Research article
International Journal of Heterocyclic Chemistry, Vol. 7, No. 2, pp. 36-52 (Spring 2017)

http://ijhc.iauahvaz.ac.ir

Synthesis of Some Quinazoline Derivatives Functionalized with3-Heterocycles Side Chain

Heba E. Hashem[a]*, Magdy M. Hemdan[b], Ahmed S.A. Youssef[b], and Fatma A. El-Mariah[a]

[a]Department of Chemistry, College for Girls, Ain Shams University, Helioplis, Cairo 11457, Egypt
[b]Department of Chemistry, Faculty of Science, Ain Shams University, Abbassia, Cairo 11566, Egypt

*E-mail: hebahashem89@yahoo.com

Recieved:16 April 2017 Revised: 26 June 2017 Accepted: 2 July 2017

Abstract:
Utilization of benzoxazinone for synthesis quinazolinone derivatives with 3-heterocycle side chain. treatment of benzoxazinon **1** with cyano acetohydrazide or thionocarbohydrazide gave the quinazolinone derivatives **2** or **12**. quinazolinone **2** has been utilized as synthon for new pyridinone, oxazet, thiazole, thiazolidinone and quinazolinone derivatives. Thiosemicarbazide and thiosemicarbazone derivatives are synthesized from quinazolinone **12** by different route. The structures of the new compounds were established on the basis of IR, ^{1}HNMR, mass spectral data, and elemental analysis.

Keywords: quinazolinone, oxazet, thiazole, thiazolidinone, tetrazine, thiosemicarbazone.

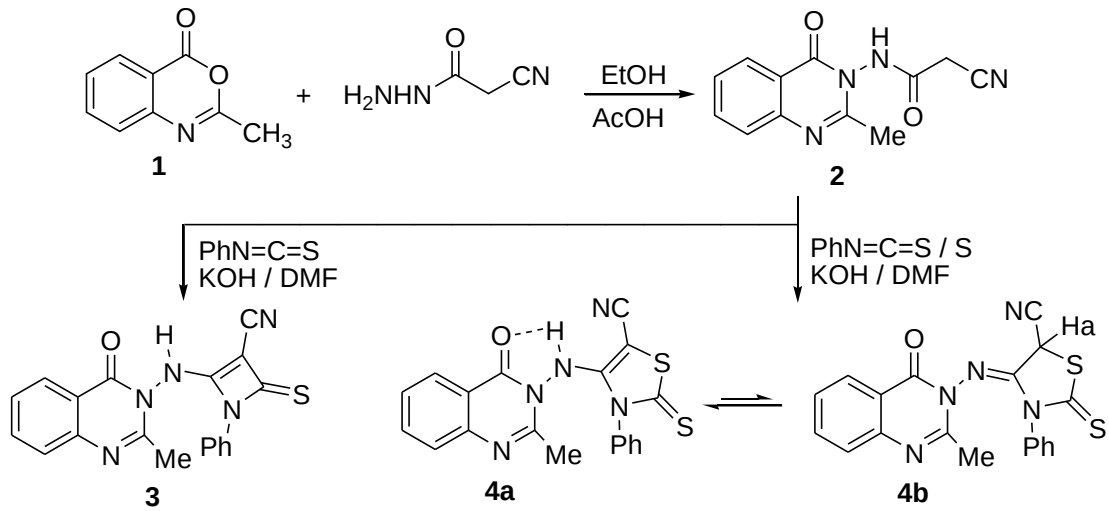
Introduction:

The quinazoline ring system is found in many types of bioactive natural and synthetic products. Many natural products containing quinazoline moiety were found to have different application in the medicinal field as biologically active molecules,[1–3] including antimicrobial[4,5], antioxidant[5], anticancer[6,7], antihypertensive[8], anti-HIV[9] ,anticonvulsant[10] and antiviral activities[11]. The present work aimed to utilize 2-methyl-4Hbenzo[*d*][3,1]oxazin-4-one[12] with cyanoacetohydrazide or

thiocarbonohydrazide as a source of bioactive quinazoline derivatives functionalized with 3-heterocycles side chain.

Results and Discussion

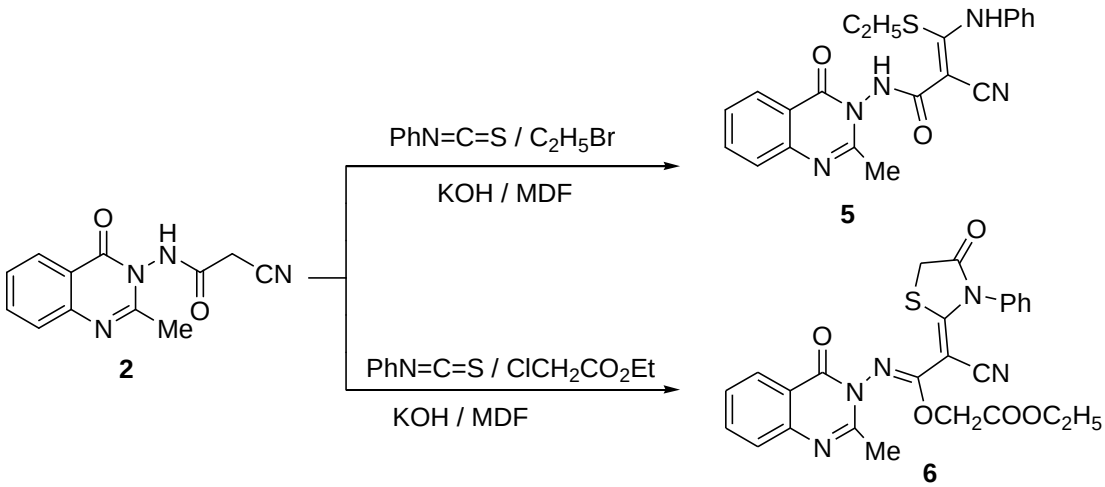
Treatment of quinazolinone derivative **2** with equivalent amounts of phenyl isothiocyanate by stirring at room temperature in dimethylformamide and catalytic amount of potassium hydroxide produced azete derivative **3** as shown in Scheme 1. On the other hand, refluxing compound **2** under similar conditions and in the presence of elemental sulfur gave thiazole derivative **4**. ^{1}HNMR spectrum of compound **4** showed its existence in dimethylsulphoxide solution as amine – imine tautomer **4a** and **4b** in the ratio of 83: 17 % respectively. The microanalytical and spectral data support the structures of the synthesized compounds **3** and **4** respectively (see Experimental section).



Scheme 1

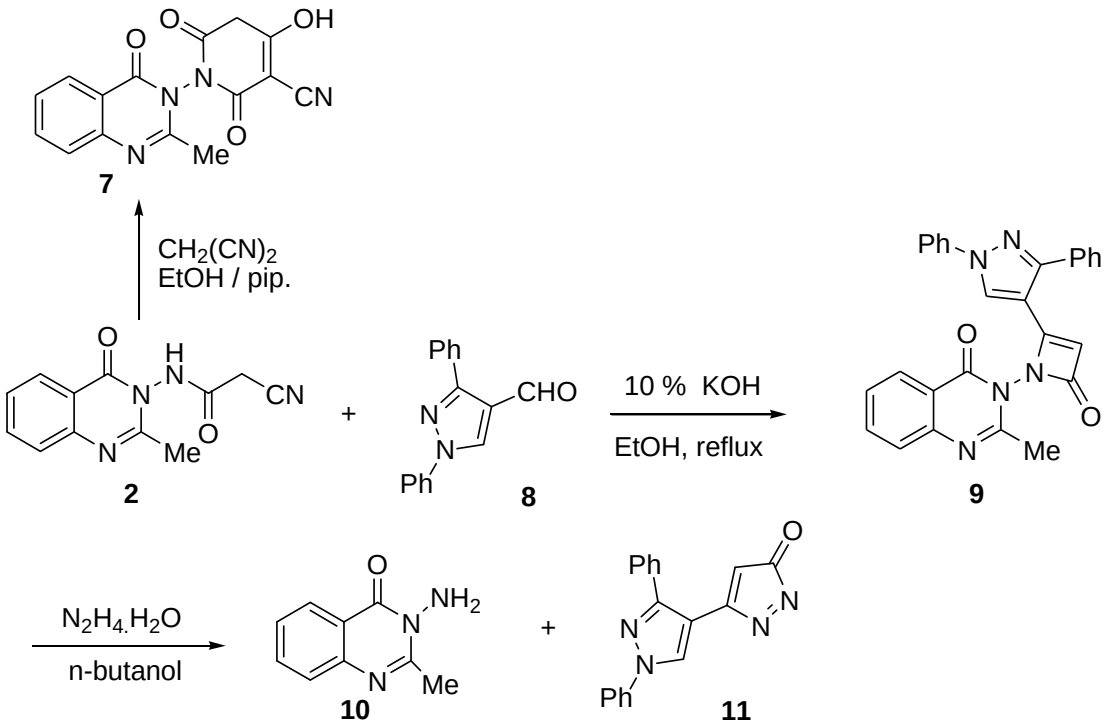
Reaction of quinazoline derivative **2**, phenyl isothiocyanate and ethyl bromide by stirring at room temperature in dimethyl formamide and catalytic amount of potassium hydroxide gave an adduct **5**. On the other hand, the reaction of **2** under similar conditions with two molar equivalent of ethyl chloroacetate afforded thiazolidinone derivative **6** in good yield (Scheme 2).

Inspection of ^{1}HNMR spectrum of compound **6** revealed doublet of doublet signals with coupling constant J = 15.9 Hz for thiazolidinone methylene protons. This suggests the two geminal protons of methylene group are magnetically nonequivalent.



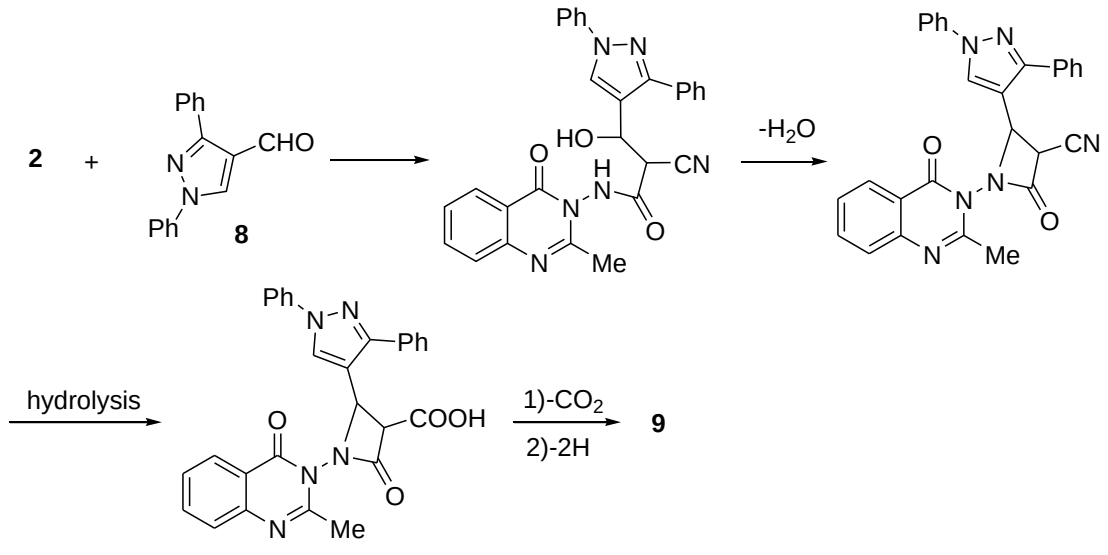
Scheme 2

Treatment a solution of compound **2** in ethanol with an equivalent amount of malononitrile and catalytic amount of pipridine yielded pyridine derivative **7** as shown in Scheme 3. The infrared spectrum of compound **7** showed absorption due vibrational coupling of the two carbonyl groups of pyridine ring at 1779 and 1708 cm[1]. Moreover, its ^{1}HNMR displayed a geminal coupling of the two methylene protons J_{gem} = 18.6 Hz which suggests that they are magnetically nonequivalent. The reaction of **2** with 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (**8**) in 10% alc. potassium hydroxide furnished pyrazole derivative **9**. Treating compound **9** with hydrazine hydrate in boiling n-butanol produced a mixture of amino quinazoline derivative **10**[13] and pyrazole derivative **11**. The proposed mechanism for the formation of compound **9** is illustrated in Scheme 4.



Scheme 3

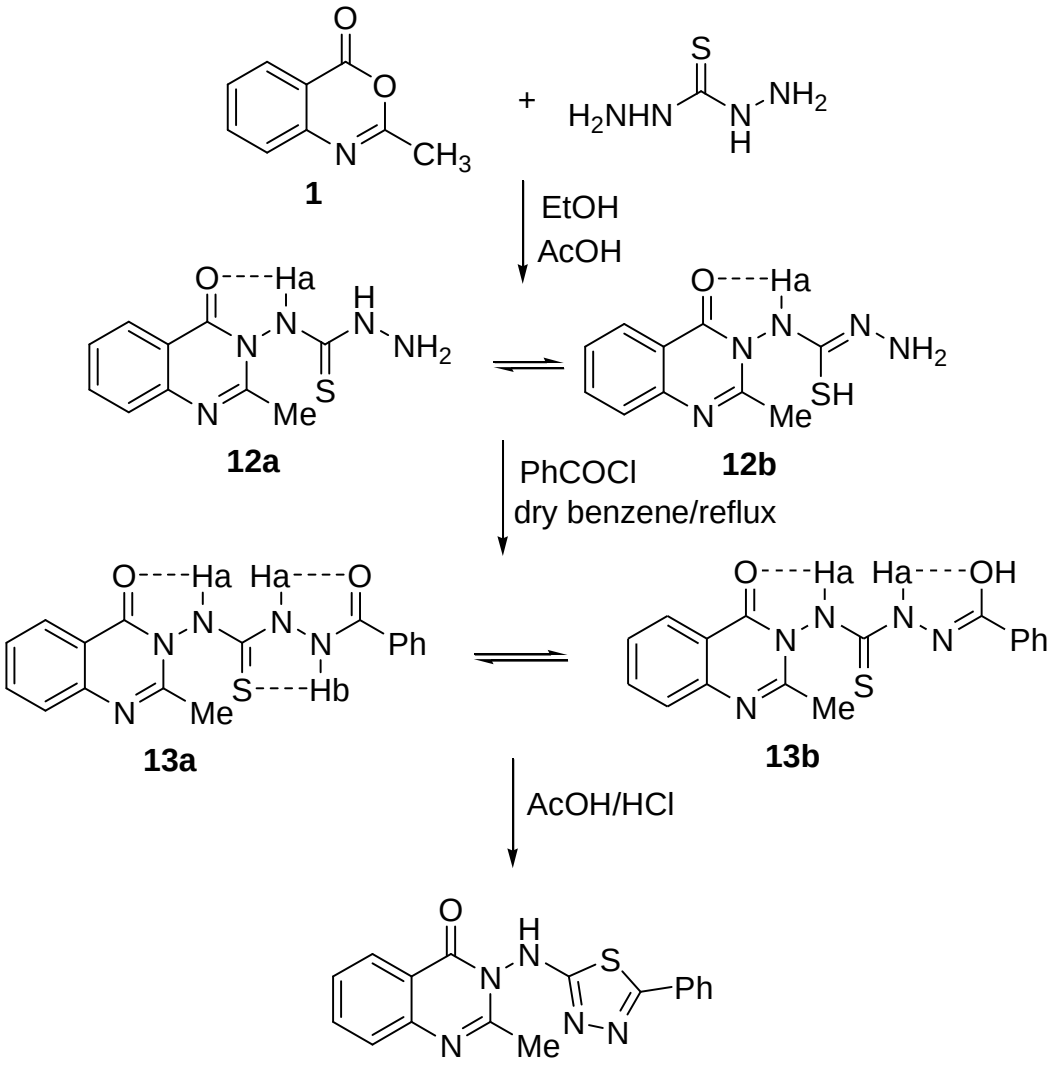
The proposed mechanism for the formation of compound **9** is illustrated in Scheme 4.



Scheme 4: The proposed mechanism of formation of compound **9.**

Further synthesis of quinazoline derivatives were achieved by reaction of benzooxazinone **1** with thiocarbonohydrazide as shown in Scheme 5**.** Thus reaction of benzooxazinone **1** with

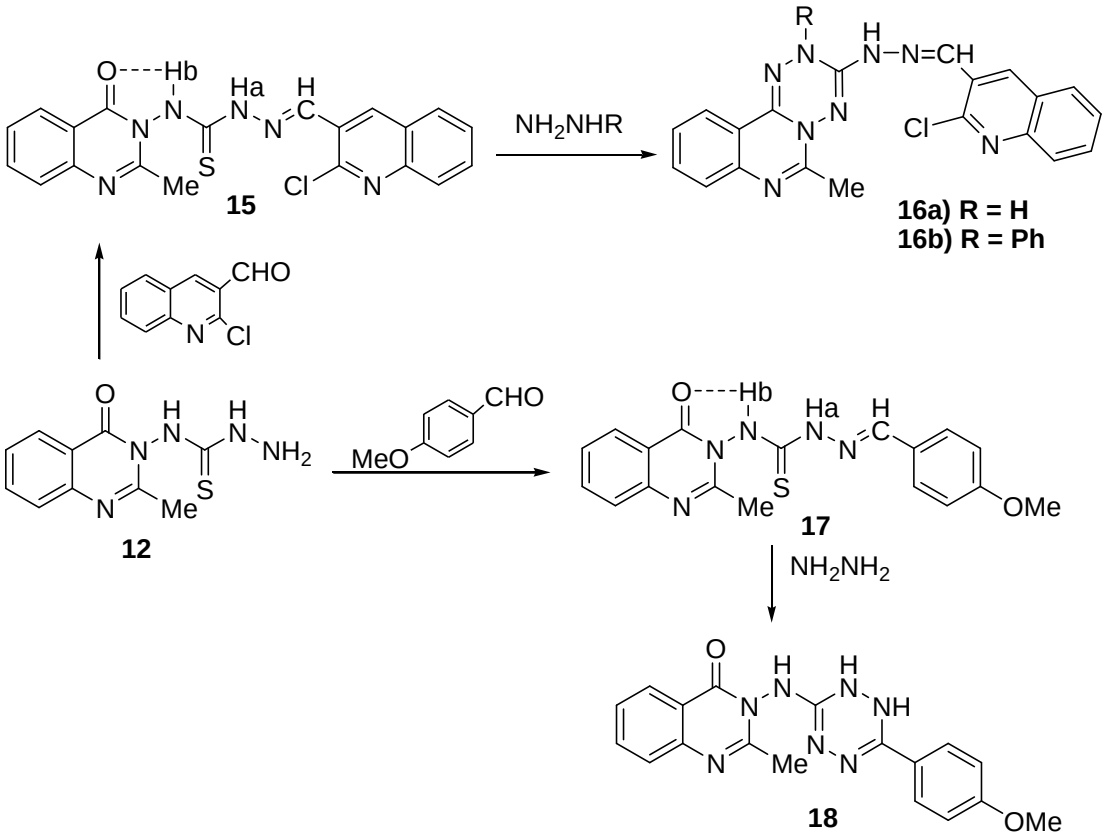
thiocarbonohydrazide in absolute ethanol with the presence of few drops of glacial acetic acid produced quinazoline derivative **12** in a good yield. Compound **12** is used as useful building block for the synthesis of further quinazoline derivatives functionalized with a 3-substitued side chain. Treatment a solution of compound **12** in a dry benzene with benzoyl chloride yielded thiosemicarbazide **13**. Boiling of thiosemicarbazide **13** in equimolar ratio of acetic and hydrochloric acids afforded thiadiazole derivative **14** in a good yield. The structures of compounds **12-14** were evidenced from their microanalytical and spectral data. ^{1}HNMR spectrum of compound **12** showed its existence in DMSO solution as thione – thiol tautomers **12a** and **12b** in approximately equal ratio; moreover, the higher δ value of Ha confirms cheleation shown in Scheme 5. ^{1}HNMR spectrum of compound **13** supports its existence as diasteriomeric mixture of **13a** and **13b** in 3 : 2 ratio, since it showed two absorption singlet signals corresponding to the two methyl protons as well as the extra exchangeable broad signals due to OH proton for compound **13b**.



Scheme 5

The reaction of thiosemicarbazide derivative **12** with aromatic aldehydes namely 2-chloroquinoline-3-carbaldehyde and 4-methoxybenzaldehyde afforded thiosemicarbazone **١٥** and **١٧** respectively (Scheme 6). Treatment thiosemicarbazone derivative **١٥** with hydrazine hydrates or phenyl hydrazine furnished the fused tetrazinoquinazoline derivatives **١٦a** and **١٦b** respectively. Similar treatment of thiosemicarbazone derivative **١٧** with hydrazine hydrate gave tetrazine derivative **١٨**. The microanalytical and spectral data of compounds **15-18** confirm their suggested structures rigidly (see Experimental).

The appearance of extra signal for methyl protons in the ^{1}HNMR spectra of compounds **1٥** and **1٧** suggest their existence as Syn / Anti sterioisomers in the ratio 2 : 3 and 1 : 4 ratio respectively.



Scheme 6

Experimental

All commercially available solvents and reagents of analytical grade were used without further purification. Melting points were determined in open capillary tubes on an electrothermal melting point apparatus and were uncorrected. The elemental analysis were performed on a Perkin-Elemer 2400 CHN elemental analyzer. The FTIR were recorded on Perkin-Elemer Modle 297 Infrared spectrometer using the KBr wafer technique. The ^{1}H-NMR spectra were measured on Varian Gemini 300MHz spectrometer, with chemical shift (δ) expressed in ppm downfield with tetramethylsilane (TMS) as internal standard, in DMSO-d_6. Mass spectra were determined on Shimadzu GC-MSQP 1000 EX instrument operating at 70 eV. Thin layer chromatography

(TLC) was run using TLC aluminum sheets silica gel F_{254} (Merck). It was carried out the monitoring of the progress of all reactions and homogeneity of the synthesized compounds.

4-(2-methyl-4-oxoquinazolin-3(4H)-ylamino)-1-phenyl-2-thioxo-1,2-dihydroazete-3-carbonitrile (3): To a stirred solution of 2 (0.01 mol) in dimethyl formamide (20 ml) at room temperature, phenyl isothicyanate (0.01 mol) and catalytic amount of potassium hydroxide were added. The stirring is continued for further 6h. Poured onto ice/ HCl, The solid product that obtained was filtered off and recrystallized from ethyl alcohol to give compound **3**. Yield:92%; yellow crystals; m.p. 208-210^{o}C (EtOH); IR (KBr) (υ, cm^{-1}): 3348, 3262 (NH), 3059 (CH_{arom}), 2927(CH_{alkyl}), 2175 (CN), 1713 (C=O), 1637 (C=N), 1266 (C=S); ^{1}H NMR (DMSO-d_6) δ: 2.02 (s, 3H, CH_3), 7.02 – 7.27 (m, 4H, Ar-H), 7.35 (br.s, 1H, NH, exchangeable), 7.73- 8.13 (m, 5H, Ar-H); MS (70 eV) m/z (%): 361 ($M^{\cdot+}$ +2, 1), 318 (5), 242 (71), 224 (37), 196 (5), 183 (3), 131 (2), 117 (9), 90 (23), 76 (12), 65 (11), 52 (3); Anal. calcd for $C_{19}H_{13}N_5OS$ (359.4): C, 63.49; H, 3.65; N, 19.49**.** Found: C, 63.16; H, 3.44; N, 19.33 %.

4-(2-methyl-4-oxoquinazolin-3(4H)-ylamino)-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbonitrile (4): To a solution of **2** (0.01 mol) in dimethyl formamide (20 ml), phenyl isothiocyanate (0.01 mol), elemental sulfur (0.01 mol) and catalytic amount of potassium hydroxide was added. The reaction mixture was heated under reflux for 6h. The solvent was distilled off under reduced pressure and the residue was poured onto ice/HCl. The solid obtained was filtered off and recrystallized to give compound **4**. yield: 56%; yellow crystals; m.p. >300^{o}C (EtOH); IR (KBr) (υ, cm^{-1}): 3395, 3114 (NH), 3078,3020 (CH_{arom}), 2966, 2829 (CH_{alkyl}), 2216 (CN), 1624 (C=O), 1612 (C=N), 1231 (C=S); ^{1}H NMR (DMSO-d_6) δ: 2.91 (s, 3H, CH_3), 7.59 – 8.26 (m, 18H, Ar-H), 14.6 (br.s, 1H, NH, exchangeable); MS (70 eV) m/z (%): 391 ($M^{\cdot+}$, 1), 316 (1), 225 (26), 224 (100), 199 (1), 167 (3), 160 (1), 135 (1), 118 (1), 105 (3), 104 (32), 91 (1), 76 (13), 52 (1); Anal. calcd for $C_{19}H_{13}N_5OS_2$ (391.47): C, 58.29; H, 3.35; N, 17.89**.** Found: C, 58.38; H, 3.11; N, 17.61 %.

2-cyano-3-(ethylthio)-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-(phenylamino)acrylamide (5): To a stirred solution of **2** (0.01 mol) in dimethyl formamide (20 ml); phenyl isothicyanate (0.01 mol) and a catalytic amount of potassium hydroxide were added. The stirring at room temperature was continued for 6h. Ethyl bromide (0.01 mol) was added drop wise, the reaction

mixture was stirred for further 2h. A solid product was obtained, that was filtered off and recrystallized to give compound **5**. Yield: 40 %; yellow crystals; mp 210-212 ^{o}C (toluene); IR (KBr) (υ, cm^{-1}): 3184 (NH), 3064 (CH_{arom}), 2969, 2930 (CH_{alkyl}), 2197 (CN), 1704 (C=O), 1597 (C=N); ^{1}H NMR (DMSO-d_6) δ: 1.04 (t, 3H, $CH_2\underline{CH_3}$, J = 7.2Hz), 2.07 (s, 3H, CH_3), 2.44 (q, 2H, $\underline{CH_2}CH_3$, J = 7.5Hz), 7.19 – 8.09 (m, 9H, Ar-H), 11.32 (br.s, 1H, NH, NHPh, exchangeable), 13.15 (br.s, 1H, NH, NHCO, exchangeable); MS (70 eV) m/z (%): 405 ($M^{+\cdot}$, 12), 344 (2), 313 (11), 246 (2), 233 (100), 170 (4), 160 (4), 116 (10); Anal. calcd for $C_{21}H_{19}N_5O_2S$ (405.47): C, 62.21; H, 4.72; N, 17.27. Found: C, 61.93; H, 4.51; N, 16.90 %.

Ethyl2-(-2-cyano-1-(2-methyl-4-oxoquinazolin-3(4H)-ylimino)-2-(4-oxo-3-phenylthiazolidin-2-ylidene)ethoxy)acetate (6): To a stirred solution of **2** (0.01 mol) in dimethyl formamide (20 ml), phenyl isothicyanate (0.01 mol) and catalytic amount of potassium hydroxide were added. The reaction mixture was stirred at room temperature for 6h. Then ethyl chloroacetate (0.02 mol) was added drop wise. And the reaction mixture was stirred for further 3h. Poured onto ice water, the solid obtained was filtered off and recrystallized to give compound **6**. Yield: 94 %; Orange crystals; m.p. 142-144 ^{o}C (EtOH); IR (KBr) (υ, cm^{-1}): 3063 (CH_{arom}), 2988, 2954 (CH_{alkyl}), 2205 (CN), 1755, 1736, 1725 (C=O), 1632 (C=N); ^{1}H NMR (DMSO-d_6) δ: 1.15 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.2Hz), 2.12 (s, 3H, CH_3), 4.09 (s, 2H, OCH_2CO), 4.12 (q, 2H, $O\underline{CH_2}CH_3$, J = 5.9 Hz), 4.68, 4.80 (dd, 2H, $S\underline{CH_2}CO$, J_{gem} = 15.9 Hz), 7.2 – 8.13 (m, 9H, Ar-H); MS (70 eV) m/z (%): 503 (M+., 20), 505 ($M^{\cdot+}$+2, 2), 400 (3), 384 (1), 339 (3), 288 (4), 186 (3), 159 (4), 119 (8), 117 (13), 104 (26), 103 (18), 77 (100), 41 (9); Anal. calcd for $C_{25}H_{21}N_5O_5S$ (503.53): C, 59.63; H, 4.20; N, 13.91. Found: C, 59.88; H, 3.94; N, 13.76 %.

2-hydroxy-1-(2-methyl-4-oxoquinazolin-3(4H)-yl)-4,6-dioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (7): A mixture of compound **2** (0.01 mole) and malononitrile (0.01 mole) was

refluxed in ethanol (30 mL) and few drops of piperidine for 6 hrs. The solvent was distilled under reduced pressure and the residue was poured onto crushed ice. The solid obtained was filtered off and recrystallized to give compound **7**. Yield: 40 %; brown crystals; m.p. 232 -234 ^{o}C; **(**ethanol/ pet. ether (40-60^{o}C)); IR (KBr) (υ, cm-1): 3343 (OH), 3068, 3040 (CH_{arom}), 2939, 2865 (CH_{alkyl}), 2202 (CN), 1779, 1708 (C=O), 1600 (C=N); ^{1}H NMR (DMSO-d_6) δ: 2.04 (s, 3H, CH_3), 3.90, 4.03 (AB quartet, 2H, CO$\underline{CH_2}$CO, J_{gem} = 18.6, 10.8 Hz), 7.53-8.13 (m, 4H, Ar-H), 13.3 (br. s, 1H, OH, exchangeable); MS (70 eV) m/z (%): 310 ($M^{\cdot+}$, 1), 266 (3), 199 (6), 140 (5), 128 (13), 112 (12), 103 (33), 100 (100), 81 (21); Anal. calcd for $C_{15}H_{10}N_4O_4$ (310.26):C, 58.07; H, 3.25; N, 18.06. Found: C, 57.79; H, 2.85; N, 17.92 %.

3-(4-(1,3-diphenyl-1H-pyrazol-4-yl)-2-oxoazet-1(2H)-yl)-2-methylquinazolin-4(3H)-one (9): A mixture of compound **2** (0.01 mol) and 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (**8**) (0.01 mol) was refluxed in 10% alc. KOH (30 mL) for 8hrs. Acidifying the ice cooled reaction mixture with dilute HCl gave solid product that was filtered off and recrystallized from ethyl acetate to give compound **9**. Yield: 78 %; pale yellow crystals; mp 224 -226 ^{o}C; IR (KBr) (υ, cm^{-1}): 3060 (CH_{arom}), 2927, 2857 (CH_{alkyl}), 1710 (C=O), 1624 (C=N); ^{1}H NMR (DMSO-d_6) δ: 2.20 (s, 3H, CH_3), 4.53 (, 1H, CH=), 7.27 – 7.88 (m, 14H, Ar-H), 8..49 (s, 1H, pyrazolo-H); MS (70 eV) m/z (%): 445 ($M^{\cdot+}$, 100), 428 (5), 370 (27), 326 (11), 279 (7), 241 (24), 233 (18), 172 (36), 140 (25), 82 (23); Anal. calcd for $C_{27}H_{19}N_5O_2$ (445.47): C, 72.80; H, 4.30; N, 15.72. Found: C, 72.62; H, 4.11; N, 15.43 %.

5-(1,3-diphenyl-1H-pyrazol-4-yl)-3H-pyrazol-3-one (11): A mixture of compound **9** (0.01 mol) and hydrazine hydrate (0.01 mol) was refluxed in n-butanol (30 mL) for 4 hrs. A solid product was obtained after cooling to room temperature, filtered off and recrystallized from ethanol to give compound **11**. Yield: 90 %; yellow crystals; m.p. 210 -212 ^{o}C (EtOH); IR (KBr) (υ, cm^{-1}): 3142 (NH), 3053 (CH_{arom}), 1723 (C=O), 1618 (C=N); ^{1}H NMR (DMSO-d_6) δ: 4.53 (,

1H, CH=), 7.12 – 8.66 (m, 10H, Ar-H), 9.14 (s, 1H, pyrazolo-H); MS (70 eV) m/z (%): 305 ($M^{\cdot+}$, 2), 244 (3), 223 (5), 219 (4), 194 (3), 159 (3), 106 (9), 81 (22), 77 (100), 64 (15), 44 (83); Anal. calcd for $C_{18}H_{12}N_4O$ (300.31): C, 71.99; H, 4.03; N, 18.66. Found: C, 71.81; H, 3.76; N, 18.39 %.

4-(2-methyl-4-oxoquinazolin-3(4H)-yl)thiosemicarbazide (12): To a solution of benzoxazinone **1** (0.01 mol) in ethanol (30 mL), thiocarbonohydrazide (0.01 mol) and few drops of glacial acetic acid were added. The reaction mixture was refluxed for 6 hrs. The solvent was distilled under reduced pressure and the residue was poured onto crushed ice. The solid obtained was filtered off and recrystallized to give compound **12**. Yield: 80 %; colorless crystals; m.p. 238-240 ^{o}C; (EtOH); IR (KBr) (υ, cm^{-1}): 3271, 3177, 3112 (NH), 3063 (CH_{arom}), 2948 (CH_{alkyl}), 1629 (C=O), 1607 (C=N), 1219 (C=S); ^{1}H NMR (DMSO-d_6) δ: 2.22 (s, 3H, CH_3), 5.49 (br.s, 2H, NH_2, exchangeable), 6.47 (t, 1H, *J* = 7.2), 6.70 (d, 1H, *J* = 8.0), 7.11 – 7.21 (m, 1H, Ar-H, *J* =7.5), 7.65 (d, 1H, *J* = 6.8), 13.33 (br.s, 1H, NHa, exchangeable), **For 12a:** 12.66 (br.s, 1H, NH, exchangeable), **For 12b:** 5.23 (br.s, 1H, SH, exchangeable); MS (70 eV) m/z (%): 249 ($M^{\cdot+}$, 1), 190 (1), 160 (3), 146 (64), 132 (3), 118 (7), 105 (3), 104 (4), 76 (7), 56 (26).; Anal. calcd for $C_{10}H_{11}N_5OS$ (249.29): C, 48.18; H, 4.45; N, 28.09. Found: C, 47.87; H, 4.33; N, 27.58 %.

1-Benzoyl-4-(2-methyl-4-oxoquinazolin-3(4H)-yl)thiosemicarbazide (13): A mixture of compound **12** (3 mmole) and benzoyl chloride (3 mmole) in a dry benzene (30 ml) was refluxed for 8 hrs. A solid product was obtained after cooling the reaction mixture to room temperature that was filtered off and recrystallized from ethanol to give compound **13**. Yield: 95 %; colorless crystals; mp 202 - 204 ^{o}C; IR (KBr) (υ, cm^{-1}): 3272, 3176, 3112 (NH), 3070 (CH_{arom}), 2949, 2782 (CH_{alkyl}), 1683, 1630 (C=O), 1601, 1549 (C=N), 1218 (C=S); ^{1}H NMR (DMSO-d_6) δ: 2.18 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 7.56 (t, 3H, *J* = 7.6), 7.66 (t, 2H, *J* = 7.2), 7.97 (d, 4H, *J* = 8.8),

11.76 (br.s, 1H, OH, excheangeable), 13.37 (br.s, 2H, NHa, excheangeable), 13.70 (br.s, 1H, NHb, excheangeable); MS (70 eV) m/z (%): 353 ($M^{\cdot+}$, 1.4), 333 (3), 310 (5), 260 (13), 224 (64), 196 (16), 127 (24), 105 (100), 91 (17), 77 (83); Anal. calcd for $C_{17}H_{15}N_5O_2S$ (353.4): C, 57.78; H, 4.28; N, 19.82. Found: C, 57.51; H, 4.09; N, 19.48 %.

2-Methyl-3-(5-phenyl-1,3,4-thiadiazol-2-ylamino)quinazolin-4(3H)-one (14): Boil compound **13** (3 mmole) with a mixture of equal volumes of acetic and hydrochloric acids (30 ml) for two hrs. Cool the reaction mixture to room temperature, and poured onto crushed ice. A solid product was obtained, filtered off and recrystallized from acetic acid to give compound **14**. 91 %; colorless crystals; mp 118-120 ^{o}C; IR (KBr) (υ, cm^{-1}): 3211 (NH), 3070 (CH_{arom}), 2892 (CH_{alkyl}), 1671 (C=O), 1602, 1581 (C=N); ^{1}H NMR (DMSO-d_6) δ: 2.47 (s, 3H, CH_3), 6.88-6.94 (m, 1H, Ar-H), 7.48-7.51 (m, 2H, Ar-H), 7.58-7.62 (m, 3H, Ar-H), 7.77 (d, 1H, *J* = 7.6), 7.92 (d, 2H, *J* = 6.8), 12.94 (br.s, 1H, NH, excheangeable); MS (70 eV) m/z (%):335 ($M^{+\cdot}$, 3), 320 (9), 306 (10), 214 (1), 176 (1), 123 (1), 121 (2), 105 (16), 76 (15), 52 (13)., Anal. calcd for $C_{17}H_{13}N_5OS$ (335.38): C, 60.88; H, 3.91; N, 20.88. Found: C, 60.61; H, 3.76; N, 20.59 %.

General procedure: To a solution of thiosemicarbazide derivative **12** (3 mmole) in ethanol (30 mL), 2-chloroquinoline-3-carbaldehyde or 4-methoxybenzaldehyde (3 mmole) and few drops of glacial acetic acid were added. The reaction mixture was refluxed for 8-12 hrs (TLC). Cool to ambient temperature, a solid product was obtained, filtered off and recrystallized from the suitable solvents to give compounds **15** or **17** respectively. .

1-((2-chloroquinolin-3-yl)methylene)-4-(2-methyl-4-oxoquinazolin-3(4H)-yl)thiosemicarbazide (1°): yield: 85 %; orange crystals; mp 288 - 290 ^{o}C (acetic acid); IR (KBr) (υ, cm^{-1}): 3163 (NH), 3047 (CH_{arom}), 2945, 2894 (CH_{alkyl}), 1696 (C=O), 1660, 1611 (C=N), 1218 (C=S); ^{1}H NMR (DMSO-d_6) 7.20 (t, 1H, *J* = 7.6), 7.33 (d, 1H, *J* = 8.4), 7.52 (t, 1H, *J* = 7.2), 7.72 (d, 1H, *J* = 8.0), 7.79 (t, 1H, *J* = 7.6), 7.98 (t, 1H, *J* = 7.2), 8.09 (d, 1H, *J* = 8.8),

8.16 (d, 1H, *J* = 8.0), 8.90 (d, 1H, *J* = 8.0), **For Syn isomer:** δ: 2.22 (s, 3H, CH_3), 8.52 (s, 1H, CH=), **For Anti isomer:** 2.41 (s, 3H, CH_3), 8.61 (s, 1H, CH=)**,** 10.33 (br.s, 1H, NHa, excheangeable), 12.04 (br.s, 1H, NHb, excheangeable); MS (70 eV) m/z (%): 422 ($M^{\cdot+}$, 1), 262 (1), 260 (1), 248 (3), 224 (14), 218 (4),188 (4), 174 (4), 170 (80), 162 (2), 77 (71), 74 (13), 64 (12).; Anal. calcd for $C_{20}H_{15}ClN_6OS$ (422.89): C, 56.80; H, 3.58; N, 19.87. Found: C, 57.04; H, 3.29; N, 19.53 %.

1-(4-methoxybenzylidene)-4-(2-methyl-4-oxoquinazolin-3(4H)-yl)thiosemicarbazide (1٧): yield: 80 %; colorless crystals; mp 210 - 212 ^{o}C (EtOH); IR (KBr) (υ, cm^{-1}): 3114 (NH), 3067 (CH_{arom}), 2941 (CH_{alkyl}), 1607, 1586 (C=N), 1258 (C=S); ^{1}H NMR (DMSO-d_6) δ: 7.07 – 7.10 (m, 4H, Ar-H), 7.83 – 7.86 (m, 4H, Ar-H), 5.50 (br.s, 1H, NHa, exchangeable), 9.69 (s, 1H, CH=), 13.66 (br.s, 1H, NHb, exchangeable) **For Syn isomer:** 2.22 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3); **For Anti isomer:** 2.31 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3); MS (70 eV) m/z (%): 367 ($M^{\cdot+}$, 1), 329 (2), 264 (14), 241 (5), 158 (6), 131 (50), 100 (29), 76 (14), 58 (83), 44 (100); Anal. calcd for $C_{18}H_{17}N_5O_2S$ (367.42): C, 58.84; H, 4.66; N, 19.06. Found: C, 58.69; H, 4.31; N, 18.80 %.

General procedure: A mixture of compound **15** (3 mmole) and hydrazine hydrate (3 mmole) or phenyl hydrazine (3 mmole) was refluxed in ethanol or n-butanol (20 mL) for 6 hrs. The solvent was evaporated and the residue was treated with cold water. the solid product was filtered off and recrystallized from the suitable solvents to give compounds **16a or 16b** respectively.

3-(2((2-chloroquinolin-3-yl)methylene)hydrazinyl)-6-methyl-2H-[1,2,4,5]tetrazino[1,6-c]quinazoline (1٦a): 68 %; pale yellow crystals; mp 218 - 220 ^{o}C (ethyl alcohol); IR (KBr) (υ, cm^{-1}): 3389, 3286, 3187 (NH), 3030 (CH_{arom}), 2973, 2931 (CH_{alkyl}), 1614, 1583 (C=N); ^{1}H NMR (DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 5.70 (br.s, 2H, NH, exchangeable), 7.43 – 7.62 (m, 7H, Ar-H),

7.87 (d, 1H, *J* = 8.0 Hz), 7.99 (s, 1H, CH=), 8.25 (s, 1H, Ar-H); MS (70 eV) m/z (%): 402 ($M^{\cdot+}$, 4), 367 (6), 360 (7), 341 (29), 285 (10), 240 (3), 213 (12), 204 (9), 198 (2), 189 (4), 162 (5), 157 (2), 118 (12), 104 (10), 76 (11); Anal. calcd for $C_{20}H_{15}ClN_8$ (402.84): C, 59.63; H, 3.75; N, 27.82. Found: C, 59.28; H, 2.66; N, 27, 61 %.

3-(2((2-chloroquinolin-3-yl)methylene)hydrazinyl)-6-methyl-2-phenyl-2H-[1,2,4,5]tetrazino[1,6-c]quinazoline (1ٮb): 63 %; yellow crystals; mp 244 - 246 ^{o}C (MeOH); IR (KBr) (υ, cm^{-1}): 3330, 3171 (NH), 3036 (CH_{arom}), 2977, 2945 (CH_{alkyl}), 1610, 1581 (C=N); ^{1}H NMR (DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 5.73 (br.s, 1H, NH, exchangeable), 7.21 – 7.29 (m, 3H, Ar-H), 7.53 (d, 2H, *J* = 7.6 Hz), 7.76 (t, 2H, *J* = 7.2 Hz), 7.95 (t, 2H, *J* = 7.2 Hz), 8.06 (d, 2H, *J* = 8.4 Hz), 8.12 (d, 2H, *J* = 7.2 Hz), 8.47 (s, 1H, CH=), 8.81 (s, 1H, Ar-H); MS (70 eV) m/z (%): 478 ($M^{\cdot+}$, 1.77), 409 (33), 351 (14), 261 (14), 244 (59), 219 (15), 136 (34), 102 (72), 89 (100), 77 (80); Anal. calcd for $C_{26}H_{19}ClN_8$ (478.94): C, 65.20; H, 4.00; N, 23.40. Found: C, 64.89; H, 3.71; N, 23.22 %.

3-(6-(4-methoxyphenyl)-1,2-dihydro-1,2,4,5-tetrazin-3-ylamino)-2-methylquinazolin-4(3H)-one (1ٰ): To compound **17** (3 mmole) in ethanol (30 mL), hydrazine hydrate (3 mmole) was added. The reaction mixture was refluxed for 5 hrs. A solid product was obtained after cooling to room temperature, filtered off and recrystallized from diluted ethanol to give compound **18**. Yield: 70 %; yellow crystals; m.p. 150 - 152 ^{o}C; IR (KBr) (υ, cm^{-1}): 3271, 3175, 3110 (NH), 3061 (CH_{arom}), 2938 (CH_{alkyl}), 1623 (C=O), 1602, 1583(C=N); ^{1}H NMR (DMSO-d_6) δ: 2.22 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.50 (br.s, 2H, 2NH, exchangeable), 7.02 – 7.80 (m, 8H, Ar-H), 13.40 (br.s, 1H, 1NH, exchangeable), MS (70 eV) m/z (%): 364 ($M^{\cdot+}$ +1, 2), 256 (2), 215 (2), 203 (4), 174 (4), 159 (1), 148 (2), 118 (3), 105 (36), 83 (65), 76 (18), 52 (9); Anal. calcd for $C_{18}H_{17}N_7O_2$ (363.37): C, 59.50; H, 4.72; N, 26.98. Found: C, 59.11; H, 4.63; N, 26.76 %.

References:

1. Michael, J.P., Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep*., *24*, 223–246**, 2007**.

2. Mhaske, S.B.; Argade, N. P., The chemistry of recently isolated naturally occurring quinazolinone alkaloids. *Tetrahedron*, *62*, 9787–9826**, 2006**.

3. Tseng, M.-C.; Yang, H.-Y.; Chu, Y. H., Total synthesis of asperlicin C, circumdatin F, demethylbenzomalvin A, demethoxycircumdatin H, sclerotigenin, and other fused quinazolinones. *Org. Biomol. Chem*., *8*, 419–427, **2010**.

4. Ghorab, M. M.; Ismail, Z. H.; Abdalla, M.; Radwan, A. A., Synthesis, antimicrobial evaluation and molecular modelling of novel sulfonamides carrying a biologically active quinazoline nucleus. *Archives of Pharmacal Research*, *36*, 660–670. DOI: 10.1007/s12272-013-0094-6, **2013**.

5. Grover, G.; Kini, S. G., Synthesis and evaluation of new quinazolone derivatives of nalidixic acid as potential antibacterial and antifungal agents. *European Journal of Medicinal Chemistry*, *41*, 256–262. DOI: 10.1016/j.ejmech.2005.09.002, **2006**.

6. Roopan, S. M.; Maiyalagan, T.; Khan, F. N., Solvent-free syntheses of some quinazolin-4(3*H*)-ones derivatives. *Canadian Journal of Chemistry*, *86*, 1019–1025. DOI: 10.1139/v08-149, **2008**.

7. Chandrika, P. M.; Yakaiah, T.; Rao, A. R. R.; Narsaiah, B.; Reddy, N. C.; Sridhar, V.; Rao, J. V., Synthesis of novel 4,6-disubstituted quinazoline derivatives, their anti-inflammatory and anti-cancer activity (cytotoxic) against U937 leukemia cell lines. *European Journal of Medicinal Chemistry*, *43*, 846–852. DOI: 10.1016/j.ejmech.2007.06.010, **2008**.

8. Khalil, A. A.; Abdel Hamide, S. G.; Al-Obaid, A. M.; El-Subbagh, H. I., Substituted quinazolines, part 2. Synthesis and in-vitro anticancer evaluation of new 2-substituted mercapto-3*H*-quinazoline analogs. *Archiv der Pharmazie*, *336*, 95–103. DOI: 10.1002/ardp.200390011, **2003**.

9. Alagarsamy, V.; Pathak, U. S., Synthesis and antihypertensive activity of novel 3-benzyl-2-substituted-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-ones. *Bioorganic & Medicinal Chemistry*, *15*, 3457–3462. DOI: 10.1016/j.bmc.2007.03.007, **2007**.

10. Alagarsamy, V.; Murugesan, S.; Dhanabal, K.; Murugan, M.; de Clercq, E., AntiHIV, antibacterial and antifungal activities of some novel 2-methyl-3-(substituted methylamino)-(3*H*)-quinazolin-4-ones. *Indian Journal of Pharmaceutical Sciences, 69*, 304–307. DOI: 10.4103/0250-474x.33167**, 2007**.

10. Laddha, S. S.; Bhatnagar, S. P.; Rapid microwave-assisted solution phase synthesis of 6,8-disubstituted 2-phenyl-3-(substituted benzothiazol-2-yl)-4-[3*H*] quinazolinones as novel anticonvulsants. *Phosphorus, Sulfur, and Silicon and the Related Elements*, *183*, 2262–2273. DOI: 10.1080/10426500801957766**, 2008**.

11. Schleiss, M.; Eickhoff, J.; Auerochs, S.; Leis, M.; Abele, S.; Rechter, S.; Choi, Y.; Anderson, Y.; Scott, G.; Rawlinson, W.; Michel, D.; Ensminger, S.; Klebl, B.; Stamminger, T.; Marschall, M., Protein kinase inhibitors of the quinazoline class exert anti-cytomegaloviral activity in vitro and in vivo. *Antiviral Research, 79*, 49–61. DOI: 10.1016/j.antiviral.2008.01.154, **2008**.

12. Jain, P.; Gudaparthi, V.; Parikh, A.; Parikh, H., Facile Synthesis of Pyrazoline Derivatives Derived from Quinazolin-4(3H)-ones as Potential Biological Agents, *Pharma Science Monitor*, 3(4). 2839-2849**, 2012**.

13. Chhabra, G.S.; Tiwari, R., Syntheses and Antimicrobial Activities of Derivatives of 3-Amino-2-methyl-quinazolin-4-(3H)-one. *Asian Journal of Chemistry*, *22*(5), 3390-3396, **2010**.