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SYNTHESIS, CHARACTERIZATION, MOLECULAR DOCKING AND ANTI-BACTERIAL ACTIVITY OF 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, Mass and Elemental Analysis. Docking study of the synthesized compounds were carried out by Auto Dock software using Biotin Carboxylase as Target Protein. The Synthesized compounds were screened for their *in- vitro* anti-bacterial activity.

KEYWORDS: Quinazolinone, Lamivudine, Biotin Carboxylase, Anti-bacterial 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] anti-inflammatory,[16,17] antihistaminic,[17] anthelmintic,[18] anti-tubercular[19] andanticonvulsant[20] activity etc. Considering the biological significance of quinazolinone nucleus were synthesized in the present research study a series of some novel 2,3-disubstituted Quinazolin-4-(3*H*)-one derivatives and optimized with Auto Dock 4.0 to investigate the interaction between the target ligand and the amino acid residues of Biotin carboxylase and screen them for their antibacterial activity.

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 spectra were recorded with 400 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 ThermoScientific High Resolution Magnetic Sector MS DFS by chemical ionization (CI) or negative-ion electrospray 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&S) 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-(3*H*)-one

A cold solution of Lamivudine (0.05 mole) in anhydrous pyridine (10ml) 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.

Molecular Docking

Molecular docking was performed for the synthesized compounds using the Auto Dock 4.0 version. Thetarget enzyme of Biotin carboxylase (PDB ID: 3JZI) was downloaded from protein data bank (PDB).The molecular interaction between the designed structure and target enzyme were studied by Auto Dock software version 4.0.Theinteractions and the docking score were mentioned in table 1 and 2. The binding modes of compounds in the activesite of Biotin carboxylase along with the interacting amino acids were shown in Figure 1to 5.

Table-1: Docking score of the synthesized compounds.

Sl. No.	Compound Code	Binding Energy (Kcal/mol)	Inhibitory Constant	Vdw. Desolvation Energy
1	L1	-5.17	124.83	-6.28
2	L2	-4.91	0.18	-5.67
3	L3	-5.28	135.51	-7.02
4	**L4**	**-8.01**	**1.34**	**-9.78**
5	L5	-6.15	30.85	-7.33
6	L6	-4.17	845.18	-5.42
7	L7	-5.51	91.91	-6.67
8	L8	-4.64	339.18	-5.73
9	**L9**	**-7.52**	**3.09**	**-8.71**
10	L10	-4.92	0.15	-5.87
11	L11	-5.45	0.17	-6.33
12	L12	-6.9	8.82	-8.06
13	**L13**	**-9.1**	**213.58**	**-10.38**
14	L14	-6.02	38.44	-7.14
15	L15	-5.34	122.05	-6.47
16	L16	-4.01	1.15	-5.53
17	L17	-5.44	103.58	-6.44
18	L18	-4.5	498.74	-5.54
19	L19	-4.02	1.13	-5.22
20	L20	-4.99	220.04	-5.84
21	L21	-5.27	136.51	-6.51
22	L22	-3.71	1.9	-4.86
23	L23	-4.57	448.68	-5.6
24	L24	-5.35	119.97	-6.65
25	L25	-5.37	127.87	-6.53
26	L26	-5.34	120.9	-6.48
27	L27	-5.31	127.42	-6.53
28	L28	-6.1	30.89	-4.1
29	L29	-5.25	141.61	-6.45
30	**L30**	**-9.01**	**248.55**	**-10.2**

Table 2: Interactions of the synthesized compounds with amino acids at the active site of the protein Biotin carboxylase.

Sl. No.	Compound Code	Number of Hydrogen bonds formed	Amino acids involved in hydrogen bond interactions	Distance between donor and acceptor (A^o)
1	L1	1	GLU 393(O)	2.936
2	L2	1	CYS 130(N)	2.727
3	L3	1	ILE152(O)	2.853
4	L4	3	GLU288(O) LYS238(N) ARG292(N)S	2.892 2.979 2.863
5	L5	0	-	-

6	L6	2	ARG151(O) LYS202(N)	2.682 2.946
7	L7	1	ALA176(N)	2.927
8	L8	1	VAL128(O)	2.729
9	L9	1	GLU446(O)	2.842
10	L10	2	ILE152(O) LYS202(N)	2.853 2.659
11	L11	1	LYS202(N)	2.947
12	L12	1	GLU288(O)	2.972
13	L13	2	GLU288(O) LYS202(O)	2.787 2.991
14	L14	1	ARG151(O)	2.936
15	L15	1	ILE 152 (O)	2.853
16	L16	1	TYR154 (O)	2.706
17	L17	1	ILE 152 (O)	2.887
18	L18	2	ILE152 (O) LYS202(N)	2.786 2.885
19	L19	1	CYS130(N)	2.925
20	L20	2	GLU280(O) LYS202(N)	2.734 2.69
21	L21	1	VAL128(O)	2.605
22	L22	1	ARG151(O)	2.809
23	L23	1	LYS202(N)	2.831
24	L24	2	LYS202(N) ARG151(N)	2.585 2.781
25	L25	0	-	-
26	L26	2	ILE152(O) ILE152(O)	2.739 2.821
27	L27	1	CYS(O)	2.765
28	L28	1	MET169(S)	2.604
29	L29	1	VAL128(O)	2.715
30	L30	1	GLU276(O)	2.991

Binding mode of compounds in the active site of Biotin carboxylase

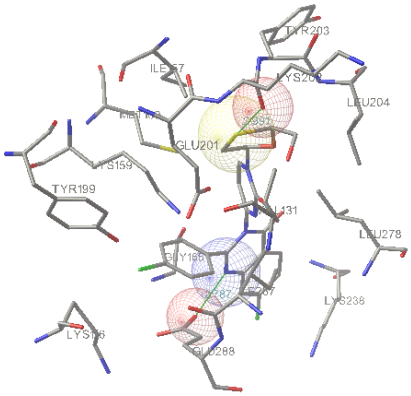

Figure 1: Docking study of Compound L13.

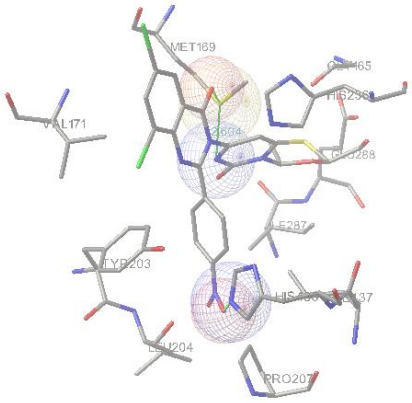

Figure 2: Docking study of compound L28.

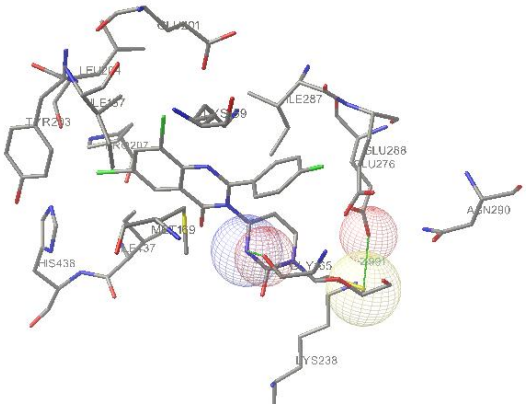

Figure 3: Docking study of compound L30.

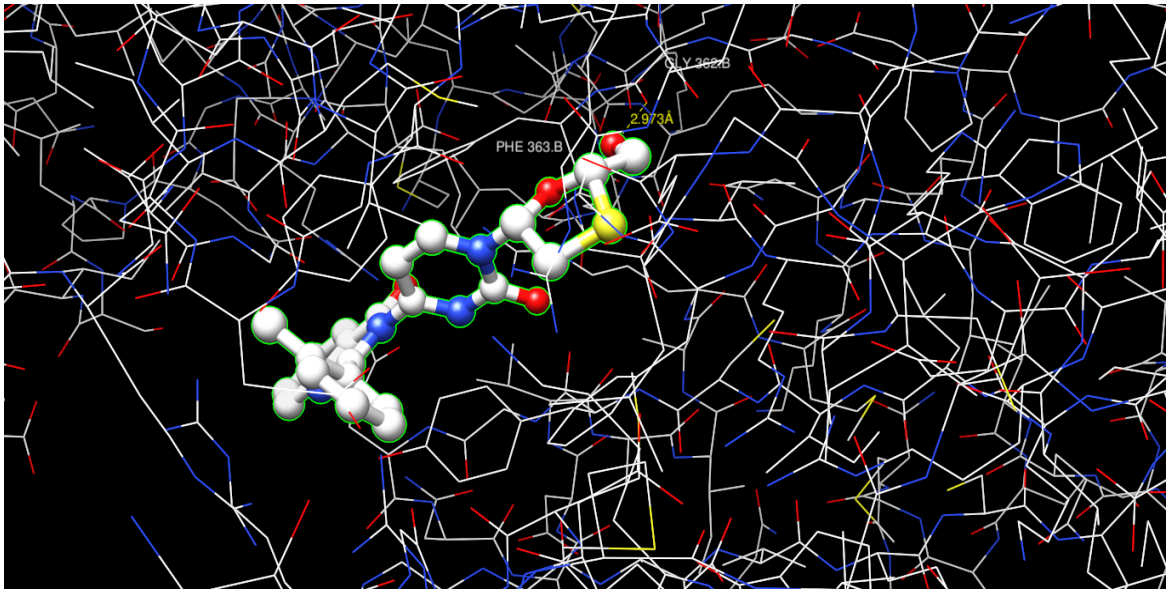

Figure 4: Docking study of compound L1.

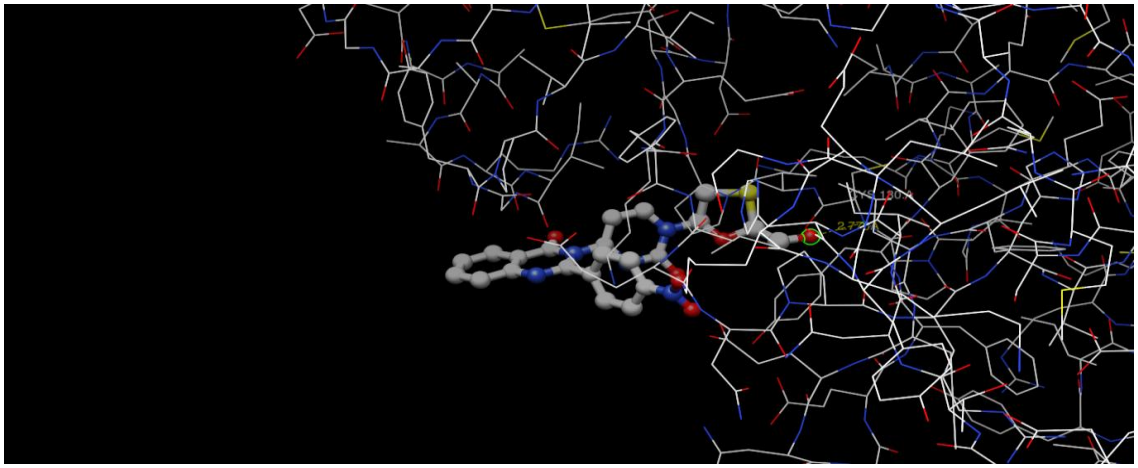

Figure 5: Docking study of compound L2.

Anti-Bacterial activity

The synthesized compounds were screened to evaluate their antibacterial activity by paper disc diffusion method against two kinds of Gram positive micro organisms *Staphylococcus aureus* (MTCC 96) and *Bacillus subtilis* and two kinds of Gram negative micro organisms *Pseudomonas aeruginos*a (MTCC 1688) and *Escherichia coli* (MTCC 443). The antibacterial activities of the Compounds L1 to L30 assessed for antibacterial activity as evidenced by the Zone of Inhibition exhibited by the compounds by using an Antibiotic Zone Reader (MZR-2).

Table 3: Antibacterial activity of the synthesized compounds.

Compound ID	Gram positive strains		Gram negative strains	
	S.aureus	***B.subtilis***	***P.aeruginosa***	***E.coli***
L1	9	11	12	12
L2	10	11	12	12
L3	10	12	12	12
L4	14	17	19	19
L5	12	14	16	15
L6	8	10	13	13
L7	8	9	13	14
L8	8	8	12	13
L9	10	10	12	12
L10	8	10	11	12
L11	9	10	11	11
L12	9	11	11	11
L13	8	8	10	10
L14	12	14	16	16
L15	9	10	11	11
L16	9	11	12	12
L17	8	10	11	11
L18	8	9	10	10
L19	9	10	12	12
L20	8	10	12	12
L21	8	11	12	12
L22	9	10	12	12
L23	8	9	12	13
L24	8	10	11	12
L25	9	11	12	12
L26	8	10	11	11
L27	8	10	12	12
L28	13	17	16	15
L29	9	10	12	12
L30	14	19	20	20
Ampicillin Standard	16	21	25	26

Inhibitory zone diameters in mm; concentration of standard and Compounds 100 µg/ml

Compound L1: 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^+).

CompoundL2:3-(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 L3:2-(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: 3.98IR (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.

CompoundL4: 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.

CompoundL5: 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 L6:2-(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 L7: 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 L8:2-(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 L9:2-(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 L10:7-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 L11: 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 L12:7-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 L13:7-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 L14:6,8-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 L15:6,8-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; LogP: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 L16: 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 $C_{23}H_{19}ClN_4O_5S$: 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 L17:7-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 ^{o}C; 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);^{1}H 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 L18:2-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 ^{o}C; 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 L19:2-(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 ^{o}C; 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);^{1}H 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 L20:6,8-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-*d6*, 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 L21:6,8-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 L22:6,8-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$C_{23}H_{18}Cl_2N_4O_4S$: 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.

CompoundL23:6,8-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.

CompoundL24:6,8-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-*d6*, 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 L25:6,8-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 ^oC; TLC R_f = 0.63;^1H 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 L26: 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 ^oC; TLC R_f = 0.71; ;Log P: 6.06; ^1H 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.

CompoundL27: 3-(1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-6,8-diiodo-2-(p-tolyl)quinazolin-4(3H)-one

Yield: 52%; m.p 214-216 ^oC; TLC R_f = 0.63; ;Log P: 7.03; ^1H 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 L28: 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 ^oC; TLC R_f = 0.63;^1H 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 L29: 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 L30:2-(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. Molecular docking study of the synthesized derivatives was performed to identify their interaction with the target site of Biotin carboxylase enzyme and the results were shown in table 1and 2.The synthesized compounds were screened for their *in vitro* anti-bacterial activity at a concentration of 100µg/ml in DMSO by paper disc diffusion method against *E.coli*, *B.substilis*, *P.aeruginosa*, *S.aureus* and the results were shown in Table 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. Molecular docking study of the synthesized derivatives was performed to identify their interaction with the target site of Biotin carboxylase enzyme and the results were shown in table 1&2. Compounds L4, L5, L13, L14, L28 and L30exhibited good hydrogen bond interactions between the atoms of the synthesized compounds and the amino acid residues of Biotin carboxylase receptor. The synthesized compounds were screened for their *in vitro* anti-bacterial activity at a concentration of 100µg/ml in DMSO by paper disc diffusion method against *E.coli*, *B.substilis*, *P.aeruginosa*, *S.aureus.* All studied compounds exhibited moderate to potent antibacterial activity at a concentration of 100 µg/ml. Compounds L4 & L30 exhibited significant anti-bacterial activity compared to the standard.

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