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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis and biological evaluation of some novel substituted 2-mercapto-3-phenethylquinazolines as antitumor agents

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Abstract A novel series of 2-(substituted thio)-3-phenethylquinazolin-4(3*H*)-one and 2-([5-mercapto-4-(substituted)-4*H*-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3*H*)-one (**1**–**25**) were designed, synthesized, and evaluated for their in vitro antitumor activity. A single dose (10 μM) of the test compounds was used in the National Cancer Institute (NCI) 60 cell lines panel assay. Compound **2** showed sensible selective activities toward renal and breast cancer cell lines, whereas breast cancer cell lines showed moderate sensitivity to compound **13**. At the same time, compound **22** yielded reasonable selective activities toward leukemia and non-small cell lung cancer cell lines. The results achieved can be used as a useful template for future development and further derivatization or modification to obtain more potent and selective antitumor agents.

Keywords Synthesis · Quinazoline · In-vitro antitumor evaluation · Selective activity · NCI

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Introduction

Cancer is continuing to be a major health problem in developed as well as undeveloped countries (Xue *et al.*, 2004; Honkanen *et al.*, 1983; Zhou *et al.*, 2004; Pannerselvam *et al.*, 2003; Refaie *et al.*, 2005). The great cancer incidence worldwide increases the search for new, safer and efficient anticancer agents, aiming the prevention or the cure of this illness. In spite of all the efforts to combat cancer, the success of the treatment of certain types of tumors has shown little progress due to their aggressiveness and the mechanisms of malignant cell metastasis. Although many classes of drugs are being used for the treatment of cancer, the need for more potent selective antitumor agents is still not precluded.

Quinazolines are frequently used in medicine because of their wide spectrum of biologic activities (Zhou *et al.*, 2004; Aziza *et al.*, 1996; El-Azab, 2007; Habib *et al.*, 2000; Al-Omar *et al.*, 2006; Alafeefy *et al.*, 2008; Kumar *et al.*, 2003; Alagarsamy *et al.*, 2007; El-Azab *et al.*, 2011; El-Azab and Eltahir, 2012a, b; Kashaw *et al.*, 2009; Archana and Kumar, 2004; El-Azab and Eltahir, 2012a, b; Al-Omary *et al.*, 2010; Al-Obaid *et al.*,2009; El-Azab *et al.*, 2010; Al-Rashood *et al.*, 2006; Abdel Gawad *et al.*, 2010). In the scope of identifying various chemical substances which may serve as leads for designing novel antitumor agents, we are particularly interested in the present study with quinazoline derivatives which have been identified as a new class of cancer chemotherapeutic agents with significant therapeutic efficacy against solid tumors (Al-Omary *et al.*, 2010; Al-Obaid *et al.*,2009; El-Azab *et al.*, 2010; Al-Rashood *et al.*, 2006; Abdel Gawad *et al.*, 2010).

Quinazolines as anticancer agents have attracted increased interest since the discovery of raltitrexed **I** and thymitaq **II** (Fig. 1), Moreover, many quinazolines

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contributed to the quest for an ultimate antitumor chemotherapeutic agent (Al-Omary *et al.*, 2010; Al-Obaid *et al.*, 2009). Interestingly, it was reported that 2-thioxo-3-benzylquinazolinones and their S-methylthioether counterparts **IV** (Fig. 1) showed promising antitumor potency (Abdel Gawad *et al.*, 2010). In addition, 2-(2-oxo-2-substituted phenylethylthio)-4(3*H*)-quinazolinone (**III**) (Fig. 1) revealed effective antitumor activity (Abdel Gawad *et al.*, 2010).

We have recently studied a series of substituted quinazoline derivatives which were evaluated for their antitumor activities (El-Azab and Eltahir, 2012a; Al-Obaid *et al.*, 2009; El-Azab *et al.*, 2010). Continuing our studies on quinazoline derivatives as attractive antitumor candidates, we have designed a number of new quinazoline derivatives containing 2-substituted mercapto fragments and have biologically evaluated their in vitro antitumor activities (Fig. 1).

In the present study, the substitution pattern at the 2-substituted mercaptoquinazoline pharmacophores was selected based on different electronic environments which would affect the lipophilicity, and hence the activity of the target molecules. The objective of forming these hybrids is an attempt to attain an active antitumor agent with potentiated activity and selectivity toward cancerous cells.

Results and discussion

Chemistry

Synthesis of 2-mercapto-3-phenethylquinazolin-4(3*H*)-one (**1**) as a first key intermediate was achieved by the reaction of anthranilic acid with 2-phenylethyl isothiocyanate in absolute ethanol in 78 % yield. Reaction of compound **1** with various halides in acetone in the presence of potassium carbonate at room temperature gave the corresponding 2-(substituted thio)-3-phenethylquinazolin-4(3*H*)-ones **2**–**14** in 81–95 % yield, (Scheme 1).

On the other hand, 2-mercapto-3-phenethylquinazolin-4(3*H*)-one (**1**) was reacted with ethyl bromoacetate in dry acetone in the presence of potassium carbonate at room temperature thereby affording 95 % yield of ethyl-2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetate (**15**) which was treated with hydrazine hydrate in ethanol at room temperature to furnish 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (**16**) as a second key intermediate in 90 % yield. Reaction of acid hydrazide **16** with various isothiocyanates in ethanol at room temperature produced *N*-(substituted)-2-[2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetyl]hydrazinecarbothioamides **17**–**21** in 80–86 % yield. Compounds **17**–**21** were cyclized according to the reported procedure (El-Azab *et al.*, 2011) to the corresponding 2-([5-mercapto-4-(substituted)-4*H*-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3*H*)-ones **22**–**25** by boiling in ethanol containing triethylamine. Compounds **22**–**25** were also obtained in another pathway by treatment of **16** with various isothiocyanates in boiling ethanol containing triethylamine in 85–90 % yield (Scheme 2).

Antitumor screening

The synthesized compounds **1**–**25** were subjected to the National Cancer Institute (NCI) in vitro disease-oriented human cells screening panel assay for in vitro antitumor activity. A single dose (10 μM) of the test compounds was used in the full NCI 60 cell lines panel assay which includes nine tumor subpanels, namely Leukemia, Non-small cell lung, Colon, CNS, Melanoma, Ovarian, Renal, Prostate, and Breast cancer cells. (Grever *et al.*, 1992;

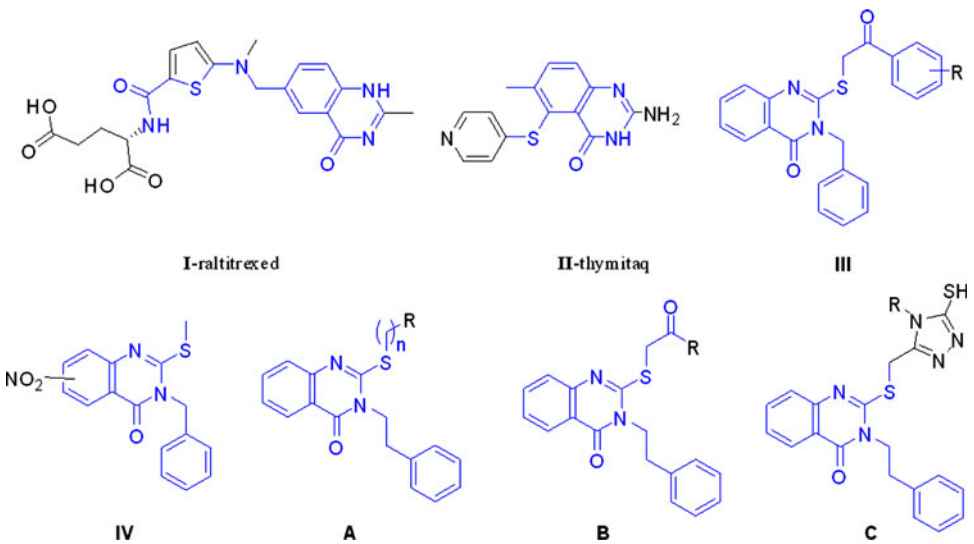
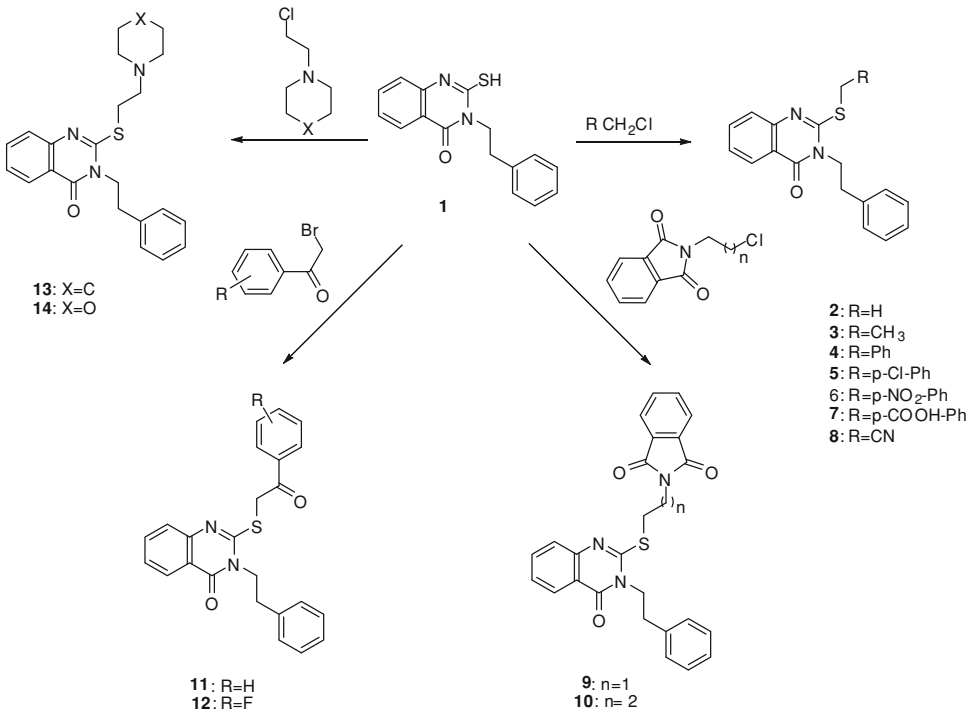
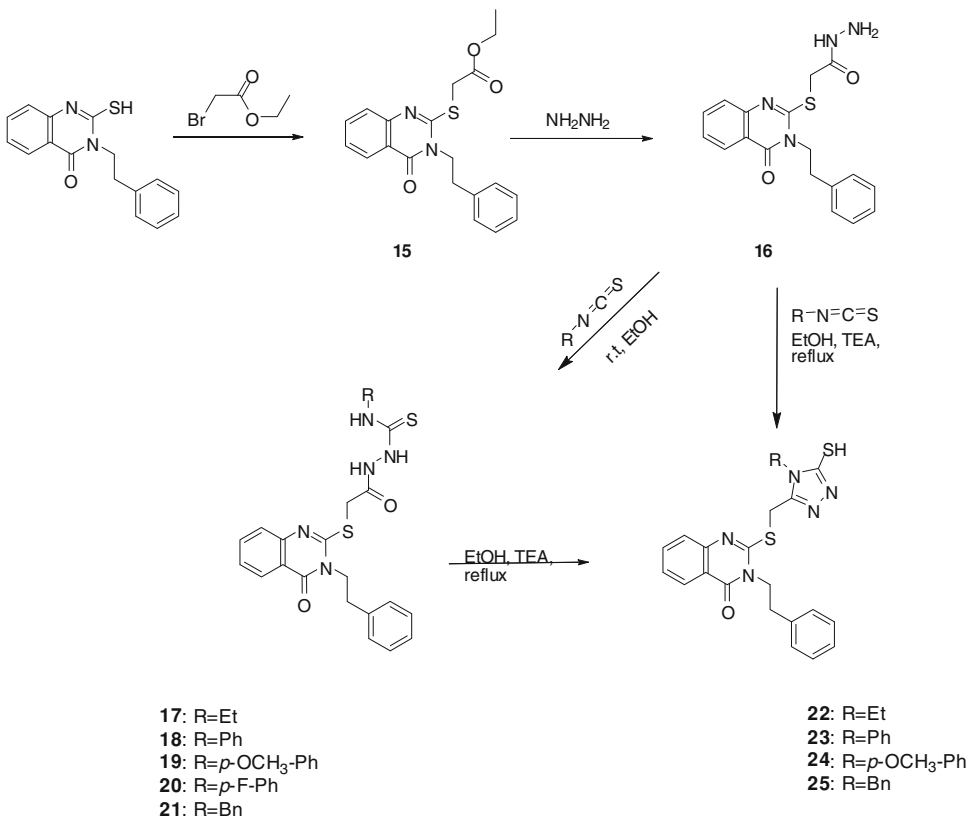


Fig. 1 Reported and proposed quinazoline derivatives as antitumor agents.

Scheme 1 Reactions of 2-mercapto-3-phenethylquinazolin-4(3*H*)-one (**1**) with various halides



Scheme 2 Synthesis and reactions of 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (**16**)



Monks *et al.*, 1991; Boyd and Paull, 1995). The data reported as mean-graph of the percent growth of the treated cells, and presented as percentage growth inhibition (GI %) caused by the test compounds (Table 1).

With regard to selective antitumor activity, close examination of the data presented in Table 1 revealed that compound **2** showed sensible selective activities toward renal and breast cancer cell lines, whereas compound **22**

Table 1 Percentage growth inhibition (GI %) of in vitro subpanel tumor cell lines at 10 μM concentration

Subpanel tumor cell lines	% Growth inhibition (GI %)											
	1	**2**	**6**	**10**	**11**	**12**	**13**	**14**	**22**	**23**	**24**	**25**
Leukemia												
HL-60(TB)	11	nt	nt	nt	nt	nt	nt	nt	30	nt	nt	nt
MOLT-4	23	nt	nt	nt	nt	nt	nt	nt	29	nt	nt	nt
CCRF-CEM	16	nt	nt	nt	nt	nt	nt	nt	27	28	13	13
Non-small cell lung cancer												
A549/ATCC	–	12	16	18	18	11	13	10	16	–	–	12
EKVX	18	29	19	16	18	16	30	–	15	31	31	17
HOP-62	26	12	–	–	–	–	11	–	22	24	–	–
NCI-H226	–	11		–	–	–	–	–	35	–	–	22
NCI-H23	–	16	15	–	–	20	23	–	–	–	–	–
NCI-H322 M	–	–	–	–	–	13	–	–	27	–	–	–
NCI-H460	–	–	–	–	–	–	–	–	31	–	–	
NCI-H522	–	10	–	13	11	–	11	–	L	–	–	46
Colon cancer												
COLO 205	–	19	–	–	–	–	25	–	–	–	–	–
HCC-2998	–	–	–	–	–	–	–	–	–	–	–	–
HCT-116	18	37	20	21	19	18	27	–	35	–	–	24
HCT-15	–	39	–	31	–	–	20	–	12	25	25	–
HT29	–	–	15	13	–	–	70	–	–	–	–	–
KM12	–	28	–	–	–	–	–	–	–	–	–	–
SW-620	–	12	–	–	–	–	11	–	–	–	–	–
CNS cancer												
SF-268	–	10	–	–	–	25	–	–	–	–	–	–
SF-295	13	–	–	–	18	–	13	–	–	12	12	–
SF-539	–	–	–	–	–	13	10	–	–	–	–	–
SNB-19	–	–	–	–	–	–	–	–	–	–	–	–
SNB-75	–	–	–	–	18	–	13	–	–	–	–	–
U251	–	12	–	15	11	19	14	–	–	11	11	–
Melanoma												
LOX IMVI	–	11	–	–	–	–	19	–	26	10	10	14
MALME-3M	–	–	–	–	14	–	–	–	–	–	–	–
M14	–	–	–	–	–	–	–	–	12	–	–	–
MDA-MB-435	–	47	–	–	–	–	–	–	16	–	–	–
SK-MEL-28	–	–	–	–	–	–	–	–	–	–	–	–
SK-MEL-5	13	19	–	43	–	–	24	–	18	24	24	–
UACC-257	–	–	–	–	–	–	–	–	12		–	–
UACC-62	20	12	22	26	16	–	–	–	15	19	19	17
Ovarian cancer												
IGROV1	–	24	–	–	–	21	22	–	–	16	16	–
OVCAR-3	–	–	–	–	–	–	–	–	–	–	–	–
OVCAR-4	–	21	–	–	–	–	14	–	15	–	–	–
OVCAR-5	–	–	–	–	–	–	12	–	–	–	–	–
OVCAR-8	–	–	–	–	15	31	–	–	11	–	–	–
NCI/ADR-RES	–	18	12	–	10	10	13	–	27	–	–	16
SK-OV-3	–	–	–	12	–	–	–	–	–	–	–	–
Renal cancer												
786-0	–		–	13	10	32	14	–	19	–	–	–

Table 1 continued

Subpanel tumor cell lines	% Growth inhibition (GI %)											
	1	**2**	**6**	**10**	**11**	**12**	**13**	**14**	**22**	**23**	**24**	**25**
A498	46	18	–	20	46	–	17	–	–	41	51	–
ACHN	–	34	–	–	–	24	–	–	15	–	–	–
CAKI-1	–	–	17	34	22	21	27	–	–	17	17	–
RXF 393	–	30	–	–	–	–	19	–	–	–	–	–
SN12C	–	–	–	–	–	–	–	–	–	–	–	–
TK-10	–	–	–	–	–	–	–	–	–	–	–	–
UO-31	33	37	–	19	22	42	43	14	24	30	30	–
Prostate cancer												
PC-3	13	33	–	51	14	13	–	14	17	30	30	12
DU-145	–	–	24	–	–	–	11	–	–	–	–	–
Breast cancer												
MCF7	31	34	–	–	–	10	37	–	16	28	28	27
MDA-MB-231/ATCC	–	30	19	14	11	23	34	–	18	20	20	28
HS 578T	–	14	19		–	25	–	–	–	–	–	–
BT-549	–	–	–	–	–	–	14	–	28	–	–	–
T-47D	–	59	15	30	–	18	35		27	38	–	38
MDA-MB-468	22	84	3	–	14	–	–	–	15	–	38	–

nt not tested, – GI < 10 %, *L* compound proved lethal to the cancer cell line

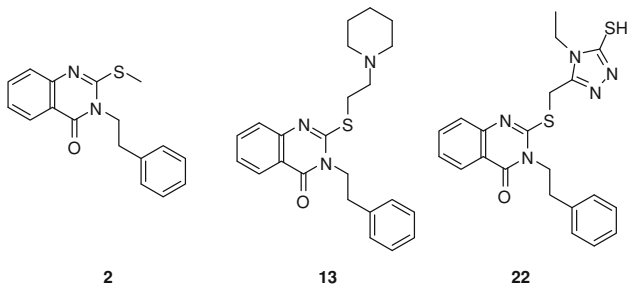


Fig. 2 Structures of the most active antitumor agents

yielded reasonable selective activities toward leukemia and non-small cell lung cancer cell lines. At the same time, breast cancer cell lines showed moderate sensitivity to compound **13** (Fig. 2).

Regarding the activity toward individual cell lines, compounds **1** and **22** showed selective activities against leukemia cell lines HL-60 (TB), MOLT-4, and CCRF-CEM with GI values of 11, 23, 16 % and 30, 29, 27 %, respectively, while compounds **23** and **25** illustrated certain activities against leukemia CCRF-CEM cell lines with GI values of 28 and 13 %, respectively.

Non-small cell lung EKVX cell line proved to be selectively sensitive to **2**, **13**, **23,**, and **24** with GI values of 29, 30, 31, and 31 %, respectively. In addition, compounds **1**, **22**, and **23** proved to be susceptible to the HOP-62 cell line with GI values of 26, 22, and 24 %, respectively. Compounds **12** and **13** have sensible activity against NCI-H23 cell lines with GI values of 20 and 23 %; meanwhile, compound **22** showed moderate activity against NCI-H322 M cell line in 27 %, NCI-H226 in 35 %, and lethal effect on NCI-H522 cancer cells. Compound **25** showed practical effect against NCI-H226 and NCI-H522 cancer cells in 22 and 46 %, respectively.

With respect to colon cancer, compounds **2**, **5**, **10**, **13**, **22**, and **25** showed GI values of 37, 20, 21, 27, 35, and 24 % with colon HCT-116 cell line, while **2**, **10**, **13**, **23,**, and **24** demonstrated moderate activities against HCT-15 cancer cell line with GI values 39, 34, 20, 25, and 25 %, respectively. On the other hand, compound **15** verified sensitivity in 25 and 70 % to colon COLO 205 and HT29 cancer cells, while compound **2** showed activity toward colon KM12 cell line with GI value 28 %.

Concerning CNS cancer, compound **12** showed certain activities against CNS SF-268 and U251 cancer cells lines with GI values of 25 and 19, respectively.

Regarding Melanoma, compounds **2** and **22** are active against MDA-MB-435 and LOX IMVI cell lines with GI values of 47 and 26 %, respectively. Compounds **10**, **13**, **23**, and **24** showed moderate activity toward SK-MEL-5 cell line with GI values of 43, 24, 24, and 24 %, respectively. Compounds **1**, **5**, and **10** illustrated certain activities through Melanoma UACC-62 cell line with GI values of 20, 22, and 26 %, respectively.

With respect to ovarian cancer, compounds **2**, **12**, and **13** showed moderate activities against Ovarian IGROV1 cell

line with GI values of 24, 21, and 22 %, while compounds **2** and **22** were active against Ovarian OVCAR-4 and Ovarian NCI/ADR-RES cell lines with GI values of 21 and 27 %, respectively.

In relation to renal cancer, renal CAKI-1 cell line was sensitive to compounds **10**, **11**, **12**, and **13** with GI values of 34, 22, 21, and 27 %; in addition, compounds **1**, **2**, **11**, **12**, **13**, **22**, **23,** and **24** showed certain activities against renal UO-31cell line with GI values of 33, 37, 22, 42, 43, 24, 30, and 30 %, respectively. Compounds **10**, **11**, **22**, **23**, and **24** were responsive to renal A498 cell line with GI values of 20, 46, 41, 51, and 46 %, while compounds **2** and **12** were active against renal ACHN cell line with GI values of 34 and 24 %. Finally, compounds **2** and **12** showed certain selectivities against renal RXF 393 and 786-0 cell lines with GI values of 30 and 32 %, respectively.

Prostate DU-145 cell line proved to be selectively sensitive to compound **5** with GI value of 24 %, while compounds **2**, **10**, **23**, and **24** showed GI effectiveness against Prostate PC-3 cell line with values of 33, 51, 30, and 30 %, respectively.

Pertaining to breast cancer, breast MCF7 cell line proved to be selectively sensitive to compounds **1**, **2**, **22**, **23**, **24**, and **25** with GI values of 31, 34, 28, 28, and 27 %, respectively. Compounds **2**, **10**, **13**, **22**, **23**, and **25** showed GI effectiveness against breast T-47D cell line with values of 59, 30, 35, 27, 38, and 38 %; concomitantly, **2**, **12**, **23**, **24**, and **25** demonstrated activities against breast cancer MDA-MB-231/ATCC cell line with GI values of 30, 23, 20, 20, and 28 %, respectively. Concurrently, compounds **1**, **2**, and **24** showed remarkable potencies against breast MDA-MB-468 cell line with GI values of 22, 84, and 38 %; at the same time, compounds **12** and **22** showed certain activities toward breast HS 578T and BT-549 cell lines with GI values of 25 and 28 %, respectively.

Structure–activity correlations

Compounds of the present investigation that belong to 2-(substituted thio)-3-phenethylquinazolin-4(3*H*)-one and 2-([5-mercapto-4-(substituted)-4*H*-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3*H*)-one revealed that compound **14** was devoid of any antitumor potency.

Structure–activity correlation revealed that replacement of the hydrogen atom of thiol function of compound **1** with variety of substituted alkyl or aralkyl groups produced 2-(substituted thio)-3-phenethylquinazolin-4(3*H*)-ones (**1**–**25**) analogs with variable potency. Alkylation of compound **1** with methyl iodide gave 2-(methylthio)-3-phenethylquinazolin-4(3*H*)-one (**2**) with increase in the antitumor activity.

Substitution of methyl group of compound **2** with 4-chlorobenzyl group produced compound **5** with a mild reduction of the antitumor activity. Changeover of 4-chlorobenzyl group of 2-(chlorobenzylthio)-3-phenethylquinazolin-4(3*H*)-one (**5**) with propylisoindoline-1,3-dione function enhanced the antitumor activity in compound **10**.

Exchange of the 2-methylthio group of compound **2** with 2-phenacylthio, 2-[2-(piperidin-1-yl)ethylthio], and/or 2-(2-morpholinoethylthio) groups afforded compounds **11**–**14** accompanied with decrease in the antitumor activities. The presence of electron-withdrawing group such as fluorine atom at aromatic ring of 2-(2-oxo-2-phenylethylthio)-3-phenethylquinazolin-4(3*H*)-one (**11**) increases the antitumor activity match up to unsubstituted phenyl ring; for example, compound **11** was less active than compound **12**. Substitution of piperidine moiety into morpholine moiety improved the antitumor activity, such as compound **13** is more active than **14**.

Replacement of the 2-methylthio group of compound **2** with 2-[(5-Mercapto-4-substituted-4*H*-1,2,4-triazol-3-yl)methylthio] groups afforded compounds **22**–**25** accompanied with reduction of the antitumor activities. Replacement of ethyl group of 2-[(4-ethyl-5-mercapto-4H-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3*H*)-one (**22**) with phenyl, 4-methoxyphenyl, and/or benzyl groups produced compounds **23**–**25** with a mild reduction of the antitumor activities. Substitution of benzyl moiety of 2-[(4-benzyl-5-mercapto-4*H*-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3*H*)-one (**25**) with phenyl and/or 4-methoxyphenyl moieties gave compounds **23**–**24** with mildly improved antitumor activities.

Conclusion

New derivatives of 4(3*H*)-quinazolinones (**1**–**25**) were synthesized and evaluated for their in vitro antitumor activity. A single dose (10 μM) of the test compounds was used in the National Cancer Institute (NCI) 60 cell lines panel assay. The results of this study demonstrated that compound **2** showed sensible selective activities (Fig. 3) toward colon cancer cell lines (HCT-116 and HCT-15), melanoma cancer cell lines (MDA-MB-435), renal cancer cell lines (AHCN, RXF 393, and UO-31), prostate cancer cell line (PC-3), and breast cancer cell lines (MCF7, MDA-MB-231/ATCC, T-47D, and MDA-MB-468). Compound **22** yielded reasonable selective activities (Fig. 4) toward leukemia cell line (HL-60(TB), MOLT-4, and CCRF-CEM), non-small Cell lung cancer cell lines (NCI-H226, NCI-H460, and NCI-H522), and colon cancer cell line (HCT-116). In addition, non-small cell lung cancer cell line (EKVX), colon cancer cell line (HT29), renal cancer cell line (UO-31), and breast cancer cell lines (MCF7, MDA-MB-231/ATCC, and T-47D) showed moderate sensitivity to compound **13** (Fig. 5).

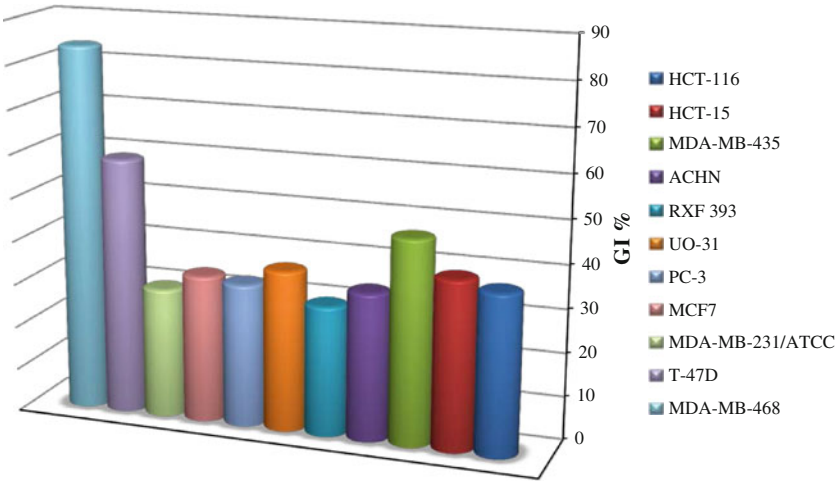


Fig. 3 The percentages of growth inhibition of compound **2** over the most sensitive tumor cell lines at 10 μM concentration

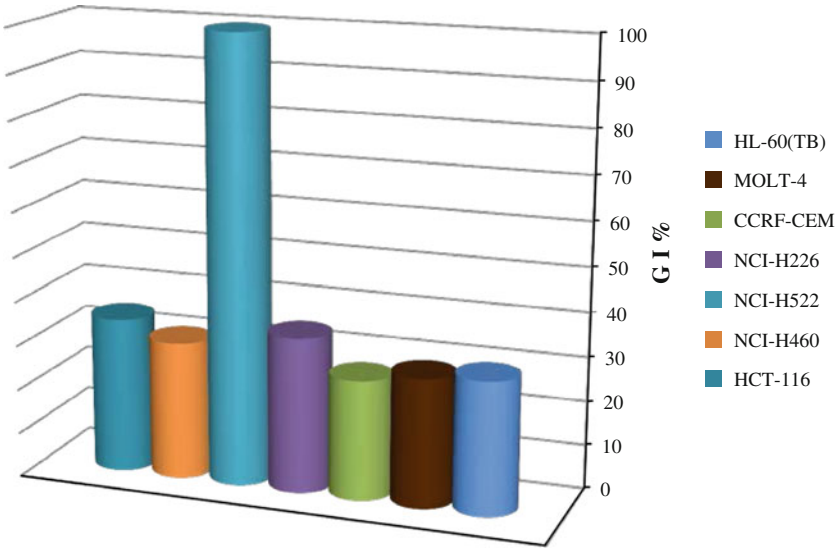


Fig. 4 The percentages of growth inhibition of compound **22** over the most sensitive tumor cell lines at 10 μM concentration

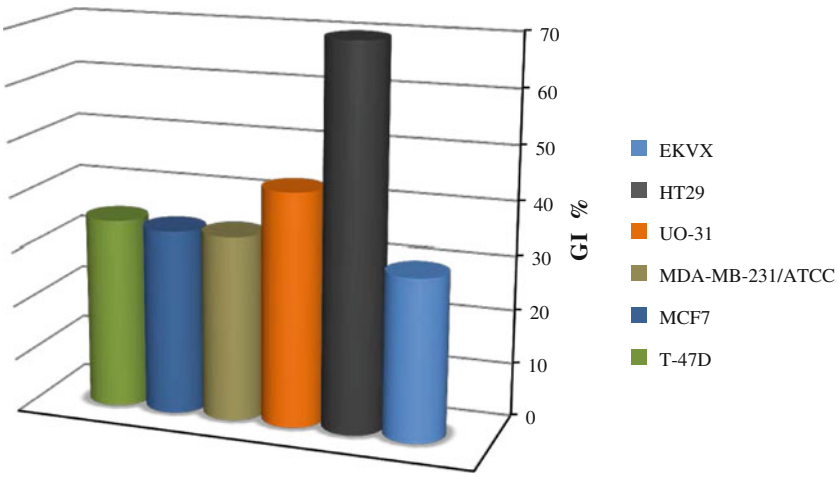


Fig. 5 The percentages of growth inhibition of compound **13** over the most sensitive tumor cell lines at 10 μM concentration

Experimental

Melting points (corrected) were recorded on Barnstead 9100 Electrothermal melting apparatus. IR spectra were recorded on a Perkine-Elmer spectrometer. ^{1}H NMR and ^{13}C NMR were recorded in DMSO-d_6, $CDCl_3$, and/or $CDCl_3$-TFA on a Jeol 500 MHz instrument using TMS as an internal standard (chemical shifts in δ ppm). Mass

spectra were recorded on a Shimadzu PQ-5000 GC–MS apparatus. Solvent evaporation was performed under reduced pressure using Buchan Rotatory Evaporator unless otherwise stated. T.L.C. was performed on precoated silica gel plates (60- F254, 0.2 mm), manufactured by E.M. Sciences, Inc, and shortwave UV (254) nm was used to detect the U.V. absorbing compounds (CH_2Cl_2, EtOH 10:1).

Chemistry

*2-Mercapto-3-phenethylquinazolin-4(3H)-one (**1**)*

A mixture of anthranilic acid (7 mmol, 960 mg) and 2-phenylethylisothiocyanate (7 mmol, 955 mg) in 25 ml absolute ethanol containing triethylamine (7 mmol, 710 mg) was heated under reflux for 2 h. The reaction mixture was filtered while hot, the solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized from ethanol.

Mp: 244–245 °C, yield, 78 %, ^{1}H NMR ($CDCl_3$, TFA): δ 11.37(s, 1H), 8.19 (d, 1H, $J = 7.5$ Hz), 7.77 (t, 1H, $J = 7.5$, 8.0 Hz), 7.45–7.30 (m, 7H), 4.75 (t, 2H, $J = 7.5$, 8.0 Hz), 3.13 (t, 2H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$, TFA): δ 31.0, 48.5, 125.9, 126.8, 128.4, 128.7, 129.0, 136.2, 137.8, 138.5, 159.5, 159.9, 160.2, 160.5, 175.7. MS: ($M^+ = 282$, 191, 100 %).

*General procedure for the synthesis of compounds (**2**–**14**)*

A mixture of 2-mercapto-3-phenethylquinazolin-4(3*H*)-one (**1**) (2 mmol, 564 mg) and the appropriate alkyl, aryl, and/or aralkyl halide (2.1 mmol) in 15 ml acetone containing anhydrous potassium carbonate (3 mmol, 415 mg) was stirred at room temperature for 10–12 h. The reaction mixture was filtered, the solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized from ethanol.

*2-(Methylthio)-3-phenethylquinazolin-4(3H)-one (**2**)* Mp: 120–122 °C, yield 95 %, ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, $J = 7.0$), 7.60 (t, 1H, $J = 7.0$), 7.49 (d, 1H, $J = 8.0$), 7.31–7.17 (m, 6H), 4.23 (t, 2H, $J = 8.0$, 8.5 Hz), 2.98 (t, 2H, $J = 8.0$, 8.5 Hz), 2.60 (s, 3H), ^{13}C NMR ($CDCl_3$): δ 15.0, 34.1, 46.1, 119.3, 125.7, 126.1, 126.8, 126.9, 128.7, 128.9, 134.3, 138.0, 147.5, 156.6, 161.6. MS: ($M^+ = 296$, 281, 100 %), IR (KBr, cm^{-1}) *v:* 3022 (Ar. CH), 2988 (Al. CH), 1674 (CO), 1611 (C=N).

*2-(Ethylthio)-3-phenethylquinazolin-4(3H)-one (**3**)* Mp: 83–85 °C, yield 90 %, ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 1H, $J = 7.5$), 7.71 (t, 1H, $J = 7.0$), 7.58 (d, 1H, $J = 8.0$ Hz), 7.42–7.24 (m, 6H), 4.34 (t, 2H, $J = 8.0$, 8.5 Hz), 3.35 (q, 2H, $J = 7.0$, 7.5 Hz), 3.09 (t, 2H, $J = 8.0$, 8.5 Hz), 1.48 (t, 3H, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$): δ 14.1, 26.6, 34.1, 46.0, 119.4, 125.6, 126.1, 126.7, 126.9, 128.7, 129.0, 134.2, 138.0, 147.6, 156.2, 161.7. MS: $M^+ = 310$, 281, 100 %), IR (KBr, cm^{-1}) *v:* 3043 (Ar. CH), 2976 (Al. CH), 1680 (CO), 1609 (C=N).

*2-(Benzylthio)-3-phenethylquinazolin-4(3H)-one (**4**)* Mp: 92–94 °C, yield 87 %, ^{1}H NMR ($CDCl_3$): δ 8.28 (d, 1H, $J = 7.0$), 7.75 (t, 1H, $J = 7.0$, 6.5 Hz), 7.66 (d, 1H, $J = 7.0$ Hz), 7.53 (d, 2H, $J = 7.0$ Hz), 7.45–7.29 (m, 9H), 4.61 (s, 2H), 4.33 (t, 2H, $J = 8.0$ Hz), 3.09 (t, 2H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 34.2, 36.6, 46.1, 119.5, 125.8, 126.1, 126.8, 127.0, 127.7, 128.7, 129.0, 129.5, 134.4, 136.5, 137.9, 147.5, 155.9, 161.6. MS: ($M^+ = 372$, 177, 100 %), IR (KBr, cm^{-1}) *v:* 3021 (Ar. CH), 2980 (Al. CH), 1669 (CO), 1614 (C=N).

*2-(4-Chlorobenzylthio)-3-phenethylquinazolin-4(3H)-one (**5**)* Mp: 140–142 °C, yield 88 %, ^{1}H NMR ($CDCl_3$): δ 8.27 (d, 1H, $J = 8.0$), 7.34 (t, 1H, $J = 7.0$ Hz), 7.63 (d, 1H, $J = 8.0$ Hz), 7.45–7.42 (m, 3H), 7.35–7.26 (m, 7H), 4.54 (s, 2H), 4.31 (t, 2H, $J = 8.0$, 8.5 Hz), 3.07 (t, 2H, $J = 8.0$, 8.5 Hz). ^{13}C NMR ($CDCl_3$): δ 34.2, 35.7, 46.2, 119.5, 126.0, 126.1, 126.8, 127.0, 128.7, 128.8, 129.0, 130.7, 133.5, 134.4, 135.2, 137.8, 147.3, 155.5, 161.1. MS: $M^+ = 406$, $M + 2 = 408$, 191, 100 %), IR (KBr, cm^{-1}) *v:* 3019 (Ar. CH), 2992 (Al. CH), 1682 (CO), 1618 (C=N), 755 (C–Cl).

*2-(4-Nitrobenzylthio)-3-phenethylquinazolin-4(3H)-one (**6**)* Mp: 144–146 °C, yield 86 %, ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 2H, $J = 8.5$ Hz), 8.20 (d, 2H, $J = 8.0$ Hz), 7.75 (t, 1H, $J = 7.0$ Hz), 7.69 (d, 2H, $J = 8.5$ Hz), 7.60–7.59 (m, 2H), 7.44 (t, 1H, $J = 7.0$, 7.5 Hz), 7.33-7.30 (m, 3H), 4.63 (s, 2H), 4.31 (t, 2H, $J = 8.0$ Hz), 3.06 (t, 2H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 34.2, 35.3, 46.2, 119.5, 123.8, 125.9, 126.1, 126.8, 127.1, 128.7, 128.9, 130.2, 134.5, 137.3, 144.8, 147.1, 147.3, 154.7, 161.5. MS: ($M^+ = 417$, 281, 100 %). IR (KBr, cm^{-1}) *v:* 3023 (Ar. CH), 2991 (Al. CH), 1685 (CO), 1613 (C=N).

*4-[(4-Oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio) methyl]benzoic acid (**7**)* Mp: 185–187 °C, yield 81 %, ^{1}H NMR ($CDCl_3$): δ 8.27 (br. s, 1H), 7.82 (d, 1H, $J = 6.5$ Hz), 7.72 (d, 1H, $J = 7.0$ Hz), 7.63 (d, 2H, $J = 3.5$ Hz), 7.54-7.53 (m, 4H), 7.35–7.30 (m, 5H), 4.69 (s, 2H), 4.39 (t, 2H, $J = 7.5$ Hz), 3.09 (t, 2H, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$): δ 33.9, 36.3, 45.1, 118.5, 125.3, 127.0, 127.1, 127.2, 128.6, 128.8, 128.9, 129.5, 130.9, 135.5, 137.1, 142.7, 143.7, 146.2, 156.1. MS: ($M^+ = 416$, 145, 100 %). IR (KBr, cm^{-1}) *v:* 3420 (OH), 3021 (Ar. CH), 2987 (Al. CH), 1695, 1676 (CO), 1609 (C=N).

*2-(4-Oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetonitrile (**8**)* Mp: 151–153 °C, yield 92 %, ^{1}H NMR ($CDCl_3$): δ 8.16 (d, 1H, J = 6.5 Hz), 7.76–7.64 (m, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.38–7.35 (m, 1H), 7.27–7.17 (m, 5H), 4.16 (t, 2H, J = 8.0, 8.5 Hz), 4.01 (s, 2H), 2.97 (t, 2H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 17.7, 34.2, 46.5, 115.8, 119.5, 126.4, 126.7, 127.0, 128.8, 128.9, 134.7, 137.3, 146.8, 152.1, 161.2. MS: (M^+ = 321, 122, 100 %). IR (KBr, cm^{-1}) *v:* 3021 (Ar. CH), 2940 (Al. CH), 2259 (CN), 1686 (CO), 1607 (C=N).

*2-[2-(4-Oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)-ethyl]isoindoline-1,3-dione (**9**)* Mp: 202–204 °C, yield 84 %, ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 1H, J = 7.5 Hz), 7.71 (dd, 2H, J = 3.0 Hz), 7.62–7.56 (m, 4H), 7.30 (t, 1H, J = 7.0 Hz), 7.21–7.15 (m, 5H), 4.17 (t, 2H, J = 8.0 Hz), 4.10 (t, 2H, J = 6.5 Hz), 3.54 (t, 2H, J = 6.5 Hz), 2.94 (t, 2H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 30.0, 34.0, 37.0, 46.1, 119.4, 123.3, 125.8, 126.3, 126.7, 126.8, 128.6, 128.9, 131.9, 134.0, 134.3, 137.9, 147.3, 154.8, 161.5, 168.1. MS: (M^+ = 455, 63, 100 %). IR (KBr, cm^{-1}) *v:* 3015 (Ar. CH), 2963 (Al. CH), 1771, 1719, 1668 (CO), 1603 (C=N).

*2-[3-(4-Oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)propyl]isoindoline-1,3-dione (**10**)* Mp: 116–118 °C, yield 82 %, ^{1}H NMR ($CDCl_3$): δ 8.23 (d, 1H, J = 7.5 Hz), 7.88–7.86 (m, 2H), 7.74–7.73 (m, 2H), 7.64 (t, 1H, J = 6.5, 7.0 Hz), 7.44–7.22 (m, 7H), 4.30 (t, 2H, J = 8.5, 8.0 Hz), 3.91 (t, 2H, J = 6.5 Hz), 3.44 (t, 2H, J = 6.5 Hz), 3.06 (t, 2H, J = 8.0 Hz), 2.19 (t, 2H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$): δ 28.3, 29.2, 34.1, 37.0, 46.0, 119.4, 123.3, 125.7, 126.1, 126.7, 126.8, 128.7, 129.0, 132.1, 134.0, 134.2, 138.0, 147.3, 156.6, 161.6, 168.4. MS: (M^+ = 469, 146, 100 %). IR (KBr, cm^{-1}) *v:* 3022 (Ar. CH), 2951 (Al. CH), 1771, 1715, 1674 (CO), 1609 (C=N).

*2-(2-Oxo-2-phenylethylthio)-3-phenethylquinazolin-4(3H)-one (**11**)* Mp: 154–156 °C, yield 88 %, ^{1}H NMR ($CDCl_3$): δ 8.22 (d, 1H, J = 7.0 Hz), 8.15 (d, 2H, J = 7.0 Hz), 7.69–7.58 (m, 4H), 7.40–7.37 (m, 5H), 7.30–7.28 (m, 1H), 7.17 (d, 1H, J = 7.5 Hz), 4.76 (s, 2H), 4.39 (t, 2H, J = 8.0 Hz), 3.15 (t, 2H, J = 8.0 Hz).^{13}C NMR ($CDCl_3$): δ 34.2, 39.2, 46.5, 119.4, 125.8, 126.8, 126.9, 128.5, 128.7, 128.8, 128.9, 133.6, 134.2, 136.4, 137.7, 147.1, 155.0, 161.4, 193.5. MS: (M^+ = 400, 119, 100 %). IR (KBr, cm^{-1}) *v:* 3020 (Ar. CH), 2957 (Al. CH), 1682, 1674 (CO), 1611 (C=N).

*2-[2-(4-Fluorophenyl)-2-oxoethylthio]-3-phenethylquinazolin-4(3H)-one (**12**)* Mp: 141–143 °C, yield 91 %, ^{1}H NMR ($CDCl_3$): δ 8.28–8.17 (m, 3H), 7.61 (t, 1H, J = 7.0 Hz), 7.39–7.37 (m, 5H), 7.30-7.23 (m, 3H), 7.16 (d, 1H, J = 8.0 Hz), 4.71 (s, 2H), 4.38 (t, 2H, J = 8.5 Hz), 3.14 (t, 2H, J = 8.0 Hz).^{13}C NMR ($CDCl_3$): δ 34.2, 38.9, 46.5, 115.9, 116.0, 119.4, 125.7, 126.0, 126.8, 127.0, 128.7, 129.0, 131.2, 131.3, 132.8, 134.3, 137.7, 147.0, 154.9, 161.4, 192.0. MS: (M^+ = 418, 107, 100 %). IR (KBr, cm^{-1}) *v:* 3027 (Ar. CH), 2994 (Al. CH), 1692, 1673 (CO), 16107 (C=N).

*3-Phenethyl-2-[2-(piperidin-1-yl)ethylthio]quinazolin-4(3H)-one (**13**)* Mp: >330 °C, yield 82 %, ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 1H, J = 8.0 Hz), 7.71 (t, 1H, J = 7.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.42–7.26 (m, 6H), 4.35 (t, 2H, J = 8.0, 8.5 Hz), 3.48 (t, 2H, J = 7.5 Hz), 3.09 (t, 2H, J = 8.0, 8.5 Hz), 2.75 (t, 2H, J = 7.0, 7.5 Hz), 2.57 (s, 4H), 1.65 (s, 4H), 1.49 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 18.4, 25.9, 29.1, 34.1, 46.0, 54.4, 63.4, 119.4, 125.6, 126.0, 126.7, 126.9, 128.6, 128.9, 134.2, 138.0, 147.5, 156.2, 161.6. MS: (M^+ = 393, 104, 100 %). IR (KBr, cm^{-1}) *v:* 3030, 3021 (Ar. CH), 2940 (Al. CH), 1676 (CO), 1604 (C=N).

*2-(2-Morpholinoethylthio)-3-phenethylquinazolin-4(3H)-one (**14**)* Mp: >330 °C, yield 83 %, ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 1H, J = 6.5 Hz), 7.72 (t, 1H, J = 6.5 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.41–7.37 (m, 6H), 4.36 (t, 2H, J = 8.0 Hz), 3.78 (s, 4H), 3.50 (t, 2H, J = 7.0 Hz), 3.09 (t, 2H, J = 8.0, 8.5 Hz), 2.80 (t, 2H, J = 6.5 Hz), 2.57 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 28.9, 34.1, 46.0, 53.5, 57.5, 66.9, 119.4, 125.7, 125.9, 126.7, 126.9, 128.6, 128.9, 134.3, 137.9, 147.4, 156.0, 161.6. MS: (M + 1 = 396, 120, 100 %). IR (KBr, cm^{-1}) *v:* 1674 (CO), 1603 (C=N).

*Ethyl 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)-acetate (**15**)*

A mixture of 2.82 g 2-mercapto-3-phenethylquinazolin-4(3*H*)-one (**1**, 10 mmol), 1.84 g ethyl bromoacetate (11 mmol), and 1.66 g anhydrous potassium carbonate (12 mmol) in 50 ml dry acetone was stirred at room temperature for 6 h. The reaction mixture was filtered, the solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized from ethanol. Mp: 132–134 °C, yield 95 %, ^{1}H NMR ($CDCl_3$): δ 8.24 (d, 1H, J = 7.0 Hz), 7.72 (t, 1H, J = 7.0 Hz), 7.52 (d, 1H, J = 8.0 Hz), 7.43-7.29 (m, 6H), 4.35 (t, 2H, J = 7.0, 7.5 Hz), 4.29 (q, 2H, J = 7.0, 7.5 Hz), 4.08 (s, 2H), 3.12 (t, 2H, J = 7.0, 7.5 Hz), 1.34 (t, 3H, J = 7.5, 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 14.2, 34.2, 34.5, 46.3, 61.9, 119.4, 126.0, 126.1, 126.8, 126.9, 128.7, 128.9, 134.3, 137.7, 147.2, 154.7, 161.4, 168.5. MS: (M^+ = 368, 63, 100 %). IR (KBr, cm^{-1}) *v:* 3035, 3026 (Ar. CH), 2980 (Al. CH), 1726, 1680 (CO), 1601 (C=N).

*2-(4-Oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (**16**)*

A mixture of 3.68 g ester **15** (10 mmol) and 750 mg hydrazine hydrate (15 mmol) in 50 ml absolute ethanol was stirred at room temperature for 8 h. The reaction mixture was filtered and dried. Mp: 160–162 °C, yield 90 %, ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 1H, $J = 7.0$ Hz), 7.75 (t, 1H, $J = 7.0$ Hz), 7.58 (d, 1H, $J = 8.0$ Hz), 7.46 (t, 1H, $J = 7.0$, 7.5 Hz), 7.36–7.29 (m, 5H), 4.32 (t, 2H, $J = 8.0$ Hz), 3.97 (s, 2H), 3.93 (s, 2H), 3.08 (t, 2H, $J = 8.0$ Hz). ^{13}C NMR (DMSO-d_6): δ 33.1, 34.1, 46.5, 119.4, 125.7, 126.5, 126.9, 127.2, 128.7, 129.0, 134.7, 137.4, 146.7, 155.9, 161.1, 169.2. MS: ($M^+ = 354$, 49, 100 %). IR (KBr, cm^{-1}) *v:* 3325, 3285 (NH), 3026(Ar. CH), 2926 (Al. CH), 1719, 1680 (CO), 1609 (C=N).

*General procedure for the synthesis of compounds (**17–21**)*

A mixture of 708 mg acid hydrazide **16** (2.0 mmol) and appropriate isothiocyanate (2.0 mmol) in 20 ml absolute ethanol was stirred at room temperature for 9–12 h. The solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized from ethanol.

*N-Ethyl-2-(2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetyl)hydrazinecarbothioamide (**17**)* Mp: 114–116 °C, yield 86 %, ^{1}H NMR (DMSO-d_6): δ 10.19 (s, 1H), 9.35 (s, 1H), 8.09 (d, 1H, $J = 7.0$ Hz), 7.99 (dd, 2H, $J = 8.5$ Hz), 7.62 (d, 1H, $J = 8.0$ Hz), 7.47 (t, 1H, $J = 7.0$, 7.5 Hz), 7.36–7.26 (m, 5H), 4.26 (t, 2H, $J = 7.5$, 8.0 Hz), 4.12 (s, 2H), 3.41 (q, 2H, $J = 6.5$, 7.0 Hz), 3.02 (t, 2H, $J = 7.5$, 8.0 Hz), 0.98 (t, 3H, $J = 6.5$, 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 14.3, 33.3, 34.3, 38.4, 45.4, 118.7, 126.1, 126.3, 126.7, 128.5, 128.6, 134.6, 137.6, 146.6, 155.5, 155.7, 160.3, 166.6, 180.8. MS: ($M^+ = 441$, 63, 100 %). IR (KBr, cm^{-1}) *v:* 3465, 3181 (NH), 3033 (Ar. CH), 2967 (Al. CH), 1685, 1654(CO), 1608 (C=N), 1252 (CS).

*2-[2-(4-Oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetyl]-N-phenylhydrazinecarbothioamide (**18**)* Mp: 192–194 °C, yield 81 %, ^{1}H NMR (DMSO-d_6): δ 10.43 (s, 1H), 9.81 (s, 1H), 9.55 (s, 1H), 8.08 (d, 1H, $J = 7.0$ Hz), 7.55 (t, 1H, $J = 7.5$, 6.5 Hz), 7.60 (d, 1H, $J = 8.0$ Hz), 7.45 (t, 1H, $J = 7.0$, 7.5 Hz), 7.39–7.16 (m, 10H), 4.27 (t, 2H, $J = 7.5$, 8.0 Hz), 4.19 (s, 2H), 3.03 (t, 2H, $J = 7.5$, 8.0 Hz). ^{13}C NMR (DMSO-d_6): δ 33.4, 34.4, 45.5, 118.8, 125.2, 126.0, 126.1, 126.3, 126.7, 128.1, 128.5, 128.6, 134.6, 137.6, 138.9, 146.6, 155.6, 160.3, 166.7, 180.8. MS: ($M^+ = 489$, 49, 100 %). IR (KBr, cm^{-1}) *v:* 3319, 3208, 3152 (NH), 3028 (Ar. CH), 2968 (Al. CH), 1685, 1653 (CO), 1607 (C=N), 1230 (CS).

*N-(4-Methoxyphenyl)-2-[2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetyl]hydrazinecarbothioamide (**19**)* Mp: 184–186 °C, yield 83 %, ^{1}H NMR (DMSO-d_6): δ 10.39 (s, 1H), 9.71 (s, 1H), 9.45 (s, 1H), 8.08 (d, 1H, $J = 7.0$ Hz), 7.75 (t, 1H, $J = 7.0$ Hz), 7.59 (d, 1H, $J = 8.0$ Hz), 7.45 (t, 1H, $J = 7.0$ Hz), 7.40-7.23 (m, 7H), 6.89 (d, 2H, $J = 8.5$ Hz), 4.27 (t, 2H, $J = 7.5$, 8.0 Hz), 4.19 (s, 2H), 3.75 (s, 3H), 3.03 (t, 2H, $J = 7.5$, 8.0 Hz). ^{13}C NMR (DMSO-d_6): δ 33.4, 34.4, 45.5, 55.2, 113.3, 114.1, 118.3, 118.7, 126.0, 126.1, 126.3, 126.7, 127.3, 128.5, 128.6, 131.7, 134.6, 137.7, 146.6, 155.6, 156.8, 160.3, 166.7, 181.1. MS: ($M^+ = 519$, 56, 100 %). IR (KBr, cm^{-1}) *v:* 3322, 3212 (NH), 3024 (Ar. CH), 2971 (Al. CH), 1688, 1654 (CO), 1609 (C=N), 1248 (CS).

*N-(4-Fluorophenyl)-2-(2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetyl)hydrazinecarbothioamide (**20**)* Mp: 94–96 °C, yield 80 %, ^{1}H NMR (DMSO-d_6): δ 10.43 (s, 1H), 9.86 (s, 1H), 9.56 (s, 1H), 8.08 (d, 1H, $J = 7.5$ Hz), 7.75 (t, 1H, $J = 7.0$ Hz), 7.60 (d, 1H, $J = 8.0$ Hz), 7.45 (t, 1H, $J = 7.0$, 7.5 Hz), 7.36–7.26 (m, 7H), 7.15 (t, 2H, $J = 8.5$ Hz), 4.27 (t, 2H, $J = 7.5$, 8.0 Hz), 4.19 (s, 2H), 3.03 (t, 2H, $J = 7.5$, 8.0 Hz). ^{13}C NMR (DMSO-d_6): δ 33.4, 34.4, 45.5, 114.6, 114.8, 118.7, 126.0, 126.1, 126.3, 126.7, 128.0, 128.5, 128.6, 134.6, 135.2, 137.6, 146.5, 155.6, 158.5, 160.3, 166.7, 181.1. MS: ($M^+ = 507$, 40, 100 %). IR (KBr, cm^{-1}) *v:* 3256, 3150 (NH), 3022 (Ar. CH), 2965 (Al. CH), 1717, 1676 (CO), 1609 (C=N), 1216 (CS).

*N-Benzyl-2-(2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetyl)hydrazinecarbothioamide (**21**)* Mp: 1018 °C, yield 86 %, ^{1}H NMR (DMSO-d_6): δ 10.37 (s, 1H), 9.61 (s, 1H), 8.22 (t, 1H, $J = 7.0$ Hz), 8.04 (d, 1H, $J = 7.5$ Hz), 7.78 (t, 1H, $J = 7.0$ Hz), 7.57 (d, 1H, $J = 8.0$ Hz), 7.45 (t, 1H, $J = 7.5$ Hz), 7.37–7.21 (m, 7H), 7.17 (d, 1H, $J = 7.5$ Hz), 7.14 (d, 2H, $J = 6.5$ Hz), 4.65 (d, 2H, $J = 5.0$), 4.22 (t, 2H, $J = 8.0$ Hz), 4.12 (s, 2H), 2.99 (t, 2H, $J = 8.0$ Hz). ^{13}C NMR (DMSO-d_6): δ 33.3, 34.2, 45.4, 46.6, 118.7, 125.9, 126.0, 126.3, 126.5, 126.6, 126.7, 127.3, 127.9, 128.5, 128.6, 134.6, 137.7, 138.7, 146.5, 155.9, 160.2, 166.8, 181.9. MS: ($M^+ = 503$, 44, 100 %). IR (KBr, cm^{-1}) *v:* 3277, 3132 (NH), 3031 (Ar. CH), 2974 (Al. CH), 1684, 1647 (C), 1606 (C=N), 1292 (CS).

*General procedure for the synthesis of compounds (**22–25**)*

Method A A mixture of 708 mg acid hydrazide **16** (2.0 mmol) and appropriate isothiocyanate (2.0 mmol) in 20 ml absolute ethanol containing 405 mg TEA (4 mmol) was refluxed for 10–12 h. The reaction mixture was allowed to cool, the solvent was removed under reduced

pressure, and the solid obtained was washed with water, dried, and recrystallized from ethanol.

Method B *N*-Substituted hydrazinecarbothioamide **17–21** (1.0 mmol) was refluxed in 20 ml absolute ethanol in the presence of 203 mg TEA (1.5 mmol) for 6–8 h. The reaction mixture was allowed to cool, the solvent was removed under reduced pressure, and the solid obtained was washed with water, dried, and recrystallized from ethanol.

2-[(4-Ethyl-5-mercapto-4H-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3H)-one ***(22)*** Mp: 196–198 °C, yield 90 %, ^{1}H NMR ($CDCl_3$): δ 12.29 (s, 1H), 8.28 (d, 1H, $J = 7.0$ Hz), 7.74 (t, 1H, $J = 6.5$, 7.0 Hz), 7.54 (d, 1H, $J = 8.0$ Hz), 7.46 (t, 1H, $J = 7.0$ Hz), 7.32–7.26 (m, 5H), 4.71 (s, 2H), 4.31 (t, 2H, $J = 7.5$, 8.0 Hz), 4.23 (dd, 2H, $J = 7.5$ Hz), 3.07 (t, 2H, $J = 8.0$ Hz), 1.45 (t, 3H, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$): δ 14.0, 25.7, 34.2, 39.7, 36.4, 119.4, 125.8, 126.5, 127.0, 127.2, 128.7, 128.9, 134.7, 137.4, 146.7, 148.5, 153.6, 161.3. MS: ($M^+ = 423$, 44, 100 %). IR (KBr, cm^{-1}) *v:* 3022 (Ar. CH), 2989 (Al. CH), 1673 (CO), 1609 (C=N).

2-[(5-Mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3H)-one ***(23)*** Mp: 194–196 °C, yield 85 %, ^{1}H NMR (DMSO-d_6): δ 13.92 (s, 1H), 8.32 (s, 1H), 8.05 (d, 1H, $J = 7.0$ Hz), 7.81 (t, 1H, $J = 7.5$ Hz), 7.75-7.72 (m, 1H), 7.54-7.47 (m, 4H), 7.40–7.7.23 (m, 6H), 4.57 (s, 2H), 4.13 (t, 2H, $J = 8.0$ Hz), 2.90 (t, 2H, $J = 8.0$ Hz). ^{13}C NMR (DMSO-d_6): δ 25.8, 33.3, 45.4, 118.7, 125.8, 126.2, 126.4, 126.7, 128.3, 128.6, 129.3, 129.4, 133.3, 134.7, 137.5, 146.2, 148.5, 154.0, 160.2, 168.2. MS: ($M^+ = 471$, 41, 100 %). IR (KBr, cm^{-1}) *v:* 3020 (Ar. CH), 2987 (Al. CH), 1680 (CO), 1609 (C=N).

2-([5-Mercapto-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-yl) methylthio]-3-phenethylquinazolin-4(3H)-one ***(24)*** Mp: 221–223 °C, yield 88 %, ^{1}H NMR ($CDCl_3$): δ 11.73 (s, 1H), 8.38 (d, 1H, $J = 7.0$ Hz), 7.23 (t, 1H, $J = 6.5$, 7.0 Hz), 7.42 (dd, 2H, $J = 7.0$, 8.5 Hz), 7.35–7.28 (m, 7H), 6.78 (d, 2H, $J = 8.5$ Hz), 4.61 (s, 2H), 4.28 (t, 2H, $J = 8.0$ Hz), 3.64 (s, 3H), 3.01 (t, 2H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 25.9, 34.1, 46.2, 55.3, 114.9, 119.3, 125.1, 126.0, 126.2, 126.9, 128.7, 128.9, 129.0, 134.5, 137.4, 146.6, 153.1, 160.6, 161.1. MS: ($M^+ = 501$, 177, 100 %). IR (KBr, cm^{-1}) *v:* 3021 (Ar. CH), 2988 (Al. CH), 1685 (CO), 1606 (C=N).

2-[(4-Benzyl-5-mercapto-4H-1,2,4-triazol-3-yl)methylthio]-3-phenethylquinazolin-4(3H)-one ***(25)*** Mp: 165–167 °C, yield 90 %, ^{1}H NMR ($CDCl_3$): δ 12.42, (s, 1H), 8.28 (d, 1H, $J = 1.0$, 1.5 Hz), 7.73 (t, 1H, $J = 7.0$ Hz), 7.45 (dd, 2H, $J = 7.0$ Hz), 7.47–7.25 (m, 10H), 5.46 (s, 2H), 4.68 (s, 2H), 4.18 (t, 2H, $J = 8.0$ Hz), 2.97 (t, 2H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$): δ 25.9, 34.1, 46.3, 47.4, 119.4, 125.9, 126.4, 126.9, 127.2, 127.5, 128.2, 128.7, 128.9, 133.1, 134.4, 134.7, 137.4, 146.7, 149.0, 153.5, 161.3, 168.7. MS: ($M^+ = 485$, 106, 100 %). IR (KBr, cm^{-1}) *v:* 3026 (Ar. CH), 2991 (Al. CH), 1681(CO), 1609 (C=N).

Antitumor screening

Under a sterile condition, cell lines were grown in RPMI 1640 media (Gibco, NY, USA) supplemented with 10 % fetal bovine serum (Biocell, CA, USA); 5×10^5 cell/ml was used to test the growth inhibition activity of the synthesized compounds. The concentrations of the compounds ranging from 0.01 to 100 μM were prepared in phosphate buffer saline. Each compound was initially solubilized in dimethyl sulfoxide (DMSO); however, each final dilution contained less than 1 % DMSO. Solutions of different concentrations (0.2 ml) were pipetted into separate wells of a microtiter tray in duplicate. Cell culture (1.8 ml) containing a cell population of 6×10^4 cells/ml was pipetted into each well. Controls, containing only phosphate buffer saline and DMSO at identical dilutions, were also prepared in the same manner. These cultures were incubated in a humidified incubator at 37 °C. The incubator was supplied with 5 % CO_2 atmosphere. After 48 h, cells in each well were diluted ten times with saline and counted using a coulter counter. The counts were corrected for the dilution (Grever *et al.*, 1992; Monks *et al.*, 1991; Boyd and Paull, 1995).

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