European Journal of Medicinal Chemistry 93 (2015) 381–391

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Discovery and optimization of novel dual dithiocarbamates as potent anticancer agents

Ri-Dong Li [a], Hui-Ling Wang [a], Ying-Bo Li [a, b], Zhong-Qing Wang [a], Xin Wang [a], Yi-Tao Wang [b], Ze-Mei Ge [a, *], Run-Tao Li [a, *]

[a] State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, PR China
[b] State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao 999078, PR China

ARTICLE INFO

Article history:
Received 5 October 2014
Received in revised form
27 January 2015
Accepted 19 February 2015
Available online 20 February 2015

Keywords:
Dual dithiocarbamate
Anti-tumor activity
Synthesis
Structure–activity relationship

ABSTRACT

A series of dual dithiocarbamates were synthesized and evaluated for their in-vitro anticancer activities on human non-small cell lung cancer cell line H460. Nine compounds exhibited significant anti-proliferative activities with IC_{50} less than 1 μM. Among them, compound **14m** showed the highest inhibitory activity against H460 cell and inhibited the growth of nine types of tumor cells with IC_{50} values less than 1 μM. It also achieved IC_{50} of 54 nM and 23 nM against HepG2 and MCF-7 cell lines, respectively. Preliminary structure–activity relationship study indicated that: a) when the methyl group (region A) is substituted with benzene rings, ortho substitution on the benzene ring is favored for activity; b) substitution with heterocyclic structures at region A exhibited greater impact on the anti-tumor activity of compounds, in which pyridine ring, thiazole ring, coumarin and benzo[b]thiophene are favored and quinoline ring is the most favored; c) substitution with different amines (region B) also showed marked effect on the activity of compounds and dimethylamine and morpholine are preferred to other tested amines.

1. Introduction

Malignant cancer is one of the most life-threatening diseases. Despite major breakthroughs in many areas of modern medicine, there still remain significant challenges in the successful treatment of cancer partly because of the development of drug resistance [1]. Therefore, it is still urgent to discover new anticancer agents of novel chemical entity. Target-based approaches to drug discovery are extensively used in the academic and pharmaceutical industry. However, phenotypic screening is still a very important method for drug discovery as an original screening paradigm [2].

Dithiocarbamates, a common class of molecular scaffold, have been attracting considerable interest due to their diverse biological activities, such as anti-fungal [3], anti-bacterial [4] and carbonic anhydrase inhibiting activities [5,6]. In particular, some molecules containing the dithiocarbamate groups as pivotal pharmacophores exhibited anticancer activity. For examples, Zahran et al. have revealed a series of novel thalidomide dithiocarbamates (**1**) which displayed anti-tumor activity against Ehrlich ascites carcinoma (EAC) cell line and exhibited potent cytotoxic activity [7]. Yang et al. have described a series of chromone derivatives bearing dithiocarbamate moieties (**2**) which displayed apoptosis-inducing effects on tumor cell lines [8]. Cao's group reported that a series of quinazolinone and 2,4-diaminoquinazoline derivatives with dithiocarbamate side chains (**3**,**4**) showed antiproliferative activity against human cancer cell lines [9]. In addition, Liu's group discovered a series of butenolide-containing dithiocarbamates (**5**), and several compounds exhibited good anticancer activities [10]. Recently, Liu's group published a novel type of 1,2,3-triazole-dithiocarbamate hybrids (**6**) which acted as selective lysine specific demethylase 1 (LSD1) inactivators (Fig. 1) [11].

In our effort to discover new types of anticancer drugs, we have identified several novel dithiocarbamate compounds with potent anticancer activity (**7**–**10**, Fig. 2) [12]. To study the structure–activity relationship of compound **8**, we attempted to prepare compound **8a** from the reaction of Mannich base, a precursor of the Michael acceptor, with pyridin-3-ylmethanamine and carbon disulfide (Scheme 1). However, two products (**8a** and **11**) were obtained and the dual dithiocarbamate **11** was the main product. The mechanism for the formation of compound **11** could be stepwise

* Corresponding authors.
E-mail addresses: zmge@bjmu.edu.cn (Z.-M. Ge), lirt@bjmu.edu.cn (R.-T. Li).

http://dx.doi.org/10.1016/j.ejmech.2015.02.030
0223-5234/

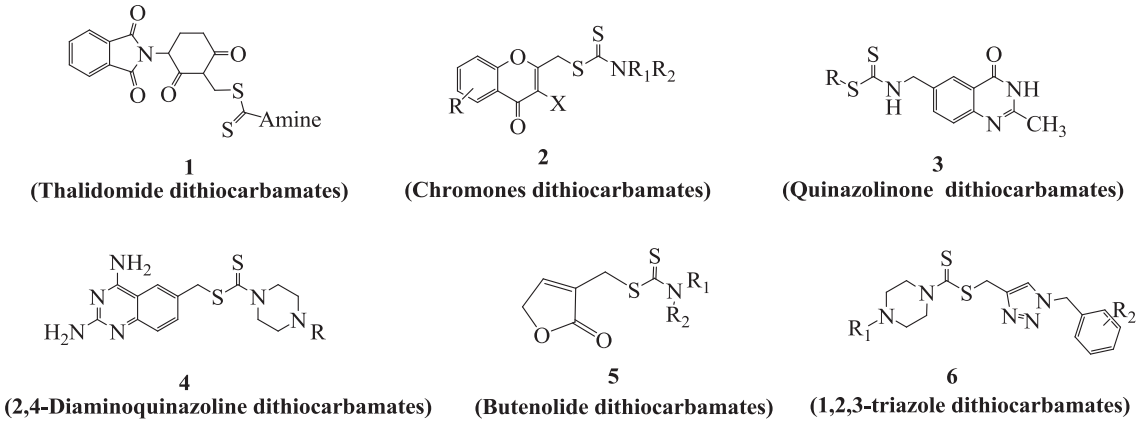


Fig. 1. Structures of some dithiocarbamates with anticancer activities.

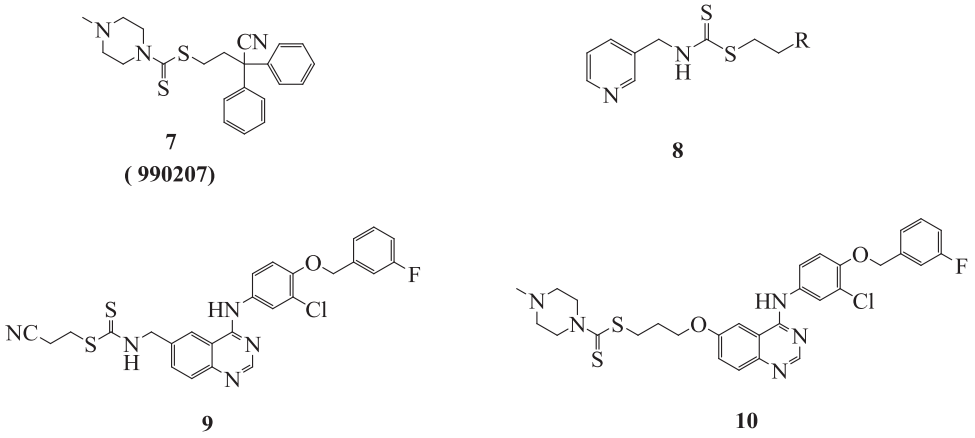
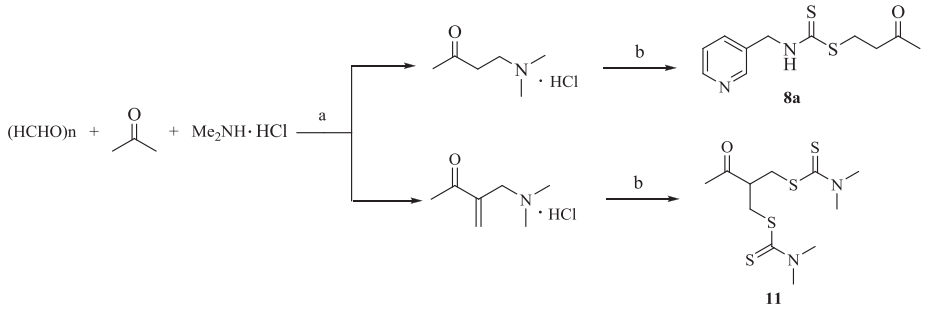


Fig. 2. Dithiocarbamate derivatives showed appreciable anticancer activities in vitro.



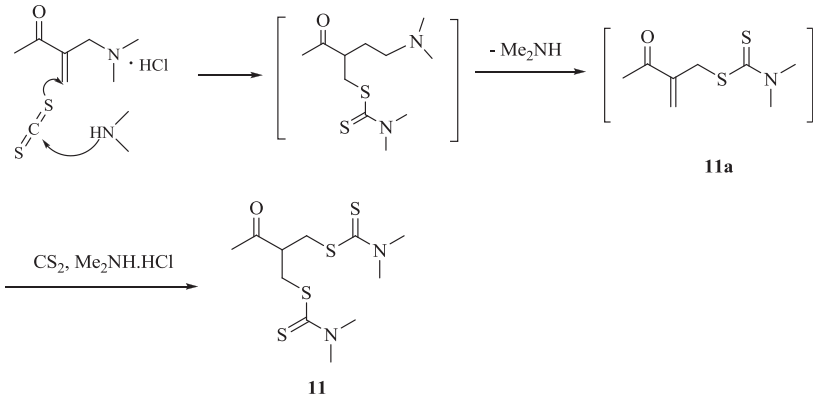
Scheme 1. Synthesis of compound **8a** and **11**. Reagents and conditions: (a) H_2O-i-PrOH, reflux; (b) pyridin-3-ylmethanamine, CS_2, TEA, H_2O, r.t.

double Michael addition reaction, which was supported by the isolation of key intermediate **11a** (Scheme 2) [13]. To the best of our knowledge, this type of dual dithiocarbamates has not been synthesized before. More interestingly, these novel dual dithiocarbamates showed significant anti-tumor activities in the preliminary anti-tumor screening. Especially, compound **11** exhibited potent anticancer activities with 92.3%, 42.9%, 87.8%, 88.2%, 88.7%, 88.8% and 95.8% inhibition rates against H460, HepG2, BGC823, Hela, HCT116, MDA-MB-231 and HL-60 cell lines at 10 μM in vitro, respectively. Furthermore, the IC_{50} of compound **11** against human non-small cell lung cancer (NSCLC) cell line H460 was 0.89 μM. These results demonstrate that compound **11** is a valuable lead compound for the development of drugs to treat lung cancer.

The SAR study of compound **11** was carried out in two aspects based on its structure. At first, the methyl group (called region A) was modified with various substituted aromatic and heterocyclic rings, and the dimethylamino group (called region B) remained intact. Afterwards, with the most favored substitution at region A, region B was modified with different secondary amines (Fig. 3). All synthesized compounds were evaluated for their activities against the human non-small cell lung cancer cell line H460.

2. Results and discussion

The modification of region A is outlined in Scheme 3. A variety of acetyl substituted aromatic or heterocyclic compounds **12a**–**12t**,



Scheme 2. Possible mechanism for the formation of compound **11**.

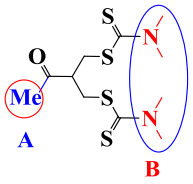
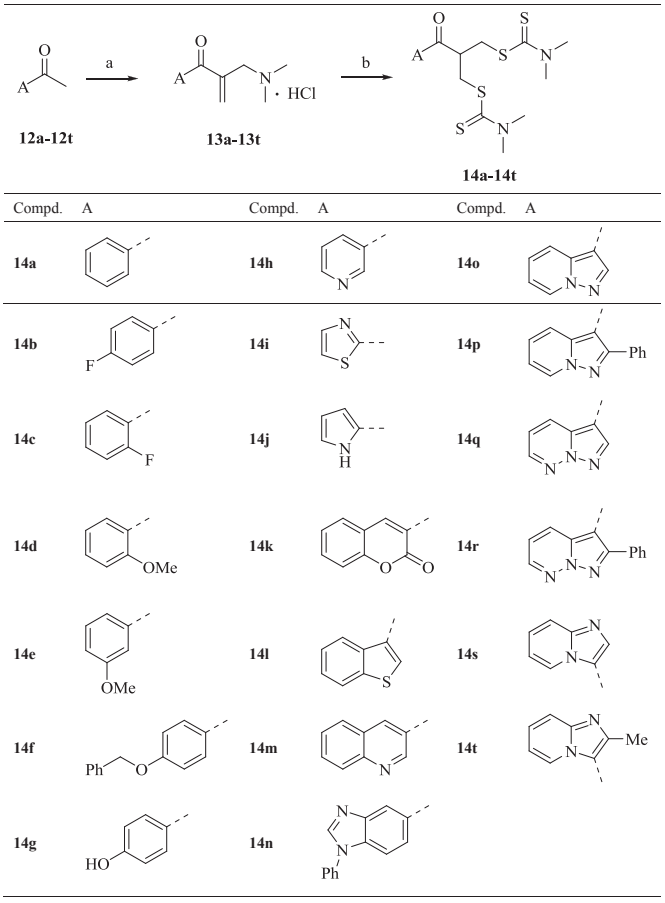


Fig. 3. Lead compound **11** and overall strategy for its structural modification.

which were commercially available or prepared by literature procedures, reacted with paraformaldehyde and dimethylamine hydrochloride in refluxing acetic acid to afford the corresponding key intermediates **13a**–**13t** [13]. Without further purification, compounds **13a**–**13t** reacted with carbon disulfide and dimethylamine hydrochloride, generating the target compounds **14a**–**14t**. The preparation of **14a**–**14j** was carried out using water as solvent and potassium carbonate as base. Since intermediates **13k**–**13t** were insoluble in water, N,N-dimethylformamide (DMF) was used as solvent and triethylamine as base for the preparation of compounds **14k**–**14t**.

The synthetic routes for the starting materials **12n**–**12t** are depicted in Scheme 4. 1-Bromo-2-nitro-4-acetyl-benzene (**15**) was treated with aniline and sodium acetate in DMF to obtain compound **16**. The nitro moiety of **16** was reduced under catalytic hydrogenation conditions to yield compound **17**. Benzimidazole **12n** was obtained from the cyclization of **17** with formic acid in 4 N hydrochloric acid solution [14]. Under basic conditions, but-3-yn-2-one (**18**) and 4-phenylbut-3-yn-2-one (**19**) reacted with 1-aminopyridinium iodide to provide the compound **12o** and **12p**, respectively [15]. Pyridazine (**20**) was treated with hydroxylamine-O-sulfonic acid (HOSA) to provide the intermediate 1-aminopyridazinium salt (**21**). The subsequent addition of but-3-yn-2-one (**18**) and 4-phenylbut-3-yn-2-one (**19**) in the presence of a base afforded compound **12q** and **12r**, respectively [16]. Compound **12s** was synthesized by the condensation of 2-aminopyridine (**22**) with dimethylformamide dimethylacetal followed by treatment with bromoacetone. Compound **12t** was obtained by cyclization of 2-aminopyridine (**22**) with 3-chloropentane-2,4-dione in refluxing EtOH [17].

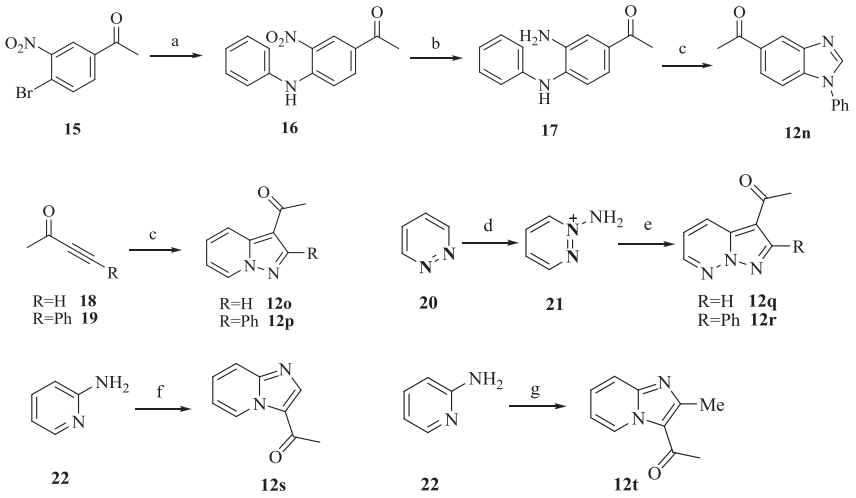
The activities of compounds **14a**–**14t** modified at region A are shown in Table 1. The results indicated that most of the compounds showed good activity against H460 cells with IC_{50} less than 1 μM. Among them, compounds **14k** and **14m** showed the highest inhibitory activity. Replacing the methyl moiety of lead compound **11** (IC_{50} = 0.89 μM) with benzene ring resulted in slight reduction



Scheme 3. Synthesis of compounds **14a**–**14t**. Reagents and conditions: (a) $Me_2NH.HCl$, (HCHO)n, AcOH, reflux; (b) $Me_2NH.HCl$, CS_2, K_2CO_3 or Et_3N, H_2O or DMF.

of activity (**14a**, IC_{50} = 1.93 μM). However, the nature and position of the substituents on the benzene ring greatly affected their activity. Introducing an ortho substitution on the benzene ring, such as **14c** (2-F, IC_{50} = 0.92 μM) and **14d** (2-OMe, IC_{50} = 0.81 μM), increased the activity to that of compound **14a**. On the contrary, substitution at para-position of the benzene ring led to a 5- to 15-fold decrease in potency (**14f**, 4-OBn, IC_{50} = 9.77 μM; **14g**, 4-OH, IC_{50} = 30 μM) comparing with **14a**.

The different heterocyclic structures at region A showed great impact on the anti-tumor activity. The compounds with pyridine



Scheme 4. Synthetic routes for the starting materials **12n**–**12t**. Reagents and conditions: (a) Aniline, AcONa, CuI, DMF; (b) H_2, Pd(C), THF, rt; (c) HCOOH, HCl; (c) 1-aminopyridinium iodide, KOH, K_2CO_3, DMSO; (d) HOSA, aqueous $KHCO_3$, pH 5.0; (e)3-butyne-2-ones or 4-Phenylbut-3-yn-2-one, KOH, CH_2Cl_2, rt; (f) (i) $Me_2NCH(OMe)_2$, reflux; (ii) bromoacetone, EtOH; (g) 3-chloropentane-2,4-dione, EtOH, reflux.

ring (**14h**, IC_{50} = 0.87 μM), thiazole ring (**14i**, IC_{50} = 0.84 μM), coumarin (**14k**, IC_{50} = 0.66 μM), benzo[b]thiophene (**14l**, IC_{50} = 0.85 μM) and quinoline ring (**14m**, IC_{50} = 0.40 μM) exhibited similar or more potent activity comparing with the lead compound **11**. In contrast, the activities of the compounds containing other heterocyclic structures decreased significantly and some lost activity completely, such as **14n** (IC_{50} = 2.20 μM), **14s** (IC_{50} = 13.03 μM), **14o** (IC_{50} = 31.46 μM), **14j** (IC_{50} = 97.28 μM), **14t** (IC_{50} = 151.4 μM). Compounds **14k** and **14m** deserve further investigation due to their excellent activity and drug-like scaffold.

Based on the optimization results of region A, we used compound **14m** as lead structure to study the influence of the amino moiety with respect to the anticancer activity. We kept 3-quinoline as region A and varied amino moiety of region B. Compounds **25a**–**25g** were obtained by replacing the dimethylamine moiety of compound **14m** with various secondary amines, including acyclic and cyclic amines (Scheme 5).

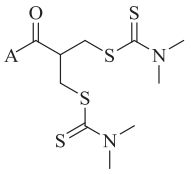
Table 2 shows the biological activities of those compounds with modified region B. Most of the amine modifications were unfavorable for the activity. For example, the compounds with bulky amines, such as diethylamine (**25a**), pyrrolidine (**25d**) and piperidine (**25e**), showed 13-fold, 2-fold and 10-fold decrease of activity (IC_{50}), respectively. For the six-membered cyclic amine modifications, the heteroatoms in the cyclic amines also greatly affected the activity. When modified with *N*-methyl piperazine (**25b**) and morpholine (**25c**) amines, the activity was increased by 2-fold and 8-fold respectively, comparing with modification by piperidine amine (**25e**). However, modification with thiomorpholine amine (**25f**, IC_{50} = 124.7 μM) led to the complete loss of activity. The compound (**25g**) derived from *N*-methyl-1-(pyridin-3-yl)methanamine also lost the activity. With regard to the biological activity, the amino moiety in the dithiocarbamate is very crucial for the inhibitory activity. The dimethyl amine and morpholine as region B are more favorable structural features.

To investigate the antiproliferative effect of these novel dual dithiocarbamates on various tumor cell lines, we selected the most potent compound **14m** to evaluate its IC_{50} against ten human tumor cell lines including HepG2 (hepatocellular carcinoma), MCF-7 (breast adenocarcinoma), MDA-MB-453 (breast adenocarcinoma), SW480 (colorectal cancer), H522 (human non-small cell lung cancer), PC3 (prostate cancer), H1299 (lung cancer), A375 (melanoma), H460 (human non-small cell lung cancer) and COLO205 (colorectal cancer). The results (Table 3) show that compound **14m** can inhibit the growth of nine types of tumor cells with IC_{50} less than 1 μM. It achieved IC_{50} of 54 nM and 23 nM against cell lines HepG2 and MCF-7, respectively. In order to investigate whether these compounds can selectively kill tumor cells and non-tumor cells, we also chose compound **14m** to test its cytotoxicity against two non-tumor cell lines (human hepatic cell line LO2 and human embryonic kidney cell line HEK293). The results indicated that compound **14m** exhibited 27-fold and 22-fold decrease of cytotoxic activity against human hepatic cell line LO2 (IC_{50} = 13.13 μM) and human embryonic kidney cell line HEK293 (IC_{50} = 10.81 μM) respectively, comparing with H460 cell line (IC_{50} = 0.476 μM), which suggested that compound **14m** has obvious selectivity for tumor cells and non-tumor cells. Further studies on the antitumor mechanisms of **14m** are currently underway.

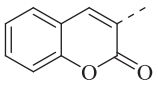
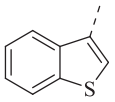
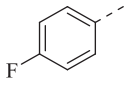
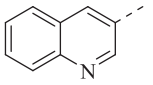
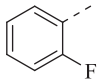
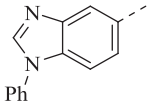
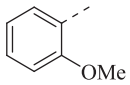
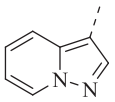
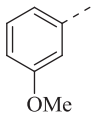
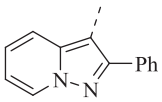
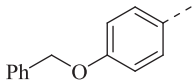
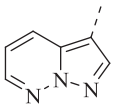
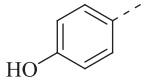
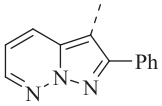
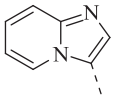
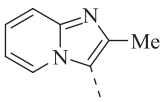
3. Conclusion

Systematic structural modification was carried out based on the structure of the lead compound **11**. A series of novel dual dithiocarbamates were synthesized and they were evaluated for their in vitro anti-tumor activities. Among them, nine compounds showed significant proliferation inhibition activities on human non-small cell lung cancer cell line H460 with IC_{50} less than 1 μM. The most potent compound **14m** inhibited the growth of nine types of tumor cells with IC_{50} less than 1 μM. And compound **14m** showed IC_{50} of 54 nM and 23 nM against cell lines HepG2 and MCF-7, respectively. Our investigation revealed the following structure–activity relationships (SAR): a) when region A is substituted with benzene rings, the ortho substituent on the benzene ring is favored for the activity; b) the different heterocyclic structures at region A show great impact on the anti-tumor activity of compounds, in which pyridine ring, thiazole ring, coumarin and benzo [b] thiophene are favored and quinoline ring is the most favored substituent; c) different amines at region B showed great effect on the activity of compounds and dimethylamine and morpholine are more favored than other examined amines. These results provide valuable

Table 1
Antiproliferative activities of compounds **14a**–**14t** modified at region A against H460 cell line.[a]

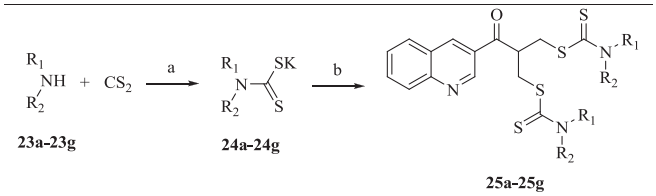


14a-14t

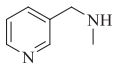
Compd.	A	IC_{50}[b] (μM)	Compd.	A	IC_{50}[b] (μM)
11		0.89	**14k**		0.66
14a		1.93	**14l**		0.85
14b		1.21	**14m**		0.40
14c		0.92	**14n**		2.20
14d		0.81	**14o**		31.46
14e		1.24	**14p**		4.09
14f		9.77	**14q**		4.55
14g		30	**14r**		1.00
14h		0.87	**14s**		13.03
14i		0.84	**14t**		151.4
14j		97.28			

[a] H460 cell line: human non-small cell lung cancer.
[b] Dose–response curves were determined at five concentrations. The IC_{50} values are the concentrations needed to inhibit cell growth by 50% as determined from these curves.

information for the further investigation of this type of potent anti-tumor compounds.

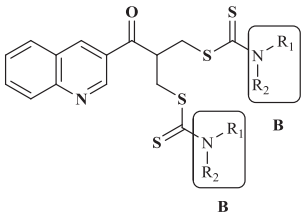


23a-23g **24a-24g** **25a-25g**

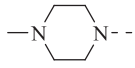
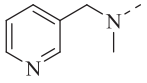
Compd.	R_1R_2NH	Compd.	R_1R_2NH	Compd.	R_1R_2NH
25a		**25d**		**25g**	
25b		**25e**			
25c		**25f**			

Scheme 5. Synthesis of compounds **25a**–**25g**. Reagents and conditions: (a) K_2CO_3, acetone; (b) **13m**, DMF, H_2O.

Table 2
Antiproliferative activities of compounds **25a**–**25g** modified at region B against H460 cell line.[a]



25a-25g

Compd.	B	IC_{50}[b] (μM)	Compd.	B	IC_{50}[b] (μM)
14m		0.40	**25d**		0.79
25a		5.16	**25e**		4.65
25b		2.51	**25f**		124.7
25c		0.58	**25g**		58.20

[a] H460 cell line: human non-small cell lung cancer.
[b] Dose–response curves were determined at five concentrations. The IC_{50} values are the concentrations needed to inhibit cell growth by 50% as determined from these curves.

4. Experiment

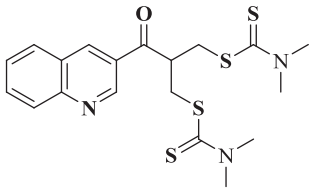
4.1. General

All reagents and solvents were purchased from commercial sources and were used without further purification. Melting points were determined on X4 microscope and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCEIII 400 MHz and 100 MHz spectrometer respectively. Elemental analyses were performed on a Vario EL III (Germany) instrument.

4.2. The procedure for synthesis of lead compound *11*

A mixture of acetone (2.33 g, 40 mmol), paraformaldehyde

Table 3
Antiproliferative activities of compounds **14m** against various tumor cell lines and non-tumor cell lines.[a]



14m

Cell line	IC_{50}[b] (μM)	Cell line	IC_{50}[b] (μM)	Cell line	IC_{50} (μM)
HepG2	0.054	H522	0.139	H460	0.476[b]
MCF-7	0.023	PC3	0.431	COLO205	0.325[b]
MDA-MB-453	0.162	H1299	0.622	LO2	13.13[c]
SW480	6.350	A375	0.439	HEK293	10.81[c]

[a] HepG2: hepatocellular carcinoma; MCF-7, MDA-MB-453: breast adenocarcinoma; SW480, COLO205: colorectal cancer; H522, H460: human non-small cell lung cancer; PC3: prostate cancer; H1299: lung cancer; A375: melanoma; LO2: human hepatic cell line; HEK293: human embryonic kidney cell line.

[b] Dose–response curves were determined at five concentrations. The IC_{50} values are the concentrations needed to inhibit cell growth by 50% as determined from these curves.

[c] Dose–response curves were determined at eight concentrations. The IC_{50} values are the concentrations needed to inhibit cell growth by 50% as determined from these curves.

(0.72 g, 24 mmol) and dimethylamine hydrochloride (1.63 g, 20 mmol) in H_2O (5 mL) and i-PrOH (0.5 mL) was heated under reflux for 16 h. The reaction mixture was cooled to room temperature and used directly without further purification. A mixture of dimethylamine hydrochloride (3.27 g, 40 mmol), triethylamine (8.10 g, 80 mmol) and H_2O (30 mL) was stirred for 15 min, and CS_2 (3.81 g, 50 mmol) was added dropwise. After stirring 30 min, the reaction mixture of previous reaction was added. The reaction mixture was stirred at room temperature for 17 h. The mixture was extracted with ethyl acetate (20 mL × 3), the combined organic phase was washed with water (20 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The crude product was purified by recrystallization from the mixture solvents of ethyl acetate and petroleum ether to give pure lead compound **11**.

4.2.1. 2-Acetylpropane-1,3-diyl bis(dimethylcarbamodithioate) (**11**)

Yield 20%. While solid. Mp: 98–99 °C. ^{1}H NMR (400 MHz, CDCl3): δ = 2.33 (s, 3H), 3.37 (s, 6H), 3.51–3.54 (m, 9H), 3.67–3.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.99, 37.45, 41.52, 45.43, 50.88, 196.36, 208.58; Anal. Cald for $C_{11}H_{20}N_2OS_4$: C, 40.71; H, 6.21; N, 8.63; Found: C, 40.90; H, 6.34; N, 8.72.

4.3. General procedure for the synthesis of compounds **14a–14j**

A mixture of the acetyl substituted aromatic or heterocyclic compound (5 mmol), paraformaldehyde (0.30 g, 10 mmol) and dimethylamine hydrochloride (0.82 g, 10 mmol) in acetic acid (10 mL) was heated under reflux for 12 h. The reaction mixture was concentrated under vacuum to afford the intermediate (**13a–13j**), which was used directly without further purification. A mixture of dimethylamine hydrochloride (0.82 g, 10 mmol), potassium carbonate (2.77 g, 20 mmol) and H_2O (25 mL) was stirred for 15 min, and CS_2 (1.15 g, 15 mmol) was added dropwise. After stirring 30 min, the intermediate (**13a–13j**) was added. The reaction mixture was stirred at room temperature for 12 h. The mixture was extracted with ethyl acetate (15 mL × 3), the combined organic phase was washed with water (15 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The crude product was purified by recrystallization from the mixture solvents of ethyl acetate and petroleum ether to give pure compound (**14a–14j**).

4.3.1. 2-Benzoylpropane-1,3-diyl bis(dimethylcarbamodithioate) (**14a**)

Yield 43%. Pale yellow solid. Mp: 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23 (s, 6H), 3.45 (s, 6H), 3.57–3.62 (m, 2H), 3.67–3.73 (m, 2H), 4.43–4.50 (m, 1H), 7.37–7.41 (m, 2H), 7.48–7.52 (m, 2H), 8.00–8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.57, 41.56, 44.49, 45.35, 128.62, 128.98, 133.51, 136.48, 196.40, 201.02; Anal. Cald for $C_{16}H_{22}N_2OS_4$: C, 49.71; H, 5.74; N, 7.25; Found: C, 49.46; H, 5.69; N, 7.09.

4.3.2. 2-(4-Fluorobenzoyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14b**)

Yield 27%. Pale yellow solid. Mp: 133–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (s, 6H), 3.52 (s, 6H), 3.62–3.67 (m, 2H), 3.72–3.77 (m, 2H), 4.50 (s, 1H), 7.11–7.15 (m, 2H), 8.12–8.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.52, 41.60, 44.47, 45.39, 115.72 (d, *J* = 22 Hz), 131.77 (d, *J* = 10 Hz), 132.94, 166.08 (d, *J* = 254 Hz), 196.21, 199.55; Anal. Cald for $C_{16}H_{21}FN_2OS_4$: C, 47.50; H, 5.23; N, 6.92; Found: C, 47.75; H, 5.36; N, 7.03.

4.3.3. 2-(2-Fluorobenzoyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14c**)

Yield 20%. Pale yellow solid. Mp: 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.33 (s, 6H), 3.51 (s, 6H), 3.68–3.73 (m, 2H), 3.76–3.81 (m, 2H), 4.32–4.39 (m, 1H), 7.09–7.14 (m, 1H), 7.20–7.27 (m, 1H), 7.49–7.54 (m, 1H), 7.83–7.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.99, 41.47, 45.32, 48.95, 116.72 (d, *J* = 23 Hz), 124.37 (d, *J* = 4 Hz), 125.39 (d, *J* = 11 Hz), 131.08, 134.65 (d, *J* = 9 Hz), 161.31 (d, *J* = 254 Hz), 196.26, 198.69; Anal. Cald for $C_{16}H_{21}FN_2OS_4$: C, 47.50; H, 5.23; N, 6.92; Found: C, 47.42; H, 5.21; N, 6.90.

4.3.4. 2-(2-Methoxybenzoyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14d**)

Yield 44%. White solid. Mp: 93–94 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.29 (s, 6H), 3.43 (s, 6H), 3.50–3.55 (m, 2H), 3.59–3.64 (m, 2H), 3.82 (s, 3H), 4.31–4.38 (m, 1H), 7.01–7.05 (m, 1H), 7.14 (d, *J* = 8.40 Hz, 1H), 7.50–7.56 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.70, 41.14, 44.86, 48.38, 55.78, 112.37, 120.50, 126.99, 129.95, 133.96, 157.95, 194.62, 201.55; Anal. Cald for $C_{17}H_{24}N_2O_2S_4$: C, 49.01; H, 5.81; N, 6.72; Found: C, 49.26; H, 5.85; N, 6.83.

4.3.5. 2-(3-Methoxybenzoyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14e**)

Yield 20%. White solid. Mp: 96–98 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.26 (s, 6H), 3.43 (s, 6H), 3.55–3.65 (m, 4H), 3.81 (s, 3H), 4.38–4.45 (m, 1H), 7.23–7.26 (m, 1H), 7.44–7.48 (m, 2H), 7.58 (d, *J* = 7.60 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.19, 41.48, 44.07, 45.16, 55.54, 113.02, 120.07, 121.01, 130.17, 137.68, 159.62, 194.48, 200.39; Anal. Cald for $C_{17}H_{24}N_2O_2S_4$: C, 49.01; H, 5.81; N, 6.72; Found: C, 48.91; H, 5.95; N, 6.84.

4.3.6. 2-(4-(Benzyloxy)benzoyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14f**)

Yield 50%. Pale yellow solid. Mp: 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.29 (s, 6H), 3.50 (s, 6H), 3.50–3.67 (m, 2H), 3.72–3.77 (m, 2H), 4.43–4.50 (m, 1H), 5.12 (s, 2H), 7.00 (d, *J* = 8.80 Hz, 2H), 7.33–7.43 (m, 5H), 8.08 (d, *J* = 9.20 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.73, 41.59, 44.05, 45.53, 70.13, 114.65, 127.48, 128.24, 128.69, 129.70, 131.42, 136.16, 163.09, 196.44, 199.32; Anal. Cald for

$C_{23}H_{28}N_2O_2S_4$: C, 56.06; H, 5.73; N, 5.69; Found: C, 56.38; H, 6.07; N, 5.36.

4.3.7. 2-(4-Hydroxybenzoyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14g**)

Yield 11%. White solid. Mp: 152–153 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.27 (s, 6H), 3.44 (s, 6H), 3.49–3.62 (m, 4H), 4.27–4.33 (m, 1H), 6.88 (d, J = 8.80 Hz, 2H), 7.89 (d, J = 8.80 Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 38.76, 41.77, 43.75, 45.46, 115.79, 128.10, 131.60, 162.09, 194.97, 198.60; Anal. Cald for $C_{16}H_{22}N_2O_2S_4$: C, 47.73; H, 5.51; N, 6.96; Found: C, 47.87; H, 5.54; N, 6.94.

4.3.8. 2-Nicotinoylpropane-1,3-diyl bis(dimethylcarbamodithioate) (**14h**)

Yield 25%. Yellow solid. Mp: 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23 (s, 6H), 3.43 (s, 6H), 3.57–3.69 (m, 4H), 4.40–4.47 (m, 1H), 7.33–7.36 (m, 1H), 8.28 (d, J = 8.00 Hz, 1H), 8.69–8.70 (m, 1H), 9.15 (d, J = 1.60 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.29, 41.54, 45.01, 45.38, 123.44, 131.93, 136.16, 150.20, 153.66, 195.75, 200.38; Anal. Cald for $C_{15}H_{21}N_3OS_4$: C, 46.48; H, 5.46; N, 10.84; Found: C, 46.63; H, 5.49; N, 10.96.

4.3.9. 2-(Thiazole-2-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14i**)

Yield 15%. Gray solid. Mp: 123–125 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.28 (s, 6H), 3.42 (s, 6H), 3.70–3.81 (m, 4H), 4.48–4.54 (m, 1H), 8.18 (d, J = 3.20 Hz, 1H), 8.25 (d, J = 2.80 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.98, 41.77, 45.56, 46.24, 129.33, 145.76, 165.85, 193.03, 194.47; Anal. Cald for $C_{13}H_{19}N_3OS_5$: C, 39.67; H, 4.87; N, 10.67; Found: C, 39.65; H, 4.91; N, 10.60.

4.3.10. 2-(1H-pyrrole-2-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14j**)

Yield 34%. Colorless solid. Mp: 169–170 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.27 (s, 6H), 3.44 (s, 6H), 3.49–3.61 (m, 4H), 3.95–4.02 (m, 1H), 6.22 (d, J = 2.40 Hz, 1H), 7.04 (d, J = 2.80 Hz, 1H), 7.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.95, 41.76, 44.63, 45.43, 110.60, 118.34, 127.18, 131.63, 188.93, 195.02; Anal. Cald for $C_{14}H_{21}N_3OS_4$: C, 44.77; H, 5.64; N, 11.19; Found: C, 44.87; H, 5.67; N, 11.36.

4.4. General procedure for the synthesis of compounds **14k–14t**

A mixture of the acetyl substituted heterocyclic compound (5 mmol), paraformaldehyde (0.60 g, 20 mmol) and dimethylamine hydrochloride (0.82 g, 10 mmol) in acetic acid (10 mL) was heated under reflux for 12 h. The reaction mixture was concentrated under vacuum to afford the intermediate (**13k–13t**) which was used directly without further purification. A mixture of dimethylamine hydrochloride (0.82 g, 10 mmol), triethylamine (3.04 g, 30 mmol) and DMF (25 mL) was stirred for 15 min, and CS_2 (0.92 g, 12 mmol) was added dropwise. After stirring 30 min, the intermediate (**13k–13t**) was added. The reaction mixture was stirred at room temperature for 24 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (15 mL × 3), the combined organic phase was washed with water (15 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The crude product was purified by column chromatography to afford the pure product (**14k–14t**).

4.4.1. 2-(2-Oxo-2H-chromene-3-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14k**)

Yield 32%. Pale yellow solid. Mp: 121–123 °C (eluent: petroleum ether/ethyl acetate = 6:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.30 (s, 6H), 3.38 (s, 6H), 3.65–3.75 (m, 4H), 4.42–4.48 (m, 1H), 7.41–7.49 (m, 2H), 7.74–7.78 (m, 1H), 7.95 (d, J = 7.60 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 37.18, 41.23, 45.08, 47.92, 116.13, 118.14, 123.78, 124.97, 130.73, 134.71, 147.95, 154.61, 158.19, 194.54, 196.91; Anal. Cald for $C_{19}H_{22}N_2O_3S_4$: C, 50.19; H, 4.88; N, 6.16; Found: C, 50.14; H, 5.04; N, 5.98.

4.4.2. 2-(Benzo[b]thiophene-3-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14l**)

Yield 48%. Pale yellow solid. Mp: 118–120 °C (eluent: petroleum ether/ethyl acetate = 6:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.26 (s, 6H), 3.43 (s, 6H), 3.67–3.70 (m, 4H), 4.32–4.39 (m, 1H), 7.48–7.55 (m, 2H), 8.09 (d, J = 7.88 Hz, 1H), 863 (d, J = 8.00 Hz, 1H), 8.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.30, 41.30, 45.00, 46.16, 122.90, 124.73, 125.53, 125.87, 133.60, 136.13, 139.43, 140.85, 194.36, 195.16; Anal. Cald for $C_{18}H_{22}N_2OS_5$: C, 48.83; H, 5.01; N, 6.33; Found: C, 48.78; H, 5.00; N, 6.34.

4.4.3. 2-(Quinoline-3-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14m**)

Yield 41%. Pale yellow solid. Mp: 130–131 °C (eluent: petroleum ether/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.26 (s, 6H), 3.42 (s, 6H), 3.71–3.79 (m, 4H), 4.55–4.58 (m, 1H), 7.73–7.76 (m, 1H), 7.93–7.97 (m, 1H), 8.11–8.18 (m, 2H), 9.13 (s, 1H), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.79, 41.28, 44.89, 45.04, 126.29, 127.74, 128.30, 128.76, 129.86, 132.49, 137.96, 148.79, 149.13, 194.24, 199.60; Anal. Cald for $C_{19}H_{23}N_3OS_4$: C, 52.14; H, 5.30; N, 9.60; Found: C, 52.23; H, 5.34; N, 9.72.

4.4.4. 1-(1-Phenyl-1H-benzo[d]imidazol-5-yl)ethanone (**16**)

To a solution of 1-(4-bromo-3-nitrophenyl)ethanone (1.23 g, 5 mmol) and aniline (0.56 g, 6 mmol) in DMF (20 mL) was added sodium acetate (0.82 g, 10 mmol). The mixture was heated 10 h at 120 °C and then cooled to room temperature. H_2O (30 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (15 mL × 3), the combined organic phase was washed with brine (15 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The crude product was purified by column chromatography (eluent: petroleum ether/ethyl acetate = 10:1) to afford **16** as a red solid (1.02 g, 79%). Mp: 104–105 °C (Lit.Mp [18]: 112 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57 (s, 3H), 7.17 (d, J = 9.08 Hz, 1H), 7.28–7.34 (m, 3H), 7.45–7.48 (m, 2H), 7.96 (d, J = 9.04 Hz, 1H), 8.82 (d, J = 1.60 Hz, 1H), 9.85 (s, 1H).

4.4.5. 1-(1-Phenyl-1H-benzo[d]imidazol-5-yl)ethanone (**12n**)

To a solution of **16** (1.02 g, 4 mmol) dissolved in THF (20 mL) was added 5% Pd/C (0.21 g). The mixture was stirred at room temperature overnight at 50 psi. The mixture was filtered and the solvent was evaporated to afford compound **17**, which was used in the next step without further purification. Compound **17** was dissolved in 4 N hydrochloric acid solution (27.5 mL) and formic acid (2 mL), the reaction mixture was refluxed for 8 h and then cooled to room temperature. The pH of the reaction mixture was adjusted to 7 with 10% NaOH aqueous solution. The mixture was extracted with dichloromethane (15 mL × 3), the combined organic phase was washed with brine (20 mL × 2), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate = 2:1) to afford **12n** as a brown solid (0.33 g, 35%). Mp: 94–96 °C. ^{1}H NMR (400 MHz, CDCl3): δ = 2.70 (s, 3H), 7.51–7.63 (m, 6H), 8.02 (d, J = 8.56 Hz, 1H), 8.20 (s, 1H), 8.49 (s, 1H).

*4.4.6. 2-(1-Phenyl-1H-benzo[d]imidazole-5-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithio-ate) (**14n**)*

Yield 21%. Pale yellow solid. Mp: 73–75 °C (eluent: petroleum ether/ethyl acetate = 2:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.26 (s, 6H), 3.44 (s, 6H), 3.65–3.66 (m, 4H), 4.54–4.57 (m, 1H), 7.53–7.56 (m, 1H), 7.64–7.73 (m, 5H), 7.79 (d, J = 8.48 Hz, 1H), 8.48 (s, 1H), 8.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.31, 41.30, 43.76, 44.98, 111.09, 121.54, 123.84, 123.95, 128.22, 130.10, 131.10, 135.38, 136.71, 143.43, 145.65, 194.39, 199.69; Anal. Cald for $C_{23}H_{26}N_4OS_4$: C, 54.95; H, 5.21; N, 11.14; Found: C, 54.73; H, 5.24; N, 11.04.

*4.4.7. 1-(Pyrazolo[1,5-a]pyridin-3-yl)ethanone (**12o**)*

but-3-yn-2-one (0.71 g, 10.4 mmol) and 1-aminopyridinium iodide (2.69 g, 12 mmol) were dissolved in DMSO (21 mL) and treated with K_2CO_3 (1.30 g, 9.36 mmol) and KOH (1.17 g, 20.8 mmol). The mixture was stirred for 6 h at room temperature. Then the reaction mixture was poured in water (50 mL) and extracted with ethyl acetate (15 mL × 3), the combined organic phase was washed with brine (20 mL × 2), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate = 4:1) to provide **12o** as a pale yellow solid (0.53 g, 31%). Mp: 94–96 °C (Lit.Mp [19]: 102–103 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (s, 3H), 7.01 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 8.34–8.40 (m, 2H), 8.54 (d, J = 8.0 Hz, 1H).

*4.4.8. 2-(Pyrazolo[1,5-a]pyridine-3-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14o**)*

Yield 57%. Pale yellow solid. Mp: 159–160 °C (eluent: petroleum ether/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.29 (s, 6H), 3.46 (s, 6H), 3.61–3.72 (m, 4H), 4.10–4.17 (m, 1H), 7.26 (t, J = 6.76 Hz, 1H), 7.69–7.31 (m, 1H), 8.31 (d, J = 8.72 Hz, 1H), 8.71 (s, 1H), 8.93 (d, J = 6.80 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 38.33, 41.29, 44.98, 46.05, 111.69, 115.56, 118.87, 130.00, 130.07, 139.77, 145.06, 192.89, 194.60; Anal. Cald for $C_{17}H_{22}N_4OS_4$: C, 47.86; H, 5.20; N, 13.13; Found: C, 47.81; H, 5.20; N, 13.14.

*4.4.9. 1-(2-Phenylpyrazolo[1,5-a]pyridin-3-yl)ethanone (**12p**)*

4-Phenylbut-3-yn-2-one (0.75 g, 5.2 mmol) and 1-aminopyridinium iodide (1.34 g, 6.04 mmol) were dissolved in DMSO (10.5 mL) and treated with K_2CO_3 (0.65 g, 4.68 mmol) and KOH (0.58 g, 10.4 mmol). The mixture was stirred for 3 h at room temperature. Then the reaction mixture was poured in water (50 mL) and extracted with ethyl acetate (15 mL × 3), the combined organic phase was washed with brine (15 mL × 2), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate = 10:1) to provide **12p** as a yellow solid (0.77 g, 59%). Mp: 90–91 °C (Lit.Mp [19]: 94–95 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 7.02 (t, J = 8.0 Hz, 1H), 7.46–7.50 (m, 4H), 7.57–7.60 (m, 2H), 8.44 (d, J = 8.0 Hz, 1H), 8.52 (d, J = 8.0 Hz, 1H).

*4.4.10. 2-(2-Phenylpyrazolo[1,5-a]pyridine-3-carbonyl)propane-1,3-diyl bis(dimethylcarbamodith-ioate) (**14p**)*

Yield 61%. Off-white solid. Mp: 118–120 °C (eluent: petroleum ether/ethyl acetate = 5:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.25 (s, 6H), 3.40 (s, 6H), 3.45–3.47 (m, 4H), 3.64–3.70 (m, 1H), 7.22–7.26 (m, 1H), 7.41–7.44 (m, 3H), 7.47–7.55 (m, 2H), 7.65–7.69 (m, 1H), 8.23 (d, J = 8.84 Hz, 1H), 8.89 (d, J = 6.80 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.33, 41.14, 44.94, 46.43, 109.75, 115.41, 118.90, 128.25, 128.94, 129.48, 129.61, 132.55, 141.47, 155.78, 194.30, 194.38; Anal. Cald for $C_{23}H_{26}N_4OS4$: C, 54.95; H, 5.21; N, 11.14; Found: C, 54.97; H, 5.30; N, 10.98.

*4.4.11. 1-(Pyrazolo[1,5-b]pyridazin-3-yl)ethanone (**12q**)*

To a solution of hydroxylamine-O-sulfonic acid (4.2 g, 37.5 mmol) neutralized with 2.5 M potassium bicarbonate to pH 5 was added pyridazine (2.0 g, 25 mmol) at 70 °C over 15 min. The reaction mixture was stirred at 70 °C for 2 h followed by cooling to room temperature. After neutralization of the reaction mixture to pH 8, but-3-yn-2-one (0.85 g, 12.5 mmol) in 50 mL of dichloromethane and potassium hydroxide (2.6 g, 46.8 mmol) were added, and the mixture was stirred at room temperature for 24 h. The reaction mixture was extracted with dichloromethane (20 mL × 3), and the combined organic layer was washed with brine (15 mL × 2), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate = 10:1) to afford **12q** as a brown solid (1.06 g, 52%). Mp: 171–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (s, 3H), 7.27–7.33 (m, 1H), 8.43–8.47 (m, 2H), 8.75 (d, J = 8.0 Hz, 1H).

*4.4.12. 2-(Pyrazolo[1,5-b]pyridazine-3-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14q**)*

Yield 55%. Pale yellow solid. Mp: 168–170 °C (eluent: petroleum ether/ethyl acetate = 3:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.28 (s, 6H), 3.44 (s, 6H), 3.65–3.69 (m, 4H), 4.14–4.19 (m, 1H), 7.61–7.65 (m, 1H), 8.70–8.74 (m, 2H), 8.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.00, 41.31, 45.02, 46.25, 111.76, 121.84, 128.42, 134.41, 142.39, 145.21, 193.79, 194.41; Anal. Cald for $C_{16}H_{21}N_5OS_4$: C, 44.94; H, 4.95; N, 16.38; Found: C, 44.97; H, 4.99; N, 16.49.

*4.4.13. 1-(2-Phenylpyrazolo[1,5-b]pyridazin-3-yl)ethanone (**12r**)*

To a solution of hydroxylamine-O-sulfonic acid (2.72 g, 24 mmol) neutralized with 2.5 M potassium bicarbonate to pH 5 was added pyridazine (1.28 g, 16 mmol) at 70 °C over 15 min. The reaction mixture was stirred at 70 °C for 3 h followed by cooling to room temperature. After neutralization of the reaction mixture to pH 8, 4-phenylbut-3-yn-2-one (1.15 g, 8 mmol) in 32 mL of dichloromethane and potassium hydroxide (1.68 g, 30 mmol) were added, and the mixture was stirred at room temperature for 24 h. The reaction mixture was extracted with dichloromethane (15 mL × 3), and the combined organic layer was washed with brine (15 mL × 2), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate = 6:1) to afford **12r** as a yellow solid (1.50 g, 79%). Mp: 162–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19 (s, 3H), 7.29–7.33 (m, 1H), 7.52 (d, J = 2.68 Hz, 3H), 7.63 (s, 2H), 8.47 (d, J = 2.56 Hz, 1H), 8.75–8.77 (m, 1H).

*4.4.14. 2-(2-Phenylpyrazolo[1,5-b]pyridazine-3-carbonyl)propane-1,3-diyl bis(dimethylcarbamodi-thioate) (**14r**)*

Yield 46%. Off-white solid. Mp: 63–64 °C (eluent: petroleum ether/ethyl acetate = 2:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.25 (s, 6H), 3.38 (s, 6H), 3.46–3.53 (m, 4H), 3.69–3.74 (m, 1H), 7.43–7.52 (m, 1H), 7.56–7.61 (m, 1H), 8.56–8.58 (m, 1H), 8.72 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.91, 41.16, 44.99, 47.12, 109.91, 121.17, 128.34, 128.41, 129.20, 129.65, 131.83, 135.90, 144.96, 152.98, 194.14, 195.10; Anal. Cald for $C_{22}H_{25}N_5OS_4$: C, 52.46; H, 5.00; N, 13.90; Found: C, 52.43; H, 5.03; N, 13.93.

*4.4.15. 1-(Imidazo[1,2-a]pyridin-3-yl)ethanone (**12s**)*

2-Aminopyridine (1.88 g, 20 mmol) in 1,1-dimethoxyN,N-dimethylmethanamine (3.82 g, 32 mmol) was refluxed for 23 h and then evaporated. The resulting residue was dissolved in EtOH (35 mL), 1-bromoacetone (3.12 g, 22.75 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated and the residue was purified by column chromatography (eluent: dichloromethane/

methanol = 40:1) to afford **12s** as a pale yellow solid (2.06 g, 64%). Mp: 95–96 °C (Lit.Mp [20]: 98–99 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.61 (s, 3H), 7.08 (t, *J* = 6.80 Hz, 1H), 7.50 (t, *J* = 8.00 Hz, 1H), 7.76 (d, *J* = 9.00 Hz, 1H), 8.34 (s, 1H), 9.65 (d, *J* = 6.84 Hz, 1H).

4.4.16. 2-(Imidazo[1,2-a]pyridine-3-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithioate) (**14s**)

Yield 41%. White solid. Mp: 166–167 °C (eluent: petroleum ether/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.27 (s, 6H), 3.43 (s, 6H), 3.67–3.69 (m, 4H), 4.18–4.21 (m, 1H), 7.31–7.35 (m, 1H), 7.68–7.72 (m, 1H), 7.88 (d, *J* = 8.44 Hz, 1H), 8.59 (s, 1H), 9.58 (d, *J* = 6.72 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.29, 41.32, 44.99, 45.66, 115.94, 117.48, 123.44, 128.29, 130.23, 144.31, 148.67, 188.61, 194.36; Anal. Cald for $C_{17}H_{22}N_4OS_4$: C, 47.86; H, 5.20; N, 13.13; Found: C, 47.81; H, 5.12; N, 13.06.

4.4.17. 1-(2-Methylimidazo[1,2-a]pyridin-3-yl)ethanone (**12t**)

A mixture of 2-aminopyridine (0.94 g, 10 mmol) and 3-chloropentane-2,4-dione (1.35 g, 10 mmol) in ethanol (6 mL) was refluxed for 10 h. After evaporation, the residue was purified by column chromatography (eluent: dichloromethane/methanol = 50:1) to afford **12**t as a pale yellow solid (0.58 g, 33%). Mp: 107–108 °C (Lit.Mp [21]: 108–110 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3H), 2.80 (s, 3H), 7.01 (t, *J* = 6.68 Hz, 1H), 7.45 (t, *J* = 8.00 Hz, 1H), 7.63 (d, *J* = 8.84 Hz, 1H), 9.74 (d, *J* = 6.92 Hz, 1H).

4.4.18. 2-(2-Methylimidazo[1,2-a]pyridine-3-carbonyl)propane-1,3-diyl bis(dimethylcarbamodithi-oate) (**14t**)

Yield 22%. Pale yellow solid. Mp: 128–130 °C (eluent: petroleum ether/ethyl acetate = 2:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.69 (s, 3H), 3.27 (s, 6H), 3.43 (s, 6H), 3.63–3.73 (m, 4H), 4.23–4.26 (m, 1H), 7.23–7.26 (m, 1H), 7.63–7.67 (m, 1H), 7.74 (d, *J* = 8.64 Hz, 1H), 9.66 (d, *J* = 6.64 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.32, 38.64, 41.29, 45.02, 45.79, 115.26, 116.31, 121.21, 128.58, 130.20, 146.48, 153.06, 189.47, 194.36; Anal. Cald for $C_{18}H_{24}N_4OS_4$: C, 49.06; H, 5.49; N, 12.71; Found: C, 48.82; H, 5.55; N, 12.50.

4.5. General procedure for the synthesis of compounds **25a**–**25g**

A mixture of 3-acetylquinoline (0.34 g, 2 mmol), paraformaldehyde (0.24 g, 8 mmol) and dimethylamine hydrochloride (0.33 g, 4 mmol) in acetic acid (5 mL) was heated under reflux for12 h. The reaction mixture was concentrated under vacuum to afford the intermediate **13m** which was used directly without further purification. A mixture of secondary amine (4 mmol), potassium carbonate (1.11 g, 8 mmol) and acetone (10 mL) was stirred for 15 min, and CS_2 (0.37 g, 4.8 mmol) was added dropwise. After stirring 1 h, the reaction mixture was concentrated to give the intermediate (**24a**–**24g**). The intermediate (**24a**–**24g**) was dissolved in water (5 ml) and the DMF (5 ml) solution of **13m** was added. The reaction mixture was stirred at room temperature for 12 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (15 mL × 3), the combined organic phase was washed with water (20 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The crude product was purified by column chromatography to obtain the pure product (**25a**–**25g**).

4.5.1. 2-(Quinoline-3-carbonyl)propane-1,3-diyl bis(diethylcarbamodithioate) (**25a**)

Yield 24%. White solid. Mp: 103–104 °C (eluent: petroleum ether/ethyl acetate = 8:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.06–1.12 (m, 12H), 3.63–3.78 (m, 8H), 3.92 (s, 4H), 4.61–4.64 (m, 1H), 7.72–7.75 (m, 1H), 7.72–7.96 (m, 1H), 8.10–8.14 (m, 2H), 9.08 (s, 1H), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 11.20, 12.16, 37.29, 44.62, 46.52, 49.20, 126.30, 127.70, 128.70, 128.76, 129.79, 132.42, 137.80, 148.69, 149.16, 192.84, 200.15; Anal. Cald for $C_{23}H_{31}N_3OS_4$: C, 55.95; H, 6.33; N, 8.51; Found: C, 55.93; H, 6.33; N, 8.52.

4.5.2. 2-(Quinoline-3-carbonyl)propane-1,3-diyl bis(4-methylpiperazine-1-carbodithioate) (**25b**)

Yield 17%. White solid. Mp: 133–134 °C (eluent: ethyl acetate/methanol = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.23 (s, 8H), 2.39–2.40 (m, 6H), 3.78–3.83 (m, 8H), 4.31 (s, 4H), 4.74–4.77 (m, 1H), 7.61–7.64 (m, 1H), 7.82–7.86 (m, 1H), 8.00 (d, *J* = 7.88 Hz, 1H), 8.15 (d, *J* = 8.32 Hz, 1H), 9.03 (s, 1H), 9.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.84, 44.69, 45.42, 54.22, 126.72, 127.40, 129.00, 129.40, 129.76, 132.12, 138.39, 149.48, 149.88, 195.41, 200.54; Anal. Cald for $C_{25}H_{33}N_5OS_4$: C, 54.81; H, 6.07; N, 12.78; Found: C, 54.85; H, 6.09; N, 12.73.

4.5.3. 2-(Quinoline-3-carbonyl)propane-1,3-diyl dimorpholine-4-carbodithioate (**25c**)

Yield 15%. White solid. Mp: 124–125 °C (eluent: petroleum ether/ethyl acetate = 2:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.31–3.57 (m, 8H), 3.77–3.79 (m, 8H), 4.17 (s, 4H), 4.63–4.66 (m, 1H), 7.73–7.76 (m, 1H), 7.93–7.97 (m, 1H), 8.11–8.17 (m, 2H), 9.09 (s, 1H), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.11, 44.60, 51.32, 65.42, 126.28, 127.78, 128.56, 128.78, 129.87, 132.53, 137.88, 148.79, 149.17, 194.51, 199.76; Anal. Cald for $C_{23}H_{27}N_3O_3S_4$: C, 52.95; H, 5.22; N, 8.05; Found: C, 52.98; H, 5.20; N, 8.01.

4.5.4. 2-(Quinoline-3-carbonyl)propane-1,3-diyl dipyrrolidine-1-carbodithioate (**25d**)

Yield 35%. Pale yellow solid. Mp: 162–163 °C (eluent: petroleum ether/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 8H), 3.40–3.80 (m, 12H), 4.58 (s, 1H), 7.53 (s, 1H), 7.75 (s, 1H), 7.92 (d, *J* = 6.92 Hz, 1H), 8.05 (d, *J* = 7.44 Hz, 1H), 9.04 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.08, 25.81, 37.18, 45.44, 50.65, 54.95, 126.63, 127.28, 128.66, 129.24, 129.62, 131.98, 138.48, 149.45, 149.74, 191.39, 200.22; Anal. Cald for $C_{23}H_{27}N_3OS_4$: C, 56.41; H, 5.56; N, 8.58; Found: C, 56.30; H, 5.51; N, 8.61.

4.5.5. 2-(Quinoline-3-carbonyl)propane-1,3-diyl dipiperidine-1-carbodithioate (**25e**)

Yield 15%. Off-white solid. Mp: 110–111 °C (eluent: petroleum ether/ethyl acetate = 6:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.48–1.50 (m, 12H), 3.67–3.76 (m, 8H), 4.14 (s, 4H), 4.65–4.68 (m, 1H), 7.72–7.75 (m, 1H), 7.92–7.96 (m, 1H), 8.09–8.15 (m, 2H), 9.05 (s, 1H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.38, 37.35, 44.44, 51.02, 52.52, 126.30, 127.74, 128.75, 128.86, 129.85, 132.46, 137.79, 148.76, 149.16, 192.53, 200.18; Anal. Cald for C25H31N3OS4: C, 57.99; H, 6.03; N, 8.12; Found: C, 57.96; H, 6.01; N, 8.13.

4.5.6. 2-(Quinoline-3-carbonyl)propane-1,3-diyl dithiomorpholine-4-carbodithioate(**25f**)

Yield 26%. Pale green solid. Mp: 136–137 °C (eluent: petroleum ether/ethyl acetate = 5:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.50–2.63 (m, 8H), 3.77 (s, 4H), 4.11–4.12 (m, 4H), 4.45 (s, 4H), 4.66–4.68 (m, 1H), 7.75 (d, J = 7.04 Hz, 1H), 7.92–7.96 (m, 1H), 8.10–8.16 (m, 2H), 9.07 (s, 1H), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.46, 37.28, 44.37, 54.12, 126.29, 127.83, 128.65, 128.82, 129.84, 132.53, 137.85, 148.76, 149.19, 194.08, 199.91; Anal. Cald for $C_{23}H_{27}N_3OS_6$: C, 49.88; H, 4.91; N, 7.59; Found: C, 49.72; H, 4.89; N, 7.64.

4.5.7. 2-(Quinoline-3-carbonyl)propane-1,3-diyl bis(methyl(pyridin-3-ylmethyl)carbamodithioate) (**25g**)

Yield 18%. Pale yellow solid. Mp: 55–56 °C (eluent: ethyl acetate/methanol = 100:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.27–3.44 (m, 7H), 3.80 (s, 4H), 4.68 (s, 1H), 5.03 (s, 1H), 5.32 (s, 2H), 7.16–7.47 (m, 3H), 7.63–7.65 (m, 1H), 7.72–7.76 (m, 1H), 7.95 (s, 1H), 8.12–8.14 (m, 2H), 8.40–8.53 (m, 4H), 9.10–9.13 (m, 1H), 9.33–9.36 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d6): δ = 38.00, 44.61, 54.54, 56.52, 123.54, 126.32, 127.76, 128.37, 128.80, 129.88, 131.39, 132.51, 134.46, 135.00, 137.97, 148.69, 148.83, 149.19, 196.63, 199.64; Anal. Cald for $C_{29}H_{29}N_5OS_4$: C, 58.85; H, 4.94; N, 11.83; Found: C, 58.84; H, 4.97; N, 11.75.

4.6. Antiproliferative activity assays

4.6.1. Antiproliferative activity against tumor cells

The antiproliferative activity of the target compounds was determined by MTT assay on human non-small cell lung cancer cell line H460 and the antiproliferative activity of the compound **14m** was determined by MTT assay on the following cell lines: HepG2, MCF-7, MDA-MB-453, SW480, H522, PC3, H1299, A375, H460 and COLO205. All cells used in the research were prepared at 3.5 × 10^3 cells/mL concentration and each 100 μL cell suspension was seeded onto 96-well microtiter plates for 24 h (37 °C, 5% CO_2). Then various appropriate dilutions of tested compounds were added and incubated for 72 h. For the control group, equivalent concentration of DMSO (final concentration 0.5%) was added. MTT (3-[4,5-dimethylthiazol-2yl]-diphenyl tetrazolium bromide) method was used to measure the number of surviving cells and recorded the OD value at 492/620 nm. The IC_{50} values were calculated using Prism Graphpad software of the triplicate experiment.

4.6.2. Antiproliferative activity against non-tumor cells

The antiproliferative activity of compound **14m** was determined by Alamar Blue assay on human hepatic cell line LO2 and human embryonic kidney cell line HEK293. Two cells used in the research were prepared at 3.5 × 10^3 cells/mL concentration and each 100 μL cell suspension was seeded onto 96-well microtiter plates for 24 h (37 °C, 5% CO_2). Then various appropriate dilutions of compound **14m** were added and incubated for 72 h. For the control group, equivalent concentration of DMSO (final concentration 0.5%) was added. Alamar Blue method was used to measure the number of surviving cells and recorded the OD value at 492/620 nm. The IC_{50} values were calculated using Prism Graphpad software of the triplicate experiment.

Acknowledgments

The authors thank the National Natural Science Foundation of China (No. 21172011 and 21372019) and the Macao Science and Technology Development Fund (077/2011/A3) for financial support.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.02.030.

References

[1] H.-Y. Hung, E. Ohkoshi, M. Goto, K.F. Bastow, K. Nakagawa-Goto, K.-H. Lee, Antitumor agents. 293. nontoxicdimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethylenedi oxybiphenyl-2,2′ -dicarboxylate (DDB) analogues chemosensitize multidrug-resistant cancer cells to clinical anticancer drugs, J. Med. Chem. 55 (2012) 5413–5424.

[2] D.C. Swinney, J. Anthony, How were new medicines discovered, Nat. Rev. Drug Discov. 10 (2011) 507–519.

[3] C. Len, A.S. Boulogne-merlot, D. Postel, G. Ronco, P. Villa, C. Goubert, E. Jeufrault, B. Mathon, H. Simon, Synthesis and antifungal activity of novel bis(dithiocarbamate) derivatives of glycerol, J. Agric. Food Chem. 44 (1996) 2856–2858.

[4] H. Imamura, N. Ohtake, R. Nagano, S. Abe, K. Yamada, T. Hashizume, H. Morishima, Dicationic dithiocarbamate carbapenems with anti-MRSA activity, Bioorg. Med. Chem. 9 (2001) 1571–1578.

[5] F. Carta, M. Aggarwal, A. Maresca, R. McKenna, E. Masini, C.T. Supuran, Dithiocarbamates strongly inhibit carbonic anhydrases and show antiglaucoma action in vivo, J. Med. Chem. 55 (2012) 1721–1730.

[6] F. Carta, C.T. Supuran, Dithiocarbamates: a new class of carbonic anhydrase inhibitors. Crystallographic and kinetic investigations, Chem. Commun. 48 (2012) 1868–1870.

[7] M.A.-H. Zahran, T.A.-R. Salem, R.M. Samaka, H.S. Agwa, A.R. Awad, Design, synthesis and antitumor evaluation of novel thalidomide dithiocarbamate and dithioate analogs against ehrlich ascites carcinoma-induced solid tumor in Swiss albino mice, Bioorg. Med. Chem. 16 (2008) 9708–9718.

[8] W. Huang, Y. Ding, Y. Miao, M.Z. Liu, Y. Li, G.F. Yang, Synthesis and antitumor activity of novel dithiocarbamate substituted chromones, Eur. J. Med. Chem. 44 (2009) 3687–3696.

[9] (a) S.L. Cao, Y.P. Feng, Y.Y. Jiang, S.Y. Liu, G.Y. Ding, R.T. Li, Synthesis andin vitro antitumor activity of 4(3H)-quinazolinone derivatives with dithiocarbamate side chains, Bioorg. Med. Chem. Lett. 15 (2005) 1915–1917;
(b) S.L. Cao, Y.P. Feng, X.L. Zheng, Y.Y. Jiang, M. Zhang, Y. Wang, M. Xu, Synthesis of substituted-benzylamino- and heterocyclylmethylamino-carbodithioate derivatives of 4(3H)-quinazolinone and their cytotoxic activity, Arch. Pharm. 339 (2006) 250–254;
(c) S.L. Cao, Y. Wang, L. Zhu, J. Liao, Y.W. Guo, L.L. Chen, H.Q. Liu, X. Xu, Synthesis and cytotoxic activity of N-((2-methyl-4(3H)-quinazolinon-6-yl) methyl)dithiocarbamates, Eur. J. Med. Chem. 45 (2010) 3850–3857;
(d) S.L. Cao, Y. Han, C.Z. Yuan, Y. Wang, Z.-K. Xiahou, J. Liao, R.T. Gao, B.B. Mao, B.L. Zhao, Z.F. Li, X. Xu, Synthesis and antiproliferative activity of 4-substituted-piperazine -1-carbodithioate derivatives of 2,4-diaminoquinazoline, Eur. J. Med. Chem. 64 (2013) 401–409.

[10] X.J. Wang, H.W. Xu, L.L. Guo, X. Guo, C.X. Zheng, H.M. Liu, Synthesis and in vitro antitumor activity of new butenolide-containing dithiocarbamates, Bioorg. Med. Chem. Lett. 21 (2011) 3074–3077.

[11] (a) Y.C. Duan, Y.C. Ma, E. Zhang, X.J. Shi, M.M. Wang, X.W. Ye, H.M. Liu, Design and synthesis of novel 1,2,3-triazole-dithiocarbamate hybrids as potential anticancer agents, Eur. J. Med. Chem. 62 (2013) 11–19;
(b) Y.C. Duan, Y.C. Zheng, X.C. Li, M.M. Wang, X.W. Ye, Y.Y. Guan, G.Z. Liu, J.X. Zheng, H.M. Liu, Design, synthesis and antiproliferative activity studies of novel 1,2,3-triazole-dithiocarbamate-urea hybrids, Eur. J. Med. Chem. 64 (2013) 99–110;
(c) Y.C. Zheng, Y.C. Duan, J.L. Ma, R.M. Xu, X.L. Zi, W.L. Lv, M.M. Wang, X.W. Ye, S. Zhu, D. Mobley, Y.Y. Zhu, J.W. Wang, J.F. Li, Z.R. Wang, W. Zhao, H.M. Liu, Triazole–dithiocarbamate based selective lysine specific demethylase 1 (LSD1) inactivators inhibit gastric cancer cell growth, invasion, and migration, J. Med. Chem. 56 (2013) 8543–8560.

[12] (a) B.G. Guo, Z.M. Ge, T.M. Cheng, R.T. Li, Synthesis and anti-tumor activity of 1,4-bis[3-(aminodithiocarboxyl)propionyl]piperazine derivatives, Acta Pharmacol. Sin. 36 (2001) 185–187;
(b) Z.M. Ge, R.T. Li, T.M. Cheng, J.R. Cui, Synthesis and biological activities of dipiperazinium salts containing dithiocarboxyl, Arch. Pharm. Pharm. Med. Chem. 334 (2001) 173–176;
(c) X.L. Hou, Z.M. Ge, T.M. Wang, W. Guo, J.R. Cui, T.M. Cheng, C.S. Lai, R.T. Li, Dithiocarbamic acid esters as anticancer agent. Part 1: 4-Substituted-piperazine-1-carbodithioic acid 3-cyano-3,3-diphenyl-propyl esters, Bioorg. Med. Chem. Lett. 16 (2006) 4214–4219;
(d) X.L. Hou, Z.M. Ge, T.M. Wang, W. Guo, J. Wu, J.R. Cui, C.S. Lai, R.T. Li, Synthesis and structure-activity relationships of a novel class of dithiocarbamic acid esters as anticancer agent, Arch. Pharm. Chem. Life Sci. 11 (2011) 320–332;
(e) R.D. Li, X. Zhang, Q.Y. Li, Z.M. Ge, R.T. Li, Novel EGFR inhibitors prepared by combination of dithiocarbamic acid esters and 4-anilinoquinazolines, Bioorg. Med. Chem. Lett. 21 (2011) 3637–3640;
(f) X. Zhang, R.D. Li, K. Qiao, Z.M. Ge, L.R. Zhang, T.M. Cheng, R.T. Li, Novel dithiocarbamic acid esters derived from 6-aminomethyl- 4-anilinoquinazolines and 6-aminomethyl-4-anilino-3-cyanoquinolines as potent EGFR inhibitors, Arch. Pharm. Chem. Life Sci. 346 (2013) 44–52;
(g) N. Zhang, W. Guo, L. Wang, W. Huang, B. Xu, Z.M. Ge, M. Li, R.T. Li, J.R. Cui, Effect of TM208 on QGY-7703 xenograft tumor growth, Anti-Cancer Drugs 19 (2008) 593–598;
(h) Y.B. Li, Z.Q. Wang, X. Yan, M.W. Chen, J.L. Bao, G.S. Wu, Z.M. Ge, D.M. Zhou, Y.T. Wang, R.T. Li, IC-4, a new irreversible EGFR inhibitor, exhibits prominent anti-tumor and anti-angiogenesis activities, Cancer Lett. 340 (2013) 88–96.

[13] H.N. Pati, U. Das, I.J.R. amirez-E rosa, D.M. Dunlop, R.A. Hickie, J.R. Dimmock, α-substituted 1-aryl-3-dimethylaminopropanone hydrochlorides: potent cytotoxins towards human WiDr colon cancer cells, Chem. Pharm. Bull. 55 (2007) 511–515.

[14] D.I. Perez, V. Palomo, C. Perez, C. Gil, P.D. Dans, F.J. Luque, S. Conde, A. Martínez, Switching reversibility to irreversibility in glycogen synthase kinase 3 inhibitors: clues for specific design of new compounds, J. Med. Chem. 54 (2011) 4042–4056.

[15] S. Patnaik, H.C. Dietz, W. Zheng, C. Austin, J.J. Marugan, Multi-gram scale

synthesis of FR180204, J. Org. Chem. 74 (2009) 8870–8873.
[16] F.X. Tavares, J.A. Boucheron, S.H. Dickerson, R.J. Griffin, F. Preugschat, S.A. Thomson, T.Y. Wang, H.-Q. Zhou, N-phenyl-4-pyrazolo[1,5- b]pyridazin-3-ylpyrimidin-2-amines as potent and selective inhibitors of glycogen synthase kinase 3 with good cellular efficacy, J. Med. Chem. 47 (2004) 4716–4730.
[17] M. Hayakawa, H. Kaizawa, K. Kawaguchi, N. Ishikawa, T. Koizumi, T. Ohishi, M. Yamano, M. Okada, M. Ohta, S. Tsukamoto, F.I. Raynaud, M.D. Waterfield, P. Parker, P. Workman, Synthesis and biological evaluation of imidazo [1,2-a] pyridine derivatives as novel PI3 kinase p110α inhibitors, Bioorg. Med. Chem. 15 (2007) 403–412.
[18] D. Gerard, R. Bernard, 2-Nitrodiphenylamine, Meml. Poudres 40 (1958) 225–239.
[19] M. asuyoshi, N. Noriko, H. Hiroko, T. Shoji, Acid-catalyzed reactions of 3-(hydroxymethyl)- and 3-(1-hydroxyethyl)pyrazolo[1,5-a]pyridines, J. Heterocycl. Chem. 26 (1989) 1739–1745.
[20] S. Kurt, K. Fritz, K. Botho, Imidazopyridines and related ring systems. I. Syntheses of imidazopyridines. 1, Chem. Ber. 88 (1955) 1093–1102.
[21] J.E. Starrett Jr., T.A. Montzka, A.R. Crosswell, R.L. Cavanagh, Synthesis and biological activity of 3-substituted imidazo[1,2-a]pyridines as antiulcer agents, J. Med. Chem. 32 (1989) 2204–2210.