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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES OF 3-SUBSTITUTED SCHIFF BASES OF QUINAZOLINE2,4-DIONES

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Keywords:

3-Substituted Schiff base, Quinazoline2,4-diones, Greener method, Conventional method, Characterization, Anti-bacterial study, Disc diffusion method

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ABSTRACT: Objective: 3-Substituted Schiff bases of Quinazolne-2,4-diones belongs to the N-containing heterocyclic compounds. The aim of the present study is to synthesis and characterization of ten novel derivatives of 3-Substituted Schiff bases of Quinazoline2,4-diones and their pharmacological study. In the current course of work the novel Schiff bases of Quinazolne-2,4-diones which are synthesized are evaluated for Anti-bacterial study. **Materials and Methods**: Present research synthesis work of 3-Substituted Schiff bases of Quinazoline 2,4-diones involve two step along with greener method and conventional method of synthesis. 3-Substituted Schiff bases of Quinazoline 2,4-diones have been evaluated for Anti-bacterial study by disc diffusion method. **Result:** The Schiff bases of quinazoline2,4-diones have been synthesized successfully as per the designed scheme of synthesis which includes Greener and conventional method. The greener method found to the more advantageous as compared to the conventional method. These compounds are characterized by various physicochemical and spectral analysis by the FT-IR spectral analysis and 1H-NMR. The Synthesized compounds possessed the antibacterial activity. **Conclusion**: The result of the present research study thus demonstrates the Anti-bacterial activity of newly synthesized 3-Substituted Schiff bases of Quinazolne-2,4-diones.

INTRODUCTION: Heterocyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of modern publications [1]. Heterocycles are an important class of compounds, making up more than half of all known organic compounds. Quinazoline is a fused six-member aromatic ring (a benzene ring and a pyrimidine ring are fused). Quinazoline is a fused bicyclic compound earlier known as benzo-1, 3-diazine [2].

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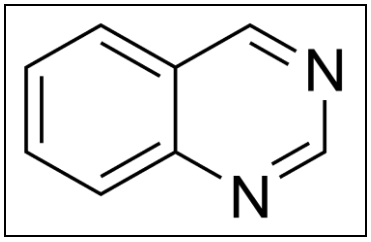


In the current study, one such versatile, heteroaromatic system, Quinazoline2,4-diones in their Schiff base form , has been explored for its biological potential.

A Schiff base is a compound with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group [3]. They are usually formed by condensation of primary amine with the carbonyl compound.

They have occupied an important position in the modern inorganic and organic chemistry [4, 5].

The present synthesis work is involve greener method by microwave synthesis. Microwave synthesis is the new lead which is being used as the source of heating in the organic synthetic reaction [6]. It is the major breakthrough in the synthetic organic chemistry whereas the conventional heating is the inefficient and time-consuming. Protozoa, Bacteria, Fungi and Virus are the pathogenic micro-organisms that cause diseases and disorders [7].

Out of the above stated causes, Bacterial infections are the most prominent reason for the health problems and they are caused by pathogenic Bacteria [8]. Resistance development is the most common drawback for any anti-bacterial agent and this forms the rational or the basis to discover new and novel anti-bacterial agents of either natural or synthetic origin to fight the viable organisms [9].

MATERIALS AND METHODS:

Chemicals and instruments: All chemicals and solvents used were of analytical grade and purchased. The melting points were determined in open capillaries and are uncorrected. Purity of the compounds was checked by TLC having silica as adsorbent using hexane and ethyl acetate (2:1) as mobile phase. IR spectra were recorded FTIR spectrophotometer. 1H NMR spectra were obtained in DMSO.

Materials: All the chemicals and reagents were of analytical grade and used without further purification. The starting material was obtained from Anshul Specialty Molecules Ltd, Mumbai, India as a gift sample and used as such without purification.

Materials for antibacterial test: Mueller Hinton Agar, Nutrient Agar and Nutrient Broth were purchased from Hi Media Laboratories. Bacterial strains used were; *Escherichia coli* and *Bacillus subtilis.*

Experimental Section:

General Scheme of Synthesis:

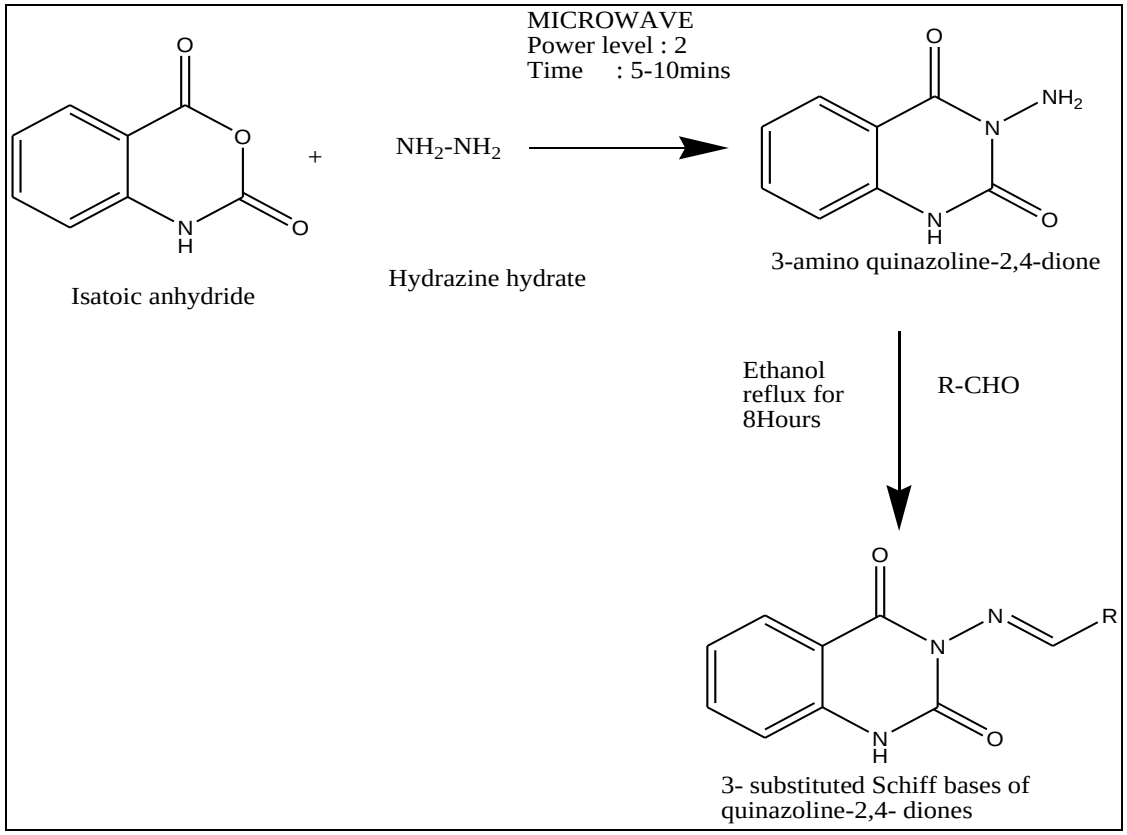


FIG. 1: GENERAL SCHEME OF SYNTHESIS

Scheme for Synthesis Of Schiff's Base:

Step 1: Synthesis of 3-amino quinazoline-2,4-dione

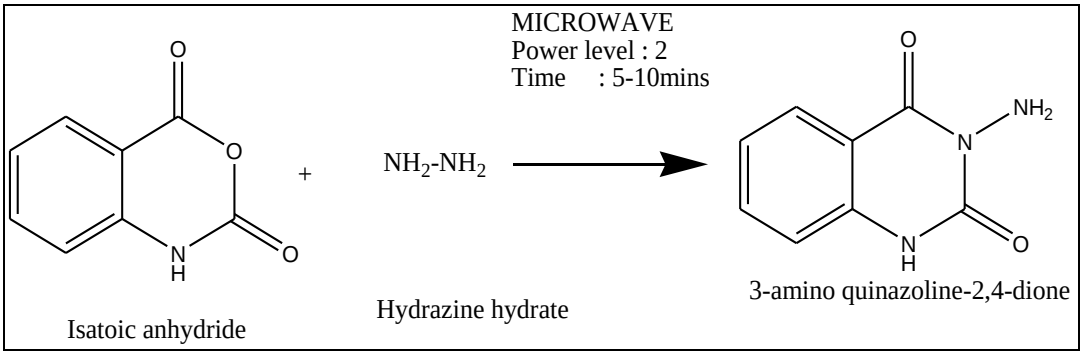


FIG. 2: SYNTHESIS OF 3-AMINO QUINAZOLINE-2,4-DIONE

An equimolar quantity of isatoic anhydride and hydrazine hydrate were taken in a 500ml round bottom flask and kept in Microwave assisted radiation for 5-10mins under Power level 2. The reaction mixture was cooled and poured into Petri plates to get white crystals, which was filtered washed with distilled water and recrystallized from aqueous ethanol [10].

Step 2: General procedure for the synthesis of 3- substituted Schiff bases of quinazoline-2, 4- diones

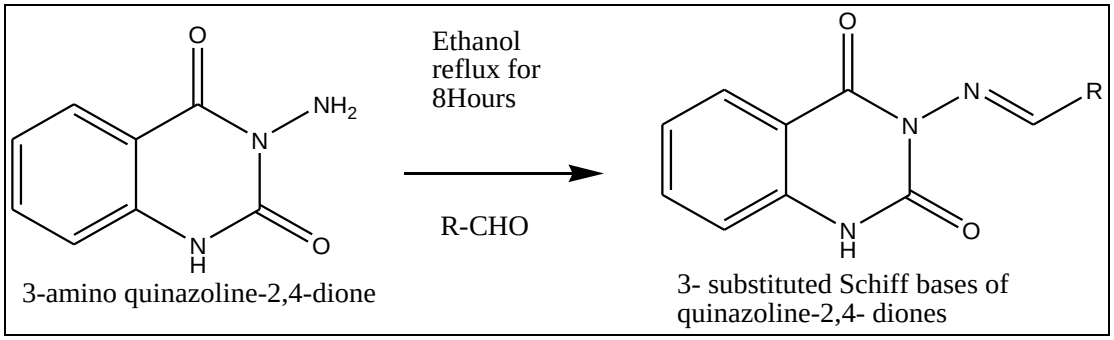


FIG. 3: SYNTHESIS OF 3- SUBSTITUTED SCHIFF BASES OF QUINAZOLINE-2, 4- DIONES

Quinazoline-2,4-dione (0.01mol) was taken in 100ml round bottom flask and ethanol (30ml) was added to dissolve the compound. The substituted aromatic aldehydes (0.01mol) were added and refluxed for about 8hrs [10]. The progress of the reaction was monitored by TLC, The excess of solvent was distilled off, the crystals formed on cooling were collected [10].

General structure for Schiff's bases of quinazoline-2,4- dione

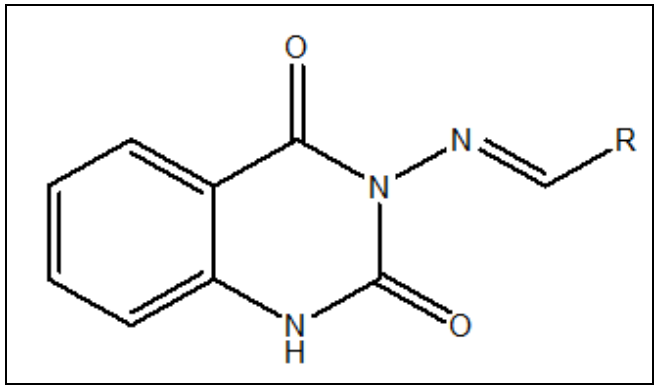
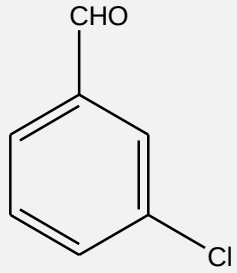
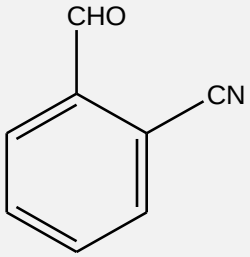
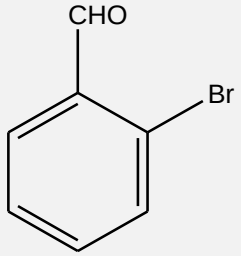
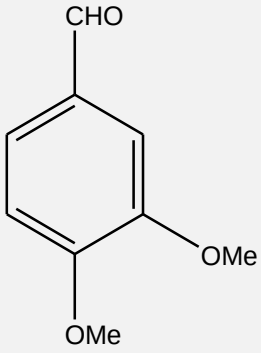
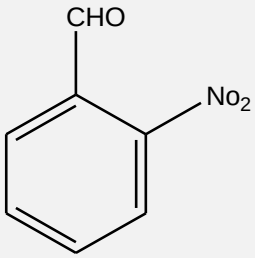
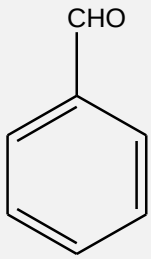
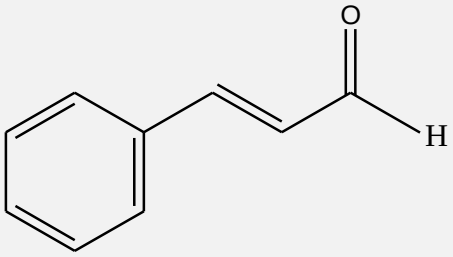
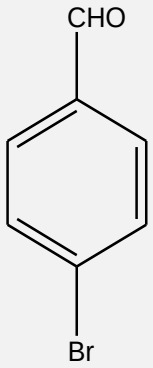
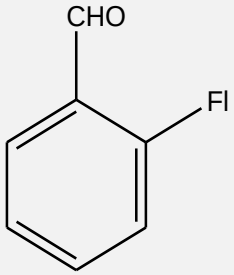
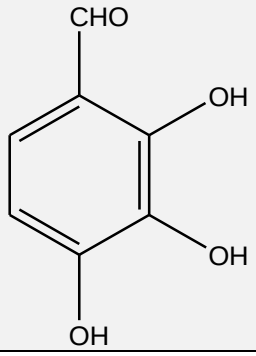


FIG. 4: GENERAL STRUCTURE FOR SCHIFF'S BASES OF QUINAZOLINE-2,4- DIONE

TABLE 1: NAME OF USED ALDEHYDES

Compounds	R	Structure
A	3-Chloro Benzaldehyde	
B	2-Cyano Benzaldehyde	
C	2-Bromo Benzaldehyde	
D	3,4-dimethoxy Benzaldehyde	
E	2-Nitro Benzaldehyde	
F	Benzaldehyde	

G	Cinnamaldehyde	
H	4-Bromo Benzaldehyde	
I	2-Fluro Benzaldehyde	
J	2,3,4-TrihydroxyBenzaldehyde	

The newly synthesized 3-Substituted Schiff bases of Quinazoline2,4-diones in this research work are as follow in **Table 2**.

TABLE 2: THE NEWLY SYNTHESIZED 3-SUBSTITUTED SCHIFF BASES OF QUINAZOLINE2,4-DIONES IN THIS RESEARCH WORK

Compounds	Name of the compounds
1	3-[(3-Chlorophenyl)methylene] aminoquinazoline-2,4(1H,3H)-dione
2	3-[(2-Cyanophenyl)methylene] aminoquinazoline-2,4(1H,3H)-dione
3	3-[(2-Bromo phenyl)methylene] aminoquinazoline-2,4(1H,3H)-dione
4	3-[(3,4-dimethoxy phenyl)methylene] aminoquinazoline-2,4(1H,3H)-dione
5	3-[(2-Bromo phenyl)methylene] aminoquinazoline-2,4(1H,3H)-dione
6	3-[(3,4-dimethoxy phenyl)methylene] aminoquinazoline-2,4(1H,3H)-dione
7	3-((E)-3-phenylallylideneamino)quinazoline-2,3(1H,3H)-dione.
8	3-[(4-Bromophenyl)methylene] aminoquinazoline-2,4(1H,3H)-dione
9	3-[(2-Flurophenyl)methylene] aminoquinazoline-2,4(1H,3H)-dione
10	3-[(2,3,4-Trihydroxy phenyl)methylene] aminoquinazoline-2,4(1H,3H)-dione

Antibacterial Assay: The effect of various Schiff bases on the bacterial strains was assayed by Disc diffusion method and on the fungal strains by Agar well diffusion method [11].

Sterilization: Sterilization was achieved by autoclaving at 394K and 100 kPa for 15 minutes.

Principle: The method used to study the anti-bacterial activity is Disc Diffusion method. In this well-known procedure, agar plates are inoculated with a standardized inoculums of the test microorganism. Then, filter paper discs (about 6 mm in diameter), containing the test compound at a desired concentration, are placed on the agar surface. The Petri dishes are incubated under suitable conditions [12, 13]. Generally, antimicrobial agent diffuses into the agar and inhibits germination and growth of the test microorganism and then the diameters of inhibition growth zones are measured.

Disk-diffusion assay offers many advantages over other methods: simplicity, low cost, the ability to test enormous numbers of microorganisms and antimicrobial agents, and the ease to interpret results provided.

Reagents:

1. **Muller Hinton Agar Medium (1 L):** The medium was prepared by dissolving 33.9 g of the commercially available Muller Hinton Agar Medium (HiMedia) in 1000ml of distilled water. The dissolved medium was autoclaved at 15 lbs pressure at 121°C for 15 minutes. The autoclaved medium was mixed well and poured onto 100mm petriplates (25-30ml/plate) while still molten[14-16].
2. **Nutrient broth (1L):** One litre of nutrient broth was prepared by dissolving 13 g of commercially available nutrient medium (HiMedia) in 1000ml distilled water and boiled to dissolve the medium completely [17]. The medium was dispensed as desired and sterilized by autoclaving at 15 lbs pressure (121ºC) for 15 minutes.

Procedure: Muller Hinton Agar plates were prepared and the test microorganisms were inoculated by the spread plate method. Filter paper discs approximately 6mm in diameter were soaked and placed in the previously prepared agar plates. Each disc was pressed down to ensure complete contact with the agar surface and distributed evenly so that they are no closer than 24 mm from each other [18-20]. The agar plates were then incubated at 37ºC. After 48hrs of incubation, each plate was examined. The resulting zones of inhibition were uniformly circular with a confluent lawn of growth. The diameters of the zones of complete inhibition were measured, including the diameter of the disc.

RESULT AND DISCUSSIONS: Physical characteristic parameter of final synthesised compounds were the synthesised compounds are produce in good yields described in **Table 3.**

The FT-IR spectra of final compounds shows various functional groups which are illustrated in **Table 4,** the band in a range 1730-1760cm^{-1} for (-C=O) group, the N-N Stretch was noted at a range of 1500cm^{-1} value, –NH group present at 3700cm^{-1} value, aromatic band in a range of 700-850cm^{-1}.

^{1}H-NMR of the final compounds are illustrated in Table 5 were the in ppm with no of 'H' & splitting patterns are represented for protons present in the compounds.

Anti-bacterial studies: Antibacterial study was done by using the disc diffusion method of synthesised compounds. The antibacterial activity was tested against the gram positive (*B. subtilis*) & gram negative (*E. coli*) strains. The Zone of inhibition diameter values were determined and tabulated in **Table 6.**

Physical Characteristic Data:

TABLE 3: PHYSICAL CHARACTERISTIC

Compound	Colour	Melting point	Rf value	Percent Yield (in %)
A	Brown	178ºC	0.65	86
B	Buff	210ºC	0.7	89
C	Off white	170ºC	0.72	86
D	Off white	215ºC	0.55	80
E	Yellow	176ºC	0.5	87
F	Off white	155ºC	0.77	87
G	Yellow	182ºC	0.79	86
H	Buff	180ºC	0.82	86
I	Brown	175ºC	0.81	89
J	Yellow	186ºC	0.80	87

[*Mobile Phase Solvents: n-hexane: ethyl acetate (3: 2)

TABLE 4: FT-IR SPECTRAL DATA (FREQUENCY VALUES IN CM^{-1}) FOR FINAL COMPOUNDS

Compound No.	ν (-C=O)	ν (-NH-)	ν Amide (-C=O)	ν (-N-N)	ν (Aromatic)
A	1743	3724	1639	1510	750
B	1740	3729	1645	1517	742
C	1748	3734	1630	1514	811
D	1743	3729	1635	1520	810
E	1746	3730	1643	1521	750
F	1752	3726	1645	1515	803
G	1762	3717	1639	1514	827
H	1737	3747	1630	1510	738
I	1745	3728	1629	1507	682
J	1756	3734	1649	1517	678

^{1}H-NMR Data:

TABLE 5: ^{1}H- NMR SPECTRA FOR FINAL COMPOUND

Compound No.	^{1}H- NMR (δppm; No. of H; splitting pattern)
A	δ=6.5(1H,s,-NH); δ=6.8(1H,m,ArH); δ=7.4(1H,m,ArH); δ=7.6(2H,m,ArH); δ=7.3(2H,m,ArH); δ=8.0(1H,m,-N=C-H).
B	δ=6.3(1H,s,-NH); δ=7.0(1H,m,ArH); δ=7.2(1H,m,ArH); δ=7.4(2H,m,ArH); δ=7.8(2H,m,ArH); δ=8.5(1H,m,-N=C-H).
C	δ=6(1H,s,-NH); δ=6.7(1H,m,ArH); δ=7.3(1H,m,ArH); δ=7.9(2H,m,ArH); δ=7.2(2H,m,ArH); δ=8.2(1H,m,-N=C-H).
D	δ=6.1(1H,s,-NH); δ=6.3(1H,m,ArH); δ=7.5(1H,m,ArH); δ=7.7(2H,m,ArH); δ=7.2(2H,m,ArH); δ=8.0(1H,m,-N=C-H).
E	δ=6.4(1H,s,-NH); δ=6.4(1H,m,ArH); δ=7.1(1H,m,ArH); δ=7.8(2H,m,ArH); δ=7.2(2H,m,ArH); δ=8.4(1H,m,-N=C-H).
F	δ=6.2(1H,s,-NH); δ=6.5(1H,m,ArH); δ=7.8(1H,m,ArH); δ=7.2(2H,m,ArH); δ=7.7(2H,m,ArH); δ=8.5(1H,m,-N=C-H).
G	δ=6.5(1H,s,-NH); δ=6.6(1H,m,ArH); δ=7.4(1H,m,ArH); δ=7.7(2H,m,ArH); δ=7.6(2H,m,ArH); δ=8.2(1H,m,-N=C-H).
H	δ=6.6(1H,s,-NH); δ=6.7(1H,m,ArH); δ=7.1(1H,m,ArH); δ=7.2(2H,m,ArH); δ=7.1(2H,m,ArH); δ=7.4(1H,m,-N=C-H).
I	δ=6.6(1H,s,-NH); δ=6.8(1H,m,ArH); δ=7.4(1H,m,ArH); δ=7.7(2H,m,ArH); δ=7.3(2H,m,ArH); δ=8.6(1H,m,-N=C-H).
J	δ=6.5(1H,s,-NH); δ=6.8(1H,m,ArH); δ=7.5(1H,m,ArH); δ=7.7(2H,m,ArH); δ=7.2(2H,m,ArH); δ=8.3(1H,m,-N=C-H).

[*δ values in ppm; s=singlet; m=multiplte; d=doublet; t=triplet; q=quartet; Ar=Aromatic

Antibacterial Activity: The difference in anti-bacterial activities of the investigated Schiff bases and their parent drugs were studied by the disc diffusion technique. The zone of inhibition was measured against *Bacillus Subtilis* (Gram positive) and *E. coli* (Gram negative) and the results are presented. The cursory view of the data indicates the following trend in antibacterial activity of the substances under investigation A clearing zone around the disc indicates the inhibitory activity of the compound on the organism.

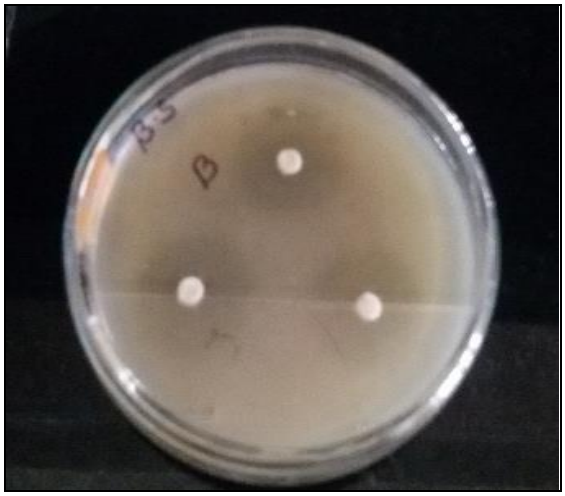
TABLE 6: THE ANTIBACTERIAL ACTIVITY (ZONE OF INHIBITION) (MM) DATA

Compounds	Inhibition zone (mm)					
	Bascillus Subtilis(Gram positive)			*E. coli* (Gram negative)		
	25µg/ml	50 µg/ml	100 µg/ml	25µg/ml	50 µg/ml	100 µg/ml
Standard	1	13	15	12	14	15
1	2	22	23	22	25	26
2	18	19	24	20	22	23
3	20	22	26	22	25	26
4	18	20	23	2	22	24
5	16	20	22	20	23	24
6	20	23	25	21	22	24
7	24	26	28	22	24	26

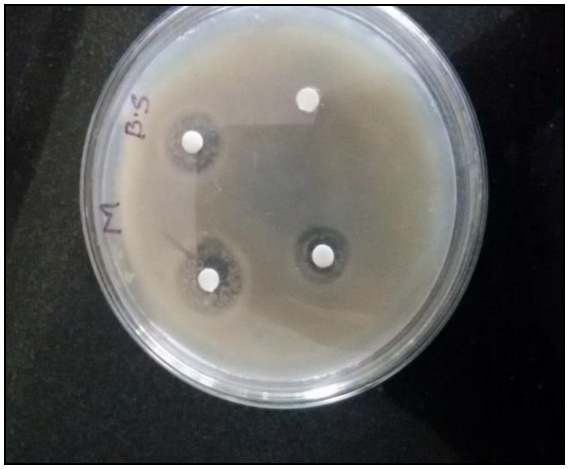
8	2	17	25	20	22	20
9	19	22	26	8	11	26
10	22	23	27	20	22	24
Control	-	-	-	-	-	-

Zone of inhibition of Compound A ,B and standard against *Bacillus Subtilis:*

Zone of inhibition of A

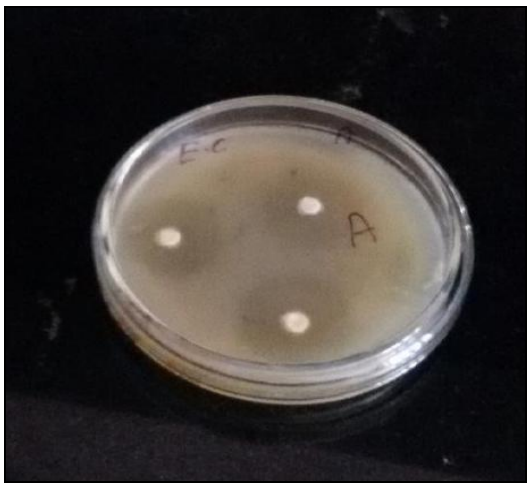


Zone of inhibition of B



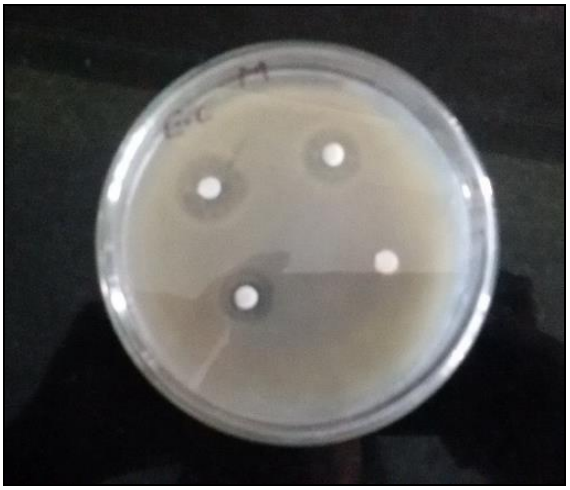
Zone of inhibition of Standard against *Bascillus Subtilis* (M)

Zone of inhibition of Compound A ,B and standard against *E.coli:*



Zone of inhibition of A

Zone of inhibition of B



Zone of inhibition of Standard against *E. coli* (M)

FIG. 5: ZONE OF INHIBITION OF SYNTHESIZED COMPOUNDS AGAINST *BASCILLUS SUBTILIS* AND *E. COLI*
[*values in **mm** for Zone of inhibition]

CONCLUSION: This research work includes chemistry of Schiff bases which have been synthesized using different aromatic aldehydes and study of their biological activity.

The Schiff bases of quinazoline 2,4-diones have been synthesized successfully as per the designed scheme of synthesis which includes Greener and conventional method.

Greener synthesis method i.e Microwave synthesis is the new lead which is being used as the source of heating in the organic synthetic reaction. It is the major breakthrough in the synthetic organic chemistry whereas the conventional heating is the inefficient and time-consuming. These compounds are characterized by various physicochemical and spectral analyses by the FT-IR spectral analysis and 1H-NMR.

The Schiff bases possessed the antibacterial activity. The anti-bacterial activities of the investigated Schiff bases were studied by the disc diffusion technique.

The zone of inhibition was measured against *Bascillus Subtilis* (Gram positive) and *E. coli* (Gram negative) and the results are presented. Results revealed that most of the compounds exhibit antibacterial.

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CONFLICT OF INTEREST: The authors do not have any conflict of interest.

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