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Synthesis, Characterization and i*n vitro* Antioxidant Study of Some Novel 2, 3-Disubstituted Quinazolin-4(3*h*)-Ones

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ABSTRACT

A series of some novel 2,3-disubstituted quinazolin-4(3*H*) ones were synthesized by condensing 2-substituted-4*H*-3,1-Benzoxazin-4-one with Lamivudine to yield the title compounds. The starting material 2-substituted-4*H*-3, 1-Benzoxazin-4-one was synthesized from anthranilic acid and substituted benzoyl chloride. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C- NMR, Mass and Elemental Analysis. The Synthesized compounds were screened for their *in vitro* anti-oxidant activity.

Keywords: Quinazolines, Quinazolinone, Lamivudine, anticancer, *in vitro* anti-oxidant activity

INTRODUCTION

Quinazolinone and their derivatives have been found to possess potent wide spectrum of activities like antibacterial[1-5], antifungal[6-9], anticancer[10,11], antiviral[12-15], Cytotoxic activity[12-15&21], anti-inflammatory[16,17], antihistaminic[17], anthelmintic[18], anti-tubercular[19], anticonvulsant[20] and anti-oxidant activity[10,22&23] etc. Considering the biological significance of them, quinazolinone nucleus was synthesized. In the present research study a series of some novel 2,3-disubstituted Quinazolin-4-(3*H*)-one derivatives were synthesized and screen them for their anti-oxidant activity using three different standard models viz. DDPH, Hydrogen peroxide and Nitric oxide free radical scavenging activities.

EXPERIMENTAL

Materials and Methods

The reaction condition was optimized by using thin layer chromatography on readymade silica gel plates (Merck) using chloroform-methanol (9.5:0.5) and n hexane-ethyl acetate (9:1) as solvent system. Iodine was used as developing agent. Melting point determination was carried in capillary tubes on melting point apparatus which are uncorrected. IR spectrum was recorded by KBr disc method in Thermo Nicolet 6700 FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded with 400 MHz and 100 MHz Bruker Advance-II NMR instrument. Elemental analysis of all the compounds was performed on Elementar Vario EL-II CHNS analyzer. Mass spectra (MS) were recorded on a Thermo Scientific High Resolution Magnetic Sector MS DFS by chemical ionization (CI) or negative-ion electro spray ionization (ESI) method.

Spectral data (IR, NMR, and mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds was ascertained by microanalysis. Elemental analysis (C,H,N) indicated that the calculated and observed values were within the acceptable limits (±0.4%).

STEP 1:

Synthesis of 2-substituted-4H-3,1-benzoxazin-4-one

A solution of substituted benzoyl chloride (0.01mole) was slowly added to a solution of anthranilic acid/substituted anthranilic acid (0.01mole) in anhydrous pyridine (15ml) at 0^{o}C with constant stirring. The reaction mixture was stirred for 30 minutes with magnetic stirrer at room temperature and set aside for one hour. The stirred solution was treated with aqueous sodium bicarbonate to remove the unreacted acid until the effervescence ceases. The solution was filtered and washed with water to remove the inorganic materials and adhered pyridine. The crude benzoxazine thus obtained was dried and recrystallized from absolute ethanol.

STEP 2:

Synthesis of 2,3 disubstituted quinazolin-4-(3H)-one

A cold solution of Lamivudine (0.05 mole) in anhydrous pyridine (10 ml) was added drop wise with constant stirring to 10 ml of cold solution of 2-substituted-4(H)-3,1-benzoxazine-4-one (0.05 mole) in glacial acetic acid. The resultant reaction mixture was stirred vigorously for 30 minutes at room temperature and subsequently heated under reflux for 36-48 hours under anhydrous reaction condition. It

was allowed to cool at room temperature and poured to ice cold water. On standing for 12 hours, solidification occurred which was allowed to settle down. It was filtered off, dried in vacuum and purified by column chromatography.

ANTI-OXIDANT ACTIVITY

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers the electrons from a substance to an oxidizing agent. Oxidation reaction can produce free radicals which start chain reaction that damage cells. Antioxidant terminates these chain reactions by being oxidized themselves. Although oxidation reaction are crucial for life, they can also be damaging, hence plants and animals maintain complex system a of multiple steps of antioxidant such as glutathione, vitamin C, E as well as enzymes such as catalyst, superoxide dismutase. Low level of antioxidant or inhibition of the antioxidant enzymes cause oxidative stress and may damage or kill cells. As oxidative stress might be an important part of many human diseases. Anti-oxidants are used in the treatment of stroke and neurodegenerative disease. Antioxidants are also widely used ingredients in dietary supplements in the hope of maintain health and preventing disease such as cancer and coronary heart disease. In addition to uses in medicine, anti-oxidant have industrial uses also like preservative in food and cosmetics and preventing the degradation of rubber and gasoline.

***In vitro* Anti-oxidant activity**

The antioxidant activity of all the synthesized compounds was determined using

1. DPPH Radical Scavenging method
2. Hydrogen peroxide radical scavenging activity
3. Nitric oxide scavenging activity assay

DPPH Radical Scavenging Activity:

To evaluate the antioxidant potential of all the compounds *in-vitro* by free radical scavenging activity using DPPH (2, 2-diphenyl-1-picryl hydrazyl) reduction.

Procedure:

1. Preparation of Control (DPPH) Solution:

10 mg of DPPH was dissolved in 10 ml of methanol. From this stock solution dilutions were made to obtain concentrations of 10 µg/ ml,50 µg/ ml,100 µg/ ml, 150 µg/ ml and 250 µg/ ml. The absorbance was recorded at 517 nm.

2. Preparation of standard solution (Ascorbic acid):

10 mg of Ascorbic acid was dissolved in 10 ml of methanol. From this stock solution dilution were made to obtain concentrations of 10 µg/ ml,50 µg/ ml,100 µg/ ml, 150 µg/ ml and 250 µg/ ml to which 1 ml of DPPH solution was added and volume was made up to 10 ml. The absorbance was recorded at 517 nm after duration of 30 min.

3. Preparation of test or sample solutions:

The test solutions were prepared in similar manner as that of standard ascorbic acid and the absorbance were recorded at 517 nm after duration of 30 min.

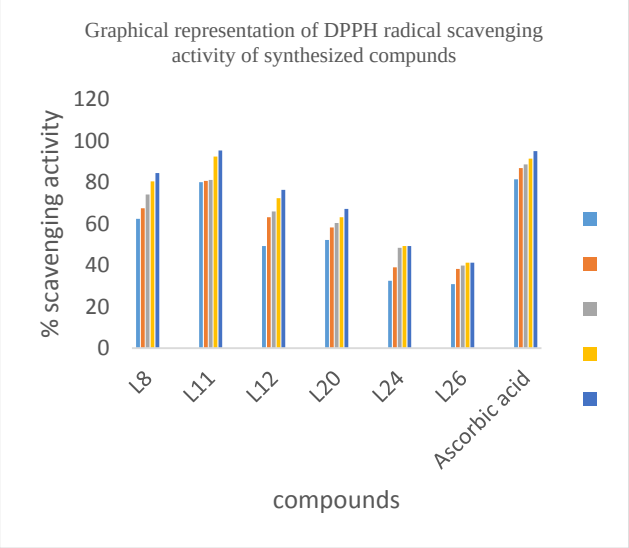
% inhibition was calculated by

$$Scavenging = \frac{Absorbance\ (DPPH) - Absorbance\ (Sample)}{Absorbance\ (DPPH)} \times 100$$

Table 1: Anti-oxidant activity of synthesized compounds by DPPH Radical Scavenging method

S.No.	Compound code	% Scavenging activity				
		10 µg/mL	50 µg/mL	100 µg/mL	150 µg/mL	250 µg/mL
1	**L8**	62.48	67.54	74.15	80.52	84.52
2	**L11**	**80.13**	**80.73**	**81.21**	**92.47**	**95.47**
3	**L12**	49.29	63.19	65.98	72.41	76.41
4	**L20**	52.22	58.25	60.47	63.25	67.25
5	**L24**	32.53	39.03	48.43	49.31	49.31
6	**L26**	**30.96**	**38.30**	**39.92**	**41.27**	**41.27**
7	**Ascorbic acid**	81.55	86.90	88.74	91.51	95.12

Figure 1:



Hydrogen peroxide radical scavenging activity :

Hydrogen peroxide produces hydroxyl radicals in cells. Scavenging of these radicals by the test drug is used as a test for antioxidant activity. Reaction mixture containing test samples/standard (Ascorbic acid) at different concentrations in 10-250µg/mL) was added to 0.6ml of Hydrogen peroxide solution in phosphate buffer (pH7.4). After incubating for10 minutes at 37°C, the absorbance was measured at 230nm. The absorbance of hydrogen peroxide in phosphate buffer as control was measured at 230nm.

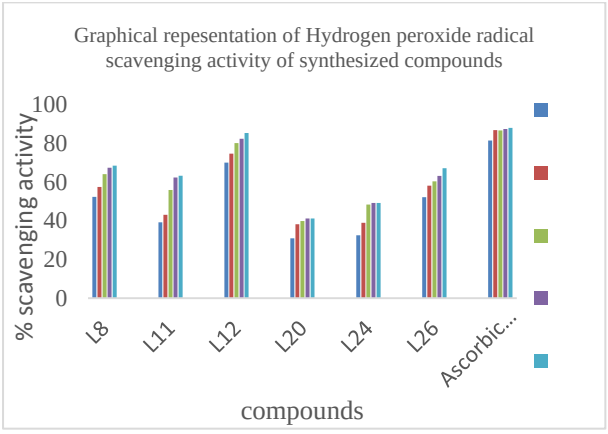
% inhibition was calculated by

$$Scavenging = \frac{Absorbance\ (Control) - Absorbance\ (Sample)}{Absorbance\ (Control)} \times 100$$

Table 2: Anti-oxidant activity of synthesized compounds by Hydrogen peroxide radical scavenging method

S.No	Compound code	% Scavenging activity				
		10 µg/mL	50 µg/mL	100 µg/mL	150 µg/mL	250 µg/mL
1	L8	52.38	57.54	64.15	67.52	68.52
2	L11	39.29	43.19	55.98	62.41	63.34
3	**L12**	**70.13**	**74.73**	**80.21**	**82.47**	**85.47**
4	**L20**	**30.96**	**38.30**	**39.92**	**41.27**	**41.27**
5	L24	32.53	39.03	48.43	49.31	49.31
6	L26	52.22	58.25	60.47	63.25	67.25
7	Ascorbic acid	81.55	86.90	86.74	87.51	88.12

Figure 2:



Nitric Oxide Radical Scavenging Activity:

In addition to reactive oxygen species, nitric oxide is also implicated in inflammation, cancer, and other pathological conditions. Sodium nitroprusside (SNP) in aqueous solution at Physiological pH spontaneously generates nitric oxide which interacts with oxygen to produce nitrite ions that can be estimated using Griess reagent. Scavengers of nitric oxide compete with oxygen, leading to the reduced production of nitrite ions. Suppression of the released NO may be partially attributed to direct NO scavenging.

The method of Garrat was adopted to determine the nitric oxide radical scavenging activity of the synthesized molecules. Sodium nitroprusside in aqueous solution at physiological pH spontaneously generates nitric oxide which interacts with oxygen to produce nitrite ions determined by the use of Griess reagents.

To 2 mL of 10 mM sodium nitroprusside dissolved in 0.5 mL phosphate buffer saline (pH 7.4) was mixed with 0.5 mL of sample solution at various concentrations (50–250 μg/mL). The mixture was incubated at 25∘ C. After 150 min, 0.5 mL of incubation solution was withdrawn and mixed with 0.5 mL of Griess reagent [1.0 mL sulfanilic acid reagent with 1 mL of naphthylethylenediamine dichloride (0.1% w/v)]. The mixture was incubated at room temperature for 30 min. The absorbance was measured at 540 nm.

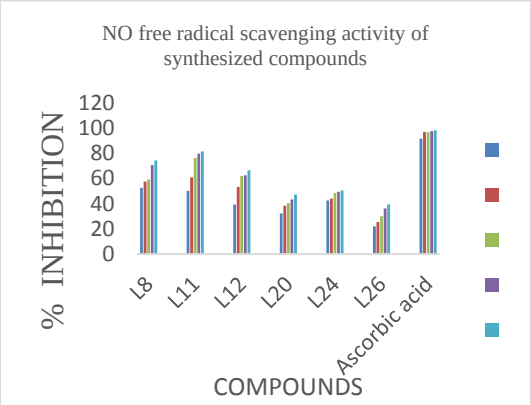
The amount of nitric oxide radical was calculated using the following equation:

% inhibition of NO = $[A_0 - A_t]\ A_0 \times 100$, where A_0 is the absorbance before the reaction and A_t is the absorbance after the reaction.

Table 3: The Anti-oxidant activity of the synthesized compounds by Nitric oxide scavenging method

S.No	Compound code	% Scavenging activity				
		10 µg/mL	50 µg/mL	100 µg/mL	150 µg/mL	250 µg/mL
1	**L8**	52.48	57.54	59.15	70.52	74.22
2	**L11**	**50.13**	**60.73**	**76.21**	**79.54**	**81.32**
3	**L12**	39.29	53.19	61.98	62.41	66.41
4	**L20**	32.22	38.25	40.47	43.25	47.25
5	**L24**	42.53	44.03	48.43	49.31	50.31
6	**L26**	**21.96**	**25.30**	**29.92**	**36.17**	**39.27**
7	Ascorbic acid	91.55	96.90	96.74	97.51	98.12

Figure 3:



Compound RajL1: 3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(o-tolyl)quinazolin-4(3H)-one

Yield: 68%; m.p 192-194 ^{o}C; TLC R_f = 0.73; Log P: 4.31;IR (KBr) cm^{-1} : 1671.32(C=O str.), 1597.97 (ring C=N str.), 3108.85(O-H str. for –OH); Anal.Calcd. for $C_{23}H_{20}N_4O_4S$: C, 61.59; H, 4.49; N, 12.49; S, 7.15; Found: C, 61.63; H, 4.51; N, 12.47; S, 7.14; MS (m/z): 448.12 (M^+)

Compound RajL2: 3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydro pyrimidin-4-yl)-2-(4-nitrophenyl)quinazolin-4(3H)-one

Yield: 66%; m.p 202-204 ^{o}C; TLC R_f = 0.74; IR (KBr) cm^{-1} :1671.32(C=O str.), 1594.28 (ring C=N str.), 3108.85 (O-H str. for –OH);^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.46 (s, 1H), 8.29 – 8.12 (m, 2H), 8.05 (d, *J* = 31.1 Hz, 2H), 7.93 – 7.75 (m, 2H), 7.56 (s, 1H), 7.51 (s, 1H), 7.41 (s, 1H), 5.82 (s, 1H), 4.34 (s, 1H), 4.17 (s, 1H), 3.93 (d, *J* = 7.4 Hz, 2H), 3.45 (s, 1H), 2.71 (s, 1H); MS (m/z): 480.09 (M^+ +1);Anal.Calcd. for $C_{22}H_{17}N_5O_6S$: C, 55.11; H, 3.57; N, 14.61; S, 6.69;Found : C, 55.15; H, 3.59; N, 14.59; S, 6.65

Compound RajL3: 2-(4-fluorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 62%; m.p 204-206 ^{o}C; TLC R_f = 0.67; Log P: 3.98 IR (KBr) cm^{-1} : 1683.48(C=O str.), 1606.95 (ring C=N str.);^{1}H NMR ((DMSO-*d*6, δ in ppm): δ 8.47 (s, 1H), 8.08 (s, 1H), 7.87 (s, 1H), 7.57 (t, *J* = 4.5 Hz, 3H), 7.50 (s, 1H), 7.40 (s, 1H), 7.06 – 6.99 (m, 2H), 5.84 (s, 1H), 4.34 (s, 1H), 4.17 (s, 1H), 3.93 (d, *J* = 7.6 Hz, 2H), 3.46 (s, 1H), 2.71 (s, 1H); MS (m/z): 452.10 (M^+); Anal.Calcd. for $C_{22}H_{17}FN_4O_4S$: C, 58.40; H, 3.79; N, 12.38; S, 7.09; Found: C, 58.42; H, 3.81; N, 12.36; S, 7.11

Compound RajL4: 3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydro pyrimidin -4-yl)-2-(4-methoxyphenyl)quinazolin-4(3H)-one

Yield: 63%; m.p 222-224 ^{o}C; TLC R_f = 0.73; Log P: 3.7; IR (KBr) cm^{-1} :1686.27(C=O str.), 1608.55 (ring C=N str.), 3125.92 (O-H str. for –OH); ^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.47 (s, 1H), 8.08 (s, 1H), 7.80 (s, 1H), 7.66 – 7.53 (m, 3H), 7.50 (s, 1H), 7.39 (s, 1H), 6.99 – 6.81 (m, 2H), 5.84 (s, 1H), 4.34 (s, 1H), 4.17 (s, 1H), 3.93 (d, *J* = 7.5 Hz, 2H), 3.81 – 3.76 (m, 3H), 3.46 (s, 1H), 2.71 (s, 1H); MS (m/z): 465.12 (M^+ +1); Anal.Calcd. for $C_{23}H_{20}N_4O_5S$: C, 59.47; H, 4.34; N, 12.06; S, 6.90; Found: C, 59.51; H, 4.38; N, 12.04; S, 6.92

Compound RajL5: 3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydro pyrimidin-4-yl)-2-(p-tolyl)quinazolin-4(3H)-one

Yield:74%; m.p:182-184 ^{o}C; TLC R_f = 0.71; Log P:4.31; IR (KBr) cm^{-1} :1696.19(C=O str.), 1610.59 (ring C=N str.), 3122.10 (O-H str. for –OH);^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.32 (s, 1H), 8.08 (s, 1H), 7.83 (s, 1H), 7.64 – 7.46 (m, 4H), 7.40 (s, 1H), 7.25 – 7.07 (m, 2H), 5.67 (s, 1H), 4.34 (s, 1H), 4.17 (d, *J* = 34.7 Hz, 2H), 3.91 (s, 1H), 3.45 (s, 1H), 2.71 (s, 1H), 2.35 – 2.30 (m, 3H); MS (m/z): 449.12 (M^++1); Anal.Calcd. for $C_{23}H_{20}N_4O4S$: C, 61.59; H, 4.49; N, 12.49; S, 7.15; Found: C, 61.61; H, 4.53; N, 12.47; S, 7.11

Compound RajL6: 2-(4-(chloromethyl)phenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 68%; m.p 196-198 ^{o}C; TLC R_f = 0.74; Log P:4.48; IR (KBr) cm^{-1} :1671.32(C=O str.), 1594.28 (ring C=N str.), 3108.85 (O-H str. for –OH);^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.37 (s, 1H), 8.08 (s, 1H), 7.64 (s, 1H), 7.61 – 7.53 (m, 3H), 7.50 (s, 1H), 7.41 (s, 1H), 7.36 – 7.18 (m, 2H), 6.35 (s, 1H), 4.52 – 4.47 (m, 2H), 4.35 (d, *J* = 10.6 Hz, 2H), 4.15 (s, 1H), 3.94 (s, 1H), 3.43 (s, 1H), 3.18 (s, 1H);MS (m/z): 482.08 (M^+); Anal.Calcd. for $C_{23}H_{19}ClN_4O_4S$: C, 57.20; H, 3.97; N, 11.60; S, 6.64; Found: C, 57.22; H, 3.95; N, 11.62; S, 6.62

Compound RajL7: 2-(2-chlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 68%; m.p 199-201^{o}C; TLC R_f = 0.67; Log P: 4.38;^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.44 (s, 1H), 8.09 (s, 1H), 7.94 (s, 1H), 7.58 (d, *J* = 16.9 Hz, 2H), 7.50 (s, 1H), 7.41 (s, 1H), 7.30 – 7.18 (m, 3H), 5.79 (s, 1H), 4.34 (s, 1H), 4.17 (s, 1H), 3.92 (d, *J* = 11.6 Hz, 2H), 3.46 (s, 1H), 2.71 (s, 1H); MS (m/z): 468.07 (M^+); Anal. Calcd. for $C_{22}H_{17}ClN_4O_4S$: C, 56.35; H, 3.65;N,11.95; S, 6.84; Found: C, 56.33; H, 3.67;N,11.93; S, 6.86

Compound RajL8: 2-(2,3-dichlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 64%; m.p 186-188 ^{o}C; TLC R_f = 0.67; Log P: 4.94; ^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.37 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.56 (s, 1H), 7.50 (d, *J* = 3.5 Hz, 2H), 7.41 (s, 1H), 7.28 (s, 1H), 7.16 (s, 1H), 5.68 (s, 1H), 4.40 (s, 1H), 4.34 (s, 1H), 4.14 (s, 1H), 3.92 (s, 1H), 3.40 (s, 1H), 3.20 (s, 1H); MS (m/z): 504.02 (M^+ + 2); Anal. Calcd. for $C_{22}H_{16}Cl_2N_4O_4S$: C, 52.49; H, 3.20; N, 11.13; S, 6.37; Found: C, 52.47; H, 3.22; N, 11.15; S, 6.36

Compound RajL9: 2-(furan-2-yl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 66%; m.p 224-226 ^{o}C; TLC R_f = 0.68; Log P:2.24;^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.46 (s, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.74 (d, *J* = 19.7 Hz, 2H), 7.58 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 6.79 (s, 1H), 5.93 (s, 1H), 4.34 (s, 1H), 4.17 (s, 1H), 4.11 (s, 1H), 3.94 (s, 1H), 3.46 (s, 1H), 2.71 (s, 1H); MS(m/z): 424.08 (M^+); Anal. Calcd. for $C_{20}H_{16}N_4O_5S$: C, 56.60; H, 3.80; N, 13.20; S, 7.55; Found: C, 56.62; H, 3.82; N, 13.18; S, 7.57

Compound RajL10: 7-chloro-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(p-tolyl)quinazolin-4(3H)-one

Yield: 61%; m.p 182-184 ^{o}C; TLC R_f = 0.68; Log P: 4.87; MS (m/z): 482.08 (M^+); Anal. Calcd. for $C_{23}H_{19}ClN_4O_4S$: C, 57.20; H, 3.97; N, 11.60; S, 6.64; Found: C, 57.18; H, 3.96; N, 11.63; S, 6.62;

Compound RajL11: 7-chloro-2-(2-chlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 64%; m.p 196-198 ^{o}C; TLC R_f = 0.62; Log P:4.94; IR (KBr) cm^{-1} :1670.88(C=O str.), 1577.17 (ring C=N str.), 3165.90 (O-H str. for –OH); MS (m/z): 502.03 (M^+) ; Anal. Calcd. for $C_{22}H_{16}Cl_2N_4O_4S$: C, 52.49; H, 3.20; N, 11.13; S, 6.37; Found: C, 52.47; H, 3.22; N, 11.15; S, 6.35

Compound RajL12: 7-chloro-2-(2,3-dichlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 64%; m.p 188-190 ^{o}C; TLC R_f = 0.67; Log P:5.5; IR (KBr) cm^{-1} :1678.66(C=O str.), 1577.08 (ring C=N str.), 3150.64 (O-H str. for –OH); ^{1}H NMR ($CDCl_3$, δ in ppm) δ 8.20 (s, 1H), 7.99 (s, 1H), 7.60 (s, 1H), 7.47 (d, *J* = 5.4 Hz, 2H), 7.38 (s, 1H), 7.26 (s, 1H), 7.14 (s, 1H), 5.60 (s, 1H), 4.34 (s, 1H), 4.27 (s, 1H), 3.97 (s, 1H), 3.56 (s, 1H), 3.16 (s, 1H), 0.84 (s, 1H); MS (m/z): 535.99 (M^+); Anal. Calcd. for $C_{22}H_{15}Cl_3N_4O_4S$: C, 49.13; H, 2.81; N, 10.42; S, 5.96; Found: C, 49.15; H, 2.83; N, 10.40; S, 5.94

Compound RajL13: 7-chloro-2-(4-chlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 66%; m.p 190-192 ^{o}C; TLC R_f = 0.74; Log P:4.94; IR (KBr) cm^{-1} :1659.45(C=O str.), 1607.66 (ring C=N str.), 3115.28 (O-H str. for –OH);^{1}H NMR ($CDCl_3$, δ in ppm) δ 8.20 (s, 1H), 7.99 (s, 1H), 7.60 (s, 1H), 7.59 – 7.48 (m, 2H), 7.32 (dd, *J* = 30.3, 7.3 Hz, 4H), 5.59 (s, 1H), 4.34 (s, 1H), 4.27 (s, 1H), 3.97 (s, 1H), 3.55 (s, 1H), 3.15 (s, 1H), 0.83 (s, 1H); MS (m/z): 502.03 (M^+); Anal.Calcd. for $C_{22}H_{16}Cl_2N_4O_4S$: C, 52.49; H, 3.20;N, 11.13; S, 6.37; Found: C, 52.47; H, 3.22;N, 11.15; S, 6.3

Compound RajL14: 6,8-dibromo-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(o-tolyl)quinazolin-4(3H)-one

Yield: 63%; m.p 212-214 ^{o}C; TLC R_f = 0.66; Log P:5.97; IR (KBr) cm^{-1} :1649.48(C=O str.), 1612.90 (ring C=N str.), 3281.12 (O-H str. for –OH); ^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.29 (d, *J* = 23.1 Hz, 2H), 7.82 (d, *J* = 11.5 Hz, 2H), 7.60 (s, 1H), 7.23 (d, *J* = 14.6 Hz, 2H), 7.12 (s, 1H), 5.51 (s, 1H), 4.52 (s, 1H), 4.34 (s, 1H), 4.13 (s, 1H), 3.92 (s, 1H), 3.39 (s, 1H), 3.19 (s, 1H), 2.24 – 2.19 (m, 3H); MS (m/z): 605.94 (M^+); Anal.Calcd. for $C_{23}H_{18}Br_2N_4O_4S$: C, 45.56; H, 2.99; N, 9.24; S, 5.29

Compound RajL15: 6,8-dibromo-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(p-tolyl)quinazolin-4(3H)-one

Yield: 63%; m.p 208-210 ^{o}C; TLC R_f = 0.68; Log P:5.97; IR (KBr) cm^{-1} :1650.49(C=O str.), 1608.26 (ring C=N str.), 3108.85 (O-H str. for –OH); ^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.33 (s, 1H), 8.26 (s, 1H), 7.83 – 7.77 (m, 2H), 7.64 – 7.46 (m, 2H), 7.25 – 7.07 (m, 2H), 5.67 (s, 1H), 4.34 (s, 1H), 4.20 (d, *J* = 18.4 Hz, 2H), 3.92 (s, 1H), 3.45 (s, 1H), 2.71 (s, 1H), 2.35 – 2.30 (m, 3H); MS (m/z): 605.94 (M^+ + 2); Anal.Calcd. for $C_{23}H_{18}Br_2N_4O_4S$: C, 45.56; H, 2.99; N, 9.24; S, 5.29; Found: : C, 45.58; H, 2.98; N, 9.22; S, 5.31

Compound RajL16: 7-chloro-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(4-methoxyphenyl)quinazolin-4(3H)-one

Yield: 64%; m.p 222-224 ^{o}C; TLC R_f = 0.67; Log P:4.26; IR (KBr) cm^{-1} :1656.94(C=O str.), 1607.07 (ring C=N str.), 3173.51 (O-H str. for –OH); ^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.76 (s, 1H), 8.41 (s, 1H),

7.99 (s, 1H), 7.69 (s, 1H), 7.66 – 7.51 (m, 2H), 7.42 (s, 1H), 7.01 – 6.83 (m, 2H), 5.94 (s, 1H), 4.35 (d, *J* = 5.8 Hz, 2H), 4.18 (s, 1H), 3.95 (s, 1H), 3.82 – 3.77 (m, 3H), 3.42 (s, 1H), 2.71 (s, 1H); MS (m/z): 498.08 (M^+); Anal.Calcd. for $C_{23}H_{19}Cl\ N_4O_5S$: C, 55.37; H, 3.84; N, 11.23; S, 6.43; Found: : C, 55.39; H, 3.86; N, 11.21; S, 6.41

Compound RajL17: 7-chloro-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(o-tolyl)quinazolin-4(3H)-one

Yield: 63%; m.p 196-198 ^oC; TLC R_f = 0.68; Log P: 4.87; IR (KBr) cm^{-1} :1672.83(C=O str.), 1603.89 (ring C=N str.), 3170.10 (O-H str. for –OH); ^1H NMR (DMSO-*d*6, δ in ppm): δ 8.32 (s, 1H), 8.02 (s, 1H), 7.84 (s, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.41 (s, 1H), 7.23 (d, *J* = 15.3 Hz, 2H), 7.12 (s, 1H), 5.50 (s, 1H), 4.52 (s, 1H), 4.34 (s, 1H), 4.13 (s, 1H), 3.92 (s, 1H), 3.39 (s, 1H), 3.19 (s, 1H), 2.24 – 2.19 (m, 3H); MS (m/z): 482.08 (M^+) ; Anal. Calcd. for $C_{23}H_{19}ClN_4O_4S$: C, 57.20; H, 3.97; N, 11.60;S, 6.64; Found: C, 57.18; H, 3.99; N, 11.62; S, 6.63

Compound RajL18: 2-cyclohexyl-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 58%; m.p 208-210 ^oC; TLC R_f = 0.67; Log P: 3.9; IR (KBr) cm^{-1}:1698.73.(C=O str.), 1611.53 (ring C=N str.), 3182.40 (O-H str. for –OH);

Compound RajL19: 2-(4-chlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 68%; m.p 182-184 ^oC; TLC R_f = 0.64; Log P:4.38; IR (KBr) cm^{-1} :1662.56(C=O str.), 1607.38 (ring C=N str.), 3314.73 (O-H str. for –OH); ^1H NMR (DMSO-*d*6, δ in ppm): δ 8.58 (s, 1H), 8.39 (s, 1H), 8.04 (s, 1H), 7.68 – 7.49 (m, 4H), 7.42 (s, 1H), 7.39 – 7.24 (m, 2H), 5.96 (s, 1H), 4.35 (d, *J* = 7.0 Hz, 2H), 4.18 (s, 1H), 3.95 (s, 1H), 3.42 (s, 1H), 2.71 (s, 1H); Ms (m/z): 468.07 (M^+) ; Anal.Calcd. for $C_{22}H_{17}ClN_4O_4S$: C, 56.35; H, 3.65; N, 11.95;S, 6.84

Compound RajL20: 6,8-dibromo-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylquinazolin-4(3H)-one

Yield: 56%; m.p 202-204 ^oC; TLC R_f = 0.72; Log P: 5.48; IR (KBr) cm^{-1} :1671.32(C=O str.), 1610.02 (ring C=N str.), 3283.36 (O-H str. for –OH); ^1H NMR (DMSO-*d*6, δ in ppm): δ 8.29 (d, *J* = 23.7 Hz, 2H), 7.82 (d, *J* = 6.4 Hz, 2H), 7.68 – 7.54 (m, 2H), 7.29 (t, *J* = 4.8 Hz, 3H), 5.67 (s, 1H), 4.34 (s, 1H), 4.21 (s, 1H), 3.86 (d, *J* = 41.5 Hz, 2H), 3.48 (s, 1H), 2.71 (s, 1H);

MS (m/z): 591.92 (M^+ + 2); Anal.Calcd. for $C_{22}H_{16}Br_2N_4O_4S$: C, 44.61; H, 2.72; N, 9.46; S, 5.41; Found: C, 44.63; H, 2.76; N, 9.42; S, 5.40

Compound RajL21: 6,8-dibromo-2-(4-chlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 56%; m.p 202-204 ^oC; TLC R_f = 0.65; Log P: 6.04; ^1H NMR ($CDCl_3$, δ in ppm) δ 8.21 (d, *J* = 3.5 Hz, 2H), 7.76 (s, 1H), 7.60 – 7.42 (m, 2H), 7.30 (t, *J* = 9.1 Hz, 3H), 5.59 (s, 1H), 4.34 (s, 1H), 4.28 (s, 1H), 3.97 (s, 1H), 3.51 (s, 1H), 3.15 (s, 1H), 1.17 (s, 1H); MS (m/z): 625.88 (M^+ + 2); Anal.Calcd. for $C_{22}H_{15}Br_2ClN_4O_4S$: C, 42.16; H, 2.41;N, 8.94; S, 5.12; Found: C, 42.19; H, 2.44;N, 8.91; S, 5.11

Compound RajL22: 6,8-dichloro-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(p-tolyl)quinazolin-4(3H)-one

Yield: 68%; m.p 198-200 ^oC; TLC R_f = 0.71; Log P: 5.43; ^1H NMR ($CDCl_3$, δ in ppm) δ 8.21 (s, 1H), 8.01 (s, 1H), 7.61 – 7.46 (m, 2H), 7.43 (s, 1H), 7.19 (t, *J* = 32.9 Hz, 2H), 7.12 (s, 1H), 5.59 (s, 1H), 4.34 (s, 1H), 4.27 (s, 1H), 3.97 (s, 1H), 3.55 (s, 1H), 3.15 (s, 1H), 2.36 – 2.31 (m, 3H), 0.83 (s, 1H); MS (m/z): 516.04 (M^+); Anal.Calcd. for $C_{23}H_{18}Cl_2\ N_4O_4S$: C, 53.39; H, 3.51; N, 10.83;S, 6.20; Found: C, 53.41; H, 3.50; N, 10.81;S, 6.22

Compound RajL23: 6,8-dichloro-2-(2-chlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan -5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 62%; m.p 192-194 ^oC; TLC R_f = 0.69; ; Log P: 5.5; ^1H NMR ($CDCl_3$, δ in ppm) δ 8.24 (s, 1H), 8.01 (s, 1H), 7.58 (s, 1H), 7.44 (d, *J* = 2.0 Hz, 2H), 7.27 – 7.17 (m, 3H), 5.75 (s, 1H), 4.34 (s, 1H), 4.19 (s, 1H), 3.98 (s, 1H), 3.47 (s, 1H), 3.27 (s, 1H), 1.53 (s, 1H); MS (m/z): 535.99 (M^+); Anal.Calcd. for $C_{22}H_{15}Cl_3N_4O_4S$: C, 49.13; H, 2.81; N, 10.42; S, 5.96; Found: C, 49.15; H, 2.80; N, 10.40; S, 5.95

Compound RajL24: 6,8-dichloro-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(4-methoxyphenyl)quinazolin-4(3H)-one

Yield: 56%; m.p 224-226 ^oC; TLC R_f = 0.72; ; Log P:4.82; ^1H NMR (DMSO-*d*6, δ in ppm): δ 8.53 (s, 1H), 7.70 (s, 1H), 7.69 – 7.50 (m, 3H), 7.41 (s, 1H), 7.00 – 6.82 (m, 2H), 5.82 (s, 1H), 4.34 (s, 1H), 4.17 (s, 1H), 3.93 (d, *J* = 8.0 Hz, 2H), 3.80 – 3.75 (m, 3H), 3.51 (s, 1H), 2.71 (s, 1H); MS (m/z): 532.04 (M^+); Anal.Calcd. for $C_{23}H_{18}Cl_2N_4O_5S$: C, 51.79; H, 3.40; N, 10.50; S, 6.01; Found: C, 51.77; H, 3.41; N, 10.51; S, 6.03

Compound RajL25: 6,8-dichloro-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(4-nitrophenyl)quinazolin-4(3H)-one

Yield: 64%; m.p 224-226 ^{o}C; TLC R_f = 0.63; ^{1}H NMR ($CDCl_3$, δ in ppm) δ 8.26 (s, 1H), 8.23 – 8.05 (m, 2H), 8.01 (s, 1H), 7.91 – 7.72 (m, 2H), 7.52 (s, 1H), 7.44 (s, 1H), 5.79 (s, 1H), 4.34 (s, 1H), 4.19 (s, 1H), 3.98 (s, 1H), 3.47 (s, 1H), 3.27 (s, 1H), 1.20 (s, 1H); MS (m/z): 547.01 (M^+); Anal.Calcd. for $C_{22}H_{15}Cl_2N_5O_6S$: C, 48.19; H, 2.76; N, 12.77; S, 5.85; Found: C, 48.21; H, 2.74; N, 12.79; S, 5.84

Compound RajL26: 6,8-dichloro-2-(2,3-dichlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)quinazolin-4(3H)-one

Yield: 59%; m.p 202-204 ^{o}C; TLC R_f = 0.71; ; Log P: 6.06; ^{1}H NMR ($CDCl_3$, δ in ppm) δ 8.26 (s, 1H), 8.01 (s, 1H), 7.53 (s, 1H), 7.46 (d, *J* = 16.2 Hz, 2H), 7.26 (s, 1H), 7.13 (s, 1H), 5.94 (s, 1H), 4.34 (s, 1H), 4.19 (s, 1H), 3.98 (s, 1H), 3.47 (s, 1H), 3.27 (s, 1H), 1.34 (s, 1H); MS (m/z): 569.95 (M^+); Anal.Calcd. for $C_{22}H_{14}Cl_4N_4O_4S$: C, 46.17; H, 2.47; N, 9.79; S, 5.60; Found: C, 46.20; H, 2.45; N, 9.77; S, 5.62

Compound RajL27: 3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydro pyrimidin-4-yl)-6,8-diiodo-2-(p-tolyl)quinazolin-4(3H)-one

Yield: 52%; m.p 214-216 ^{o}C; TLC R_f = 0.63; ; Log P: 7.03; ^{1}H NMR ($CDCl_3$, δ in ppm) δ 8.44 (s, 1H), 8.17 (s, 1H), 7.95 (s, 1H), 7.73 (s, 1H), 7.62 – 7.44 (m, 2H), 7.26 – 7.08 (m, 2H), 4.34 (s, 1H), 4.19 (s, 1H), 3.96 (s, 1H), 3.38 (d, *J* = 33.1 Hz, 2H), 3.16 (s, 1H), 2.39 – 2.34 (m, 3H), 1.72 (s, 1H); MS (m/z): 699.91 (M^+) ; Anal. Calcd. for $C_{23}H_{18}I_2N_4O_4S$: C, 39.45; H, 2.59; N, 8.00; S, 4.58; Found: : C, 39.46; H, 2.57; N, 8.02; S, 4.57

Compound RajL28: 3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-6,8-diiodo-2-(4-nitrophenyl)quinazolin-4(3H)-one

Yield: 52%; m.p 224-226 ^{o}C; TLC R_f = 0.63; ^{1}H NMR ($CDCl_3$, δ in ppm) δ 8.45 (s, 1H), 8.21 (d, *J* = 18.3 Hz, 2H), 8.16 – 8.02 (m, 2H), 7.85 – 7.68 (m, 2H), 7.45 (s, 1H), 5.64 (s, 1H), 4.34 (s, 1H), 4.29 (s, 1H), 3.98 (s, 1H), 3.72 (s, 1H), 3.19 (s, 1H), 2.70 (s, 1H); MS (m/z): 730.88 (M^+); Anal. Calcd. for $C_{22}H_{15}I_2N_5O_6S$: C, 36.13; H, 2.07; N, 9.58; S, 4.38; Found: C, 36.11; H, 2.09; N, 9.55; S, 4.39

Compound RajL29: 2-(2-chlorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-6,8-diiodoquinazolin-4(3H)-one

Yield: 52%; m.p 220-222 ^{o}C; TLC R_f = 0.65; Log P:7.1; ^{1}H NMR (DMSO-*d*6, δ in ppm): δ 8.46 (d, *J* = 24.0 Hz, 2H), 8.23 (s, 1H), 7.93 (s, 1H), 7.61 (s, 1H), 7.30 – 7.20 (m, 3H), 5.79 (s, 1H), 4.34 (s, 1H), 4.17 (s, 1H), 3.92 (d, *J* = 11.6 Hz, 2H), 3.46 (s, 1H), 2.71 (s, 1H); MS (m/z): 719.86 (M^+); Anal.Calcd. for $C_{22}H_{15}ClI_2N_4O_4S$: C, 36.66; H, 2.10; N, 7.77; S, 4.45; Found: C, 36.69; H, 2.11; N, 7.73; S, 4.44

Compound RajL30: 2-(4-fluorophenyl)-3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-6,8-diiodoquinazolin-4(3H)-one

Yield: 53%; m.p 212-214 ^{o}C; TLC R_f = 0.65; Log P: 6.7;^{1}H NMR ($CDCl_3$, δ in ppm) δ 8.43 (s, 1H), 8.20 (d, *J* = 19.3 Hz, 2H), 7.59 – 7.54 (m, 2H), 7.33 (s, 1H), 7.04 – 6.97 (m, 2H), 5.59 (s, 1H), 4.34 (s, 1H), 4.27 (s, 1H), 3.97 (s, 1H), 3.51 (s, 1H), 3.15 (s, 1H), 1.14 (s, 1H); MS (m/z): 703.89 (M^+); Anal. Calcd. for $C_{22}H_{15}FI_2N_4O_4S$: C, 37.52; H, 2.15; N, 7.96; S, 4.55; Found: C, 37.54; H, 2.14; N, 7.94; S, 4.56

RESULTS AND DISCUSSION:

In the present study, thirty novel 2,3-disubstituted quinazolin-4(3*H*)one derivatives were synthesized, purified by column chromatography and characterized by using FT-IR, ^{1}H-NMR, Mass spectra and Elemental analysis.The synthesized compounds were screened for their *invitro* anti-oxidant activity using three different standard model viz. DPPH, Hydrogen peroxide and Nitric oxide scavenging method and the results were shown in Table 1-3 and Figure 1-3.

CONCLUSION:

In the present study, thirty novel 2, 3-disubstituted quinazoline derivatives were synthesized and purified by column chromatography. The spectral data of the titled compounds were in correlation with the expected structure. The anti-oxidant activity of the synthesized compounds were studied using three different standard models viz. DPPH, Hydrogen peroxide and Nitric oxide free radical scavenging activities. Those compounds which showed good *in vitro* cytotoxic activity and good docking values in molecular docking studies were selected for the study. The compounds L11 and L20 showed the highest free radical scavenging activity in DPPH and Nitric oxide model. The compound L12 showed the highest free radical scavenging activity in Hydrogen peroxide model.

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