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# Synthesis, Molecular Docking and Anti-Bacterial Activity of 3-Sulfonamido Substituted Quinazolinone Derivatives

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## Abstract
Quinazolines have inhabited a distinctive position in heterocyclic chemistry and its derivatives have attracted considerable interests in recent years for their variable properties in chemistry and pharmacology. Quinazolines are nitrogen containing heterocyclic ring which possesses biological and pharmaceutical importance owing to its diversified activities like antibacterial, anti-tumor, anti-viral, anti-retroviral etc. The 3-sulfonamido substituted Quinazolines were synthesized and the title compounds were then characterized by melting point, TLC, IR, NMR and Mass spectral data. Docking studies were conducted for these derivatives on the PDB ID: 1AJO by using AutoDOCK software. The anti-bacterial activity was checked by using *E. coli, B.subtilis, P.aerugenosa* and *S.aureus.*

**Keywords**
Quinazolines, nitrogen containing heterocycles, antibacterial activity.

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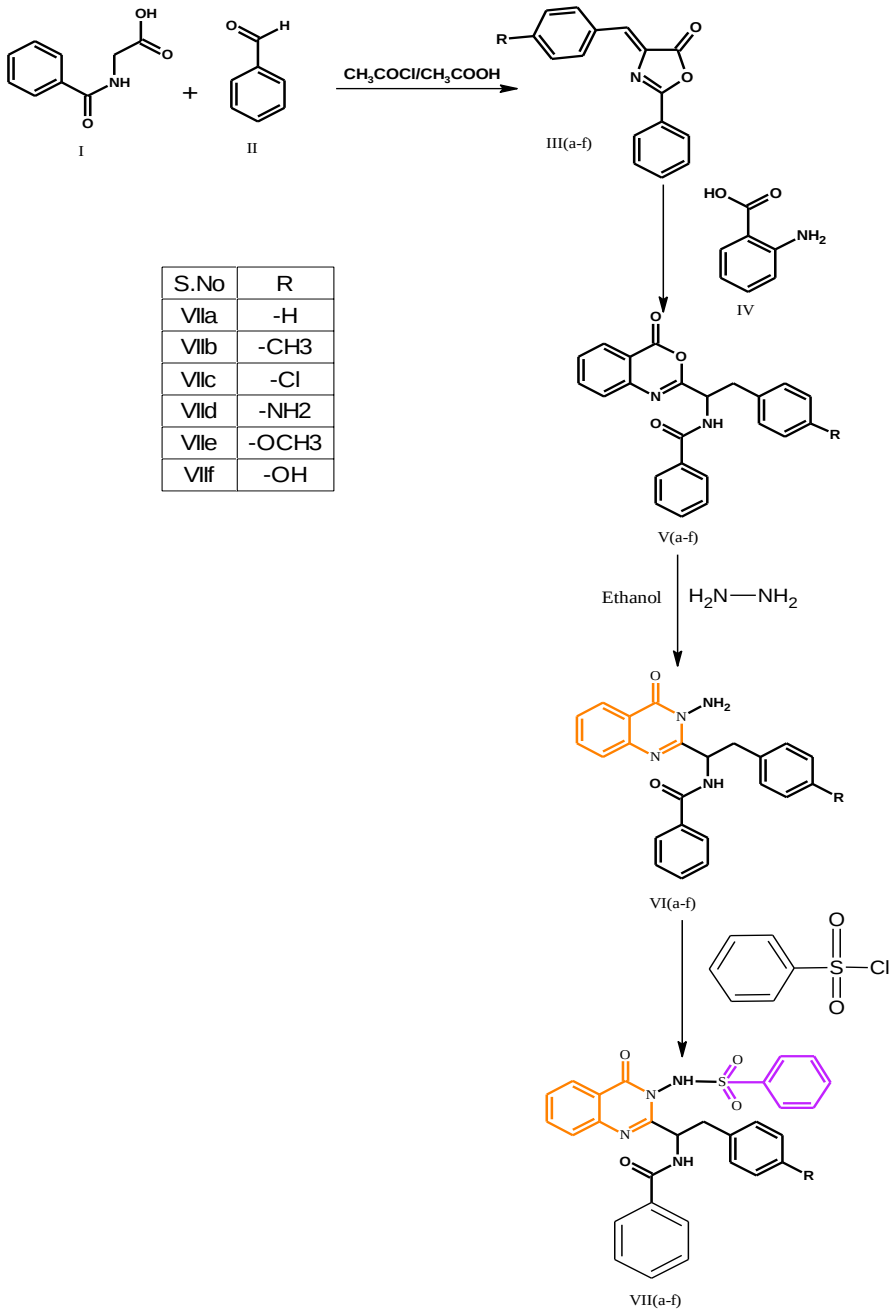
## INTRODUCTION
Resistance is a natural phenomenon, and it is inevitable that it will develop to all antibiotics at some time. As misuse and overuse of antibiotics speed up the growth of resistance, antibiotics should be used more liably and new antibacterial treatments should be developed to hinder pop up resistance. However, these are challenges, which both scientific- for the discovery of new antibiotics – and economic for ensuring investment into research and development.

Quinazoline is an interesting molecule, and its pharmacological activities are well documented. It has been reported as anti-microbial, anti-viral, anti-HIV, anti-convulsant, anti-inflammatory, antihistaminic, anti-tubercular, and anti-cancer activity, etc. It is known for its antiviral activity against selected viruses, and some of its derivatives such as 2, 3-disubstituted quinazoline derivatives also show anti-HIV and anticancer activity. Millions of people worldwide are affected by infectious diseases caused by viruses. Further, widespread viral resistance has renewed the interest in the quest for new antiviral agents. A large number of quinazolines have been synthesized and evaluated for various activities. The present study deals with the synthesis of 3-Sulfonamide Substituted Quinazoline derivatives and its evaluation of antibacterial activity against *E. coli, B.subtilis, P.aerugenosa and S.aureus.*

## RESULTS AND DISCUSSION
### Chemistry
### Synthetic Scheme




| S.No | R |
|---|---|
| VIIa | -H |
| VIIb | -CH3 |
| VIIc | -Cl |
| VIId | -NH2 |
| VIIe | -OCH3 |
| VIIf | -OH |

**Experimental**

Melting points of the synthesized compounds were taken in the open capillary tubes using the Chemline company CL726 melting apparatus. The purity of the compounds was checked by thin-layer chromatography using silica gel G as the stationary phase and various combinations of the mobile phase. The spots resolved were visualized by using the UV and iodine chamber. The IR spectra of the synthesized compounds were recorded on a Fourier Transform IR spectrometer (model Shimadzu 8400s) in the range of 400-4000 using KBr pellets and the values of $V_{max}$ were reported in cm. H-NMR spectra were recorded in bruce 500 MHz-NMR spectrometer (Astra Zeneca Pharma India Ltd) using $CDCl_3$ and chemical shifts were reported in parts per million downfield from internal reference Tetramethylsilane (TMS). Mass spectra were recorded in Shimadzu Mass Spectrometer.

**Step-1: Synthesis of 4-Arylidine-2-Phenyl-Oxazolones:**

Mixture of aromatic aldehydes (0.25moles),Hippuric acid (44.8 gm, 0.25 moles) / acetyl glycine (29 gm, 0.25 moles), anhydrous sodium acetate (15 gm), and acetic anhydride (59 ml) was heated at 110°C, with constant stirring. The mixture become almost solid, and then as the temperature rises, it gradually liquefies and turns deep yellow in color. The

completion of the reaction monitored by TLC, the reaction Mixture was allowed to cool, and ethanol (100 ml) is added slowly to the contents of the flask. After allowing the reaction mixture was left to stand overnight, the yellow color product was filtered and washed with ice cold ethanol and finally with boiling water and recrystallized in ethanol.

**Step-2: Synthesis of 2-aryl Benzamido-4-Benzoxazin-4-one:** A mixture of 4-Arylidine-2-Phenyl Oxazolones (0.01mole) and anthranilic acid (0.01moles) was refluxed in 20 ml of acetic acid for 6h, cooled and poured into cold water. A yellow ppt. was formed, M.p.219 - 220°C. TLC: hexane: ethyl acetate (60:40).

**Step- 3: Synthesis of 3-Amino Quinazoline 4-one:** To a solution of compound (benzaxazine-4one) (0.0lmole) in 50 ml of absolute ethanol and hydrazine hydrate (0.03moles), was added and the reaction mixture was refluxed for 6hrs, on cooling, the precipitate formed was filtered off, recrystallization by ethanol.TLC:hexane: ethyl acetate (60:40).

**Step-4: Synthesis of 3-Sulfonamide Substituted Quinazoline:** Equimolar quantities of quinazoline derivative (0.003mole) and benzene sulphonyl chloride (0.42ml, 0.003 moles) and dioxane 10ml and few drops of triethylamine refluxed for 8 hrs. The progress of the reaction was maintained by TLC. The mixture was cooled at room temperature and poured into ice-cold water. A pale-yellow colored solid was obtained the product obtained was crystallization by ethanol.

## RESULTS AND DISCUSSION

**(Z)-N-(1-(4-oxo-3-(phenylsulfonamido)-3,4-dihydroquinazolin-2-yl)-2-phenylvinyl) benzamide (VII a):**

Pale yellow crystalline solid; M. Pt: 125$^0$C. IR (KBr, cm$^{-1}$) 1160 cm$^{-1}$(S=O stretching ), 1076.28 (C-N stretching), 3442.44 (N-H amide stretching) and 3523.9 (N-H($SO_2NH$) stretching), Mass spectra m/z peak is observed at 498; $^1$H NMR: 11.75(S,1H,-$SO_2NH$)9.79(s,1H, -CONH), 7.85(d, 4H, IPArH), 7.36-7.61(m, 10H, ArH), 7.25-7.30(m, 3H, ArH), 7.18(t, 2H, IPArH).$^1$H NMR: δ 7.02 (1H, s, C=C-H), 7.19-7.36 (3H, 7.31 (m, *J* = 8.2, 7.6, 1.7, 0.5 Hz, Ar-H), 7.24 (m, *J* = 7.6, 1.5 Hz, Ar-H)), 7.41-7.66 (11H, 7.55 (m, *J* = 7.3, 1.5, 0.4 Hz, C8-quinazoline-H), 7.57 (m, *J* = 7.5, 1.5 Hz, Ar-H), 7.58 (m, *J* = 8.5, 7.5, 1.4, 0.4 Hz, Ar-H), 7.48 (m, *J* = 7.9, 7.7, 1.5 Hz, C6-quinazoline-H), 7.44 (m, *J* = 8.2, 1.8, 1.5, 0.5 Hz, Ar-H), 7.46 (m, *J* = 7.7, 7.3, 1.4 Hz, C7-quinazoline-H), 7.63 (m, *J* = 7.6, 1.5 Hz, Ar-H), 7.54 (m, *J* = 8.0, 7.6, 1.5, 0.4 Hz, Ar-H)), 7.76 (2H, m, *J* = 8.0, 1.5, 0.4 Hz, Ar-H), 8.01 (2H, m, *J* = 8.5, 1.8, 1.5, 0.4 Hz, Ar-H), 8.15 (1H, m, *J* = 7.9, 1.4, 0.4 Hz, C5-quinazoline-H).

**Z)-N-(1-(4-oxo-3-(phenylsulfonamido)-3,4-dihydroquinazolin-2-yl)-2-(p-tolyl) vinyl) benzamide (VII b):**

White crystalline solid; M. Pt: 122°C.

$^1$H NMR: δ 2.15 (3H, s, CH3), 7.07 (1H, s, C=C-H), 7.21 (2H, m, *J* = 8.0, 1.6, 0.5 Hz, Ar-H), 7.38-7.66 (11H, 7.55 (m, *J* = 7.4, 1.5, 0.5 Hz, C8-quinazoline-H), 7.57 (m, *J* = 7.5, 1.5 Hz, Ar-H), 7.58 (m, *J* = 8.5, 7.5, 1.4, 0.4 Hz, Ar-H), 7.48 (m, *J* = 7.9, 7.7, 1.5 Hz, C6-quinazoline-H), 7.43 (m, *J* = 7.7, 7.4, 1.4 Hz, C7-quinazoline-H), 7.63 (m, *J* = 7.6, 1.5 Hz, Ar-H), 7.54 (m, *J* = 8.0, 7.6, 1.5, 0.4 Hz, Ar-H), 7.41 (m, *J* = 8.0, 1.9, 0.5 Hz, Ar-H)), 7.76 (2H, m, *J* = 8.0, 1.5, 0.4 Hz, Ar-H), 8.01 (2H, m, *J* = 8.5, 1.6, 1.5, 0.4 Hz, Ar-H), 8.13 (1H, m, *J* = 7.9, 1.4, 0.5 Hz, C5-quinazoline-H).

**VII c (Z)-N-(2-(4-chlorophenyl) -1- (4-oxo- 3 - (phenyl sulfonamido)- 3, 4- dihydroquinazolin-2-yl) vinyl) benzamide (VII c):** Pale yellow crystalline solid; M.Pt: 130°C.

$^1$H NMR: δ 7.04 (1H, s, C=C-H), 7.33-7.66 (15H, 7.59 (m, *J* = 8.5, 1.6, 1.5, 0.4 Hz), 7.57 (m, *J* = 7.5, 1.5 Hz), 7.58 (m, *J* = 8.5, 7.5, 1.4, 0.4 Hz, Ar-H), 7.63 (m, *J* = 7.6, 1.5 Hz, Ar-H), 7.54 (m, *J* = 8.0, 7.6, 1.5, 0.4 Hz, Ar-H), 7.48 (m, *J* = 7.9, 7.7, 1.5 Hz, C6-quinazoline-H), 7.44 (m, *J* = 7.7, 7.3, 1.4 Hz, C7-quinazoline-H), 7.44 (m, *J* = 8.4, 1.6, 0.5 Hz, Ar-H), 7.37 (m, *J* = 8.4, 1.7, 0.5 Hz, Ar-H), 7.53 (m, *J* = 7.3, 1.5, 0.5 Hz, C8-quinazoline-H)), 7.76 (2H, m, *J* = 8.0, 1.5, 0.4 Hz, Ar-H), 8.14 (1H, m, *J* = 7.9, 1.4, 0.5 Hz, C5-quinazoline-H).

**(Z)-N-(2-(4-aminophenyl)-1-(4-oxo-3-(phenyl sulfonamido)-3, 4-dihydroquinazolin-2-yl) vinyl) benzamide (VII d):** White crystalline solid; M. Pt: 125°C.

$^1$H NMR: δ 6.66 (2H, m, *J* = 8.1, 1.2, 0.5 Hz, Ar-H), 6.95 (1H, s, C=C-H), 7.14 (1H, m, *J* = 7.6, 1.5, 0.5 Hz, C8-quinazoline-H), 7.37-7.49 (2H, 7.42 (m, *J* = 7.6, 1.4 Hz, C7-quinazoline-H), 7.44 (m, *J* = 7.9, 7.6, 1.5 Hz, C6-quinazoline-H)), 7.49-7.66 (8H, 7.54 (m, *J* = 8.0, 7.6, 1.5, 0.4 Hz, Ar-H), 7.57 (m, *J* = 7.5, 1.5 Hz, Ar-H), 7.58 (m, *J* = 8.5, 7.5, 1.4, 0.4 Hz, Ar-H), 7.60 (m, *J* = 8.1, 1.7, 0.5 Hz, Ar-H), 7.63 (m, *J* = 7.6, 1.5 Hz, Ar-H)), 7.76 (2H, m, *J* = 8.0, 1.5, 0.4 Hz, Ar-H), 8.01 (2H, m, *J* = 8.5, 1.6, 1.5, 0.4 Hz, Ar-H), 8.20 (1H, m, *J* = 7.9, 1.4, 0.5 Hz, C5-quinazoline-H).

**(Z)-N-(2-(4-methoxyphenyl)-1-(4-oxo-3-(phenylsulfonamido)-3,4-dihydroquinazolin-2-yl) vinyl) benzamide (VII e):** Black crystalline powder; M. Pt: 132°C.

$^1$H NMR: δ 3.89 (3H, s, O-CH3), 7.02 (1H, s, C=C-H), 7.10 (2H, m, *J* = 8.8, 1.3, 0.4 Hz, Ar-H), 7.38-7.66 (11H, 7.44 (m, *J* = 7.2, 1.5, 0.5 Hz, C8-quinazoline-H), 7.42 (m, *J* = 7.9, 7.6, 1.5 Hz, C6-quinazoline-H), 7.43 (m, *J* = 7.6, 7.2, 1.4 Hz, C7-quinazoline-H), 7.46 (m, *J* = 8.8, 1.8, 0.4 Hz, Ar-H), 7.54 (m, *J* = 8.0, 7.6, 1.5, 0.4

Hz, Ar-H), 7.57 (m, *J* = 7.5, 1.5 Hz, Ar-H), 7.58 (m, *J* = 8.5, 7.5, 1.4, 0.4 Hz, Ar-H), 7.63 (m, *J* = 7.6, 1.5 Hz, Ar-H)), 7.76 (2H, m, *J* = 8.0, 1.5, 0.4 Hz, Ar-H), 8.01 (2H, m, *J* = 8.5, 1.6, 1.5, 0.4 Hz, Ar-H), 8.20 (1H, m, *J* = 7.9, 1.4, 0.5 Hz, C5-quinazoline-H).

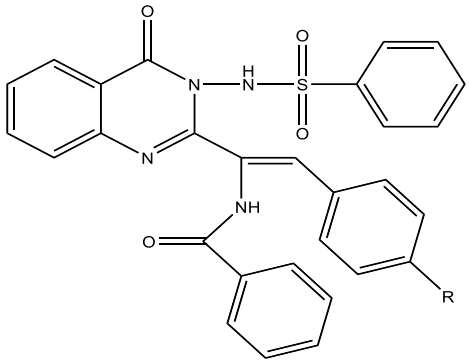
**(Z)-N-(2-(4-hydroxyphenyl)-1-(4-oxo-3-(phenyl sulfonamido)- 3, 4-dihydroquinazolin-2-yl) vinyl) benzamide (VII f):** White crystalline solid; M. Pt: 135°C.

$^1$H NMR: δ 6.91 (2H, m, *J* = 8.3, 1.3, 0.5 Hz, Ar-H), 7.01 (1H, s, C=C-H), 7.38-7.66 (11H, 7.44 (m, *J* = 7.2, 1.5, 0.5 Hz, C8-quinazoline-H), 7.43 (m, *J* = 7.9, 7.6, 1.5 Hz, C6-quinazoline-H), 7.44 (m, *J* = 7.6, 7.2, 1.4 Hz, C7-quinazoline-H), 7.47 (m, *J* = 8.3, 1.9, 0.5 Hz, Ar-H), 7.54 (m, *J* = 8.0, 7.6, 1.5, 0.4 Hz, Ar-H), 7.57 (m, *J* = 7.5, 1.5 Hz, Ar-H), 7.58 (m, *J* = 8.5, 7.5, 1.4, 0.4 Hz, Ar-H), 7.63 (m, *J* = 7.6, 1.5 Hz, Ar-H)), 7.76 (2H, m, *J* = 8.0, 1.5, 0.4 Hz, Ar-H), 8.01 (2H, m, *J* = 8.5, 1.6, 1.5, 0.4 Hz, Ar-H), 8.21 (1H, m, *J* = 7.9, 1.4, 0.5 Hz, C5-quinazoline-H).

**MOLECULAR PROPERTY CALCULATION AND TOXICITY PREDICTION**

The molecular properties of the newly synthesized compounds (VII-f) were calculated values of some basic molecular descriptions such as log**P**, log**S**, molecular weight, Polar Surface Area, number of hydrogen bonds donor and number of hydrogen bonds acceptor in molecule membrane hydrophobicity and bioavailability were predicted.

Table-2: Lipinski rule of five (Lipinski rule *et al* 1997) was adopted to sort out the drug-likeness of synthesized compounds. The results are presented in the following table:




| S. No | R | Mol wt. | C log P | Logs | DL | MUT | REP | Rotatable bonds |
|---|---|---|---|---|---|---|---|---|
| VII a | -H | 497.56 | 2.124 | -3.52 | -1.247 | None | None | 3 |
| VII b | -CH3 | 526.6 | 4.463 | -4.3 | -8.0 | None | None | 4 |
| VII c | -Cl | 546.0 | 0.706 | -0.734 | -7.734 | None | None | 2 |
| VII d | -NH2 | 488.5 | 4.049 | -3.90 | -7.913 | None | None | 3 |
| VII e | -OCH3 | 544.7 | 4.016 | -4.0 | -7.176 | None | None | 5 |
| VII f | -OH | 512.5 | 3.774 | -3.684 | -7.737 | None | None | 4 |

**MOLECULAR DOCKING**

**Table 3: Binding interactions of title compounds with DHPS enzyme**

| Compounds | Kcal/mol | Binding Interactions | Hydrophobic interactions | H-Bonds |
|---|---|---|---|---|
| VII a | -4.8 | Cys532, Thr529, Phe595, Val471 | Phe595 | |
| VII b | -5.9 | Cys532, Trp531, Gly530, | - | Thr529 |
| VII c | -5.4 | - | Ile513, Ile592 | - |
| VII d | -5.9 | Phe595, Thr529, Gln513 and Leu514, Lys483 | - | - |
| VII e | -6.8 | Leu505 | Phe595, Val471, Asp594 | Cys532 |
| VIIf | -5.8 | - | Ile513 | - |
| **Sulphamethoxazole** | -5.5 | Cys532, Thr529, Phe595, Leu514, Lys483 and Val471 | Phe595 | Cys532 |

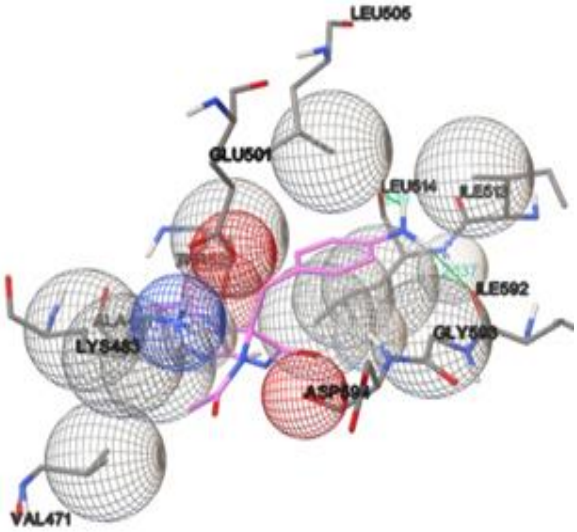



**Fig-No.3: Three-dimensional representation of binding mode of compounds VII b (purple) in DHPS (PDBID:1AJO) binding site and interacting amino acid residues.**

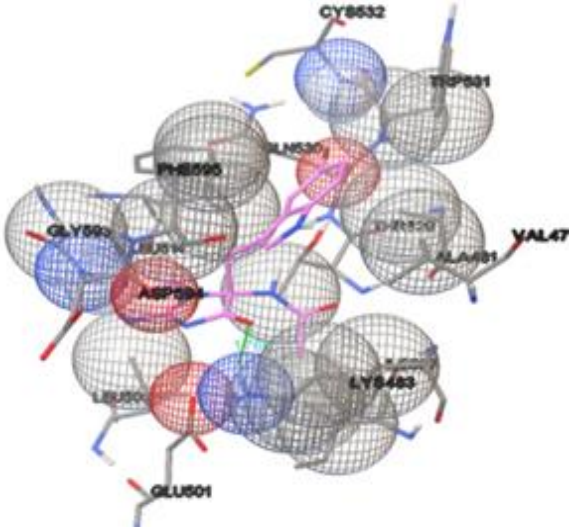



**Fig No-4: Three-dimensional representation of binding mode of compounds VII d (purple) in DHPS (PDBID:1AJO) binding site and interacting amino acid residues.**

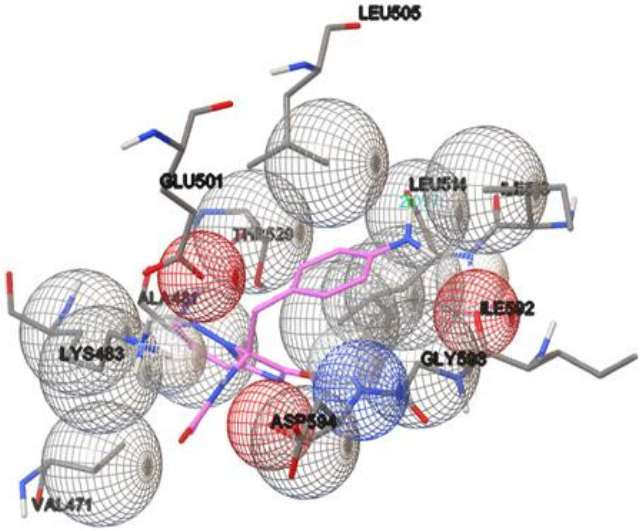



**Fig No-5: Three-dimensional representation of binding mode of compounds VII e (purple) in DHPS (PDBID:1AJO) binding site and interacting amino acid residues.**

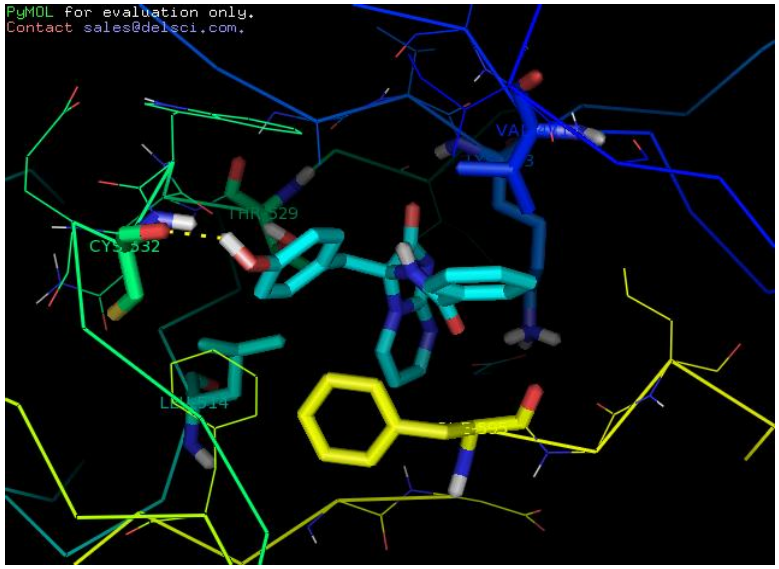



**Fig No-6: Three-dimensional representation of binding mode of compounds Sulfamethoxazole (purple) in DHPS (PDBID: 1AJO) binding site and interacting amino acid residues.**

All the compounds **VII (a-f)** showed binding interactions of the title compounds with the active site of the protein is the hydrophobic pocket comprising of amino acids Asp594, ILe592, Thr529, Phe595 which was similar to that of Sulfamethoxazole (reference standard drug) protein interaction as shown in fig 6. The compounds also demonstrated hydrophobic interactions with the hydrophobic pocket. The target protein amino acid residues Cys532, Thr529, Phe595, Leu514, Lys483, and Val471 were similar to that of sulfamethoxazole protein interaction.

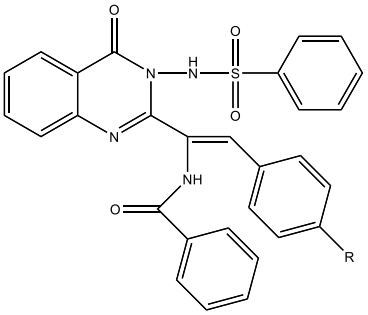
Further, compound VII e (Figure 5) formed one strong hydrogen bond with the Cys532 and compound VII b (Figure 4) formed another hydrogen bond with the amino acid residue Thr529 which is crucial for inhibition of the DHPS enzyme.

It can be summarized that the synthesized compounds form the complex with the target at the lowest energy and showed a better affinity towards the DHPS enzyme suggested that for further in vitro anti-bacterial studies.

**ANTIBACTERIAL ACTIVITY**

The antibacterial activity of the synthesized quinazolinones was evaluated using the agar cup plate method. Accordingly, the compounds were screened against Gram-negative organisms, namely, *Escherichia coli* and *Pseudomonas aeruginosa* and Gram-positive organisms *Bacillus subtilis* and *Staphylococcus aureus* using the cup plate method. Sulphamethoxazole was employed as a reference standard to compare the results. The results are presented in the following table

**Table 4: Zone of inhibition caused by various bacterial species:**



| S.No | Compound | Zone of Inhibition in mm | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | ***Escherichia coli* (-ve)** | | ***Pseudomonas aeruginosa* (-ve)** | | ***Bacillus subtilis* (+ve)** | | ***Staphylococcus aureus* (+ve)** | |
| | | **1000µg** | **500µg** | **1000µg** | **500µg** | **1000µg** | **500µg** | **1000µg** | **500µg** |
| 01 | VII a | 12 | 10 | 10 | - | - | - | - | - |
| 02 | VII b | 18 | 16 | 17 | 15 | - | - | - | - |
| 03 | VII c | 16 | 15 | 15 | 13 | - | - | - | - |
| 04 | VII d | **18** | **13** | **15** | **13** | - | - | - | - |
| 05 | VII e | **24** | **22** | **17** | **15** | - | - | - | - |
| 06 | VII f | 16 | 14 | 13 | 12 | - | - | - | - |
| 07 | Sulphamethoxazole (250 µg) | **35** | **33** | **35** | **33** | 15 | 13 | 17 | 15 |
| 08 | Solvent control | - | - | - | - | - | - | - | - |

All the synthesized quinazolinones were screened for their antibacterial activity using the agar cup plate method. Accordingly, Sulfamethoxazole was sensitive at 250 µg/mL on gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* with the zone of inhibitions at 35 and 33 mm respectively and was found to be inactive on gram-positive bacteria at the same concentration. The antibacterial activity of the synthesized quinazolinones in comparison with Sulfamethoxazole is shown in Figures 7-8. Compounds VII e (24 mm) and VII d (18 mm) exhibited significant antibacterial activity against Gram-negative bacteria at 1000 µg/mL concentration. However, the general activity of the synthesized quinazolinones against Gram-positive bacteria was found to be negative.

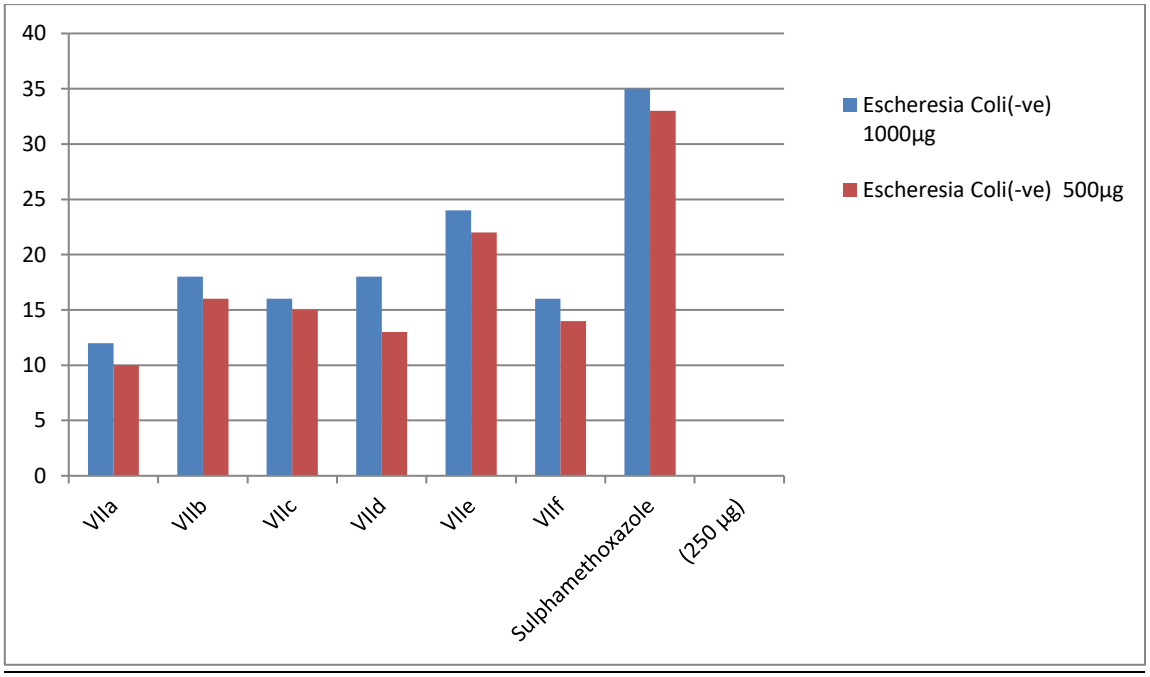



**Fig: 7: Antibacterial activity of the synthesized quinazolinones on *EscherichiaColi* (-ve) at 1000ug/ML concentration.**

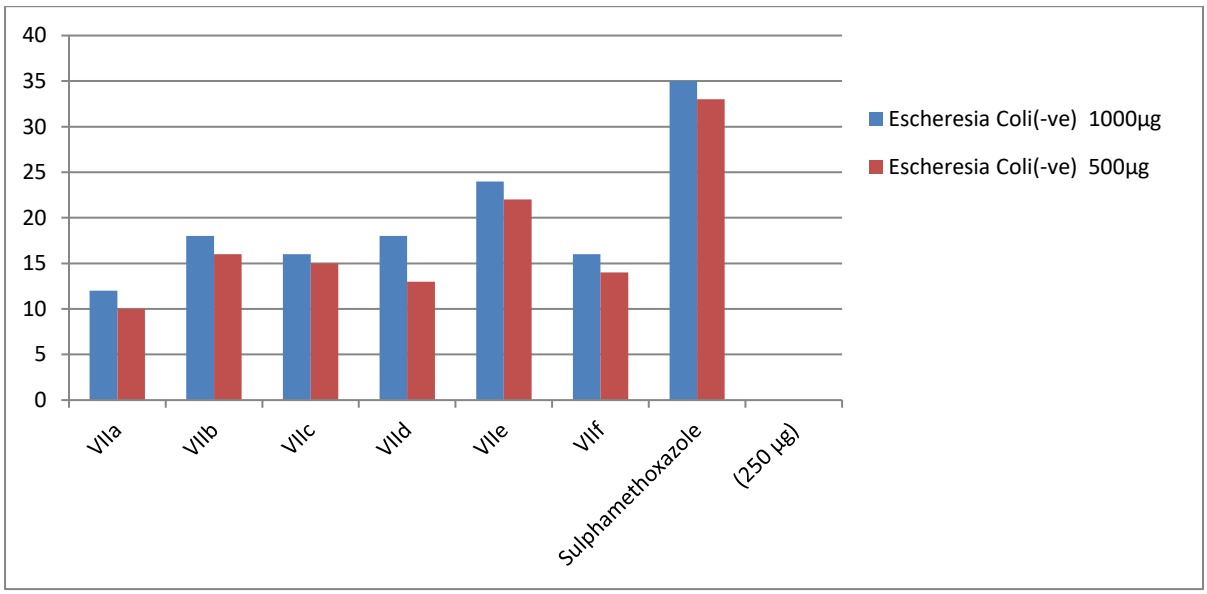



**Fig 8: Antibacterial activity of the synthesized quinazolinones on *Pseudomonas aeruginosa* (-ve) at 1000ug/ML concentration.**

Among all the synthesized quinazolinone compounds VIIe exhibited significant activity against Gram-negative bacteria, which may be due to structural similarity of it with the standard drug and also because of the presence of methoxy group which mediated its interactions with DHPS enzyme. However, the activity of the synthesized quinazolinones against Gram-positive bacteria was low. Further synthetic work on these derivatives is to optimize its potential on Gram-positive bacteria and also to further increase its activity against Gram-negative bacteria.

## CONCLUSION

In the present investigation, a new series of 3- new Sulphonamido substituted quinazolinones (VIIa-f) were synthesized. All the synthesized compounds characterized by physical and spectral data. The molecular docking studies of the title compounds were carried out on DHPS kinase (PDB ID: IAJO) to identify potential molecules. Molecular properties were also predicted to assess the drug likeness of the synthesized compounds. All the synthesized compounds were screened for their activity against Gram-negative organisms and Gram-positive organisms by agar cup plate method and the results are correlated with the docking results for their possible DHPS Kinase inhibitory activity. All the synthesized compounds have shown their antibacterial activity selectively towards gram-negative bacteria rather than gram-positive bacteria. However, among the tested compounds, VIId was found to more potent antibacterial activity. Further synthetic work on these derivatives is to optimize its potential on Gram-positive bacteria and also to further increase its activity against Gram-negative bacteria.

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