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Original article

Synthesis and antitumor activity of some 2, 3-disubstituted quinazolin-4(3*H*)-ones and 4, 6- disubstituted- 1, 2, 3, 4-tetrahydroquinazolin-2*H*-ones

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ABSTRACT

The synthesis of some new 3-substituted quinazolin-4(3*H*)-ones and 3,4-dihydro-quinazolin-2(1*H*)-one derivatives and their biological evaluation as antitumor agents using the National Cancer Institute (NCI), disease oriented antitumor screening protocol are investigated. Compounds 2-[2-(4-chlorophenyl)-2-oxo-ethylthio]-3-(4-methoxyphenyl)quinazolin-4(3*H*)-one (**3b**), and 3-(4-chlorophenyl)-2-[2-(4-methoxyphenyl)-2-oxo-ethylthio]quinazolin-4(3*H*)-one (**3d**), are broad-spectrum antitumors showing effectiveness toward numerous cell lines that belong to different tumor subpanels, Compounds **3b**, **3d** are the most active members in this study. Those two quinazoline analogues could be considered as useful templates for future development to obtain more potent antitumor agent(s).

1. Introduction

Quinazolines are considered to be an important chemical synthon of various physiological significance and pharmaceutical utility. They possess variety of biological effects including antihypertensive [1,2], antimicrobial [3,4], antihyperlipidemic [5,6] anti-inflammatory [7,8] and anticonvulsant [9–13] activities. Moreover, many quinazolines contributed to the quest for an ultimate antitumor chemotherapeutic agent [14–18]. It was reported that 2-thioxo-3-substituted quinazolinones (**I**) [19] and their *S*-methyl thioether counterparts (**II**), in addition to the 6-substituted quinazolinone derivatives (**III**) [20] showed promising antitumor potency, (Chart 1).

The aforementioned compounds have inspired the idea of synthesizing hybrid derivatives where heterocyclic moieties reported to possess antitumor activity, such as thiadiazole [21], imidazole [22], uracil [23] and sulfonamides [24] could be incorporated into the quinazoline nucleus. In the present study, a new series of substituted quinazolinone derivatives were designed to be combined with imidazole, thiadiazole, and pyrimidine heterocycles, in addition to substituted phenyl moieties, in one molecule, as hybrid compounds anticipated acquiring antitumor efficacy.

2. Results and discussion

2.1. Chemistry

The strategy to synthesize the target quinazoline derivatives is depicted in Schemes 1–3. 3-Substituted-2-thioxo-2,3-dihydro-quinazolin-4(1*H*)-ones (**1a–d**) were synthesized according to reported methods [25–28]. Compounds **1a–d** were then reacted with the appropriate freshly prepared substituted phenacyl bromides **2a,b** [29] to yield 2-(2-(4-substituted phenyl)-2-oxo-ethylthio)-3-substituted-quinazolin-4(3*H*)-ones (**3a–e**). On the other hand, the reaction of **1a–d** with dimethyl sulphate in ethanolic sodium hydroxide afforded the 2-methylthio derivatives **4a–d** [25–28]. Nucleophilic displacement of the $-SCH_3$ function of **4a–d** by 2-amino-5-aryl-1′,3′,4′-thiadiazoles (**5a–c**), produced the target compounds 2-(5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl-amino)-3-substituted-quinazolin-4(3*H*)-ones (**6a–f**); Scheme 1. Further nucleophilic displacements of the 2-SCH_3 function in **4a–d** using imidazole, 6-aminouracil, substituted sulfonamides and 6-amino-2-mercaptopyrimidin-4-ol afforded the corresponding derivatives **7a–d**, **8a–d**, **9a–g** and **10a–d** respectively; Scheme 2. Fusion of 1,1′-(4-substituted-phenyl-methylene)diurea derivatives (**11a,b**) with different aromatic amines such as 4-aminobenzoic acid, 4-methylaniline and sulfapyridine afforded the corresponding target compounds 4-(4-substituted phenyl)-2-oxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acids (**12a,b**); 4-(4-substituted-phenyl)-6-methyl-3,4-dihydro-quinazolin-2(1*H*)-ones (**15a,b**) and

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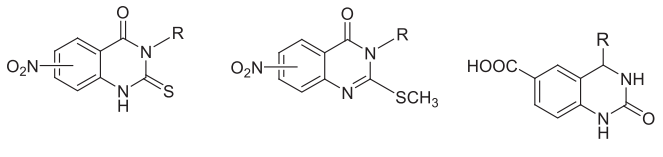


I, R= Et, Ph, Bn **II**, R= Et, Ph, Bn **III**, R = H, Ph

Chart 1.

4-(4-substituted-phenyl)-2-oxo-*N*-(pyridin-2-yl)-1,2,3,4-tetrahydro-quinazoline-6-sulfonamides (**18a**,**b**), respectively. Compounds **12a**,**b** were converted to their corresponding acid chlorides **13a**,**b** and allowed to react with 2-aminopyridine to yield 4-(4-substituted-phenyl)-2-oxo-*N*-(pyridin-2-yl)-1,2,3,4-tetrahydro-quinazoline-6-carboxamide (**14a**,**b**). The 6-methyl groups of **15a**,**b** were brominated using NBS to give the 6-bromomethyl derivatives **16a**,**b** which were subsequently reacted with 2-aminopyridine to afford the targets 4-(4-substituted-phenyl)-6-(pyridin-2-yl-aminomethyl)-3,4-dihydro-quinazolin-2(1*H*)-one (**17a**,**b**); Scheme 3.

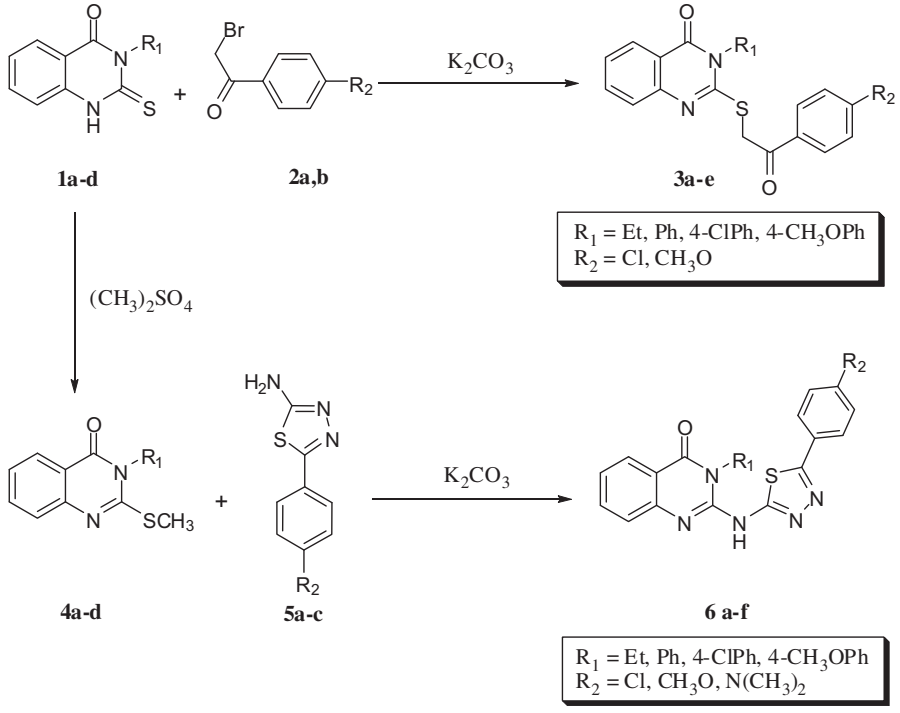
2.2. Preliminary in-vitro antitumor screening

The synthesized compounds (**3**–**18**; Schemes 1–3), were subjected to the NCI's disease-oriented human cell lines screening assay to be evaluated for their *in-vitro* antitumor activity. A single high 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 cancer, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancer cells [30–33]. The data were reported as mean graph of the percent growth of treated cells, and presented as percentage growth inhibition (GI %), Tables 1 and 2. The obtained results of the tested quinazoline derivatives **3a**–**e**, **4a**, **4c**, **4d**, **6a**, **6c**, **7a**–**d**, **9c**, **9d**, **10c**, **14a**, **b** and **17d** showed GI values >30%, distinctive potential pattern of selectivity, as well as broad-spectrum antitumor activity.

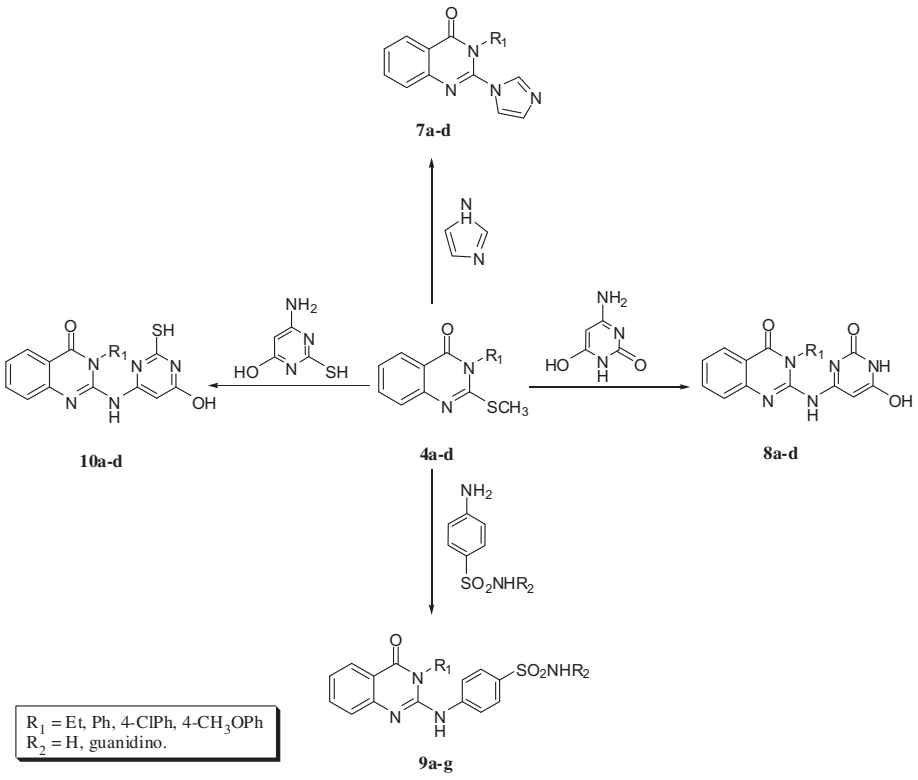
Regarding the activity toward individual cell lines; compounds **6f** and **8c** showed selective potency against leukemia K-562 and MOLT-4 cell lines with GI values of 52.0 and 34.6%, respectively; while ovarian cancer IGORV1 proved to be selectively sensitive to **8b** with GI value of 72.3%. Compounds **8d** and **10a** showed activity against CNS cancer SF-295 with GI values of 80.8 and 59.9%, respectively. Compounds **17a** and **18b** showed GI values of 43.9% and 40.5% against breast T-47D and renal UO-31 cancer cells, respectively. Meanwhile, **3b** showed a remarkable activity against non small cell lung cancer NCI-H226, melanoma UACC-62, and breast cancer HS 578T with GI values of 75.6, 68.6, and 80.6%, respectively; **3d** showed GI effectiveness against CNS cancers SNB-75, U251; and ovarian cancer OVCAR-8 with values of 71.1, 65.1, and 76.2%, respectively; **6a** and **7b** showed remarkable potency against ovarian cancer IGORV1 and non small cell lung cancer HOP-92 with GI values of 65.9 and 76.6%, respectively. In addition, compounds **3c** and **6c** proved lethal to the ovarian cancer cell line OVCAR-8; the same was observed in case of **4d** and **7d** toward non small cell lung cancer HOP-92. With regard to broad-spectrum antitumor activity; close examination of the data presented in Tables 1 and 2, revealed that compounds **3b** and **3d** are the most active members of this study, showing effectiveness toward numerous cell lines that belong to different tumor subpanels. The same analogy indicated that **14a** possess a moderate antitumor activity, while compounds **3e**, **4c**, **9c** and **10c** possess selective potency toward leukemia cell lines; and **17b** possess selective activity toward breast cancer cell lines.

2.3. Structure–activity correlation

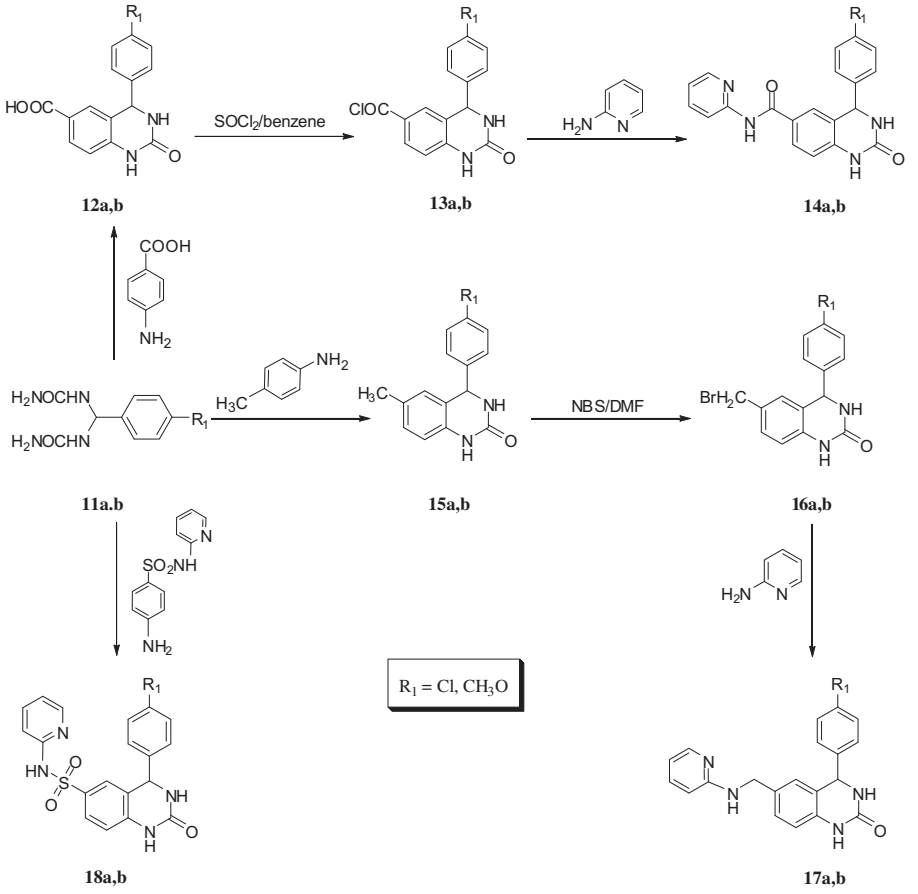
Structure–activity correlation, based on the number of cell lines proved sensitive toward each of the synthesized individual compounds, revealed that, 3-substituted quinazolin-4(3*H*)-ones heterocycles (**3**–**10**) are more active antitumors than 3,4-dihydro-quinazolin-2(1*H*)-one counterparts (**12**–**18**). The presence of aromatic substitution at position 3- of the quinazolin-4(3*H*)-one nucleus proved essential for activity rather than the aliphatic



Scheme 1. Syntheses of the target compounds **3a**–**e**, **4a**–**d** and **6a**–**f**.



Scheme 2. Syntheses of the target compounds **7a**–**d**, **8a**–**d**, **9a**–**g**, and **10a**–**d**.



Scheme 3. Syntheses of the target compounds **14a**,**b**, **15a**,**b**, **17a**,**b**, and **18a**,**b**.

Table 1
Percentage growth inhibition (GI %) of *in-vitro* subpanel tumor cell lines at 10 μM concentration of compounds **3a**–**6c**.

Subpanel tumor cell lines	% Growth Inhibition (GI %)[a]									
	Compd	3a	3b	3c	3d	3e	4a	4c	4d	6a	6c
Leukemia											
CCRF-CEM		–	–	–	nt	**70.3**	49.5	nt	–	–	–
HL-60(TB)		–	33.3	–	–	43.0	34.8	32.0	–	–	–
K-562		–	nt	nt	nt	nt	–	44.1	30.1	–	–
MOLT-4		–	–	–	–	49.4	–	31.4	–	–	–
SR		–	–	–	–	34.9	–	nt	–	–	–
RPMI-8226		–	nt	nt	nt	nt	–	35.8	–	–	–
Non small cell lung cancer											
A549/ATCC		–	nt	–	nt	30.8	–	–	–	–	–
HOP-92		–	nt	–	nt	–	60.8	–	**L**	–	–
NCI-H226		–	**75.6**	–	–	–	–	–	–	–	–
NCI-H23		–	41.1	–	–	–	–	–	–	–	–
NCI-H522		52.6	23.0	–	–	–	–	–	–	31.9	–
Colon cancer											
COLO 205		–	53.1	–	48.9	–	–	–	–	–	58.9
HCT-116		–	54.6	–	–	–	–	–	–	–	–
KM12		–	41.8	–	–	–	–	–	–	–	–
CNS cancer											
SF-268		–	49.0	–	48.8	–	–	–	–	–	–
SF-539		–	**68.6**	–	48.6	–	–	–	–	–	–
SNB-75		–	47.4	–	**71.1**	–	–	–	–	–	–
U251		–	31.6	–	**65.1**	–	–	–	–	–	–
Melanoma											
M14		–	–	–	38.4	–	–	–	–	–	–
SK-MEL-2		–	–	–	34.2	–	–	–	–	–	–
SK-MEL-28		–	–	–	37.3	–	–	–	–	–	–
UACC-62		–	**76.7**	–	42.2	–	–	–	–	–	–
Ovarian cancer											
IGORV1		43.7	45.7	–	48.9	–	–	–	–	**65.9**	–
OVCAR-4		–	32.1	–	53.5	–	–	–	–	–	–
OVCAR-8		nt	nt	**L**	**76.2**	–	–	–	–	–	**L**
SK-OV-3		–	31.9	–	44.7	–	–	–	–	–	–
Renal cancer											
786–0		–	31.1	–	41.3	–	–	–	–	–	–
CAKI-1		–	nt	–	nt	nt	42.9	–	–	–	–
SN12C		–	32.5	–	–	–	–	–	–	–	–
UO-31		–	–	31.6	37.2	30.3	–	–	–	–	–
Prostate cancer											
PC-3		nt	55.3	–	–	–	–	50.3	–	–	–
Breast cancer											
MCF7		–	34.3	–	–	–	–	–	–	–	–
MDA-MB-231/ATCC		–	33.3	–	40.9	–	–	–	–	–	–
HS 578T		–	**80.6**	–	–	–	–	–	–	–	–
T-47D		–	–	–	–	–	–	47.0	–	–	–
MDA-MB-468		–	41.4	–	35.4	30.8	–	–	–	–	–

[a] –, GI ‘ 30%; nt, not tested; L, compound proved lethal to the cancer cell line.

substituent, as in case of **3c**, **6b**, **9a**, **9e**, **10a**. Among the compounds of 2-(4-substituted phenyl)-2-oxo-ethylthio- series (**3a**–**e**); electronegativity of substituent at the aromatic rings manipulated the magnitude of activity. The two chlorine atoms of **3a** (4-chlorophenyl-ethylthio and 3-chlorophenyl-quinazoline) rendered the compound merely active, while their replacement by two methoxy groups enhanced the activity with selectivity toward leukemia cell lines as in **3e**. Mixed electronegative substituents at the said positions produced compounds **3b** and **3d**; the most active members of this study, with broad-spectrum antitumor activity (Fig. 1). Introduction of 2-[5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl-amino]- to the quinazoline nucleus afforded the hybrid series **6a**–**f**, with diminished activity. The pattern of the effect of electronegative functions on activity has been repeated in this series as well. Unsubstituted phenyl moiety at position 3- of the quinazoline nucleus favor the potency rather than substituted phenyls and chloro group at 4-chlorophenyl-1,3,4-thiadiazole contributed to activity rather than methoxy moiety (**6a** versus **6d**–**f**). The same analogy was observed upon the introduction of 2-(1*H*-imidazole), **7a**–**d**. Introducing other heterocycles to position 2- of the quinazoline moiety, such as 6-hydroxy-2-oxo-1,2-dihydropyrimidin-4-yl-amino- (**8a**–**d**), benzene sulfonamides or sulfonylguanidines (**9a**–**g**), and 6-hydroxy-2-mercaptopyrimidin-4-yl-amino- (**10a**–**d**) did not contribute to the enhancement of the antitumor activity.

3. Conclusion

Compounds 2-[2-(4-chlorophenyl)-2-oxo-ethylthio]-3-(4-methoxyphenyl)quinazolin-4(3*H*)-one (**3b**), and 3-(4-chlorophenyl)-2-[2-(4-methoxyphenyl)-2-oxo-ethylthio]quinazolin-4(3*H*)-one (**3d**), (Fig. 1); are broad-spectrum antitumors showing effectiveness toward numerous cell lines that belong to different tumor subpanels, Compounds **3b**, **3d** are the most active members in this study. Those two quinazoline derivatives could be considered as useful templates for future development to obtain more potent antitumor agent(s).

4. Experimental

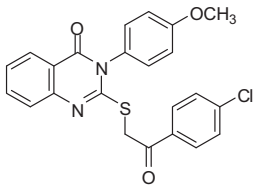
Unless specified all chemicals were of commercial grade, used without further purification and were obtained from Aldrich Chemical Co. (Milwaukee, WI). Solvents used for work ups were

Table 2
Percentage growth inhibition (GI %) of *in-vitro* subpanel tumor cell lines at 10 μM concentration of compounds **7a**–**17b**.

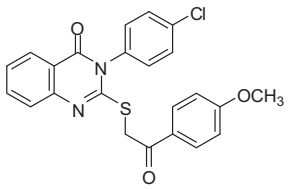
Subpanel tumor cell lines	% Growth Inhibition (GI %)[a]									
Compd	7a	7b	7c	7d	9c	9d	10c	14a	14b	17b
Leukemia										
CCRF-CEM	–	–	nt	–	–	–	–	–	–	–
HL-60(TB)	–	–	–	–	–	–	–	–	–	–
K-562	37. 9	–	37.1	30.8	34.3	47.1	36.5	–	–	–
MOLT-4	nt	–	47.7	nt	38.1	–	30.8	33.9	–	–
SR	nt	nt	nt	nt	30.2	–	36.4	–	–	–
RPMI-8226	–	–	–	–	–	–	–	–	–	–
Non small cell lung cancer										
A549/ATCC	–	–	–	–	–	–	–	–	–	–
HOP-92	–	**76.6**	–	**L**	–	–	–	–	–	–
NCI-H226	–	–	–	–	–	–	–	–	–	–
NCI-H23	–	–	–	–	–	–	–	30.4	–	–
NCI-H522	–	–	–	–	–	–	–	–	–	–
Colon cancer										
COLO 205	–	nt	–	–	–	–	–	–	–	–
HCT-116	–	–	–	–	33.6	36.7	–	39.8	–	36.8
HT29	–	–	–	–	–	–	–	37.4	–	–
KM12	–	–	–	–	–	–	–	–	–	–
CNS cancer										
SF-268	–	–	–	–	–	–	–	–	–	–
SF-539	–	–	–	–	–	–	–	–	–	–
SNB-75	–	–	–	–	–	–	–	–	–	–
U251	–	–	–	–	–	–	–	–	–	–
Melanoma										
M14	–	–	–	–	–	–	–	–	–	–
SK-MEL-2	–	–	–	–	–	–	–	–	–	–
SK-MEL-28	–	–	–	–	–	–	–	–	–	–
UACC-62	–	–	–	–	–	–	–	–	–	–
Ovarian cancer										
IGORV1	nt	nt	–	–		–	–	–	–	–
OVCAR-4	–	–	–	–	–	–	–	–	–	–
OVCAR-8	–	–	–	–	–	–	–	–	–	–
SK-OV-3	–	–	–	–	–	–	–	–	–	–
Renal cancer										
786–0	–	–	–	–	–	–	–	–	–	–
CAKI-1	46.3	–	–	–	–	–	–	–	–	–
SN12C	–	–	–	–	–	–	–	–	–	–
UO-31	–	–	–	–	–	–	–	41.8	34.3	–
Prostate cancer										
PC-3	–	–	40.3	–	–	–	–	32.9	–	–
Breast cancer										
MCF7	–	–	–	–	–	–	–	39.2	–	–
MDA-MB-231/ATCC	–	–	–	–	–	–	–	–	–	30.2
HS 578T	–	–	–	–	–	–	–	–	–	–
BT-549	–	–	–	–	–	–	–	31.8	–	–
T-47D	–	–	39.0	–	–	–	–	44.9	37.6	33.1
MDA-MB-468	–	–	–	–	–	37.5	–	–	–	–

[a] –, GI ‘ 30%; nt, not tested; L, compound proved lethal to the cancer cell line.

dried over $MgSO_4$, filtered and removed on a rotary evaporator. Melting points were carried out by the open capillary tube method using a Gallenkamp digital melting point Griffin apparatus 1901 and they are uncorrected. Elemental Microanalyses were recorded using Heraew and Vario El III (elemntar), CHNS analyzer (Germany) at the Micro Analytical Center, Faculty of Science, Cairo University. Infrared Spectra were recorded on Bruker FT-IR spectrophotometer Vector 22, Schimadzu 435, Perkin–Elmer 457 and Jasco FT-IR plus 460 Japan, and expressed in wave number (cm^{-1}), using potassium bromide discs. ^1H NMR Spectra were carried out using a Varian Gemini 200 MHz spectrophotometer. The chemical shifts were expressed in δ ppm units using trimethylsilane as the internal standard. The exchangeable protons were exchanged by D_2O. Mass Spectra were recorded on Shimadzu QP-2010 plus. All reactions were monitored by thin layer chromatography. Silica gel/TLC-cards DC-Alufolien-Kieselgel with fluorescent indicator 254 nm; layer thickness 0.2 mm; 20 × 20 cm aluminum cards were used. Petroleum ether:ethyl acetate (1:1) or (1:2) was the adopted solvent system. Compounds **1a**–**d**, **4a**–**d** [25–28] and **2a**,**b** [29] were prepared according to reported procedures.



3b



3d

Fig. 1. Structures of the active antitumor agents.

4.1. Chemistry

4.1.1. General procedure for the preparation of 2-[2-(4-substituted phenyl)-2-oxo-ethylthio]-3-substituted quinazolin-4(3H)-ones ***3a***–***e***

A mixture of 2-thioxo-dihydro-quinazolinones **1a**–**d** (10 mmol) and the appropriate freshly prepared substituted phenacyl bromide **2a**,**b** (10 mmol) was refluxed in dry acetone (30 mL) in the presence

of anhydrous potassium carbonate (1.37 g, 10 mmol) for 24 h. The reaction mixture was then filtered while hot and the filtrate was evaporated to dryness. The obtained solid was recrystallized from acetone.

4.1.1.1. 3-(4-Chlorophenyl)-2-[2-(4-chlorophenyl)-2-oxo-ethylthio] quinazolin-4(3H)-one ***3a***. Yield: 67; mp 218–219 °C; IR (KBr, cm^{-1}): 3065 (CH aromatic), 2920, 2852 (CH aliphatic), 1691 (br., C=Os), 1591, 1548 (C=C), 769 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 4.67 (s, 2H, SC$\underline{H}_2$), 7.06–8.11 (m, 12H, Ar–H); Anal. Calcd. For $C_{22}H_{14}Cl_2N_2O_2S$: C, 59.87; H, 3.20; N, 6.35. Found: C, 60.00; H, 3.10; N, 5.97.

4.1.1.2. 2-[2-(4-Chlorophenyl)-2-oxo-ethylthio]-3-(4-methoxyphenyl)-quinazolin-4(3H)-one ***3b***. Yield: 65; mp 212–213 °C; IR (KBr, cm^{-1}): 3061 (CH aromatic), 2966, 2952 (CH aliphatic), 1693 (br., C=Os), 1586, 1548 (C=C), 769 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 3.85 (s, 3H, OC$\underline{H}_3$), 4.69 (s, 2H, SC$\underline{H}_2$), 7.06–8.12 (m, 12H, Ar–H); EIMS, *m/z*: 436 (M^+); Anal. Calcd. For $C_{23}H_{17}ClN_2O_3S$: C, 63.23; H, 3.92; N, 6.41. Found: C, 63.10; H, 3.92; N, 6.10.

4.1.1.3. 3-Ethyl-2-[2-(4-methoxyphenyl)-2-oxo-ethylthio]quinazolin-4(3H)-one ***3c***. Yield: 68; mp 130–131 °C; IR (KBr, cm^{-1}): 2965, 2922 (CH aliphatic), 1675 (br., C=Os), 1567, 1545 (C=C); ^{1}H NMR (DMSO-d_6): δ 1.34 (t, 3H, C$\underline{H}_3$CH$_2$, *J* = 8.4 Hz), 3.89 (s, 3H, OC$\underline{H}_3$), 4.16 (q, 2H, CH$_3$C$\underline{H}_2$, *J* = 7.8 Hz), 4.85 (s, 2H, SC$\underline{H}_2$), 7.10–8.08 (m, 8H, Ar–H); ^{13}C NMR (DMSO-d_6): δ 14.97 (CH$_2$C$\underline{H}_3$), 38.67 (C$\underline{H}_2$CH$_3$), 38.95 (S$\underline{C}$H$_2$), 55.58 (O$\underline{C}$H$_3$), 120.67, 125.84, 125.99, 126.49, 129.47, 131.39, 134.86 (arom. C), 147.0 (C=C–N), 153.4 (N–$\underline{C}$=N), 160.6 ($\underline{C}$–OCH$_3$), 161.0 (N–$\underline{C}$=O), 194.10 (H$_2$CS–$\underline{C}$=O); EIMS, *m/z*: 355 (M + 1); Anal. Calcd. For $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90. Found: C, 64.20; H, 5.00; N, 7.96.

4.1.1.4. 3-(4-Chlorophenyl)-2-[2-(4-methoxyphenyl)-2-oxo-ethylthio]-quinazolin-4(3H)-one ***3d***. Yield: 68; mp 217–218 °C; IR (KBr, cm^{-1}): 3064 (CH aromatic), 2956, 2919 (CH aliphatic), 1682 (br., C=Os), 1548, 1489 (C=C), 758 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 3.87 (s, 3H, OC$\underline{H}_3$), 4.72 (s, 2H, SC$\underline{H}_2$), 7.11–8.07 (m, 12H, Ar–H); Anal. Calcd. For $C_{23}H_{17}ClN_2O_3S$: C, 63.23; H, 3.92; N, 6.41. Found: C, 63.35; H, 4.21; N, 6.16.

4.1.1.5. 3-(4-Methoxyphenyl)-2-[2-(4-methoxyphenyl)-2-oxo-ethylthio]quinazolin-4(3H)-one ***3e***. Yield: 65; mp 204–205 °C; IR (KBr, cm^{-1}): 3051 (CH aromatic), 1682 (br., C=Os) 1545, 1503 (C=C); ^{1}H NMR (CDCl$_3$): δ 3.78, 3.87 (2 s, 6H, 2OC$\underline{H}_3$), 4.56 (s, 2H, SC$\underline{H}_2$), 6.85–8.22 (m, 12H, Ar–H); Anal. Calcd. For $C_{24}H_{20}N_2O_4S$: C, 66.65; H, 4.66; N, 6.48. Found: C, 66.75; H, 4.56; N, 6.10.

4.1.2. General procedure for the preparation of 2-[5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl-amino]-3-substituted quinazolin-4 (3H)-ones ***6a–f***

A mixture of 2-methylthio-quinazolinone derivatives **4a–d** (10 mmol) and 2-amino-5-(4-substituted phenyl)-1,3,4-thiadiazol (**5a–c**, 10 mmol) in absolute ethanol (20 mL) was refluxed for 24 h in the presence of anhydrous potassium carbonate (1.37 g, 10 mmol). The reaction mixture was filtered while hot; the filtrate was evaporated to dryness and the obtained solid was recrystallized from methanol.

4.1.2.1. 2-[5-(4-Chlorophenyl)-1,3,4-thiadiazol-2-ylamino]-3-phenyl-quinazolin-4(3H)-one ***6a***. Yield: 78; mp 207–209 °C; IR (KBr, cm^{-1}): 3270 (NH), 3087 (CH aromatic), 2959, 2919 (CH aliphatic), 1686 (C=O), 1597 (NH bending), 1569, 1514 (C=C), 828 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 7.54–8.13 (m, 13H, Ar–H), 8.80 (s, 1H, N$\underline{H}$); EIMS, *m/z*: 433 (M + 2), 431 (M^+); Anal. Calcd. For $C_{22}H_{14}ClN_5OS$: C, 61.18; H, 3.27; N, 16.22. Found: C, 61.00; H, 3.10; N 16.44.

4.1.2.2. 3-Ethyl-2-[5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-ylamino] quinazolin-4(3H)-one ***6b***. Yield: 59; mp 204–205 °C; IR (KBr, cm^{-1}): 3251 (NH), 3108 (CH aromatic), 2959, 2922 (CH aliphatic), 1670 (C=O), 1609 (NH bending), 1550, 1464 (C=C); ^{1}H NMR (DMSO-d_6): δ 1.21 (t, 3H, CH$_2$C$\underline{H}_3$, *J* = 6.7 Hz), 3.79 (s, 3H, OC$\underline{H}_3$), 4.45 (q, 2H, C$\underline{H}_2$CH$_3$, *J* = 5.1 Hz), 6.98–7.91 (m, 8H, Ar–H), 8.60 (s, 1H, N$\underline{H}$); ^{13}C NMR (DMSO-d_6): δ 12.08 (CH$_2$C$\underline{H}_3$), 37.63 (C$\underline{H}_2$CH$_3$), 55.29 (O$\underline{C}$H$_3$), 114.46, 120.68, 123.48, 126.86, 127.74, 134.71 (arom. C), 152.0 (H$\underline{N}$–$\underline{C}$=N), 160.6 ($\underline{C}$–OCH$_3$), 166.6 (N–$\underline{C}$=N), 168.81 ($\underline{C}$=O), 185.59 (S–$\underline{C}$=N); EIMS, *m/z*: 379 (M^+); Anal. Calcd. For $C_{19}H_{17}N_5O_2S$: C, 60.14; H, 4.52; N, 18.46. Found: C, 59.44; H, 4.04; N, 18.19.

4.1.2.3. 2-[5-(4-Methoxyphenyl)-1,3,4-thiadiazol-2-yl-amino]-3-phenyl-quinazolin-4(3H)-one ***6c***. Yield: 68; mp 172–173 °C; IR (KBr, cm^{-1}): 3265 (NH), 3060 (CH aromatic), 2928 (CH aliphatic), 1686 (C=O), 1605 (NH bending), 1544, 1515 (C=C); ^{1}H NMR (DMSO-d_6): δ 3.87 (s, 3H, OC$\underline{H}_3$), 7.08–8.13 (m, 13H, Ar–H), 12.62 (s, 1H, N$\underline{H}$); Anal. Calcd. For $C_{23}H_{17}N_5O_2S$: C, 64.62; H, 4.01; N, 16.38. Found: C, 64.60; H, 4.00; N, 16.30.

4.1.2.4. 3-(4-Chlorophenyl)-2-[5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-ylamino]-quinazolin-4(3H)-one ***6d***. Yield: 65; mp 157–158 °C; IR (KBr, cm^{-1}): 3292 (NH), 3063 (CH aromatic), 2976, 2924 (CH aliphatic), 1688 (C=O), 1607 (NH bending), 1544, 1487 (C=C), 766 (C–Cl); ^{1}H NMR(DMSO-d_6): δ 3.90 (s, 3H, OC$\underline{H}_3$), 6.95–8.15 (m, 13H, 12Ar–H + N$\underline{H}$); Anal. Calcd. For $C_{23}H_{16}ClN_5O_2S$: C, 59.80; H, 3.49; N, 15.16. Found: C, 60.09; H, 3.54; N, 15.05.

4.1.2.5. 3-(4-Methoxyphenyl)-2-[5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-ylamino]- quinazolin-4 (3H)-one ***6e***. Yield: 62; mp 129–130 °C; IR (KBr, cm^{-1}): 3285 (NH), 3060 (CH aromatic), 3001, 2926 (CH aliphatic), 1685 (C=O), 1607 (NH bending), 1546, 1509 (C=C); ^{1}H NMR (DMSO-d_6): δ 3.83, 3.86 (2s, 6H, 2OC$\underline{H}_3$), 7.05–8.08 (m, 13H, 12Ar–H + N$\underline{H}$); Anal. Calcd. For $C_{24}H_{19}N_5O_3$: C, 63.01; H, 4.19; N, 15.31. Found: C, 63.21; H, 4.32; N, 15.38.

4.1.2.6. 2-[5-(4-(Dimethylamino)phenyl)-1,3,4-thiadiazol-2-ylamino]-3-phenyl-quinazolin-4(3H)-one ***6f***. Yield: 62; mp 117–118 °C; IR (KBr, cm^{-1}): 3347 (NH), 3057 (CH aromatic), 2925 (CH aliphatic), 1686 (C=O), 1603 (NH bending), 1544, 1466 (C=C); ^{1}H NMR (CDCl$_3$): δ 2.46 (s, 6H, 2CH$_3$), 7.18–8.19 (m, 14H, 13Ar–H + N$\underline{H}$); EIMS, *m/z*: 440 (M^+); Anal. Calcd. For $C_{24}H_{20}N_6OS$: C, 65.44; H, 4.58; N, 19.08. Found: C, 65.24; H, 4.71; N, 19.50.

4.1.3. General procedure for the preparation of 3-substituted-2-(1H-imidazol-1-yl)-quinazolin-4(3H)-ones ***7a–d***

A mixture of 2-methylthio-quinazolinone derivatives **4a–d** (10 mmol) and imidazole (0.68 g, 10 mmol) was refluxed for 22 h in dry dimethyl formamide (20 mL). The reaction mixture was poured onto crushed ice; the precipitated solid was filtered, washed with water, dried and recrystallized from acetone.

4.1.3.1. 3-Ethyl-2-(1H-imidazol-1-yl)quinazolin-4(3H)-one ***7a***. Yield: 62; mp 68–69 °C; IR (KBr, cm^{-1}): 3050 (CH aromatic), 2970, 2849 (CH aliphatic), 1680 (C=O), 1594, 1466 (C=C); ^{1}H NMR(DMSO-d_6): δ 1.17 (t, 3H, C$\underline{H}_3$CH$_2$, *J* = 7.0 Hz), 4.43 (q, 2H, CH$_3$C$\underline{H}_2$, *J* = 7.2 Hz), 7.36–8.11 (m, 7H, Ar–H); Anal. Calcd. For $C_{13}H_{12}N_4O \cdot 1/2H_2O$: C, 62.63; H, 5.26; N, 22.46. Found: C, 62.11; H, 5.70; N, 22.13.

4.1.3.2. 2-(1H-Imidazol-1-yl)-3-phenylquinazolin-4(3H)-one ***7b***. Yield: 56; mp 124–125 °C; IR (KBr, cm^{-1}): 3059, 3005 (CH aromatic), 2956, 2850 (CH aliphatic), 1687 (C=O), 1573, 1464 (C=C); ^{1}H NMR (DMSO-d_6): δ 7.39–8.10 (m, 12H, Ar–H); Anal. Calcd. For $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.75; H, 4.42; N, 19.68.

4.1.3.3. 3-(4-Chlorophenyl)-2-(1H-imidazol-1-yl)quinazolin-4(3H)-one ***7c***. Yield: 58; mp 104–106 °C; IR (KBr, cm^{-1}): 3087, 3065 (CH aromatic), 2938, 2850 (CH aliphatic), 1687 (C=O), 1570, 1545 (C=C), 766 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 7.47–8.10 (m, 11H, Ar–H); EIMS, *m*/*z*: 321 (M − 1), 319 (M − 3); Anal. Calcd. For $C_{17}H_{11}ClN_4O$: C, 63.23; H, 3.44; N, 17.36. Found: C, 63.35; H, 3.65; N, 17.48.

4.1.3.4. 2-(1H-Imidazol-1-yl)-3-(4-methoxyphenyl)quinazolin-4(3H)-one ***7d***. Yield: 50; mp 166–167 °C; IR (KBr, cm^{-1}): 3059, 3002 (CH aromatic), 2957, 2849 (CH aliphatic), 1688 (C=O), 1571, 1545 (C=C); ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H, OCH_3), 7.03–8.22 (m, 11H, Ar–H); ^{13}C NMR (DMSO-d_6): δ 55.44 (OCH_3), 114.55, 118.81, 119.43, 120.87, 124.34, 125.39, 125.95, 126.51. 126.69, 127.74, 128.37, 129.43, 130.51 (arom. C), 134.67 (N–C=N), 147.27 (C=C–N), 158.63 (C–OCH_3), 160.81 (C=O), 162.04 (N=C-N(N)); EIMS, *m*/*z*: 319 (M + 1); Anal. Calcd. For $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 68.55; H, 4.76; N, 17.89.

4.1.4. General procedure for the preparation of 3-substituted-2-(6-hydroxy-2-oxo-1,2-dihydro-pyrimidin-4-yl-amino)quinazolin-4(3H)-ones ***8a–d***

A mixture of 2-methylthio-quinazolinone derivatives **4a–d** (10 mmol) and 6-aminouracil (1.27 g, 10 mmol) was refluxed for 36 h in absolute ethanol (20 mL) in the presence of anhydrous potassium carbonate (1.37 g, 10 mmol). The reaction mixture was filtered while hot, the filtrate evaporated to dryness and the obtained solid was recrystallized from acetone.

4.1.4.1. 3-Ethyl-2-(6-hydroxy-2-oxo-1,2-dihydro-pyrimidin-4-yl-amino)quinazolin-4(3H)-one ***8a***. Yield: 48; mp 197–198 °C; IR (KBr, cm^{-1}): 3474 (OH), 3196, 3136 (NHs), 3077 (CH aromatic), 2982, 2926 (CH aliphatic), 1716, 1645 (C=Os), 1622 (NH bending), 1502, 1467 (C=C); ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 3H, CH_3, *J* = 7.0 MHz), 4.11 (q, 2H, CH_2, *J* = 7.2 MHz), 7.39–8.08 (m, 5H, 4Ar–H + C_5H of pyrimidine ring), 10.2 (s, 2H, 2NHs), 10.5 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 14.40 (CH_3), 38.95 (CH_2), 62.23 (C=N–C–OH), 118.66, 125.60, 125.76, 126.22, 134.38 (arom. C), 146.77 (C–OH), 156.73, 160.16 (2 C=Os), 168.37 (HN–C=N); Anal. Calcd. For $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.38; N, 23.40. Found: C, 56.44; H, 4.64; N, 23.50.

4.1.4.2. 2-(6-Hydroxy-2-oxo-1,2-dihydro-pyrimidin-4-yl-amino)-3-phenyl-quinazolin-4(3H)-one ***8b***. Yield: 52; mp 144–145 °C; IR (KBr, cm^{-1}): 3406 (OH), 3194, 3140 (NHs), 3058 (CH aromatic), 2922, 2851 (CH aliphatic), 1727, 1686 (C=Os), 1604 (NH bending), 1544, 1490 (C=C); ^{1}H NMR (DMSO-d_6): δ 7.44–8.10 (m, 13H, 9Ar–H + 2NH + OH + C_5H of pyrimidine ring); EIMS, *m*/*z*: 347 (M^+); Anal. Calcd. For $C_{18}H_{13}N_5O_3$: C, 62.24; H, 3.77; N, 20.16. Found: C, 62.44; H, 3.97; N, 20.42.

4.1.4.3. 3-(4-Chlorophenyl)-2-(6-hydroxy-2-oxo-1,2-dihydro-pyrimidin-4-yl-amino)-quinazolin-4(3H)-one ***8c***. Yield: 49; mp 125–127 °C; IR (KBr, cm^{-1}): 3294 (OH), 3196 (br., NHs), 3087, 3065 (CH aromatic), 2979, 2925 (CH aliphatic), 1731, 1687 (C=Os), 1607 (NH bending), 1544, 1489 (C=C), 768 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 7.21–8.15 (m, 12H, 8Ar–H + 2NH + OH + C_5H of pyrimidine ring); Anal. Calcd. For $C_{18}H_{12}ClN_5O_3$: C, 56.63; H, 3.17; N, 18.34. Found: C, 56.82; H, 3.37; N, 18.32.

4.1.4.4. 2-(6-Hydroxy-2-oxo-1,2-dihydro-pyrimidin-4-yl-amino)-3-(4-methoxy-phenyl)-quinazolin-4(3H)-one ***8d***. Yield: 46; mp 139–140 °C; IR (KBr, cm^{-1}): 3344 (OH), 3297 (br., NHs), 3059, 3036 (CH aromatic), 2971, 2927 (CH aliphatic), 1687 (br., C=Os), 1607 (NH bending), 1545, 1507 (C=C); ^{1}H NMR (DMSO-d_6): δ 3.81 (s, 3H, OCH_3), 6.99–7.97 (m, 11H, 8Ar–H + C_5H of pyrimidine ring + 2NHs), 12.91 (s, 1H, OH); Anal. Calcd. For $C_{19}H_{15}N_5O_4$: C, 60.47; H, 4.01; N, 18.56. Found: C, 60.99; H, 4.09; N, 18.79.

4.1.5. General procedure for the preparation of 4-[(3-substituted-4-oxo-3,4-dihydro-quinazolin-2-yl) amino]benzene sulfonamides or sulfonylguanidines ***9a–g***

A mixture of 2-methylthio-quinazolinone derivatives **4a–d** (10 mmol) and the appropriate sulfonamide (10 mmol) was refluxed for 24 h in dry dimethyl formamide (10 mL). The reaction mixture was poured onto crushed ice; the precipitated solid was filtered, washed with water, dried and recrystallized from aqueous ethanol.

4.1.5.1. 4-(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl-amino)benzenesulfonamide ***9a***. Yield: 70; mp 57–59 °C; IR (KBr, cm^{-1}): 3345, 3190 (NH_2, NH), 3074, 3017 (CH aromatic), 2979, 2923 (CH aliphatic), 1678 (C=O), 1604 (NH bending), 1564, 1467 (C=C), 1353, 1163 (SO_2); ^{1}H NMR (DMSO-d_6): δ 1.19 (t, 3H, CH_2CH_3, *J* = 7.2 Hz), 4.41 (q, 2H, CH_2CH_3, *J* = 7.2 Hz), 7.37–8.11 (m, 11H, 8Ar–H + NH_2 + NH); Anal. Calcd. For $C_{16}H_{16}N_4O_3S$: C, 55.80; H, 4.68; N, 16.27. Found: C, 56.00; H, 4.46; N, 16.25.

4.1.5.2. 4-(4-Oxo-3-phenyl-3,4-dihydroquinazolin-2-yl-amino)benzenesulfonamide ***9b***. Yield: 75; mp 97–98 °C; IR (KBr, cm^{-1}): 3362 (br., NH_2, NH), 3058(CH aromatic), 2989, 2922 (CH aliphatic), 1688 (C=O), 1609 (NH bending), 1544, 1490 (C=C), 1318, 1206 (SO_2); ^{1}H NMR (DMSO-d_6): δ 7.37–8.10 (m, 16H, 13Ar–H + NH_2 + NH); EIMS, *m*/*z*: 393 (M + 1); Anal. Calcd. For $C_{20}H_{16}N_4O_3S$: C, 61.21; H, 4.11; N, 14.28. Found: C, 61.30; H, 3.80; N, 14.29.

4.1.5.3. 4-(3-(4-Chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl-amino)benzene-sulfonamide ***9c***. Yield: 68; mp 147–149 °C; IR (KBr, cm^{-1}): 3300, 3198 (NH_2, NH), 3087 (CH aromatic), 2921, 2850 (CH aliphatic), 1685 (C=O), 1606 (NH bending), 1545, 1487 (C=C), 1321, 1205 (SO_2); ^{1}H NMR (DMSO-d_6): δ 7.47–7.80 (m, 15H, 12Ar–H + NH_2 + NH); Anal. Calcd. For $C_{20}H_{15}ClN_4O_3S$: C, 56.27; H, 3.54; N, 13.12. Found: C, 55.79; H, 4.10; N, 12.86.

4.1.5.4. 4-(3-(4-Methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl-amino)benzene-sulfonamide ***9d***. Yield: 65; mp 305–306 °C; IR (KBr, cm^{-1}): 3362, 3195 (NH_2, NH), 3066 (CH aromatic), 2927, 2854 (CH aliphatic), 1722 (C=O), 1603 (NH bending), 1512, 1488 (C=C), 1341, 1154 (SO_2); ^{1}H NMR (DMSO-d_6): δ 3.86 (s, 3H, OCH_3), 7.04–7.98 (m, 15H, 11Ar–H + NH_2 + NH); ^{13}C NMR (DMSO-d_6): δ 55.27 (OCH_3), 113.85, 114.43, 116.33, 121.43, 127.31, 128.80, 129.92, 134.62, 141.95, 151.23 (arom. C), 158.54 (C–OCH_3), 162.71 (C=O), 168.37 (N=C–N); Anal. Calcd. For $C_{21}H_{18}N_4O_4S$: C, 59.70; H, 4.29; N, 13.26. Found: C, 60.01; H, 4.45; N, 12.87.

4.1.5.5. 4-(3-Ethyl-4-oxo-3,4-dihydroquinazolin-2-yl-amino)benzenesulfonylguanidine ***9e***. Yield: 67; mp 186–187 °C; IR (KBr, cm^{-1}): 3325, 3291, 3245 (NH_2, NHs), 3050 (CH aromatic), 2922 2851 (CH aliphatic), 1674 (C=O), 1611 (NH bending), 1533, 1490 (C=C), 1375, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 1.29 (t, 3H, CH_3, *J* = 6.59 Hz), 4.11 (q, 2H, CH_2, *J* = 5.79 Hz), 5.75 (s, 2H, 2NHs), 6.60 (s, 3H, NH and NH_2), 7.44–8.14 (m, 8H, Ar–H); EIMS, *m*/*z*: 386 (M^+); Anal. Calcd. For $C_{17}H_{18}N_6O_3S$: C, 52.84; H, 4.70; N, 21.75. Found: C, 52.42; H, 5.13; N, 21.85.

4.1.5.6. 4-(3-(4-Chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl-amino)benzene-sulfonylguanidine ***9f***. Yield: 65; mp 193–194 °C; IR (KBr, cm^{-1}): 3487, 3401, 3341, 3221 (NH_2, NHs), 3098, 3062 (CH aromatic), 2927, 2850 (CH aliphatic), 1682 (C=O), 1617 (NH bending), 1549, 1488 (C=C), 1301, 1131 (SO_2), 812 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 5.75 (s, 2H, 2NHs), 6.61 (s, 3H, NH and NH_2),

7.42–8.15 (m, 12H, Ar–H); Anal. Calcd. For $C_{21}H_{17}ClN_6O_3S$: C, 53.79; H, 3.65; N, 17.92. Found: C, 53.51; H, 3.79; N, 18.19.

4.1.5.7. 4-(3-(4-Methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl-amino)benzene-sulfonylguanidine ***9g***. Yield: 63; mp 303–304 °C; IR (KBr, cm^{-1}): 3433, 3400, 3343, 3221 (NH_2, NHs), 3065 (CH aromatic), 2922, 2852 (CH aliphatic), 1620 (C=O), 1573 (NH bending), 1535, 1507 (C=C), 1302, 1132 (SO_2); ^1H NMR (DMSO-d_6): δ 3.86 (s, 3H, OCH_3), 5.75 (s, 2H, 2NHs), 6.57 (s, 3H, NH and NH_2), 6.61–7.46 (m, 12H, CH aromatic); Anal. Calcd. For $C_{22}H_{20}N_6O_4S$: C, 56.89; H, 4.34; N, 18.09. Found: C, 56.91; H, 4.42; N, 18.49.

4.1.6. General procedure for the preparation of 3-substituted-2-(6-hydroxy-2-mercaptopyrimidin-4-yl-amino) quinazolin-4(3H)-ones ***10a–d***

A mixture of 2-methylthio-quinazolinone derivatives **4a–d** (10 mmol) and the freshly prepared 6-amino-2-mercaptopyrimidin-4-ol (1.43 g, 10 mmol) was refluxed in absolute ethanol (20 mL) in the presence of anhydrous potassium carbonate (1.37 g, 10 mmol) for 36 h. The reaction mixture was then filtered while hot, the filtrate evaporated to dryness and the obtained solid was recrystallized from aqueous ethanol.

4.1.6.1. 3-Ethyl-2-(6-hydroxy-2-mercaptopyrimidin-4-yl-amino)quinazolin-4(3H)-one ***10a***. Yield: 62; mp 93–94 °C; IR (KBr, cm^{-1}): 3304, 3258, 3198 (OH, NH, SH), 3055, (CH aromatic), 2916 (CH aliphatic), 1678 (C=O), 1596 (NH bending), 1570, 1462 (C=C); ^1H NMR (DMSO-d_6): δ 1.23 (t, 3H, CH_2CH_3, J = 6.80 Hz), 4.45 (q, 2H, CH_2CH_3, J = 7.40 Hz), 7.40–8.12 (m, 7H, 4CH aromatic + C_5H of pyrimidine ring + OH + NH), 9.20 (s, 1H, SH); ^{13}C NMR (DMSO-d_6): δ 13.81 (CH_3), 35.98 (CH_2), 63.94 (C=N–C–OH), 118.09, 123.95, 125.06, 126.25, 134.05 (arom. C), 146.57 (C–OH), 152.08 (C=O), 161.22 (C–SH); Anal. Calcd. For $C_{14}H_{13}N_5O_2S$: C, 53.32; H, 4.16; N, 22.21. Found: C, 53.60; H, 4.70; N, 22.43.

4.1.6.2. 2-(6-Hydroxy-2-mercaptopyrimidin-4-yl-amino)-3-phenyl-quinazolin-4(3H)-one ***10b***. Yield: 64; mp 127–129 °C; IR (KBr, cm^{-1}): 3324, 3281, 3190 (OH, NH, SH), 3057, (CH aromatic), 2922 (CH aliphatic), 1687 (C=O), 1602 (NH bending), 1572, 1544 (C=C); ^1H NMR (DMSO-d_6): δ 6.99–8.13 (m, 12H, 9Ar–H + C_5H of pyrimidine ring + OH + NH), 8.95 (s, 1H, SH); Anal. Calcd. For $C_{18}H_{13}N_5O_2S$: C, 59.49; H, 3.61; N, 19.27. Found: C, 59.68; H, 3.38; N, 19.00.

4.1.6.3. 3-(4-Chlorophenyl)-2-(6-hydroxy-2-mercaptopyrimidin-4-yl-amino)quinazolin-4(3H)-one ***10c***. Yield: 62; mp 117–119 °C; IR (KBr, cm^{-1}): 3295 (br., OH, NH, SH), 3086, 3065, (CH aromatic), 2922, 2851 (CH aliphatic), 1686 (C=O), 1607 (NH bending), 1545, 1487 (C=C), 767 (C–Cl); ^1H NMR (DMSO-d_6): δ 6.81–8.21 (m, 11H, 8Ar–H + C_5H of pyrimidine ring + OH + NH), 9.12 (s, 1H, SH); Anal. Calcd. For $C_{18}H_{12}ClN_5O_2S$: C, 54.34; H, 3.04; N, 17.60. Found: C, 54.60; H, 3.50; N, 17.82.

4.1.6.4. 2-(6-Hydroxy-2-mercaptopyrimidin-4-yl-amino)-3-(4-methoxyphenyl)quinazolin-4(3H)-one ***10d***. Yield: 59; mp 135–136 °C; IR (KBr, cm^{-1}): 3295 (br., OH, NH, SH), 3060, (CH aromatic), 2922, 2851 (CH aliphatic), 1687 (C=O), 1606 (NH bending), 1545, 1509 (C=C); ^1H NMR (DMSO-d_6): δ 3.81 (s, 3H, OCH_3), 7.01–8.15 (m, 11H, 8Ar–H + C_5H of pyrimidine ring + OH + NH), 9.05 (s, 1H, SH); EIMS, m/z: 393 (M^+); Anal. Calcd. For $C_{19}H_{15}N_5O_3S$: C, 58.01; H, 3.84; N, 17.80. Found: C, 57.88; H, 3.46; N, 17.96.

4.1.7. General procedure for the preparation of 1,1′-(4-substituted-phenylmethylene)-diurea ***11a,b***

A mixture of the appropriate aldehyde (10 mmol) and urea (1.5 g, 25 mmol) was dissolved in absolute ethanol (50 mL) and the reaction mixture was heated under reflux for 4 h. Ethanol was distilled off and the residue was left to solidify, the obtained solid was recrystallized from methanol/chloroform (3:1).

4.1.7.1. 1,1′-(4-Chloro-phenylmethylene)diurea ***11a***. Yield: 85; mp 195–197 °C; IR (KBr, cm^{-1}): 3444, 3336 (NH_2s, NHs), 3000 (CH aromatic), 2974, 2923 (CH aliphatic), 1666 (br., C=Os), 1601 (NH bending), 1541, 1489 (C=C), 816 (C–Cl); ^1H NMR (DMSO-d_6): δ 5.16 (s, 4H, $2NH_2$), 5.82 (s, 1H, CH aliphatic), 7.38–7.95 (m, 4H, 4Ar–H), 10.00 (s, 2H, 2NH); Anal. Calcd. For $C_9H_{11}ClN_4O_2$: C, 44.55; H, 4.57; N, 23.09. Found: C, 44.64; H, 4.67; N, 23.28.

4.1.7.2. 1,1′-(4-Methoxy-phenylmethylene)diurea ***11b***. Yield: 82; mp 193–194 °C; IR (KBr, cm^{-1}): 3449, 3342 (NH_2s, NHs), 3006 (CH aromatic), 2962, 2935 (CH aliphatic), 1674 (C=Os), 1599 (NH bending), 1599, 1543 (C=C); ^1H NMR (DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 5.60 (s, 4H, $2NH_2$), 6.14 (s, 1H, CH), 7.36–7.93 (m, 4H, 4Ar–H), 9.97 (s, 2H, 2NH); EIMS, m/z: 241 (M + 3); Anal. Calcd. For $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.03; H, 6.00; N, 23.68.

4.1.8. General procedure for the preparation of 4-(4-substituted-phenyl)-2-oxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid ***12a,b***

1,1′-(4-Substituted-phenylmethylene)diurea **11a,b** (60 mmol) and 4-aminobenzoic acid (11.0 g, 80 mmol) were fused together at 145–150 °C for 4 h on a sand bath. A clear liquid was obtained on heating which solidified on cooling at room temperature. On triturating the solid using 1 M hydrochloric acid (50 mL), a solid was separated, filtered off, washed with water, dried and recrystallized from aqueous ethanol.

4.1.8.1. 4-(4-Chlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid ***12a***. Yield: 83; mp 298–299 °C; IR (KBr, cm^{-1}): 3317, 3215 (NHs), 3063 (CH aromatic), 2555 (OH carboxylic), 1697, 1654 (C=Os), 1594 (NH bending), 1525, 1458 (C=C), 764 (C–Cl); ^1H NMR (DMSO-d_6): δ 5.54 (s, 1H, C_4H), 7.15–8.19 (m, 7H, Ar–H), 9.27 (s, 2H, 2NH), 11.20 (s, 1H, OH); Anal. Calcd. For $C_{15}H_{11}ClN_2O_3$: C, 59.52; H, 3.66; N, 9.25. Found: C, 59.81; H, 3.90; N, 8.76.

4.1.8.2. 4-(4-Methoxyphenyl)-2-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid ***12b***. Yield: 80; mp 220–221 °C; IR (KBr, cm^{-1}): 3309, 3260 (NHs), 3100 (CH aromatic), 2947, 2917 (CH aliphatic), 2628, 2529 (OH carboxylic), 1686 (br., C=Os), 1599 (NH bending), 1511, 1480 (C=C); ^1H NMR (DMSO-d_6): δ 3.91 (s, 3H, OCH_3), 5.78 (s, 1H, C_4H), 7.29–8.35 (m, 7H, CH aromatic), 9.39 (s, 1H, NH), 11.63 (s, 1H, NH), 13.10 (s, 1H, OH); EIMS, m/z: 296 (M – 2); Anal. Calcd. For $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.80; H, 3.90; N, 9.00.

4.1.9. General procedure for the preparation of 4-(4-substituted-phenyl)-2-oxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl chloride ***13a,b***

To a mixture of 4-(4-substituted-phenyl)-2-oxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (**12a,b**; 10 mmol) in dry benzene (10 mL), thionyl chloride (1.18 mL, 10 mmol) was added and the reaction mixture was refluxed for 3 h. The solvent was distilled off under reduced pressure and the residue was azoetroped twice with dry benzene, then used in the next reaction without further purification.

4.1.10. General procedure for the preparation of 4-(4-substitued-phenyl)-2-oxo-N-(pyridin-2-yl)-1,2,3,4-tetrahydro-quinazoline-6-carboxamide ***14a,b***

A solution of freshly prepared acid chlorides **13a,b** (10 mmol) in dry dimethyl formamide (10 mL) was refluxed with 2-amino-pyridine (0.94 g, 10 mmol) in the presence of triethylamine (1 mL)

for 12 h. The reaction mixture was poured onto crushed ice and the separated solid was filtered, washed with water, dried and recrystallized from aqueous ethanol.

4.1.10.1. 4-(4-Chlorophenyl)-2-oxo-N-(pyridin-2-yl)-1,2,3,4-tetrahydro-quinazoline-6-carboxamide ***14a***. Yield: 65; mp 108–109 °C; IR (KBr, cm^{-1}): 3399, 3205 (NHs), 3048 (CH aromatic), 2824, 2771 (CH aliphatic), 1701, 1669 (C=Os), 1598 (NH bending), 1509, 1489 (C=C), 836 (C–Cl); 1H NMR (DMSO-d_6): δ 4.10 (s, 1H, C_4H), 7.60–8.04 (m, 13H, 11Ar–H + 2NHs), 9.94 (s, 1H, NH); Anal. Calcd. For $C_{20}H_{15}ClN_4O_2$: C, 63.41; H, 3.99; N, 14.79. Found: C, 63.43; H, 3.75; N, 14.30.

4.1.10.2. 4-(4-Methoxyphenyl)-2-oxo-N-(pyridin-2-yl)-1,2,3,4-tetrahydro-quinazoline-6-carboxamide ***14b***. Yield: 60; mp 230–231 °C; IR (KBr, cm^{-1}): 3421 (brs, NHs), 3050 (CH aromatic), 2923, 2853 (CH aliphatic), 1733, 1700 (C=Os), 1626 (NH bending), 1561, 1542 (C=C); ^{1}H NMR (DMSO-d_6): δ 3.79 (s, 3H, OCH_3), 4.86 (s, 1H, C_4H), 7.23–8.41 (m, 11H, Ar–H), 9.06 (s, 2H, 2NHs), 11.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 55.35 (OCH_3), 56.43 (HC_4), 112.17, 112.49, 113.84, 114.06, 128.21, 128.37, 130.63, 131.24, 131.34, 131.55, 132.06, 132.15, 133.42, 133.98 (arom. C), 120.61 (N=C-N(ph)(N)), 157.70 (HN C(NH)ONH), 158.10 (C–OCH_3), 158.50 (HN–C=N); Anal. Calcd. For $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 66.75; H, 4.65; N, 14.98.

4.1.11. General procedure for the preparation of 4-(4-substituted-phenyl)-6-methyl-3,4-dihydro-quinazolin-2(1H)-ones ***15a,b***

1,1′-(4-substituted-phenylmethylene)diurea (**11a,b**; 60 mmol) and 4-methylaniline (8.6 g, 80 mmol) were fused together at 145–150 °C for 4 h on a sand bath. A clear liquid was obtained on heating which solidified on cooling at room temperature. On triturating the solid using 1 M hydrochloric acid (50 mL), a solid was separated, filtered off, washed with water, dried and recrystallized from aqueous ethanol.

4.1.11.1. 4-(4-Chlorophenyl)-6-methyl-3,4-dihydro-quinazolin-2(1H)-one ***15a***. Yield: 68; mp 165–167 °C; IR (KBr, cm^{-1}): 3294, 3212 (NHs), 3082 (CH aromatic), 2917, 2825 (CH aliphatic), 1702 (C=O), 1565 (NH bending), 1563, 1457 (C=C), 781 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 5.5 (s, 1H, C_4H), 7.05–8.59 (m, 7H, Ar–H), 10.40 (s, 1H, NH), 11.13 (s, IH, NH); EIMS, *m/z*: 272 (M^+), 270 (M − 2); Anal. Calcd. For $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; N, 10.27. Found: C, 66.26; H, 5.00; N, 10.30.

4.1.11.2. 4-(4-Methoxyphenyl)-6-methyl-3,4-dihydro-quinazolin-2(1H)-one ***15b***. Yield: 63; mp 136–138 °C; IR (KBr, cm^{-1}): 3220 br. (NHs), 3061 (CH aromatic), 2985, 2947 (CH aliphatic), 1668 (C=O), 1599 (NH bending), 1516, 1486 (C=C); ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 5.5 (s, 1H, C_4H), 7.02–8.12 (m, 7H, Ar–H), 8.79 (s, 1H, NH), 9.86 (s, IH, NH); Anal. Calcd. For $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.81; H, 5.92; N, 10.90.

4.1.12. General procedure for the preparation of 6-(bromomethyl)-4-(4-substituted-phenyl)-3,4-dihydro-quinazolin-2(1H)-ones ***16a,b***

A solution of 4-(4-substituted phenyl)-6-methyl-3,4-dihydroquinazolin-2(1*H*)-one **15a,b** (10 mmol) and *N*-bromosuccinimide (1.76 g, 10 mmol) in dry dimethyl formamide (10 mL) was stirred at room temperature for 24 h. The reaction mixture was poured onto crushed ice; the obtained solid was filtered, washed with water, dried and recrystallized from ethanol:chloroform mixture (3:1) to give the desired compounds.

4.1.12.1. 6-(Bromomethyl)-4-(4-chlorophenyl)-3,4-dihydro-quinazolin-2(1H)-one ***16a***. Yield: 68; mp 168–169 °C; IR (KBr, cm^{-1}): 3427, 3308 (NHs), 3035 (CH aromatic), 2916, 2856 (CH aliphatic), 1644 (C=O), 1595 (NH bending), 1513, 1459 (C=C), 778 (C–Cl), 639 (C–Br); ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 2H, CH_2), 4.50 (s, 1H, C_4H), 6.70 (s, 2H, 2NH), 7.20–7.51 (m, 7H, Ar–H); Anal. Calcd. For $C_{15}H_{12}BrClN_2O$: C, 51.24; H, 3.44; N, 7.97. Found: C, 51.64; H, 3.94; N, 7.96.

4.1.12.2. 6-(Bromomethyl)-4-(4-methoxyphenyl)-3,4-dihydro-quinazolin-2(1H)-one ***16b***. Yield: 62; mp 211–212 °C; IR (KBr, cm^{-1}): 3419, 3300 (NHs), 3031 (CH aromatic), 2919, 2854 (CH aliphatic), 1638 (C=O), 1588 (NH bending), 1513, 1477 (C=C), 644 (C–Br); ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3), 5.51 (s, 1H, C_4H), 6.07 (s, 1H, NH), 7.28–8.71 (m, 7H, Ar–H), 9.88 (s, 1H, NH); EIMS, *m/z*: 349 ($M^+ + 2$); Anal. Calcd. For $C_{16}H_{15}BrN_2O_2$: C, 55.35; H, 4.35; N, 8.07. Found: C, 54.93; H, 3.92; N, 8.16.

4.1.13. General procedure for the preparation of 4-(4-substituted-phenyl)-6-(pyridin-2-yl-aminomethyl)-3,4-dihydro-quinazolin-2(1H)-ones ***17a,b***

A solution of bromomethyl analogues **16a,b** (10 mmol) in dry dimethyl formamide (10 mL) was refluxed with 2-aminopyridine (0.94 g, 10 mmol) in the presence of triethylamine (1 mL) for 12 h. The reaction mixture was poured onto crushed ice and the separated solid was filtered, washed with water, dried and recrystallized from aqueous ethanol.

4.1.13.1. 4-(4-Chlorophenyl)-6-(pyridin-2-yl-aminomethyl)-3,4-dihydro-quinazolin-2(1H)-ones ***17a***. Yield: 58; mp 232–233 °C; IR (KBr, cm^{-1}): 3451 (br., NH s), 2933 (CH aromatic), 2882 (CH aliphatic), 1718 (C=O), 1591 (NH bending), 1501, 1436 (C=C), 664 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 5.51 (s, 2H, CH_2), 5.60 (s, 1H, C_4H), 6.20 (s, 1H, NH), 7.02–8.60 (m, 11H, Ar–H), 11.96 (s, 2H, 2NHs); Anal. Calcd. For $C_{20}H_{17}ClN_4O$: C, 65.84; H, 4.70; N, 15.36. Found: C, 65.20; H, 4.71; N, 15.75.

4.1.13.2. 4-(4-Methoxyphenyl)-6-(pyridin-2-yl-aminomethyl)-3,4-dihydro-quinazolin-2(1H)-ones ***17b***. Yield: 55; mp 146–148 °C; IR (KBr, cm^{-1}): 3295 (br., NHs), 3062 (CH aromatic), 2921, 2850 (CH aliphatic), 1658 (C=O), 1596 (NH bending), 1542, 1500 (C=C); ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H, OCH_3), 5.10 (s, 1H, NH), 5.50 (s, 2H, CH_2), 5.62 (s, 1H, C_4H), 7.17–8.56 (m, 13H, 11Ar–H + 2NHs); Anal. Calcd. For $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55. Found: C, 69.54; H, 6.04; N, 16.00.

4.1.14. General procedure for the preparation of 4-(4-substituted-phenyl)-2-oxo-N-(pyridin-2-yl)-1,2,3,4-tetrahydro-quinazoline-6-sulfonamides ***18a,b***

1,1′-(4-substituted-phenylmethylene)diurea (**11a,b**; 60 mmol) and 4-amino-*N*-(pyridin-2-yl)benzenesulfonamide (19.9 g, 80 mmol) were fused together at 145–150 °C for 4 h on a sand bath. A clear liquid was obtained on heating which solidified on cooling at room temperature. On triturating the solid using 1 M hydrochloric acid (50 mL), a solid was separated, filtered off, washed with water, dried and recrystallized from aqueous ethanol.

4.1.14.1. 4-(4-Chlorophenyl)-2-oxo-N-(pyridin-2-yl)-1,2,3,4-tetrahydro-quinazoline-6-sulfonamide ***18a***. Yield: 52; mp 239–241 °C; IR (KBr, cm^{-1}): 3415, 3328, 3240 (NHs), 3050 (CH aromatic), 2924 (CH aliphatic), 1666 (C=O), 1585 (NH bending), 1523, 1499 (C=C), 1259, 1128 (SO_2), 769 (C–Cl); ^{1}H NMR (DMSO-d_6): δ 5.52 (s, 1H, C_4H), 6.03 (s, 1H, NH), 6.16 (s, 1H, NH), 6.59–8.16 (m, 11H, Ar–H), 9.17 (s, 1H, NH); EIMS, *m/z*: 416 (M + 2), 414 (M^+); Anal. Calcd. For $C_{19}H_{15}ClN_4O_3S$: C, 55.01; H, 3.64; N, 13.50. Found: C, 55.20; H, 3.20; N, 13.62.

4.1.14.2. 4-(4-Methoxyphenyl)-2-oxo-N-(pyridin-2-yl)-1,2,3,4-tetrahydro-quinazoline-6-sulfonamide ***18b***. Yield: 49; mp 341–342 °C; IR (KBr, cm^{-1}): 3359, 3217, 3123 (NHs), 3057 (CH aromatic), 2932, 2820 (CH aliphatic), 1703 (C=O), 1596 (NH bending), 1596, 1535 (C=C), 1391, 1136 (SO_2); ^1H NMR (DMSO-d_6): δ 3.89 (s, 3H, OCH_3), 5.59 (br. s, 3H, $C_4\underline{H} + 2N\underline{H}s$), 6.63–8.11 (m, 11H, Ar–H), 9.65 (s, 1H, N$\underline{H}$); Anal. Calcd. For $C_{20}H_{18}N_4O_4S$: C, 58.53; H, 4.42; N, 13.65. Found: C, 58.20; H, 4.40; N, 13.89.

4.2. 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 well of a microtiter tray in duplicate. Cell culture (1.8 mL) containing a cell population of 6×10^4 cells/mL was pippeted 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 10 times with saline and counted by using a coulter counter. The counts were corrected for the dilution [30–33].

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