforded **2**, which was subsequently reacted with 2.0 M methyl amine in tetrahydrofuran to give the corresponding compound **3** as pale-yellow crystals. Etherification of **3** with 4-aminophenol in the presence of potassium *tert*-butoxide led to the formation of the intermediate **4**. Compound **5** was prepared by reacting the intermediate **4** with thiophosgen in chloroform and sodium bicarbonate. Cyclization of **5** and thioglycolic in 1,4-dioxane furnished the key rhodanine intermediate **6** in good yield. Knoevenagel condensation of **6** and different substituted aromatic aldehydes in the presence of piperidine in ethanol gave the target compounds **7a–7x** and **8a–8e**.

Biological activities

In-vitro evaluation of the key intermediate **6** and the target compounds **7a–7x** and **8a–8e** were performed by MTT assay using three human cancer cell lines, A549, H460 and HT29. The biological activity data were presented in Table 1. Some of the compounds exhibited enhanced antitumor potency compared to sorafenib against one or more cell lines in a low micromolar range (Table 1). Especially the most promising compound **7r** inhibited the proliferation of A549, H460 and HT29 cell lines with the IC_{50} value of 0.8, 1.3 and 2.8 μM. In addition, compound **7w** exhibited the optimal activity against HT29 cell line with the IC_{50} value of 0.2 μM, and compound **7t**, the most potent compound against H460 cell line selectively, possessed an IC_{50} value of 0.3 μM.

The preliminary structure–activity relationships (SARs) suggested that substituted arylidene on the C-5″ position of the rhodanine ring is essential for the antitumoral activity. A case in point is that compound **6** exhibited less antitumor activity than the target compounds. Introduction of a heterocyclidene (e.g. pyridin-4-yl-methylene, thiophen-2-yl-methylene, and 1*H*-indol-3-yl-methylene) led to weakened antitumor activity, while 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 compounds **7g**, **7m**, **7r** and **7t** with groups on the *ortho*-position or both *ortho*- and *para*-position of the benzylidene showed a remarkable antitumor activity against A549, H460 and HT29 cell lines. Interestingly, a potential tendency was found that the position influenced the selectivity of HT29 cell line. Compounds **7w**, **7s** and **7q** with a substitution on the *para*-position of the benzylidene are relatively well tolerated against HT29 cell line than the other two cell lines. However, similar tendency



Reagents and conditions: Reagents and conditions: a) $SOCl_2$/DMF, 50°C, 10 min, r.t. 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) $HSCH_2COOH$/Et_3N/dioxane, r.t., 3 h; f) EtOH/piperidine, r.t., 2–12 h;g) EtOH/piperidine, r.t., 2–12 h.

Scheme 1. Synthesis of target compounds.

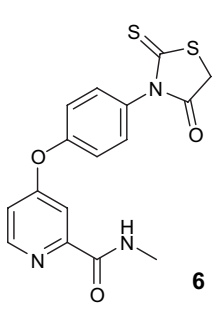
for different substituents of the benzylidene in the A549 and H460 are difficult to determine. It is noteworthy that the nature of the substituents on the benzylidene affects the antitumor activity. An electron withdrawing group exhibited moderate to significant influence on antitumor activity. Among the electron withdrawing groups, fluorine is more preferable, while other electron withdrawing groups such as chlorine, bromine, trifluoromethoxy group and the trifluoromethyl group exhibited less antitumor potency than fluorine (e.g. **7t** and the most promising compound **7r** showed more potent antitumor activity among the tested compounds). In contrast, an electron donating group including the hydroxyl group and methoxy group showed no evident influence on potency. This study may provide valuable information for further design of rhodanine-containing antitumor agents.

Experimental protocols

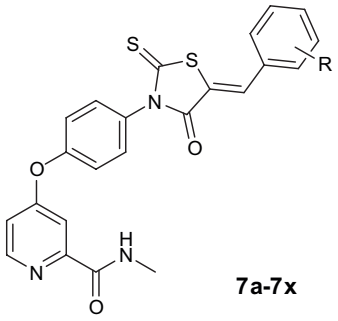
Chemistry

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 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.

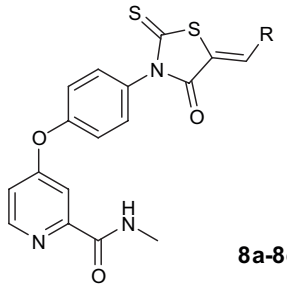
Table 1. IC_{50} value for tested compounds **7a–7x** and **8a–8e** (μM) against A549, H460 and HT29 cancer cell lines



6



7a-7x



8a-8e

Compd.	R	IC_{50} (μM)		
		A549	H460	HT29
6	–	43.6	77.2	48.0
7a	–	12.8	29.3	NA [a]
7b	2,4,6-trimethoxy	3.8	26.4	17.7
7c	2,3,4-trimethoxy	7.9	14.3	38.5
7d	3-methoxy-4-hydroxy	22.6	95.3	5.5
7e	3-hydroxy-4-methoxy	NA [a]	NA [a]	NA [a]
7f	3,4-dihydroxy	3.6	47.9	4.3
7g	2,4-dichloro	5.6	8.6	1.4
7h	2,3-dichloro	5.9	11.3	5.8
7i	3,4,5-trimethoxy	NA [a]	NA [a]	3.6
7j	3-bromo-4,5-dihydroxy	43.6	16.7	3
7k	2,3,4-trihedroxy	33.5	NA [a]	34.7
7l	4-benzo[d][1′,3′]dioxole	33.1	6.7	NA [a]
7m	2,4-dimethoxy	16.4	4.8	14.2
7n	3-hydroxy	NA [a]	NA [a]	NA [a]
7o	3,5-dimethoxy-4-hydroxy	12	59.8	17.6
7p	4-hydroxy	NA [a]	NA [a]	8.7
7q	4-methoxy	46	9.5	1.8
7r	2-fluoro	0.8	1.3	2.8
7s	4-fluoro	58.3	6.3	1.2
7t	2,4-difluoro	3.1	0.3	2.8
7u	3,4-difluoro	22.3	NA [a]	5.5
7v	2-chloro-4-fluoro	3.8	1.5	3.0
7w	4-trifluoromethoxy	3.1	NA [a]	0.2
7x	4-trifluoromethyl	46.5	64.8	17.2
8a	2-oxoindolin-3-ylidene	64.9	[a] NA	[a] NA
8b	1*H*-indol-3-yl	6.7	21.4	72.9
8c	5-hydroxythiophen-2-yl	[a] NA	[a] NA	33.7
8d	thiophen-2-yl	[a] NA	65.8	18.5
8e	pyridin-4-yl	89	[a] NA	43
Sorafenib	–	1.3	2.7	3.7

[a] NA, not active

*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 twice to give **2** as 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 nearly to 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.

*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 $(M + H)^+$; Anal. calcd. for $C_{13}H_{13}N_3O_2$ (%): C, 64.19, H, 5.38, N, 17.27, O, 13.15; found: C, 64.45, H, 5.33, N, 17.24.

*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 a 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. 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 $(M + H)^+$; Anal. calcd. for $C_{14}H_{11}N_3O_2S$ (%): C, 58.93, H, 3.89, N, 14.73, O, 11.22, S, 11.24; found: C, 58.78, H, 3.92, N, 14.73, S, 11.31.

*N-Methyl-4-(4-(4-oxo-2-thioxothiazolidin-3-yl)-phenoxy)picolinamide **6***

A mixture of 2-sulfanylacetic acid (3.8 mL, 54.1 mmol), 4-(4-isothiocyanatophenoxy)-*N*-methylpicolinamide **5** (15.4 g, 54.1 mmol) and triethylamine (7.6 mL, 54.1 mmol) in dioxane (90 mL) was refluxed for 3 h. The reaction mixture was left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from ethanol to give **6** (12.6 g, 35.2 mmol, 66%) as light yellow solid. ^{1}H-NMR (300 MHz, DMSO) δ: 8.814–8.79 (m, 1H), 8.58 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 3 Hz, 1H), 7.43–7.36 (m, 4H), 7.24–7.21 (q, J = 3 Hz, J = 5.4 Hz, 1H), 4.4 (s, 2H), 2.80 (d, J = 4.5 Hz, 3H); ESI-MS m/z: 360.1 $(M + H)^+$; Anal. calcd. for $C_{16}H_{13}N_3O_3S_2$ (%): C, 53.47, H, 3.56, N, 11.69, O, 13.35, S, 17.84; found: C, 53.35, H, 3.58, N, 11.53, S, 17.95.

*General procedure for the preparation of compounds **7a–7x** and **8a–8e***

A mixture of *N*-methyl-4-(4-(4-oxo-2-thioxothiazolidin-3-yl)-phenoxy)picolinamide **6** (0.1 g, 0.28 mmol), substituted benzaldehyde (0.42 mmol) and a drop of piperidine in absolute ethanol (5 mL) was refluxed for 2–12 h to participate the crude product. The crude product was recrystallized from proper solvent or purified by chromatography on silica gel using $MeOH/CH_2Cl_2$ to afford the solids **7a–7x** and **8a–8e**.

*(Z)-4-(4-(5-Benzylidene-4-oxo-2-thioxothiazolidin-3-yl)-phenoxy)-N-methylpicolinamide **7a***

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 66%; m.p.: 227–228°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.82–8.81 (m, 1H), 8.60 (d, J = 6.0 Hz, 1H), 7.87 (s, 1H), 7.73 (d, J = 6.9 Hz, 2H), 7.62–7.54 (m, 5H), 7.51 (d, J = 2.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.26–7.24 (q, J = 2.7 Hz, J = 6 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 447.9 $(M + H)^+$; Anal. calcd. for $C_{23}H_{17}N_3O_3S_2$ (%): C, 61.73, H, 3.83, N, 9.39, O, 10.73, S, 14.33; found: C, 62.01, H, 3.85, N, 9.32, S, 14.28.

*(Z)-N-Methyl-4-(4-(4-oxo-2-thioxo-5-(2,4,6-trimethoxybenzylidene)thiazolidin-3-yl)-phenoxy)picolinamide **7b***

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 62%; m.p.: 243–244°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.80 (m, 1H), 8.59 (d, J = 5.7 Hz, 1H), 8.01 (s, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 2.7 Hz, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.25–7.22 (q, J = 2.7 Hz, J = 5.7 Hz, 1H), 6.37 (s, 2H), 3.93 (s, 6H), 3.89 (s, 3H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 538.1 $(M + H)^+$; Anal. calcd. for $C_{26}H_{23}N_3O_6S_2$ (%): C, 58.09, H, 4.31, N, 7.82, O, 17.76, S, 11.93; found: C, 58.03, H, 4.33, N, 7.64, S, 11.97.

*(Z)-N-Methyl-4-(4-(4-oxo-2-thioxo-5-(2,3,4-trimethoxybenzylidene)thiazolidin-3-yl)-phenoxy)picolinamide **7c***

Yield: 31%; m.p.: 248–249°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.82–8.80 (m, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.87 (s, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 2.7 Hz, 1H), 7.42 (d, J = 6.9 Hz, 2H), 7.31 (d, J = 9.0 Hz, 1H), 7.26–7.23 (q, J = 2.7 Hz, J = 6.0 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 3.91 (s, 6H), 3.80 (s, 3H), 2.81 (d, J = 5.4 Hz, 3H); ESI-MS m/z: 537.9 $(M + H)^+$;

Anal. calcd. for $C_{26}H_{23}N_3O_6S_2$ (%): C, 58.09, H, 4.31, N, 7.82, O, 17.76, S, 11.93; found: C, 58.21, H, 4.29, N, 7.76, S, 11.79.

(Z)-4-(4-(5-(4-Hydroxy-3-methoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolin-amide ***7d***

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 71%; m.p.: 231–232°C. ^{1}H-NMR (300 MHz, DMSO) δ: 10.1 (br, 1H), 8.83–8.80 (m, 1H), 8.59 (d, J = 5.7 Hz, 1H), 7.79 (s, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.28–7.24 (m, 2H), 7.21–7.08 (q, J = 1.8 Hz, J = 6 Hz, 1H), 7.00 (d, J = 6 Hz, 1H), 3.86 (s, 3H), 2.81 (d, J = 4.5 Hz, 3H); ESI-MS m/z: 493.8 $(M + H)^+$; Anal. calcd. for $C_{24}H_{19}N_3O_5S_2$ (%): C, 58.40, H, 3.88, N, 8.51, O, 16.21, S, 12.99; found: C, 58.17, H, 3.85, N, 8047, S, 12.89.

(Z)-4-(4-(5-(3-Hydroxy-4-methoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7e***

Yield: 63%; m.p.: 240–241°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.80 (m, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.72 (s, 1H), 7.58 (d, J = 9.0 Hz, 2 H), 7.51 (d, J = 2.4 Hz, 1H), 7.44 (d, J = 9.0 Hz, 2 H), 7.26–7.21 (m, 2H), 7.14–7.11(m, 2H), 3.86 (s, 3H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 493.9 $(M + H)^+$; Anal. calcd. for $C_{24}H_{19}N_3O_5S_2$ (%): C, 58.40, H, 3.88, N, 8.51, O, 16.21, S, 12.99; found: C, 58.37, H, 3.85, N, 8.39, S, 13.11.

(Z)-4-(4-(5-(3,4-Dihydroxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7f***

Yield: 46%; m.p.: 237–238°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.82–8.80 (m, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.68 (s, 1H), 7.57 (d, J = 9.3 Hz, 2H), 7.52 (d, J = 3 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 7.26–7.23 (q, J = 2.7 Hz, J = 6.0 Hz, 1H), 7.11–7.09 (m, 2H), 6.93 (d, J = 8.7 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 480.2 $(M + H)^+$; Anal. calcd. for $C_{24}H_{17}N_3O_5S_2$ (%): C, 57.61, H, 3.57, N, 8.76, O, 16.68, S, 13.37; found: C, 57.30, H, 3.55, N, 8.65, S, 13.51.

(Z)-4-(4-(5-(2,4-Dichlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7g***

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 42%; m.p.: 229–230°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.91 (s, 1H), 7.87 (s, 1H), 7.72 (d, J = 10.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 7.51 (d, J = 3.0 Hz, 1H), 7.44 (d, J = 9.0 Hz, 2H), 7.26–7.24 (q, J = 3.0 Hz, J = 6.0 Hz, 1H), 2.81 (d, J = 5.1 Hz, 3H); ESI-MS m/z: 514.2, 516.2 $(M + H)^+$; Anal. calcd. for $C_{23}H_{15}Cl_2N_3O_3S_2$ (%): C, 53.49, H, 2.93, Cl, 13.73, N, 8.14, O, 9.29, S, 12.42; found: C, 53.61, H, 2.85, N, 8.08, S, 21.21.

(Z)-4-(4-(5-(2,3-Dichlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7h***

Yield: 55%; m.p.: 240–241°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.80 (m, 1H), 8.59 (d, J = 5.1 Hz, 1H), 7.93 (s, 1H), 7.84–7.81 (q, J = 1.8 Hz, J = 7.2 Hz, 1H), 7.66–7.62 (m, 2H), 7.61–7.58 (m, 2H), 7.51 (d, J = 3.0 Hz, 1H)7.43 (d, J = 6.6 Hz, 2H), 7.26–7.23 (q, J = 3.0 Hz, J = 5.1 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 514.5, 516.5 $(M + H)^+$; Anal. calcd. for $C_{23}H_{15}Cl_2N_3O_3S_2$ (%): C, 53.49, H, 2.93, Cl, 13.73, N, 8.14, O, 9.29, S, 12.42; found C, 53.68, H, 2.90, N, 7.99, S, 12.35.

(Z)-N-Methyl-4-(4-(4-oxo-2-thioxo-5-(3,4,5-trimethoxybenzylidene)thiazolidin-3-yl)-phenoxy)picolinamide ***7i***

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 68%; m.p.: 252–253°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.80 (m, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.82 (s, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 3.0 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.28–7.24 (q, J = 3.0 Hz, J = 6.0 Hz, 1H), 7.02 (s, 2H), 3.88 (s, 6H), 3.76 (s, 3H), 2.81 (d, J = 5.1 Hz, 3H); ESI-MS m/z: 538.0 $(M + H)^+$; Anal. calcd. for $C_{26}H_{23}N_3O_6S_2$ (%): C, 58.09, H, 4.31, N, 7.82, O, 17.86, S, 11.93; found: C, 58.45, H, 4.22, N, 7.96, S, 12.05.

(Z)-4-(4-(5-(3-Bromo-4-hydroxy-5-methoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7j***

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 35%; m.p.: 233–234°C. ^{1}H-NMR (300 MHz, DMSO) δ: 10.61 (br, 1H), 8.81–8.78 (m, 1H), 8.59 (d, J = 2.1 Hz, 1H), 7.78 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.51–7.49 (m, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.27–7.23 (m, 2H), 3.93 (s, 3H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 572.7 $(M + H)^+$; Anal. calcd. for $C_{24}H_{18}BrN_3O_5S_2$ (%): C, 50.35, H, 3.17, N, 13.96, O, 13.97, S, 11.20; found: C, 50.61, H, 3.22, N, 13.88, S, 11.31.

(Z)-N-Methyl-4-(4-(4-oxo-2-thioxo-5-(2,3,4-trihydroxybenzylidene)thiazolidin-3-yl)phenoxy)picolinamide ***7k***

Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 70%; m.p.: 244–245°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.80–8.79 (m, 1H), 8.59 (d, J = 5.7 Hz, 1H), 8.02 (s, 1H), 7.56–7.50 (m, 3H), 7.41 (d, J = 8.4 Hz, 2H), 7.24–7.23 (m, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 495.5 $(M + H)^+$; Anal. calcd. for $C_{23}H_{17}N_3O_6S_2$ (%): C, 55.75, H, 3.46, N, 8.48, O, 19.37, S, 12.94; found: C, 55.68, H, 3.35, N, 8.37, S, 13.09.

(Z)-4-(4-(5-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7l***

Yield: 58%; m.p.: 235–236°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.59 (d, J = 5.4 Hz, 1H), 7.80 (s, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 3 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.30–7.23 (m, 3H), 7.16 (d, J = 8.7 Hz, 1H), 6.17 (s, 2H),

2.81 (d, $J = 4.5$ Hz, 3H); ESI-MS m/z: 491.7 $(M + H)^+$; Anal. calcd. for $C_{24}H_{17}N_3O_5S_2$ (%): C, 58.64, H, 3.49, N, 8.55, O, 16.27, S, 13.05; found: C, 58.46, H, 3.53, N, 8.69, S, 12.89.

(Z)-4-(4-(5-(2,4-Dimethoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7m***
Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 61%; m.p.: 226–227°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 7.93 (s, 1H), 7.56 (d, $J = 8.7$ Hz, 2H), 7.50 (d, $J = 3.0$ Hz, 1H), 7.48 (d, $J = 8.4$ Hz, 1H), 7.42 (d, $J = 9.0$ Hz, 2H), 7.25–7.22 (q, $J = 3.0$ Hz, $J = 6.0$ Hz, 1H), 6.78–6.73 (m, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 2.81 (d, $J = 4.5$ Hz, 3H); ESI-MS m/z: 508.0 $(M + H)^+$; Anal. calcd. for $C_{25}H_{21}N_3O_5S_2$ (%): C, 59.16, H, 4.17, N, 8.28, O, 15.76, S, 12.63; found: C, 59.27, H, 3.99, N, 8.51, S, 12.79.

(Z)-4-(4-(5-(3-Hydroxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7n***
Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 65%; m.p.: 236–237°C. ^{1}H-NMR (300 MHz, DMSO) δ: 9.91(s, 1H), 8.81–8.80 (m, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 7.77 (s, 1H), 7.59 (d, $J = 8.7$ Hz, 2H), 7.51 (d, $J = 2.4$ Hz, 1H), 7.43 (d, $J = 9.0$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 1.8), 7.26–7.23 (q, $J = 2.4$ Hz, $J = 6.0$ Hz, 1H), 7.16 (d, $J = 7.5$ Hz, 1H), 7.08 (s, 1H), 6.96 (d, $J = 7.5$ Hz, 1H), 2.81 (d, $J = 4.8$ Hz, 3H); ESI-MS m/z: 463.9 $(M + H)^+$; Anal. calcd. for $C_{23}H_{17}N_3O_4S_2$ (%): C, 59.60, H, 3.70, N, 9.07, O, 13.81, S, 13.84; found: C, 59.60, H, 3.72, N, 9.01, S, 13.77.

(Z)-4-(4-(5-(4-Hydroxy-3,5-dimethoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7o***
Yield: 43%; m.p.: 241–242°C. ^{1}H-NMR (300 MHz, DMSO) δ: 9.56 (s, 1H), 8.81–8.79 (m, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 7.79 (s, 1H), 7.58 (d, $J = 8.7$ Hz, 2H), 7.51 (d, $J = 3.0$ Hz, 1H), 7.43 (d, $J = 8.7$ Hz, 2H), 7.26–7.23 (q, $J = 3.0$ Hz, $J = 6.0$ Hz, 1H), 6.99 (s, 2H), 3.86 (s, 6H), 2.81 (d, $J = 4.8$ Hz, 3H); ESI-MS m/z: 523.7 $(M + H)^+$; Anal. calcd. for $C_{25}H_{21}N_3O_6S_2$ (%): C, 57.35, H, 4.04, N, 8.03, O, 18.33, S, 12.25; found: C, 57.78, H, 4.01, N, 8.21, S, 11.99.

(Z)-4-(4-(5-(4-Hydroxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7p***
Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 39%; m.p.: 221–222°C. ^{1}H-NMR (300 MHz, DMSO) δ: 10.49 (s, 1H), 8.81–8.79 (m, 1H), 8.59 (d, $J = 6$ Hz, 1H), 7.78 (s, 1H), 7.60–7.54 (m, 4H), 7.51 (d, $J = 3.0$ Hz, 1H), 7.42 (d, $J = 8.7$ Hz, 2H), 7.26–7.24 (q, $J = 3.0$ Hz, $J = 6.0$ Hz, 1H), 6.99 (d, $J = 6.0$ Hz, 2H), 2.81 (d, $J = 4.5$ Hz, 3H); ESI-MS m/z: 463.9 $(M + H)^+$; Anal. calcd. for $C_{23}H_{17}N_3O_4S_2$ (%): C, 59.60, H, 3.70, N, 9.07, O, 13.81, S, 13.84; found: C, 59.88, H, 3.75, N, 8.86, S, 14.07.

(Z)-4-(4-(5-(4-Methoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7q***
Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 58%; m.p.: 225–226°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 7.83 (s, 1H), 7.70 (d, $J = 8.7$ Hz, 2H), 7.58 (dd, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 3.0$ Hz, 1H), 7.43 (dd, $J = 8.7$ Hz, 2H), 7.26–7.24 (q, $J = 3.0$ Hz, $J = 6.0$ Hz, 1H), 7.17 (d, $J = 4.8$ Hz, 2H), 2.81 (d, $J = 4.8$ Hz, 3H); ESI-MS m/z: 478.3 $(M + H)^+$; Anal. calcd. for $C_{24}H_{19}N_3O_4S_2$ (%): C, 60.36, H, 4.01, N, 8.80, O, 13.40, S, 13.43; found: C, 60.62, H, 40.6, N, 9.02, S, 13.59.

(Z)-4-(4-(5-(2-Fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7r***
Yield: 63%; m.p.: 228–229°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 7.82 (s, 1H), 7.68–7.57 (m, 4H), 7.51 (d, $J = 2.7$ Hz, 1H), 7.48–7.41 (m, 4H), 7.26–7.23 (q, $J = 2.7$ Hz, $J = 6.0$ Hz, 1H), 2.81 (d, $J = 4.5$ Hz, 3H); ESI-MS m/z: 465.7 $(M + H)^+$; Anal. calcd. for $C_{23}H_{16}FN_3O_3S_2$ (%): C, 59.34, H, 3.46, F, 4.08, N, 9.03, O, 10.31, S, 13.78; found: C, 59.60, H, 3.53, N, 8.89, S, 13.91.

(Z)-4-(4-(5-(4-Fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7s***
Yield: 68%; m.p.: 225–226°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 7.89 (s, 1H), 7.82–7.76 (q, $J = 5.4$ Hz, $J = 9.0$ Hz, 2H), 7.59 (d, $J = 8.7$ Hz, 2H), 7.51 (d, $J = 3.0$ Hz, 1H), 7.45–7.41(m, 4H), 7.26–7.23 (q, $J = 3.0$ Hz, $J = 6.0$ Hz, 1H), 2.81 (d, $J = 4.8$ Hz, 3H); ESI-MS m/z: 465.4 $(M + H)^+$; Anal. calcd. for $C_{23}H_{16}FN_3O_3S_2$ (%): C, 59.34, H, 3.46, F, 4.08, N, 9.03, O, 10.31, S, 13.78; found C, 59.68, H, 3.52, N, 8.97, S, 14.00.

(Z)-4-(4-(5-(2,4-Difluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7t***
Yield: 62%; m.p.: 224–225°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.59 (d, $J = 6.0$ Hz, 1H), 7.75 (s, 1H), 7.74–7.70(m, 1H), 7.59–7.55 (m, 3H), 7.50 (d, $J = 3.0$ Hz, 1H), 7.44 (dd, $J = 8.7$ Hz, 2H), 7.35–7.31 (m, 1H), 7.26–7.23 (q, $J = 3.0$ Hz, $J = 6.0$ Hz, 1H), 2.81 (d, $J = 4.8$ Hz, 3H); ESI-MS m/z: 483.2 $(M + H)^+$; Anal. calcd. for $C_{23}H_{15}F_2N_3O_3S_2$ (%): C, 57.13, H, 3.13, F, 7.86, N, 8.69, O, 9.93, S, 13.26; found: C, 56.89, H, 3.19, N, 8.81, S, 13.03.

(Z)-4-(4-(5-(3,4-Difluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7u***
Flash chromatography (silica gel, methylene chloride/methanol (30:1)). Yield: 46%; m.p.: 231–232°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.60 (d, $J = 6.0$ Hz, 1H), 7.89–7.82 (m, 2H), 7.72–7.63 (m, 1H), 7.59–7.56 (m, 3H), 7.51 (d, $J = 2.7$ Hz, 1H), 7.44 (d, $J = 8.7$ Hz, 2H), 7.26–7.24 (q, $J = 2.7$ Hz, $J = 6.0$ Hz, 1H), 2.81 (d, $J = 4.5$ Hz, 3H); ESI-MS m/z: 483.7 $(M + H)^+$; Anal. calcd.

for $C_{23}H_{15}F_2N_3O_3S_2$ (%): C, 57.13, H, 3.13, F, 7.86, N, 8.69, O, 9.93, S, 13.26; found: C, 56.95, H, 3.12, N, 8.84, S, 13.40.

(Z)-4-(4-(5-(2-Chloro-4-fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***7v***

Yield: 66%; m.p.: 235–236°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.60 (d, J = 6.0 Hz, 1H), 7.89 (s, 1H), 7.77–7.70 (m, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 2.7 Hz, 1H), 7.48 (d, J = 3.0 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.25–7.23 (q, J = 2.7 Hz, J = 5.4 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 499.1 $(M + H)^+$; Anal. calcd. for $C_{23}H_{15}ClF_2N_3O_3S_2$ (%): C, 55.25, H, 3.02, Cl, 7.09, F, 3.80, N, 8.40, O, 9.60, S, 12.83; found: C, 54.98, H, 2.93, N, 8.29, S, 12.67.

(Z)-N-Methyl-4-(4-(4-oxo-2-thioxo-5-(4-(trifluoromethoxy)benzylidene)thiazolidin-3-yl)-phenoxy)picolinamide ***7w***

Flash chromatography (silica gel, methylene chloride/methanol (25:1)). Yield: 61%; m.p.: 256–257°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.79 (m, 1H), 8.59 (d, J = 6.0 Hz, 1H), 7.91 (s, 1H), 7.87 (d, J = 9.0 Hz, 2H), 7.59–7.57 (m, 4H), 7.51 (d, J = 3.0 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.26–7.23 (q, J = 3.0 Hz, J = 6 Hz, 1H), 2.81 (d, J = 5.1 Hz, 3H); ESI-MS m/z: 531.2 $(M + H)^+$; Anal. calcd. for $C_{24}H_{16}F_3N_3O_4S_2$ (%): C, 54.23, H, 3.03, F, 10.72, N, 7.91, O, 12.04, S, 12.07; found: C, 54.65, H, 2.99, N, 8.03, S, 12.31.

(Z)-N-Methyl-4-(4-(4-oxo-2-thioxo-5-(4-(trifluoromethyl)benzylidene)thiazolidin-3-yl)-phenoxy)picolinamide ***7x***

Yield: 75%; m.p.: 241–242°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.80 (m, 1H), 8.60 (d, J = 6.0 Hz, 1H), 7.96–7.91 (d, 5H), 7.61 (d, J = 9.3 Hz, 2H), 7.51(d, J = 3.0 Hz, 1H), 7.44 (d, J = 9.3 Hz, 2H), 7.26–7.24 (q, J = 3.0 Hz, J = 6.0 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 515.7 $(M + H)^+$; Anal. calcd. for $C_{24}H_{16}F_3N_3O_3S_2$ (%): C, 55.91, H, 3.13, F, 11.06, N, 8.15, O, 9.31, S, 12.44; found: C, 56.03, H, 3.19, N, 8.41, S, 12.65.

(Z)-N-Methyl-4-(4-(4-oxo-5-(2-oxoindolin-3-ylidene)-2-thioxothiazolidin-3-yl)phenoxy)picolinamide ***8a***

Yield: 31%; m.p.: 255–256°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.78 (m, 2H), 8.59 (d, J = 3.0 Hz, 1H), 7.61–7.58 (m, 2H), 7.50–7.43 (m, 5H), 7.26–7.24 (m, 1H), 7.07–7.04 (m, 1H), 7.00 (d, J = 6.0 Hz, 2H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 489.6 $(M + H)^+$; Anal. calcd. for $C_{24}H_{16}N_4O_4S_2$ (%): C, 59.00, H, 3.30, N, 11.47, O, 13.10, S, 13.13; found: C, 61.2, H, 3.52, N, 11.63, S, 13.22.

(Z)-4-(4-(5-((1H-Indol-3-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicolinamide ***8b***

Yield: 45%; m.p.: 238–239°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.80 (m, 1H), 8.59 (d, J = 5.1 Hz, 1H), 8.13 (s, 1H), 7.98 (br, 2H), 7.58–7.52 (m, 4H), 7.43 (d, J = 8.4 Hz, 2H), 7.30–7.24 (m, 3H), 2.81 (d, J = 4.5 Hz, 3H); ESI-MS m/z: 487.2 $(M + H)^+$; Anal. calcd. for $C_{25}H_{18}N_4O_3S_2$ (%): C, 61.71, H, 3.73, N, 11.51, O, 9.86, S, 13.18; found: C, 60.25, H, 3.28, N, 10.99, S, 12.67.

(Z)-4-(4-(5-((5-Hydroxythiophen-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)phenoxy)-N-methylpicoli-namide ***8c***

Yield: 47%; m.p.: 233–234°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.79–8.77 (m, 1H), 8.57 (d, J = 4.8 Hz, 1H), 7.50–7.41 (m, 5H), 7.33 (d, J = 3 Hz, 1H), 7.24–7.22 (q, J = 2.1 Hz, J = 6.0 Hz, 1H), 7.16 (d, J = 3.6 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z:470.2 $(M + H)^+$; Anal. calcd. for $C_{21}H_{15}N_3O_4S_3$ (%): C, 53.72, H, 3.22, N, 8.95, O, 13.63, S, 20.49; found: C, 53.58, H, 3.19, N, 8.87, S, 20.21.

(Z)-N-Methyl-4-(4-(4-oxo-5-(thiophen-2-ylmethylene)-2-thioxothiazolidin-3-yl)phenoxy)picolinamide ***8d***

Yield: 51%; m.p.: 238–239°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.80 (m, 1H), 8.59 (d, J = 5.4 Hz, 1H), 8.16–8.14 (br, 2H), 7.83 (d, J = 3.3 Hz, 1H), 7.51 (d, J = 3.0 Hz, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 3.0 Hz, J = 6.0 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.37 (m, 1H), 7.26–7.23 (q, J = 3.0 Hz, J = 6.0 Hz, 1H), 2.81 (d, J = 4.5 Hz, 3H); ESI-MS m/z: 454.1 $(M + H)^+$; Anal. calcd. for $C_{21}H_{15}N_3O_3S_3$ (%): C, 55.61, H, 3.33, N, 9.26, O, 10.58, S, 21.21; found: C, 56.00, H, 3.56, N, 9.21, S, 21.50.

(Z)-N-Methyl-4-(4-(4-oxo-5-(pyridin-4-ylmethylene)-2-thioxothiazolidin-3-yl)phenoxy)picolinamide ***8e***

Yield: 63%; m.p.: 229–230°C. ^{1}H-NMR (300 MHz, DMSO) δ: 8.81–8.77 (m, 3H), 8.60 (d, J = 6.0 Hz, 1H), 7.83 (s, 1H), 7.65 (d, J = 6 Hz, 2H), 7.60–7.57(m, 2H), 7.51 (d, J = 3 Hz, 1H), 7.45–7.42 (m, 2H), 7.27–7.24 (q, J = 3.0 Hz, J = 6.0 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H); ESI-MS m/z: 448.8 $(M + H)^+$; Anal. calcd. for $C_{22}H_{16}N_4O_3S_2$ (%): C, 58.91, H, 3.60, N, 12.49, O, 10.70, S, 14.30; found: C, 57.83, H, 4.11, N, 12.31, S, 14.35.

Pharmacology

The cytotoxic activities of compounds **6**, **7a–7x** and **8a–8e** were evaluated with A549, H460 and HT29 cell lines by the standard MTT assay. The cancer cell lines were cultured in minimum essential medium (MEM) supplement with 10% fetal bovine serum (FBS). The cells were maintained at 37°C in a moisture-saturated atmosphere containing 5% CO_2. The compounds were used at concentrations ranging from 0.16 to 100 μg/mL and sorafenib at the same concentrations was introduced as positive control. The assessment of the antiproliferative activity was expressed as concentration inhibiting 50% of cancer cell growth (IC_{50}).

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 **6**, **7a–7x** and **8a–8e** at 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 and the absorbencies at 492 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) were measured with the ELISA reader. All of the compounds were tested twice in each cell line. The results expressed as IC_{50} (inhibitory concentration 50%) were the averages of two determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

This work was supported by a grant from the National Natural Science Foundation of China (No. 21002065) and National S & T Major Project (No.2009ZX09301-012).

The authors have declared no conflict of interest.

References

[1] L. Liu, Y. Cao, X. Zhang, *Cancer Res.* **2006**, *66*, 11851–11858.
[2] S. M. Wilhelm, L. Advane, P. Newell, *Mol. Cancer Ther.* **2008**, *7*, 3129–3140.
[3] T. Guida, S. Anaganti, L. Provitera, *Clin. Cancer Res* **2007**, *13*, 3363–3369.
[4] L. R. Roberts, *N. Engl. J. Med.* **2008**, *359*, 420–422.
[5] N. Kansal, O. Silakari, M. Ravikumar, *Lett. Drug Des. Discov.* **2008**, *5*, 437–448.
[6] Y. Dai, K. Hartandi, Z. Ji, *J. Med. Chem.* **2007**, *50*, 1584–1597.
[7] M. Sun, X. Wu, J. Chen, *Eur. J. Med. Chem.* **2010**, *45*, 2299–2306.
[8] P. Yao, X. Zhai, D. Liu, *Arch. Pharm.* **2008**, *343*, 17–23.
[9] M. H. Potashman, J. Bready, A. Coxon, *J. Med. Chem.* **2007**, *50*, 4351–4373.
[10] S. Ramurthy, S. Subramanian, M. Aikawa, *J. Med. Chem.* **2008**, *51*, 7049–7052.
[11] T. Tomašic, L. P. Mašic, *Curr. Med. Chem.* **2009**, *16*, 1596–1629.
[12] D. B. Boyd, *J. Mol. Struct.* **1997**, *401*, 227–234.
[13] G. A. Patani, E. J. LaVoie, *Chem. Rev.* **1996**, *96*, 3147–3176.
[14] S. Miyamoto, *Chem-Bio Inf. J.* **2002**, *2*, 74–85.

