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Synthesis and Evaluation of Aldehyde Derivatives of Sulfonyl Chloride Quinoxaline

Goyal Rakesh [1]*, Sharma Mukesh [1], Ahuja Dharmendra [2], Jain Anurekha [2]

[1] Research Scholar, Faculty of Pharmaceutical Sciences Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India

[2] Professor, Faculty of Pharmaceutical Sciences Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India

ABSTRACT

In pyrazine mesomeric interaction between the protonated & neutral nitrogen atoms probably destabilizes the cation.N, N'-diprotonation is very easier for pyrazine Synthesis of 2, 3-diphenylquinoxaline by phenylene-diamine in 16 ml of rectified spirit was added & combine solution was warm in water bath for 30 min. added water until slight colorless persist & allow to cool recrystallize the product in ethanol. Synthesis of 2, 3-diphenylquinoxaline 7-sulfonylchloride (R) using chlorosulfonic acid under ice-cold condition, then Synthesis of 2-hydroxyphenyl-2,3-diphenylquinoxaline-7-sulphonate(R1) throughresorcinol with 3ml pyridine & sulphonyl chloride derivative, Synthesis of 2-formylphenyl-2,3-diphenylquinoxaline-7-sulphonate(R7)obtained by reaction of salicylaldehyde with pyridine & sulphonyl chloride derivative then Synthesis of 3-formylphenyl-2,3-diphenylquinoxaline-7-sulphonate(R9) obtained by heating on water bath mixture of3-hydroxybenzaldehyde with pyridine & sulphonyl chloride, Synthesized quinoxaline derivatives were subjected to antimicrobial susceptibility testing by well diffusion method against gram positive (*S.aureus*, 2079) and gram negative bacteria (*E. coli*, 2685). The results of quinoxaline derivatives in terms of zone of inhibition recorded. MIC of quinoxaline derivative was determined by tube micro dilution technique against *S. aureus* and *E. coli.* The turbidity was measured by UV at about 420 nm. Hydrogen peroxide scavenging activity and 1, 1 diphenyl 2, picryl hydrazyl Method (DPPH) calculated and Most of the derivatives have shown comparable antioxidant activity in relation to standard Ascorbic acid and DPPH.

Keywords: QSAR, Sulfonyl Chloride Quinoxaline, Ant-microbial, Antioxidant

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***Address for Correspondence:**

Goyal Rakesh, Research Scholar, Faculty of Pharmaceutical Sciences Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India

INTRODUCTION:

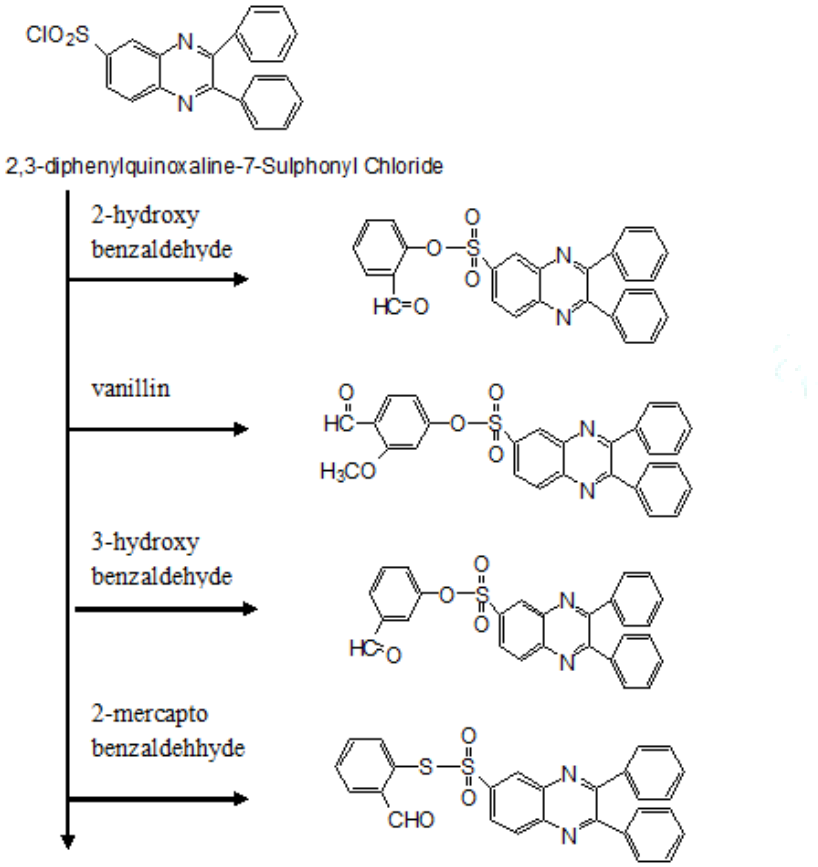
Heterocyclic chemistry To provide an understanding of principles of the medicinal chemistry, it is necessary to consider the physicochemical properties used to develop new pharmacologically active compounds and their mechanism of action, the drug's metabolism including possible biological activities of the metabolites, the importance of stereochemistry in drug design, and the methods used to determine what 'space' a drug occupies. All of the principles are based on the fundamental organic chemistry, physical chemistry and biochemistry. The diazines are essentially monobasic substances and considerably weaker as bases than pyridine. In pyrazine mesomeric interaction between the protonated & neutral nitrogen atoms probably destabilizes the cation.N, N'-diprotonation is very easier for pyrazine.[4] Chlorination of 2-methyl pyrazine occurs under such mild condition that it is almost certain that an addition / elimination sequence is involved, rather than a classical aromatic electrophilic substitution The diazines are generally resistant to oxidative attack at ring carbons through alkaline oxidizing agent can bring about degradation via intermediate produced by initial nucleophilic addition. Alkyl substituents fused aromatic rings can be oxidized to carboxylic acid residue leaving the heterocyclic ring untouched. Pyrazine N-oxide can be readily prepared by oxidation of parent heterocycle. Pyrazine N-oxide behaves like their pyridine counterparts in electrophilic substitution & nucleophilic displacement reaction involving loss of the oxygen.

The broth and agar dilution methods are to determine the lowest concentration of the assayed antimicrobial that inhibits the growth of the bacterium being tested (MIC, usually expressed in mg/ml or mg/liter). However, the MIC does not always represent an absolute value. The 'true' MIC is a point between the lowest test concentration that inhibits the growth of the bacterium and the next lower test concentration. Therefore, MIC determinations performed using a dilution series may be considered to have an inherent

variation of one dilution. Antimicrobial ranges should encompass both the interpretive criteria (susceptible, intermediate and resistant) for a specific bacterium/antibiotic combination and appropriate quality control reference organisms. Antimicrobial susceptibility dilution methods appear to be more reproducible and quantitative than agar disk diffusion. However, antibiotics are usually tested in doubling dilutions, which can produce inexact MIC data. Thus, Asuncion Burguete *et al.*, synthesized novel ring substituted 3-phenyl -1- (1, 4-di-N-oxide quinoxaline-2-yl) -2-propen-1-one derivatives and of their 4, 5-dihydro-(1H)-pyrazole analogues. Synthesized compounds were evaluated for anti-inflammatory and antioxidant activity. The tested compounds inhibit the carrageenan-induced rat paw edema (4.5-56.1%) and present important scavenging activities.[i] .M.Ali *et.al,* synthesized some novel quinoxalinone derivative and evaluated for antimicrobial activity. Condensation of 4-benzoyl-1, 2-phenylenediamine with sodium pyruvate in acetic acid furnished two product which were identified as 6-benzoyl and 7-benzoyl-3-methyl-2(1H) quinoxalinone.[ii] Alireza Hasaninejad, Abdolkarim Zare, *et.al,* reported Bentonite Clay K-10 as an Efficient Reagent for the Synthesis of Quinoxaline Derivatives at Room Temperature. Bentonite clay K-10 acts as an efficient reagent for the preparation of quinoxaline derivatives via the condensation of aryl and alkyl 1,2-diamines with α-diketones in ethyl alcohol as a green media at room temperature.[iii]

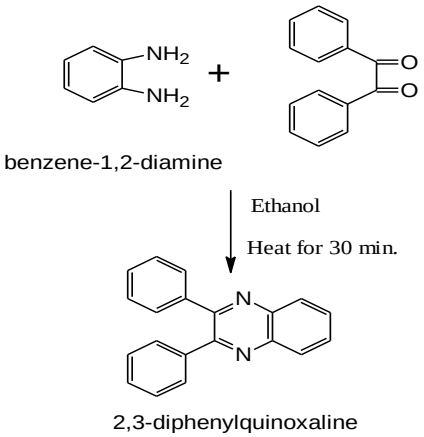
MATERIALS AND METHODS:

Derivatives of 2,3-diphenylquinoxaline-7-sulphonyl chloride with Aldehydes.



Experimental Methods:

Synthesis of 2, 3-diphenylquinoxaline



To warm solution of 4.2 gram of benzyl in 16 ml of rectified spirit, the solution of 2.2ml of o-phelyne diamine in 16 ml of rectified spirit was added & combine solution was warm in water wath for 30 min. added water until slight colourless persist & allow to cool. Filter & recrystallize the product in ethanol.

Synthesis of 2, 3-diphenylquinoxaline 7-sulfonylchloride (R)

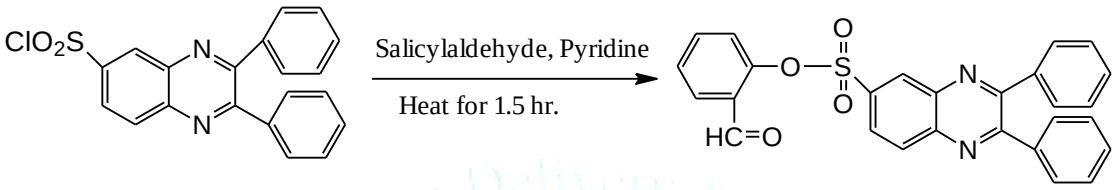
0.01 moles of 2, 3 diphenylquinoxaline (2.82g) was treated with Chlorosulfonic acid under ice-cold condition in fuming cupboard with constant stirring. The stirring was continued until the reaction reaches room temperature. The resultant mixture was poured into water to give sulfonylchloride derivative.[1]

Synthesis of phenol derivatives of 2, 3-diphenylquinoxaline-7-sulphonyl chloride:

Synthesis of 2-hydroxyphenyl-2,3-diphenylquinoxaline-7-sulphonate(R1)

Mix 1.17gm of resorcinol with 3ml pyridine & 2.34 gm of sulphonyl chloride derivative &heat on water bath for 1 hr. pour into 25 ml of cold water & stir until the oil solidifies , filter wash with cold dil HCl to remove pyridine and cold dil NaOH to remove any phenol present &them with cold water, recrystallized from methanol or ethanol.

Synthesis of 2-formylphenyl-2,3-diphenylquinoxaline-7-sulphonate(R7)

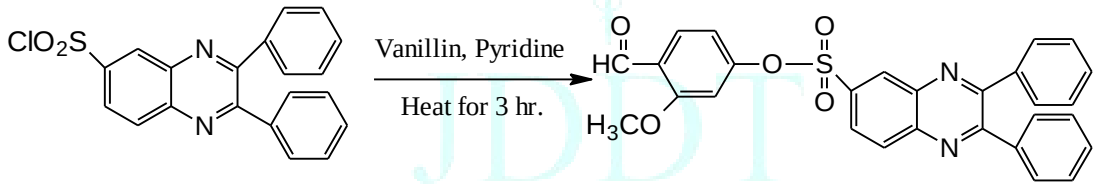


2,3-diphenylquinoxaline--7-sulphonyl chloride

2-formylphenyl-2,3-diphenyl-quinoxaline-7-sulphonate

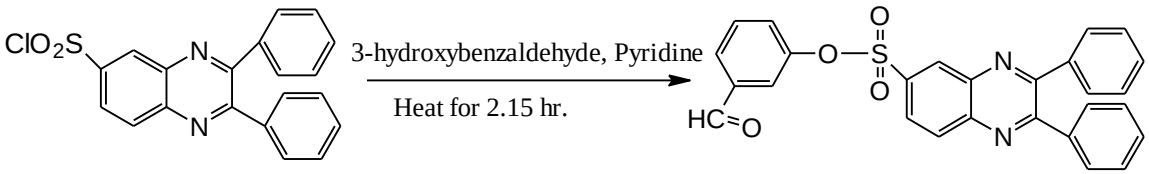
Mix 1.29 gm of salicylaldehyde with 3.22ml pyridine & 2.58 gm of sulphonyl chloride derivative &heat on water bath for 1.5 hr. pour into 25 ml of cold water & stir until the oil solidifies , filter wash with cold dil HCl to remove pyridine and cold dil NaOH to remove any phenol present &them with cold water , recrystallized from methanol or ethanol.

Synthesis of 4-formyl-3-methoxyphenyl-2,3-diphenylquinoxaline-7-sulphonate (R8)



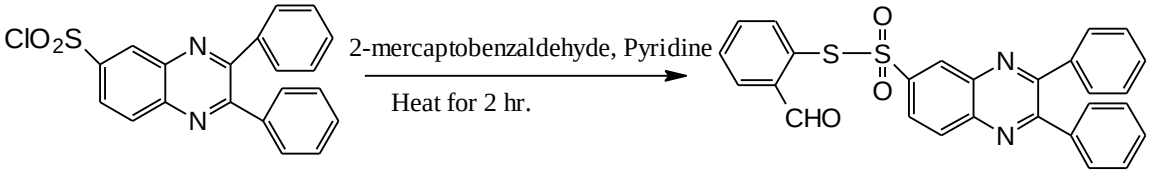
Mix 1.61 gm of vanillin with4.02 ml pyridine & 3.22 gm of sulphonyl chloride derivative & heat on water bath for 3 hr. pour into 25 ml of cold water & stir until the oil solidifies, filter wash with cold dil HCl to remove pyridine and cold dil NaOH to remove any phenol present &them with cold water, recrystallized from methanol or ethanol.

Synthesis of 3-formylphenyl-2,3-diphenylquinoxaline-7-sulphonate(R9)



Mix 1.29 gm of 3-hydroxybenzaldehyde with 3.22ml pyridine & 2.58 gm of sulphonyl chloride derivative &heat on water bath for 2.15 hr. pour into 25 ml of cold water & stir until the oil solidifies , filter wash with cold dil HCl to remove pyridine and cold dil NaOH to remove any phenol present &them with cold water , recrystallized from methanol or ethanol.

Synthesis of S-2-formylphenyl-2,3-diphenylquinoxaline-7-sulphonate(R10)



Mix 1.46 gm of 2-mercapto benzaldehyde with 3.67ml pyridine & 2.92 gm of sulphonyl chloride derivative &heat on water bath for 2 hr. pour into 25 ml of cold water & stir until the oil solidifies, filter wash with cold dil HCl to remove pyridine and cold dil NaOH to remove any phenol present &them with cold water , recrystallized from methanol or ethanol.

Identification &Characterization

The identification & characterization of prepared compound were carried out on the basis of physical, chemical, and spectral data such as Melting point (MP), thin layer chromatography (TLC), Infrared Spectroscopy (IR), Mass Spectrometry (MS), Nuclear Magnetic Resonance Spectroscopy (^{1}HNMR).

Physical Properties

Synthesized quinoxaline sulfonamide derivatives were evaluated for physical properties such as physical state, color, and melting point.

Melting point

Melting points of all derivatives were determined by Open capillary tube method.

Solubility

Solubility study of synthesized derivatives was carried out in different solvents like water, ethanol, methanol, acetone, benzene, chloroform, and DMF.

Thin layer chromatography (TLC)

All the synthesized derivatives were subjected to TLC analysis to ensure the completion of the reaction

Determination of Minimum Inhibitory Concentration:

Tube Dilution Technique

Double strength nutrient broth was prepared by dissolving 6.25 g of nutrient broth in 250 ml distilled water. The medium was boiled to aid dissolution and sterilized by autoclaving at 15 psi pressure (121˚C) for 20 min.

1ml of double strength nutrient broth was added to a set of presterilized 5 test tubes (numbered from 1-5). To the first test tube, 1ml quinoxaline derivative sample solution (conc.=1000 µg/ml) was added. After thorough mixing, 1ml of solution from test tube no.1 was transferred to test tube no.2 so as to obtain concentration of 500µg/ml. The same procedure (serial dilution) was followed for the remaining test tubes from no. 3 to no. 5 to get the concentration in the range of 250µg/ml to 62.5µg/ml from 3rd to 5th test tube. From 5th test tube 1 ml of solution was discarded so as to get the equal volume in each test tube. Thus, each tube having concentration of 1000, 500, 250, 125, 62.5µg/ml. To each test tube 20 µl of *Enterobacteria* suspension was added (inoculation). All test tubes were incubated at 37˚C for 24 hours and observed for turbidity. The sets of test tube were compared for determining the MIC. The whole experimental setup was repeated for *S. aureus* and *E. coli.*

Table 1: Preparation of Medium

Micro-organism	***S. aureus***
Media	Double strength nutrient broth
Conc. of quinoxaline derivative	1000µg/ml
Loaded volume of media	1 ml
Loaded volume of microbial suspension	20 µl
Incubation temperature	37°C
Incubation period	24 Hrs

QSAR:

Molecular Descriptors:

Molecular descriptors can be defined as a numerical representation of chemical information encoded within a molecular structure via mathematical procedure. Type of QSAR is based on the dimensionality of molecular descriptors used:

- 0D these are descriptors derived from molecular formula e.g. molecular weight, number and type of atoms etc.
- 1D A substructure list representation of a molecule can be considered as a one dimensional (1D) molecular representation and consists of a list of molecular fragments (e.g. functional groups, rings, bonds, substituents etc.).
- 2D A molecular graph contains topological or two dimensional (2D) information describes how the atoms are bonded in a molecule, both the type of bonding and the interaction of particular atoms (e.g. total path count, molecular connectivity indices etc.).
- 3D These are calculated starting from a geometrical or 3D representation of a molecule. These descriptors include molecular surface, molecular volume and other geometrical properties. There are different types of 3D descriptors e.g. electronic, steric, shape etc.
- 4D In addition to the 3D descriptors the 4th dimension is generally in terms of different conformations or any other experimental condition.

RESULT AND DISCUSSION:

Number of Rotatable Bonds – nrotb:

This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs. Rotatable bond is defined as any single non-ring bond, bounded to non terminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier.

Table 2: Predicted Values for GPCR ligands and kinase inhibitors of compounds

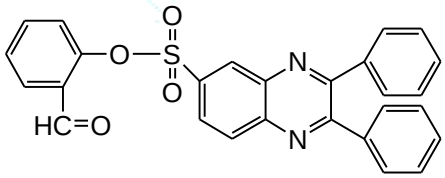
Compound	Nrotb	Vol	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand
R_1	5	382.382	-0.17	-0.24	-0.35	-0.09
R_7	5	392.381	-0.14	-0.49	-0.12	-0.21
R_8	6	417.927	-0.45	-0.68	-0.18	-0.28
R_9	5	392.381	-0.17	-0.53	-0.17	-0.22
R_{10}	5	402.024	-0.43	-0.78	-0.41	-0.55

Table 3: Physicochemical properties of synthesized quinoxaline derivatives

Code no.	M. P. (^{0}C)	Mol. wt	Rf value	Percent yield	Mol. formula
R1	92	460	0.39	80	$C_{26}H_{18}N_2O_4S$
R7	86	472	0.2	83	$C_{27}H_{18}N_2O_4S$
R8	62	502	0.44	75	$C_{28}H_{20}N_2O_5S$
R9	90	472	0.35	82	$C_{27}H_{18}N_2O_4S$
R10	94	488	0.8	84	$C_{27}H_{18}N_2O_3S_2$

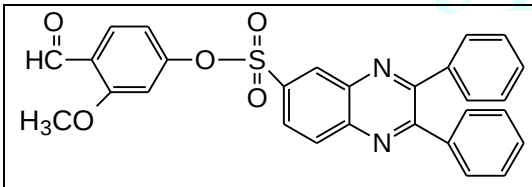
Infra-red spectroscopy:

All the synthesized derivatives were characterized by infra red spectroscopy in the range of 400-4000 cm^{-1} by KBr pellet technique. The IR spectra of all synthesized derivatives were as follows.



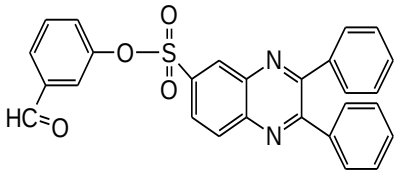
2-formylphenyl-2,3-diphenyl- quinoxaline-7-sulphonate

Fuctional group	Frequency(cm^{-1})
S=O	1132.8(1180-1130) 1330.1(1370-1300)
C=O	1695(1760-1690)
Mono sub. Aromatic ring	762.3(770-735)
CH aromatic	3046.6 (3100-3000)



4-formyl-3-methoxyphenyl-2,3--diphenyl- quinoxaline-7-sulphonate

Fuctional group	Frequency(cm^{-1})
S=O	1132.8(1180-1130) 1334.9(1370-1300)
C=O	1691(1760-1690)
Mono sub. Aromatic ring	762.4(770-735)
CH aromatic	3046.6 (3100-3000)



3-Formylphenyl-2,3-diphenylquinoxaline-7-sulphonate

Fuctional group	Frequency(cm^{-1})
S=O	1136(1180-1130) 1342.4(1370-1300)
C=O	1691(1760-1690)
Mono sub. Aromatic ring	767.6(770-735)
CH aromatic	3055 (3100-3000)

Pharmacological Screenings:

Antimicrobial Susceptibility Testing:

Synthesized quinoxaline derivatives were subjected to antimicrobial susceptibility testing by well diffusion method against gram positive (*S.aureus*, 2079) and gram negative bacteria *(E. coli*, 2685). The results of quinoxaline derivatives in terms of zone of inhibition were as follows;

Table 4: Zone of inhibition against *S. aureus*

Quinoxaline derivative	Zone of inhibition (mm.) 200µg. S.aureus	Zone of inhibition (mm.) 400 µg. S.aureus
Azithromycin (s)	18	37
R1	-	-
R7	-	-
R8	-	-
R9	11	21
R10	-	-

Table 5: Zone of inhibition against*E. coli*

Quinoxaline derivative	Zone of inhibition (mm.) 200µg. E.coli	Zone of inhibition (mm.) 400 µg. E.coli
Azithromycin (s)	17	33
R1	-	-
R7	-	-
R8	-	-
R9	09	18
R10	-	-

Azithromycin is used as Reference drug and a comparative study was done. As compare to reference drug all derivatives shows less sensitivity but R9 shows better sensitivity than other derivatives.

Determination of MIC:

MIC of quinoxaline derivative was determined by tube micro dilution technique against *S.aureus* and *E. coli*. The turbidity was measured by UV at about 420 nm. The results of MIC were found to be as follows.

Table 6: Results for MIC of quinoxaline derivatives against *S. aureus*

Quinoxaline Derivative	Absorbance at 420 nm.			
Conc. (µg/ml)	200	400	800	1000
S	0.865	0.851	0.621	0.271
R9	0.432	0.351	0.274	0.243

As per the data obtained after micro broth dilution method, the antimicrobial activity of drug derivative R4 found to be effective in between the range of 800-1000µg/ml where as that of R9 was above 1000µg against *S. aureus.*

Table 7: Results for MIC of quinoxaline derivatives against *E. coli*

Quinoxaline Derivative	Absorbance at 420 nm.			
Conc. (µg/ml)	200	400	800	1000
S	0.705	0.580	0.436	0.365
R9	0.295	0.258	0.230	0.215

As per the data obtained after micro broth dilution method, the antimicrobial activity of drug derivative R4 found to be effective in between the range of 400-800µg/ml where as that of R9 was above 1000µg against *E. coli*.

CONCLUSION:

The objective of the present study was to synthesize some new 7-sulfonate of 2, 3- Diphenyl quinoxaline which are more potential as antibacterial than parent quinoxalines.[1]QSAR study gives idea about various descriptors of different derivatives and Docking gives idea about having more affinity towards gamma Glutamyl-transpeptidase enzyme. In future similar methods can be used for 3-Methyl 2-(1*H*) quinoxalinone. Synthesis of derivatives of sulfonyl chloride quinoxaline and physicochemical and spectral characterization, in vitro antimicrobial screening against gram positive and gram negative bacteria. The reaction was carried out in the presence of base, (NaOH) was used, and all the reaction was refluxed on water bath. The reaction time required for each reaction was different it was depends on the aldehydes used. All the derivatives were confirmed by TLC, IR, and ^{1}HNMR. The spectral characterization revealed the formation of sulfonates. The newly synthesized aldehydes derivatives were screened for antimicrobial activity. All the derivatives were then subjected to antimicrobial susceptibility testing against gram positive (*S. aureus*) and gram negative bacteria (*E. coli*). Also, antimicrobial data of quinoxaline derivatives was obtained. It was found that sulfonyl chloride quinoxaline derivatives have pronounced effect as compared to antibiotic Azithromycin, present in the market against both the gram positive and gram negative bacteria.

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