Full Paper

Synthesis and Cytotoxicity Screening of Piperazine-1-carbodithioate Derivatives of 2-Substituted Quinazolin-4(3*H*)-ones

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A new series of piperazine-1-carbodithioate derivatives of 2-substituted quinazolin-4(3*H*)-ones were synthesized via a five-steps procedure starting from 2-amino-5-methylbenzoic acid. The cytotoxicity of the resulting compounds against A-549 (human lung cancer), HCT-8 (human colon cancer), HepG2 (human liver cancer), and K562 (human myelogenous leukaemia) cell lines was determined by the MTT assay. Preliminary screening results of these compounds are reported.

Keywords: Dithiocarbamate / Cytotoxicity / Quinazolin-4(3*H*)-one / Screening / Synthesis

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Introduction

Quinazolin-4(3*H*)-one analogs of folic acid have drawn considerable attention in the search for antifolates and antitumor agents [1]. In recent years, classical as well as non-classical antifolates, which differ in either containing the L-glutamic acid moiety or not, have been increasingly reported in the literature [2–8]. On the other hand, dithiocarbamate has proved to be an effective pharmacophore with cancer chemopreventive and antitumor activity [9–15]. In our previous paper, the synthesis of a series of 2-methylquinazolin-4(3*H*)-one derivatives bearing dithiocarbamate side chains was described together with their *in-vitro* antitumor activity via the MTT assay [16]. Preliminary results showed that among the compounds synthesized, **1** (Fig. 1), containing the 4-fluorophenylpiperazine-1-carbodithioate moiety, possessed significant *in-vitro* cytotoxicity against human myelogenous leukaemia K562 and human cervical cancer HeLa cell lines with IC_{50} values of 0.5 and 12.0 μM, respectively [16, 17].

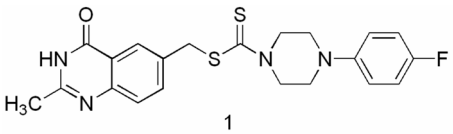

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Figure 1. Structure of compound **1**.

We noted reports that substituents at the C2 position of quinazolin-4(3*H*)-one derivatives acting as antifolate antitumor agents had much to do with their biological activity [18, 19]. Therefore, a new series of 2-substituted-quinazolin-4(3*H*)-one derivatives bearing 4-substituted-piperazine-1-carbodithioate side chains **8a–z** (Scheme 1 and Table 1) have been designed with the aim of investigating the effect of the substituents both at the C2 position of quinazolin-4(3*H*)-one and the N4 position of piperazine on the antitumor activity in search for more effec-

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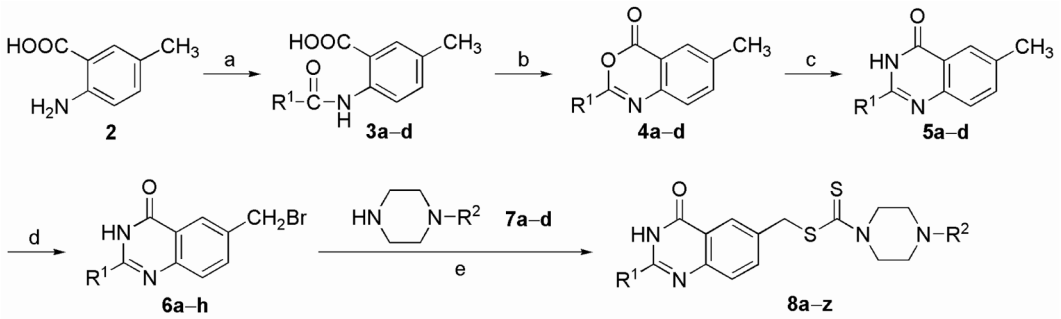
Abbreviations: 3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT); *N*-bromosuccinimide (NBS)



3a–d, **4a–d**, **5a–d**, **6a–d**: **a**: R^1 = n-Pr, **b**: R^1 = i-Pr, **c**: R^1 = 4-ClPh, **d**: R^1 = 2-Furanyl;
6e–h: **e**: R^1 = CF_3, **f**: R^1 = Et, **g**: R^1 = $PhCH_2$, **h**: R^1 = Ph;
7a–d: **a**: R^2 = Me, **b**: R^2 = $PhCH_2$, **c**: R^2 = Ph, **d**: R^2 = 4-FPh;
8a–z: for R^1 and R^2, see Table 1.

Reagents and conditions: a) RCOCl, pyridine, THF, reflux 5 h; b) Ac_2O, reflux 1.5 h; c) $HCONH_2$, 150 – 155°C, 3 h; d) NBS, $(PhCO)_2O_2$, $CHCl_3$, ν · *n*, reflux 3 h; e) CS_2, K_3PO_4, DMF, rt, 2 h.

Scheme 1. Synthetic route to compounds **8a–z**.

Table 1. Percent growth inhibition of compounds **8a–z** against A-549, HCT-8, HepG2, and K562 cell lines at the concentration of 5 μg/mL.

Compound	R^1	R^2	% Inhibition at 5 μg/mL			
			A-549	HCT-8	HepG2	K562
8a	CF_3	Me	−1.0	−3.0	12.4	2.7
8b	CF_3	$PhCH_2$	−11.0	1.2	10.6	5.0
8c	CF_3	Ph	−2.2	1.3	17.1	0.1
8d	CF_3	4-FPh	−6.4	1.5	−1.0	8.4
8e	Et	Me	6.2	−4.7	29.9	0.9
8f	Et	$PhCH_2$	−8.7	−6.5	20.5	1.4
8g	Et	Ph	−2.9	−5.0	−37.0	5.4
8h	Et	4-FPh	1.4	−5.1	6.8	4.6
8i	n-Pr	Me	−3.9	−9.8	13.5	17.6
8j	n-Pr	$PhCH_2$	4.7	17.7	20.6	6.5
8k	n-Pr	Ph	80.4	−15.6	−12.8	6.7
8l	n-Pr	4-FPh	−3.8	−21.4	16.3	5.8
8m	i-Pr	Me	10.0	−16.2	−9.7	6.5
8n	i-Pr	$PhCH_2$	−20.1	−3.4	14.3	13.1
8o	i-Pr	Ph	−27.3	12.9	−0.5	3.8
8p	i-Pr	4-FPh	−6.5	10.5	7.5	4.3
8q	$PhCH_2$	Me	−10.9	−6.3	−11.3	7.3
8r	$PhCH_2$	$PhCH_2$	−6.4	−6.7	11.5	3.9
8s	$PhCH_2$	Ph	11.1	9.5	28.6	39.1
8t	$PhCH_2$	4-FPh	−4.7	8.2	2.0	4.2
8u	Ph	Me	−14.9	−7.7	8.9	7.9
8v	Ph	$PhCH_2$	−23.6	−13.0	−0.9	11.3
8w	Ph	Ph	−22.9	8.8	−13.4	12.3
8x	Ph	4-FPh	−2.1	66.7	23.7	12.0
8y	4-ClPh	4-FPh	−0.8	−12.1	−9.5	0.3
8z	2-Furanyl	4-FPh	−2.0	16.8	44.7	6.1

tive antitumor agents. We now report the synthesis of these compounds together with their screening results of inhibitory activity against A-549, HCT-8, HepG2, and K562 tumor cell lines.

Results and discussion

As shown in Scheme 1, the reaction of 2-amino-5-methylbenzoic acid **2** with different acyl chlorides in dry tetrahydrofuran using pyridine as acid-binding agent yielded *N*-acylated products **3**. Heating **3** with an excess of acetic anhydride under reflux for 1.5 h produced benzoxazin-4-ones **4**, which were converted into 2-substituted quinazolin-4(3*H*)-ones **5** by heating together with formamide at 150-155°C. Bromination of **5** in chloroform with *N*-bromosuccinimide (NBS) gave bromomethyl compounds **6**, of which four viz., **6e–h** have been reported elsewhere [20]. Finally, the target compounds **8a–z** were prepared according to the established method [16, 21] by the reaction of compounds **6** with CS_2 and various 1-substitued-piperazines (**7a–d**) in the presence of anhydrous K_3PO_4. The structures of the synthesized compounds were confirmed by MS, ^{1}H-NMR, and elemental analysis, and the data are given in the experimental section.

The newly synthesized compounds **8a–z** were preliminarily screened at the single concentration of 5 μg/mL using the colorimetric MTT (3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyl-tetrazolium bromide) assay [21] to test their *in-vitro* cytotoxicity against A-549 (human cell lung cancer), HCT-8 (human colon cancer), HepG2 (human liver cancer), and K562 (human myelogenous leukaemia) cell lines. The cytotoxicity of the compounds tested was estimated in terms of percent growth inhibition compared with untreated control cells. From the data listed in Table 1, it was disappointing to note that all but two of the compounds did not show significant inhibitory activity. The two compounds that demonstrated inhibition, namely **8k** and **8x**, inhibited the growth of A-549 and

HCT-8 cells by 80.4% and 66.7%, respectively. In contrast with the 2-methyl-quinazolin-4(3*H*)-one derivatives previously reported [16], no compound within the new series **8a–z** displayed obvious inhibitory activity against K562 cells. These results indicate that the substituents at the C2 position of quinazolin-4(3*H*)-one instead of those at the N4 position of piperazine markedly influence the cytotoxic activity of this type of compounds.

In summary, a new series of piperazine-1-carbodithioate derivatives of 2-substituted quinazolin-4(3*H*)-ones were synthesized and the screening results revealed that the replacement of methyl at the C2 position of quinazolin-4(3*H*)-one with other alkyl, aryl, or heteroaryl group led to a decrease in cytotoxic activity.

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The authors have declared no conflict of interest.

Experimental

Melting points were determined on an XT4A microscopic melting point apparatus (Keyi Electrooptical, Beijing, China) or WRS-1B digital melting point apparatus (Shenguang, Shanghai, China) and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AC-200P spectrometer (Bruker, Zürich, Switzerland) at 200 MHz using tetramethylsilane (TMS) as internal standard. Electrospray ionization (ESI) mass spectra were recorded on a Bruker Daltonics Esquire-LC 00136 mass spectrometer (Bruker Daltonics, Bremen, Germany); chemical ionization (CI) mass spectra were recorded on a Finnigan Trace DSQ mass spectrometer (Thermo Finnigan, USA); electron impact (EI) mass spectra were recorded on a Micromass GCT mass spectrometer (Micromass, Manchester, UK). Elemental analyses were performed by Institute of Chemistry, Chinese Academy of Science, on a Flash EA 1112 elemental analyzer (Thermo Electron. Waltham, MA, USA). Column chromatography was carried out on silica gel (200-300 mesh). 2-Amino-5-methylbenzoic acid **2** was prepared according to the reported method [22], and other commercially available reagents were used without further purification.

General procedure for the synthesis of 5-methyl-2-(N-acylamino)benzoic acids *3a–d*

To a stirred solution of 2-amino-5-methylbenzoic acid **2** (3.02 g, 20 mmol) and pyridine (25 mmol) in tetrahydrofuran (34 mL) was added dropwise acyl chloride (21 mmol) in tetrahydrofuran (42 mL). The reaction mixture was heated under reflux for 5 h. After removing about 2/3 volume of tetrahydrofuran under reduced pressure, water (100 mL) was added into the residue, and the resulting mixture was acidified to pH 2–3 with dilute hydrochloride. The formed precipitate was collected by filtration and recrystallized from appropriate solvent to afford compounds **3a–d**.

*2-(Butyramido)-5-methylbenzoic acid **3a***

Yield: 80.3%, m.p.: 115.1–116.0°C (from EtOH / H_2O, 9 : 1). ESI-MS *m/z*: 222 $[M + H]^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (t, *J* = 7.3 Hz, 3H, CH_3CH_2), 1.82 (m, 2H, $CH_3CH_2CH_2$), 2.35 (s, 3H, CH_3), 2.47 (t, *J* = 7.4 Hz, 2H, CH_2CH_2), 7.41 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.94 (s, 1H, Ar-H), 8.64 (d, *J* = 8.6 Hz, 1H, Ar-H), 10.94 (s, 1H, NH), 11.70 (br s, 1H, COOH). Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.97; H, 6.72; N, 6.41.

*2-(Isobutyramido)-5-methylbenzoic acid **3b***

Yield: 94.6%, m.p.: 162.3–163.2°C (from ethanol / H_2O, 3 : 1). ESI-MS *m/z*: 220 $[M - H]^-$. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.36 (s, 3H, CH_3), 2.65 (m, 1H, $(CH_3)_2CH$), 7.43 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.95 (s, 1H, Ar-H), 8.67 (d, *J* = 8.6 Hz, 1H, Ar-H), 10.93 (s, 1H, NH). Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N 6.33. Found: C, 65.20; H, 6.79; N, 6.33.

*2-(4-Chlorobenzamido)-5-methylbenzoic acid **3c***

Yield: 83.7%, m.p.: 233.2–233.5°C (from ethyl acetate / ethanol, 2 : 1). ESI-MS *m/z*: 288 $[M - H]^-$. ^{1}H-NMR (DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 7.49 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.66 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.86 (s, 1H, Ar-H), 7.94 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.53 (d, *J* = 8.8 Hz, 1H, Ar-H). Anal. Calcd. for $C_{15}H_{12}ClNO_3$: C, 62.19; H, 4.17; N, 4.83. Found: C, 61.99; H, 4.20; N, 4.66.

*2-(Furan-2-carboxamido)-5-methylbenzoic acid **3d***

Yield: 86.5%, m.p.: 202.4–202.8°C (from acetone / H_2O, 1 : 1). ESI-MS *m/z*: 244 $[M - H]^-$. ^{1}H-NMR (DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 6.76 (m, 1H, furan-H), 7.28 (d, *J* = 3.1 Hz, 1H, furan-H), 7.47 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.88 (s, 1H, furan-H), 8.00 (s, 1H, Ar-H), 8.58 (d, *J* = 8.5 Hz, 1H, Ar-H), 12.08 (s, 1H, NH). Anal. Calcd. for $C_{13}H_{11}NO_4 \cdot H_2O$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.07; H, 4.95; N, 5.35.

General procedure for the synthesis of 2-substituted 6-methylbenzoxazin-4-ones *4a–d*

A mixture of 2-(*N*-acylamino)-5-methylbenzoic acid **3a–e** (18 mmol) and acetic anhydride (26 mL) was heated under reflux for 1.5 h. After removing excess acetic anhydride under reduced pressure, the residue solidified to afford crude products **4a** and **4b**. In the preparation of **4c** and **4d**, the reaction mixtures were cooled to room temperature and left refrigerated overnight. The separated precipitate was collected by filtration to give the crude products **4c** and **4d**. The crude products were recrystallized from appropriate solvents to give compounds **4a–d**.

*6-Methyl-2-propyl-4H-benzo[d][1,3]oxazin-4-one **4a***

Yield: 86.4%, m.p.: 70.9–71.0°C (from cyclohexane). ESI-MS *m/z*: 204 $[M + H]^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 1.86 (m, 2H, $CH_3CH_2CH_2$), 2.47 (s, 3H, CH_3), 2.66 (t, *J* = 7.5 Hz, 2H, CH_2CH_2), 7.46 (d, *J* = 8.2 Hz, 1H, benzoxazinone 8-H), 7.60 (dd, *J* = 8.2 Hz and 1.6 Hz, 1H, benzoxazinone 7-H), 8.64 (d, *J* = 1.6 Hz, 1H, benzoxazinone 5-H). Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.51; H, 6.35; N, 6.93.

2-Isopropyl-6-methyl-4H-benzo[d][1,3]oxazin-4-one ***4b***

Yield: 88.9%, m.p.: 51.6 – 51.9°C (from petroleum ether). ESI-MS *m/z*: 204 [M + H]$^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.46 (s, 3H, CH_3), 2.93 (m, 1H, $(CH_3)_2CH$), 7.47 (d, *J* = 8.2 Hz, 1H, benzoxazinone 8-H), 7.59 (d, *J* = 8.2 Hz, 1H, benzoxazinone 7-H), 7.97 (s, 1H, benzoxazinone 5-H). Anal. Calcd. for $C_{12}H_{13}NO_2 \cdot 1/6\ H_2O$: C, 69.88; H, 6.52; N, 6.79. Found: C, 69.70; H, 6.52; N, 6.61.

2-(4-Chlorophenyl)-6-methyl-4H-benzo[d][1,3]oxazin-4-one ***4c***

Yield: 91.1%, m.p.: 190.6 – 190.8°C (from ethyl acetate / ethanol, 2 : 1). ESI-MS *m/z*: 272 [M + H]$^+$. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (s, 3H, CH_3), 7.47 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.60 (m, 2H, benzoxazinone 8-H and 7-H), 8.02 (s, 1H, benzoxazinone 5-H), 8.22 (d, 2H, *J* = 8.6 Hz, Ar-H). Anal. Calcd. for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71; N, 5.16. Found: C, 66.11; H, 3.74; N, 4.99.

2-(Furan-2-yl)-6-methyl-4H-benzo[d][1,3]oxazin-4-one ***4d***

Yield: 80.4%, m.p.: 154.7 – 155.0°C (from cyclohexane). ESI-MS *m/z*: 228 [M + H]$^+$. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (s, 3H, CH_3), 6.61 (m, 1H, furan-H), 7.34 (dd, *J* = 3.4 and 0.6 Hz, 1H, furan-H), 7.65 (m, 3H, benzoxazinone 8-H, 7-H and furan-H), 8.01 (s, 1H, benzoxazinone 5-H). Anal. Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 69.09; H, 4.04; N, 6.17.

General procedure for the synthesis of 2-substituted 6-methylquinazolin-4(3*H*)-ones *5a – d*

A mixture of 2-substituted 6-methylbenzoxazin-4-one **4a – e** and formamide (40 mL) was stirred at 150-155°C for 3 h. After cooling to room temperature, water (100 mL) was added into the reaction mixture and the formed solid was collected by filtration and was recrystallized from appropriate solvent to afford compounds **5a – d**.

6-Methyl-2-propylquinazolin-4(3H)-one ***5a***

Yield: 70.5%, m.p.: 244.3 – 244.8°C (from acetic acid). ESI-MS *m/z*: 203 [M + H]$^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (t, *J* = 7.3 Hz, 3H, CH_3CH_2), 1.93 (m, 2H, $CH_3CH_2CH_2$), 2.53 (s, 3H, CH_3), 2.81 (t, *J* = 7.6 Hz, 2H, CH_2CH_2), 7.63 (m, 2H, quinazolinone 7-H and 8-H), 8.09 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{12}H_{14}N_2O \cdot 1/10$ AcOH: C, 70.46; H, 7.02; N, 13.36. Found: C, 70.46; H, 7.02; N, 13.45.

2-Isopropyl-6-methylquinazolin-4(3H)-one ***5b***

Yield: 69.4%, m.p.: 244.3 – 244.8°C (from acetic acid). ESI-MS *m/z*: 203 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (d, *J* = 6.7 Hz, 6H, $(CH_3)_2CH$), 2.42 (s, 3H, CH_3), 2.88 (m, 1H, $(CH_3)_2CH$), 7.52 (d, *J* = 8.2 Hz, 1H, quinazolinone 8-H), 7.60 (d, *J* = 8.2 Hz, 1H, quinazolinone 7-H), 7.88 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.12; H, 7.00; N, 13.64.

2-(4-Chlorophenyl)-6-methylquinazolin-4(3H)-one ***5c***

Yield: 73.4%, m.p.: 311 – 312°C (from acetic acid). ESI-MS *m/z*: 271 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.47 (s, 3H, CH_3), 7.63 (m, 4H, quinazolinone 7-H, 8-H and Ar-H), 7.96 (s, 1H, quinazolinone 5-H), 8.19 (d, *J* = 8.7 Hz, 2H, Ar-H). Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.50; H, 4.12; N, 10.06.

2-(Furan-2-yl)-6-methylquinazolin-4(3H)-one ***5d***

Yield: 56.5%, m.p.: 260.4 – 261.4°C (from methanol). ESI-MS *m/z*: 227 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 6.72 (m, 1H, furan-H), 7.21 (d, *J* = 3.4 Hz, 1H, furan-H), 7.36 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.73 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 7.95 (s, 1H, quinazolinone 5-H), 8.33 (s, 1H, furan-H), 12.64 (s, 1H, NH). Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.11; H, 4.51; N, 12.35.

General procedure for the synthesis of 2-substituted 6-bromomethylquinazolin-4(3*H*)-ones *6a – d*

2-Substituted 6-methylquinazolin-4(3*H*)-one **5a – d** (14 mmol), *N*-bromosuccinimide (NBS) (16 mmol) and benzoyl peroxide (0.2 mmol) were dissolved in trichloromethane (70 mL; for **5c**, 150 mL of trichloromethane was used). The resulting mixture was refluxed under the irradiation of 100-W tungsten lamp for 3 h. After cooling to room temperature, the separated solid was filtered and recrystallized from acetic acid to afford compounds **6a – d**.

6-Bromomethyl-2-propylquinazolin-4(3H)-one ***6a***

Yield: 66.7%, m.p.: >330°C. ESI-MS *m/z*: 281, 283 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 0.96 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 1.78 (m, 2H, $CH_3CH_2CH_2$), 2.69 (t, *J* = 7.5 Hz, 2H, CH_2CH_2), 4.88 (s, 2H, CH_2Br), 7.66 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.93 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.20 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{12}H_{13}BrN_2O$: C, 51.26; H, 4.66; N, 9.96. Found: C, 51.49; H, 4.87; N, 10.31.

6-Bromomethyl-2-isopropylquinazolin-4(3H)-one ***6b***

Yield: 50.5%, m.p.: >330°C. ESI-MS *m/z*: 281, 283 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (d, *J* = 6.7 Hz, 6H, $(CH_3)_2CH$), 2.91 (m, 1H, $(CH_3)_2CH$), 4.86 (s, 2H, CH_2Br), 7.63 (d, *J* = 8.2 Hz, 1H, quinazolinone 8-H), 7.85 (d, *J* = 8.2 Hz, 1H, quinazolinone 7-H), 8.16 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{12}H_{13}N_2OBr \cdot H_2O$: C, 50.46; H, 4.76; N, 9.81. Found: C, 50.50; H, 4.62; N, 9.66.

6-Bromomethyl-2-(4-chlorophenyl)quinazolin-4(3H)-one ***6c***

Yield: 55.3%, m.p.: 282.8 – 283.6°C. EI-MS *m/z*: 348, 350 [M$^+$]. ^{1}H-NMR (DMSO-d_6) δ: 4.87 (s, 2H, CH_2Br), 7.62 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.73 (d, *J* = 8.4 Hz, 1H, quinzolinone 8-H), 7.89 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.18 (m, 3H, quinazolinone 5-H and Ar-H). Anal. Calcd. for $C_{15}H_{10}ClNO_2Br$: C, 51.53; H, 2.88; N, 8.01. Found: C, 51.73; H, 3.01; N, 8.09.

6-(Bromomethyl)-2-(furan-2-yl)quinazolin-4(3H)-one ***6d***

Yield: 60.7%, m.p.: 265 – 267°C. EI-MS *m/z*: 304, 306 [M$^+$]. ^{1}H-NMR (DMSO-d_6) δ: 4.87 (s, 2H, CH_2Br), 6.77 (m, 1H, furan-H), 7.63 (d, *J* = 3.4 Hz, 1H, furan-H), 7.69 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.88 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 7.80 (s, 1H, furan-H), 8.19 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{13}H_9N_2O_2Br$: C, 51.17; H, 2.97; N, 9.18. Found: C, 51.40; H, 2.97; N, 9.14.

General procedure for the synthesis of compounds *8a – z*

A suspension of 1-substituted piperazine **7a – d** (2.4 mmol), carbon disulfide (0.72 mL, 12 mmol) and anhydrous potassium phosphate (0.51 g, 2.4 mmol) in *N,N*-dimethylformamide (15 mL)

was stirred at room temperature for 30 min. Then, bromomethyl compound **6** (2 mmol) was added and the stirring was continued for 2 h. The reaction mixture was poured into water (100 mL) and the formed solid was collected by filtration and purified by column chromatography (CC) on silica gel or recrystallization from appropriate solvent to give compounds **8a – z**.

(2-(Trifluoromethyl)-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-methylpiperazine-1-carbodithioate ***8a***

Yield: 64.7%, m.p.: 228.9 – 230.4°C (CC, eluent: dichloromethane / methanol, 95 : 5). CI-MS *m/z*: 403 $[M + H]^+$. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (s, 3H, NCH_3), 2.58 (t, *J* = 4.8 Hz, 4H, piperazine-H), 4.04 (br s, 2H, piperazine-H), 4.31 (br s, 2H, piperazine-H), 4.74 (s, 2H, CH_2S), 7.80 (d, *J* = 8.5 Hz, 1H, quinazolinone 8-H), 7.92 (d, *J* = 8.5 Hz, 1H, quinazolinone 7-H), 8.32 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{16}H_{17}F_3N_4OS_2$: C, 47.75; H, 4.26; N, 13.92. Found: C, 47.72; H, 4.29; N, 13.88.

(2-(Trifluoromethyl)-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-benzylpiperazine-1-carbodithioate ***8b***

Yield: 48.1%, m.p.: 201 – 203°C (CC, eluent: dichloromethane / methanol, 98 : 2). CI-MS *m/z*: 479 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.49 (s, 4H, piperazine-H), 3.55 (s, 2H, CH_2Ph), 3.93 (br s, 2H, piperazine-H), 4.24 (br s, 2H, piperazine-H), 4.77 (s, 2H, CH_2S), 7.31 (s, 5H, Ar-H), 7.76 (d, *J* = 8.5 Hz, 1H, quinazolinone 8-H), 7.91 (d, *J* = 8.5 Hz, 1H, quinazolinone 7-H), 8.18 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{22}H_{21}F_3N_4OS_2 \cdot {}^1/_3\,H_2O$: C, 54.53; H, 4.51; N, 11.56. Found: C, 54.46; H, 4.45; N, 11.97.

(2-(Trifluoromethyl)-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-phenylpiperazine-1-carbodithioate ***8c***

Yield: 54.8%, m.p.: 231 – 232°C (CC, eluent: dichloromethane / methanol, 98 : 2). CI-MS *m/z*: 465 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.29 (br s, 4H, piperazine-H), 4.08 (br s, 2H, piperazine-H), 4.38 (br s, 2H, piperazine-H), 4.80 (s, 2H, CH_2S), 6.81 (t, *J* = 7.2 Hz, 1H, Ar-H), 6.94 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.24 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.75 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.92 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.21 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{21}H_{19}F_3N_4OS_2 \cdot {}^1/_2\,H_2O$: C, 53.26; H, 4.26; N, 11.83. Found: C, 53.28; H, 4.26; N, 11.92.

(2-(Trifluoromethyl)-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-(4-fluorophenyl)piperazine-1-carbodithioate ***8d***

Yield: 67.0%, m.p.: 251.2 – 252.6°C (CC, eluent: dichloromethane / methanol, 98 : 2). CI-MS *m/z*: 483 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.22 (s, 4H, piperazine-H), 4.08 (br s, 2H, piperazine-H), 4.38 (br s, 2H, piperazine-H), 4.81 (s, 2H, CH_2S), 7.03 (m, 4H, Ar-H), 7.73 (d, *J* = 8.3 Hz, 1H, quinazolinone 8-H), 7.95 (d, *J* = 8.3 Hz, 1H, quinazolinone 7-H), 8.23 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{21}H_{18}F_4N_4OS_2$: C, 52.27; H, 3.76; N, 11.61. Found: C, 52.27; H, 3.86; N, 11.68.

(2-Ethyl-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-methylpiperazine-1-carbodithioate ***8e***

Yield: 87.5%, m.p.: 202 – 204°C (CC, eluent: dichloromethane / methanol, 9 : 1). ESI-MS *m/z*: 363 $[M + H]^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (t, *J* = 7.6 Hz, 3H, CH_3CH_2), 2.32 (s, 3H, NCH_3), 2.50 (s, 4H, piperazine-H), 2.82 (q, *J* = 7.6 Hz, 2H, CH_3CH_2), 3.91 (br s, 2H, piperazine-H), 4.34 (br s, 2H, piperazine-H), 4.71 (s, 2H, CH_2S), 7.63 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.77 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.23 (s, 1H, quinazolinone 5-H), 11.69 (br s, 1H, NH). Anal. Calcd. for $C_{17}H_{22}N_4OS_2 \cdot 4/3\,H_2O$: C, 52.82; H, 6.43; N, 14.49. Found: C, 52.84; H, 6.13; N, 14.86.

(2-Ethyl-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-benzylpiperazine-1-carbodithioate ***8f***

Yield: 65.8%, m.p.: 195.0 – 196.5°C (CC, eluent: dichloromethane / methanol, 95 : 5). ESI-MS *m/z*: 439 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (t, *J* = 7.5 Hz, 3H, CH_3CH_2), 2.45 (s, 4H, piperazine-H), 2.57 (q, *J* = 7.5 Hz, 2H, CH_3CH_2), 3.51 (s, 2H, CH_2Ph), 3.90 (br s, 2H, piperazine-H), 4.24 (br s, 2H, piperazine-H), 4.69 (s, 2H, CH_2S), 7.31 (s, 5H, Ar-H), 7.55 (d, *J* = 8.3 Hz, 1H, quinazolinone 8-H), 7.76 (d, *J* = 8.3 Hz, 1H, quinazolinone 7-H), 8.07 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{23}H_{26}N_4OS_2$: C, 62.98; H, 5.97; N, 12.77. Found: C, 62.61; H, 6.05; N, 12.77.

(2-Ethyl-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-phenylpiperazine-1-carbodithioate ***8g***

Yield: 86.6%, m.p.: 246 – 247°C (CC, eluent: dichloromethane / methanol, 99 : 1). CI-MS *m/z*: 425 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (t, *J* = 7.5 Hz, 3H, CH_3CH_2), 2.62 (q, *J* = 7.5 Hz, 2H, CH_3CH_2), 3.30 (br s, 4H, piperazine-H), 4.09 (br s, 2H, piperazine-H), 4.40 (br s, 2H, piperazine-H), 4.75 (s, 2H, CH_2S), 6.82 (t, *J* = 7.2 Hz, 1H, Ar-H), 6.95 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.25 (t, *J* = 7.9 Hz, 2H, Ar-H), 7.57 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.81 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.11 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{22}H_{24}N_4OS_2$: C, 62.23; H, 5.70; N, 13.20. Found: C, 62.36; H, 5.82; N, 13.10.

(2-Ethyl-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-(4-fluorophenyl)piperazine-1-carbodithioate ***8h***

Yield: 84.3%, m.p.: 251.1 – 251.3°C (from trichloromethane / methanol, 9 : 1). ESI-MS *m/z*: 442.1 $[M^+]$. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (t, *J* = 7.5 Hz, 3H, CH_3CH_2), 2.62 (q, *J* = 7.5 Hz, 2H, CH_3CH_2), 3.21 (br s, 4H, piperazine-H), 4.08 (br s, 2H, piperazine-H), 4.38 (br s, 2H, piperazine-H), 4.74 (s, 2H, CH_2S), 7.02 (m, 4H, Ar-H), 7.57 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.81 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.11 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{22}H_{23}FN_4OS_2$: C, 59.70; H, 5.24; N, 12.66. Found: C, 59.78; H, 5.26; N, 12.64.

(3,4-Dihydro-4-oxo-2-propylquinazolin-6-yl)methyl 4-methylpiperazine-1-carbodithioate ***8i***

Yield: 33.2%, m.p.: 225.5 – 226.0°C (CC, eluent: dichloromethane / methanol, 96 : 4). ESI-MS *m/z*: 377 $[M + H]^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (t, *J* = 6.8 Hz, 3H, CH_3CH_2), 1.92 (m, 2H, $CH_3CH_2CH_2$), 2.33 (s, 3H, NCH_3), 2.51 (br s, 4H, piperazine-H), 2.77 (t, *J* = 7.2 Hz, 2H, CH_2CH_2), 3.97 (br s, 2H, piperazine-H), 4.35 (br s, 2H, piperazine-H), 4.72 (s, 2H, CH_2S), 7.65 (d, *J* = 8.3 Hz, 1H, quinazolinone 8-H), 7.81 (d, *J* = 8.3 Hz, 1H, quinazolinone 7-H), 8.27 (s, 1H, quinazolinone 5-H), 11.86 (br s, 1H, NH). Anal. Calcd. for $C_{18}H_{24}N_4OS_2$: C, 57.42; H, 6.42; N, 14.88. Found: C, 57.28; H, 6.44; N, 14.90.

(3,4-Dihydro-4-oxo-2-propylquinazolin-6-yl)methyl 4-benzylpiperazine-1-carbodithioate ***8j***

Yield: 85.8%, m.p.: 186.3 – 186.8°C (from ethyl acetate). ESI-MS *m/z*: 452 $[M^+]$. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (t, *J* = 7.3 Hz, 3H, CH_3CH_2), 1.90

(m, 2H, $CH_3CH_2CH_2$), 2.53 (br s, 4H, piperazine-H), 2.76 (t, *J* = 7.6 Hz, 2H, CH_2CH_2), 3.54 (s, 2H, CH_2Ph), 3.93 (br s, 2H, piperazine-H), 4.35 (br s, 2H, piperazine-H), 4.71 (s, 2H, CH_2S), 7.30 (s, 5H, Ar-H), 7.63 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.80 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.25 (s, 1H, quinazolinone 5-H), 11.90 (br s, 1H, NH). Anal. Calcd. for $C_{24}H_{28}N_4OS_2$: C, 63.68; H, 6.24; N, 12.38. Found: C, 63.56; H, 6.30; N, 12.19.

(3,4-Dihydro-4-oxo-2-propylquinazolin-6-yl)methyl 4-phenylpiperazine-1-carbodithioate ***8k***

Yield: 69.6%, m.p.: 230.5 – 231.3°C (CC, eluent: dichloromethane / methanol, 99 : 1). ESI-MS *m/z*: 439 $[M + H]^+$. ^{1}H NMR ($CDCl_3$) δ: 1.08 (t, *J* = 6.4 Hz, 3H, CH_3CH_2), 1.92 (m, 2H, $CH_3CH_2CH_2$), 2.78 (t, *J* = 5.9 Hz, 2H, CH_2CH_2), 3.30 (br s, 4H, piperazine-H), 4.13 (br s, 2H, piperazine-H), 4.46 (br s, 2H, piperazine-H), 4.75 (s, 2H, CH_2S), 6.92 (m, 3H, Ar-H), 7.29 (m, 2H, Ar-H), 7.67 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.83 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.29 (s, 1H, quinazolinone 5-H), 11.60 (br s, 1H, NH). Anal. Calcd. for $C_{23}H_{26}N_4OS_2$: C, 62.98; H, 5.97; N, 12.77. Found: C, 62.82; H, 6.05; N, 12.76.

(3,4-Dihydro-4-oxo-2-propylquinazolin-6-yl)methyl 4-(4-fluorophenyl)piperazine-1-carbodithioate ***8l***

Yield: 74.6%, m.p.: 216.7 – 218.3°C (from DMF / H_2O, 2 : 1). ESI-MS *m/z*: 456 $[M^+]$. ^{1}H-NMR (DMSO-d_6) δ: 0.93 (t, *J* = 6.8 Hz, 3H, CH_3CH_2), 1.74 (m, 2H, $CH_3CH_2CH_2$), 2.61 (t, *J* = 7.2 Hz, 2H, CH_2CH_2), 3.21 (br s, 4H, piperazine-H), 4.10 (br s, 2H, piperazine-H), 4.37 (br s, 2H, piperazine-H), 4.74 (s, 2H, CH_2S), 7.03 (m, 4H, Ar-H), 7.56 (d, *J* = 8.2 Hz, 1H, quinazolinone 8-H), 7.80 (d, *J* = 8.2 Hz, 1H, quinazolinone 7-H), 8.11 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{23}H_{25}FN_4OS_2$: C, 60.50; H, 5.52; N, 12.27. Found: C, 60.41; H, 5.53; N, 12.30.

(3,4-Dihydro-2-isopropyl-4-oxoquinazolin-6-yl)methyl 4-methylpiperazine-1-carbodithioate ***8m***

Yield: 70.6%, m.p.: 242.9 – 243.9°C (CC, eluent: dichloromethane / methanol, 95 : 5). ESI-MS *m/z*: 377 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (d, *J* = 6.5 Hz, 6H, $(CH_3)_2CH$), 2.20 (s, 3H, NCH_3), 2.40 (br s, 4H, piperazine-H), 2.89 (m, 1H, $(CH_3)_2CH$), 3.91 (br s, 2H, piperazine-H), 4.23 (br s, 2H, piperazine-H), 4.71 (s, 2H, CH_2S), 7.58 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.81 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.09 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{18}H_{24}N_4OS_2$: C, 57.42; H, 6.42; N, 14.88. Found: C, 57.47; H, 6.56; N, 14.72.

(3,4-Dihydro-2-isopropyl-4-oxoquinazolin-6-yl)methyl 4-benzylpiperazine-1-carbodithioate ***8n***

Yield: 62.7%, m.p.: 215.1 – 216.9°C (from DMF / H_2O, 2 : 1). ESI-MS *m/z*: 453 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.25 (d, *J* = 6.8 Hz, 6H, $(CH_3)_2CH$), 2.45 (br s, 4H, piperazine-H), 2.90 (m, 1H, $(CH_3)_2CH$), 3.51 (s, 2H, CH_2Ph), 3.92 (br s, 2H, piperazine-H), 4.24 (br s, 2H, piperazine-H), 4.70 (s, 2H, CH_2S), 7.31 (s, 5H, Ar-H), 7.56 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.78 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.09 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{24}H_{28}N_4OS_2 \cdot \frac{1}{4}H_2O$: C, 63.06; H, 6.28; N, 12.26. Found: C, 62.98; H, 6.23; N, 12.27.

(3,4-Dihydro-2-isopropyl-4-oxoquinazolin-6-yl)methyl 4-phenylpiperazine-1-carbodithioate ***8o***

Yield: 61.2%, m.p.: 227.3 – 228.9°C (from DMF / H_2O, 2 : 1). ESI-MS *m/z*: 439 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2CH$), 2.90 (m, 1H, $(CH_3)_2CH$), 3.29 (br s, 4H, piperazine-H), 4.11 (br s, 2H, piperazine-H), 4.35 (br s, 2H, piperazine-H), 4.75 (s, 2H, CH_2S), 6.82 (t, *J* = 6.9 Hz, 1H, Ar-H), 6.95 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.25 (t, *J* = 7.9 Hz, 2H, Ar-H), 7.58 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.81 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.12 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{23}H_{26}N_4OS_2$: C, 62.98; H, 5.97; N, 12.77. Found: C, 62.84; H, 6.06; N, 12.82.

(3,4-Dihydro-2-isopropyl-4-oxoquinazolin-6-yl)methyl-4-(4-fluorophenyl)piperazine-1-carbodithioate ***8p***

Yield: 59.9%, m.p.: 243.9 – 246.3°C (from DMF / H_2O, 2 : 1). ESI-MS *m/z*: 457 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (d, *J* = 6.8 Hz, 6H, $(CH_3)_2CH$), 2.90 (m, 1H, $(CH_3)_2CH$), 3.21 (br s, 4H, piperazine-H), 4.16 (br s, 2H, piperazine-H), 4.28 (br s, 2H, piperazine-H), 4.74 (s, 2H, CH_2S), 7.02 (m, 4H, Ar-H), 7.58 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.80 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.11 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{23}H_{25}N_4OS_2$: C, 60.50; H, 5.52; N, 12.27. Found: C, 60.48; H, 5.53; N, 12.21.

(2-Benzyl-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-methylpiperazine-1-carbodithioate ***8q***

Yield: 26.8%, m.p.: 208.6 – 209.4°C (CC, eluent: dichloromethane / methanol, 95 : 5). ESI-MS *m/z*: 425 $[M + H]^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.19 (s, 3H, NCH_3), 2.38 (br s, 4H, piperazine-H), 3.93 (br s, 3H, piperazine-H and CH_2Ph), 4.22 (br s, 2H, piperazine-H), 4.71 (s, 2H, CH_2S), 7.31 (m, 5H, Ar-H), 7.56 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.78 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.07 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{22}H_{24}N_4OS_2 \cdot \frac{1}{2}H_2O$: C, 60.94; H, 5.81; N, 12.92. Found: C, 61.14; H, 5.67; N, 13.11.

(2-Benzyl-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-benzylpiperazine-1-carbodithioate ***8r***

Yield: 82.7%, m.p.: 176 – 178°C (CC, eluent: dichloromethane / methanol, 95 : 5). ESI-MS *m/z*: 500 $[M^+]$. ^{1}H-NMR (DMSO-d_6) δ: 2.44 (s, 4H, piperazine-H), 3.50 (s, 2H, CH_2Ph), 3.93 (br s, 4H, piperazine-H and CH_2Ph), 4.24 (br s, 2H, piperazine-H), 4.69 (s, 2H, CH_2S), 7.31 (s, 5H, Ar-H), 7.35 (s, 5H, Ar-H), 7.55 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.77 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.08 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{28}H_{28}N_4OS_2 \cdot 1/3\ H_2O$: C, 66.37; H, 5.70; N, 11.06. Found: C, 66.65; H, 5.69; N, 11.30.

(2-Benzyl-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-phenylpiperazine-1-carbodithioate ***8s***

Yield: 72.6%, m.p.: 218.9 – 221.6°C (from DMF / H_2O, 2 : 1). ESI-MS *m/z*: 486 $[M^+]$. ^{1}H-NMR (DMSO-d_6) δ: 3.28 (br s, 4H, piperazine-H), 3.94 (s, 2H, CH_2Ph), 4.07 (br s, 2H, piperazine-H), 4.36 (br s, 2H, piperazine-H), 4.74 (s, 2H, CH_2S), 6.82 (t, *J* = 7.3 Hz, 1H, Ar-H), 6.95 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.30 (m, 7H, Ar-H), 7.58 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.82 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.11 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{27}H_{26}N_4OS_2$: C, 66.64; H, 5.39; N, 11.51. Found: C, 66.77; H, 5.47; N, 11.44.

(2-Benzyl-3,4-dihydro-4-oxoquinazolin-6-yl)methyl 4-(4-fluorophenyl)piperazine-1-carbodithioate ***8t***

Yield: 62.5%, m.p.: 202.6 – 204.1°C (from DMF / H_2O, 2 : 1). ESI-MS *m/z*: 504 [M^+]. ^{1}H-NMR (DMSO-d_6) δ: 3.20 (br s, 4H, piperazine-H), 3.93 (s, 2H, CH_2Ph), 4.07 (br s, 2H, piperazine-H), 4.35 (br s, 2H, piperazine-H), 4.73 (s, 2H, CH_2S), 7.01 (m, 4H, Ar-H), 7.30 (m, 5H, Ar-H), 7.57 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.80 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.10 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{27}H_{25}FN_4OS_2$: C, 64.26; H, 4.99; N, 11.10. Found: C, 64.27; H, 5.05; N, 11.20.

(3,4-Dihydro-4-oxo-2-phenylquinazolin-6-yl)methyl 4-methylpiperazine-1-carbodithioate ***8u***

Yield: 41.7%, m.p.: 275.8 – 275.9°C (CC, eluent: dichloromethane / methanol, 95 : 5). ESI-MS *m/z*: 411 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.36 (s, 3H, NCH_3), 2.44 (br s, 4H, piperazine-H), 3.95 (br s, 2H, piperazine-H), 4.26 (br s, 2H, piperazine-H), 4.76 (s, 2H, CH_2S), 7.58 (m, 3H, Ar-H), 7.71 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.85 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.18 (m, 3H, quinazolinone 5-H and Ar-H). Anal. Calcd. for $C_{21}H_{22}N_4OS_2 \cdot {}^1/_3\,H_2O$: C, 60.55; H, 5.48; N, 13.45. Found: C, 60.74; H, 5.43; N, 13.44.

(3,4-Dihydro-4-oxo-2-phenylquinazolin-6-yl)methyl 4-benzylpiperazine-1-carbodithioate ***8v***

Yield: 82.6%, m.p.: 228.1 – 229.0°C (CC, eluent: dichloromethane / methanol, 97 : 3). ESI-MS *m/z*: 486 [M^+]. ^{1}H-NMR (DMSO-d_6) δ: 2.46 (br s, 4H, piperazine-H), 3.51 (s, 2H, CH_2Ph), 3.92 (br s, 2H, piperazine-H), 4.24 (br s, 2H, piperazine-H), 4.73 (s, 2H, CH_2S), 7.31 (m, 5H, Ar-H), 7.55 (m, 3H, Ar-H), 7.69 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.84 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.12 (m, 3H, quinazolinone 5-H and Ar-H). Anal. Calcd. for $C_{27}H_{26}N_4OS_2$: C, 66.64; H, 5.39; N, 11.51. Found: C, 66.64; H, 5.45; N, 11.47.

(3,4-Dihydro-4-oxo-2-phenylquinazolin-6-yl)methyl 4-phenylpiperazine-1-carbodithioate ***8w***

Yield: 32.7%, m.p.: 261.5 – 262.3°C (from DMF). ESI-MS *m/z*: 473 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.29 (s, 4H, piperazine-H), 4.08 (br s, 2H, piperazine-H), 4.38 (br s, 2H, piperazine-H), 4.78 (s, 2H, CH_2S), 6.80 (t, *J* = 7.2 Hz, 1H, Ar-H), 6.93 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.23 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.57 (m, 3H, Ar-H), 7.70 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.86 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.17 (m, 3H, quinazolinone 5-H and Ar-H), 12.56 (br s, 1H, NH). Anal. Calcd. for $C_{26}H_{24}N_4OS_2$: C, 66.07; H, 5.12; N, 11.85. Found: C, 65.86; H, 5.11; N, 12.01.

(3,4-Dihydro-4-oxo-2-phenylquinazolin-6-yl)methyl 4-(4-fluorophenyl)piperazine-1-carbodithioate ***8x***

Yield: 46.3%, m.p.: 263.3 – 264.1°C (from DMF). CI-MS *m/z*: 491 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.22 (s, 4H, piperazine-H), 4.08 (br s, 2H, piperazine-H), 4.39 (br s, 2H, piperazine-H), 4.78 (s, 2H, CH_2S), 6.99 (m, 4H, Ar-H), 7.56 (m, 3H, Ar-H), 7.70 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.86 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 8.20 (m, 3H, quinazolinone 5-H and Ar-H), 12.56 (br s, 1H, NH). Anal. Calcd. for $C_{26}H_{23}FN_4OS_2$: C, 63.65; H, 4.73; N, 11.42. Found: C, 63.59; H, 4.83; N, 11.37.

(2-(4-Chlorophenyl)-3,4-dihydro-4-oxoquinazolin-6-yl)methyl4-(4-fluorophenyl)piperazine-1-carbodithioate ***8y***

Yield: 50.2%, m.p.: 315 – 317°C (from DMF / H_2O, 2 : 1). ESI-MS *m/z*: 525 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.22 (br s, 4H, piperazine-H), 4.21 (br m, 4H, piperazine-H), 4.78 (s, 2H, CH_2S), 7.01 (m, 4H, Ar-H), 7.62 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.71 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.87 (d, *J* =8.4 Hz, 1H, quinazolinone 7-H), 8.17 (m, 3H, quinazolinone 5-H and Ar-H). Anal. Calcd. for $C_{26}H_{22}ClFN_4OS_2$: C, 59.47; H, 4.22; N, 10.67. Found: C, 59.19; H, 4.25; N, 10.50.

(2-(Furan-2-yl)-3,4-dihydro-4-oxoquinazolin-6-yl)methyl4-(4-fluorophenyl)piperazine-1-carbodithioate ***8z***

Yield: 54.6%, m.p.: 253.0 – 253.8°C (from DMF / H_2O, 2 : 1). ESI-MS *m/z*: 481 [M + H]$^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.22 (br s, 4H, piperazine-H), 4.16 (br s, 2H, piperazine-H), 4.33 (br s, 2H, piperazine-H), 4.76 (s, 2H, CH_2S), 6.75 (m, 1H, furan-H), 7.05 (m, 4H, Ar-H), 7.60 (d, *J* = 3.3 Hz, 1H, furan-H), 7.66 (d, *J* = 8.4 Hz, 1H, quinazolinone 8-H), 7.84 (d, *J* = 8.4 Hz, 1H, quinazolinone 7-H), 7.97 (s, 1H, furan-H), 8.15 (s, 1H, quinazolinone 5-H). Anal. Calcd. for $C_{24}H_{21}FN_4O_2S_2 \cdot {}^1/_5\,H_2O$: C, 59.53; H, 4.45; N, 11.57. Found: C, 59.55; H, 4.36; N, 11.59.

References

[1] I. M. Kompis, K. Islam, R. L. Then, *Chem. Rev.* **2005**, *105*, 593 – 620.

[2] D. Cunningham, J. Zalcberg, J. Maroun, R. James, *et al.*, *Eur. J. Cancer* **2002**, *38*, 478 – 486.

[3] K. Pawelczak, M. Makowski, M. Kempny, J. M. Dzik, *et al.*, *Acta Biochim. Pol.* **2002**, *49*, 407 – 420.

[4] C.-G. Cheong, D. W. Wolan, S. E. Greasley, P. A. Horton, *et al.*, *J. Biol. Chem.* **2004**, *279*, 18034 – 18045.

[5] S. T. Al – Rashood, I. A. Aboldahab, M. N. Nagi, L. A. Abouzeid, *et al.*, *Bioorg. Med. Chem.* **2006**, *14*, 8608 – 8621.

[6] E. Chu, M. A. Callender, M. P. Farrell, J. C. Schmitz, *Cancer Chemother. Pharmacol.* **2003**, *52*, S80 – S89.

[7] A. Gangjee, H. D. Jain, J. Phan, R. L. Kisliuk, *J. Heterocycl. Chem.* **2005**, *42*, 165 – 168.

[8] A. Gangjee, H. D. Jain, R. L. Kisliuk, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2225 – 2230.

[9] C. Gerhauser, M. You, J. Liu, R. M. Moriarty, *et al.*, *Cancer Res.* **1997**, *57*, 272 – 278.

[10] M. Sabol, P. Kutschy, L. Siegfried, A. Mirossay, *et al., Biologia* **2000**, *55*, 701 – 707.

[11] A. Scozzafava, A. Mastrolorenzo, C. T. Supuran, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1887 – 1891.

[12] M. Pilatova, M. Sarissky, P. Kutschy, A. Mirossay, *et al.*, *Leuk. Res.* **2005**, *29*, 415 – 421.

[13] O. Guzel, A. Salman, *Bioorg. Med. Chem.* **2006**, *14*, 7804 – 7815.

[14] P. Gaspari, T. Banerjee, W. P. Malachowski, A. J. Muller, *et al.*, *J. Med. Chem.* **2006**, *49*, 684 – 692.

[15] F. Liu, S. Y. Liu, Y. Liu, D. X. Han, *et al.*, *Chin. Sci. Bull.* **2007**, *52*, 3200 – 3206.

[16] S. L. Cao, Y. P. Feng, Y. Y. Jiang, S. Y. Liu, *et al.*, *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1915 – 1917.

[17] S. L. Cao, Y. Y. Jiang, Y. P. Feng, S. Y. Liu, *et al.*, *Yaoxue Xuebao* **2007**, *42*, 741 – 746.

[18] P. R. Marsham, P. Chambers, A. J. Hayter, L. R. Hughes, *et al.*, *J. Med. Chem*. **1989**, *32*, 569 – 575.

[19] L. R. Hughes, A. L. Jackman, J. Oldfield, R. C. Smith, *et al.*, *J. Med. Chem*. **1990**, *33*, 3060 – 3067.

[20] S. L. Cao, Y. P. Feng, H. H. Gao, K. R. Feng, *Yingyong Huaxue* **2005**, *22*, 1027 – 1029.

[21] S. L. Cao, Y. P. Feng, X. L. Zheng, Y. Y. Jiang, *et al.*, *Arch. Pharm. Chem. Life Sci.* **2006**, *339*, 250 – 254.

[22] S. L. Cao, X. Q. Ma, *Huaxue Shiji* **2004**, *26*, 27 – 28.

