

**“SYNTHESIS, CHARACTERIZATION OF 2-METHYLQUINOZOLINYL  
THIAZOLIDINES FOR ANTIMICROBIAL ACTIVITY.”**Shivanand Kolageri\*<sup>1</sup>, B. Shivakumar<sup>2</sup>, S. M. Biradar<sup>3</sup>, Santosh Karajagi<sup>4</sup> and E. N. Gaviraj<sup>5</sup><sup>1,2,4</sup>Department of Pharmaceutical Chemistry, <sup>3</sup> Pharmacology, <sup>5</sup> Pharmacognosy,  
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**ABSTRACT**

Six new derivatives of **3-(4-oxo-2-arylthiazolidin-3-yl)-2-methylquinazolin-4(3H)-one** were synthesized by condensation between **3-amino-2-methylquinazolin-4(3H)-one** and substituted aromatic aldehydes using thioglycolic acid, N,N'-dicyclohexylcarbodiimide and N,N-dimethyl formamide as solvent. The required **3-amino-2-methylquinazolin-4(3H)-one** was obtained from the reaction between 2-amino benzoic acid and acetic anhydride/acetyl chloride. The synthesized compounds containing quinazolinone nucleus coupled with thiazolidinone could yield effective biologically active derivatives. Hence the objectives of the research work are as synthesized newer heterocyclic derivatives of Quinazolinones with thiazolidinone, characterize the synthesized compounds using physical data like M.P, TLC and spectroscopic analysed FT-IR, <sup>1</sup>H-NMR Spectral and these synthesized compounds were biological evaluated for their antimicrobial screening. The prepared compounds were confirmed for antibacterial activity against *E. coli* (gram negative) and *Staphylococcus Aureus* (gram positive) by using cup-plate method. The results of antibacterial activity revealed that, among all derivatives **3-[2-(2-chloroquinolin-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-2-methylquinazolin-4(3H)-one** showed moderate to good activity and others showed moderate to weak activity at the concentration of 250µ/ml, 500µ/ml and 750µ/ml compared to Chloramphenicol drug.

**KEYWORDS:** Quinazolinones with thiazolidinone derivatives, Antibacterial activity, Cup-plate method.**INTRODUCTION**

The term 'drug' possibly originated Arabic source and may be first mentioned in ancient German term as drug, means to a kind of powder. Nature has provided plenty of plants, fungi, insects, and reptiles which are rich sources of pharmacologically active chemical substances against various co-morbidities.<sup>[1]</sup>

Even though nature has been providing many drugs for multiple diseases or disorders that mostly fall under broad spectrum class; researchers are more determined towards synthetic medications, due to their potency in narrow spectrum class (specific drug for specific disease or disorder). Most of the pharmaceutical industries synthesize drugs from heterocyclic compounds. For instance, top 200 trademarked drugs of pharmaceutical industries have 75% of heterocyclic fragments in their structure. One of the popular and interested molecules among heterocyclic compounds was a derivative of quinazolinone-4(3H)-one.<sup>[2]</sup>

The quinazolinone-4(3H)-one, previously named as benzo-1,3-diazine and its derivatives were established in more than 200 naturally occurring alkaloids. Weddige was first

proposed the name of quinazolinone (German: Chinazolin). From 1903 still quinazolinone synthesized by 3,4-dihydroquinazolinone and alkaline potassium ferricyanide through oxidation. About 50 years later scientists gained interest in the QZN molecule after the discovery of its alkaloids, Example: 3-[β-keto-g-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolinone.

Quinazolinone derivatives (specifically quinazolinone-4-ones or quinazolinones) are the most significant class among the heterocyclic compounds in Pharmacological branch. QZN nucleus stability surprised too many medicinal chemists so they synthesized many of its bioactive moieties. In the medicinal chemistry, the QZN nucleus was frequently encountered literature due to its various applications such as against of fungal, malarial, hypertension, depression, bacterial, inflammatory, epilepsy, Parkinsonism, many viral and cancer diseases.<sup>[3]</sup>

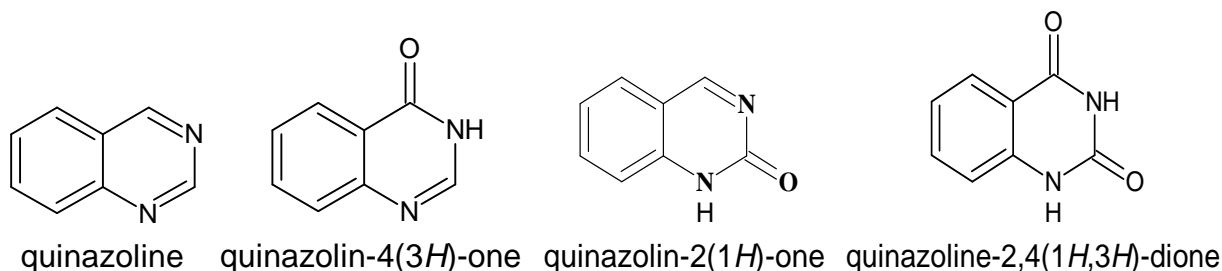
Most of the pharmacologically active organic cycles preferably had nitrogen atom it, either naturally or unnaturally available pharmaceuticals. Between them, quinazolinone and its analogues consist of a superior

category along with a various beneficial bioactive properties over bacterial, diabetic, convulsants, tumor, malarial, hypertensive, inflammatory and cholinesterase conditions. Several analogues of quinazoline had synthesized to design more efficacy plus safety drugs for multiple disorders. As soon as, the researchers have recognized the significance of QZN, due to its several applications on diseases and disorders, a number of chemical methods and analogues had discovered. Because of QZNs unavoidable attention towards pharmacological activity, I felt that, it should be noteworthy to mention its various chemical synthesis and

bioactive molecules in my review of literature section.<sup>[4]</sup>

### Chemistry of Quinazolinone Nucleus

Quinazolinone(QZN) are biologically active molecules which includes a framework of six-membered ring containing two nitrogen atoms fused with phenyl ring. Oxidation of quinazoline gives the QZNs. The framework of QZNs was distinguished by the positions of the oxygen and nitrogen (NH) present in fused ring. The major sub- classes of the QZNs fall into the following categories.<sup>[5]</sup>



Quinazolinones are commonly solid in nature with high m.p. They are insoluble in water, freely soluble in alkali and give stable salts. QZNs on nitration and bromination, the primary nitro group attaches to the 6<sup>th</sup> position and the second group attaches to the 8<sup>th</sup> position. Chemically, they are steady during oxidization, however in critical condition; they can produce 2,4-dihydroxy quinazoline.<sup>[6]</sup>

### SAR of quinazolin-4-one derivatives

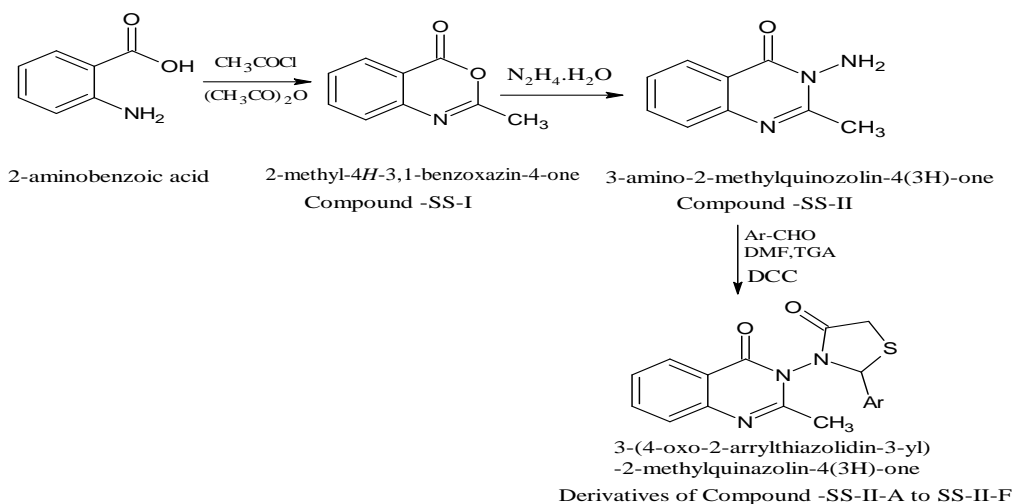
Four times improvement in the activity can be seen by attaching substituent (halogen) at C-6 position. Studies showed that minor substituent on 3<sup>rd</sup> place of phenyl group had decent biological activity and big groups attachment not showed any notable strength in activity. Studies showed that aromatic ring, methyl group existence at 3<sup>rd</sup> and 2<sup>nd</sup> position respectively were basic necessities for neurotransmitter excitation and inhibition. Effective CNS actions like sedative, hypnotic and tranquillizing actions can result by alteration of methyl

group with propyl or butyl groups.<sup>[7]</sup>

### SCHEME

For this purpose, the required 3-(4-oxo-2-arylthiazolidin-3-yl)-2-methylquinazolin-4(3H)-one has been synthesized by using specified **SCHEME-I**

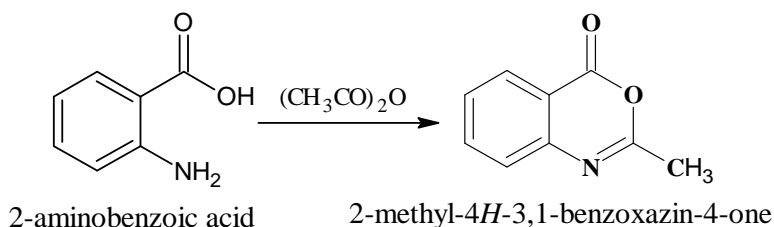
2-methyl-4H-3,1-benzoxazin-4-one (SS-I) was synthesized by reaction of anthranilic acid and acetic anhydride. The intermediate (SS-I) obtained was refluxed with hydrazine hydrate in ethanol to form 3-amino-2-methylquinazolin-4(3H)-one (SS-II). The compounds 3-(4-oxo-2-arylthiazolidin-3-yl)-2-methylquinazolin-4(3H)-one (Derivatives compound SS-II-A to SS-II-F) were synthesized by stirring with substituted aromatic aldehydes using thioglycolic acid (TGA), N,N'-dicyclohexylcarbodiimide (DCC) and N,N-dimethyl formamide (DMF) as solvent.



Ar- =Benzaldehyde and 2-Chloroquinolin-3-Carbaldehyde

**SCHEME-I****MATERIALS AND METHODS****Synthesis of intermediate 2-methyl-4H-3,1-benzoxazin-4-one (SS-I)**

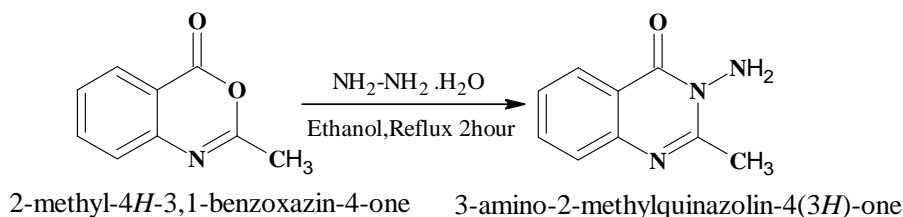
In 250ml of RBF took (0.01mole or 1.37gm) anthranilic acid (2-amino benzoic acid) to that added 15ml of acetic anhydride (excess) with porcelain chips. Reflux the solution at 35-40°C for 50- 55min on heating mantle. TLC was done using EA: n-hexane (1:1) solvent system.

**Synthesis of intermediate 3-amino-2-methyl quinoxalin-4(3H)-one (SS-II)**

To the solution of compound (SS-I) taken 0.01 mol. (1.51gm) of 2-methyl-4H-3,1-benzoxazin-4-one sample was dissolved in absolute ethanol, and further added to equi-molar quantity of 0.01mol. (0.51ml) of 99% hydrazine hydrate then reflux for 3-4hours and cooled, the product was formed 3-amino-2-methylquinoxalin-4(3H)-one then it is filtered out and dried. The TLC was

Then removed the excess solvent (acetic anhydride) at low pressure using rotatory evaporator, To the remaining solid, added petroleum ether (40-60) to extract the 2-methyl-4H-3,1-benzoxazin-4-one. Repeated petroleum ether step to extract the entire product. After drying of petroleum-ether, the crystals of 2-methyl-4H-3, 1-benzoxazin-4-one was obtained and then it was recrystallized with ethanol. <sup>[8]</sup> M.P 80-82 °C Yield 79 % Rf value 0.61.

done using ethyl acetate: n-hexane (1:1) solvent system. As the synthesis was carried out in reflux condition, the recrystallization was done from ethanol. M.P 149-151 °C Yield 75% Rf value 0.49 IR Spectrum of compound SS-II, C=O Stretching of amide 1645, C=N Stretching 1317, N-N Stretching 1242, C-H Stretching of aromatic 3060, N-H Stretching of primary amine 3315, C-CH<sub>3</sub> Stretching 2959.

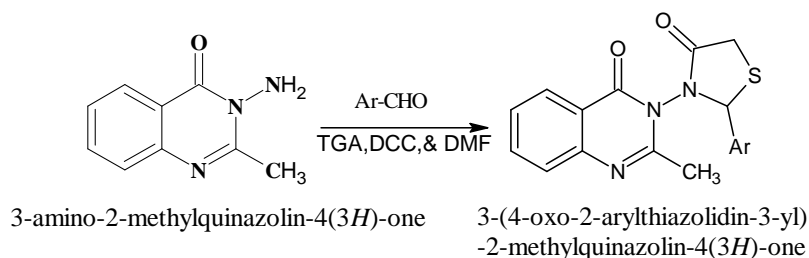
**Synthesis of 3-(4-oxo-2-arylthiazolidin-3-yl)-2-methylquinoxalin-4(3H)-one (General procedure) SS-II-A to SS-II-F**

In 250ml of dry RBF took 0.01 mol. of 3-amino-2-methyl quinoxalin-4(3H)-one and added 0.012 mol. of substituted aromatic aldehydes was stirred under cold condition in 20ml of DMF for 10 minutes. Then 0.02 mol. of thioglycolic acid solution was added and after at 0 °C temperature add 0.01 mol. of N,N-dicyclohexylcarbodiimide (DCC) and Dimethylformamide (DMF) as a solvent. The mixture was stir for 5 hours and filtered the insoluble product to remove. Then by addition of 25 ml of cold water the final product was obtained to the filtrate and then to get pure compound. It was recrystallized from acetone. TLC was done using ethyl acetate: n-hexane (1:1) solvent system. Finally insoluble product separated by filtration 3(2-Substituted aromatic aldehyde)-4-oxothiazolidin-3-yl)-2-methylquinoxalin-4(3H)-one final compound was obtained.

1283.72, C-H Stretching of aromatic 3062.05, C=O Stretching of thiazolidinone 1597.19, C-N Stretching 1442.70, C-S-C Stretching 751.25, C-CH<sub>3</sub> Stretching 2958.34

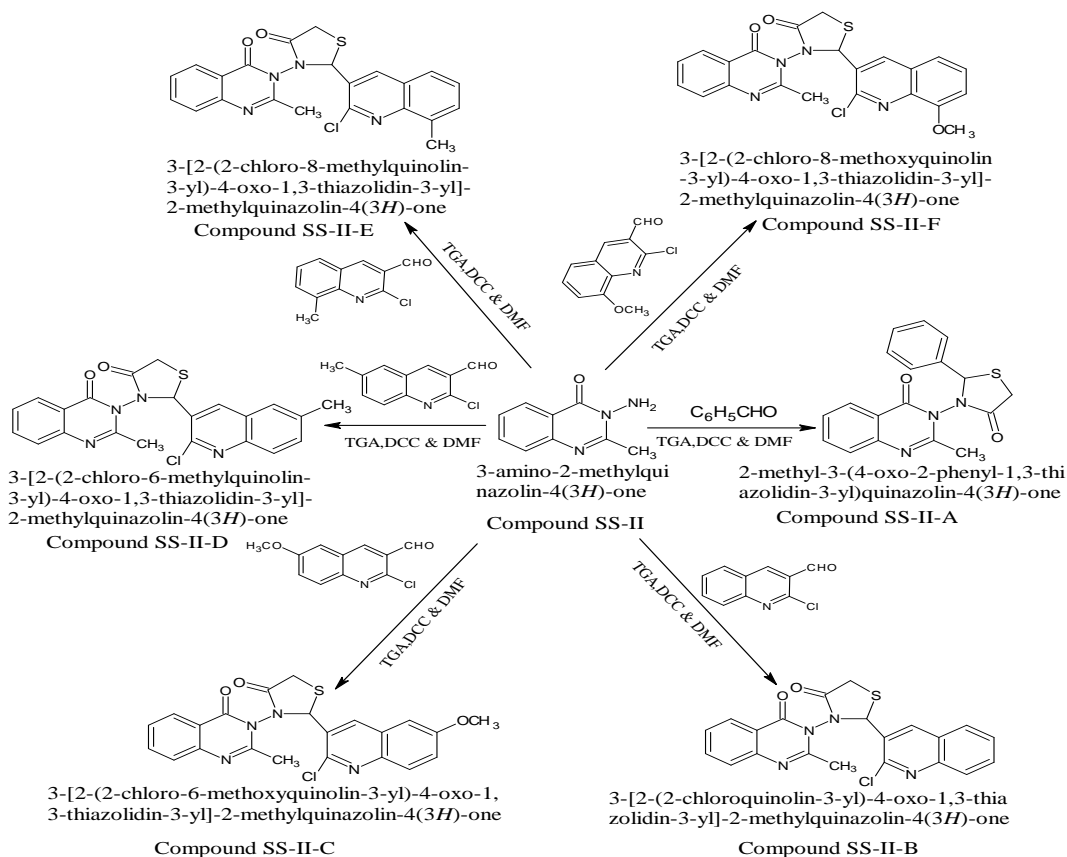
<sup>1</sup>H-NMR Spectrum SS-II-A, m 5H of phenyl on thiazolidinone-7.06-7.17 δ, m 4H of heterocyclic aromatic-7.55-7.59 δ, s 2H of CH<sub>2</sub> thiazolidinone-3.25 δ, s 1H of CH of thiazolidinone-5.95 δ, and s 3H of C-CH<sub>3</sub> - 1.24 δ.

IR Spectrum of compound SS-II-A, C=O Stretching of amide 1652, C=N Stretching 1311.64, N-N Stretching



### SYNTHESIZED DERIVATIVES

Synthesized all derivatives by adopting same above general procedures: synthesis of analogue derivatives are SS-II-A to SS-II-F.

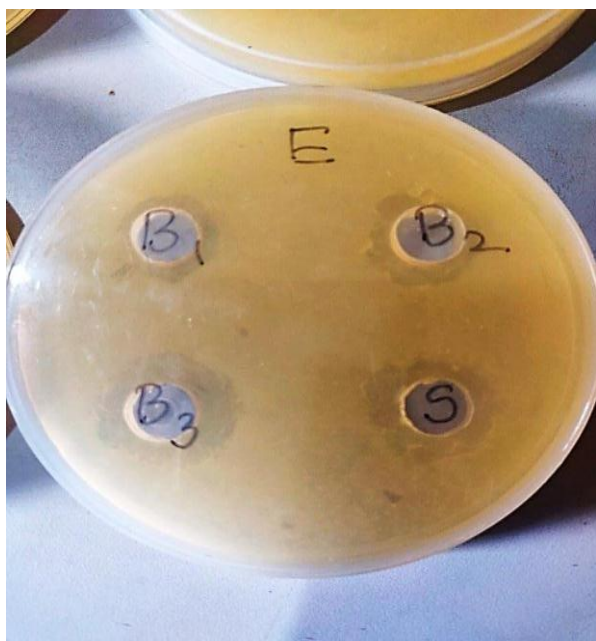


### ANTIBACTERIAL ACTIVITY

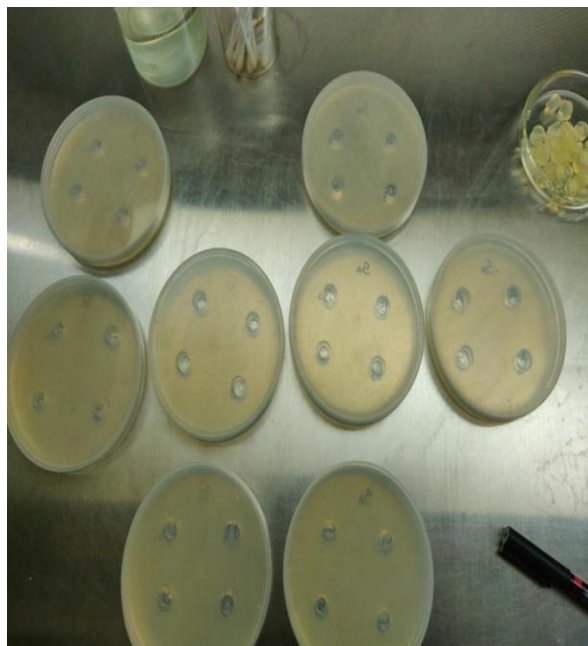
By cup plate method

Table No. 2: Antibacterial Activity of synthesized compounds.

SL. No.	Compound Code	<i>Escherichia coli</i> (gram -ve )			<i>Staphylococcus Aureus</i> (gram +ve )		
		Concentration of derivatives (µg/ml)			Concentration of derivatives (µg/ml)		
		250	500	750	250	500	750
Mean zone of Inhibition (mm)							
1	SS-II-A	12	13	14	10	11	12
2	SS-II-B	12	18	21	11	12	13
3	SS-II-C	11	12	13	09	10	11
4	SS-II-D	12	16	20	10	12	13
5	SS-II-E	09	12	14	09	10	12
6	SS-II-F	10	11	13	08	10	11
Std.	Chloramphenicol (100mcg/ml)	25			15		



**Fig. 1: Inoculation of bacteria and drugs. (Std. and sample) into Agar media.**



**Fig. 2: Zone of inhibition in SS-II-B.**

## RESULTS AND DISCUSSION

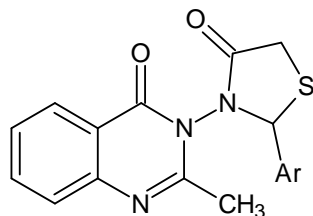
### Synthetic Methods

All synthesized analogues were prepared in noble yield, ranging from 39% to 68%, using current laboratory facilities. All analogues found to be pure when evaluated through TLC and Melting point determination.

### Physical data of the prepared derivatives

### Spectral analysis

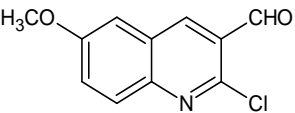
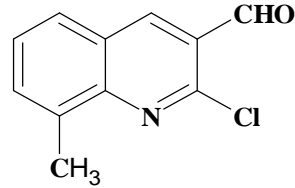
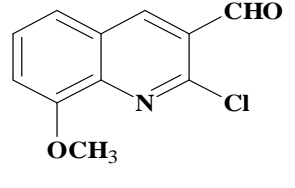
The synthesized compounds were characterized by physical and analytical spectral data like MP, TLC and IR, <sup>1</sup>H-NMR respectively. Based on the observation of spectral data the compounds could be characterization as 2-methylquinoxoliny Thiiazolidines compounds.



**Table 1: Physical data of synthesized derivatives.**

SL. No.	Comp. Code	Ar- (Aromatic aldehyde)	Molecular Formula	M.W (gm.)	M.P (°C)	Rf value	% yield
1	SS-II-A		C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	337.39	213-216 <sup>0</sup> C	0.63	68%
2	SS-II-B		C <sub>21</sub> H <sub>15</sub> ClN <sub>4</sub> O <sub>2</sub> S	422.88	288-291 <sup>0</sup> C	0.81	65%
3	SS-II-C		C <sub>22</sub> H <sub>17</sub> ClN <sub>4</sub> O <sub>2</sub> S	436.91	290-292 <sup>0</sup> C	0.45	55%



4	SS-II-D		$C_{22}H_{17}ClN_4O_3S$	452.91	291-293 <sup>0</sup> C	0.82	66%
5	SS-II-E		$C_{22}H_{17}ClN_4O_2S$	436.91	289-290 <sup>0</sup> C	0.36	39%
6	SS-II-F		$C_{22}H_{17}ClN_4O_3S$	452.91	290-293 <sup>0</sup> C	0.71	45%

TLC Solvent & ratio, Ethyl acetate and n-hexane 1:1  
Recrystallization solvent used was Ethanol.

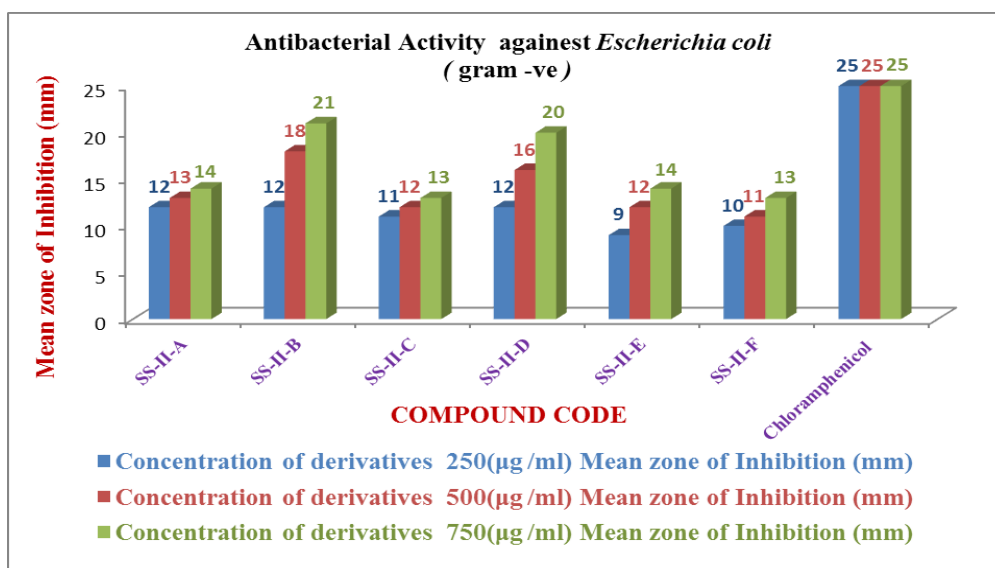
### Biological evaluation

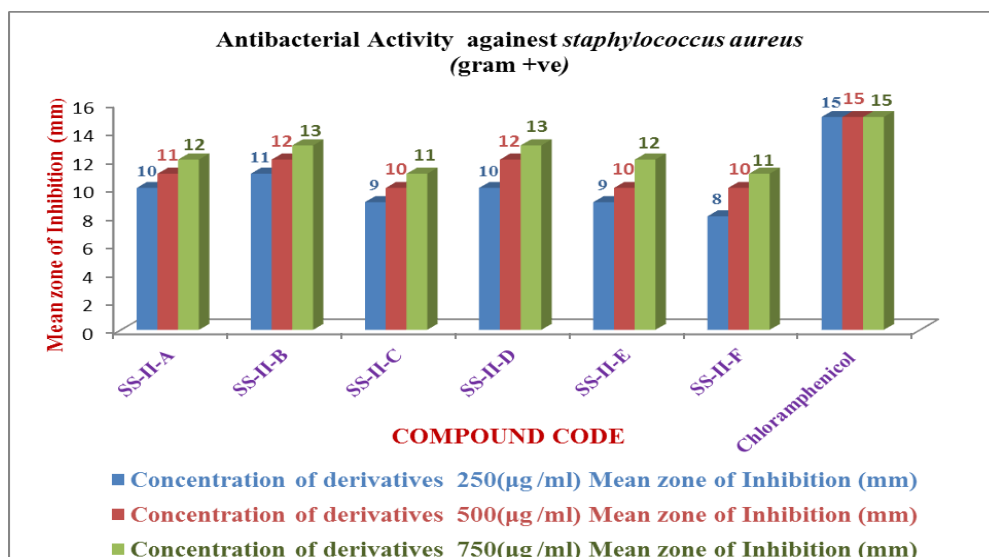
The synthesized compounds were subjected for antibacterial activity against two organisms (Gram '-'ve and Gram '+'ve) *Escherichia coli* and *Staphylococcus Aureus* respectively by using cup plate method.

The results of antibacterial activity synthesized compound 3-[2-(2-chloroquinolin-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-2-methylquinazolin-4(3H)-one (SS-II-B) reveals that moderate to good activity and others showed moderate to weak activity at the concentration of 250 $\mu$ /ml, 500 $\mu$ /ml and 750 $\mu$ /ml compared to

Chloramphenicol as reference drug.

All synthesized compound was exposed to gram negative and gram positive bacterial i.e. *Escherichia coli* and *Staphylococcus Aureus* respectively. The synthesized compound SS-II-B showed active inhibition of growth against *Escherichia coli*. SS-II-B showed noteworthy effects against *Staphylococcus Aureus*, when compare to standard drug Chloramphenicol, which showed zone of inhibition 25 mm and 15 mm against *E. Coli* and *S. Aureus* respectively.





## CONCLUSION

The novel derivatives viz., SS-II-A, SS-II-B, SS-II-C, SS-II-D, SS-II-E, and SS-II-F prepared and SS-II-A derivatives were prepared and analyzed by Infra-red and <sup>1</sup>H-NMR spectroscopy. The antibacterial activity was carried out by cup-plate method. Synthesized compound (SS-II-B) exhibited moderate to good antibacterial activity when compared to standard drug chloramphenicol. Certain derivatives showed noteworthy antibacterial activity. The aim and objectives of the present work on quinazoline had been exactly outlined. The present survey of literature had been prepared on various synthetic methods of quinazoline. It had been followed by a need for the present work and to study their antibacterial attempt had been made as follows.

As expected, quinazoline derivatives exhibited moderately to good active antibacterial activity compared to standard drug. As results showed some synthesized drugs were showed good activity and others with weak antibacterial activity.

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