Reactivity of 3-Amino-3*H*-quinazolin-4-one Derivatives Towards Some Electrophilic and Nucleophilic Reagents and using of the Products in the Building of some interesting Heterocycles as Anticancer Agent

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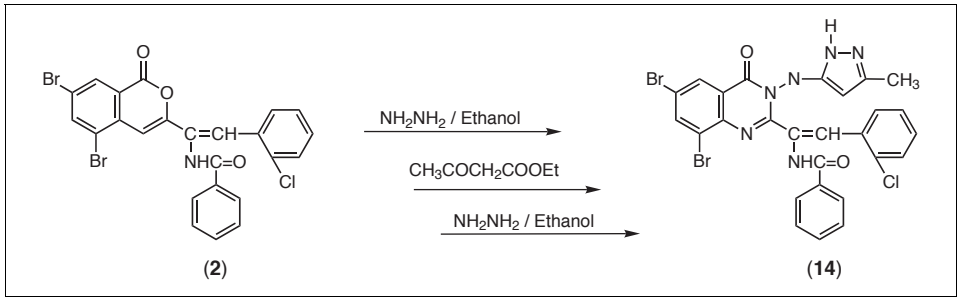

The chemical reactivity of *N*-[1-(3-amino-6,8-dibromo-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-(2-chloro-phenyl)-vinyl]benzamide (**3**) towards electrophilic and nucleophilic reagents have been reported. Structures of the products **3-24** have been confirmed by elemental analysis and spectral data (IR, ^{1}H-NMR, ^{13}C and MS). The bioassay indicates that some of the prepared compounds have a good selective anticancer activity.

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Introduction.

4*H*-3,1-Benzoxazin-4-one derivatives bear aliphatic substituents at position 2, [so called Dynamic Benzoxazinones], *e.g*. CH_3, [1], C_3H_7(iso) [2] CH_2COCH_3 [3], CH_2CN [4], C_3H_7(n) [5], CH_2CH_2COOH [6], and CH_2-C_6H5 [7], are among the more recent synthesized heterocyclic compounds. The electronically unsaturated character of these rings made difficult the synthesis of satisfactorily stable rings. New organic substituents with special properties in steric and in an electronic manner helped to solve this problem. In the last two decades, our contribution to the solving this problem includes the use of bulk substituents involving strong conjugation power (which so called static benzoxazinones) [8].

Results and Discussion.

Chemistry.

In continuation of our program involving the reactivity of the static benzoxazinone derivatives toward nitrogen and carbon nucleophiles, another derivative compound **3** was obtained *via* the interaction of *N*-[-2-(2-chloro-phenyl)-1-(6,8-dibromo-4-oxo-4*H*-benzo[*d*][1,3]-oxazin-2-yl)vinyl]benzamide (**2**) (so called Super Static benzoxazinone derivatives [9-11]) and hydrazine hydrate in absolute ethanol. The reaction takes place *via* hetero-ring opening followed by cyclization.

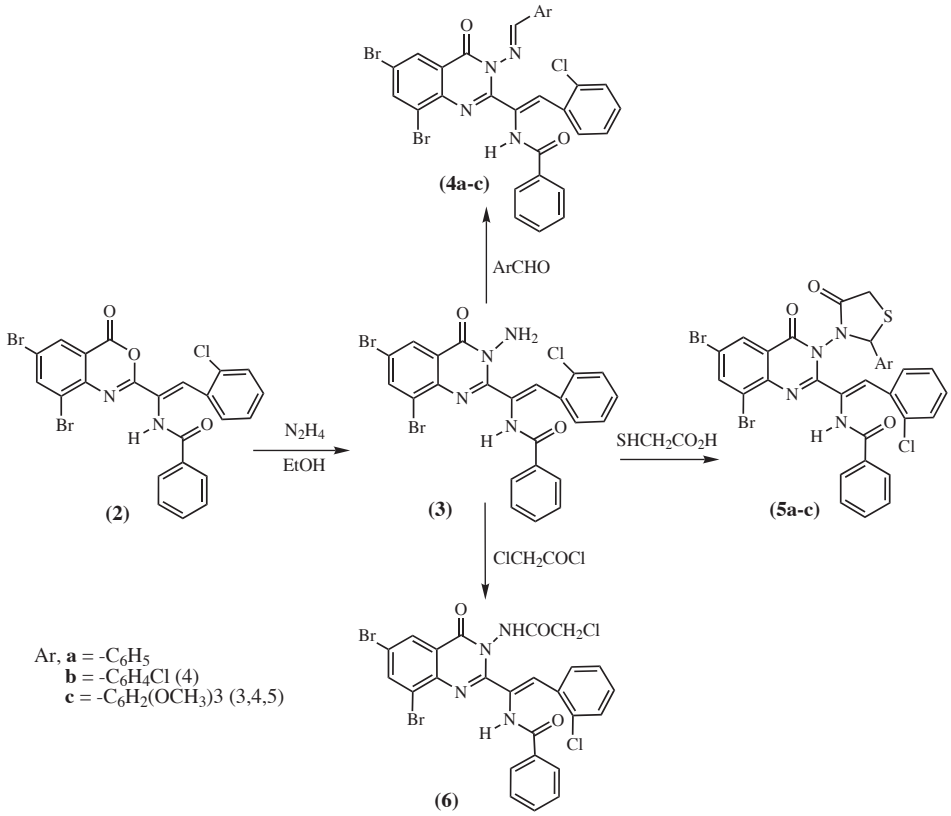
Compound **3** was used as starting material for the synthesis of various compounds, thus, when **3** was allowed to react with aromatic aldehydes namely, benzaldehyde, 4-chlorobenzaldehyde and 3,4,5-trimethoxy-benzaldehyde in boiling ethanol and in the presence of few drops of piperidine afforded (heterocyclic Schiff's bases) 2-substituted-3-arylidene-quinazoline derivatives **4a-c**, respectively, which reacted with thioglycolic acid in benzene, in the presence of few drops of piperidine, to yield 2-substituted-3-thiazolidine-quinazoline derivatives **5a-c**, respectively. The reaction takes place *via* Michael type addition followed by cyclization.

When compound **3** was allowed to react with chloro-acetyl chloride in *N*,*N*-dimethyl formamide furnished 2-substituted-3-chloro-acetylaminoquinazoline derivative **6** (Scheme 1). The reaction takes place *via* tetrahedral mechanism on the acyl moiety rather than S_N2 mechanism on the alkyl moiety.

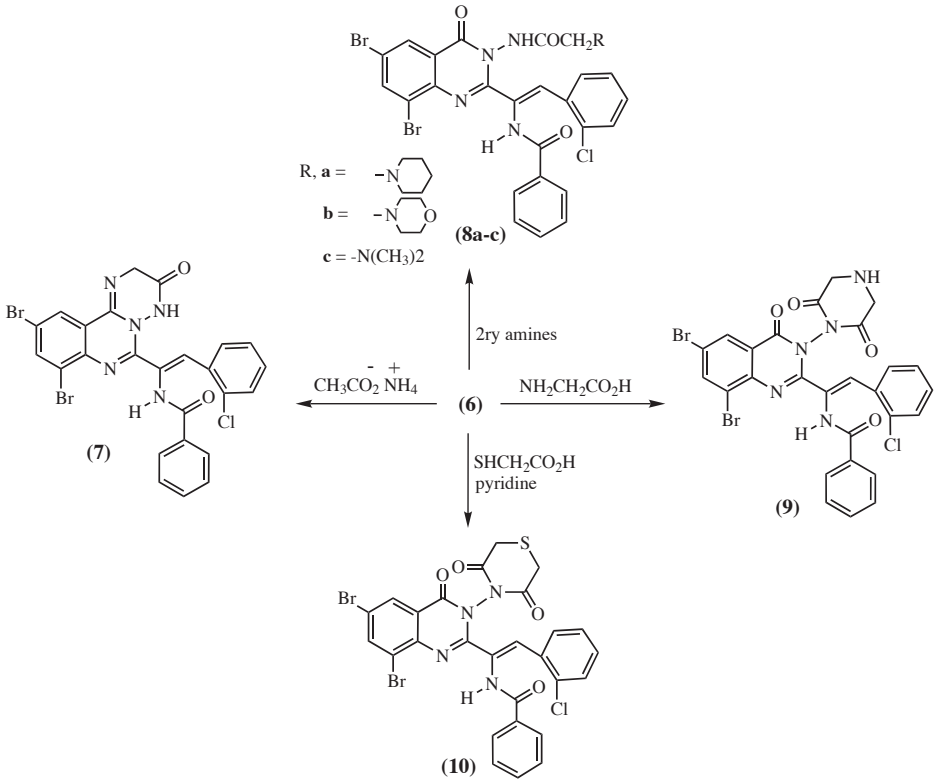
Compound **6** was used as a key starting material for synthesis of some interesting heterocyclic compounds since it has a hydrolysable halogen. Thus, when **6** reacted with ammonium acetate in *n*-butanol gave the corresponding 2-substituted-3-tetraazaphenanthrene derivative **7**. The reaction takes place *via* nucleophilic substitution of ammonia on the substituent seating (chloro-compound) through S_N2 mechanism followed by cyclization.

Refluxing of compound **6** with secondary amines namely, piperidine, morpholine and/or dimethylamine in ethanol yielded the 2-substituted-3-alkylated quinazoline derivatives **8a-c**, respectively. Moreover, compound **6**

Scheme 1



Scheme 2

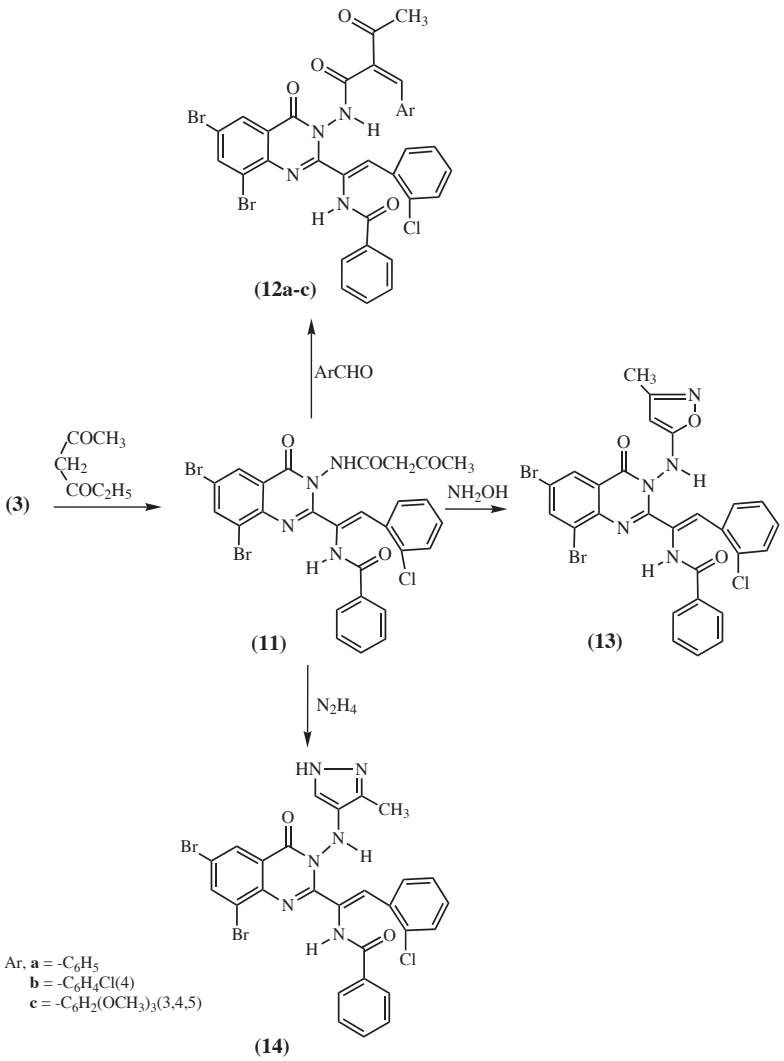


was submitted to react with glycine and/or thioglycolic acid in boiling pyridine to give 2-substituted-3-piprazinoquinazoline derivative **9** and 2-substituted-3-thiomorpholinoquinazoline derivative **10**, respectively. The reaction takes place *via* nucleophilic displacement of chlorine followed by cyclization [Scheme 2].

Reaction of **3** with ethyl acetoacetate in ethanol afforded 2-substituted-3-butyrylamino-quinazoline derivative **11**, which in turn reacted with aromatic aldehydes namely, benzaldehyde, 4-chlorobenzaldehyde and/or 3,4,5-trimethoxybenzaldehyde in the presence of piperidine to afford 2-substituted-3-acryloylamino-quinazoline derivatives **12a-c**, respectively. Also, treatment of compound **11** with either hydroxylamine hydrochloride in pyridine or hydrazine hydrate in ethanol gave 2-substituted-3-isoxazol-aminoquinazoline derivative (**13**) and 2-substituted-3-pyrazol-3-ylamino)quinazoline derivative **14**, respectively [Scheme 3].

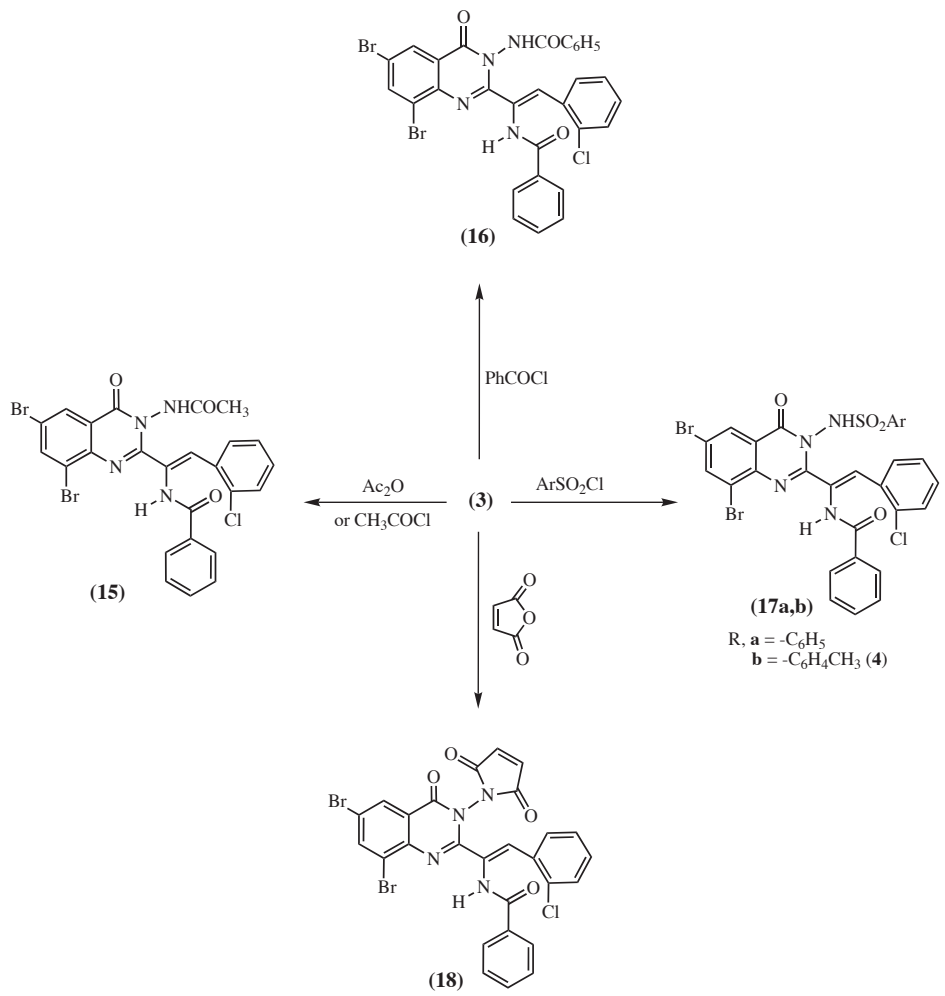
Refluxing **3** with acetic anhydride, acetylchloride and/or benzoylchloride afforded 2-substituted-3-acetyl/benzoylaminoquinazoline derivatives **15** and **16**, respectively. While refluxing **3** with benzenesulphonyl chloride and *p*-toluenesulphonyl chloride in benzene afforded 2-substituted-3-arylsulfonylaminoquinazoline derivatives **17a,b**, respectively. Fusion of **3** with maleic anhydride afforded 2-substituted-3-pyrrol-quinazoline derivative **18** [Scheme 4].

Scheme 3



Recently, [12] it has been reported that the quinazoline derivatives bearing N-H moiety reacted with phenylisocyanate in the presence of anhydrous K_2CO_3 in dry acetone to yield [*N*-(phenyl)carbamoyl]quinazoline derivatives. This prompted the author to extend his studies

Scheme 4



by reacting the amino quinazoline **3** with phenylisothiocyanate in dry benzene, phthalic anhydride in *n*-butanol, diethylmalonate in ethanol, acetylacetone in ethanol and chloroacetamide in *N*,*N*-dimethylformamid producing 2-substituted-3-(3-phenyl-thioureido)quinazoline derivative **19**, 2-substituted-3-isoindol-quinazoline derivative **20**, 2-substituted-3-malonamic acid ethyl ester-quinazoline derivative **21**, 2-substituted-3-butylideneamino-quinazoline derivative **22** and 2-substituted-3-tetraazaphenanthrene derivative **23**, respectively. Moreover, when compound **19** was treated with diethylmalonate in the presence of few drops of piperidine 2-substituted-3-pyrimidine-quinazoline derivative **24** was obtained [Scheme 5].

Pharmacology.

In Vitro Anti-tumor Testing.

Some of the new compounds have been evaluated for *in vitro* antitumor activity according to the described method of Skehan and coworkers, [13] against brain tumor cell line (**U251**) and liver carcinoma cell line (**Hepg 2**) at drug concentration between (1.00-10.00 μg/ml) using sulforhodamine **B** (**SRB**) protein assay [13]. The IC_{50} percent control of infected and uninfected response values were calculated for the various active compounds are reported in Table 3. Doxirubsin was used as positive stander. Compounds having IC_{50} < 5 μg/ml. are considered potentially active and exposed to further *in vivo* studies. The results obtained in [Table 1] showed that : 1- All the selected compounds possessed highly a significant effect on brain tumor cell line (**U251**) in the order **17b > 14 > 5b > 19 > 4 > 24 > 19 >7 > 17a**. 2- All the selected compounds are found to be lethal against liver carcinoma cell line (**Hepg 2**). 3-The compounds **17b**, **14** and **5b** possessed a highly significant effect on brain tumor cell line (**U251**), which might be due to the presence of sulfonylamino moiety in compound (**17b**), the pyrazolo moiety in compound (**14**) and the thiazolidinone moiety in compound (**5b**).

Scheme 5

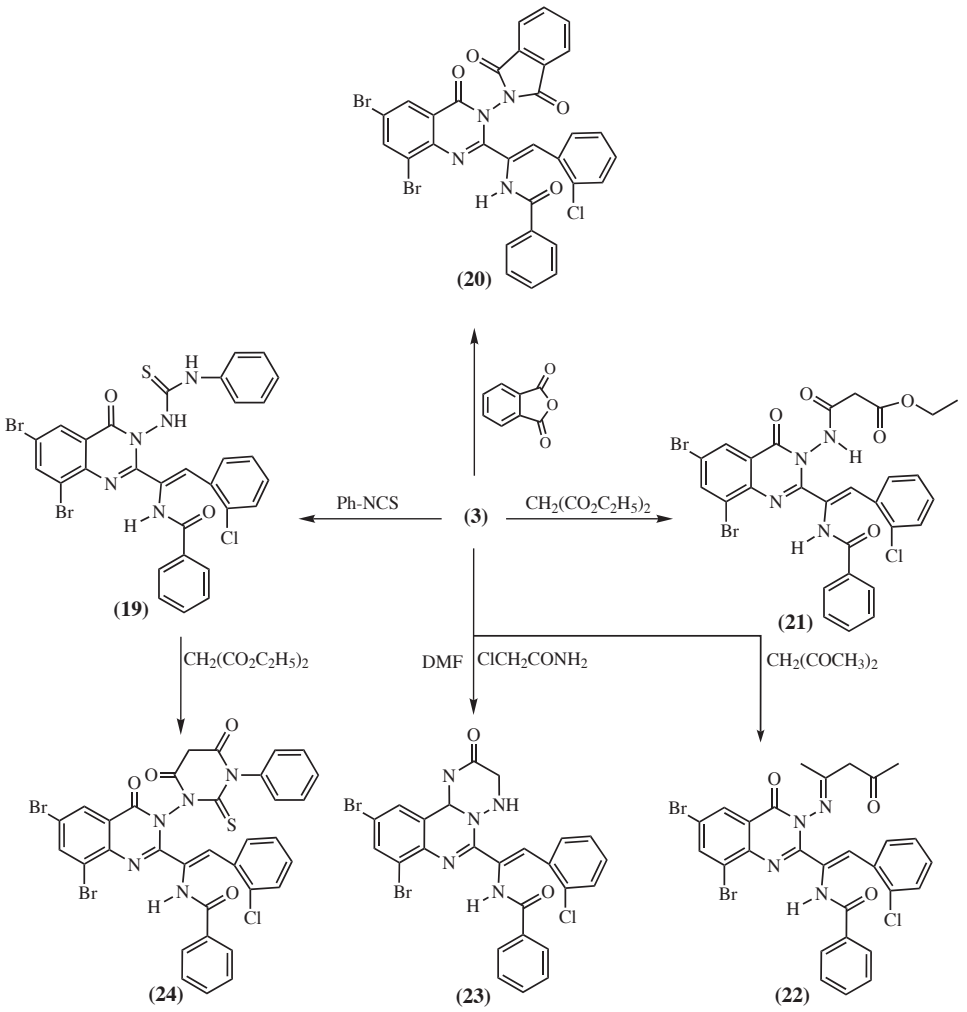


Table 1

In *vitro* antitumor activity data of some selected target new compounds.

Compds.	Cell line	**IC**$_{50}$ μg/ml
	brain tumor cell line (U251)	0.7
DOX		
DOX	liver carcinoma cell line (Hepg 2)	0.8
4	brain tumor cell line (U251)	4.36
	liver carcinoma cell line (Hepg 2)	9.04
5b	brain tumor cell line (U251)	3.74
	liver carcinoma cell line (Hepg 2)	9.76
7	brain tumor cell line (U251)	4.78
	liver carcinoma cell line (Hepg 2)	934
14	brain tumor cell line (U251)	3.21
	liver carcinoma cell line (Hepg 2)	9.36
17a	brain tumor cell line (U251)	4.83
	liver carcinoma cell line (Hepg 2)	9.54
17b	brain tumor cell line (U251)	2.14
	liver carcinoma cell line (Hepg 2)	9.00
19	brain tumor cell line (U251)	4.01
	liver carcinoma cell line (Hepg 2)	9.76
24	brain tumor cell line (U251)	4.65
	liver carcinoma cell line (Hepg 2)	9.84

IC$_{50}$**:** Dose of the drug which reduces survival to 50%.

EXPERIMENTAL

The reported melting points are uncorrected. Elemental analysis were carried out in the Microanalytical Center, Cairo University and anticancer activity in the National Center Institute, Cancer Biology Department, Pharmacology Unit, Cairo University, Egypt. IR spectra (KBr) were recorded on BRUKER VECTOR 22 FT spectrophotometer (ν_{max} in cm^{-1}), ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 MHz (Germany) using DMSO as a solvent and TMS as an internal reference δ (chemical shifts in ppm) and mass spectra were recorded on a gas chromatographic GC/MS-HEWLETT PACKARD 5988A GC/MS instrument at 70 eV. The physical data of the synthesized compounds are given in Table 2.

N-[1-(3-Amino-6,8-dibromo-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-(2-chloro-phenyl)-vinyl]-benzamide (**3**).

A mixture of **2** (0.01 mol) and hydrazine hydrate (0.75 ml, 0.015 mol) in ethanol (20 ml) was refluxed for 4 h., cooled then poured onto ice. The solid produced was collected by filtration and recrystallized from benzene to give **3** (Table 2). IR(KBr, ν_{max} in cm^{-1}): 3359 and 33379(NH_2); 3267(NH)1679(C=O); 1596(C=N). ^{1}H-NMR δ_H (DMSO-d_6): δ 2.52 (s, 2H, NH_2); 6.32(s, 1H, CH); 7.41 - 8.12 (m, 12H, [Ar-H and NH]) ppm.

N-[1-[3-(Benzylidene-amino)-6,8-dibromo-4-oxo-3,4-dihydro-quinazolin-2-yl]-2-(2-chloro-phenyl)vinyl]-benzamide (**4a**), *N*-(2-(2-Chlorophenyl)-1-{6,8-dibromo-3-[(4-chloro-benzylidene)-amino)-4-oxo-3,4-dihydro-quinazolin-2-yl}vinyl)-benzamide (**4b**) and *N*-(2-(2-Chloro-phenyl)-1-{6,8-dibromo-4-oxo-3-[(3,4,5-trimethoxy-benzylidene)-amino]-3,4-dihydro-quinazolin-2-yl}-vinyl)-benzamide (**4c**).

A solution of equimolar ratio of aminoquinazolinone **3** and benzaldehyde, 4-chlorobenzaldehyde and/or 3,4,5-trimethoxy-benzaldehyde in ethanol (30 ml) and few drops of piperidine was refluxed for 3 h., the reaction mixture was concentrated and cooled. The solid that separated was collected by filtration and recrystallized from the proper solvent to give **4a-c** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): (**4b**) 3193 (NH); 1685 and 1662 (C=O); 1567 (C=N). ^{1}H-NMR δ_H (DMSO-d_6) (**4a**): 6.32 (s, 1H, C=CH); 7.20 - 8.18 (m, 17H, [Ar-H and NH]) ppm.

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-4-oxo-3-(4-oxo-2-phenyl-thiazolidin-3-yl)-3,4-dihydroquinazolin-2-yl]-vinyl}-benzamide (**5a**), *N*-(2-(2-Chlorophenyl)-1-{6,8-dibromo-3-[2-(4-cholro-phenyl)-4-oxo-thiazolidin-3-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl}-vinyl)-benzamide (**5b**) and *N*-(2-(2-Chlorophenyl)-1-{6,8-dibromo-4-oxo-3-[4-oxo-2-(3,4,5-trimethoxy-phenyl)-thiazolidin-3-yl]-3,4-dihydro-quinazolin-2-yl}-vinyl)-benzamide (**5c**).

To a solution of **4a-c** (0.01 mol) in benzene (30 ml), thioglycolic acid (0.01 mol) was added with a few drops of piperidine and the mixture was refluxed for 1 h., then allowed to cool. The solid that separated was collected by filtration and recrystallized from the proper solvent to give **5a-c**. [Table 2]. IR(KBr, ν_{max} in cm^{-1}): (**5b**) 3243 (NH); 1720, 1641 and 1602 (C=O). ^{1}H-NMR δ_H (DMSO-d_6) (**5a**): 3.27 (s, 2H, CH_2-Thiazolidine); 6.32 - 8.12 (m, 18H, [CH-thiazolidine, N=CH, Ar-H]) and 8.24 (s, 1H, NH) ppm.; ^{13}C NMR: (**5a**) 163.2 (C-1), 159.9 (C-2), 126.0 (C-3), 132.1 (C-4), 124.6(C-5), 140.3 (C-6), 114.2 (C-7), 151.1 (C-8), 120.7 (C-9), 161.7 (C-10), 135.0 (C-11), 128.2 (C-12,C-16), 129.6 (C-13,C-15), 133.0 (C-14), 117.2 (C-17), 133.9 (C-18), 128.5 (C-19), 129.5 (C-20, C-22), 130.1 (C-21), 132.0 (C-23), 167.6 (C-24), 35.9 (C-25), 55.5 (C-26), 140 (C-27), 129.5 (C-28, C-32), 129.4 (C-29, C-31), 127.9 (C-30) ppm.

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-3-(2-chloro-acetylamino)-4-oxo-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**6**).

A mixture of **3** (0.01 mol) and chloroacetylchloride (5 ml) in DMF (20 ml) was refluxed on a water bath for 3 h., cooled and poured into cooled water. The solid obtained was collected by filtration and recrystallized from ethanol to give **6** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3248 and 3201 (NH); 1704, 1682 and 1614 (C=O); 1582 (C=N). ^{1}H-NMR δ_H (DMSO-d_6): 4.20 (s, 2H, CH_2); 6.33 (s, 1H, CH=C); 7.23 - 8.10 (m, 11H, Ar-H) and 8.18, 8.24 (s, 2H, 2NH) ppm.

N-[2-(2-Chlorophenyl)-1-(6,8-dibromo-2-oxo-2,3-dihydro-1H-1,4,9,10a-tetraaza-phenanthren-10-yl)-vinyl]-benzamide (**7**).

Ammonium acetate (0.01 mol) was added to a solution of **6** (0.01 mol) in *n*-butanol (20 ml) and the mixture was refluxed for 6 h., and allowed to cool. The solid obtained was collected by filtration and recrystallized from ethanol to give **7** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3353 and 3243 (NH); 1739, 1699 and 1653 (C=O). ^{1}H-NMR δ_H (DMSO-d_6): 4.52 (s, 2H, CH_2); 6.32 (s, 1H, CH); 7.11 - 7.98 (m, 11H, Ar-H) and 8.18 - 8.24 (s, 2H, 2NH) ppm.

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-4-oxo-3-(2-piperidin-1-yl-acetylamino)-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**8a**), *N*-{2-(2-Chloro-phenyl)-1-[6,8-dibromo-3-(2-morpholin-4-yl-acetylamino)-4-oxo-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**8b**) and *N*-{2-(2-Chloro-phenyl)-1-[6,8-dibromo-3-(2-dimethylamino-acetylamino)-4-oxo-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**8c**).

A mixture of **6** (0.01 mol) and secondary amines namely, piperidine, morpholine and/or *N*,*N*-dimethylamine (0.01 mol) in ethanol (30 ml) was refluxed for 6 h., then concentrated and cooled, the solid product separated was collected by filtration and recrystallized from the proper solvent to give (**8a-c**) [Table 2]. IR (KBr, ν_{max} in cm^{-1}): (**8a**): 3362 and 3224 (2NH); 2923 (CH of methylene group); 1701, 1681 and 1660 (C=O); 1576 (C=N). ^{1}H-NMR δ_H (DMSO-d_6) (**8c**): 2.52 (s, 6H, $2CH_3$); 3.28 (s, 2H, CH_2); 6.33 (s, H, CH); 6.81 - 7.99 (m, 11H, Ar-H) and 8.18, 18.24 (s, 2H, 2NH-C=O) ppm.

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-3-(2,6-dioxo-piprazin-1-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**9**).

To a solution of **6** (0.01 mol) in pyridine (20 ml), glycine (0. 01 mol) was added and the reaction mixture was refluxed for 8 h., then cooled and poured onto ice/HCl mixture. The solid that separated was collected by filtration and recrystallized from ethanol to give (**9**) [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3353 and 3243 (NH);1743, 1719, 1691 and 1682 (C=O); ^{1}H-NMR δ_H (DMSOd_6): 2.52 (s, 1H, NH); 3.65 (s, 2H, CH_2); 6.33 (s, 1H, CH); 7.04 - 7.97 (m, 11H, Ar-H) and 8.18 (s, 1H, NH) ppm.

N-{2-(2-Chloro-phenyl)-1-[6,8-dibromo-3-(3,5-dioxo-thiomorpholin-4-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**10**).

A mixture of **6** (0.01 mol) and thioglycolic acid (0.01 mol) in pyridine (20 ml) was refluxed for 8 h., the reaction mixture was

cooled and poured onto ice/HCl mixture. The solid that separated was collected by filtration and recrystallized from ethanol to give (**10**) [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3243 (NH); 1722, 1713, 1681 and 1668 (C=O). ^{1}H-NMR δ_H (DMSO-d_6): 3.58 (s, 4H, $2CH_2$); 6.32 (s, 1H, CH); 7.21 - 7.97 (m, 11H, Ar-H) and 8.18 (s, 1H, NH) ppm.

N-{2-(2-Chloro-phenyl)-1-[6,8-dibromo-4-oxo 3-(3-oxo-butyryl-amino)-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**11**).

An equimolar ratio of **3** (0.01 mol) and ethylacetoacetate (0.01 mol) in ethanol (30 ml) was refluxed for 6 h., then allowed to cool. The solid obtained after cooling was collected by filtration and crystallized from ethanol to give **11** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3361 and 3242 (NH); 1720, 1719, 1681 and 1639 (C=O);1576 (C=N).

N-[1-[3-(2-Acetyl-3-phenyl-acryloylamino)-6,8-dibromo-4-oxo-3,4-dihydro-quinazolin-2-yl]-2-(2-chloro-phenyl-vinyl]-benz-amide (**12a**) *N*-[1-{3-[2-Acetyl-3-(4-chloro-phenyl)acryloyl-amino]-6,8-dibromo-4-oxo-3,4-dihydro-quinazolin-2-yl}-2-(2-chlorophenyl)-vinyl]-benzamide (**12b**) and *N*-[1-{3-[2-Acetyl-3-(3,4,5-trimethoxy-phenyl)-acryloylamino]-6,8-dibromo-4-oxo-3,4-dihydro-quinazolin-2-yl}-2-(2-chloro-phenyl)-vinyl]-benz-amide (**12c**).

A mixture of **8** (0.01 mol) and benzaldehyde, 4-chloro-benzaldehyde and or 3,4,5-trimethoxy benzaldehyde (0.01 mol) in ethanol (30 ml) and few drops of piperidine was refluxed for 3 h., cooled and poured into cooled water. The solid that obtained was collected by filtration and recrystallized from the proper solvent to give **12a-c** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): (**12b**) 3461 and 3247 (NH); 1719, 1699, 1645 and 1602 (C=O).

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-3-(3-methyl-isoxazol-5-ylamino)- 4-oxo 3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**13**).

To a solution of **11** (0.01 mol) in pyridine (20 ml), hydroxylamine hydrochloride (0.01 mol) was added and the reaction mixture was refluxed for 2 hrs., cooled and poured into cooled water. The solid obtained was collected by filtration and recrystallized from ethanol to give **13** [Table 2]. IR(KBr, ν_{max} in cm^{1}):3359 and 3243 (NH); 1718 and 1672 (C=O);1605 (C=N).

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-3-(5-methyl-2*H*-pyrazol-3-ylamino)-4-oxo-3,4-dihydro-quinazolin-2-yl]-vinyl}-benz-amide (**14**).

A mixture of **11** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 ml) was refluxed for 2 h., the mixture was allowed to cool, The solid obtained after cooling was collected by filtration and recrystallized from toluene to give **14** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3469, 3342 and 3244 (NH); 1697 and 1651 (C=O).

N-[1-(3-Acety1amino-6,8-dibromo-4-oxo-3,4-dihydro-quinazo-lin-2-yl)-2-(2-chlorophenyl)-vinyl]-benzamide (**15**) and *N*-[1-(3-Benzoylamino-6,8-dibromo-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-(2-chloro-phenyl)-vinyl]-benzamide (**16**).

A solution of 3 (0.01 mol) in acetic anhydride, acetylchloride and/or benzoylchloride (20 ml) was refluxed for 2 hrs., cooled and poured into cooled water. The solid that separated was collected by filtration and recrystallized from benzene to give **15** and **16**, respectively [Table 2]. IR (KBr, ν_{max} in cm^{-1}): (15) 3339 and 3246 (2NH) 1715, 1651 and 1640 (CO) (16b): 3356 and 3245 (NH); 1687, 1672 and 1640 (C=O).; (16b): 3356 and 3245 (NH); 1687, 1672 and 1640 (C=O); ^{1}H-NMR δ_H (DMSO-d_6): (**15**): 1.83 (s, 3H, CH_3); 6.33 (s, 1H, CH); 7.16 .- 8.01 (m, 11H, Ar-H) and 8.18 - 8.20 (s, 2H, 2NH) ppm.; ^{13}C NMR: 162.8 (C-1), 160 (C-2), 126 (C-3), 132.1 (C-4), 134.6 (C-5), 140,3 (C-6), 114.0 (C-7), 157,8 (C-8), 120.7 (C-9), 161.6 (C-10), 135.0 (C-11), 128.2 (C-12,C-16), 129.6 (C-13, C-15), 133.0 (C-14), 117.2 (C-17), 133.9 (C-18), 128.5 (C-19), 127.5 (C-20, C-22), 130.1 (C-21), 132.0 (C-23), 166.7 (C=O), 25.3 (CH_3) ppm.

N-[1-(3-Benzenesulfonylamino-6,8-dibromo-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-(2-chlorophenyl)-vinyl]-benzamide (**17a**) and *N*-{2-(2-Chlorophenyl)-1-[6,8-dibromo-4-oxo-3-(toluene 4-sulfonyl-amino)- 3,4-dihydro-quinazolin-2-yl]- vinyl}-benzamide (**17b**).

A mixture of **3** (0.01 mol) with benzenesulfonyl chloride and/or *p*-toluenesulfonyl chloride (0.01 mol) in benzene (30 ml) was refluxed for 2 h., then allowed to cool. The mixture obtained after cooling was collected by filtration and recrystallized from the proper solvent to give (**17a,b**) [Table 2]. IR (KBr, ν_{max} in cm^{-1}): (**17b**) 3357 and 3287(NH), 1680 and 1640 (C=O); 1054(C=S).

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]-vinyl}-benzamide (**18**).

Compound **3** (0.01 mol) and maleic anhydride (0.01 mol) in dry benzene were refluxed on a water bath for 2 hrs., then left to cool, the solid that separated was collected by filtration and recrystallized from benzene to give **18** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3354 (NH), 1715 - 1670 (C=O). ^{1}H-NMR δ_H (DMSO-d_6): 6.33 (s, 1H, C=CH-Ph), 7.04 .- 8.05 (m, 11H , [-CH-CH-pyrrol, Ar-H]) and 8.18 (s, 1H, NH) ppm.

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-4-oxo-3-(3-phenyl-thio-ureido)-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**19**).

A mixture of **3** (0.01 mol) and phenylisothiocyanate (0.01 mol) in dry benzene (30 ml) and 0.5 g anhydrous K_2CO_3 was refluxed for 3 h. The solid that separated after cooling was collected by filtration and recrystallized from benzene to give **19** [Table 2]. IR(KBr, ν_{max} in cm^{-1}): 3448, 3213, 3114 (NH);1662 (C=O); 1213 (C=S); 1189 (C=S).

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**20**).

Compound **3** (0.01 mol) and phthalic anhydride (0.01 mol) in *n*-butanol (30 ml) were refluxed for 6 h., the mixture was allowed to cool. The solid that separated was collected by filtration and recrystallized from toluene to give **20** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3243 (NH); 1720, 1680 and 1639 (C=O).

N-{2-[1-Benzoylamino-2-(2-chloro-phenyl)-vinyl]-6,8-dibromo-4-oxo-4*H*-quinazolin-3-yl}-malonamic acid ethyl ester (**21**).

A mixture of **3** (0.01 mol) and diethylmalonate (0.01 mol) in ethanol (40 ml) was refluxed for 6h., cooled and poured into cooled water. The solid that separated was collected by filtration and recrystallized from benzene to give **21** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3379 and 3243 (NH); 1779, 1735, 1670 and 1635 (C=O). ^{1}H-NMR δ_H (DMSO-d_6): 1.51 (t, 3H, CH_3); 3.25 (s, 2H, CH_2C=O); 4.22 (q, 2H, CH_2O-C=O); 6.33 (s, 1H, CH); 6.82 - 8.09 (m, 11H, Ar-H) and 8.17 -8.19 (s, 2H, 2NH) ppm.

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-3-(1-methyl-3-oxo-butylideneamino)-4-oxo-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**22**).

An equimolar ratio of **3** (0.01 mol) and acetylacetone (0.01 mol) in ethanol (30 ml) was refluxed for 6hrs., and allowed to cool. The solid obtained was collected by filtration and recrystallized from ethanol to give **22** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3364 (NH); 1720, 1679, 1639 (C=O).^{1}H-NMR δ_H (DMSO-d_6): 1.20 (s, 3H, CH_3); 2.03 (s, 3H, $COCH_3$); 2.62 (s, 2H, CH_2CO); 6.32 (s, 1H, CH); 7.26. - 8.09 (m, 11H, Ar-H) and 8.24 (s, 1H, NH) ppm.

N-[2(2-Chlorophenyl)-1-(6,8-dibromo-3-oxo-2,3-dihydro-1*H*-1,4,9,10a-tetraazaphenanthren-10-yl)-vinyl]-benzamide (**23**).

A mixture of **3** (0.01 mol) with chloroacetamide (0.01 mol) in *N*,*N*-dimethylformamid (20 ml) was refluxed for 6 h., and allowed to cool. The solid obtained was collected by filtration and recrystallized from ethanol to give **23** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3470 and 3350 (NH); 1742, 1700 (C=O).

N-{2-(2-Chlorophenyl)-1-[6,8-dibromo-3-(4,6-dioxo-3-phenyl-2-thioxotetrahydropyrimidin-1-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-vinyl}-benzamide (**24**).

To a solution of **19** (0.01 mol) in ethanol (40 ml), diethylmalonate (0.01 mol) was added with a few drops of piperidine and the reaction mixture was refluxed for 3 h., then poured onto cold water to give a solid, which was recrystallized from ethanol to give **24** [Table 2]. IR (KBr, ν_{max} in cm^{-1}): 3427 and 3357 (NH); 2923 (CH of methylene group); 1672 and 1658 (C=O); 1157 (C=S). ^{1}H-NMR δ_H (DMSO-d_6): 3.09 (s, 2H, CH_2 of pyrimidine dervative); 6.33 (s, 1H, CH); 7.05 - 8.11 (m, 16H Ar-H) and 8.18 (s, 1H, NH) ppm.; ^{13}C NMR: 161.8 (C-1), 158.8 (C-2), 126.1 (C-3), 132.3 (C-4), 124.8 (C-5), 140.5 (C-6), 113.8 (C-7), 151.5 (C-8), 120.9 (C-9), 161.4 (C-10), 135.2 (C-11), 128.4 (C-12, C-16), 129.8 (C-13, C-15), 133.2 (C-14), 117.4 (C-17), 134.1 (C-18), 128.7 (C-19), 127.7 (C-20, C-22,), 130.4(C-21) 132.2 (C-23), 179 (C-24), 167 (C-25), 40.0 (C-26), 165.6 (C-27), 136.4 (C-28), 122.5 (C-29, C-33), 129.9 (C-30, 32), 125.3 (C-31) ppm.

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