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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Thiourea and thioether derivatives of sorafenib: synthesis, crystal structure, and antiproliferative activity

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Abstract A series of novel sorafenib derivatives containing diaryl thiourea and thioether, **9a–u**, was designed and synthesized, and their antiproliferative activities against HCT116 and MDA-MB-231 cell lines were also evaluated and described. Most compounds exhibited potent antiproliferative activity against HCT116 cells with $IC_{50} = 1.8–80.4$ μM. Compounds **9p**, **9r**, and **9s** demonstrated competitive antiproliferative activities to sorafenib, against all two cancer cell lines. The structures of all the newly synthesized compounds were determined by ^{1}H NMR, ^{13}C NMR, and HRMS, and compound **9n** was characterized by single-crystal X-ray diffraction. Primary structure–activity relationships (SAR) have also been established.

Keywords Sorafenib analogs · Antiproliferative activity · Synthesis · Crystal structure

Introduction

Sorafenib, a multiple targeted antitumor agent containing a diaryl urea and a diaryl ether skeleton, can not only inhibit Raf to block Raf/MEK/ERK signaling pathway (Liu *et al.*, 2006), but also inhibit other kinases involved in tumor proliferation and angiogenesis, such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Fms-like tyrosine kinase-3 (Flit-3), and stem-cell growth factor (c-KIT) (Liu *et al.*, 2006; Wilhelm *et al.*, 2006; Guida *et al.*, 2007; Wilhelm *et al.*, 2008). The multi-mechanisms provide sorafenib with broad-spectrum anticancer potency and well-tolerated results in combination trials, and more and more attentions are given to the optimization of sorafenib (Dai *et al.*, 2007; Potashman *et al.*, 2007; Ramurthy *et al.*, 2008; Ménard *et al.*, 2009; Sun *et al.*, 2010).

Based on the bioisosteric theory, we have previously described a series of diaryl thiourea derivatives (Yao *et al.*, 2012). In the present paper, a series of sorafenib derivatives (**9a–u**) containing both diaryl thiourea and thioether were designed and synthesized (Fig. 1). The crystal structure of **9n** was also obtained. The antiproliferative activities of 21 compounds against human colorectal carcinoma cell line (HCT116) and human breast cancer cell line (MDA-MB-231) were evaluated. Apparent growth inhibition against HCT116 cells was observed for most of the compounds, and **9h**, **9p**, **9q**, **9r**, and **9s** demonstrating potent activities against both cancer cells.

Results and discussion

Chemistry

The synthetic routes to the library compounds were illustrated as outlined in Scheme 1.

The substituted diaryl thioethers, **5a–e**, were prepared from 2-picolinic acid **1**, which was treated with $SOCl_2$ to generate 4-chloropicolinoyl chloride **2**. Then methyl 4-chloropicolinate **3** was obtained by treating **2** with methanol, which was treated with corresponding amine (methylamine, ethylamine, phenylmethanamine, cyclopropanamine, and

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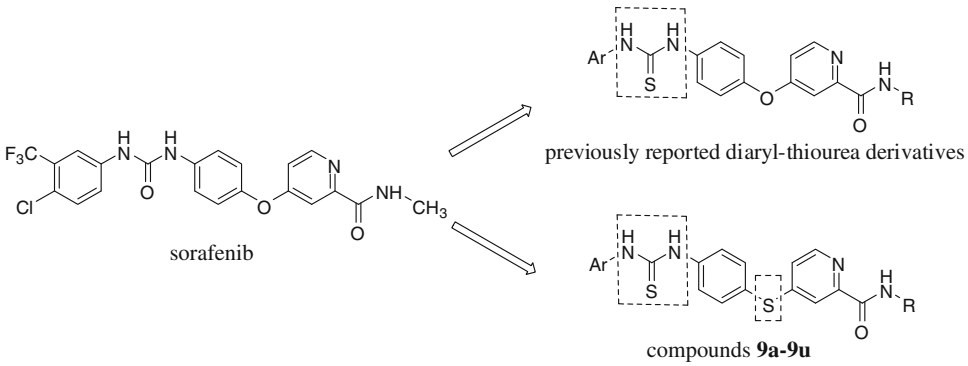
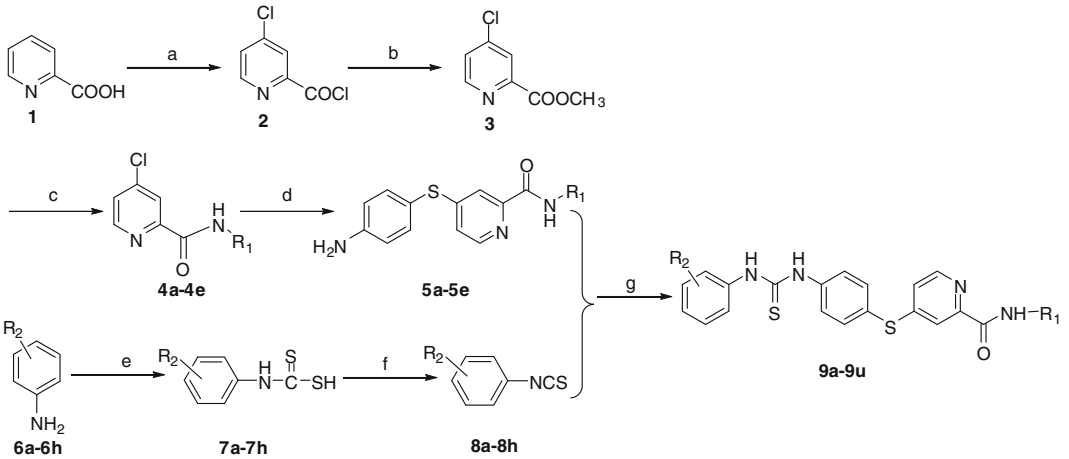


Fig. 1 Structures of sorafenib and its derivatives



Scheme 1 Reagents and conditions: (*a*) $SOCl_2$ (*b*) CH_3OH (*c*) R_1NH_2, THF (*d*) 4-aminobenzenethiol, DMF, t-BuOK (*e*) Dabco, CS_2, toluene (*f*) BTC, DCM (*g*) DCM

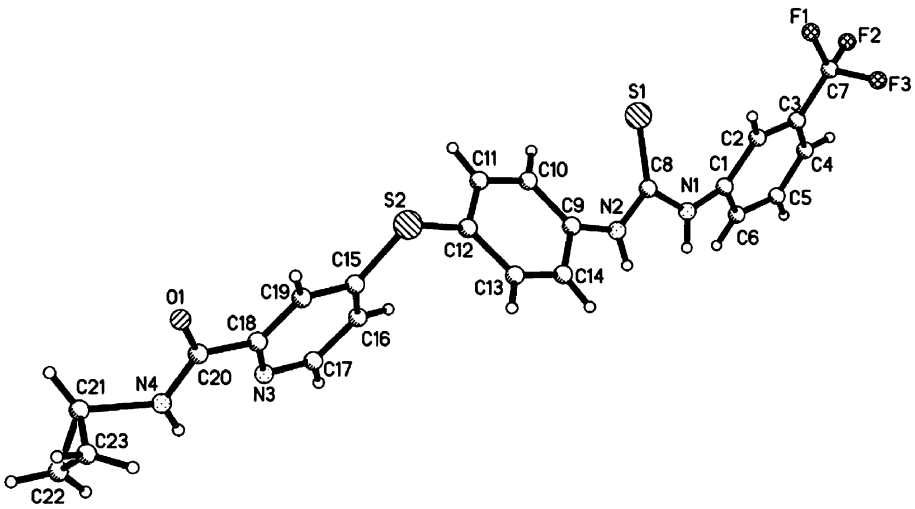


Fig. 2 The crystal structure of compound 9n. Disorderd atoms, F1′, F2′, and F3′, were omitted as clarity

cyclohexanamine) to form **4a–e**. Subsequently, they were treated with 4-aminobenzenethiol to afford corresponding diaromatic thioethers (**5a–e**) in the total yields of 40.5–56.4 %. On the other hand, virous isothiocyanates (**8a–h**) were obtained from substituted anilines (2,4-dichloroaniline, 4-chloroaniline, 3,4-difluoroaniline, 4-fluoroaniline, 3-(trifluoromethyl)aniline, 3,5-bis(trifluoromethyl)aniline, 4-chloro-3-(trifluoromethyl) aniline, or 4-(trifluoromethoxy)aniline), **6a–h**, which reacted with CS_2 to generate **7a–h**, and then treated with BTC to produce various isothiocyanates **8a–h**. Finally, these isothiocyanates were reacted with different substituted diaryl thioethers (**5a–e**) in DCM to give target compounds (**9a–u**) in 26.9–44.8 % total yields. The final products were purified by column chromatography and their

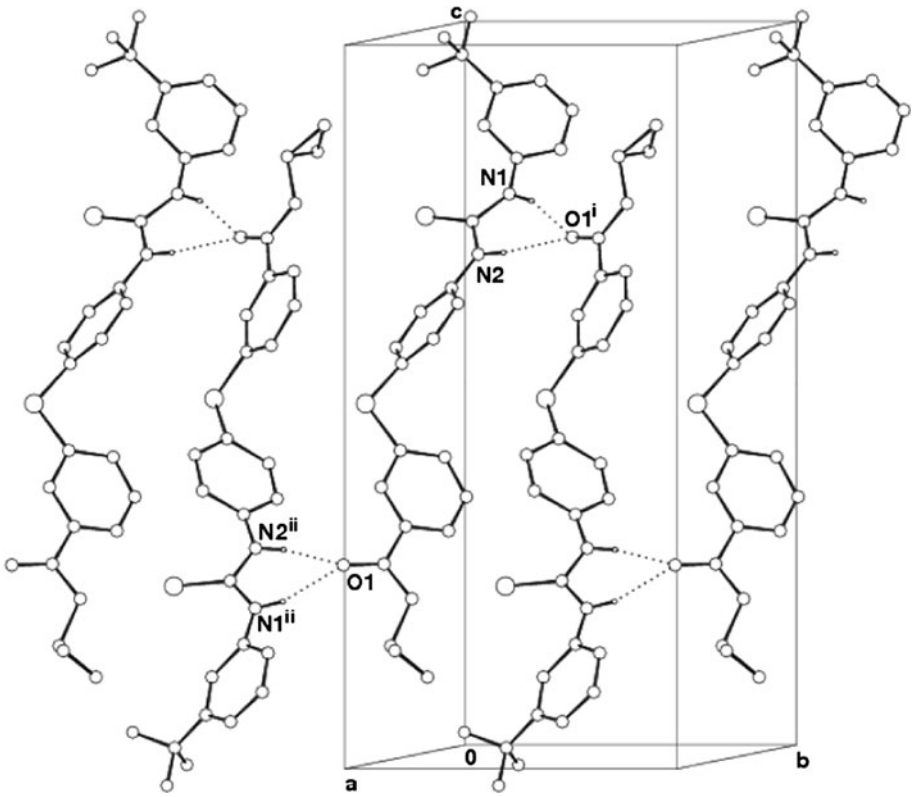


Fig. 3 A view showing the ribbon extending along the *b*-axis, formed by N–H···O hydrogen bonds (*dashed lines*). H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) 3/2 − x, 1/2 + y, 1 − z; (ii) 3/2 − x, y − 1/2, 1 − z]

structures were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.

Crystal structure of 9n

As shown in Fig. 2, the molecular structure of **9n** containing three six-membered aromatic rings and one cyclopropane ring adopts an extended conformation. The atoms F1, F2, and F3 appeared to be disordered, and were refined as two parts. Each molecular was connected by two classical hydrogen bond N1—H1′···O1^{i} and N2—H2···O1^{i} (i = 3/2 − x, 1/2 + y, 1 − z) to form an extended chain along the b axis (Fig. 3).

The plane of amide group (C18, C20, N4, and O1) forms the diangle of 9.8° with pyridine plane (C15, C16, C17, N3, C18, and C19). This value is much smaller than that of sorafenib (18.3°) (Ravikumar *et al.*, 2011). The pyridine ring connects a phenyl ring (C9, C10, C11, C12, C13, and C14) by an S atom. The angle of C12–S2–C15 is 103.85(17)°, which is much smaller than that of sorafenib (118.48°), that induces the dihedral angle between them (74.6°) to be similar with that angle of 78.4° in sorafenib.

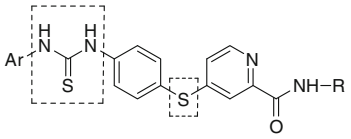
Another obvious difference between **9n** and sorafenib is that **9n** use thiourea to displace the urea in sorafenib. The dihedral angles between the thiourea group (N1, C8, N2, and S1) and the terminal phenyl planes is 35.6°. This value is much larger than that between the urea group and the phenyl plane in sorafenib (9.9°), which is perhaps due to the steric hindrance of S atom. The distance between S1 and H2 in **9n** is 2.76 Å, which is shorter than the sum (2.95 Å) of van der Waals Radius of S and H atom (Pauling and Pauling, 1975).

Although there many structure differences between sorafenib and **9n** mentioned above, the conformational flexibility of the urea and ether linkages in the molecules allow the terminal groups adopting the appropriate orientations to bind the target. On the other hand, the size of the total molecule between two structures is similar. The distance between N1 and N4 in **9n** is 13.576 Å which is a little longer than that (13.477 Å) of sorafenib. Considering that **9n** lack a Cl atom on 4-position of phenyl group compared with sorafenib, we anticipate that the compound **9s** have more similar structure with sorafenib, and the antiproliferative activities of **9s** are also comparative with those of sorafenib (Table 1).

Cell inhibition

In vitro cell cytotoxicity of the 21 new sorafenib derivatives was evaluated against HCT116 and MDA-MB-231 cells by MTT assay using sorafenib as a positive control. As shown in Table 1, compounds **9h**, **9p**, **9q**, **9r**, and **9s** showed significant inhibitory activities against both cell lines, and most compounds (except **9a**, **9b, 9e** and **9g, 9m**) exhibited potent antiproliferative activities to HCT116 cells with IC_{50} = 1.8–78.0 μM. Notably, compared with

Table 1 The structures and IC_{50} values of the target compounds



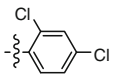
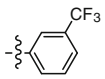
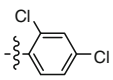
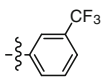
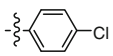
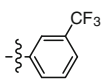
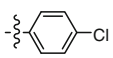
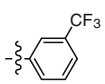
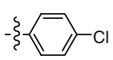
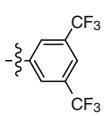
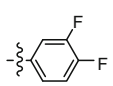
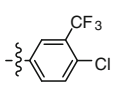
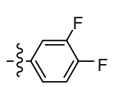
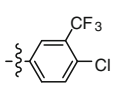
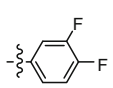
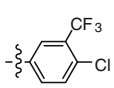
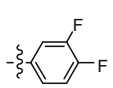
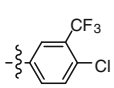
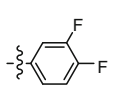
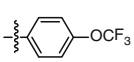
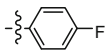
Comp. no.	Substituents		IC_{50} (μM)[a]		Comp. no.	Substituents		IC_{50} (μM)[a]	
	Ar	R	HCT116	MDA-MB-231		Ar	R	HCT116	MDA-MB-231
9a			>200	>200	**9l**			46.8 ± 2.0	>200
9b			>200	>200	**9m**			>200	>200
9c			14.5 ± 0.7	>200	**9n**			50.5 ± 3.5	>200
9d			15.8 ± 1.7	>200	**9o**			2.94 ± 0.3	>200
9e			>200	>200	**9p**			29.1 ± 0.8	38.2 ± 1.1
9f			78.0 ± 1.2	>200	**9q**			12.0 ± 2	84.0 ± 4.2
9g			>200	>200	**9r**			8.8 ± .2	53.6 ± 3.7
9h			34.5 ± 2.1	94.1 ± 5.7	**9s**			22.0 ± 2.8	50.8 ± 2.8
9i			38.5 ± 3.5	>200	**9t**			1.8 ± 0.7	>200
9j			3.3 ± 0.14	>200	**9u**			11.5 ± 1.7	>200

Table 1 continued

Comp. no.	Substituents		IC_{50} (μM)[a]		Comp. no.	Substituents		IC_{50} (μM)[a]	
	Ar	R	HCT116	MDA-MB-231		Ar	R	HCT116	MDA-MB-231
9k			47.0 ± 1.6	>200	Sorafenib	–	–	7.75 ± 1.1	36.6 ± 2.1

[a] Mean value of three experiments and standard deviation are given

sorafenib, some compounds showed good inhibitory selectivity on HCT116 cells. For example, compounds **9j**, **9o**, and **9t** which contains cyclohexyl substitute showed more potent inhibitory activities (IC_{50} = 1.8–3.3 μM) against HCT116 cells, while they have no inhibitory activities against MDA-MB-231 cell line. This trait was also found in the previously reported diaryl thiourea derivatives (Yao *et al.*, 2012), but the activities (IC_{50} = 9.15–26.15 μM) of them are weaker than those of **9j**, **9o**, and **9t**. Comparing the test data, we obtained some basic structure–activity relationships (SAR) as the following: (1) The size and shape of R on the terminal amide: **a.** Too large substitutes may diminish the cytotoxicity of the compounds. For example, all compounds (**9b**, **9e, 9g**, and **9m**) whose R substitutes are benzyl group have no antiproliferative activity to both cells. **b.** The cytotoxicity of the compounds with methyl, ethyl, and cyclopropyl substitutes have no significant differences. **c.** As mentioned above, cyclohexyl substitute may contribute to the selectivity on the HCT116 cells. (2) The substitutes on the terminal phenyl ring: **a.** 3-CF_3, 4-Cl-disubstitution on the phenyl ring may be conducive to the antiproliferative activity against MDA-MB-231 cells. All 3-CF_3, 4-Cl-disubstituted compounds (except **9t** whose R is cyclohexyl ring) showed potent cytotoxicity against MDA-MB-231 cells; the other compound having the cytotoxicity against MDA-MB-231 cells is 3,5-CF_3-disubstituted on the phenyl ring (**9p**). **b.** 2-, 4-disubstituted on phenyl group may be disadvantageous to the inhibitory activity of compounds. For example, **9a** with chloro substituted at 2-, 4-position of phenyl has no activity against both cells, while other compounds (**9c**, **9l**, **9k**, **9f**, **9p**, **9q**, and **9u**) having the same R group with **9a** showed potent activity against HCT116 cells.

Conclusion

In summary, we report here the synthesis, crystal structure, and biological evaluation of a series of new sorafenib derivatives as potential antitumor agents. Most compounds (except **9a**, **9b**, **9e, 9g**, and **9m**) exhibited potent antiproliferative activities to HCT116 cells with IC_{50} = 1.8–78.0 μM. Compounds **9h**, **9p**, **9q**, **9r**, and **9s** showed significant inhibitory activities against both HCT116 and MDA-MB-231cell lines. Notably, compared with sorafenib, most of the derivatives showed excellent selectivity toward HCT-116 over MDA-MB-231 cells, especially the compounds **9j**, **9o**, and **9t** which contains cyclohexyl substitute showed no inhibitory activities against MDA-MB-231 cells, but demonstrated more potent inhibitory activities against HCT116 cells (IC_{50} = 1.8–3.3 μM) than those of sorafenib and previously reported diarylthiourea derivatives. Further modifications of these derivatives are still required in order to improve their potency and are in progress in our laboratory.

Experimental

General

All the materials we used were purchased from commercial suppliers and used without further purification. Solvents were distilled prior to use and flash chromatography was performed using silica gel (60 Å, 200–300 mesh). Compounds **3**, **4a–e** and **8a–h** were synthesized according to the literature method (Yao *et al.*, 2012). All reactions were monitored by thin-layer chromatography on 0.25 mm silica gel plates (60F-254, Merk) and visualized with UV light, or chloride ferric. Melting points were determined on an electrothermal melting point apparatus, and the thermometer was uncorrected. ^1H, ^{13}C NMR spectra were determined on a Brucker Avance 600/300 spectrometer using TMS as an internal standard in DMSO-d_6 or $CDCl_3$ solutions. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane. ESI-MS were determined on an API 4000 spectrometer. High-resolution mass spectral (HRMS) data were conducted by Shandong Analysis and Test Center, and are reported as *m/z* (relative intensity).

General procedure for synthesis of compounds ***5a–e***

4-Aminobenzenethiol (24.8 mmol) and potassium tert-butoxide (25.0 mmol) were first dissolved in 40 mL anhydrous DMF. After stirring the resulting mixture at room temperature for 2 h, a solution of **4a–e** (24.8 mmol) and K_2CO_3 (14.9 mmol) in DMF (20 mL) was added, and the mixture was stirred at 75–80 °C for 8 h. After the temperature was back to room temperature, the mixture was diluted with water and the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined ethyl acetate extracts were washed with brine (2 × 60 mL) and then dried with anhydrous sodium sulfate. The solvent was evaporated and the resulting crude material was purified by column chromatography to afford the pure compounds.

*4-(4-Aminophenylthio)-N-methylpicolinamide (**5a**)* Yield 69.5 %, mp 123–124 °C;. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (d, $J = 5.2$ Hz, 3H), 4.09 (br s, 2H), 6.74 (d, $J = 8.5$ Hz, 2H), 6.97 (dd, $J = 5.2$, 1.9 Hz, 1H), 7.32 (d, $J = 8.5$ Hz, 2H),7.84 (d, $J = 1.7$ Hz, 1H), 8.75 (br s, 1H), 8.20 (d, $J = 5.2$ Hz, 1H); ESI-MS *m/z* 260.2 $[M + H]^+$.

*4-(4-Aminophenylthio)-N-ethylpicolinamide (**5b**)* Yield 70.6 %, mp 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ.1.24 (t, $J = 7.3$, 3H), 3.43–3.50 (m, 2H), 3.98 (br s, 2H), 6.73 (d, $J = 8.4$ Hz, 2H), 6.97 (dd, $J = 5.3$, 1.9 Hz, 1H), 7.32 (d, $J = 8.5$ Hz, 2H), 7.83 (d, $J = 1.6$ Hz, 1H), 7.96 (br s, 1H), 8.21 (d, $J = 5.2$ Hz, 1H). ESI-MS *m/z* 274.1 $[M + H]^+$.

*4-(4-Aminophenylthio)-N-benzylpicolinamide (**5c**)* Yield 66.5 %, mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (br s, 2H), 4.62 (d, $J = 6.1$ Hz, 2H), 6.73 (d, $J = 8.5$ Hz, 2H), 6.98 (dd, $J = 5.3$, 1.9 Hz, 1H), 7.29–7.34 (m, 7H), 7.85 (d, $J = 1.8$ Hz, 1H), 8.19 (d, $J = 5.3$ Hz, 1H), 8.38 (br d, 1H). ESI-MS *m/z* 336.3 $[M + H]^+$.

*4-(4-Aminophenylthio)-N-cyclohexylpicolinamide (**5d**)* Yield 72.8 %, mp 177–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.46 (m, 5H), 1.61–1.66 (m, 1H), 1.72–1.77 (m, 2H), 1.95–1.99 (m, 2H), 3.86–3.96 (m, 3H), 6.73 (d, $J = 11.0$ Hz, 2H), 6.96 (dd, $J = 5.3$, 1.8 Hz, 1H), 7.32 (d, $J = 11.0$ Hz, 2H), 7.83 (d, $J = 1.8$ Hz, 1H), 7.88 (br d, 1H), 8.20 (d, $J = 5.3$ Hz, 1H). ESI-MS *m/z* 328.2 $[M + H]^+$.

*4-(4-Aminophenylthio)-N-cyclopropylpicolinamide (**5e**)* Yield 75.7 %, mp 167–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63–0.69 (m, 2H), 0.78–0.88 (m, 2H), 2.86–2.92 (m, 1H), 4.12 (br d, 2H), 6.74 (d, $J = 11.0$ Hz, 2H), 6.96 (dd, $J = 5.3$, 1.9 Hz, 1H), 7.32 (d, $J = 11.0$ Hz, 2H), 7.82 (d, $J = 1.8$ Hz, 1H), 7.99 (br d, 1H), 8.18 (d, $J = 5.3$ Hz, 1H). ESI-MS *m/z* 286.1 $[M + H]^+$.

General procedure for synthesis of ***9a–u***

To a 10 mL DCM solution of compound **5a–e** (4.5 mmol), a DCM solution of **8a–h** (4.5 mmol) was added slowly under 0–5 °C. The mixture was stirred for 2 h in ice bath and then stirred for another 20 h at room temperature. 60 mL petroleum ether was poured into the mixture. The resulting precipitates were collected by filtration and washed with methanol to give compounds.

*4-(4-(3-(2,4-Dichlorophenyl)thioureido)phenylthio)-N-methylpicolinamide (**9a**)* Light yellow solid (yield 69.2 %), mp 158–160 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.77 (d, $J = 5.4$ Hz, 3H), 7.25 (dd, $J = 5.4$, 1.8 Hz, 1H), 7.46 (dd, $J = 6.4$, 2.4 Hz, 1H), 7.59–7.62 (m, 4H), 7.71 (d, $J = 2.4$ Hz, 1H), 7.79 (d, $J = 8.4$ Hz, 2H), 8.42 (d, $J = 4.8$ Hz, 1H), 8.74 (d, $J = 5.4$ Hz, 1H), 9.71 (s, 1H), 10.22 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.92, 118.76, 123.38, 123.42, 125.20, 128.41, 129.98, 131.97, 132.16, 132.42, 136.44, 136.62, 142.22, 149.31, 151.04, 152.87, 164.33, 181.26; HRMS(AP-ESI) *m/z*: calcd for $C_{20}H_{17}Cl_2N_4OS_2$ $[M + H]^+$ 463.0216, found 463.0211.

*N-benzyl-4-(4-(3-(2,4-dichlorophenyl)thioureido)phenylthio) picolinamide (**9b**)* Off-white solid (yield 66.4 %), mp = 126–130 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.44 (d, $J = 6.0$ Hz, 2H), 7.22 (m, 1H), 7.28 (s, 5H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.61 (m, 4H), 7.10 (d, $J = 1.8$ Hz, 1H), 7.79 (d, $J = 8.4$ Hz, 2H), 8.44 (d, $J = 4.8$ Hz, 1H), 9.32 (d, $J = 6.0$ Hz, 1H), 9.71 (s, 1H), 10.21 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.39, 118.77, 123.35, 123.43, 125.21, 127.71, 128.30, 128.42, 129.18, 129.96, 131.99, 132.12, 132.39, 136.46, 136.63, 140.34, 142.22, 149.32, 151.05, 152.87, 164.34, 181.20. HRMS(AP-ESI) *m/z*: calcd for $C_{28}H_{21}F_6N_4OS_2$ $[M + H]^+$ 607.1056, found 607.1051.

*4-(4-(3-(4-Chlorophenyl)thioureido)phenylthio)-N-methyl-picolinamide (**9c**)* Off-white solid (yield 68.3 %), mp = 174–176 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.77 (d, $J = 5.4$ Hz, 3H), 7.26 (dd, $J = 5.4$, 1.8 Hz, 1H), 7.42 (d, $J = 6.6$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.58 (m, 3H), 7.73 (d, $J = 8.4$ Hz, 2H), 8.42–8.44 (m, 2H), 10.14 (s, 1H), 10.20 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.92, 118.70, 123.08, 123.34, 125.10, 126.24, 129.38, 129.47, 136.57, 139.19, 142.44, 149.65, 151.11, 152.47, 164.75, 180.48; HRMS(AP-ESI) *m/z*: calcd for $C_{20}H_{18}ClN_4OS_2$ $[M + H]^+$ 429.0605, found 429.0611.

*4-(4-(3-(4-Chlorophenyl)thioureido)phenylthio)-N-cyclohexylpicolinamide (**9d**)* White solid (yield 71.1 %), mp = 161–164 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.09–1.15 (m, 1H), 1.25–1.32 (m, 2H), 1.34–1.41 (m, 2H), 1.58 (d, J = 12.0 Hz, 1H), 1.68–1.70 (m, 2H), 1.73–1.75 (m, 2H), 3.72 (m, 1H), 7.27 (dd, J = 5.4, 1.8 Hz, 1H), 7.41 (d, J = 6.6 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.58 (m, 3H), 7.73 (d, J = 8.4 Hz, 2H), 8.42–8.43 (m, 2H), 10.12 (s, 1H), 10.17 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.70, 26.01, 33.03, 48.95, 118.68, 123.07, 123.30, 125.06, 126.24, 129.36, 129.46, 136.53, 139.18, 142.41, 149.71, 151.16, 152.86, 163.12, 180.42; HRMS(AP-ESI) *m/z*: calcd for $C_{25}H_{26}ClN_4OS_2$ $[M + H]^+$ 497.1231, found 497.1227.

*N-benzyl-4-(4-(3-(4-chlorophenyl)thioureido)phenylthio) picolinamide (**9e**)* Light yellow solid (yield 75.6 %), mp = 100–104 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.43 (d, J = 6.6, 2H), 7.21–7.31 (m, 6H), 7.41 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.59 (m, 3H), 7.74 (d, J = 9.0 Hz, 2H), 8.44 (d, J = 6.0 Hz, 1H), 9.33 (t, J = 6.0 Hz, 2H), 10.19 (s, 1H), 10.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.37, 118.71, 123.04, 123.30, 125.05, 126.25, 127.70, 128.31, 129.18, 129.39, 129.50, 136.58, 139.18, 140.34, 142.40, 149.71, 151.16, 152.87, 164.32, 180.45; HRMS (AP-ESI) *m/z*: calcd for $C_{26}H_{22}ClN_4OS_2$ $[M + H]^+$ 505.0918, found 505.0923.

*4-(4-(3-(3,4-Difluorophenyl)thioureido)phenylthio)-N-methylpicolinamide (**9f**)* Light gray solid (yield 78.0 %), mp = 142–144 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.77 (d, J = 4.8 Hz, 3H), 7.25 (m, 2H), 7.43 (m, 1H), 7.58–7.73 (m, 6H), 8.42 (d, J = 4.8 Hz, 1H), 8.75 (d, J = 4.8 Hz, 1H), 10.11 (s, 1H), 10.18 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.92, 114.02, 114.30, 117.87, 118.16, 118.56, 121.45 (q, J = 12 Hz), 123.30, 123.37, 125.22, 136.51, 137.16 (dd, J = 36, 12 Hz), 142.28, 149.21, 151.27, 152.84, 164.28, 180.69; HRMS(AP-ESI) *m/z*: calcd for $C_{20}H_{17}F_2N_4OS_2$ $[M + H]^+$ 431.0807, found 431.0811.

*N-benzyl-4-(4-(3-(3,4-difluorophenyl)thioureido)phenylthio)picolinamide (**9g**)* Beige solid (yield 68.0 %), mp = 138–140 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.43 (d, J = 6.6 Hz, 2H), 7.21–7.31 (m, 7H), 7.41 (m, 1H), 7.59, (m, 3H), 7.69–7.73 (m, 3H), 8.44 (d, J = 2.4 Hz, 1H), 9.33 (t, J = 6.6 Hz, 1H), 10.14 (s, 1H), 10.22 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.40, 114.00, 114.26, 117.90, 118.14, 118.80, 121.43 (q, J = 12 Hz), 123.26, 123.44, 125.20, 127.71, 128.30, 129.18, 136.58, 137.18 (dd, J = 33, 12 Hz), 140.34, 142.31, 149.31, 151.07, 152.86, 164.35, 180.62; HRMS(AP-ESI) *m/z*: calcd for $C_{26}H_{21}F_2N_4OS_2$ $[M + H]^+$ 507.1119, found 507.1110.

*4-(4-(3-(3,4-Difluorophenyl)thioureido)phenylthio)-N-ethylpicolinamide (**9h**)* Light yellow solid (yield 76.5 %), mp = 138–140 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.09 (t, J = 7.8 Hz, 3H), 3.27 (m, 2H), 7.26 (m, 2H), 7.43 (m, 1H), 7.58 (m, 3H), 7.67–7.73 (m, 3H), 8.42 (d, J = 4.8 Hz, 1H), 8.75 (d, J = 4.8 Hz, 1H), 10.10 (s, 1H), 10.18 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.71, 34.66, 114.04, 114.31, 117.90, 118.13, 118.67, 121.48 (q, J = 12 Hz), 123.29, 123.38, 125.24, 136.52, 137.17 (dd, J = 36, 12 Hz), 142.26, 149.20, 151.26, 152.70, 163.97, 180.67; HRMS(AP-ESI) *m/z*: calcd for $C_{21}H_{19}F_2N_4OS_2$ $[M + H]^+$ 445.0963, found 445.0970.

*N-cyclopropyl-4-(4-(3-(3,4-difluorophenyl)thioureido) phenylthio)picolinamide (**9i**)* Off-white solid (yield 66.9 %), mp = 154–156 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.62-0.68 (m, 4H), 0.83-0.87 (m, 1H), 7.26 (m, 2H), 7.43 (m, 1H), 7.58–7.73 (m, 6H), 8.43 (d, J = 4.8 Hz, 1H), 8.76 (d, J = 4.8 Hz, 1H), 10.11 (s, 1H), 10.19 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 6.63, 23.82, 114.01, 114.32, 117.91, 118.14, 118.69, 121.49 (q, J = 12 Hz), 123.26, 123.34, 125.26, 136.50, 137.14 (dd, J = 33, 12 Hz), 142.23, 149.21, 151.23, 152.64, 165.57, 180.63; HRMS(AP-ESI) *m/z*: calcd for $C_{22}H_{19}F_2N_4OS_2$ $[M + H]^+$ 457.0963, found 457.0960.

*N-cyclohexyl-4-(4-(3-(3,4-difluorophenyl)thioureido)phenylthio)picolinamide (**9j**)* Off-white solid (yield 69.7 %), mp = 154–157 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.09–1.15 (m, 1H), 1.25–1.32 (m, 2H), 1.34–1.40 (m, 2H), 1.57 (d, J = 11.4 Hz, 1H), 1.68–1.70 (m, 2H), 1.73–1.75 (m, 2H), 3.71 (m, 1H), 7.25 (m, 2H), 7.42 (m, 1H), 7.59 (m, 3H), 7.68–7.73 (m, 3H), 8.42 (d, J = 4.8 Hz, 1H), 8.75 (d, J = 4.8 Hz, 1H), 10.10 (s, 1H), 10.18 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.71, 26.00, 33.03, 48.94, 114.02, 114.33, 117.92, 118.12, 118.61, 121.47 (q, J = 12 Hz), 123.30, 123.39, 125.25, 136.55, 137.19 (dd, J = 36, 12 Hz), 142.25, 149.19, 151.26, 152.83, 163.17, 180.63; HRMS(AP-ESI) *m/z*: calcd for $C_{25}H_{25}F_2N_4OS_2$ $[M + H]^+$ 499.1435, found 499.1428.

*4-(4-(3-(4-Fluorophenyl)thioureido)phenylthio)-N-methylpicolinamide (**9k**)* Light yellow solid (yield 82.3 %), mp = 154–157 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.77 (s, 3H), 7.20 (t, J = 8.4 Hz, 2H), 7.24 (m, 1H), 7.48 (m, 2H), 7.58 (m, 3H), 7.73 (d, J = 8.4 Hz, 2H), 8.42 (d, J = 5.4 Hz, 1H), 8.75 (d, J = 4.8 Hz, 1H), 10.01 (s, 1H), 10.09 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.92, 115.87, 116.19, 118.76, 123.28, 123.43, 125.20, 127.25 (d, J = 33 Hz), 136.52, 136.65 (d, J = 12 Hz), 142.24, 149.31, 151.20, 152.85, 164.30, 181.11; HRMS (AP-ESI)

m/z: calcd for $C_{20}H_{18}FN_4OS_2$ $[M + H]^+$ 413.0901, found 413.0898.

N-methyl-4-(4-(3-(3-(trifluoromethyl)phenyl)thioureido)phenylthio)picolinamide (**9l**) Off-white solid (yield 75.3 %), mp = 99–103 °C; ^{1}H NMR (DMSO-d_6) 2.78 (d, J = 4.8 Hz, 3H), 7.18 (dd, J = 5.6, 2.4 Hz, 1H), 7.23 (d, J = 6.6 Hz, 2H), 7.42 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 6.6 Hz, 2H), 7.77 (m, 1H), 7.97 (s, 1H), 8.45 (d, J = 5.4 Hz, 1H), 8.78 (d, J = 4.8 Hz, 1H), 10.26 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.92, 118.81, 120.72 (q), 121.83 (d, J = 15 Hz), 123.37 (m), 125.17, 126.82, 129.81, 130.22, 130.59, 136.60, 141.21, 142.20, 149.30, 151.04, 152.85, 164.31, 180.67; HRMS (AP-ESI) *m/z*: calcd for $C_{21}H_{18}F_3N_4OS_2$ $[M + H]^+$ 463.0869, found 463.0861.

N-benzyl-4-(4-(3-(3-(trifluoromethyl)phenyl)thioureido)phenylthio)picolinamide (**9m**) Beige solid (yield 76.3 %), mp = 117–120 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.44 (d, J = 6.0 Hz, 2H), 7.21–7.31 (m, 6H), 7.49 (d, J = 7.8 Hz, 1H), 7.57–7.61 (m, 4H), 7.73 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.96 (s, 1H), 8.45 (d, J = 5.4 Hz, 1H), 9.33 (t, J = 6.0 Hz, 1H), 10.27 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.4, 118.84, 120.74 (q), 121.80 (d, J = 15 Hz), 123.34 (m), 125.17, 126.81, 127.11, 128.30, 129.18, 129.82, 130.23, 130.56, 136.62, 140.34, 141.19, 142.22, 149.32, 151.08, 152.81, 164.35, 180.61; HRMS (AP-ESI) *m/z*: calcd for $C_{27}H_{22}F_3N_4OS_2$ $[M + H]^+$ 539.1182, found 539.1177.

N-cyclopropyl-4-(4-(3-(3-(trifluoromethyl)phenyl)thioureido)phenylthio)picolinamide (**9n**) Off-white solid (yield 60.8 %), mp = 160–163 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.623–0.681 (m, 4H), 0.82-0.87 (m, 1H), 7.26 (dd, J = 5.4, 1.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.58-7.60 (m, 4H), 7.73 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 8.40 (d, J = 5.4 Hz, 1H), 8.72 (d, J = 4.8 Hz, 1H), 10.26 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 6.64, 23.81, 118.82, 120.75 (q), 121.85 (d, J = 12 Hz), 123.36 (m), 125.16, 126.83, 129.81, 130.24, 130.58, 136.61, 141.20, 142.18, 149.31, 151.04, 152.63, 165.54, 180.63; HRMS (AP-ESI) *m/z*: calcd for $C_{23}H_{20}F_3N_4OS_2$ $[M + H]^+$ 489.1025, found 489.1022. Crystal data for **9n**: $C_{23}H_{19}F_3N_4OS_2$, FW = 488.56, monoclinic, space group $P2_1/a$, a = 10.494(14) Å, b = 10.538(14) Å, c = 21.69(3)Å, $\alpha = \gamma = 90°$, β = 93.92(2)°, V = 2393(6) Å^3, Z = 4, d_{calc} = 1.356 g/cm^3, R = 0.1006, wR_2 = 0.3274. The crystal structure analyses were carried out on a Bruker APEX area-detector diffractometer with graphite monochromated Mo $K\alpha$ radiation (λ = 0.71073 Å). The crystal structure was solved by the direct method followed by Fourier syntheses. Structure refinement was performed by full-matrix least-squares procedures using SHELXL-97 on F^2 (Sheldrick, 1997). All H atoms were placed in calculated positions, with C–H distance of 0.93(aromatic), 0.97 (methylene), 0.98 Å (methine), and with N–H distance of 0.86 Å, and refined as riding, with U_{iso} (H) = 1.2U_{eq} (C, N). F1, F2, and F3 appeared to be disordered, and were refined as two groups. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as CCDC No. 869085. Copies of the data can be obtained on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

N-cyclohexyl-4-(4-(3-(3-(trifluoromethyl)phenyl)thioureido)phenylthio)picolinamide (**9o**) White solid (yield 73.5 %), mp = 152–154 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ1.09–1.16 (m, 1H), 1.25–1.31 (m, 2H), 1.34–1.41 (m, 2H), 1.58 (d, J = 12.0 Hz, 1H), 1.68–1.71 (m, 2H), 1.73–1.76 (m, 2H), 3.72 (m, 1H), 7.26 (dd, J = 5.4, 1.8 Hz, 1H), 7.497 (d, J = 8.4 Hz, 1H), 7.57–7.61 (m, 4H), 7.74 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 8.41 (d, J = 5.4 Hz, 1H), 8.72 (d, J = 4.8 Hz, 1H), 10.26 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.71, 26.03, 33.04, 48.93, 118.83, 120.71 (q), 121.87 (d, J = 15 Hz), 123.32 (m), 125.15, 126.82, 129.82, 130.23, 130.58, 136.60, 141.19, 142.19, 149.31, 151.03, 152.88, 163.15,180.66; HRMS (AP-ESI) *m/z*: calcd for $C_{26}H_{26}F_3N_4OS_2$ $[M + H]^+$ 531.1495, found 531.1501.

4-(4-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)phenylthio)-N-methylpicolinamide (**9p**) Light yellow solid (yield 70.8 %), mp = 154–156 °C; HPLC purity = 98.9 %. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.77 (d, J = 4.2 Hz, 3H), 7.27 (d, J = 5.4 Hz, 1H), 7.61 (m, 3H), 7.71 (d, J = 8.4 Hz, 2H), 7.84 (s, 1H), 8.26 (s, 2H), 8.43 (d, J = 5.4 Hz, 1H), 8.75 (d, J = 5.4 Hz, 1H), 10.45 (s, 1H), 10.54 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 26.92, 118.71, 123.36, 124.15, 124.58, 125.58, 130.87, 131.31, 136.62, 141.71, 142.58, 149.30, 151.23, 152.45, 164.75, 180.78; HRMS (AP-ESI) *m/z*: calcd for $C_{22}H_{17}F_6N_4OS_2$ $[M + H]^+$ 531.0743, found 531.0750.

4-(4-(3-(4-Chloro-3-(trifluoromethyl)phenyl)thioureido)phenylthio)-N-methylpicolinamide (**9q**) Off-white solid (yield 74.6 %), mp = 158–160 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.77 (d, J = 5.4 Hz, 3H), 7.26 (dd, J = 5.4, 1.8 Hz, 1H), 7.60 (d, J = 8.4 Hz, 3H), 7.71 (t, J = 8.4 Hz, 3H), 7.82 (dd, J = 8.4, 2.4 Hz, 1H), 8.09 (d, J = 2.4 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H), 8.75 (d, J = 4.8 Hz, 1H), 10.31 (s, 1H), 10.38 (s, 1H); ^{13}C NMR

(75 MHz, DMSO-d_6) δ 26.91, 118.55, 121.85, 123.41 (m), 123.67, 125.35, 126.34 (d, $J = 6$ Hz), 127.05, 127.47, 129.51, 132.65, 136.63, 139.94, 142.02, 149.23, 151.08, 152.89, 164.34, 180.65; HRMS (AP-ESI) *m/z*: calcd for $C_{21}H_{17}ClF_3N_4OS_2$ $[M + H]^+$ 497.0479, found 497.0473.

*4-(4-(3-(4-Chloro-3-(trifluoromethyl)phenyl)thioureido) phenylthio)-N-ethylpicolinamide (**9r**)* Off-white solid (yield 63.5 %), mp = 154–156 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.08 (t, $J = 7.2$, 3H), 3.27 (m, 2H), 7.28 (dd, $J = 4.8$, 1.8 Hz, 1 H), 7.59 (m, 3H), 7.71 (m, 3H), 7.82 (dd, $J = 8.4$, 1.8 Hz, 1H), 8.09 (d, $J = 2.4$ Hz, 1H), 8.42 (d, $J = 5.4$ Hz, 1H), 8.79 (t, $J = 6.0$ Hz, 1H), 10.31 (s, 1H), 10.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.70, 34.66, 118.58, 121.83, 123.37 (m), 123.67, 125.35, 126.36 (d, $J = 6$ Hz), 127.06, 127.46, 129.48, 132.60, 136.58, 139.93, 142.01, 149.18, 151.07, 152.72, 163.97, 180.62; HRMS(AP-ESI) *m/z*: calcd for $C_{22}H_{17}ClF_3N_4OS_2$ $[M + H]^+$ 511.0635, found 511.0638.

*4-(4-(3-(4-Chloro-3-(trifluoromethyl)phenyl)thioureido) phenylthio)-N-cyclopropylpicolinamide (**9s**)* Light yellow solid (yield 69.1 %), mp = 150–154 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.63-0.69 (m, 4H), 0.83–0.87 (m, 1H), 7.27 (dd, $J = 5.4$, 1.8 Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 3H), 7.70 (m, 3H), 7.82 (dd, $J = 8.4$, 2.4 Hz, 1H), 8.09 (d, $J = 2.4$ Hz, 1H), 8.43 (d, $J = 5.4$ Hz, 1H), 8.76 (d, $J = 5.4$ Hz, 1H), 10.32 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 6.64, 23.81, 118.57, 121.83, 123.39 (m), 123.66, 125.34, 126.33 (d, $J = 6$ Hz), 127.06, 127.47, 129.50, 132.61, 136.60, 139.93, 142.02, 149.19, 151.08, 152.62, 165.52, 180.60; HRMS(AP-ESI) *m/z*: calcd for $C_{23}H_{20}ClF_3N_4OS_2$ $[M + H]^+$ 523.0636, found 523.0630.

*4-(4-(3-(4-Chloro-3-(trifluoromethyl)phenyl)thioureido) phenylthio)-N-cyclohexylpicolinamide (**9t**)* Off-white solid (yield 71.7 %), mp = 174–175 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.22 $\sim$ 1.45 (m, 6H), 1.72 (m, 4H), 3.71 (m, 1H), 7.28 (dd, $J = 5.4$, 2.0 Hz, 1H), 7.59 (d, $J = 1.8$ Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 8.09 (s, 1H), 8.43 (d, $J = 5.4$ Hz, 1H), 8.45 (s, 1H), 10.31 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.71, 26.01, 33.01, 48.98, 118.60, 121.82, 123.38 (m), 123.63, 125.35, 126.35 (d, $J = 6$ Hz), 127.05, 127.45, 129.51, 132.62, 136.60, 139.90, 142.04, 149.20, 151.08, 152.83, 163.14, 180.62; HPLC purity = 98.1 %. HRMS (AP-ESI) *m/z*: calcd for $C_{26}H_{25}ClF_3N_4OS_2$ $[M + H]^+$ 565.1105, found 565.1112.

*N-methyl-4-(4-(3-(4-(trifluoromethoxy)phenyl)thioureido) phenylthio)picolinamide (**9u**)* White solid (yield 72.7 %), mp = 163–165 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.77 (d, $J = 4.8$ Hz, 3H), 7.26 (dd, $J = 5.4$, 1.8 Hz, 1H), 7.36 (d, $J = 9.0$ Hz, 2H), 7.58–7.62 (m, 5H), 7.74 (d, $J = 8.4$ Hz, 2H), 8.42 (d, $J = 5.4$ Hz, 1H), 8.75 (d, $J = 5.4$ Hz, 1H), 10.15 (s, 1H), 10.21 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.92, 118.55, 122.23, 123.14, 123.21, 125.09, 126.19, 136.55, 139.45, 142.38, 145.66 (d, $J = 12$ Hz), 149.26, 151.18, 152.74, 164.76, 180.59. HRMS (AP-ESI) *m/z*: calcd for $C_{21}H_{18}F_3N_4O_2S_2$ $[M + H]^+$ 479.0818, found 479.0818.

Biological evaluation

Preliminary cytotoxic activity of these sorafenib derivatives (**9a–u**) on HCT116 and MDA-MB-231 cell lines was investigated in vitro. HCT116, MDA-MB-231 cell lines were plated on 96-well plates at a density of 5,000 per well and incubated overnight. The cells were treated with **9a–u** and sorafenib at final concentrations ranging from 0.5 to 200 μM, while control cells were treated with equal volume of DMSO (0.1 %). After 48 h treatment, 0.5 % MTT (Amresco, USA) solution was added to each well, and further incubated for 4 h, then cells were centrifuged at 2,500 rpm for 15 min, the culture medium was removed, and 150 μL DMSO was added to dissolve the formazan. After mixing for 5 min, optical density was detected at 570 nm on a microplate reader (Thermo, USA).

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