Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Issue 2, 2012

Research Article

DESIGN AND SYNTHESIS OF SOME QUINAZOLINE DERIVATIVES OF ANTICIPATED ANTIMICROBIAL ACTIVITY

SAMIR M EL-MOGHAZY, NAGWA M ABDEL-GAWAD, AMAL A M EISSA*, RIHAM M YOUSSEF

Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, Kasr El-Aini street, Cairo, Egypt.
Email: phd_amalabdelhaleem@hotmail.com

Received: 27 Dec 2011, Revised and Accepted: 31 Jan 2012

ABSTRACT

The present work is concerned with the synthesis of some new compounds comprising different 2, 3-disubstituted 4(3*H*) – quinazolinones as series **5- 7**, **10- 13**, **15- 17**, **19** and **20**, 2, 3, 4- trisubstituted quinazolines as in series **8** and **9** and fused quinazolines as in **14** and **18**. The building block of these different compounds is the 3-amino-2-substituted quinazolin-4(3H)-ones **5 a- d**. To study the effect of steric hindrance and positional isomerism on the antimicrobial activity; substitution in the 2 position of the quinazoline ring was accomplished by tolyl derivatives or naphthyl radicals. Also, the 2-chloro-*N*-(4-oxo-2-substituted-quinazolin-3(4*H*)-yl) acetamido **15 a-d** were synthesized and used as starting materials to prepare other new tricyclic derivatives **14** and **18**. In addition, these intermediates **15 a-d** were reacted with various hydrazides of drugs like isoniazide, norfloxacin and ofloxacin to yield the biodynamic compounds **17**, **19**, and **20**. Furthermore, reaction of the chloroacetamido intermediates **15 a-d** with potassium cyanate afforded compounds **16 a-d**. The antimicrobial activity was tested for some new compounds against Gram positive and Gram negative microorganisms and the fungus *Candida albicans.* Additionally, minimum inhibitory concentration (MIC) was determined for nine compounds. Of these **10h, 14b, 15a** were expressed as broad spectrum and **5a, 10b, 11a, 12a, 20a** as narrow spectrum against variable microorganisms.

Keywords: Synthesis of quinazoline and quinazolinone derivatives, Anti-microbial activity.

INTRODUCTION

Infectious diseases caused by bacteria and fungi affect millions of people worldwide. Concerted and systematic progresses to discover and develop new antibiotics are always done due to the development of resistance by the microorganisms to the drugs commonly used against them. The rapid rise in bacterial resistance to the traditional antibiotics such as penicillins [1] and tetracyclines [2] had encouraged a continuing search for new classes of compounds with novel modes of antibacterial activity. Quinazolines are considered a very important class of compounds that show a diversity of activities; most prominent of which are antimicrobial [3-11] and antifungal [6, 8, 12, 13], in addition to a wide range of other activities viz anti-inflammatory [14- 19], anticancer [20-23], anti-convulsant and other CNS depressant activities [24- 31], diuretic [32], anthelmentic [9, 33] and many other types of activities [34- 37].

In view of the above, the design and synthesis of newer antimicrobials containing the quinazoline moiety continues to attract the attention of an increasing number of medicinal chemists. Encouraged by previous schiff bases of quinazolinones having promising antimicrobial activity [38]; different benzylidene derivatives **6** were synthesized followed by their cyclization to afford the corresponding thiazolidinone containing compounds **7**. Furthermore, thiosemicarbazide derivatives **10** and their cyclised thiazolidines **11** and thioxo imidazolidines **12** were obtained. Also, the survey disclosed that 3-sulfonamide-2-substituted quinazolinone derivatives had potent antimicrobial activity [39]. Hence, a sulfonamide moiety was incorporated giving compounds with N_4 acetyl sulfanilamido ring in position 3 of the quinazolinone ring **13**. Hydrazone derivatives **8** and **9** were obtained through incorporation of isoniazide and the hydrazide of some sulfonamides with the benzylidene derivatives **6**. Moreover, the tricyclic compounds **14** and **18** were synthesized having a triazine ring which enhanced the antimicrobial activity of previous quinazolinones [40, 41]. Similarly, the incorporation of an imidazole moiety in the quinazoline ring increased the antimicrobial activity [41]. Hence, compounds **16** were synthesized. Hydrazides of broad spectrum antimicrobial drugs were incorporated with the quinazoline ring known to have potent antimicrobial activity to study the effect of this amalgamation on the activity of **19** and **20**.

MATERIALS AND METHODS

Chemistry

Melting points were carried out by the open capillary tube method using a Gallenkamp digital melting point apparatus and they are uncorrected. Elemental Microanalysis was carried out at the Microanalytical Center, Faculty of Science at Cairo University. Infrared Spectra were done on Bruker FT-IR spectrophotometer Vector 22, Germany and Jasco FT.IR plus 460 Japan, and expressed in wave number(cm $^{-1}$), using potassium bromide discs. ^{1}H- NMR Spectra were obtained from Varian Gemini 200 MHz and Joel Fx 90Q, 90MHz FT spectrophotometer, the chemical shifts were expressed in δ ppm units using trimethylsilane as the internal standard. Mass spectra were performed on Hewlett Packard 5988 at 70e V.

General procedure for synthesis of methyl-2-substituted acetamido benzoate 2 a- d

2-(Substituted) acetic acid (0.01 mol) was converted to its acid chloride **1 a-d** using thionyl chloride (5 ml) in dry benzene (10 ml). The mixture was refluxed for 2 hours. Excess thionyl chloride and benzene were distilled under reduced pressure and a solution of methyl anthranilate (3 gm, 0.02 mol) in dry ether (50 ml) was added to the mixture with stirring. The reaction mixture was stirred overnight; the obtained crystalline methyl anthranilate hydrochloride was filtered off and washed with dry ether. The combined ether filtrate were washed four times with 2M HCl (15 ml each), water (15 ml) and then with 20 ml 10 % NaOH before being evaporated to dryness.

Methyl 2-(2-(*p*-tolyloxy) acetamido) benzoate 2 a

Yield %: 72, **m.p:** 98- 100 °C, **I.R (cm^{-1}):** 3200 (NH), 2950, 2850 (CH_2, $CH_{3(s)}$), 1710, 1680 (C=O $_{(s)}$), 1600, 1550 (NH, C=C), **^{1}H NMR (ppm):** 3.97(s, 6H, $2CH_3$), 4.21(s, 2H, OCH_2), 7.13-8.72 (m, 8H, CH aromatic), 11.84(s, 1H, NH), Anal. Calcd for $C_{17}H_{17}NO_4$ (299.39): C, 68.20; H, 5.72; N, 4.70. Found: C, 68.10; H, 5.40; N, 4.91. **Mass m/z (%):**299(1.74), 57(100).

Methyl 2-(2-(4-chloro-3-methylphenoxy) acetamido) benzoate 2 b

Yield %: 68, **m.p:** 113- 115 °C, **I.R (cm^{-1}):** 3263 (NH), 2954, 2916 (CH_2, $CH_{3\ (S)}$), 1680 (C=O $_{(S)}$), 1589, 1527 (NH, C=C), 756 (C-Cl). Anal. Calcd for $C_{17}H_{16}ClNO_4$ (333.84): C, 61.10; H, 4.83; N, 4.20. Found: C, 61.10; H, 4.50; N, 4.23.

Methyl 2-(2-(naphthalen-1-yloxy) acetamido) benzoate 2 c

Yield %: 55, **m.p:** 117- 119 °C, **I.R (cm^{-1}):** 3270 (NH), 2916, 2846 (CH_2, CH_3), 1689 (C=O $_{(S)}$), 1589, 1520 (NH, C=C). Anal. Calcd for

$C_{20}H_{17}NO_4$.2.5 H_2O (380.39): C, 63.15; H, 5.83; N, 3.68. Found: C, 62.74; H, 5.62; N, 4.18.

Methyl 2-(2-(naphthalen-2-yloxy) acetamido) benzoate 2 d

Yield %: 60, **m.p:** 124- 126 °C, **I.R (cm^{-1}):** 3263 (NH), 2916, 2840(CH_2, CH_3), 1689 (C=O $_{(S)}$), 1589, 1527 (NH, C=C). Anal. Calcd for $C_{20}H_{17}NO_4$ (335.35): C, 71.63; H, 5.11; N, 4.18. Found: C, 71.46; H, 5.01; N, 3.97.

General procedure for synthesis of 2- substituted-4*H*-benzo[d] [1, 3] oxazin-4-one 4 c, d

Method 1

A solution of anthranilic acid (1.37 gm, 0.01 mol) in dry pyridine (10 ml) was added to the corresponding freshly prepared acid chloride (0.01 mol) **1 c, d** and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured onto ice/ethanol mixture and the precipitated solid was filtered, dried then recrystallized from methylene chloride.

Method 2

A solution of anthranilic acid (0.01 mol) in methylene chloride (10 ml) and triethylamine (5 drops) was added to the freshly prepared acid chloride (0.01 mol) **1 c, d**. The mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to yield the labile intermediate **3 c, d** to which 10 ml acetic anhydride was added and the whole mixture was refluxed for 4 hours. The reaction mixture was poured onto ice/water mixture and extracted with methylene chloride. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated in vacuum to afford the benzoxazinone derivative. The newly obtained compounds **4 c, d** were recrystallized from methylene chloride.

2-((Naphthalen-1-yloxy) methyl)-4*H*-benzo[d] [1, 3] oxazin-4-one 4 c

Yield %: 80, **m.p:** 104- 105 °C, **I.R (cm^{-1}):** 2922, 2852 (CH_2), 1695(C=O), 1610, 1510 (C=C, C=N), **^{1}H NMR (ppm):** 4.88(s, 2H, OCH_2), 6.83-8.75 (m, 11H, CH aromatic). Anal. Calcd for $C_{19}H_{13}NO_3$.1.5 H_2O (330.34): C, 69.08; H, 4.58; N, 4.24. Found: C, 69.16; H, 5.10; N, 4.21.

2-((Naphthalen-2-yloxy) methyl)-4*H*-benzo[d] [1,3]oxazin-4-one 4 d:

Yield %: 85, **m.p:** 98- 99 °C, **I.R (cm^{-1}):** 2915, 2840 (CH_2), 1681(CO), 1581, 1504 (C=C, C=N), **Mass m/z (%):** 303(4.27), 144(100). Anal. Calcd for $C_{19}H_{13}NO_3$ (303.32): C, 75.24; H, 4.32; N, 4.62. Found: C, 75.04; H, 4.31; N, 4.42.

General procedure for synthesis of 3-amino-2 substituted-quinazolin-4(3*H*)-ones 5 a-d

Method 1

The appropriate anthranilate amide **2 a-d** (0.02 mol) and hydrazine hydrate 95 % (5.01 gm, 0.1 mol) were refluxed together in butanol (10 ml) for 8 hours. Addition of ethanol (2 ml) to the reaction mixture gave the desired product as white precipitate which was recrystallized from aqueous ethanol.

Method 2

The chosen benzoxazinones **4 c, d** (0.02 mol) and hydrazine hydrate 95 % (0.1 mol) were refluxed together in absolute ethanol (10 ml) for 24 hours. The excess solvent was then distilled and the solid residue was left to dry and recrystallized from aqueous ethanol.

3-Amino-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-one 5 a

Yield %: 85, **m.p:** 143- 145 °C, **I.R (cm^{-1}):** 3308, 3252 (NH_2), 2918, 2852 (CH_2, CH_3), 1688 (C=O), 1607, 1512, 1471 (NH_2, C=C, C=N), **^{1}H NMR (ppm):** 2.30(s, 3H, CH_3), 5.28 (s, 4H, OCH_2 and NH_2), 6.93-7.77 (m, 7H, CH aromatic), 8.27(d, *J*= 1.5 Hz, 1H, H on C_5 of the quinazolinone ring). Anal. Calcd for $C_{16}H_{15}N_3O_2$ (281.32): C, 68.31; H, 5.37; N, 14.94. found: C, 68.10; H, 5.40; N, 14.90.

3-Amino-2-((4-chloro-3-methylphenoxy)methyl)quinazolin-4(3*H*)-one 5 b

Yield %:74, **m.p:** 156- 157 °C, **I.R (cm^{-1}):** 3500, 3300 (NH_2), 2900 (CH_2, CH_3), 1660 (C=O), 1600, 1560, 1540 (NH_2, C=C, C=N), 770 (C-Cl), **Mass m/z (%):**315 (37.69), 145(100). Anal. Calcd for $C_{16}H_{14}ClN_3O_2$ (315.77): C, 60.86; H, 4.47; N, 13.31. Found: C, 60.90; H, 4.70; N, 13.32.

3-Amino-2-((naphthalen-1-yloxy) methyl) quinazolin-4(3*H*)-one 5c

Yield %: 50, **m.p:** 182- 183 °C, **I.R (cm^{-1}):** 3350, 3250 (NH_2), 2950 (CH_2), 1660 (C=O), 1620, 1580, 1550 (NH_2, C=C, C=N). Anal. Calcd for $C_{19}H_{15}N_3O_2$. H_2O (335.36): C, 68.05; H, 5.11; N, 12.53. Found: C, 67.76; H, 5.96; N, 13.14.

3-Amino-2-((naphthalen-2-yloxy) methyl) quinazolin-4(3*H*)-one 5 d

Yield %: 53, **m.p:** 203- 204 °C, **I.R (cm^{-1}):** 3350, 3200 (NH_2), 2950 (CH_2), 1670 (C=O), 1620, 1580, 1560 (NH_2, C=C, C=N). Anal. Calcd for $C_{19}H_{15}N_3O_2$ (317.35): C, 71.91; H, 4.76; N, 13.24. Found: C, 72.00; H, 4.80; N, 13.20.

General procedure for synthesis of 3-(4-substitutedbenzylideneamino)-2-substituted-quinazolin-4(3*H*)-one 6 a- j

A reaction mixture compounded of 3-amino-2-substituted quinazolin-4(3*H*)-one **5 a-d** (0.01 mol) and the appropriate benzaldehyde (0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 6 hours. It was then poured onto ice/cold water and the solid product obtained was filtered, washed well with water, left to dry and then recrystallized from aqueous ethanol.

3-(4-Chlorobenzylideneamino)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-one 6 a

Yield %: 86, **m.p:** 150- 151 °C, **I.R (cm^{-1}):** 2924, 2854 (CH_2, CH_3), 1689 (C=O), 1589, 1504(C=C, C=N), 756 (C-Cl), **^{1}H NMR (ppm):** 2.15(s, 3H, CH_3), 5.20 (s, 2H, OCH_2), 6.17-7.58 (m, 11H, CH aromatic), 8.25(d, *J*= 1.6 Hz, 1H, H on C_5 of the quinazolinone ring), 8.90 (s, 1H, N=CH). Anal. Calcd for $C_{23}H_{18}ClN_3O_2$ (403.86): C, 68.04; H, 4.49; N, 10.40. Found: C, 68.64; H, 4.29; N, 10.35.

3-(4-Chlorobenzylideneamino)-2-((4-chloro-3-methylphenoxy) methyl)quinazolin -4(3*H*)-one 6 b

Yield %: 78, **m.p:** 174- 175 °C, **I.R (cm^{-1}):** 2950, 2850 (CH_2, CH_3), 1680 (C=O), 1620, 1600 (C=C, C=N), 770 (C-Cl), **^{1}H NMR (ppm):** 2.29(s, 3H, CH_3), 5.33 (s, 2H, OCH_2), 6.70-7.82 (m, 10H, CH aromatic), 8.35(d, *J*= 1.6 Hz, 1H, H on C_5 of the quinazolinone ring), 9.23(s, 1H, N=CH), **Mass m/z (%):**438(4.22), 159 (100). Anal. Calcd for $C_{23}H_{17}Cl_2N_3O_2$ (438.31): C, 63.03; H, 3.91; N, 9.59. Found: C, 63.42; H, 4.34; N, 9.70.

3-(4-Chlorobenzylideneamino)-2-((naphthalen-1-yloxy)methyl) quinazolin-4(3*H*)-one 6 c

Yield %: 45, **m.p:** 124- 125 °C, **I.R (cm^{-1}):** 2924, 2854 (CH_2), 1689 (C=O), 1589, 1496 (C=C, C=N), 764 (C-Cl), **Mass m/z (%):**439(0.08), 145 (100). Anal. Calcd for $C_{26}H_{18}ClN_3O_2$ (439.89): C, 70.99; H, 4.12; N, 9.55. Found: C, 70.95; H, 4.41; N, 9.39.

3-(4-Chlorobenzylideneamino)-2-((naphthalen-2-yloxy)methyl)quinazolin-4(3*H*)-one 6 d

Yield %: 46, **m.p:** 140- 141°C, **I.R (cm^{-1}):** 2950, 2854(CH_2), 1674 (C=O), 1581, 1500 (C=C, C=N), 748 (C-Cl), **^{1}H NMR (ppm):** 5.60 (s, 2H, OCH_2), 7.24-7.50 (m, 16H, CH aromatic), 8.70 (s, 1H, N=CH). Anal. Calcd for $C_{26}H_{18}ClN_3O_2$ (439.89): C, 70.99; H, 4.12; N, 9.55. Found: C, 70.80; H, 3.90; N, 9.59.

3-(4-Hydroxybenzylideneamino)-2-(*p*-tolyloxymethyl)quinazolin-4(3*H*)-one 6 e:

Yield %: 88, **M.P:** 181- 183 °C, **I.R (cm^{-1}):** 3450(OH), 2925(CH_2, CH_3), 1700 (C=O), 1600, 1560, 1540 (C=C, C=N). Anal. Calcd for

$C_{23}H_{19}N_3O_3$. ½ H_2O (394.42): C, 70.04; H, 5.11; N, 10.65. Found: C, 69.50; H, 5.30; N, 10.65.

3-(4-Hydroxybenzylideneamino)-2-((4-chloro-3-methylphenoxy) methyl) quinazolin-4(3*H*)-one 6 f:

Yield %: 77, **M.P:** 158- 159 °C, **I.R (cm^{-1}):** 3417(OH), 2916, 2846(CH_2, CH_3), 1628 (C=O), 1581, 1458(C=C, C=N), 764(C-Cl). Anal. Calcd for $C_{23}H_{18}ClN_3O_3$. H_2O (437.88): C, 63.09; H, 4.60; N, 9.60. Found: C, 63.69; H, 5.00; N, 9.36.

3-(4-Fluorobenzylideneamino)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-one 6 g

Yield %: 73, **M.P:** 129- 130 °C, **I.R (cm^{-1}):** 2924, 2854(CH_2), 1680 (C=O), 1600, 1512 (C=C, C=N), 1234 (C-F), **Mass m/z (%):**385(73.08), 158 (100). Anal. Calcd for $C_{23}H_{18}FN_3O_2$ (387.41): C, 71.31; H, 4.68; N, 10.85. Found: C, 71.28; H, 4.52; N, 11.02.

3-(4-Fluorobenzylideneamino)-2-((4-chloro-3-methylphenoxy) methyl)quinazolin -4(3*H*)-one 6 h

Yield %: 75, **M.P:** 147- 149 °C, **I.R (cm^{-1}):** 2916, 2854(CH_2, CH_3), 1690 (C=O), 1605, 1481(C=C, C=N), 1220 (C-F), 771 (C-Cl), **^{1}H NMR (ppm):** 2.20 (s, 3H, CH_3), 5.28 (s, 2H, OCH_2), 7.00-7.80 (m, 12 H, CH aromatic), 9.10 (s, 1H, N=CH). Anal. Calcd for $C_{23}H_{17}ClFN_3O_2$ (421.85): C, 65.48; H, 4.06; N, 9.96. Found: C, 64.93; H, 4.33; N, 9.81.

3-(4-Methoxybenzylideneamino)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-one 6 i:

Yield %: 72, **M.P:** 100- 101 °C, **I.R (cm^{-1}):** 2950, 2850(CH_2, $CH_{3(s)}$), 1680 (C=O), 1610, 1570(C=C, C=N). Anal. Calcd for $C_{24}H_{21}N_3O_3$ (399.44): C, 72.16; H, 5.30; N, 10.52. Found: C, 71.94; H, 5.23; N, 10.44.

3-(4-Methoxybenzylideneamino)-2-((4-chloro-3-methylphenoxy) methyl) quinazolin-4(3*H*)-one 6 j:

Yield %: 78, **M.P:** 184- 186 °C, **I.R (cm^{-1}):** 2924, 2846(CH_2, $CH_{3(s)}$), 1674 (C=O), 1600, 1480, (C=C, C=N), 780 (C-Cl), **^{1}H NMR (ppm):** 2.22(s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.26 (s, 2H, OCH_2), 6.70-7.76 (m, 10H, CH aromatic), 8.40 (d, *J*= 1.7 Hz, 1H, H on C_5 of the quinazolinone ring), 8.93 (s, 1H, N=CH). Anal. Calcd for $C_{24}H_{20}ClN_3O_3$ (433.89): C, 66.44; H, 4.65; N, 9.68. Found: C, 66.68; H, 4.86; N, 9.64.

General procedure for synthesis of 2-substituted-3-(2-(4-substituted-phenyl)-4-oxothiazolidin-3-yl) quinazolin-4(3*H*)-one 7 a- d

A mixture of 3-(4-chlorobenzylideneamino)-2-(substituted) quinazolin-4(3*H*)-one **6** (0.01 mol) and thioglycolic acid (0.92 gm, 0.01 mol) was refluxed for 8 hours in the presence of anhydrous zinc chloride (1.36 gm, 0.01 mol). The reaction mixture was then poured onto ice/cold water. The precipitated solid was filtered, washed with water, left to dry then recrystallized from aqueous ethanol.

3-(2-(4-Chlorophenyl)-4-oxothiazolidin-3-yl)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-one 7 a

Yield %:71, **m.p:** 256- 257 °C, **I.R (cm^{-1}):** 2920, 2850 (CH_2, CH_3), 1716, 1697 (C=O $_{(s)}$), 1608, 1558(C=C, C=N), 773 (C-Cl), **^{1}H NMR (ppm):** 2.24(s, 3H, CH_3), 5.34 (s, 3H, OCH_2 and CH of the oxothiazolidine ring), 5.72(s, 2H, CH_2 of the oxothiazolidine ring), 6.93-7.81 (m, 11H, CH aromatic), 8.17(d, *J*= 1.8 Hz, 1H, H on C_5 of the quinazolinone ring), **Mass m/z (%):**476 (40.91), 55 (100). Anal. Calcd for $C_{25}H_{20}ClN_3O_2S$ (477.96): C, 62.82; H, 4.22; N, 8.79. Found: C, 62.98; H, 4.22; N, 8.50.

2-((4-Chloro-3-methylphenoxy) methyl)-3-(2-(4-chlorophenyl)-4-oxothiazolidin -3-yl) quinazolin-4(3*H*)-one 7 b:

Yield %: 85, **m.p:** 184- 185 °C**, I.R (cm^{-1}):** 2947, 2893 ($CH_{2\,(s)}$, $CH_{3(s)}$), 1665 (C=O $_{(s)}$), 1566, 1504, (C=C, C=N), 748 (C-Cl). Anal. Calcd for $C_{25}H_{19}Cl_2N_3O_3S$ (512.41): C, 58.60; H, 3.74; N, 8.20. Found: C, 58.66; H, 3.88; N, 8.68.

3-(2-(4-Hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-one 7 c

Yield %: 65, **m.p:** 110- 112 °C**, I.R (cm^{-1}):** 3247 (OH), 2924, 2854($CH_{2\,(s)}$, CH_3), 1670 (C=O $_{(s)}$), 1600, 1511, 1457, 1473 (C=C, C=N). Anal. Calcd for $C_{25}H_{21}N_3O_4S$ (459.52): C, 65.34; H, 4.61; N, 9.14. Found: C, 65.08; H, 4.95; N, 9.76.

2-((4-Chloro-3-methylphenoxy)methyl)-3-(2-(4-hydroxyphenyl) -4-oxo thiazolidin-3-yl) quinazolin-4(3*H*)-one 7 d

Yield %: 85, **m.p:** 132- 134°C**, I.R (cm^{-1}):** 3248 (OH), 2924, 2854 ($CH_{2\,(s)}$, CH_3), 1666 (C=O $_{(s)}$), 1604, 1473 (C=C, C=N), 771 (C-Cl), **^{1}H NMR (ppm):** 2.28(s, 3H, CH_3), 5.34 (s, 3H, OCH_2 and CH of the oxothiazolidine ring), 5.71(s, 2H, CH_2 of the oxothiazolidine ring), 6.92-7.71 (m, 10H, CH aromatic), 8.10(d, *J*= 1.6 Hz, 1H, H on C_5 of the quinazolinone ring). Anal. Calcd for $C_{25}H_{20}ClN_3O_4S$ (493.96): C, 60.79; H, 4.08; N, 8.51. Found: C, 61.43; H, 4.15; N, 8.38.

General procedure for synthesis of *N'*-(3-(4-Substituted-benzylideneamino)-2-substituted-quinazolin-4(3*H*)-ylidene) isonicotinohydrazide 8 a- d

Isoniazide (1.37 gm, 0.01 mol) was added to a solution of the benzylidene derivative **6** (0.01 mol) in absolute ethanol (20 ml) and anhydrous sodium acetate (3.28 gm, 0.04 mol) was then added. The reaction mixture was heated under reflux for 8 hours. The solvent was then removed under reduced pressure and the remaining solid was left to dry then recrystallized from aqueous ethanol.

***N'*-(3-(4-Chlorobenzylideneamino)-2-(*p*-tolyloxymethyl)quinazolin-4(3*H*)-ylidene)isonicotinohydrazide 8 a:**

Yield %: 79, **m.p:** 116- 118 °C**, I.R (cm^{-1}):** 3448(NH), 2920, 2850 (CH_2, CH_3), 1666 (C=O), 1604, 1565, 1512(NH, C=C, C=N), **^{1}H NMR (ppm):** 2.24(s, 3H, CH_3), 5.31 (s, 2H, OCH_2), 6.91-7.85(m, 13H, CH aromatic) 8.17(d, J= 1.6 Hz, 1H, H on C_5 of the quinazolinone ring), 8.47(s, 1H, N=CH), 8.79 (s, 2H $_a$ on the pyridine ring) and 12.17 (s, 1H, NH), **Mass m/z (%):**522 (0.06), 106 (100). Anal. Calcd for $C_{29}H_{23}ClN_6O_2$ (522.98): C, 66.60; H, 4.43; N, 16.07. Found: C, 66.20; H, 3.90; N, 16.41.

***N'*-(3-(4-Chlorobenzylideneamino)-2-((4-chloro-3-methylphenoxy) methyl) quinazolin-4(3*H*)-ylidene) isonicotinohydrazide 8 b**

Yield %: 79, **m.p:** 167- 169 °C**, I.R (cm^{-1}):** 3147 (NH), 2924, 2854 (CH_2, $CH_{3\,(s)}$), 1674 (C=O), 1612, 1566, 1512 (NH, C=C, C=N), 748 (C-Cl). Anal. Calcd for $C_{29}H_{22}Cl_2N_6O_2$ (557.43): C, 62.49; H, 3.98; N, 15.08.Found: C, 62.06; H, 4.67; N, 14.74.

***N'*-(3-(4-Methoxybenzylideneamino)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-ylidene)isonicotinohydrazide 8 c**

Yield %: 79, **m.p:** 167- 169 °C, **I.R (cm^{-1}):** 3201 (NH), 2924, 2854 (CH_2, $CH_{3\,(s)}$), 1658 (C=O), 1590, 1512 (NH, C=C, C=N). Anal. Calcd for $C_{30}H_{26}N_6O_3$ (518.57): C, 69.48; H, 5.05; N, 16.21. Found: C, 69.41; H, 5.24; N, 16.31.

***N'*-(3-((4-Methoxybenzylideneamino)-2-((4-chloro-3-methylphenoxy) methyl) quinazolin-4(3*H*)-ylidene) isonicotinohydrazide 8 d:**

Yield %: 78, **m.p:** 149- 150°C**, I.R (cm^{-1}):** 3350 (NH), 2924, 2854 (CH_2, $CH_{3\,(s)}$), 1682 (C=O), 1589, 1511 (NH, C=C, C=N), 756 (C-Cl). Anal. Calcd for $C_{30}H_{25}ClN_6O_3$ (553.01): C, 65.16; H, 4.56; N, 15.20. Found: C, 65.74; H, 4.55; N, 15.42.

General procedure for synthesis of 4-(2-(3-(4-substituted benzylideneamino)-2-substituted-quinazolin-4(3*H*)-ylidene) hydrazinyl)-*N*-(substituted-2-yl)benzene sulfonamide 9 a- d

The freshly prepared sulphonamide hydrazide (0.01 mol) was refluxed for 12 hours with the benzylidene derivative **6** (0.01 mol) in absolute ethanol (20 ml) with few drops of dry DMF. The brown solution obtained was concentrated and poured onto ice/cold water. The solid precipitated was filtered, washed with water, dried then recrystallized from DMF.

4-(2-(3-(4-Chlorobenzylideneamino)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-ylidene) hydrazinyl)-*N*-(pyrimidin-2-yl) benzenesulfonamide 9 a

Yield %: 67, **m.p:** 281- 283 °C**, I.R (cm^{-1}):** 3295(NH $_{(s)}$), 2921, 2851 (CH_2, CH_3), 1591, 1540, 1493(NH, C=C, C=N), 1332, 1148 (SO_2), 771

(C-Cl).**^{1}H NMR (ppm):** 2.51(s, 3H, CH_3), 5.27 (s, 2H, OCH_2), 5.74 (s, 1H, N-NH), 6.85-8.20 (m, 18H, CH aromatic), 8.51(d, *J*= 1.5 Hz, 1H, H on C_5 of the quinazolinone ring), 9.14 (s, 1H, N= CH), and 10.99 (s, 1H, SO_2NH). Anal. Calcd for $C_{33}H_{27}ClN_8O_3S$ (651.14): C, 60.87; H, 4.18; N, 17.21. Found: C, 60.70; H, 4.75; N, 17.62.

4-(2-(3-(4-Chlorobenzylideneamino)-2-((4-chloro-3-methylphenoxy)methyl)quinazolin-4(3*H*)-ylidene) hydrazinyl) -*N*-(pyrimidin-2-yl)benzenesulfonamide 9 b

Yield %: 76, **m.p:** 227- 228 °C**, I.R (cm^{-1}):** 3294 (NH s), 2924, 2854 (CH_2, CH_3), 1605, 1481 (NH s, C=C, C=N), 1296, 1173 (SO_2), 771(C-Cl). Anal. Calcd for $C_{33}H_{26}Cl_2N_8O_3S$ (685.58): C, 57.81; H, 3.82; N, 16.34. Found: C, 57.75; H, 3.96; N, 16.43.

4-(2-(3-(4-Hydroxybenzylideneamino)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-ylidene)hydrazinyl)benzenesulfonamide 9 c:

Yield %: 74, **m.p:**137- 139 °C**, I.R (cm^{-1}):** 3463, 3293, 3170 (OH, NH_2, NH), 2925, 2854 (CH_2, CH_3), 1597, 1504 (NH_2, NH, C=C, C=N), 1326, 1149 (SO_2), **Mass m/z (%):**551(0.20), 57(100). Anal. Calcd for $C_{29}H_{26}N_6O_4S$ (554.62): C, 62.80; H, 4.73; N, 15.15. Found: C, 63.00; H, 4.81; N, 15.49.

4-(2-(3-(4-Hydroxybenzylideneamino)-2-((4-chloro-3-methylphenoxy) methyl) quinazolin-4(3*H*)-ylidene) hydrazinyl) benzenesulfonamide 9 d

Yield %: 71, **m.p:** 239- 241 °C**, I.R (cm^{-1}):** 3533, 3417, 3286, 3194 (OH, NH_2, NH), 2924, 2850 (CH_2, CH_3), 1605, 1473 (NH_2, NH, C=C, C=N), 1296, 1173 (SO_2), 764 (C-Cl). Anal. Calcd for $C_{29}H_{25}ClN_6O_4S.H_2O$ (607.08): C, 57.37; H, 4.48; N, 13.84. Found: C, 57.75; H, 3.95; N, 13.97.

General procedure for synthesis of 1-substituted-3-(4-oxo-2-substituted-quinazolin-3(4*H*)-yl) thiourea (10 a- k)

A mixture of the respective 3-amino-2 substituted-quinazolin-4(3*H*)-ones **5** (0.01 mol) and the appropriate isothiocyanate (0.015 mol) in methylene chloride (15 ml) and 5 drops triethylamine was refluxed for 12 hours. The excess solvent was distilled off and the separated solid was dried and recrystallized from aqueous ethanol.

1-Ethyl-3-(4-oxo-2-*(p*-tolyloxymethyl)quinazolin-3(4*H*)-yl)thiourea 10 a

Yield %: 82, **m.p:** 83- 84°C**, I.R (cm^{-1}):** 3294, 3200($NH_{(s)}$), 2967, 2916 ($CH_{2\,(s)}$, $CH_{3\,(s)}$), 1682 (C=O), 1606, 1511 ($NH_{(s)}$, C=C, C=N), 1180 (C=S), **Mass m/z (%):** 368(6.71), 57(100). Anal. Calcd for $C_{19}H_{20}N_4O_2S$ (368.45): C, 61.94; H, 5.47; N, 15.21. Found: C, 61.60; H, 5.25; N, 15.35.

1-(2-((4-Chloro-3-methylphenoxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)-3-ethyl thiourea 10 b

Yield %: 78, **m.p:** 155- 156°C**, I.R (cm^{-1}):** 3309, 3178 (NH s), 2916, 2846 ($CH_{2(s)}$, $CH_{3\,(s)}$), 1690 (C=O), 1605, 1481 (NHs, C=C, C=N), 1180 (C=S). Anal. Calcd for $C_{19}H_{19}ClN_4O_2S$ (402.9): C, 56.64; H, 4.75; N, 13.91. Found: C, 55.92; H, 5.20; N, 13.88.

1-Ethyl-3-(2-((naphthalen-1-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)thiourea 10 c

Yield %: 52, **m.p:** 222- 224°C**, I.R (cm^{-1}):** 3294 (NH s), 2924, ($CH_{2(s)}$, CH_3), 1660 (C=O), 1512, 1458 (NHs, C=C, C=N), 1157 (C=S), **Mass m/z (%):**407(3.44), 57(100). Anal. Calcd for $C_{22}H_{20}N_4O_2S$ (404.48): C, 65.33; H, 4.98; N, 13.85. Found: C, 65.74; H, 4.55; N, 13.90.

1-Ethyl-3-(2-((naphthalen-2-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)thiourea 10 d

Yield %: 65, **m.p:** 142- 143°C**, I.R (cm^{-1}):** 3302, 3194 (NH s), 2916, 2854 ($CH_{2(s)}$, CH_3), 1680 (C=O), 1600, 1512 (NHs, C=C, C=N), 1180 (C=S). Anal. Calcd for $C_{22}H_{20}N_4O_2S$ (404.48): C, 65.33; H, 4.98; N, 13.85. Found: C, 65.22; H, 5.07; N, 13.40.

1-(2-((4-Chloro-3-methylphenoxy) methyl)-4-oxoquinazolin-3(4*H*)-yl)-3-(prop-1-enyl) thiourea 10 e:

Yield %:77, **m.p:** 144- 145°C**, I.R (cm^{-1}):** 3286, 3232 (NH s), 2962, 2893 (CH_2, $CH_{3(s)}$), 1689 (C=O), 1600, 1473 (NHs, C=C, C=N), 1173 (C=S), 779 (C-Cl), **^{1}H NMR (ppm):** 2.30(s, 3H, CH_3), 5.35(s, 2H, 2NH s), 5.73 (s, 2H, OCH_2), 6.96-7.66 (m, 6H, CH aromatic), 8.07 (d, *J*= 1.6 Hz, 1H, H on C_5 of the quinazolinone ring). Anal. Calcd for $C_{20}H_{19}N_4O_2SCl$. ½ H_2O (423.92): C, 56.67; H, 4.76; N, 13.22. Found: C, 56.36; H, 5.15; N, 13.45.

1-(4-Oxo-2-(*p*-tolyloxymethyl)quinazolin-3(4*H*)-yl)-3-propylthiourea 10 f

Yield %: 80, **m.p:** 85- 86°C**, I.R (cm^{-1}):** 3300, 3200 (NH s), 2950, 2850 ($CH_{2(s)}$, $CH_{3(s)}$), 1680 (C=O), 1600, 1520 (NHs, C=C, C=N), 1180 (C=S). Anal. Calcd for $C_{20}H_{22}N_4O_2S$ (382.48): C, 62.80; H, 5.80; N, 14.65. Found: C, 62.79; H, 5.77; N, 14.50.

1-(2-((4-Chloro-3-methylphenoxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)-3-propyl thiourea 10g

Yield %:77, **m.p:** 158- 159°C**, I.R (cm^{-1}):** 3300, 3200 (NH s), 2950, 2850 ($CH_{2(s)}$, $CH_{3(s)}$), 1680 (C=O), 1600, 1520 (NHs, C=C, C=N), 1180 (C=S). Anal. Calcd for $C_{20}H_{21}N_4O_2SCl$ (416.92): C, 57.62; H, 5.08; N, 13.44. Found: C, 57.83; H, 5.13; N, 13.44.

1-(4-Oxo-2-(*p*-tolyloxymethyl)quinazolin-3(4*H*)-yl)-3-phenylthiourea 10 h

Yield %: 56, **m.p:** 178- 181°C**, I.R (cm^{-1}):** 3209, 3109 (NH s), 2947 (CH_2, CH_3), 1705 (C=O), 1605, 1543(NHs, C=C, C=N), 1196(C=S). Anal. Calcd for $C_{23}H_{20}N_4O_2S.2\ H_2O$ (452.53): C, 61.05; H, 5.35; N, 12.38. Found: C, 61.90; H, 4.79; N, 11.66.

1-(2-((4-Chloro-3-methylphenoxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)-3-phenyl thiourea 10i

Yield %:71, **m.p:**147- 149°C**, I.R (cm^{-1}):** 3209, 3109 (NH s), 2947 (CH_2, CH_3), 1705 (C=O), 1605, 1543(NHs, C=C, C=N), 1196(C=S), **^{1}H NMR (ppm):** 2.74(s, 3H, CH_3), 4.82 (s, 2H, OCH_2), 7.09-7.85(m, 11H, CH aromatic), 8.20(d, *J*= 1.7 Hz, 1H, H on C_5 of the quinazolinone ring), 9.35(s, 2H, 2NH s). Anal. Calcd for $C_{23}H_{19}ClN_4O_2S$ (450.94): C, 61.26; H, 4.25; N, 12.42. Found: C, 61.00; H, 4.49; N, 12.52.

1-(2-((Naphthalen-1-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)-3-phenylthiourea 10 j

Yield %:47, **m.p:** 193- 195°C**, I.R (cm^{-1}):** 3201, 3170 (NH s), 2916, 2854 (CH_2), 1682 (C=O), 1612, 1512(NHs, C=C, C=N), 1160 (C=S). Anal. Calcd for $C_{26}H_{20}N_4O_2S.\ H_2O$ (470.54): C, 66.37; H, 4.71; N, 11.91. Found: C, 66.27; H, 4.00; N, 11.76.

1-(2-((Naphthalen-2-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)-3-phenylthiourea 10 k

Yield %: 59, **m.p:**202- 204°C, **I.R (cm^{-1}):** 3170 (NH s), 2924, 2854 (CH_2), 1670 (C=O), 1605, 1512(NHs, C=C, C=N), 1165 (C=S). Anal. Calcd for $C_{26}H_{20}N_4O_2S$ (452.53): C, 69.01; H, 4.45; N, 12.38. Found: C, 68.34; H, 5.18; N, 12.18.

General procedure for synthesis of 2-substituted-3-(3,[4-disubstituted-thiazol-2(3*H*)-ylideneamino)quinazolin-4(3*H*)-one 11 a-h

A reaction mixture compromised of the 1-substituted-3-(4-oxo-2-(substituted) quinazolin-3(4*H*)-yl) thiourea **10** (0.01 mol), phenacyl bromide (1.55 gm, 0.01 mol) in absolute ethanol (20 ml) and anhydrous sodium acetate (3.28 gm, 0.04 mol) was refluxed for 8 hours. The solvent was removed under reduced pressure and the remaining solid was left to dry then recrystallized from aqueous ethanol.

3-(3-Ethyl-4-phenylthiazol-2(3*H*)-ylideneamino)-2-(*p*-tolyloxymethyl)quinazolin-4(3*H*)-one 11 a

Yield %:71, **m.p:** 92- 93°C**, I.R (cm^{-1}):** 2920, 2850 ($CH_{2\,(s)}$, $CH_{3\,(s)}$), 1685 (C=O), 1606, 1587 (C=C, C=N), **^{1}H NMR (ppm):** 2.14(s, 3H, CH_3), 2.22-2.51(q, 2H, CH_2CH_3), 3.27-3.44(t, 3H, CH_2CH_3), 5.29(s, 2H, OCH_2), 5.72 (s, 1H, CH of the thiazolidine ring), 6.90-8.13 (m, 12H, CH aromatic), 8.15(d, *J*= 1.8 Hz, 1H, H on C_5 of the quinazolinone ring), **Mass m/z (%):**468(54.17), 89 (100). Anal. Calcd for $C_{27}H_{24}N_4O_2S.1_{1/2}H_2O$ (495.61): C, 65.43; H, 5.49; N, 11.3. Found: C, 64.93; H, 6.10; N, 11.99.

2-((4-Chloro-3-methylphenoxy)methyl)-3-(3-ethyl-4-phenylthiazol-2(3*H*)ylidene amino)quinazolin-4(3*H*)-one 11 b

Yield %: 81, **m.p:** 159- 160°C, **I.R (cm^{-1}):** 2950, 2850 ($CH_{2(s)}$, $CH_{3\,(s)}$), 1690 (C=O), 1610, 1510 C=C, C=N), **Mass m/z (%):** 503(36.36), 83(100). Anal. Calcd for $C_{27}H_{23}ClN_4O_2S.2H_2O$ (539.07): C, 60.16; H, 5.05; N, 10.39. Found: C, 60.18; H, 5.46; N, 10.17.

3-(3-Ethyl-4-phenylthiazol-2(3*H*)-ylideneamino)-2-((naphthalen-1-yloxy) methyl) quinazolin-4(3*H*)-one 11 c:

Yield %: 54, **m.p:**241- 242°C, **I.R (cm^{-1}):** 2916, 2846 ($CH_{2(s)}$, CH_3), 1697 sh. (C=O), 1581 (C=C, C=N). Anal. Calcd for $C_{30}H_{24}N_4O_2S$ (504.62): C, 71.41; H, 4.79; N, 11.10. Found: C, 71.29; H, 5.62; N, 11.62.

3-(3-Ethyl-4-phenylthiazol-2(3*H*)-ylideneamino)-2-((naphthalen-2-yloxy)methyl) quinazolin-4(3*H*)-one 11 d

Yield %: 67, **m.p:** 128- 129°C, **I.R (cm^{-1}):** 2920, 2854 ($CH_{2(s)}$, CH_3), 1674 (C=O), 1589(br.) C=C, C=N). Anal. Calcd for $C_{30}H_{24}N_4O_2S$ (504.62): C, 71.41; H, 4.79; N, 11.10. Found: C, 71.50; H, 4.50; N, 11.42.

3-(3, 4-Diphenylthiazol-2(3*H*)-ylideneamino)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-one 11 e

Yield %: 70, **m.p:** 99- 100°C, **I.R (cm^{-1}):** 2924, 2854 (CH_2, CH_3), 1670 (C=O), 1610, 1550(C=C, C=N), **^{1}H NMR (ppm):** 2.24(s, 3H, CH_3), 5.10(s, 2H, OCH_2), 5.32 (s, 1H, CH of the thiazolidine ring), 7.03-7.73 (m, 17H, CH aromatic), 8.14 (d, *J*= 1.9 Hz, 1H, H on C_5 of the quinazolinone ring). Anal. Calcd for $C_{31}H_{24}N_4O_2S$ (516.63): C, 72.07; H, 4.68; N, 10.85. Found: C, 71.95; H, 4.76; N, 10.52.

2-((4-Chloro-3-methylphenoxy)methyl)-3-(3,4-diphenylthiazol-2(3*H*)-ylidene amino)quinazolin-4(3*H*)-one 11 f

Yield %: 83, **m.p:** 88- 90°C, **I.R (cm^{-1}):** 2920, 2850 (CH_2, CH_3), 1690 (C=O), 1612, 1510(C=C, C=N), 773 (C-Cl), **^{1}H NMR (ppm):** 2.29(s, 3H, CH_3), 5.40(s, 2H, OCH_2), 5.80 (s, 1H, CH of the thiazolidine ring), 7.19-7.75 (m, 16H, CH aromatic), 8.20 (d, *J*= 1.9 Hz, 1H, H on C_5 of the quinazolinone ring). Anal. Calcd for $C_{31}H_{23}ClN_4O_2S$ (551.07): C, 67.57; H, 4.21; N, 10.17. Found: C, 67.65; H, 4.34; N, 9.79.

3-(3, 4-Diphenylthiazol-2(3*H*)-ylideneamino)-2-((naphthalen-1-yloxy)methyl) quinazolin-4(3*H*)-one 11 g

Yield %: 55, **m.p:** 240- 241°C, **I.R (cm^{-1}):** 2924, 2854 (CH_2), 1697 (C=O), 1581, 1504(C=C, C=N), **Mass m/z (%):**553(33.33), 55(100). Anal. Calcd for $C_{34}H_{24}N_4O_2S$ (552.66): C, 73.89; H, 4.38; N, 10.14. Found: C, 73.92; H, 4.14; N, 9.86.

3-(3, 4-Diphenylthiazol-2(3*H*)-ylideneamino)-2-((naphthalen-2-yloxy)methyl) quinazolin-4(3*H*)-one 11 h

Yield %: 69, **m.p:** 208- 209°C, **I.R (cm^{-1}):** 2916, 2846 (CH_2), 1690 (C=O), 1574, 1466 (C=C, C=N). Anal. Calcd for $C_{34}H_{24}N_4O_2S$ (552.64): C, 73.89; H, 4.38; N, 10.14. Found: C, 73.90; H, 4.10; N, 10.60.

General procedure for synthesis of 2-substituted-3-(5-oxo-3-substituted-2-thioxo imidazolidin-1-yl)quinazolin-4(3*H*)-one 12 a- f

Quinazolinone thiosemicarbazide **10** (0.01 mol), chloroacetic acid (0.95 gm, 0.01 mol) and anhydrous sodium acetate (3.28 gm, 0.04 mol) were refluxed in absolute ethanol for 12 hours. The solvent was distilled off and the solid was left to dry then recrystallized from aqueous ethanol.

3-(3-Ethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(*p*-tolyloxymethyl) quinazolin-4(3*H*)-one 12 a

Yield %: 75, **m.p:** 102- 103°C, **I.R (cm^{-1}):** 2950, 2850 ($CH_{2\,(s)}$, $CH_{3\,(s)}$), 1690 (C=O $_{(s)}$), 1610, 1510 (C=C, C=N), 1180 (C=S), **^{1}H NMR (ppm):** 2.51(t, 3H, CH_3), 5.31 (s. 2H, CH_2 of the thioxoimidazole ring), 5.74 (s, 2H, OCH_2), 6.88- 8.13 (m, 11H, CH aromatic), 8.20(d, *J*= 1.8 Hz, 1H, H on C_5 of the quinazolinone ring), **Mass m/z (%):**407(1.03), 145(100). Anal. Calcd for $C_{21}H_{20}N_4O_3S$ (408.49): C, 61.75; H, 4.94; N, 13.72. Found: C, 61.40; H, 4.79; N, 13.66.

2-((4-Chloro-3-methylphenoxy)methyl)-3-(3-ethyl-5-oxo-2-thioxoimidazolidin-1-yl)quinazolin-4(3*H*)-one 12 b

Yield %:75, **m.p:** 160- 161°C**, I.R (cm^{-1}):** 2916, 2846 ($CH_{2(s)}$, $CH_{3(S)}$), 1674 (C=O $_{(s)}$), 1605, 1466 (C=C, C=N), 1180 (C=S), 756 (C-Cl), **Mass m/z (%):**439(22.47), 60(100). Anal. Calcd for $C_{21}H_{19}ClN_4O_3S$ (442.93): C, 56.95; H, 4.32; N, 12.65. Found: C, 57.00; H, 4.07; N, 12.60.

3-(3-Ethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-((naphthalen-1-yloxy)methyl) quinazolin-4 (3*H*)-one 12 c:

Yield %: 62**, m.p:** 210- 212°C, **I.R (cm^{-1}):** 2950, 2848 ($CH_{2(s)}$, CH_3), 1660 (C=O $_{(s)}$), 1620, 1585 (C=C, C=N), 1180 (C=S). Anal. Calcd for $C_{24}H_{20}N_4O_3S$ (444.52): C, 64.85; H, 4.54; N, 12.60. Found: C, 64.50; H, 4.30; N, 11.91.

3-(3-Ethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-((naphthalen-2-yloxy)methyl) quinazolin-4(3*H*)-one 12 d

Yield %: 78, **m.p:** 206- 207°C, **I.R (cm^{-1}):** 2920, 2854 ($CH_{2(s)}$, CH_3), 1670 (C=O $_{(s)}$), 1520, 1466 (C=C, C=N), 1180 (C=S), **^{1}H NMR (ppm):** 2.50(t, 3H, CH_3), 3.35 (q, 2H, CH_2), 5.50 (s. 2H, CH_2 of the thioxoimidazole ring), 5.79 (s, 2H, OCH_2), 7.26- 7.78 (m, 10H, CH aromatic), 8.13(d, *J*= 1.6 Hz, 1H, H on C_5 of the quinazolinone ring), **Mass m/z (%):**442 (0.12), 115 (100). Anal. Calcd for $C_{24}H_{20}N_4O_3S.H_2O$ (462.53): C, 62.32; H, 4.79; N, 12.11. Found: C, 62.31; H, 5.00; N, 12.56.

3-(5-Oxo-3-phenyl-2-thioxoimidazolidin-1-yl)-2-(*p*-tolyloxymethyl)quinazolin-4(3*H*)-one 12 e

Yield %: 88, **m.p:** 107- 108°C, **I.R (cm^{-1}):** 2900, 2850 (CH_2, CH_3), 1690 (C=O $_{(s)}$), 1600, 1510 (C=C, C=N), 1180 (C=S), **^{1}H NMR (ppm):** 2.28(s, 3H, CH_3), 5.28(s, 4H, OCH_2 and CH_2 of the thioxoimidazole ring), 6.93- 7.78 (m, 12H, CH aromatic), 8.27(d, *J*= 1.6 Hz, 1H, H on C_5 of the quinazolinone ring). Anal. Calcd for $C_{25}H_{20}N_4O_3S$ (456.53): C, 65.77; H, 4.42; N, 12.27. Found: C, 66.10; H, 4.20; N, 12.84.

2-((4-Chloro-3-methylphenoxy)methyl)-3-(5-oxo-3-phenyl-2-thioxoimidazolidin-1-yl) quinazoline-4(3*H*)-one 12 f

Yield %: 87, **m.p:** 149- 150°C, **I.R (cm^{-1}):** 2990, 2850 (CH_2, CH_3), 1680 (C=O $_{(s)}$), 1600, 1560, 1540 (C=C, C=N), 1170 (C=S), 770 (C-Cl), **^{1}H NMR (ppm):** 2.28(s, 3H, CH_3), 5.35 (s. 2H, CH_2 of the thioxoimidazole ring), 5.72 (s, 2H, OCH_2), 6.96- 7.63 (m, 11H, CH aromatic), 8.10 (d, *J*= 1.5 Hz, 1H, H on C_5 of the quinazolinone ring). Anal. Calcd for $C_{25}H_{19}ClN_4O_3S$ (490.98): C, 61.16; H, 3.90; N, 11.41. Found: C, 60.70; H, 4.20; N, 11.88.

General procedure for synthesis of 3-(*p*-acetamidophenylsulphonylamino)-2-(substituted)quinazolin-4(3H)-one 13 a- d

An equimolar amount of 3-amino-4(3*H*) quinazolinone derivative **5** and *p*-acetamido benzenesulfonyl chloride was warmed for 4 hours in dimethylformamide (15 ml). The reaction mixture was then poured onto ice/cold water and the separated solid was filtered, washed well with water, dried and then recrystallized from aqueous ethanol.

3-(*p*-Acetamidophenylsulphonylamino)-2-*(p*-tolyloxymethyl) quinazolin-4(3*H*)-one 13 a

Yield %: 69, **m.p:** 97- 98°C, **I.R (cm^{-1}):** 3294 (NH $_{(s)}$), 2924, 2850 (CH_2, $CH_{3\,(s)}$), 1666 (C=O $_{(s)}$), 1600, 1481 (NH, C=C, C=N), 1288, 1165 (SO_2), **^{1}H NMR (ppm):** 2.22 (s, 3H, $COCH_3$), 3.33(s, 3H, CH_3), 5.29(s, 2H, OCH_2), 5.71(s, 2H, 2 NH), 6.90-7.84 (m, 11H, CH aromatic), 8.15 (d, *J*= 1.7 Hz, 1H, H on C_5 of the quinazolinone ring), **Mass m/z (%):**478(0.30),145(100). Anal. Calcd for $C_{24}H_{22}N_4O_5S$ (478.53): C, 60.24; H, 4.63; N, 11.71. Found: C, 60.30; H, 4.70; N, 11.70.

3-(*p*-Acetamidophenylsulphonylamino)-2-((4-chloro-3-methylphenoxy)methyl) quinazolin-4(3*H*)-one 13 b

Yield %: 79, **m.p:** 137- 138°C, **I.R (cm^{-1}):** 3300, 3198 (NH $_{(s)}$), 2919, 2850 (CH_2, $CH_{3\,(s)}$), 1676 (C=O $_{(s)}$), 1612, 1572, (NH, C=C, C=N), 1286, 1172 (SO_2), 771 (C-Cl). Anal. Calcd for $C_{24}H_{21}ClN_4O_5S$ (512.98): C, 56.20; H, 4.13; N, 10.92. Found: C, 56.06; H, 4.52; N, 10.89.

3-(*p*-Acetamidophenylsulphonylamino)-2-((naphthalen-1-yloxy)methyl) quinazolin-4(3*H*)-one 13 c

Yield %: 52, **m.p:** 191- 193°C, **I.R (cm^{-1}):** 3400-3200(br) (NH $_{(s)}$), 2950, 2850 (CH_2, CH_3), 1660 (C=O $_{(s)}$), 1590, 1500, (NH, C=C, C=N), 1360, 1150 (SO_2). Anal. Calcd for $C_{27}H_{22}N_4O_5S$ (514.56): C, 63.02; H, 4.31; N, 10.89. Found: C, 63.66; H, 4.70; N, 11.38.

3-(*p*-Acetamidophenylsulphonylamino)-2-((naphthalen-2-yloxy)methyl) quinazolin-4(3*H*)-one 13 d

Yield %: 63, **m.p:** 180- 181°C, **I.R (cm^{-1}):** 3294, 3248 (NH $_{(s)}$), 2916, 2854 (CH_2, CH_3), 1680 (C=O $_{(s)}$), 1612, 1511, (NH, C=C, C=N), 1296, 1188 (SO_2). Anal. Calcd for $C_{27}H_{22}N_4O_5S$ (514.56): C, 63.02; H, 4.31; N, 10.89. Found: C,63.60; H,4.68; N,10.98.

General procedure for synthesis of 6-substituted-3,4-dihydro-[1,2,4]triazino [2,3-c] quinazolin-2-one 14 a-d

Equivalent weights of 3-amino-4(3*H*) quinazolinone derivative **5** and chloroacetamide (0.93 gm) were refluxed overnight in DMF (15 ml). The desired compound was obtained through pouring the reaction solution onto ice/cold water and the precipitated was collected, washed with water, dried and then recrystallized from aqueous ethanol.

6-(*p*-Tolyloxymethyl)-3,4-dihydro-[1,2,4]triazino[2,3-c]quinazolin-2-one 14 a

Yield %: 71, **m.p:** 85- 86°C, **I.R (cm^{-1}):** 3400- 3300 (br.) (NH), 2950, 2850 (CH_2, CH_3), 1690 (C=O), 1610, 1510 (NH, C=C, C=N), **^{1}H NMR (ppm):** 2.28(s, 3H, CH_3), 5.28(s, 4H, OCH_2 and CH_2 of the triazine ring), 6.93-7.77 (m, 7H, CH aromatic and 1H, NH), 8.27(d, *J*= 1.9 Hz, 1H, H on C_5 of the quinazolinone ring), **Mass m/z (%):**319(0.34), 145(100). Anal. Calcd for $C_{18}H_{16}N_4O_2$ (320.35): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.49; H, 4.89; N, 17.50.

6-((4-Chloro-3-methylphenoxy)methyl)-3,4-dihydro-[1,2,4] triazino[2,3-c] quinazolin-2-one 14 b

Yield %: 80, **m.p:** 153- 155°C, **I.R (cm^{-1}):** 3200 (NH), 2950, 2850 ($CH_{2(s)}$, CH_3), 1670 (C=O), 1610, 1570, 1540 (NH, C=C, C=N), 770 (C-Cl). Anal. Calcd for $C_{18}H_{15}ClN_4O_2$ (354.80): C, 60.94; H, 4.26; N, 15.79. Found: C, 61.04; H, 4.60; N, 15.49.

6-((Naphthalen-1-yloxy)methyl)-3,4-dihydro-[1,2,4]triazino [2,3-c]quinazolin-2-one 14 c

Yield %: 60, **m.p:** 142- 145°C, I.**R (cm^{-1}):** 3232 (br.) (NH), 2924, 2854 ($CH_{2(s)}$), 1659 (C=O), 1589, 1504(NH, C=C, C=N). Anal. Calcd for $C_{21}H_{16}N_4O_2$ (356.39): C, 70.77; H, 4.53; N, 15.72. Found: C, 70.65; H, 4.63; N, 15.75.

6-((Naphthalen-2-yloxy)methyl)-3,4-dihydro-[1,2,4]triazino [2,3-c]quinazolin-2-one 14 d

Yield %: 75, **m.p:** 162- 163°C, **I.R (cm^{-1}):** 3286 (NH), 2924, 2854 ($CH_{2(s)}$), 1674 (C=O), 1581, 1466(NH, C=C, C=N), **Mass m/z (%):**355(3.04), 144(100). Anal. Calcd for $C_{21}H_{16}N_4O_2.H_2O$ (374.40): C, 67.37; H, 4.85; N, 14.96. Found: C, 68.06; H, 5.36; N, 15.76.

General procedure for synthesis of 2-Chloro-*N*-(4-oxo-2-substituted-quinazolin-3(4*H*)-yl) acetamido 15 a-d

Chloroacetyl chloride (1.69 gm, 0.015 mol) was added dropwise to the 3-amino-4(3*H*) quinazolinone derivative **5** (0.01 mol) in dimethylformamide (15 ml) with stirring for one hour at room temperature. The reaction mixture was poured onto ice; the separated solid was filtered, washed well with water, left to dry then recrystallized from the aqueous ethanol.

2-Chloro-*N*-(4-oxo-2-(*p*-tolyloxymethyl) quinazolin-3(4*H*)-yl) acetamido 15 a

Yield %: 84, **m.p:** 169 -70°C, **I.R (cm^{-1}):** 3250 (NH), 2950(CH_2 $_{(s)}$, CH_3), 1690 (C=O $_{(s)}$), 1610, 1560, 1520 (NH, C=C, C=N), 770 (C-Cl), **^{1}H NMR (ppm):** 2.28(s, 3H, CH_3), 5.29(s, 4H, 2 CH_2), 6.86-7.79 (m, 7H, CH aromatic), 9.13(s, 1H, NH), 8.22(d, *J*= 1.5 Hz, 1H, H on C_5 of the quinazolinone ring), **Mass m/z (%):**357(11.48), 250(100). Anal. Calcd for $C_{18}H_{16}ClN_3O_3$ (357.80): C, 60.42; H, 4.51; N, 11.74. Found: C, 60.52; H, 4.16; N, 11.72.

2-Chloro-*N*-(2-((4-chloro-3-methylphenoxy)methyl)-4-oxoquinazolin-3(4*H*)-yl) acetamido 15 b

Yield %:82, **m.p:** 149- 150°C, **I.R (cm^{-1}):** 3200 (NH), 1721 (C=O $_{(s)}$), 1609, 1574, 1519 (NH, C=C, C=N), 766 (C-$Cl_{(s)}$). Anal. Calcd for $C_{18}H_{15}Cl_2N_3O_3$ (392.24): C, 55.12; H, 3.85; N, 10.71. Found: C, 55.28; H, 3.62; N, 10.70.

2-Chloro-*N*-(2-((naphthalen-1-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-yl) acetamido 15 c

Yield %: 54, **m.p:** 215- 216°C, **I.R (cm^{-1}):** 3186 br. (NH), 2924 (CH_2 (s), CH_3), 1659 (C=O $_{(s)}$), 1581, 1504 (NH, C=C, C=N), 764 (C-Cl). Anal. Calcd for $C_{21}H_{16}ClN_3O_3$ (393.84): C, 64.05; H, 4.09; N, 10.67. Found: C, 64.20; H, 4.08; N, 10.32.

2-Chloro-*N*-(2-((naphthalen-2-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-yl) acetamido 15 d

Yield %: 67, **m.p:** 160- 161°C, **I.R (cm^{-1}):** 3217 (NH), 2950, 2850 (CH_2 (s), CH_3), 1697 (C=O $_{(s)}$), 1612, 1512 (NH, C=C, C=N), 756 (C-Cl). Anal. Calcd for $C_{21}H_{16}ClN_3O_{3.1/2}H_2O$ (402.84): C, 62.61; H, 4.25; N, 10.43. Found: C, 61.84; H, 4.53; N, 10.57.

General procedure for synthesis of 1-(4-oxo-2-substituted)quinazolin-3(4*H*)-yl)-1*H*-imidazole-2, 5-dione 16 a-d

A suspension of the chloroacetyl chloride derivative **15** (0.005 mol) and potassium cyanate (0.81 gm, 0.01 mol) in absolute ethanol (20 ml) was refluxed for 6 hours. The solvent was removed under reduced pressure and the remaining solid was dried and then recrystallized from aqueous ethanol.

1-(4-Oxo-2-(*p*-tolyloxymethyl)quinazolin-3(4*H*)-yl)-1*H*-imidazole-2,5-dione 16 a

Yield %: 80, **m.p:** 150- 152°C, **I.R (cm^{-1}):** 2919, 2850(CH_2, CH_3), 1678 (C=O $_{(s)}$), 1600, 1509(C=C, C=N), **^{1}H NMR (ppm):** 5.32(s, 1H, CH=N of the imidazoledione), 5.76 (s, 2H, OCH_2), 7.00-7.71 (m, 8H, CH aromatic), 8.11(d, *J*= 1.7 Hz, 1H, H on C_5 of the quinazolinone ring), **Mass m/z (%):**364(1.68), 132(100). Anal. Calcd for $C_{19}H_{14}N_4O_4$ (362.35): C, 62.98; H, 3.89; N, 15.46. Found: C, 63.29; H, 4.12; N, 15.57.

1-(2-((4-Chloro-3-methylphenoxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)-1*H*-imidazole-2,5-dione 16 b

Yield %: 83, **m.p:** 147- 148°C, **I.R (cm^{-1}):** 2924, 2854 (CH_2, CH_3), 1690 (C=O $_{(s)}$), 1570, 1510(C=C, C=N), **^{1}H NMR (ppm):** 2.33(s, 3H, CH_3), 5.20(s, 1H, CH=N of the imidazoledione), 5.27(s, 2H, OCH_2), 6.80-7.81 (m, 6H, CH aromatic), 8.26(d, *J*= 1.7 Hz, 1H, H on C_5 of the quinazolinone ring). Anal. Calcd for $C_{19}H_{13}ClN_4O_4$. 2 ½ H_2O (441.84): C, 51.65; H, 4.11; N, 12.68. Found: C, 51.34; H, 3.62; N, 12.13.

1-(2-((Naphthalen-1-yloxy) methyl)-4-oxoquinazolin-3(4*H*)-yl)-1*H*-imidazole-2,5-dione 16 c

Yield %: 50, **m.p:** 198- 199°C, **I.R (cm^{-1}):** 2950, 2854 (CH_2), 1682 (C=O $_{(s)}$), 1581, 1504 (C=C, C=N). Anal. Calcd for $C_{22}H_{14}N_4O_4$ (398.38): C, 66.33; H, 3.54; N, 14.06. Found: C, 66.03; H, 3.89; N, 14.21.

1-(2-((Naphthalen-2-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-yl)-1*H*-imidazole-2,5-dione 16 d

Yield %: 66, **m.p:** 214- 215°C, **I.R (cm^{-1}):** 2950, 2854 (CH_2), 1682 (C=O $_{(s)}$), 1566, 1504 (C=C, C=N). Anal. Calcd for $C_{22}H_{14}N_4O_4$ (398.38): C, 66.33; H, 3.54; N, 14.06. Found: C, 65.91; H, 3.30; N, 14.48.

General procedure for synthesis of *N'*-(2-(2-substituted)-4-oxoquinazolin-3(4*H*)-ylamino)-2-oxoethyl)isonicotinohydrazide 17 a-d

A dimethylformamide solution (10 ml) of 2-chloro-*N*-(4-oxo-2-(substituted quinazolin-3(4*H*)-yl) acetamido **15** (0.01 mol), isonicotinic acid hydrazide (1.37 gm, 0.01 mol) and 5 drops of triethylamine was refluxed for 8 hours. The reaction mixture was then poured onto ice/cold water and the separated solid was then filtered, washed with water, left to dry then recrystallized from dimethylformamide.

***N'*-(2-oxo-2-(4-oxo-2-(*p*-tolyloxymethyl)quinazolin-3(4*H*)-ylamino)ethyl) isonicotinohydrazide 17 a**

Yield %: 66, **m.p:** 192- 193°C, **I.R (cm^{-1}):** 3194 (br.) (NH $_{(s)}$), 2924, 2854(CH_2, CH_3), 1670 (C=O $_{(s)}$), 1612, 1512 (C=C, C=N), **^{1}H NMR (ppm):** 2.27 (s, 3H, CH_3), 5.09 (s, 2H, CH_2NH), 5.28(s, 2H, OCH_2), 6.88-8.22 (m, 11H, CH aromatic), 8.40(d, *J*= 1.6 Hz, 1H, H on C_5 of the quinazolinone ring), 10.10(s, 1H, $CH_2NHNHCO$), 12.15 (s, 2H, NHNHCO and CONH). Anal. Calcd for $C_{24}H_{22}N_6O_4$ (458.48): C, 62.87; H, 4.84; N, 18.33. Found: C, 63.10; H, 5.09; N, 18.24.

***N'*-(2-(2-((4-chloro-3-methylphenoxy)methyl)-4-oxoquinazolin-3(4*H*)-ylamino)-2-oxoethyl)isonicotinohydrazide 17 b**

Yield %:76, **m.p:** 248- 249°C, **I.R (cm-1):** 3347, 3244 (NH s), 2917, 2849 ($CH_{2\ (s)}$, CH_3), 1695 (C=O $_{(s)}$), 1581, 1510, 1448 (NH s, C=C, C=N), 755 (C-Cl). Anal. Calcd for $C_{24}H_{21}ClN_6O_4$ (492.93): C, 58.48; H, 4.29; N, 17.05. Found: C, 58.50; H, 4.30; N, 17.15.

***N'*-(2-(2-((naphthalen-1-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-ylamino)-2-oxoethyl)isonicotinohydrazide 17 c**

Yield %: 54, **m.p:** 128- 129°C, **I.R (cm^{-1}):** 3170 (br.) (NH s), 2924, 2854 ($CH_{2\ (s)}$), 1690 (C=O $_{(s)}$), 1581, 1504 (NH s, C=C, C=N). Anal. Calcd. For $C_{27}H_{22}N_6O_4$ (494.51): C, 65.58; H, 4.48; N, 16.99. Found: C, 65.72; H, 4.68; N, 17.19.

***N'*-(2-(2-((naphthalen-2-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-ylamino)-2-oxoethyl)isonicotinohydrazide 17 d**

Yield %: 67, **m.p:** 126- 127°C, **I.R (cm^{-1}):** 3294, 3201 (NH s), 2924, 2854 ($CH_{2\ (s)}$), 1690 (C=O $_{(s)}$), 1605, 1504, 1466 (NH s, C=C, C=N), **Mass m/z (%):**495(0.30), 115(100). Anal. Calcd for $C_{27}H_{22}N_6O_4$ (494.51): C, 65.58; H, 4.48; N, 16.99. Found: C, 66.10; H, 4.20; N, 17.19.

General procedure for synthesis of 6-substituted-2*H*-[1,2,4]triazino[2,3-c] quinazolin-3(4*H*)-one 18 a, b

An equimolar amount of the chloroacetylchloride derivative **15** and ammonium acetate (0.77 gm) in glacial acetic acid (15 ml) were refluxed for 3 hours. It was then poured onto ice/cold water and the deposited solid was then filtered, washed with water, left to dry and then crystallized from aqueous ethanol.

6-(*p*-Tolyloxymethyl)-2*H*-[1, 2, 4]triazino[2,3-c]quinazolin-3(4*H*)-one 18 a

Yield %: 69, **m.p:** 159- 160°C, **I.R (cm^{-1}):** 3225 (NH), 2950, 2850($CH_{2\ (s)}$, CH_3), 1700 (C=O), 1610, 1515 (NH, C=C, C=N), **^{1}H NMR (ppm):** 2.28(s, 3H, CH_3), 5.04(s, 4H, OCH_2 and CH_2 of the triazine ring), 6.88-7.82 (m, 7H, CH aromatic), 8.21(d, *J*= 1.5 Hz, 1H, H on C_5 of the quinazolinone ring), 9.21(s, 1H, NH), **Mass m/z (%):**318(50), 57(100). Anal. Calcd for $C_{18}H_{16}N_4O_2$ (320.35): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.62; H, 5.71; N, 18.02.

6-((4-Chloro-3-methylphenoxy)methyl)-2*H*-[1, 2, 4]triazino [2,3-c]quinazolin-3(4*H*)-one 18 b

Yield %: 74, **m.p:** 165- 166°C, **I.R (cm^{-1}):** 3209 (NH), 2924, 2850($CH_{2(s)}$, CH_3), 1700 (C=O), 1612, 1481 (NH, C=C, C=N), 771 (C-Cl). Anal. Calcd for $C_{18}H_{15}ClN_4O_2$ (354.80): C, 60.94; H, 4.26; N, 15.79. Found: C, 60.70; H, 4.20; N, 15.99.

General procedure for synthesis of *N'*-(2-(2-substituted-4-oxoquinazolin-3(4*H*)-ylamino)-2-oxoethyl)-1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydro quinoline-3-carbohydrazide 19 a-d, *N'*-(2-(2-Substituted-4-oxo quinazolin-3(4*H*)-ylamino)-2-oxoethyl)-9-fluoro-3-methyl-10-(4-methyl piperazin-1-yl)-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-ij]quinoline-6-carbohydrazide 20 a-d

The 2-chloro-*N*-(4-oxo-2-(substituted) quinazolin-3(4*H*)-yl) acetamido **15** (0.01 mol) and norfloxacin hydrazide (3.34 gm, 0.01 mol) in dimethylformamide (15 ml) with 5 drops triethylamine was refluxed for 8 hours. The reaction mixture was then poured onto ice/cold water and the separated solid was then filtered, washed with water and left to dry then recrystallized from dimethylformamide. Compounds **20 a-d** were prepared through the same procedure but using ofloxacin hydrazide instead of norfloxacin hydrazide and they were recrystallized from dimethylformamide**.**

1-Ethyl-6-fluoro-4-oxo-N'-(2-oxo-2-(4-oxo-2-(*p*-tolyloxymethyl) quinazolin-3 (4*H*) -ylamino) ethyl)-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbohydrazide 19 a

Yield %: 64, **m.p:** 160- 161°C, **I.R (cm^{-1}):** 3356, 3308, 3251 (NH $_{(s)}$), 2922, 2853($CH_{2\ (s)}$, CH_3), 1688, 1656 (C=O $_{(s)}$), 1606, 1512, 1469 (NH $_s$, C=C, C=N), 1250 (C-F), **Mass m/z (%):**654(50), 105(100). Anal. Calcd for $C_{34}H_{35}FN_8O_5.H_2O$ (672.72): C, 60.71; H, 5.54; N, 16.66. Found: C, 60.89; H, 6.04; N, 16.60.

***N'*-(2-(2-((4-chloro-3-methylphenoxy)methyl)-4-oxoquinazolin-3(4*H*)-ylamino)-2-oxoethyl)-1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydro quinoline-3-carbohydrazide 19 b**

Yield %: 74, **m.p:** 272- 273°C, **I.R (cm^{-1}):** 3433 (br.), 3224, 3186 (NH s), 2924, 2850 ($CH_{2\ (s)}$, CH_3), 1689, 1628 (C=O $_{(s)}$), 1473, 1403 (NH s, C=C, C=N), 1250 (C-F), 770 (C-Cl), **Mass m/z (%):**687(0.21), 160 (100). Anal. Calcd for $C_{34}H_{34}FClN_8O_5$ (689.15): C, 59.26; H, 4.97; N, 16.26. Found: C, 59.33; H, 5.28; N, 16.32.

1-Ethyl-6-fluoro-*N'*-(2-(2-((naphthalen-1-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-ylamino)-2-oxoethyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbo hydrazide 19 c

Yield %:57, **m.p:**106- 107°C, **I.R (cm-1):** 3294, 3255, 3178 (NH s), 2924, 2854 ($CH_{2\ (s)}$), 1690 (C=O $_{(s)}$), 1566, 1504, 1458 (NH s, C=C, C=N), 1251 (C-F). Anal. Calcd for $C_{37}H_{35}FN_8O_5$ (690.74): C, 64.34; H, 5.11; N, 16.22. Found: C, 64.35; H, 5.14; N, 16.90.

1-Ethyl-6-fluoro-*N'*-(2-(2-((naphthalen-2-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-ylamino)-2-oxoethyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbo hydrazide 19 d

Yield %: 67, **m.p:** 230- 232°C**, I.R (cm^{-1}):** 3450-3200 (br.) (NH s), 2950, 2850 ($CH_{2\ (s)}$), 1690, 1660 (C=O $_{(s)}$), 1620, 1510, 1480 (NH s, C=C, C=N), 1250 (C-F). Anal. Calcd for $C_{37}H_{35}FN_8O_5.H_2O$ (708.75): C, 62.70; H, 5.26; N, 15.81. Found: C, 62.56; H, 5.26; N, 16.32.

9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-*N'*-(2-oxo-2-(4-oxo-2-(*p*-tolyloxymethyl)quinazolin-3(4*H*)-ylamino)ethyl)-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-ij] quinoline-6-carbohydrazide 20 a

Yield %: 55, **m.p:** 229- 231°C, **I.R (cm^{-1}):** 3450-3300 (br.) (NH s), 2900 ($CH_{2\ (s)}$), CH_3), 1690, 1655 (C=O $_{(s)}$), 1610, 1515, 1475 (NH s, C=C, C=N), 1250 (C-F), **^{1}H NMR (ppm):** 1.17(s, 3H, CH_3 on oxazine), 2.23(s, 6H, N-CH_3 and CH_3 on phenyl), 2.51(s, 4H, 2 CH_2 on piperazine), 3.37(s, 7H, 2 CH_2 on piperazine, CO-CH_2-NH and CH of oxazine), 4.98 (s, 4H, OCH_2 and CH_2 of morpholino), 6.93-7.87 (m, 9H, CH aromatic), 8.13(d, *J*= 1.6 Hz, 1H, H on C_5 of the quinazolinone ring), 12.48(s, 3H, 3NH s), **Mass m/z (%):**694(0.05), 132(100). Anal. Calcd for $C_{36}H_{37}FN_8O_6$ (696.74): C, 62.06; H, 5.35; N, 16.08. Found: C, 61.75; H, 5.52; N, 15.98.

***N'*-(2-(2-((4-chloro-3-methylphenoxy)methyl)-4-oxoquinazolin-3(4*H*)-ylamino)-2-oxoethyl)-9-fluoro-3-methyl-10-(4-methyl piperazin-1-yl)-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-ij] quinoline-6-carbohydrazide 20 b**

Yield %: 60, **m.p:** 257- 258°C, **I.R (cm^{-1}):** 3450-3200 (br.) (NH s), 2923, 2850 ($CH_{2\ (s)}$), $CH_{3(s)}$), 1683, 1653 (C=O $_{(s)}$), 1620, 1514, 1471 (NH s, C=C, C=N), 1246 (C-F), 771 (C-Cl). Anal. Calcd for $C_{36}H_{36}ClFN_8O_6$ (731.19): C, 59.14; H, 4.96; N, 15.33. Found: C, 59.50; H, 4.99; N, 15.39.

9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-*N'*-(2-(2-((naphthalen-1-yloxy)methyl)-4-oxoquinazolin-3(4*H*)-ylamino) -2-oxoethyl)-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-ij] quinoline-6-carbohydrazide 20 c

Yield %: 55, **m.p:**162-164°C, **I.R (cm-1):** 3170(br.) (NH s), 2924, 2854 ($CH_{2\ (s)}$), $CH_{3(s)}$), 1690 (C=O $_{(s)}$), 1581, 1504, 1458 (NH s, C=C, C=N), 1234 (C-F). Anal. Calcd for $C_{39}H_{37}FN_8O_6$ (732.78): C, 63.93; H, 5.09; N, 15.29. Found: C, 64.52; H, 4.40; N, 15.33.

9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-N'-(2-(2-((naphthalen-2-yloxy)methyl)-4-oxoquinazolin-3(*4H*)-ylamino)-2-oxoethyl)-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-ij] quinoline-6-carbohydrazide 20 d

Yield %: 63, **m.p:** 189- 190°C**, I.R (cm-1):** 3278, 3232 (NH s), 2924, 2850 ($CH_{2\ (s)}$), 1682 (C=O $_{(s)}$), 1612, 1465 (NH s, C=C, C=N), 1257 (C-F), **Mass m/z (%):**731(0.99), 142(100). Anal. Calcd for $C_{39}H_{37}FN_8O_6$ (732.78): C, 63.93; H, 5.09; N, 15.29. Found: C, 64.50; H, 4.30; N, 15.43.

Microbiological Screening

Disc diffusion method

The compounds were tested at a concentration of 5.2 mg ml-1. They were dissolved in dimethylsulfoxide (DMSO) which showed no antimicrobial activity against either the tested bacteria or fungi. Ciprofloxacin and fluconazole [42, 43] were used as reference standards for bacteria and fungi respectively and were screened under similar conditions for comparison. Solvent control was also maintained under similar conditions. The inoculum of each of the standard bacterial strains was prepared by transferring a single well-isolated colony taken from overnight culture on nutrient agar plate in 10 ml of nutrient broth. The resulting suspension was vortexed for15 seconds and incubated at 37± 1°C for 4 h. The turbidity was adjusted to match the 0.5 McFarland standards. Muller Hinton Agar plates for bacteria and Sabbaroud Agar for fungi were inoculated with the inoculum using a sterile cotton swab and allowed to dry for 5 min. The sterile disks were impregnated with different compounds. The disks were suitably placed apart on the medium and the plates were incubated aerobically at 37 ± 1°C for 24- 48 h. After incubation, the inhibition zone diameter around each disk was measured using a ruler.

Agar streak dilution method

For each tested compound, a stock solution of 100 mg/ml in DMSO was prepared and tenfold serial dilution was made in the same solvent. Each dilution was added to 20 mL of molten nutrient agar medium, held at 45 ^{o}C to yield the final test concentrations in the agar medium ranging from 0.0005 - 3.6 mg/ml. The activity of tested samples was challenged against standard plates supplemented with ciprofloxacin and was examined side by side to determine the MIC of the tested compounds. Controls were prepared using the same quantities of DMSO as blank. The mixtures were mixed and poured into sterile Petri dishes, allowed to harden at room temperature. The agar surface was inoculated with a standardized suspension of the tested microorganism and incubated at 37ºC for 24-48 hours [44, 45]. The MIC was defined as the lowest concentration of an antibacterial agent that inhibited visible growth after incubation at 37°C for 24 and 48 h for bacteria and yeast respectively.

RESULTS

Chemistry

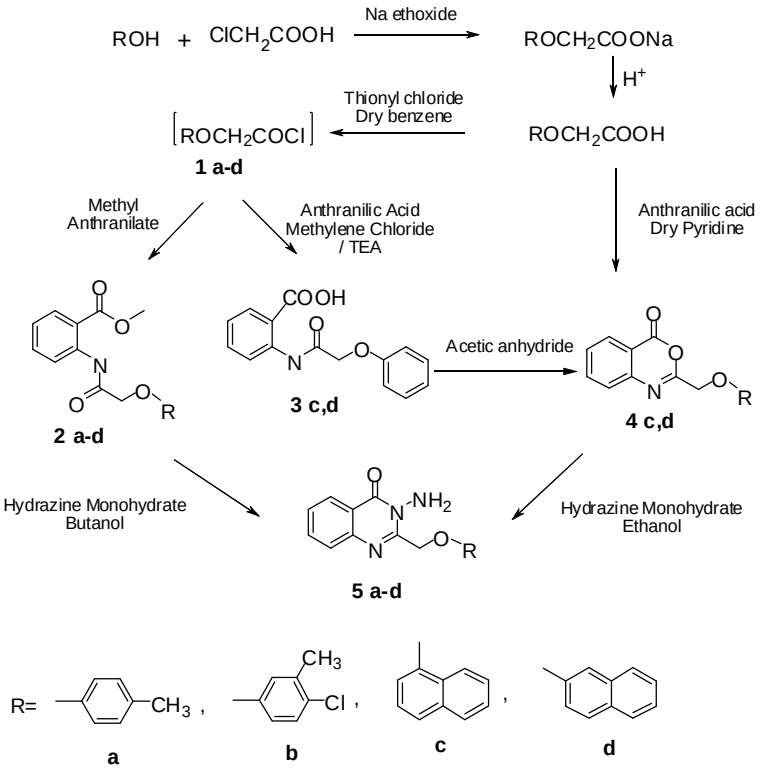
The aimed for amino derivatives **5** were obtained from the freshly prepared corresponding acid chloride **1** [46- 48] via two routes. The first through reaction of this in sito generated acid chloride with methyl anthranilate to yield **2** [49] followed by reaction with hydrazine monohydrate in butanol. The second through generation of the benzoxazine intermediates **4** [50- 52] followed by reaction with hydrazine monohydrate in ethanol giving the designed amino **5** in better yield (scheme 1). These amino quinazolinones **5** were the building blocks for the preparation of all the desired new compounds. Condensation of these amino quinazolinones with various aldehydes in glacial acetic acid gave the corresponding benzylidene derivatives **6** in high yield. Further reaction with thioglycolic acid in the presence of anhydrous zinc chloride in dry dimethylformamide yielded the oxothiazolidine derivatives **7**. The reaction of the amino intermediates with isonicotinic acid hydrazide in absolute ethanol and anhydrous sodium acetate was accomplished to reach the aimed for derivatives **8**. The hydrazones **9** were obtained via the reaction of benzylidene derivatives **6** with the prepared sulphonamide hydrazides in absolute ethanol (scheme 2). The amino quinazolinones **5** were changed into another intermediate namely 1-substituted-3-(4-oxo-2-substituted-quinazolin-3(4*H*)-yl) thiourea **10** by reflux with the appropriate isothiocyanates in methylene chloride and triethylamine. These thiourea intermediates **10** were used to synthesize the corresponding thiazolidine containing compounds **11** and thioxoimidazolidines derivatives **12** via the reflux with phenacyl bromide or monochloroacetic acid in absolute ethanol respectively. Moreover, the amino quinazolinones **5** were reacted with 4-acetamido benzenesulfonyl chloride in dry dimethylformamide to give the corresponding acetamido phenyl sulphonyl amino quinazolinone derivatives **13**. The oxotriazine containing compounds **14** was obtained through the reaction of 3- amino quinazolinones **5** with chloroacetamide in dimethylformamide [41]. Another dynamic intermediate **15** was synthesized with several target compounds in mind. This intermediate **15** was reached by the reaction of the amino quinazolinones **5** with the good acylating synthon chloroacetyl chloride in dry dimethylformamide to obtain the active chloroacetamido derivative **15** (scheme 3). The deemed for imidazole containing compounds **16** were prepared by reacting potassium cyanate in absolute ethanol [41] while reacting the acetyl chloride congeners **15** with isoniazide in dry dimethylformamide, led to the isonicotinohydrazide quinazolinone derivatives **17**. The positional isomers of the tricyclic compounds **14** were obtained via the cyclization [53] of the acetyl chloride congeners **15** with ammonium acetate in glacial acetic acid to give compounds **18**. The well known norfloxacin and ofloxacin were converted to the corresponding acid hydrazides, which were reacted with the chloroacetyl chloride intermediates **15** in dry dimethylformamide to yield the designed compounds **19** and **20** (scheme 4). The I.R, ^{1}H NMR and mass spectra are in agreement with the proposed structures.

Microbiological Screening

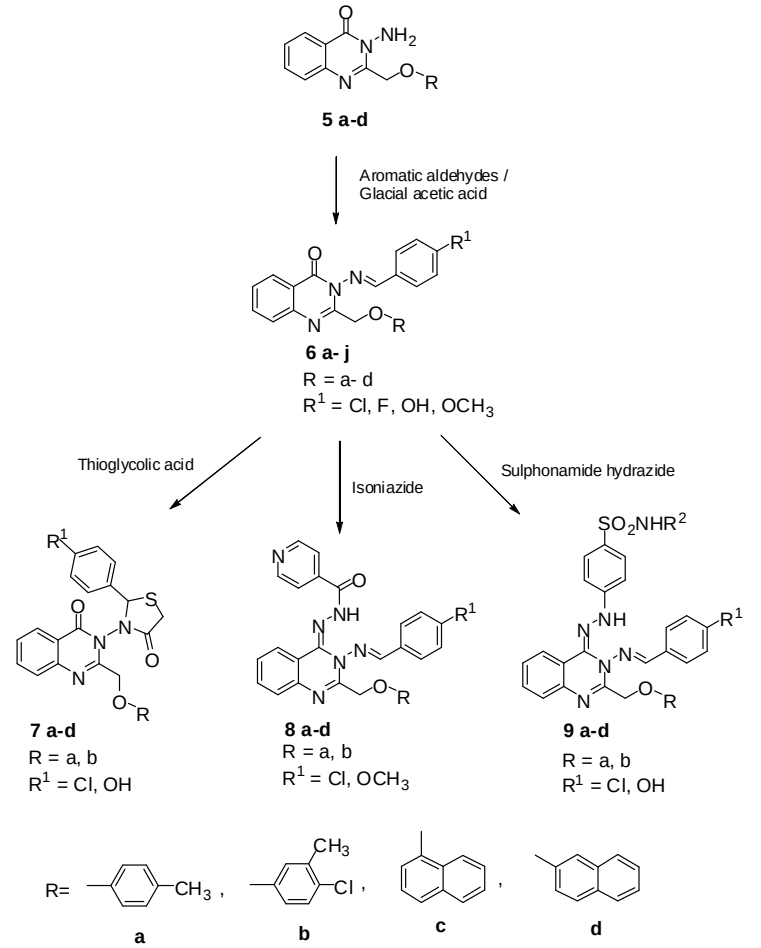
Several series of various quinazoline derivatives were synthesized. The structures of these derivatives include quinazolinones, fused ring systems from quinazoline; all substituted at the 2-position with p-tolyl, chloro- tolyl and/ or 1-naphthyl, 2-naphthyl moieties. This was done to test the anti-microbial effect of these substituents among others on the new structures obtained. Most of the newly synthesized compounds were evaluated in vitro against gram positive Staphylococcus aureus, the gram negative E. coli and Pseudomonas aeruginosa and the fungus Candida albicans using the preliminary disc diffusion method [54- 59].

From the preliminary testing; compounds **6c** and d showed fair activity against gram-positive Staphylococcus aureus, while **7a** and **b** had slight activity against both gram negative micro-organisms; **8a** and **b** were more active especially against E. coli. Fortunately, compound **9b** was effective against both gram positive and negative organisms. Some of series **10** (**h**, **i**, **j**, **k**) were with slight antifungal activity. Derivatives **11c**, **d**, **e** and f showed fair to good activity against E. coli and so did **14a** while **14c** and **d** was active against Pseudomonas aeruginosa. All series **15** was active against Staphylococcus aureus while **16a** had broad spectrum of activity; active against Staphylococcus aureus, E. coli, Pseudomonas aeruginosa and Candida albicans as well. Compounds of the series **16** were characterized by acquiring antifungal activity and so did **17c** and **d**. **18**, **19** and **20b** were anti gram positive. On the other hand, all series **19** except **19d**, **20b**, **c** and d showed activity against E. coli.

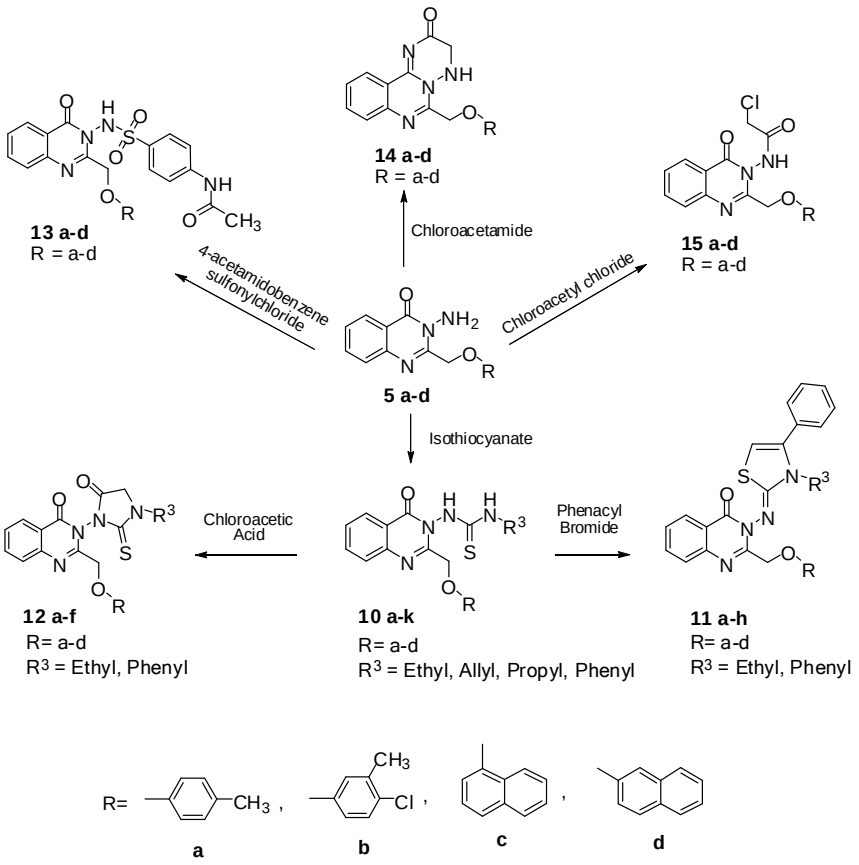
On estimation of the MIC of some compounds; **5a** was active against Staphylococcus epidermidis, **11a**, **12e** and **14b** were active against Streptococcus pyogens and Staphylococcus epidermidis. Also, **14b** and **15a** showed activity against Salmonella typhi. The rest of the tested compounds were found inactive against the tested micro-organisms.



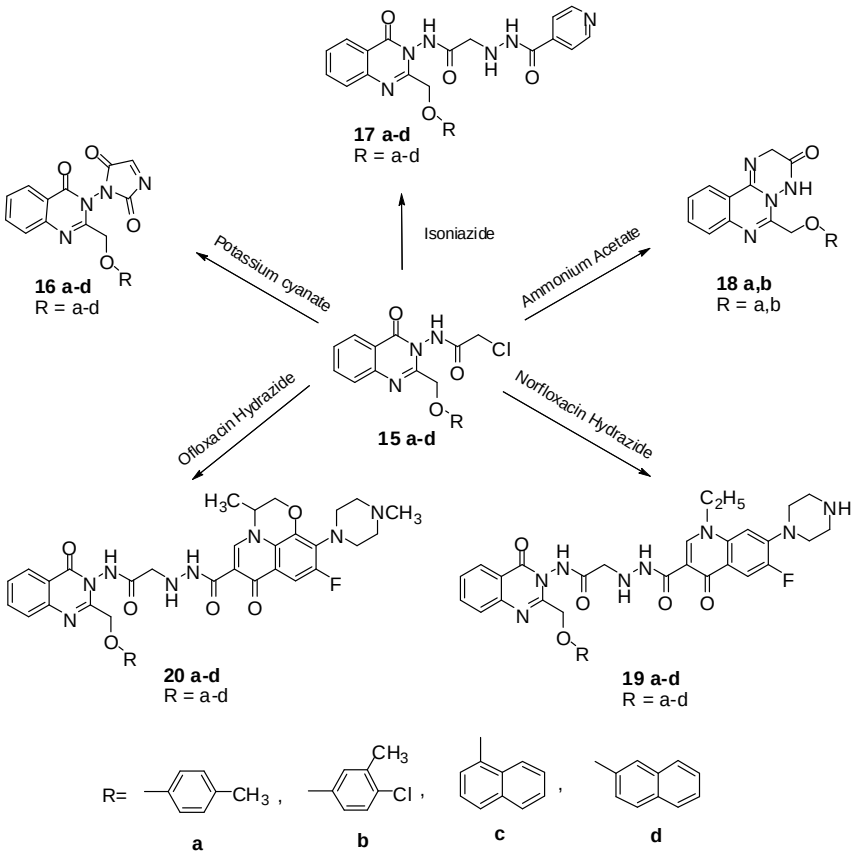
Scheme 1



Scheme 2



Scheme 3



Scheme 4

DISCUSSION

By analyzing & studying the results of the testing (Table 1); it became apparent that the various substitutions & cyclization reactions performed caused variation in activity. Unfortunately, the amino intermediate (**5**), showed no activity against those chosen. When this intermediate was changed to the substituted oxothiazolidine- containing compounds **7**; it showed some activity against the gram negative E. Coli & Pseudomonas aeruginosa. The quinazolinone derivatives having either of the naphthyl radicals (**6c** and **d**) at position 2- showed slight activity against the gram-positive Staphylococcus aureus. Replacing the oxo- group at position 4- of the quinazolinone derivatives (**6 a** and **b**) by the isonicotinohydrazide moiety; the resulting compounds (**8 a** and **b**) acquired good activity against gram negative E. Coli. On the other hand, replacing this oxo group in the quinazolinone congener (**6 b**) by the hydrazide of N-pyrimidinyl benzene sulfonamide; produced broader spectrum quinazoline derivative (**9 b**) against both gram positive and negative micro organisms. Increasing the lipophilic character of compounds **5** by substitution of its amino group at position 3- by thiourea moiety (**10**) and specially the phenyl substituted ones (**10 h- k**) led to the corresponding quinazolinone compounds that showed moderate activity against E. Coli and Candida albicans. The quinazolinone derivative having a phenyl substituted thiourea (**10h**) gave in addition moderate activity against gram positive Staphylococcus aureus. Moreover, cyclization of thiourea- containing compounds **10** into the corresponding thiazolidine (**11**) or the thioxo-imidazolidine (**12**) led to decrease in the activity against E. Coli. Acylation of the amino group in the quinazolinone intermediates (**5**) with chloroacetylchloride was fruitful as their corresponding chloro acetamido counterparts (**15**) acquired broader spectrum activity against gram positive Staphylococcus aureus and the gram negative E. Coli or Pseudomonas aeruginosa. Reaction of the chloro acetamido derivatives with potassium cyanate, afforded the corresponding imidazole dione derivatives (**16**) that showed slight activity against Candida albicans. The imidazole-dione derivative-bearing the tolyloxy methyl moiety (**16 a**)- showed activity against the gram positive and all the gram negative micro-organisms. The positional isomers **14** and **18** showed varied activities against the tested micro- organisms. Amalgamation of quinazolinone ring with norfloxacin hydrazide (**19**) or ofloxacin hydrazide gave the corresponding adducts (**19** and **20**) respectively, that gave in most of the cases vaiable activities against gram positive Staphylococcus aureus and gram negative E. Coli.

The rest of the tested compounds were with mild activity or devoid of activity. (Table 1) Comparing the activity of the new compounds with quinazolines/ones from literature; most previously prepared and tested compounds had a substituent; mostly phenyl that's directly attached to N at position 3 of quinazoline ring; while compounds in this work have at least an N=CH spacer or directly attached to a heterocyclic ring also at N-3. The activity was also mild to moderate [8, 11, 45] except in case where a morpholinyl moiety was placed [56].

On applying the minimum inhibitory concentration test (MIC) for representative compounds against other types of micro organisms, in addition to those used in the preliminary test (Table 2). All the tested compounds were active against gram-positive bacteria except **10h**, **14b** and **15a** were active against gram-negative E-Coli and Salmonella Typhi. The preliminary compound **4c** had no antimicrobial activity against all the tested microorganisms. Compounds **5a, 11a, 12e** and **20a** showed narrow spectrum anti gram positive activity mainly against Streptococci and Staphylococci. Derivatives **10h** and **14b** showed remarkable broad spectrum antibacterial activity against both gram positive and negative especially Streptococcus pyogenes, Staphylococcus epidermidis, Salmonella typhi and E. Coli.

In general, it could be concluded that the p-tolyloxy methyl placed at position 2- of the quinazolinone ring is favored for any activity to appear after which comes the chlorotolyloxy congener. The oxo-group of the quinazolinone ring is also important since it lent the compounds narrow spectrum of activity against gram positive microorganisms and even those who showed broad spectrum of activity had an oxo- group.

Table 1: The inhibition zones of the tested compounds measured in mm:

Compound	Gram +ve	Gram -ve		Fungi
	Staph.aureus	*E. coli.*	*Ps. aeruginosa*	*Candida albicans*
Ciprofloxacin	35	40	40	-
Fluconazole	-	-	-	25
5 a	-	-	-	-
5 b	-	-	-	-
5 c	-	-	-	-
5 d	-	-	-	-
6 a	-	-	-	-
6 b	-	-	-	-
6 c	10	-	-	-
6 d	10	-	-	-
6 g	-	-	-	-
7 a	-	16	10	-
7 b	-	12	10	-
8 a	-	24	-	-
8 b	-	12	8	-
9 a	-	-	-	-
9 b	15	25	10	-
10 a	-	-	-	-
10 b	-	-	-	-
10 c	-	-	-	-
10 d	-	-	-	-
10 f	-	-	-	-
10g	-	-	-	*10*
10 h	*25*	*25*	-	*10*
10 i	-	*20*	-	-
10 j	-	*15*	-	*10*
10 k	-	*10*	-	-
11 a	-	-	-	*10*
11 b	-	-	-	-
11 c	-	*10*	-	-
11 d	-	*15*	-	-

11 e	-	*20*	-	-
11 f	-	*15*	-	-
11 g	-	-	-	-
11 h	-	-	-	-
12 a	-	-	-	-
12 b	-	-	-	-
12 d	-	-	-	-
12 e	-	*10*	-	-
12 f	-	*10*	-	-
13 a	-	-	*10*	-
13 b	-	-	-	-
13 c	-	-	-	-
13 d	-	-	-	-
14 a	-	*18*	-	-
14 b	-	-	-	-
14 c	-	-	*10*	-
14 d	-	-	*10*	-
15 a	*20*	-	-	-
15 b	*23*	*22*	-	-
15 c	*10*	-	*10*	-
15 d	*18*	-	-	-
16 a	*20*	*18*	*10*	*10*
16 b	-	*20*	-	*10*
16 c	-	-	-	*10*
16 d	-	-	-	*10*
17 a	*8*	-	-	-
17 b	-	-	-	-
17 c	-	-	-	*10*
17 d	-	-	-	*10*
18 a	*20*	-	-	-
18 b	*15*	-	-	-
19 a	*8*	*12*	-	-
19 b	*20*	*12*	-	-
19 c	*25*	*22*	-	-
19 d	-	-	-	-
20 a	-	-	-	-
20 b	*20*	*27*	-	-
20 c	-	*12*	-	-
20 d	-	*23*	*10*	*10*

Table 2: **Estimated minimum inhibitory concentrations (MIC) in µg ml^{-1} of some tested compounds against tested standard microorganisms.**

Compounds	**4c**	**5a**	**10b**	**10h**	**11a**	**12e**	**14b**	**15a**	**20a**
Test organism	3	2	24	8	9	10	25	13	18
Streptococcus pyogenes	NS	NS	NS	0.39	6.25	6.25	0.39	NS	0.39
Staphylococcus aureus	NS	NS	0.39	12.5	NS	NS	NS	NS	12.5
Staphylococcus epidermidis	NS	0.39	NS	NS	12.5	6.25	0.39	0.39	NS
Salmonella typhi	NS	NS	NS	NS	NS	NS	3.125	25	NS
E. coli	NS	NS	NS	6.25	NS	NS	NS	NS	NS
Pseudomonas aeruginosa	NS	NS	NS	NS	NS	NS	NS	NS	NS
Candida albicans	NS	NS	NS	NS	NS	NS	NS	NS	NS

NS = not significant antimicrobial effect.

ACKNOWLEDGEMENT

The authors are thankful for Dr. Ahmed Sameer; Lecturer of microbiology, Microbiology Department, Faculty of Veterinary Medicine, Cairo University for performing MIC.

REFERENCES

1. Nathwami D, Wood MJ Penicillins: A current review of their clinical pharmacology and therapeutic use. Drugs 1993; 45: 866-894.
2. Schnappinger D, Hillen W Tetracyclines: antibiotic action, uptake and resistance mechanisms. Arch Microbiol 1996; 165: 359-369.
3. Beena KP, Akelesh T Synthesis and antibacterial activity of quinazolinone derivatives. Int J Pharm Pharm Sci 2010; 2: 166-168.
4. Said MM, Hussein MMM Synthesis of some novel 4(3H)-quinazolinones as antimicrobial agents. Bull Fac Pharm Cairo Univ 1994; 32: 341-347.
5. Kung PP, Casper DM, Cook LK, Lingaldo WL, Risen ML, Vickers AT Structure- activity relationships of novel 2-substitutedquinazoline antibacterial agents. J Med Chem 1999; 42, 4705-4713.
6. Pandeya NS, Sriram D, Nath G, De Clercq E Synthesis, antibacterial, antifungal and anti- HIV evaluation of Sciff and Mannich bases of isatin derivatives with 3-amino-2-methylmercaptoquinazolin-4(3H)-one. Pharmaceutica Acta Helvetica 1999; 74: 11-17.
7. Jantova S, Stankovsky S, Spirkova K In vitro antibacterial activity of ten series of substituted quinazolines. Biologica Bratislava 2004; 59: 741-752.

8. Grover G, Kini GS Synthesis and evaluation of new quinazolone derivatives of nalidixic acid as potent antibacterial and antifungal agents. Eur J Med Chem 2006; 41: 256-262.
9. Afzal-Azam Md, Sahu KS, Banerjee M, Samatray A, Behera C Synthesis, characterization and biological activity of 2-methyl-3-aminoquinazolin-4(3H)-ones Schiff bases. J Braz Chem Soc 2008; 19: 963-970.
10. Abdel-Aal TM, Abdel-Aleem AA, Ibahim IL, Zein LA Synthesis and antimicrobial activity of novel 5-amino-4-cyano-1H-pyrazole and quinazolin-4(3H)- one derivatives. Arch Pharm Res 2010; 33 :1891-900.
11. Girija, K., and Hemalatha, K., Synthesis, preliminary QSAR study and antimicrobial activity of some novel 2,3-disubstituted quinazolinone derivatives. Int J Pharm BioSci 2010; 1: 254-259.
12. Bartroli J, Turmo E, Alquero M, Boncompte E, Vericat LM; Conte L; Ramis J, Merlos M, Garcia-Rafanell J, Forn J New azole antifungals. 3. Synthesis and antifungal activity of 3-substituted-4(3H)-quinazolinones. J Med Chem 1998; 41: 1869-1882.
13. Ryu CK, Shim JY, Yi YJ, Choi IH, Chae MJ, Han JY, Jung OJ Synthesis and antifungal activity of 5,8-quinazolinedione derivatives modified at positions 6 and 7. Arch Pharm Res 2004; 27: 990-996.
14. Hemalatha K, Girija K Synthesis of some novel 2, 3-disubstituted quinazolinone derivatives as analgesic and anti-inflammatory agents. Int J Pharm Pharm Sci 2011; 3: 103-106.
15. Kumar A, Sharma S, Archana A, Bajaj K, Sharma S, Panwar H, Singh T, Srivastava KV Some new 2,3,6-trisubstitutedquinazolinones as potent anti-inflammatory, analgesic and COX-II inhibitors. Bioorg Med Chem 2003; 11: 5293-5299.
16. Laddha SS, Wadodkar GS, Meghal KS Studies on some biologically active substituted 4(3H)-quinazolinone: Part. 1. Synthesis, characterization and anti-inflammatory-antimicrobial activity of 6, 8-disubstituted, 2-phenyl-3-[substituted-benzothiazole-2-yl]-4[3H]-quinazolinone. Arkivoc 2006; 11: 1-20.
17. Algarsamy V, Murugesan S Synthesis and pharmacological evaluation of some 3-(4-methoxyphenyl)-2-substitutedamino-quinazolin-4(3H)-ones as analgesic and anti-inflammatory agents. Chem Pharm Bull 2007; 55: 76-80.
18. Algarsamy V, Solomon RV, Dhanabal K Synthesis and pharmacological evaluation of some 3-phenyl-2-substituted-3H-quinazolin-4-one as analgesic, anti-inflammatory agents. Biorg Med Chem 2007; 15: 235-241.
19. Rather AB, Raj T, Reddy A, Ishar SPM, Sivakumar S, Paneerselvam P Synthesis and evaluation of novel 2-substituted-quinazolin-4(3H)-ones as potent analgesic and anti-inflammatory agents. Arch Pharm 2010; 343: 108-113.
20. Al-Obaid MA, Abdel-Hamide GS, El-Kashef AH, Abdel-Aziz AA, El-Azab SA, Al-Khamees AH, El-Subbagh IH Substituted quinazolines, part 3. Synthesis, in vitro antitumor activity and molecular modeling study of certain 2-thieno-4(3H)-quinazolinone analogs. Eur J Med Chem 2009; 44: 2379-2391.
21. Raghavendra NM, Gurubasavarajaswamy PM, Nagaranavile KS, Parameshwaran T Antitumor actions of imidazolyl-(4-oxoquinazolin-3(4H)-yl)-acetamides against Ehrlich Ascites Carcinoma. Arch Pharm Res 2009; 32: 431-436.
22. Abdel Gawad MN, Georgey HH, Youssef MR, El Sayed AN Synthesis and antitumor activity of some 2,3-disubstitutedquinazolin-4(3H)-ones and 4,6-disubstituted-1,2,3,4-tetrahydroquinazolin-2H-ones. Eur J Med Chem 2010; 45: 6058-6067.
23. Kamal A, Bharathi VE, Reddy SJ, Ramaiah JM, Dastagiri D, Reddy KM, Viswanath A, Reddy LT, Shaik BT, Pushpavali NS, Bhadra PM Synthesis and biological evaluation of 3,5-diarylisoxazoline/ isoxazole linked 2,3-dihydro quinazolinone hybrids as anticancer agents. Eur. J Med Chem 2011; 46: 691-703.
24. Rastogi KV, Parmar SS, Singh PS, Akers KT Synthesis of 2-methyl-3-(3,5-diallyl-4-hydroxyphenyl)-4-quinazolones as possible anticonvulsants. J Heterocyclic Chem 1978; 15: 497-499.
25. Tani J, Yamada Y, Oine T, Ochiai T, Ishida R, Inoue I Studies on biologically active halogenated compounds. 1. Synthesis and central nervous system depressant activity of 2-(fluoromethyl)-3-aryl-4(3H)-quinazolinone derivatives. J Med Chem 1979; 22: 95-99.
26. Misra SV, Gupta NP, Pandey NR, Nath C, Gupta PG Search for potential anticonvulsant agents. Synthesis of 2-phenyl/ methyl-3-[o-,m- or p-(benzimidazol-2'-yl)phenyl]-6 or 6,8-substituted/ unsubstitutedquinazolin(3H)-4-ones. Pharmazie 1980; 35: 400-401.
27. Ochiai T, Fukuchi I, Ego H, Yamamura M, Kudo Y, Ishida R General pharmacology of 6-amino-2-fluoromethyl-3-(o-tolyl)-4(3H)-quinazolinone (afloqualone), a new centrally acting muscle relaxant. II. Effects on the peripheral system. Nippon Yakurigaku Zasshi 1981; 78: 359-380.
28. Wolfe FJ, Rathman LT, Sleevi CM, Campbell AJ, Greenwood DT Synthesis and anticonvulsant activity of some new 2-substituted 3-aryl4(3H)-quinazolinones. J Med Chem 1990; 33: 161-166.
29. El-Feky HAS, Abd el-Samii KZ Synthesis and anticonvulsant properties of some novel quinazolone thiosemicarbazone and 4-thiazolidone derivatives. J Chem Technol Biotechnol 1991; 51: 61-66.
30. Abdel Hamide GS, El-Hakim EA, El-Helby AA Synthesis of 2-[1(5-ethyl-5-phenyl)-barbituryl]methylcarbonyl-thioquinazolin-4-one for hypnotic and anticonvulsant activities. Az J Pharm Sci 1996; 17**:** 35-40.
31. El-Helby AA, Abdel Wahab HM Design and synthesis of some new derivatives of 3H-quinazolin-4-one with promising anticonvulsant activity. Acta Pharm 2003; 53: 127-138.
32. Maarouf RA, El-Bendary RE, Goda EF Synthesis and evaluation of some novel quinazolinone derivatives as diuretic agents. Arch Pharm 2004; 337: 527-532.
33. Gupta PD, Ahmad S, Kumar A, Shanker K Newer quinazolinone derivatives as anthelmentic agents. Ind J Chem 1988; 27 B: 1060-1062.
34. Parmar SS, Arora CR Synthesis of quinazolone hydrazides and mono amine oxidase inhibitors. Can J Chem 1966; 44: 2100-2102.
35. Saravanan S, Selvam P, Kumar S, De Clercq E Synthesis, anti-viral and cytotoxicity studies of some 2-phenyl-3substituted quinazolin-4(3H)-ones. Int J Pharm Pharm Sci 2010; 2: 71-79.
36. Saravanan G, Algarsamy V, Prakash RC Synthesis and evaluation of antioxidant activities of novel quinazolinone derivatives. Int J Pharm Pharm Sci 2010; 2: 83-86.
37. Pannerselvam P, Pradeep chandran VR, Sridhar KS Synthesis and characterization and biological activities of novel 2-methyl-quinazolin-4(3H)-ones. Ind J Pharm Sci 2003; 65: 268-273.
38. Mishra P, Gupta NP, Shakya KA Synthesis of Schiff bases of 3-amino-2-methylquinazolin-4(3H)-ones and their antimicrobial activities. J Ind Chem Soc 1991; 68: 618-619.
39. Zhou Y, Murphy ED, Sun Z, Gregor EV Novel parallel synthesis of N-(4-oxo-2-substituted-4H-quinazolin-3-yl)-substituted sulfonamides. Tetrahedron Letters 2004; 45: 8049-8051.
40. Schneller WS, Christ JW The synthesis of "stretched-out" analogs of Lumazine,6,7-dimethyllumazine and 2-amino-5,6,7,8-tetrahydro-6,7-dimethyl-4-pteridinone. J Heterocyclic Chem 1981; 18: 539-542.
41. Ibrahim KM Synthesis and antimicrobial evaluation of certain new 6,8-dichloro-2-phenyl-4(3H)quinazolinone derivatives. Egypt J Pharm Sci 1998; 39: 519-531.
42. Oon LL, Yeo GM Fluconazole susceptibility of Candida species in Singapore by disc diffusion test. Ann Acad Med 2002; 31: 497-501.
43. Kustimer S, Kalkanci A, Mansuroglu H, Senel K Evaluation of the disc diffusion method with a comparison study of fluconazole susceptibility of Candida strains. Chinese Medical Journal 2003; 116: 633-636.
44. Asahina Y, Araya I, Iwase K, Iinuma F, Hosaka M, Ishizaki T Synthesis and antibacterial activity of the 4-quinolone-3-carboxylic acid derivatives having a trifluoromethyl group as a novel N-1-substituent. J Med Chem 2005; 48: 3443-3446.

45. Mohamed SM, Kamel MM, Kassem MME, Abotaleb N, Abd El-Moez IS, Ahmed FM Novel 6,8-dibromo-4(3H)quinazolinone derivatives of anti-bacterial and anti-fungal activities. Eur J Med Chem 2010; 45: 3311-3319.
46. Giacosa Vortheilhafte Phenolglycolsaure der Darstellung und uber die Pyrogallol triglycolsaure. J Prakt Chem (2) 1879; 19: 396-399.
47. Clinton OR, Laskowski CS Coumarins. I. Derivatives of coumarin-3- and 4-carboxylic acids. J Am Chem Soc 1949; 71: 3602-3606.
48. Loudon SA, Radhakrishna RM, Almond KJ, Blodget MG, Boutin HR Conversion of aliphatic amides into amines with (I,I-bis(trifluoroacetoxy)iodo) benzene. 1. Scope of the reaction. J Org Chem 1984; 49: 4272-4276.
49. Atkinson SR, Gawad AN Intramolecular reactions of N-nitrenes: oxidation of 3-amino-2-(2,4-dimethoxyphenylbutyl)quinazolin-4(3H)-ones. J Chem Soc Perkin Trans 1, 1985; 825-830.
50. Smith K, El-Hiti AG, Abdel-Megeed FM, Abdo AM Lithiation of 3-(acylamino)-2-unsubstituted-, 3-(acylamino)-2-ethyl-,and 3-(acylamino)-2-propyl-4(3H)-quinazolinones: convenient syntheses of more complex quinazolinones (1). J Org Chem 1996; 61: 647-655.
51. Zahran AM Synthesis of quinazolinoquinoxalines and quinazolino[2,3:6,1] pyridazino[4,5-b]quinoxalines. J Indian Chem Soc 2000; 77, 494-496.
52. Madkour FMH Reactivity of 4H-3,1-benzoxazin-4-ones towards nitrogen and carbon nucleophilic reagents: applications to the synthesis of new heterocycles. Arkivoc 2004; 1: 36-54.
53. Van Zyl FE A survey of reported synthesis of methaqualone and some positional and structural isomers. Forensic Science International 2001; 122: 142-149.
54. Barry L Antibiotics in Laboratory Medicine, 2nd ed, V Lorian: Williams & Wilkins, Baltimore; 1986. p. 1–26.
55. Isenberg IH Essential procedures in clinical microbiology. ASM Press, Washington, DC. Koneman, EW, SD Allen, WM Janda; 1998. p. 207-254.
56. Bedi SMP, Kumar V, Mahajan PM, Synthesis and biological activity of novel antibacterial quinazolines. Biorg Med Chem Lett 2004; 14: 5211-5213.
57. Kidwai K, Saxena S, Khan RKM, Thukral SS Synthesis of 4-aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-one/thione-5-one derivatives and evaluation as antibacterials. Eur J Med Chem 2005; 40: 816-819.
58. Samie A, Obi LC, Bessong OP, Namrita L Activity profiles of fourteen selected medicinal plants from Rural Venda Communities in South Africa against fifteen clinical bacterial species. Afr J Biotechnol 2005; 4: 1443-1451.
59. Andrews MJ BSAC Working party on susceptibility testing: BSAC standardized disc susceptibility testing method (version 6). J Antimicrob Chemother 2007; 60: 20-41.