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Design, synthesis and biological evaluation of 2-mercapto-3-phenethylquinazoline bearing anilide fragments as potential antitumor agents: Molecular docking study

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ABSTRACT

A novel series of 2-(3-phenethyl-4(3*H*)quinazolin-2-ylthio)-N-substituted anilide and substituted phenyl 2-(3-phenethyl-4(3*H*) quinazolin-2-ylthio)acetate were designed, synthesized and evaluated for their in-vitro antitumor activity. Compound **15** possessed remarkable broad-spectrum antitumor activity which almost sevenfold more active than the known drug 5-FU with GI_{50} values of 3.16 and 22.60 μM, respectively. Compound **15** exhibited remarkable growth inhibitory activity pattern against renal cancer (GI_{50} = 1.77 μM), colon cancer (GI_{50} = 2.02 μM), non-small cell lung cancer (GI_{50} = 2.04 μM), breast cancer (GI_{50} = 2.77 μM), ovarian cancer (GI_{50} = 2.55 μM) and melanoma cancer (GI_{50} = 3.30 μM). Docking study was performed for compound **15** into ATP binding site of EGFR-TK which showed similar binding mode to erlotinib.

Cancer is continuing to be a major health problem in developed as well as undeveloped countries.[1–5] The great cancer incidence worldwide increases the search for new, safer and efficient anticancer agents, aiming the prevention or the cure of this illness. 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 biological activities.[6–23] It is well known that quinazoline derivatives are potent inhibitors of epidermal growth factor receptor (EGFR).[24–36] The epidermal growth factor receptor (EGFR) is cellular trans-membrane tyrosine kinases that are over-expressed in a significant number of human tumors (e.g., breast, ovarian, colon, renal, and prostate).[37–40] Overexpression of EGFR family receptors have always been observed in these tumors, approximately in 60% of all tumors. A number of small molecule EGFR kinase inhibitors have been evaluated in cancer clinical trials.[24–40] For example, anilinoquinazoline-containing compounds erlotinib (**A**) (TarcevaTM),[31] gefitinib (**B**) (IressaTM),[28–40] lapatinib (**C**) (TykerbTM, also known as GW-572016) and Vandetanib (ZactimaTM) were recently approved for the treatment of breast cancer and non-small-cell lung cancer.[32–36] Moreover a series of salicylanilides (**D**) were synthesized and determined their inhibitory activity against tyrosine kinases (Fig. 1), some of them indeed proved to be potent and selective EGFR tyrosine kinase inhibitors (Fig. 1).[41] We have recently studied a series of 4-substituted quinazoline derivatives which were evaluated for their antitumor activities (**E**) (Fig. 1).[20,21] Owing to our continues studies on quinazoline derivatives as an attractive candidates as antitumor agents, we have designed a number of new quinazoline derivatives containing anilide fragments[41] (**F**) and biologically evaluated there in-vitro antitumor activities (Fig. 1). In the present study, the substitution pattern at the 2-substituted quinazoline pharmacophores was selected based on different electronic environment 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. Molecular docking methodology was used to identify the structural features required for the antitumor properties of these new series. These models are necessary to obtain a consistent and more precise picture of the biological active molecules at the atomic level and furthermore, provide new insights that can be used to design novel therapeutic agents.[21,42–49] Moreover, the results of this molecular docking could support the postulation

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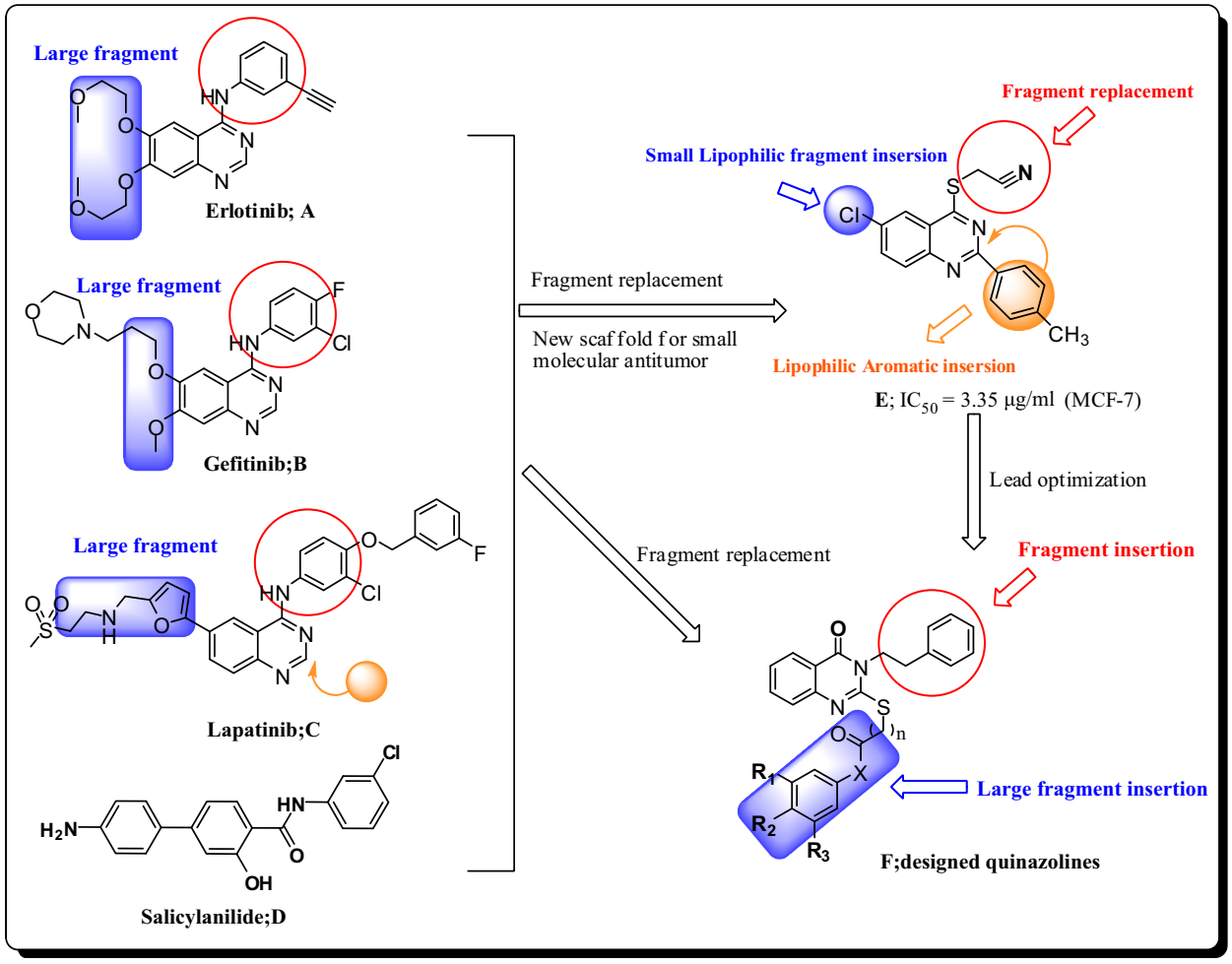


Figure 1. Reported and proposed quinazoline derivatives as antitumor.

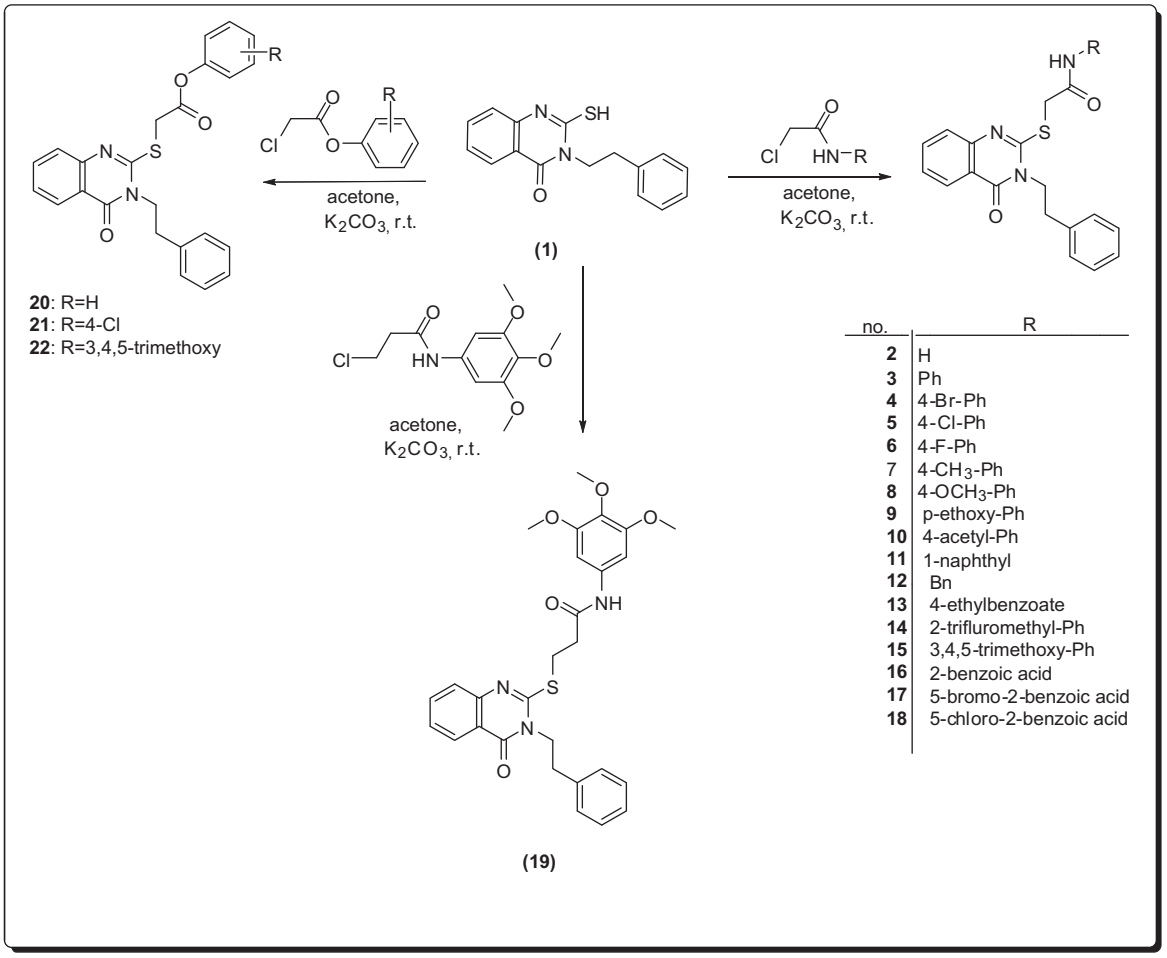
that our active compounds may act on the same enzyme target where EGFR inhibitor acts confirming the molecular design of the reported class of antitumor agents.

Synthesis of 2-mercapto-3-phenethylquinazolin-4(3*H*)-one (**1**) as a key intermediate was achieved by the reaction of anthranilic acid with 2-phenylethyl isothiocyanate in absolute ethanol in 78% yield. The reaction of compound **1** with various 2-chloro-N-substituted phenylacetamide and/or substituted phenyl-2-chloroacetate in anhydrous acetone in the presence of potassium carbonate gave 2-(quinazolin-2-ylthio)-N-substituted anilide and/or 2-(quinazolin-2-ylthio) substituted acetate derivatives **2**–**22** in 84–95% yield (Scheme 1).

The synthesized compounds **1**–**22** 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 were 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.[50–52] 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).

Concerning broad spectrum antitumor activity; the results of this study demonstrated that compounds **15**, **16** and **19** are the most remarkable broad spectrum antitumor agents. Close examination of the data presented in Table 1, revealed that compound **15** are the most active member of this study showing effectiveness toward numerous cell lines belong to different tumor subpanels. Consequently, compound **15** was carried over and tested against a panel of 60 different tumor cell lines at a 5-log dose range.[50–52] Three response parameters, GI_{50}, TGI, and LC_{50} were calculated for each cell line, using the known drug 5-Fluorouracil (5-FU) as a positive control. Compound **15** exhibited remarkable growth inhibitory activity pattern against renal cancer (GI_{50} = 1.77 µM), colon cancer (GI_{50} = 2.02 µM), non-small cell lung cancer (GI_{50} = 2.04 µM), breast cancer (GI_{50} = 2.77 µM), ovarian cancer (GI_{50} = 2.55 µM) and melanoma cancer (GI_{50} = 3.30 µM). Compound **15** is almost sevenfold more active than the known drug 5-FU with GI_{50} values of 3.16 and 22.60 µM, respectively (Table 2).

Regarding the activity toward individual cell lines; Non-small cell lung; compounds **8**, **15** and **16** proved to be susceptible to the HOP-62 cancer cell line with GI values of 52%, 91% and 49% respectively. NCI-H522 cell line proved to be selectively sensitive to compounds **10**, **15**, **16** and **19** with GI values of 51, lethal, 85% and 52%, respectively. In addition, compound **15** showed strong activity against A549/ATCC, NCI-H226, NCI-H23, NCI-H322M and NCI-H460 cancer cell lines in 76%, lethal, 74%, 73% and lethal respectively. Respecting colon cancer; compound **15** verified strong selectively sensitive to colon HCT-116, HCC-2998, COLO 205, HT29, KM12 and SW-620 cancer cell lines in lethal, 71%, 66%, 85%, 93% and 52%, respectively. Concerning CNS cancer; Compounds **5**, **8**, **15** and **16** showed GI values of 63%, 72%, lethal and 74% to SNB-75 cancer cell line respectively, while compounds **15** and **19** illustrated potent activity against SF-539 cancer cell line



Scheme 1. Reactions of 2-mercapto-3-phenethylquinazolin-4(3*H*)-one (**1**) with various 2-chloro-*N*-phenylanilide and/or phenyl 2-chloroacetate.

in lethal and 70%, respectively. On the other hand, compound **15** showed lethal activities against CNS U251, SF-295 and SNB-19 cancer cell lines and strong activity against SF-268 with GI value of 87%. Regarding Melanoma; compounds **15** and **19** showed selective activities against LOX IMVI, MALME-3M, UACC-257 cancer cell lines with GI values of 70%, 59%, 61%, 54%, 77% and 72% respectively. Compound **15** showed moderate sensitivity towards M14, SK-MEL-28 cancer cell lines with GI values of 68% and 63%, whilst compound **15** proved to be lethal to MDA-MB-435 and SK-MEL-5 cancer cell lines. Respecting ovarian cancer; compounds **15** and **16** showed moderate activities against Ovarian OVCAR-8 cell line with GI values of 70% and 61%. Ovarian SK-OV-3 cell line was responsive to compound **16** with GI value of 53% while compound **15** active against IGROV1 cancer cell line with GI value of 92%. Ovarian OVCAR-4 cell line receptive to compounds **19**, **20** and **21** with GI values of 51%, 59% and 59% respectively, additionally compound **15** demonstrated lethal activities to OVCAR-3 and SK-OV-3 cancer cell lines. Relating to renal cancer; renal CAKI-1 cancer cell line was sensitively selective to compound **19** with GI value of 74%. Additionally, compound **15** showed certain activity against renal RXF 393 and SN12C cancer cell lines with GI values of 55% and 75%, as well lethal to renal 786-0, A498, ACHN, TK-10 and UO-31cancer cell lines. Prostate PC-3 and DU-145 cancer cell lines proved to be selectively sensitive to compound **15** with GI value of 59% and 55%, respectively. Pertaining to breast cancer; breast HS 578T cancer cell line convinced responsive to compounds **15** and **19** with GI values of 64% and 67% respectively. Compounds **5** and **19** showed GI effectiveness against breast T-47D and MDA-MB-231/ATCC cancer cell lines with values of 56% and 67%, respectively. Concurrently, compound **15** showed remarkable potency against breast MDA-MB-468 cancer cell line with GI value of 71%, at the same time as showed lethal activities against breast BT-549, T-47D and MDA-MB-231/ATCC cancer cell lines (Table 1).

The antitumor activity correlation of the newly synthesized compounds revealed that compounds **2**, **3**, and **18** devoid any potent antitumor activities. Replacement of the hydrogen atom of amino function of 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetamide (**2**) or phenyl ring of 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)-N-phenylacetamide (**3**) with variety of substituted phenyl produced (N-substituted phenyl)acetamide analogs with variable potency. The presence of electron withdrawing or electron donating groups at aromatic ring of compound **3** afforded N-(4-substituted phenyl)-2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetamides (**5**–**10**) with improvement of the antitumor activity as shown in compound **3** matched up to compounds **5**–**10**. Introduction of electron donating group such as 3,4,5-trimethoxy moiety at aromatic ring of compound **3** produced *N*-(3,4,5-trimethoxyphenyl)acetamide **15** and *N*-(3,4,5-trimethoxyphenyl)propanamide **19** with enhancement of the antitumor activities compared to compounds containing unsubstituted phenyl or electron withdrawing group (**3**–**6**). The length of the carbon chain linking of the N-substituted anilide proved crucial and manipulated the antitumor activity; accordingly one carbon length favored the antitumor activities such as 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)-*N*-(3,4, 5-trimethoxyphenyl)acetamide (**15**) rather than two carbon lengths like

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

Subpanel tumor cell lines	% Growth inhibition (GI %)[a]																
	2	**3**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**13**	**15**	**16**	**18**	**19**	**20**	**21**	**22**
Leukemia																	
HL-60(TB)	nt	17	nt	25	–	nt	nt	nt	nt	nt	nt	nt	nt	27	11	nt	nt
MOLT-4	nt	–	nt	26	–	nt	10	nt	nt	nt	nt	nt	nt	40	23	nt	nt
Non-small cell lung cancer																	
A549/ATCC	12	16	16	23	21	25	13	29	17	27	76	46	–	29	12	–	10
EKVX	10	16	29	24	29	25	19	29	25	34	35	25	20	34	nt	28	36
HOP-62	–	–	40	–	42	52	36	22	36	45	91	49	–	45	nt	10	–
NCI-H226		–	24	–	–	–	31	16	13	25	L	26	–	10	nt	13	16
NCI-H23	–	11	21	12	–	–	–	12	10	13	74	26	–	28	14	25	–
NCI-H322M	–	–	13	17	15	19	23	27	26	23	73	19	–	28	25	–	11
NCI-H460	–	–	32	–	22	25	11	31	29	23	L	41	–	17	14	–	26
NCI-H522		10	45	31	22	–	11	51	28	26	L	85	–	52	37	37	–
Colon cancer																	
COLO 205	–	–	15	–	15	–	–	12	–	22	71	35	–	20	–	–	–
HCC-2998	––	–	–	–	–	–	–	–	–	–	66	–	–	–	–	–	–
HCT-116	–	15	23	19	13	13	16	37	27	14	L	45	–	40	21	–	20
HCT-15	–	–	16	10	10	–	–	21	20	–	11	12	–	18	–	25	48
HT29	–	–	–	10	–	–	10	12	–	12	85	11	–	18	–	–	–
KM12	–	–	14	–	11	16	–	18	–	11	93	10	–	39	–	–	–
SW-620	–	–	11	–	10	11	–	14	–	11	52	21	–	14	–	–	–
CNS cancer																	
SF-268		–	40	–	19	47	25	32	28	33	87	33	–	26	16	–	–
SF-295	–	–	32	13	12	21	–	21	27	25	49	18	–	10	20	–	13
SF-539	–	–	41	–	19	10	–	–	38	–	L	44	–	70	–	–	–
SNB-19	–	–	30	–	22	41	–	20	17	36	73	40	–	12	–	–	–
SNB-75	–	12	63	–	12	72	21	41	38	39	L	74	20	38	28	28	12
U251	–	–	25	17	11	29	27	10	24	28	L	nt	–	25	nt	–	26
Melanoma																	
LOX IMVI		11	23	18	14	–	11	25	17	22	70	38	–	54	16	14	–
MALME-3M	–	–	–	11	17	40	37	13	14	23	59	18	–	77	16	–	–
M14	–	10	–	18	–	25	10	21	14	21	68	12	–	40	13	–	–
MDA-MB-435	–	–	13	–	17	10	14	23	19	16	L	35	–	38	19	–	–
SK-MEL-28	–	–	10	–	22	11	–	23	12	14	63	17	–	42	–	–	–
SK-MEL-5	–	13	22	16	22	10	–	25	22	21	L	35	–	31	–	–	–
UACC-257	–	–	18	–	17	14	–	36	–	29	61	35	–	72	11	–	–
UACC-62	–	16	34	25	20	13	–	28	29	29	25	21	–	30	19	11	23
Ovarian cancer																	
IGROV1		–	36	16	20	18	21	20	39	31	92	42	–	21	10	15	11
OVCAR-3	–	–	32	–	–	10	–	23	10	13	L	29	–	11	–	–	–
OVCAR-4	–	–	14	–	–	–	–	25	13	10	47	23	–	51	59	59	–
OVCAR-5	–	–	–	–	–	–	–	10	–	15	35	–	–	–	–	–	–
OVCAR-8	–	–	39	–	27	40	29	42	40	37	70	61	–	28	23	–	–
NCI/ADR-RES	–	–	21	–	–	15	–	33	19	19	64	34	–	13	22	10	11
SK-OV-3	–	14	43	25	20	25	–	17	14	19	L	53	–	44	28	28	–
Renal cancer																	
786-0		–	13	–	–	–	–	–	15	–	L	16	–	29	13	–	–
A498	–	11	–	10	–	–	–	–	–	–	L	26	10	37	18	10	–
ACHN	34	–	22	16	21	–	12	30	38	21	L	34	–	21	10	–	10
CAKI-1	12	–	42	22	13	13	12	16	32	19	nt	–	17	74	–	27	28
RXF 393	–	–	22	13	10	21	13	–	16	14	55	25	–	12	–	–	–
SN12C	–	–	13	19	–	–	–	13	20	–	75	–	–	16	16	–	10
TK-10	–	–	19	–	–	10	–	–	20	–	L	19	–	17	–	–	–
UO-31	–	–	28	31	–	–	26	10	33	10	L	–	18	22	16	–	37
Prostate cancer																	
PC-3	–	10	30	16	14	–	–	20	29	10	59	–	–	25	14	25	–
DU-145	–	–	12	–	–	–	–	11	13	10	55	30	–	–		–	–
Breast cancer																	
MCF7		19	30	18	23	11	12	16	21	12	49	21	–	33	15	34	34
MDA-MB-231/ATCC	–	35	37	22	23	39	25	39	37	48	L	45	–	66	15	33	20
HS 578T	–	–	45	16	41	49	–	33	37	33	64	45	–	67	–	41	–
BT-549	–	–	nt	10	–	10	–	–	–	12	L	10	10	13	–	15	10
T-47D	–	13	56	25	44	–	15	19	20	17	L	27	–	47	14	14	26
MDA-MB-468	–	18	36	23	29	13	10	14	–	18	71	14	–	27	–	–	–

Nt, not tested; –, GI <10%; L, GI >100%.

3-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio) *N*-(3,4,5-trimethoxyphenyl)propanamide (**19**). Replacement of acetamide function of *N*-(4-chlorophenyl)-2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetamide (**5**) and 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)-*N*-(3,4,5-trimethoxyphenyl) acetamide (**15**) by acetate function produced 4-chlorophenyl-2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetate (**21**) and 3,4,5-trimethoxyphenyl-2-(4-oxo-3-phenethyl-3,4-dihydroquinazo-

Table 2
Compound **15** median growth inhibitory (GI_{50}, μM), total growth inhibitory (TGI, μM) and median lethal (LC_{50}, μM) concentration of in-vitro subpanel tumor cell lines.

Compound	Supbanel tumor cell lines[a]									MG-MID[b]
	Activity	I	II	III	IV	V	VI	VII	VIII	IX	
15	GI_{50}	c	2.04	2.02	2.73	3.30	2.55	1.77	4.98	2.77	3.16
	TGI	c	43.09	c	13.45	76.60	52.03	3.63	c	44.06	25.0
	LC_{50}	c	c	c	75.03	94.47	84.50	54.18	c	81.86	77.6
5-FU	GI_{50}	15.1	c	8.4	72.1	70.6	61.4	45.6	22.7	76.4	22.60
	TGI	c	c	c	c	c	c	c	c	c	c
	LC_{50}	c	c	c	c	c	c	c	c	c	c

[a] I, leukemia; II, non-small cell lung cancer; III, colon cancer; IV, CNS cancer; V, melanoma; VI, ovarian cancer; VII, renal cancer; VIII, prostate cancer; IX, breast cancer.
[b] Full panel mean-graph midpoint (μM).
[c] Compound showed values >100 μM.

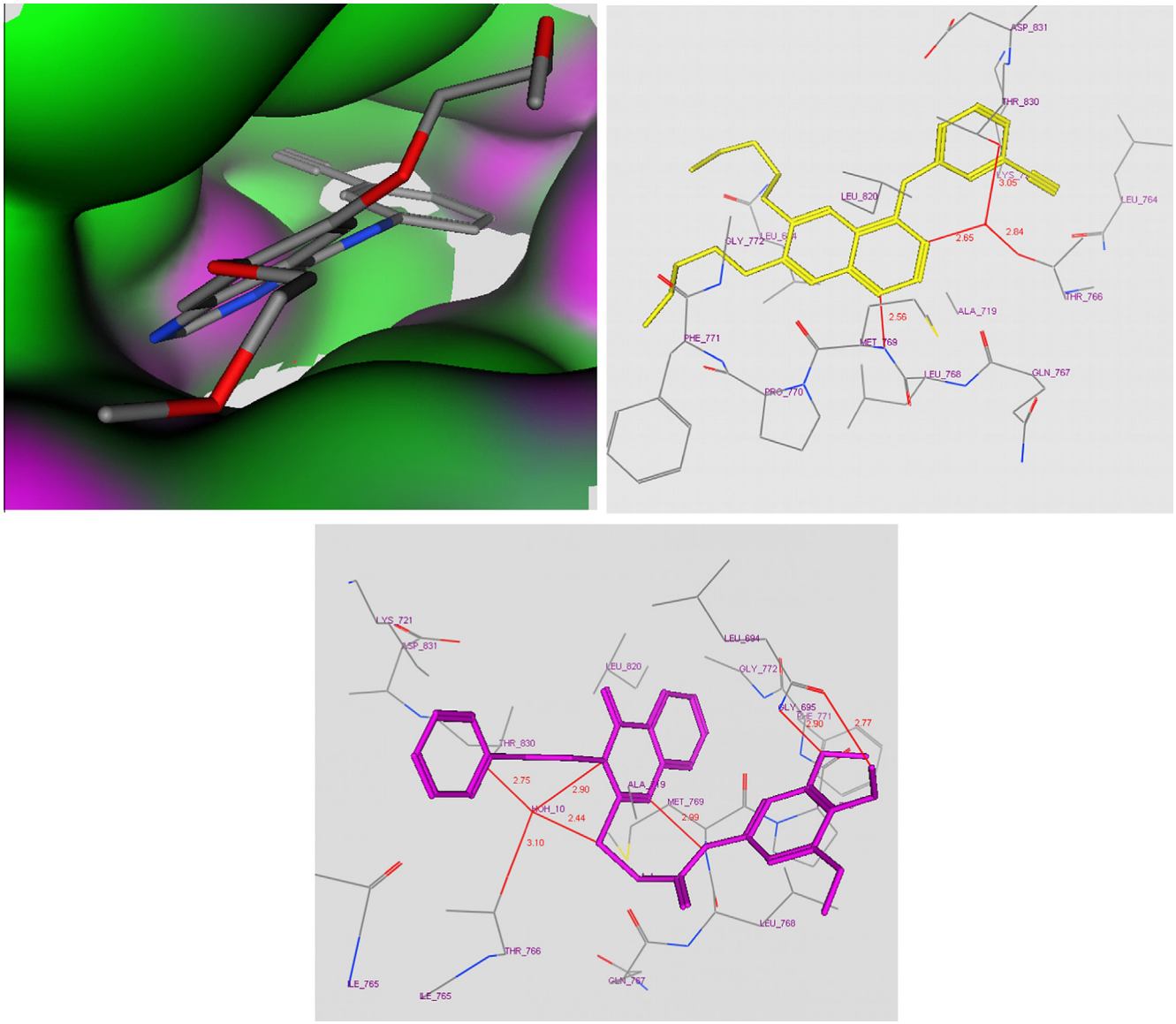


Figure 2. Docking of the erlotinib inhibitor and compound **15** into the active site of epidermal growth factor receptor.

lin-2-ylthio)acetate (**22**) with a dramatically reduction of the antitumor activities. Substitution of ethoxy group of *N*-(4-ethoxyphenyl)-2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio) acetamide (**9**) by methoxy group gave *N*-(4-methoxyphenyl)-2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetamide (**8**) with development of the antitumor activities. Displacement of chlorine atom of 5-chloro-2-(2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio) acetamido)benzoic acid (**18**) produced 2-(2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetamido)benzoic acid (**16**) with improvement of the antitumor activities. The carbon bridge linking potentiate the antitumor activity of *N*-benzyl-2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)acetamide (**12**) compared to 2-(4-oxo-3-phenethyl-3,4-dihydroquinazolin-2-ylthio)-*N*-phenylacetamide (**3**).

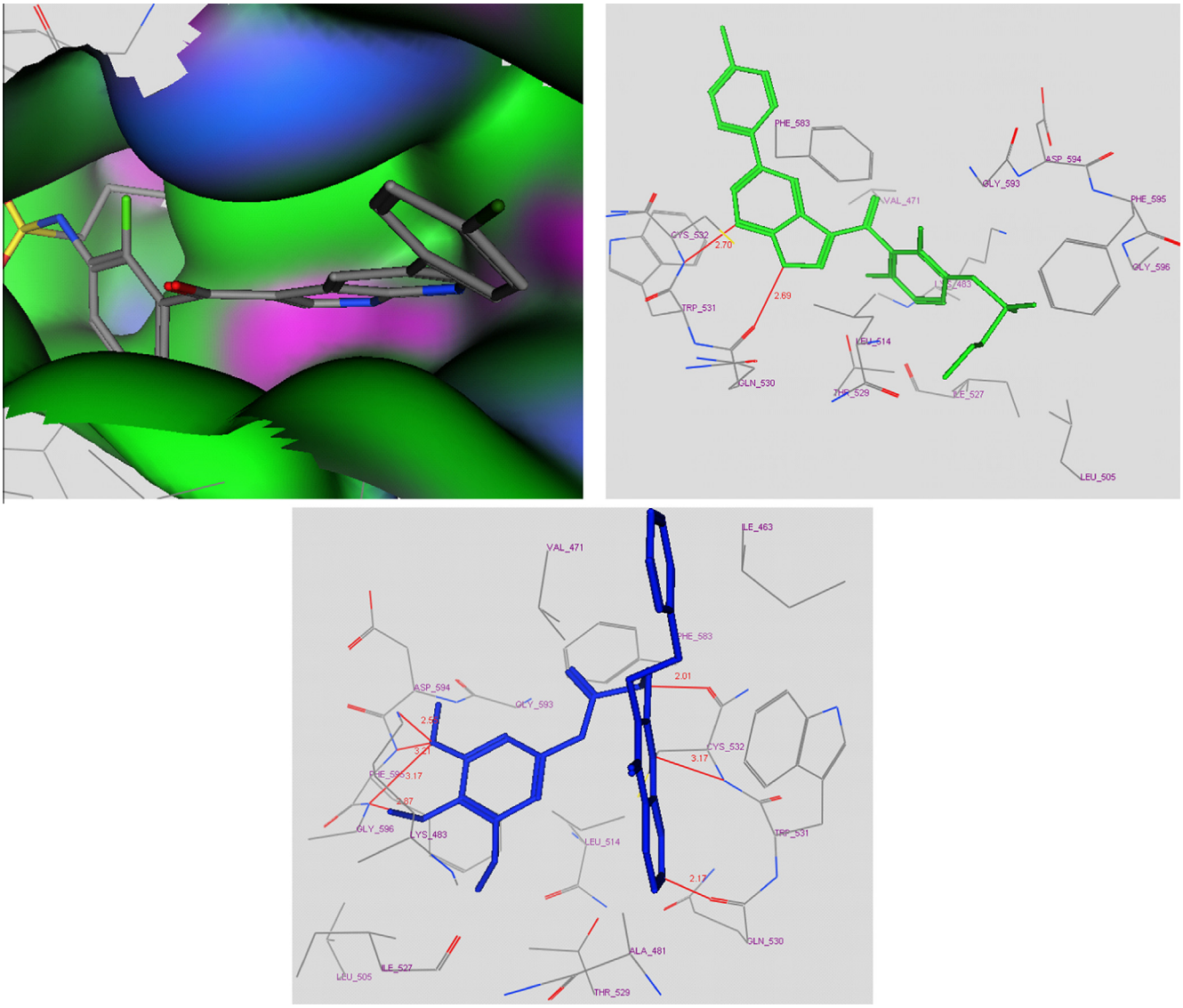


Figure 3. Docking of the PLX4032 inhibitor and compound **15** into the V600E-B-RAF kinase domain.

Molecular docking studies; The level of antitumor activities of the compound **15** over breast cancer, colon, renal, small lung and melanoma cancer cells, in which epidermal growth factor receptor (EGFR) and GG V600E-B-RAF kinase is highly expressed,[37–40,53] prompted us to perform molecular docking into the ATP binding site of EGFR and V600E-B-RAF kinase to predict if this compound **15** has analogous binding mode to the EGFR and V600E-B-RAF kinase inhibitors. We assumed that the active target compound **15** might demonstrates antiproliferative activities against breast cancer, colon, renal, small lung and melanoma cell lines through inhibition of EGFR and V600E-B-RAF respectively. Compound **15** was docked into receptor active site of both EGFR and V600E-B-RAF kinase along with their inhibitors. All the calculations were performed using MOE 2008.10 software[54] installed on 2.0G Core 2 Duo. The crystal structure of epidermal growth factor receptor with erlotinib (*Tarceva*™) (PDB code: 1M17)[37–40,55–57] and the crystal structure of V600E-BRAF kinase in complex with PLX4032 (PDB code: 3OG7)[53,58,59] were obtained from protein data bank (PDB). The automated docking program of MOE 2008.10 was used to dock compound **15** along with the inhibitors erlotinib and PLX4032 into ATP binding site of EGFR and domain of V600E-BRAF kinase, respectively. The complexes were energy-minimized with a MMFF94 force field[60] till the gradient convergence 0.01 kcal/mol was reached. The binding energies of compound **15** and erlotinib docked into the active site of EGFR were −27.21 and −24.00 kcal/mol, respectively (Fig. 2). These docking studies have revealed that the quinazoline ring binds to a narrow hydrophobic pocket in the N-terminal domain of EGFR-TK where N-1 of the quinazoline ring interacts with the backbone NH of Met-769 via a hydrogen bond. Similarly, a water (HOH-10) molecule-mediated hydrogen bonding interaction is observed among the N-3 and S-atom of the quinazoline ring, Thr-830 and Thr-766 side chain. These interactions revealed the importance of quinazoline ring for binding and the subsequent inhibitory capacity. Compound **15** complexed with EGFR-TK in a fashion similar to erlotinib and showed the occurrence of three hydrogen bonds with Met-769 (2.99 Å) and HOH-10 (2.90 Å, 2.44 Å) mediated hydrogen bonding interaction with Thr-830 side chain (2.75 Å) and Thr-766 side chain (3.10 Å). Moreover the anilide trimethoxyphenyl fragment showed two additional hydrogen bonds with Gly-695 (2.90 Å, 2.77 Å). On the other hand, the binding energies of compound **15** and PLX4032 docked into the active site of V600E-BRAF kinase were −39.89 and −36.11 kcal/mol, respectively (Fig. 3). The docking study has revealed that the ligand **15** has bound in the active site of one of

the protomers in the protein dimer through the formation of seven hydrogen bonds with Gln-530 (2.17 Å), Cys-532 (2.01, 3.17 Å), Lys-483 (2.55 Å), Phe-595 (3.21 Å) and Gly-596 (3.17 Å, 2.87 Å). Moreover there are one arene π–π and two CH-arene interactions between the binding site and the ligand. The arene π–π interaction occurred between quinazoline fragment and Trp-531 while CH–arene interaction occurred between the phenethyl fragment and Ile-463 and Val-471.

In conclusion, an interesting class of novel 2-mercapto-3-phenethyl-4(3*H*)-quinazolinone analogs were designed, synthesized and evaluated for their in-vitro antitumor activity. A single dose (10 μM) of the test compounds were used in the National Cancer Institute (NCI) 60 cell lines panel assay. The results of this study demonstrated that compounds **15**, **16** and **19** possessed the most remarkable broad spectrum antitumor agents. Additionally; the results of antitumor activity revealed that compound **15** possessed the most broad-spectrum antitumor activities; consequently compound **15** was carried over and tested against a panel of 60 different tumor cell lines at a 5-log dose rang. Three response parameters, GI_{50}, TGI and LC_{50} were calculated for each cell line, using the known drug 5-Fluorouracil (5-FU) as a positive control. Compound **15** is almost sevenfold more active than the positive control 5-FU, with GI_{50}, TGI, and LC_{50} values of 3.16, 25.0, and 77.60 μM, respectively. Molecular docking into the ATP binding site of EGFR and V600E-B-RAF kinase further helps in understanding the antitumor selectivity over tested cell lines. Molecular docking studies further supported the inhibitory activity of **15** and helped in understanding the various interactions between the ligands and enzyme active sites; thereby help to design novel potent inhibitors. Further optimizations of antitumor and pharmacokinetic profiling of these series are currently ongoing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.04.056.

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