WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 6, 1482-1497. Research Article ISSN 2277 – 7105

IN SILICO DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF QUINAZOLIN-4-ONE DERIVATIVES AS POTENTIAL MULTITARGET AGENTS.

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Article Received on
30 June 2014,

Revised on 25 July 2014,
Accepted on 20 August 2014

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ABSTRACT

An applied simple computational technique of molinspiration and Hex6.3 software are emphasized us to designing the synthetical path way of quinazolin-4-one derivatives. The biological scoring activity was provided by molinspiration software while the energies minimization values(E.total values) of quinazolin-4-one derivatives were obtained from Hex 6.3 docking soft ware by interaction of target proteins *(E.coli-3GI9, S.aureus-4AE5 and S.typhi-3FHU*). As per the standard drug protocol, the synthesized compounds ($4a_{1\text{-}6}$) were found to have highly drug likeness properties due to the highly negative E. total energies. Therefore it was observed that the both in vitro and insilico methods parallely determined the antibacterial activity which revealed that the synthesized compounds quinazolin-4-one derivatives act as antibacterial agents. The Structures of synthesized quinazolin-4-ones were established by spectrophotometers (FT-IR, ^{1}HNMR and MS).

KEY WORDS- Docking study, Biological activity scoring, Synthesis of Quinazoline-4-ones derivatives and Antibacterial study.

INTRODUCTION

In our earlier continuous research works was found that quinazoline derivatives have various biological properties like analgesic, anti-inflammatory, antimicrobial activity and

anthelmintic activities[1-5]. The compounds ($4a_{1-6}$) of quinazolin-4-ones were designed, synthesized based on the efficacy of biological activity by interaction with the target molecules in insilico method. The targeted macro molecules were derived from protein data bank (RCSB) and are encoded by the name *E.coli* (pdb 3GI9)[4], *S. aureus* (pdb-4AE5)[5] and *S. typhi* (pdb-3FHU)[6] .Normally *Escherichia coli* is remarkable for urinary tract infection (UTI).The *E,coli* (3GI9[4]) receptor acts as amino acid, polyamine, and organocation (APC) transporters which recycle the neurotransmitter to uptake of nutrient and regulate the ionic homeostasis. Various types of infected diseases caused by *Staphylococcus aureus. The S.aureus (*4AE5[5]) was contained fibrogen –binding clumping factor (ClfB) as like as dermokine peptide binding mode of (ClfB) (glycine-serine-rich, GSR) which binds with the quinazolin-4-ones and exert the antibacterial activity by blocking DNA replication. While the main causative agent of typhoid is *Salmonella typhi.* The S.typhi (3FHU[6]) is the entero pathogenic bacteria of major adhesion factor into gastrointestinal epithelial cells which contains Pilus protein. Its target the first extracellular domain of cystic fibrosis trans membrane conductance regulator (CFTR). The CFTR are involved in binding with the pilin protein and gives us insight on the amino acids that are essential for binding and the role of a conserved disulfide bridge in pilus formation. The subunit structure and pilus functions for designing the suitable antibacterial analogs. The physico-chemical parameters and biological activity score of the compounds were found from on line software Molinspiration[9].

MATERIALS AND METHOD

1. Drawing of these structures, energy minimization and docking of Quinazolin-4-one derivatives were done by using Chem sketch, Hex-6.3 .
2. The entire chemicals were supplied by S. D. Fine Chem. (Mumbai), Finar Chem. Ltd (Ahmedabad) and Loba Chemie. Pvt. Ltd. (Mumbai).
3. Melting points were determined by open tube capillary method and were uncorrected.
4. Purity of compounds were checked by thin layer chromatography (TLC) on silicagel-G in solvent system benzene: ethyl acetate (7:2) and the spots were located under UV light.
5. IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr pallet.
6. $^{[1]}$H NMR were recorded on Bruker DPX-300 MHz spectrometer in deuteriochloroform with trimethylsilane as internal standard (chemical shift in δ ppm).

7. Mass spectra were obtained using Perkin-Elmer Hitachi RMU-6L MS-30 spectrometer at 70 ev and a 90 ^{0}C inlet temperature.

Experimental Designing

Computational works (Insilico methods)

Biological activity scoring and calculation of logp value

The logp values of the quinazoline-4-ones derivatives were calculated in Molinspiration software which indicates that the compounds are hydrophobic in nature and having log p values < 5. The biological activity scoring studies furnished the quinazolin-4-one derivatives as antibacterial analogs due to all these compounds act as protease and enzyme inhibitors. As compared to the standard drug ciprofloxacin the synthesized compounds were shown good potency towards the both inhibitors and was seen in table-01.

Macromolecules (Antimicrobial receptors)

The X-ray crystallographic structure of antimicrobial receptors were derived from protein data bank of RCSB which were encoded by pdb codes 3GI9, 4AS5 and 3FHU with named as *Escherichia coli , Staphylococcus aureus and Salmonella typhi.* The energy minimization of these protein was done in Argus Lab.4.0.1.

Hex 6.3and docking procedure of Hex-6.3

It is an interactive macromolecular graphical program which is used for the calculating and docking the ligand (drug) with protein molecule (receptor) in pdb format by pop up the spherical polar Fourier correlations in their 3D shape. It is also reads the DNA and protein molecules. This docking software has high tendency to calculated the each docking molecular modeled by 3D parametric functions such as surface shape ,electrostastic charge ,scaling factors and the docking score can be interpreted in the interaction energy of ligand and receptor. In order to run the docking calculation in Hex 6.3, first load the pdb format of both receptor and ligand in Hex. Example. Then open the file of ligand and receptor one after another. Thus the docking can be carried out by using option, controls – Docking – Activate and the docking result is saved in dock example of hex 6.3[10].

Docking of Quinazoline-4-ones derivatives

Various docking steps procedure of Hex6.3 were carried out in ligands against the micro organisms, E.coli (pdb code-3GI9), staphylococcus aureus (pdb code -4AS5) and Salmonella typhi (pdb code -3FHU) and calculated the E. total values. The standard drug (ciprofloxacin)

was docked with above three microorganisms and observed that, the E. total values of these compounds have higher as compared to the standard one. Hence it was shown that, the quinazoline-4-one derivatives drugs have highly antibacterial activity than the standard drug. The E. total values were given in table- I.

Against *Escherichia coli* (pdb code-3GI9)

All series of quinazoline-4-one derivatives were found to have higher E.total values than the standard Ciprofloxacin and are given in table-I.

Against *Staphylococcus aurous (pdbcode-4AS5)*

As compared to the standard, this series of compounds were shown promising E. total values which indicates their drug activities and the E. total values were shown in table-II.

Against *Salmonella typh (pdb code-3FHU)*

Except a_1, all the compounds of the series have highly active against the micro organisms due to the E. total value was higher than the standard one and the E. total values were given in table-III.

Chemistry

Quinazolin-4-ones synthetical works-

3-Amino-6,8-dibromo -2-methylquinazolin-4(3H)-one **2** were prepared according to the literature procedures[12,13,14] Compounds **2a** were condensed with isatin in ethanol to afford the corresponding Schiff's bases **3** in 71 % yields (**Table VI).** The N-Mannich bases of the above Schiff's base were synthesized by condensing acidic imino group of isatin with formaldehyde and various secondary amines in 51-73 % yields. All the synthesized compounds were characterized by their elemental analysis, FT-IR, ^{1}H NMR, and mass spectroscopy. For example, the IR spectrum of **3** shows an absorption band at 3471 cm^{-1} corresponding to the stretching vibration of NH group, while bands at 1670 and 1732 cm^{-1} correspond to the characteristic keto group of quinazolinone and isatin, respectively. The IR spectrum of **$4a_1$** shows an absorption band at 2818 and 1314 cm^{-1} corresponding to the methylene and di alkyl amino methyl groups, respectively present at 1^1position of isatin moiety. The ^{1}H NMR of **3** showed the absence of the signal for the NH_2 group, while the isatin imino NH signal appeared as a singlet at 8.57 ppm. Diagnostically important signals in the nuclear magnetic resonance (^{1} H NMR) spectrum of **$4a_1$** were two singlet at 2.50 and 4.43 ppm attributed to the $N(CH_3)_2$ and CH_2 groups, respectively. Aromatic protons of

quinazolinone and isatin moieties all appeared at the expected chemical shifts. The structures of **3** and **4a$_1$** were also confirmed by its mass spectrum that shows molecular ion peaks (M^+) at m/z 462 and m/z 519.

General method for the preparation of Schiff's bases[3].

To a solution of isatin (0.005 mol) in ethanol (50 mL) was added the appropriate 3-amino-6,8-dibromo 2-methylquinazolin-4(3H)-one **2** (0.005 mol) and a few drops of acetic acid. The reaction mixture was refluxed for 17 hrs. on a water bath and then allowed to cool. The separated solid was filtered, washed with aqueous ethanol, and recrystallized from benzene.

3-{(2^1-Oxo-1^1, 2^1-dihydroindole-3H-ylidene) amino}-6, 8-dibromo-2-methylquinazolin-4-(3H)-one (3). IR (KBr): 3471 (NH), 3076(Ar-CH), 1732 (C=O), 1670 (C=O), 1607 (C=N), 1570 (C=N), 1307 (CN)680(C-Br str.); MS: (m/z) 462 (M^+); ^{1}H NMR ($CDCl_3$)δ: 8.57 (s, 1H, NH), 8.06 (m, 9H, ArH), 6.48-7.73 (m, 4H, ArH)

General method for the preparation of Mannich bases (4a$_{1-6}$)

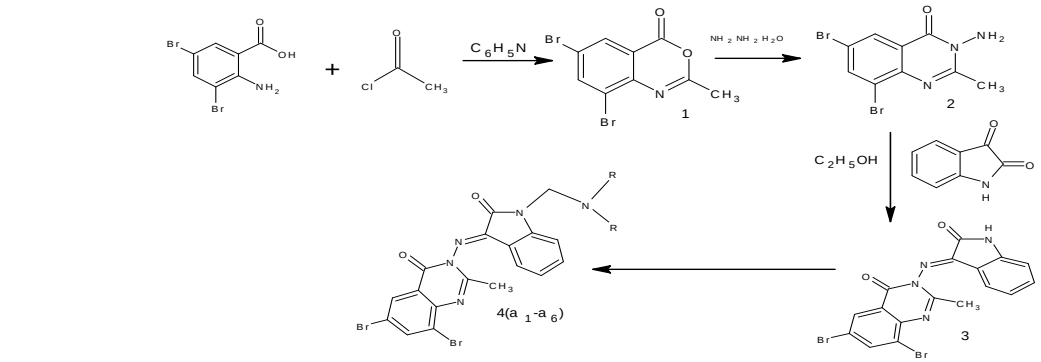
To a mixture of **3** (0.005 mol) and 37 % formalin (1mL) in ethanol (20 mL) was added drop wise appropriate secondary amines (0.005 mol) with stirring over 15 min. The stirring was continued for 1hr. at room temperature and the reaction mixture then warmed for 15 min. on a water bath. The mixture was poured into ice-cold water and stored in a refrigerator. The crude product, which separated, was washed with water, dried and recrystallized from ethanol.

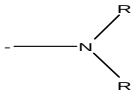
3-{(1^1-Dimethylaminomethyl-2^1-oxo-1^1,2^1-dihydroindole-3^1-ylidene)amino}-6,8-dibromo-2-methyl quinazolin-4-(3H)-one (4a$_1$)

IR (KBr) : 3066 (Ar-CH), 2818 (CH_2), 1726 (C=O), 1675 (C=O), 1604 (C=N), 1560 (C=N), 1314 (CN); MS: m/z 519,489,437,314,235,203,201,176,159 (M^+); ^{1}H NMR ($CDCl_3$) δ : 2.50 [s, 6H, $N(CH_3)_2$], 4.43 (s, 2H, CH_2), 6.40-7.25 (m, 4H, ArH), 7.55-8.23 (m, 9H, ArH).

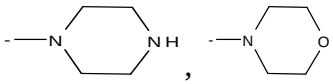
Compounds **4a$_{2-6}$** was prepared similarly.

SCHEME





= N Me_2, N Et_2, $N(C_6H_5)_2$, $N(C_6H_{11})_2$,

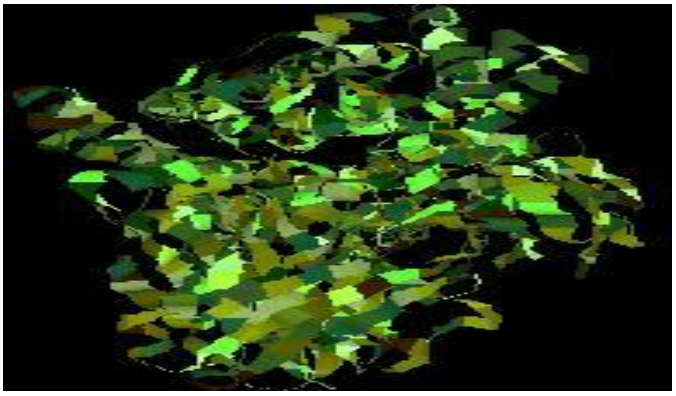


Antibacterial activity[21]

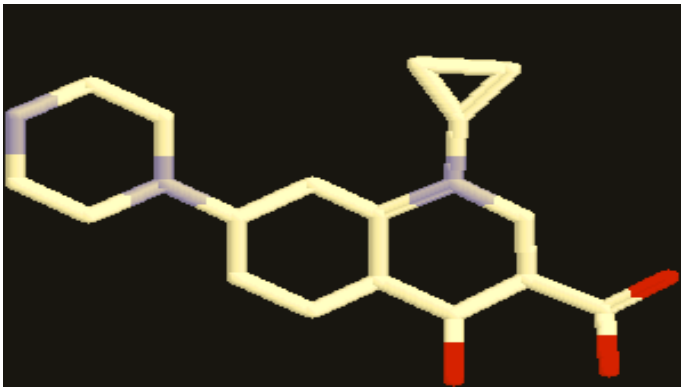
All the synthesized compounds were screened for antibacterial activity by cup plat method. The concentration100µg / ml of the compounds were prepared as a stock solution by using DMF solution. The standard drug ciprofloxacin of concentration 20 µg /ml was prepared in distill water and determined the zone of inhibition. As compared to the standard, the synthesized compounds were shown promising inhibition activity against *E. coli* as well as *S. aureus* and significant activity against *S. typhi*. Then it was observed that the antibacterial activity was determined by both In vitro and Insilco methods parallel. The result revealed that these quinzolin-4-one derivatives can be used as an antimicrobial agent. The zones of inhibition of the compounds were shown in table-VII.

RESULTS AND DISCUSSION

The syntheses of a new series of quinazolin-4-ones were done by TLC monitoring and established these structures in FT-IR, ^{1}HNMR and mass spectra. The biological activity scoring and docking energies indicate that these synthesized compounds have drug likeness properties and were predicted the high efficacy activities against the human pathogens like *E.coli, S.aureus and S.typhi*. The comparison activity of quinazoline-4one derivatives against the micro organisms by insilico model revealed that, the compounds 4(a_1-a_6) were found to possess higher drug activity against *Escherichia Coli* as well as *Staphylococcus aureus.* While in case of *Salmonella typhi* the compounds possess significant activity.

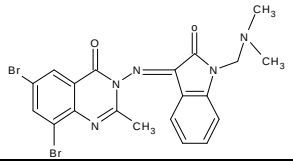
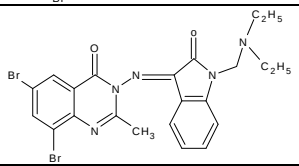
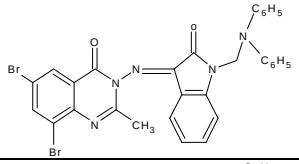
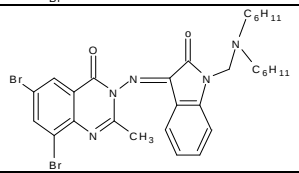


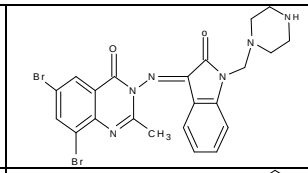
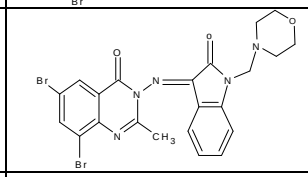
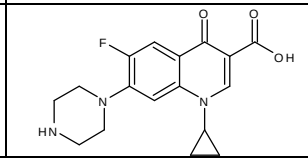
3GI9

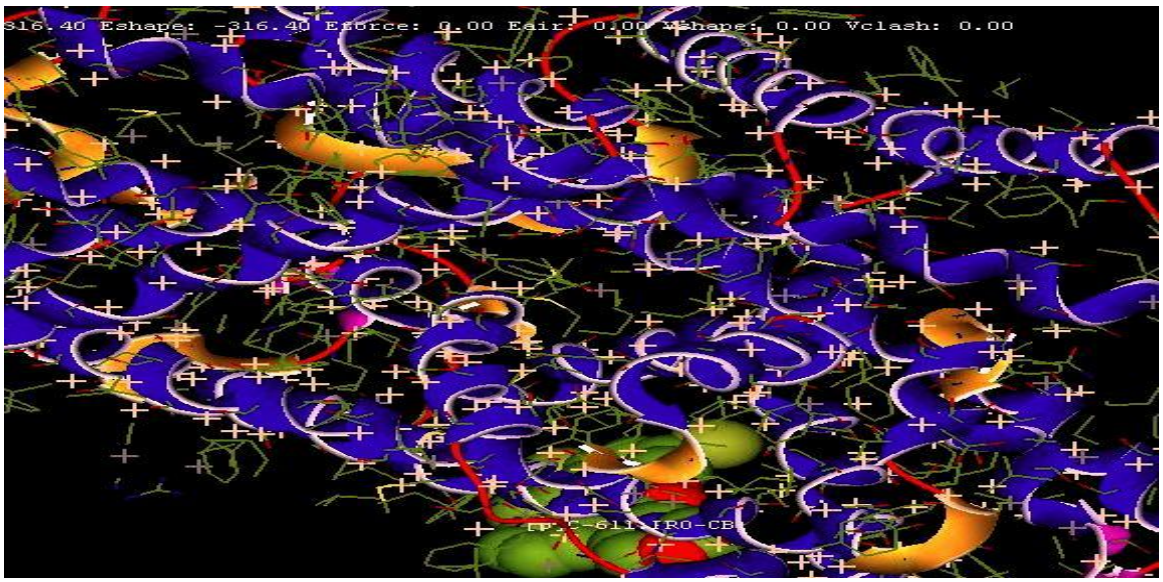


Ciprofloxacin

Table I- Physical data and E.total values of quinazolne-4-ones against E.coli.

Code Nos	Molecular Structure	Molecular Volume	Optimization Energy	E.Total Value	Binding Sites
$4a_1$		358.864	205.87	-284.64	[O]C-497:LYS-CD
$4a_2$		392.467	153.53	-296.09	[O]C-486:ILE-CB
$4a_3$		486.599	194.40	-295.62	[O]C-486:ILE-CD
$4a_4$		505.731	181.39	-310.42	[O]C-753:GLU-C

$4a_5$		394.s509	122.33	-307.81	[O]C-806:ILE-CB
$4a_6$		391.092	117.43	-316.40	[O]C-611:PRO-CB
Ciproflox acin		280.528	202.74	-242.02	[O]C-840:PHE –CD



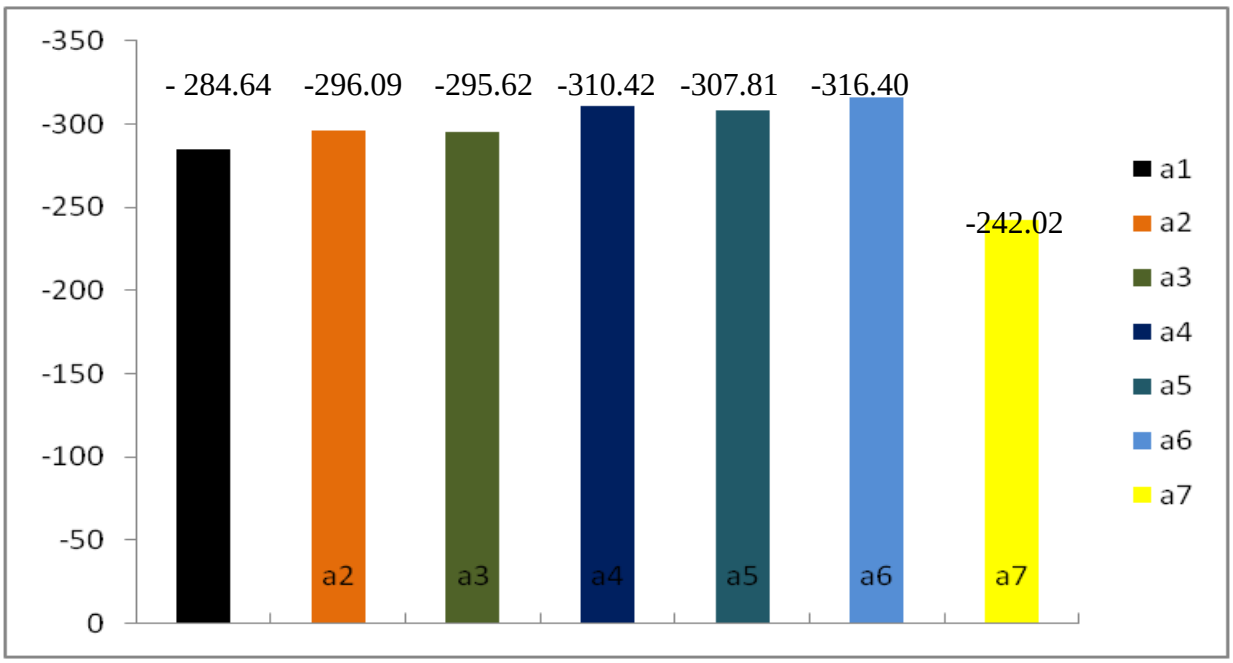
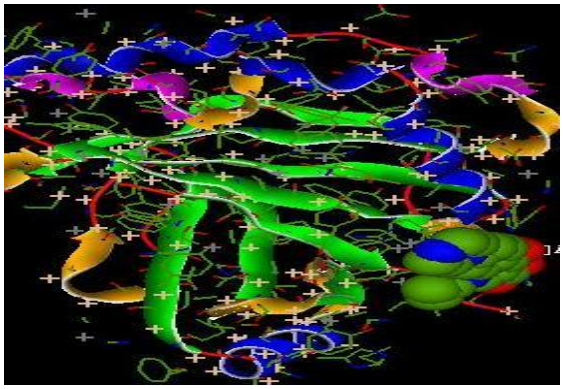


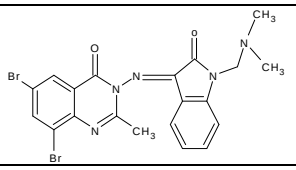
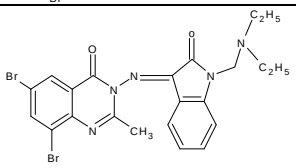
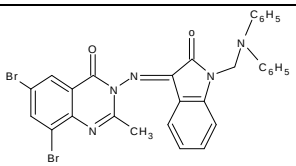
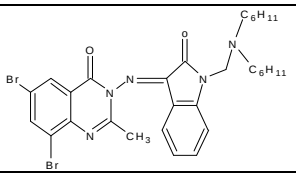
Fig .1 –Hex6.3 docking of quinazoline-4ones against *Escherichia coli.*

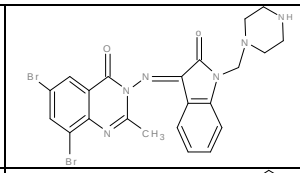
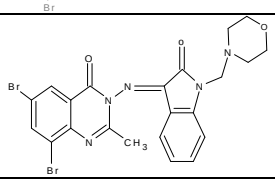
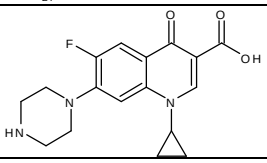


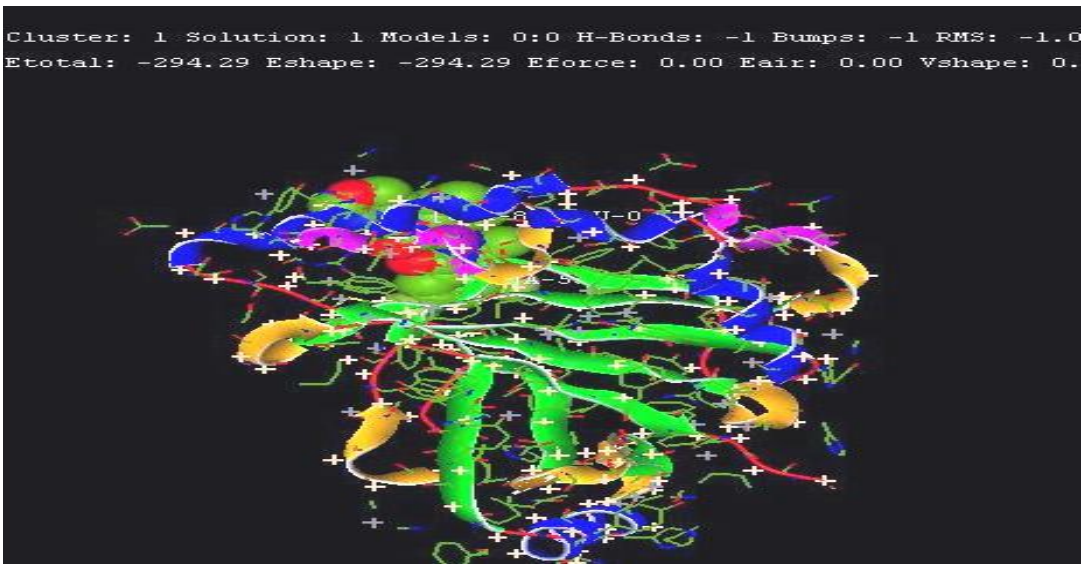
4AE5 +ciprofloxacin

4AE5+4a$_5$

Table-II- Physical data and E.total values of quinazolne-4-ones against S.a.

Code Nos	Molecular Structure	Molecular Volume	Optimization Energy	E.Total Value	Binding Sites
4a$_1$		358.864	205.87	-268.09	[O]A-65:HIS-O
4a$_2$		392.467	153.53	-268.19	[O]A-65:HIS-O
4a$_3$		486.599	194.40	-269.94	[O]A-37:ILU-C
4a$_4$		505.731	181.39	-270.15	[O]A-139:PHE-CE1 [O]A-138:HIS-CB

$4a_5$		394.509	122.33	-293.36	[O]A-73:ILU-CG1
$4a_6$		391.092	117.43	-294.29	[O]A-84:HIS-GLU-O
Ciproflo Cin		280.528	202.74	-222.14	[O]A-65:HIS-CB



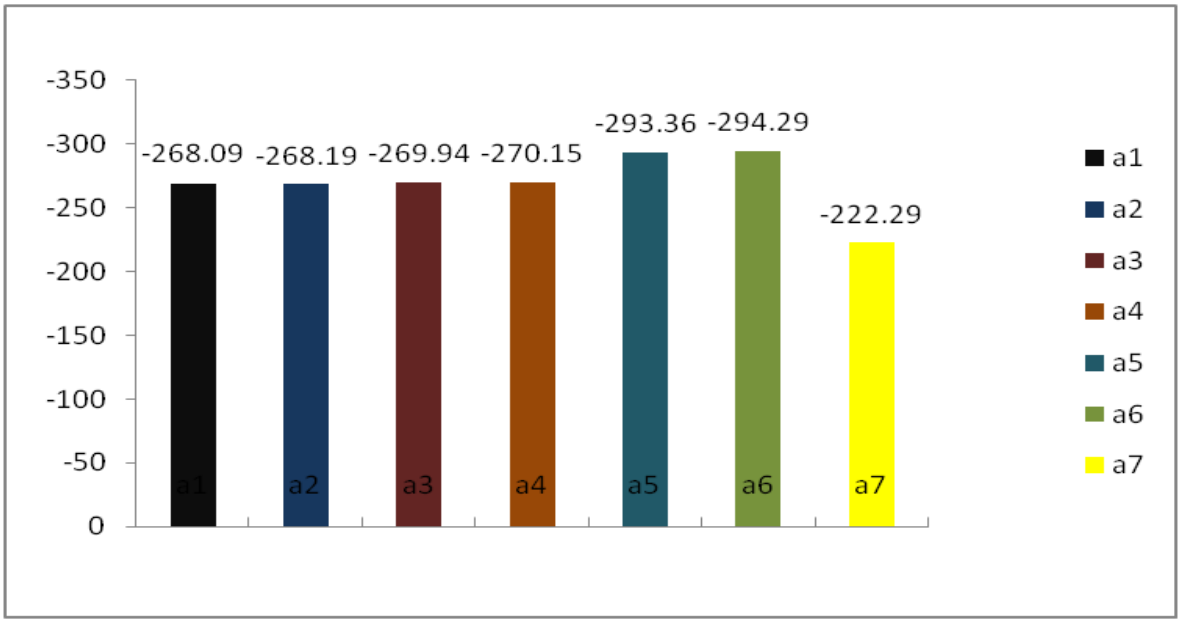
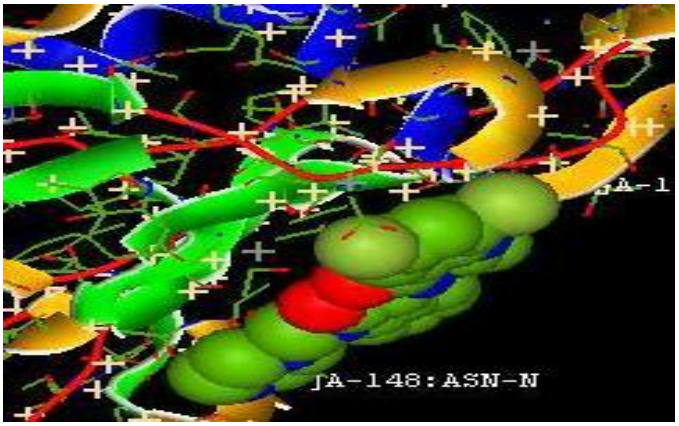
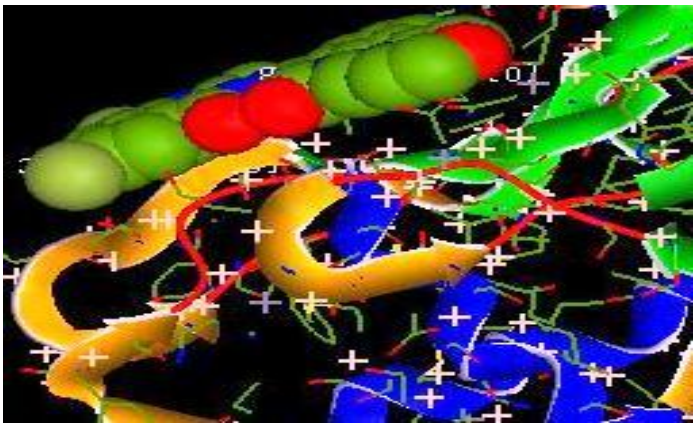


Fig.2 –Hex6.3 docking ofquinazoline-4ones against *Staphylococcus aureus.*

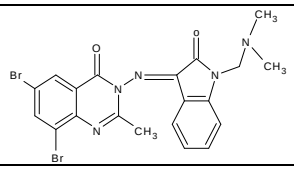
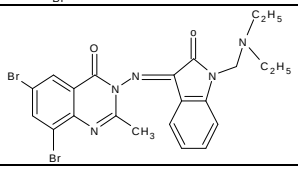
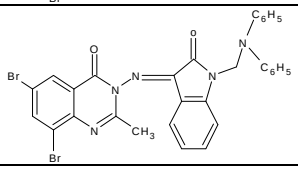
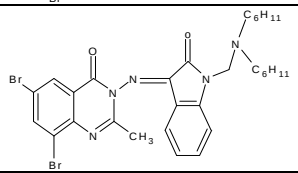


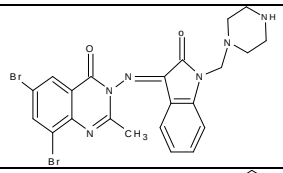
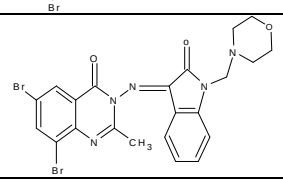
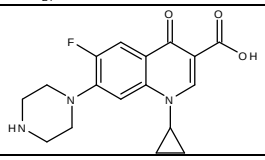
3FHU+4a5

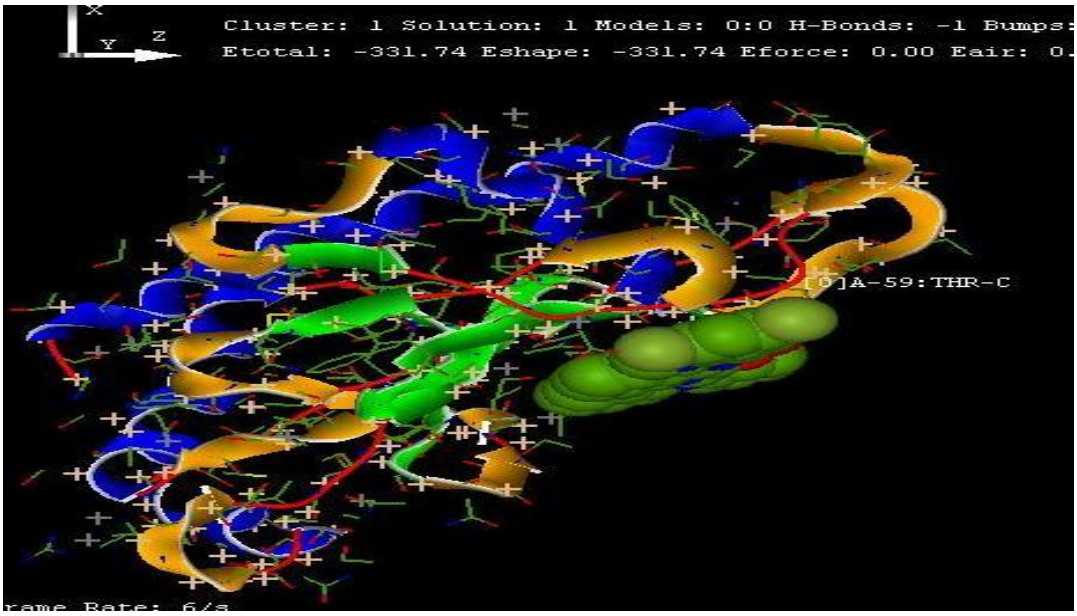


3FHU+4a$_6$

Table III- Physical data and E.total values of quinazolne-4-ones against *S.typhi*

Code Nos	Molecular Structure	Molecular Volume	Optimization Energy cal/mole	E.total Value	Binding Sites
4a$_1$		358.864	205.87	-96.97	[O]A-143:LYS-CD
4a$_2$		392.467	153.53	-268.91	[O]A-143:LYS-CE
4a$_3$		486.599	194.40	-271.65	[O]A-105:ALA-N
4a$_4$		505.731	181.39	-331.74	[O]A-79:THR-C

$4a_5$		394.509	122.33	-279.80	[O]A-148:ASN-N
$4a_6$		391.092	117.43	-282.60	[O]A-117:THR-CB [O]A-103:ASP-C
Ciprofloxacin		280.528	202.74	-230.41	[O]A-104:THR –CB



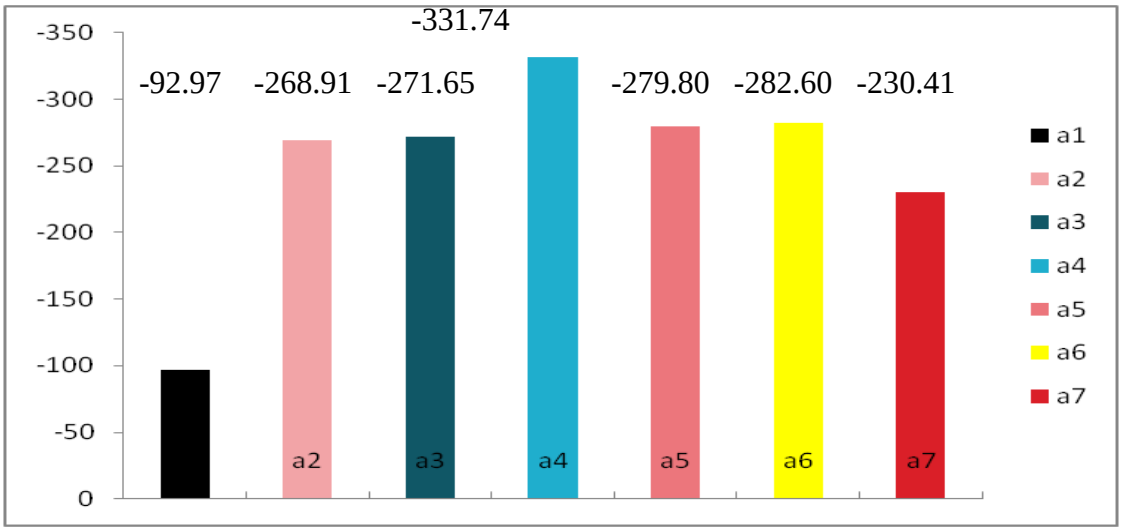


Fig3:–Hex6.3 docking of quinazoline-4ones against *Salmonella typhi*

Table IV- Enzyme inhibitors of Quinazoline-4-ones.

Code Nos	Biological Activities	Scoring	LogP	Violations	H-Acceptor/ Donor	
					ON	OHNH
$4a_1$	Enzyme inhibitor	-0.54	3.95	O1	07	01
$4a_2$	Enzyme inhibitor	-0.48	4.70	01	07	01
$4a_3$	Enzyme inhibitor	-0.39	7.35	02	07	01
$4a_4$	Enzyme inhibitor	-0.37	7.76	02	07	01
$4a_5$	Enzyme inhibitor	-0.43	3.24	01	07	O1
$4a_6$	Enzyme inhibitor	-0.47	3.79	01	07	01
Ciprofloxacin	Enzyme inhibitor	0.29	0.18	0	06	02

Table V- Protease inhibitors of Quinazoline-4-ones.

Code Nos	Biological Activities	Scoring	LogP	Violations	H-Acceptor/Donor	
					ON	OHNH
$4a_1$	protease inhibitor	-0.84	3.95	O1	07	01
$4a_2$	protease inhibitor	-0.85	4.70	01	07	01
$4a_3$	protease inhibitor	-0.57	7.35	02	07	01
$4a_4$	protease inhibitor	-0.54	7.76	02	07	01
$4a_5$	protease inhibitor	-0.37	3.24	01	07	O1
$4a_6$	protease inhibitor	-0.80	3.79	01	07	01
Ciprofloxacin	protease inhibitor	- 0.25	0.18	0	06	02

Table-VI Physical data of synthesized compounds 3 and $4a_{1-6}$

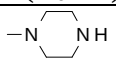
Compd. Code	-NRR	Molecular Formula	M.p (^{0}C)	Yield (%)	Rf Value
3	---	$C_{17}H_{10}Br_2N_4O_2$	174	71	0.76
$4a_1$	$-N(CH_3)_2$	$C_{20}H_{17}Br_2N_5O_2$	108	63	0.69
$4a_2$	$-N(C_2H_5)_2$	$C_{22}H_{21}Br_2N_5O_2$	109	64	0.81
$4a_3$	$-N(C_6H_5)_2$	$C_{30}H_{21}Br_2N_5O_2$	142	73	0.67
$4a_4$	$-N(C_6H_{11})_2$	$C_{30}H_{33}Br_2N_5O_2$	126	57	0.73
$4a_5$		$C_{22}H_{20}Br_2N_6O_2$	143	56	0.68
$4a_6$		$C_{22}H_{19}Br_2N_5O_3$	129	51	0.71

Table:-VII- Antibacterial screening of compounds $4a_{1-6}$ by cup plate method

Compound code	Inhibition of zone*(mm) 100µg / ml		
	E.coli	*S. aureus*	*S. typhi*
$4a_1$	28	20	12
$4a_2$	30	21	23
$4a_3$	31	21	27
$4a_4$	33	23	33
$4a_5$	32	26	28
$4a_6$	34	28	30
ciprofloxacin	30	29	27
10%DMSO control	…….	…….	……

#Average of three reading *E. c.* - *Escherichia coli, S. a.* - *Staphylococcus areus, S. t.* - *Salmonella typhi*

CONCLUSION

In conclusion, the utilized molecular docking application of the title compounds reveals for better activity and indicating that quinazolin-4-one rings scaffold influences the pharmacological activity. From the best posed energy and activity data, the compounds having saturated rings such as hexyl, piperazine and morphine are found to be more activity as compared to others. It is observed that the both saturated homo and hetero Lagos six member rings increases the activity. However, the difference in activity profile with structural modifications provides further scope to explore these compounds for better bioactivity.

ACKNOWLEDGEMENT

The authors are grateful to the authorities of University Department of Pharmaceutical Sciences, Utkal University, Bhubaneswar, Odisha, India for providing the necessary facility to carry out this research work. We are also thankful to Dr. P. K. Mohanta, USA, for his valuable suggestions to make the research work successful.

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