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SYNTHESIS, CHARACTERIZATION OF 2-METHYLQUINOZOLINYL THIAZOLIDINES FOR ANTI-MICROBIAL ACTIVITY

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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-methylquinozolin-4(3H)-one and substituted aromatic aldehydes using thioglycolic acid, N, N'-dicylohexylcarbodiimide and N, N-dimethyl formamide as solvent. The required 3-amino-2-methylquinozolin-4(3H)-one was obtained from the reaction between 2-amino benzoic acid and acetic anhydride/acetyl chloride. The synthesized compounds containing quinazoline nucleus coupled with thiazolidinone could yield effective biologically active derivatives. Hence the objectives of the research work are as synthesize newer heterocyclic derivatives of Quinazolinones with thiazolidinone, characterize the synthesized compounds using physical data like M.P, TLC and spectroscopic analysed FT-IR, ^{1}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 goodactivity and others showed moderate to weak activity at the concentration of 250 µ/mL, 500 µ/mL and 750 µ/mL compared to Chloramphenicol drug.

Keywords-*Antibacterial activity, Quinazolinones, Thiazolidinone derivatives, 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[1].

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 quinazoline-4(3H)-one[2].

The quinazoline-4(3H)-one, previously named as benzo-1,3-diazine and its derivatives were establish in more than 200 naturally occurring alkaloids. Weddige was first proposed the name of quinazoline (German: Chinazolin).From 1903 still quinazoline synthesized by 3, 4–dihydroquinazoline 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-quinazolone. Quinazoline derivatives (specifically quinazolin-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 synthesizedmany 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[3].

Most of the pharmacologically active organic cycles preferably had nitrogen atom it, either naturally or unnaturally available pharmaceuticals. Between them, quinazoline 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[4].

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[5] as shown in Figure 1.

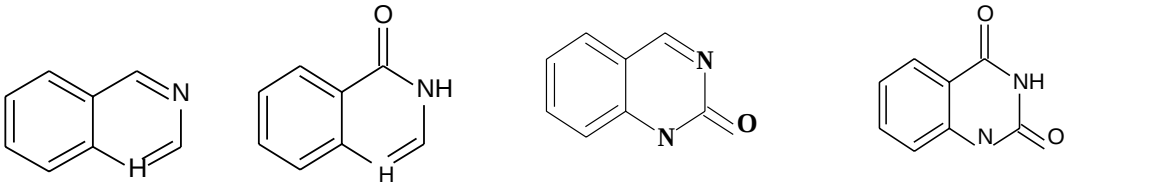


Fig. 1: Quinazolinones

Quinazolinones are commonly solid in nature with high melting point. 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 6th position and the second group attaches to the 8th position. Chemically, they are steady during oxidization, however in critical condition; they can produce 2, 4-dihydroxy quinazoline[5,6].

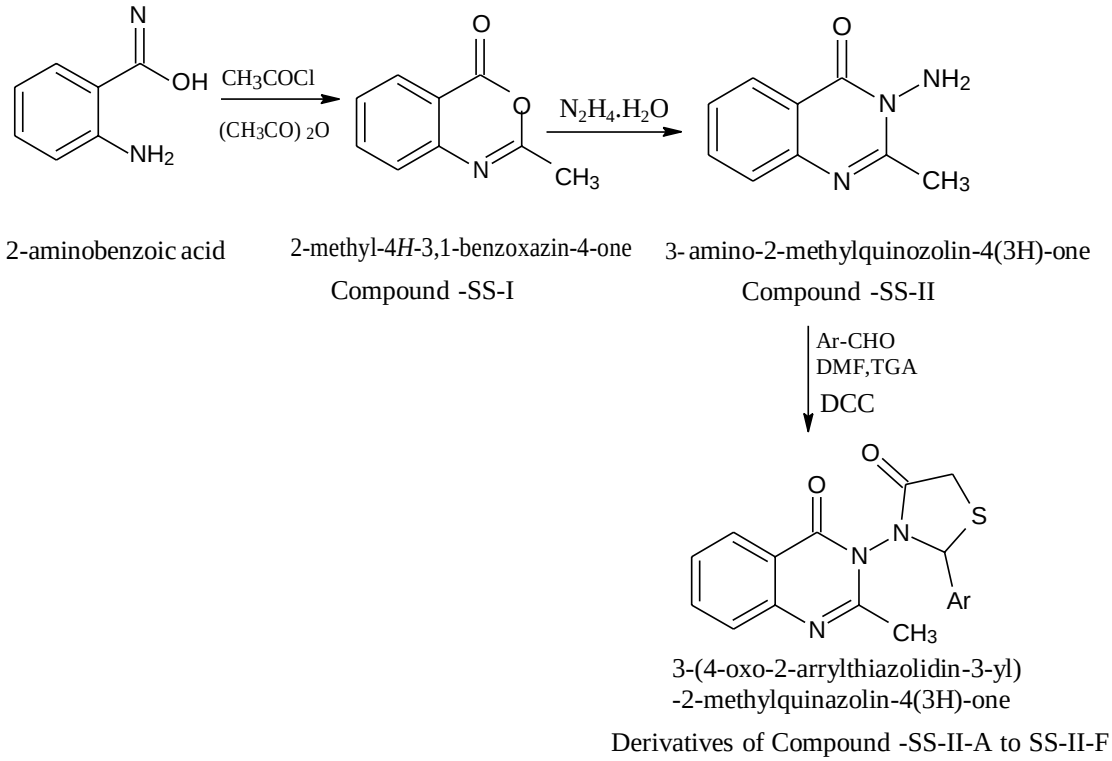
SAR of quinazolin-4-one derivatives

Four times improvement in the activity can be seen by attaching substituent (halogen) at C-6 position. Studies showed that minor substituent on 3rd 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 3rd and 2nd 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[7].

Scheme

For this purpose, the required 3-(4-oxo-2-arrylthiazolidin-3-yl)-2-methylquinazolin-4(3H)-one has been synthesized by using specified scheme (Figure 2).

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'-dicylohexylcarbodiimide (DCC) and N,N-dimethyl formamide (DMF) as solvent.



2-aminobenzoic acid

2-methyl-4*H*-3,1-benzoxazin-4-one
Compound -SS-I

3- amino-2-methylquinozolin-4(3H)-one
Compound -SS-II

3-(4-oxo-2-arrylthiazolidin-3-yl)
-2-methylquinazolin-4(3H)-one

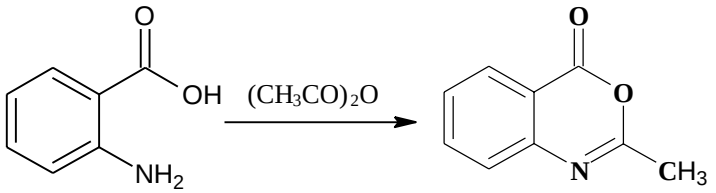
Derivatives of Compound -SS-II-A to SS-II-F

Fig. 2: Synthesis of 3-(4-oxo-2-arrylthiazolidin-3-yl)-2-methylquinazolin-4(3H)-one (Ar-=Benzaldehyde and 2-Chloroquinolin-3-Carbaldehyde)

MATERIALS AND METHODS

Synthesis of intermediate 2-methyl-4H-3,1-benzoxazin-4-one (SS-I)

In 250 mL of RBF took (0.01 mole or 1.37 gm) anthranilic acid (2-amino benzoic acid) to that added 15 mL of acetic anhydride (excess) with porcelain chips. Reflux the solution at 35-40 ℃ for 50-55 min on heating mantle. TLC was done using EA: n-hexane (1:1) solvent system. Then remove 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[8].M.P 80-82℃, Yield79%, Rf value 0.61 (Figure 3).



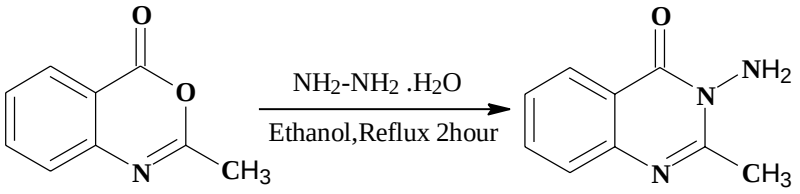
2-aminobenzoic acid

2-methyl-4*H*-3,1-benzoxazin-4-one

Fig. 3: Synthesis of 2-methyl-4*H*-3,1-benzoxazin-4-one

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

To the solution of compound (SS-I) taken 0.01 mol. (1.51 gm) of 2-methyl-4H-3,1-benzoxazin-4-one sample was dissolved in absolute ethanol, and further added to equi-molar quantity of 0.01 mol. (0.51 mL) of 99% hydrazine hydrate then reflex for 3-4 hours and cooled, the product was formed 3-amino-2-methylquinozolin-4(3H)-one then it is filtered out and dried. The TLC was done using ethyl acetate: n-hexane (1:1) solvent system[9] . 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_3 Stretching 2959 (Figure 4).



2-methyl-4*H*-3,1-benzoxazin-4-one 3-amino-2-methylquinazolin-4(3*H*)-one

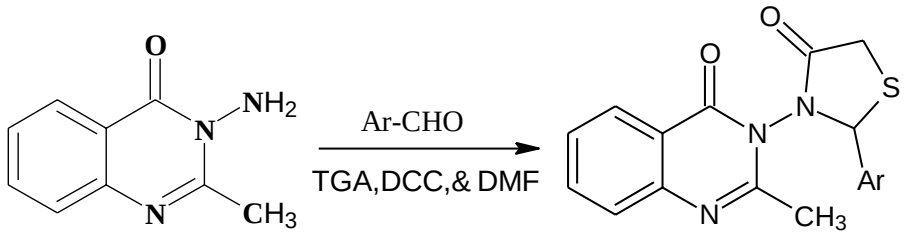
Fig. 4: Synthesis of intermediate 3-amino-2-methyl quinozolin-4(3H)-one

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

In 250 mL of dry RBF took 0.01 mol. of 3-amino-2-methyl quinozolin-4(3H)-one and added 0.012 mol. of substituted aromatic aldehydes was stirred under cold condition in 20 mL 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-dicylohexylcarbodiimide (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[10] . TLC was done usnig ethyl acetate: n-hexane (1:1) solvent system. Finally insoluble product separated by filtration 3(2-Substituted aromatic aldehyde)-4-oxothiazolidin-3-yl)-2-methylquinazolin-4(3H)-one final compound was obtained[11].

IR Spectrum of compound SS-II-A, C=O Stretching of amide 1652, C=N Stretching 1311.64, N-N Stretching 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_3 Stretching 29 58.34

1H-NMR Spectrum SS-II-A, m 5H of phenyl[12,13] on thiazolidinone-7.06-7.17 δ, m 4H of heterocyclic aromatic-7.55-7.59 δ, s 2H of CH_2 thiazolidinone-3.25 δ, s 1H of CH of thiazolidinone-5.95 δ, and s 3H of C-CH_3-1.24 δ (Figure 5).



3-amino-2-methylquinazolin-4(3*H*)-one 3-(4-oxo-2-arylthiazolidin-3-yl) -2-methylquinazolin-4(3*H*)-one

Fig. 5: Synthesis of 3-(4-oxo-2-arylthiazolidin-3-yl)-2-methylquinazolin-4(3*H*)-one

Synthesized derivatives

Synthesized all derivatives by adopting same above general procedures. Synthesis of analogue derivatives is SS-II-A to SS-II-F (Figure 6).

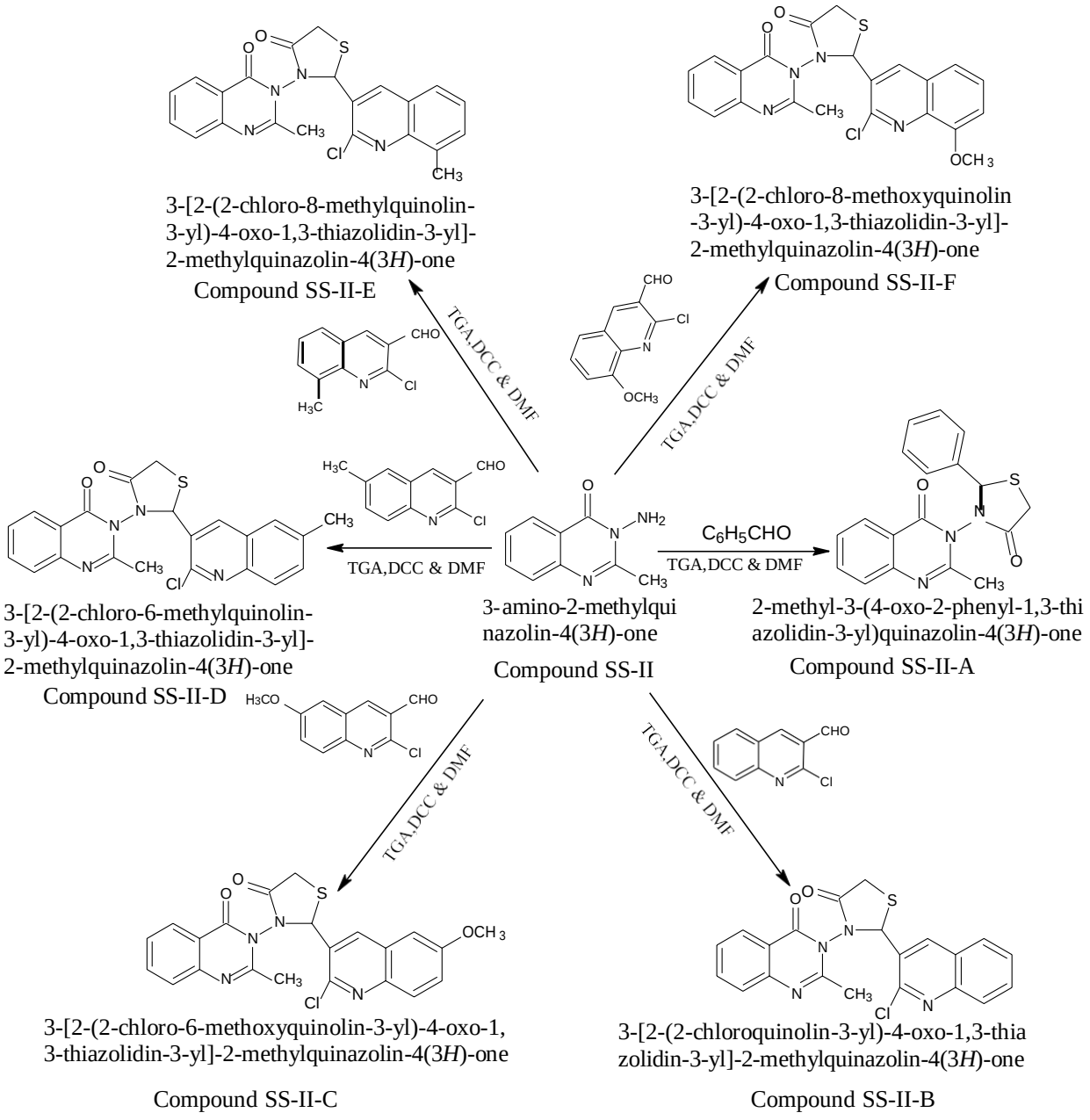


Fig. 6: Synthesis of analogue derivatives are SS-II-A to SS-II-F

Antibacterial activity

Anti-bacterial activity is performed by using Cup-Plate Method[14.] Agar is used as nutrient medium. *Escherichia coli* and *Staphylococcus aureus* are the two different strains of bacteria used in study (Table 1 and Figures 7 and 8).

Table 1: Antibacterial Activity of synthesized compounds

SL No.	Compound code	*Escherichia coli*(gram -ve)			*Staphylococcus aureus*(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	25	25	25	15	15	15

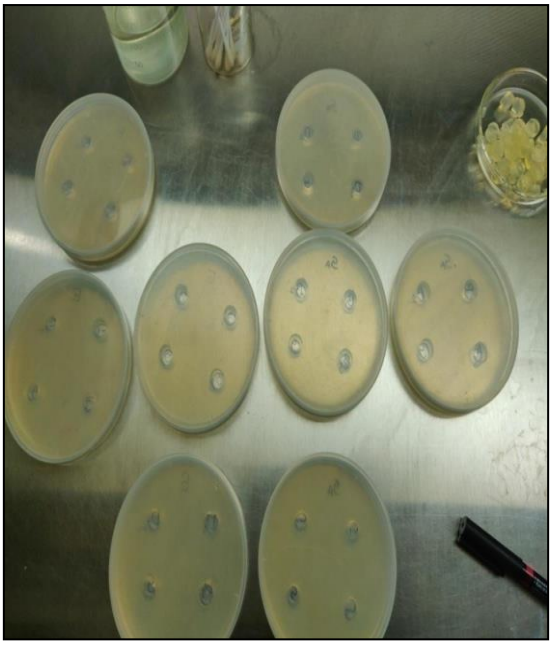


Fig. 7: Inoculation of bacteria and drugs (Std. and sample) into Agar media

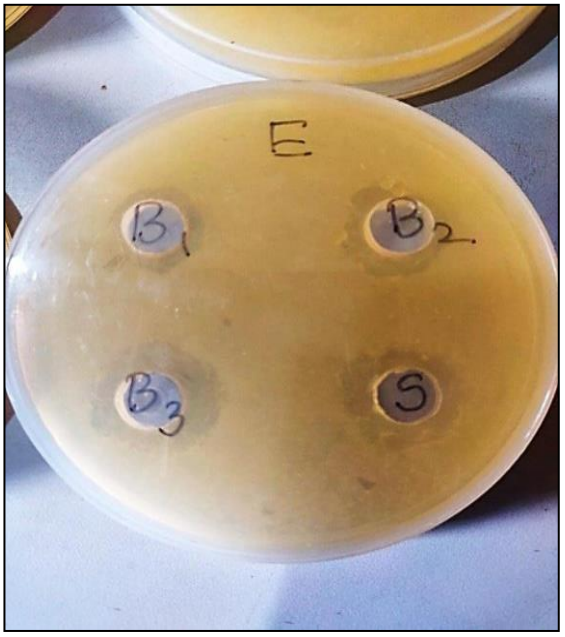


Fig. 8: Zone of inhibition in SS-II-B

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.

Spectral analysis

The synthesized compounds were characterized by physical and analytical spectral data like MP, TLC and IR, ^{1}H-NMR respectively. Based on the observation of spectral data the compounds could be characterization as 2-methylquinozolinyl Thiazolidines compounds.

Physical data of the prepared derivatives

It is shown in Figure 9 and Table 2.

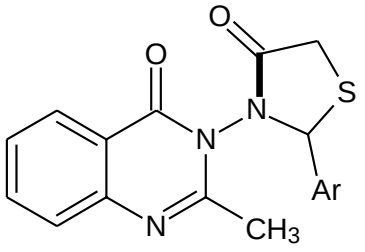
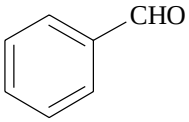
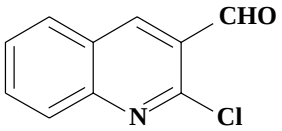
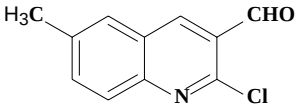
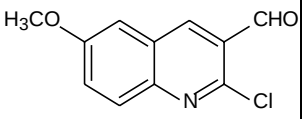
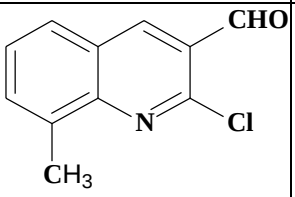
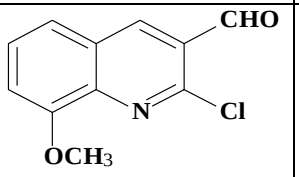


Fig. 9: Chemical Structure of 3-(4-oxo-2-arylthiazolidin-3-yl)-2-methylquinazolin-4(3*H*)-one

Table 2: 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		$C_{18}H_{15}N_3O_2S$	337.39	213-216 °C	0.63	68%
2	SS-II-B		$C_{21}H_{15}ClN_4O_2S$	422.88	288-291 °C	0.81	65%
3	SS-II-C		$C_{22}H_{17}ClN_4O_2S$	436.91	290-292 °C	0.45	55%
4	SS-II-D		$C_{22}H_{17}ClN_4O_3S$	452.91	291-293 °C	0.82	66%
5	SS-II-E		$C_{22}H_{17}ClN_4O_2S$	436.91	289-290 °C	0.36	39%
6	SS-II-F		$C_{22}H_{17}ClN_4O_3S$	452.91	290-293 °C	0.71	45%
Note: TLC Solvent and 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 µ/mL, 500 µ/mL and 750 µ/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 (Figures 10 and 11).

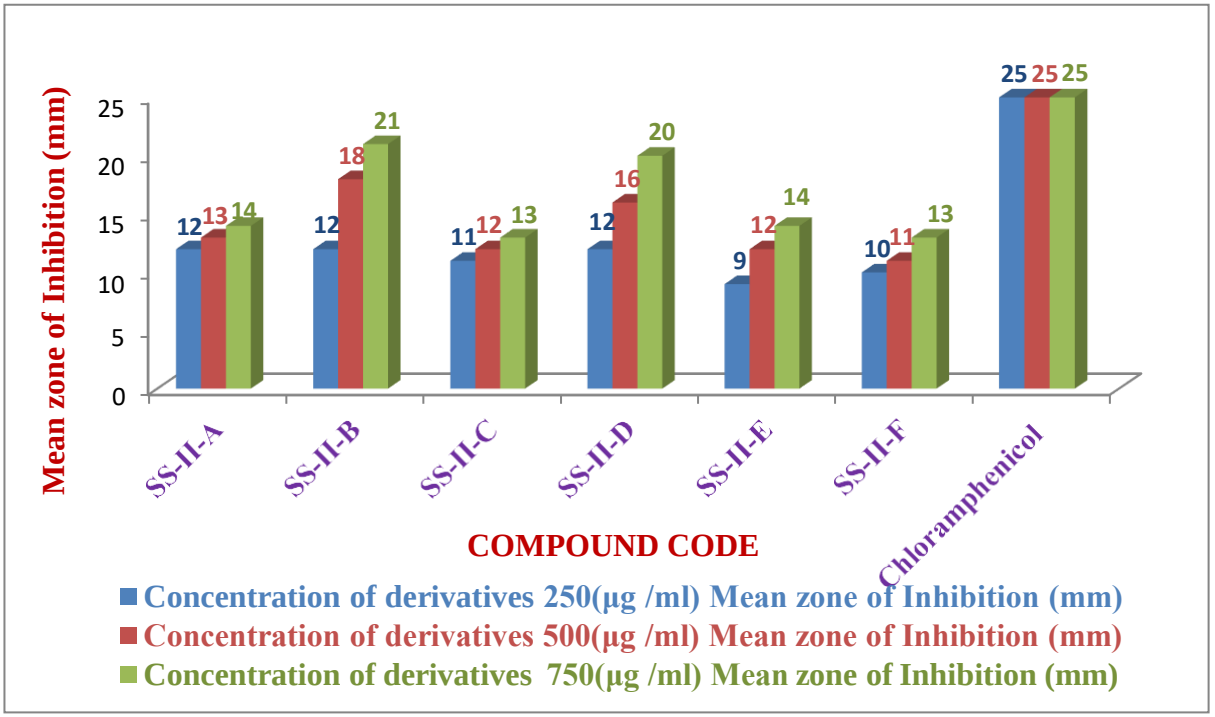


Fig. 10: Anti-bacterial activity against *Escherichia coli* (Gram -ve bacteria)

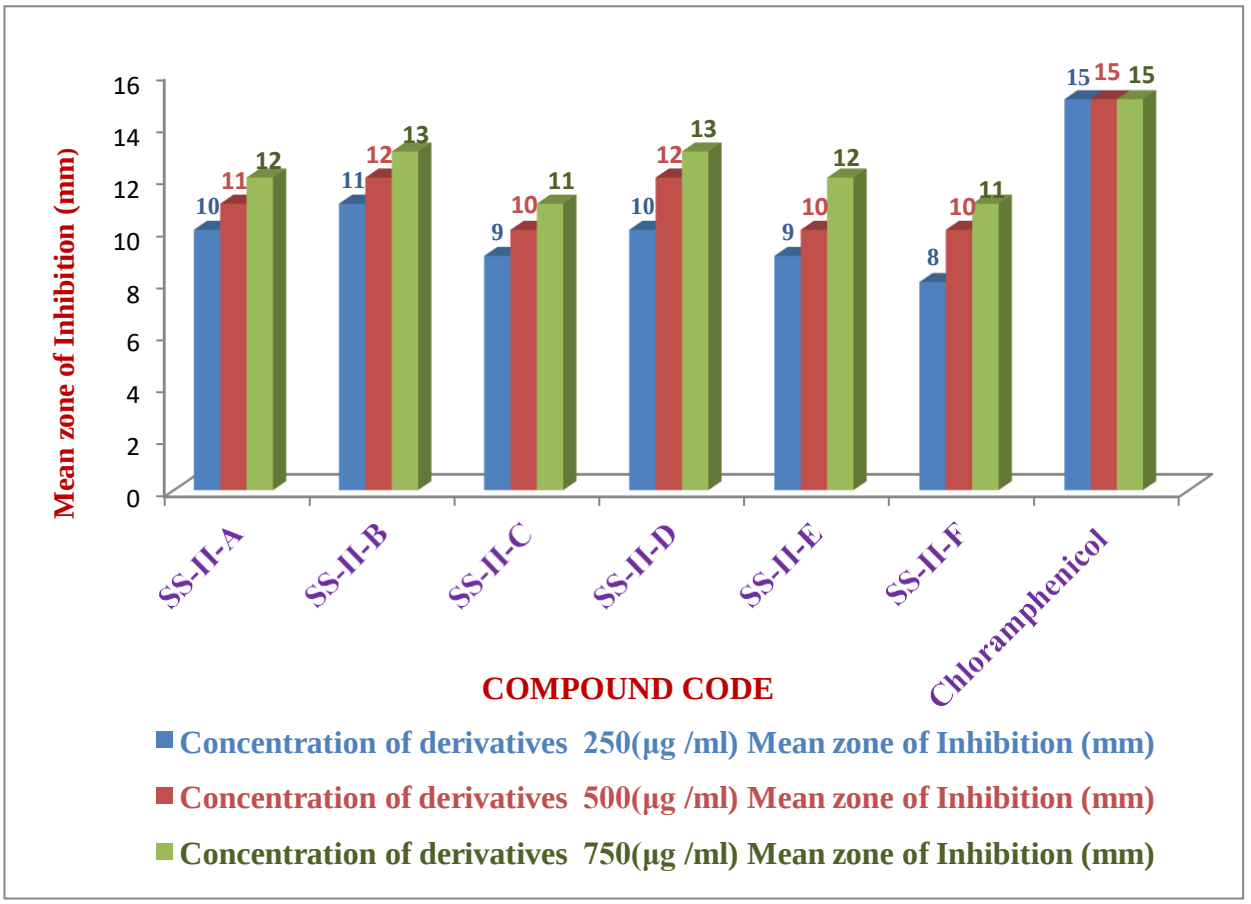


Fig. 11: Anti-bacterial activity against *Staphylococcus aureus* (Gram +ve bacteria)

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 ^{1}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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