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Synthesis and Evaluation of Phenol Derivatives of Sulfonyl Chloride Quinoxaline

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ABSTRACT

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. The present study was synthesis of derivatives of sulfonyl chloride quinoxaline and physicochemical and spectral characterization, in vitro antimicrobial screening against gram positive and gram negative bacteria.The concentration of derivatives used as 200 and 400 microgram initially. When 200 µg concentrations was used R6 shows sensitivity towards *S. aureus* and R6 shows sensitivity towards gram negative *E. coli* organism. When 400 µg used then R3, R5, and R6 shows sensitivity in case of gram positive organism. And in case of gram negative organism R5, R6 shows sensitivity.Azithromycin is used as Reference drug and a comparative study was done. As compare to reference drug all derivatives shows less sensitivity than S- Standard and R- quinoxaline derivatives.

Keywords: Diphenyl quinoxaline, QSAR, Quinoxaline, Phenol derivatives

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1. INTRODUCTION:

Quinoxaline is also called as benzopyrazine. It is heterocyclic compound containing benzene ring & pyrazine ring. Pyrazine are stable, colorless compound which are soluble in water. Unlike pyridine, they are expensive & not readily available & so are seldom used as starting material for synthesis of their derivative. Diazines are fused to benzene ring to form quinoxaline. The pyrazine ring system is found in the fungal metabolite aspergillic acid and in dihydro form in luciferin of several bettles including the fire fly is responsible for the chemiluminescence of this ostracod. Methoxy pyrazine are very important component of aroma of many fruit's and vegetable such as Peas and Capsicum peppers and also of wines.

Antimicrobial agent shows activity against bacteria, fungi, mycobacterium species, called antibacterial, antifungal, antituberculer activity respectively. There are various quinoxaline derivatives showing antimicrobial activity. Quinoxaline core antibiotics like Echinomycin, Triostin A showing antimicrobial activity by having DNA cleaving property. Design of quinoxaline antibiotics have undertaken by several workers, but they posses limited application due to their toxic effect. It is believed that the antimicrobial potency of the quinoxaline due to the facilitate approach of the structure to prevent DNA directed RNA synthesis by virtue binding to CPG site on DNA (Ali et.al, 2003).

Ganapaty *et.al.,* 2007 has synthesized some new 2-substituted hydrazino/benzylidino/methyl hydrazones and 7-sulfonamides of 1H, 4H 3-oxo-quinoxalines from 1H, 4H-quinoxalin-2,3diones. All the compounds were evaluated for their in vitro antimicrobial activity against the gram-positive bacteria *Staphyllococus aureus*, the gram-negative *Psudomonas aeruginosa*, *Proteus vulgaris* and *Escherichia coli*, the fungi *Aspergillus niger, Candida albicans* and the *Mycobacterium tuberculosis*H_{37}*Rv* species. Antibacterial and antifungal screening was carried out by agar plate disc diffusion method at 100µg/disc concentration in triplicate and its results were reported as zone of inhibition in millimeter. The antituberculer screening was performed by Micro plate Alamar Blue Assay method.

M. M. Ali synthesized some novel quinoxalinone derivatives.[i] The antimicrobial activities of the synthesized compounds were determined by the agar diffusion technique. The organisms tested were *Staphyloccus aureus* (NCTC 7447),

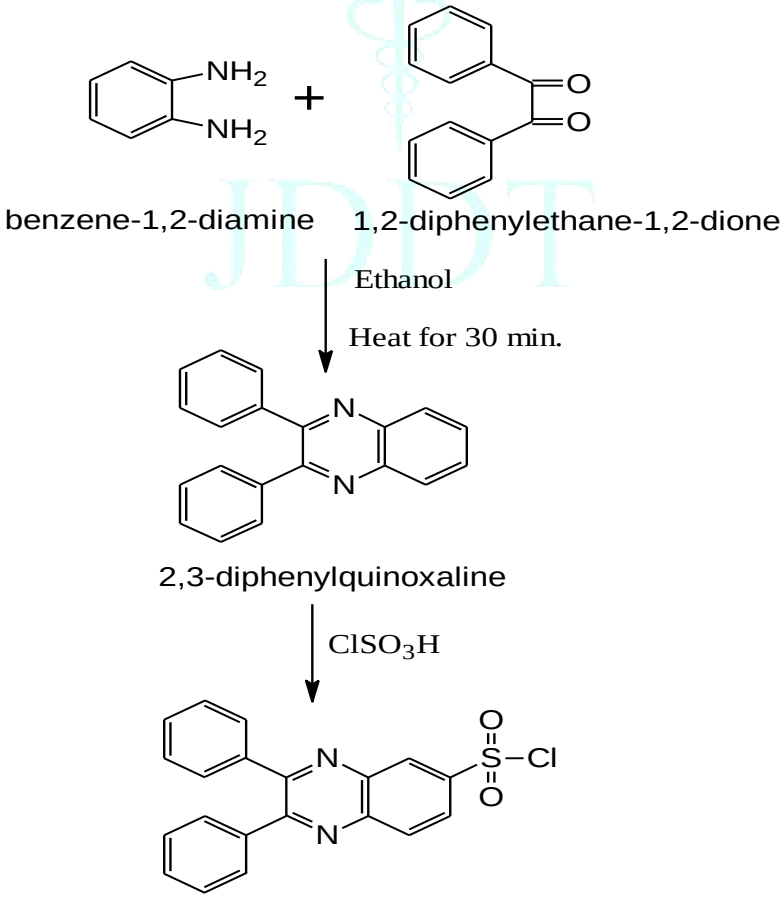
Bacillus cereus (ATCC-14579), *Serratia marcescens* (IMRU 70), *Proteus merabitis* (NCTC-289), *Aspergillus ochraceus,* Wilhelm (AUCC-230) and *Penicillium chrysogenum*, Thom (AUCC-530). Disk diffusion refers to the diffusion of an antimicrobial agent of a specified concentration from disks, tablets or strips, into the solid culture medium that has been seeded with the selected inoculum isolated in a pure culture. Disk diffusion is based on the determination of an inhibition zone proportional to the bacterial susceptibility to the antimicrobial present in the disk.

The diffusion of the antimicrobial agent into the seeded culture media results in a gradient of the antimicrobial. When the concentration of the antimicrobial becomes so diluted that it can no longer inhibit the growth of the test bacterium, the zone of inhibition is demarcated. The diameter of this zone of inhibition around the antimicrobial disk is related to minimum inhibitory concentration (MIC) for that particular bacterium/antimicrobial combination; the zone of inhibition correlates inversely with the MIC of the test bacterium. Generally, the larger the zone of inhibition, the lower the concentration of antimicrobial required to inhibit the growth of the organisms. However, this depends on the concentration of antibiotic in the disk and its diffusibility.

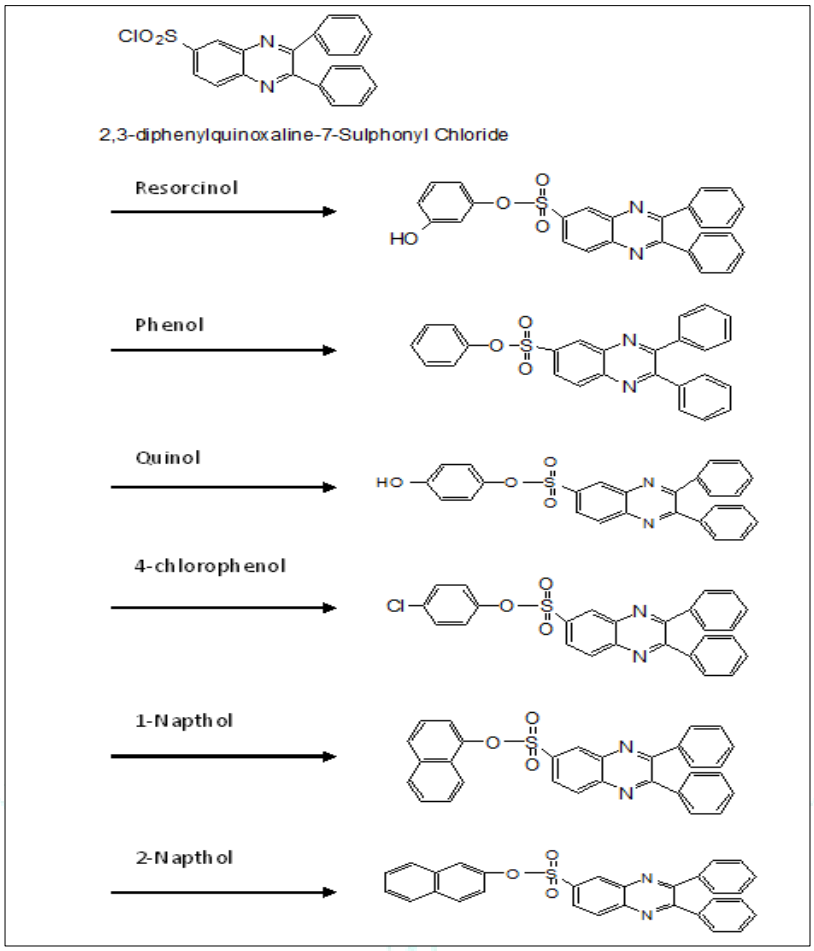
Quinoxalines are becoming the attractive target of extensive research due to its inherent diverse properties. Various potential activities of the quinoxalines have been explored recently like, antimicrobial agents, cytotoxic agents, anti-tubercular, anxiolytic, anti-HIV, anti-inflammatory, antioxidant etc. In the recent year, 2, 3 Disubstituted quinoxalines reported to posse's significant antimicrobial potential against bacteria, fungi, and mycobacterium (Ganapaty S. *et al* 2007). Design of quinoxaline antibiotics have undertaken by several workers, but they posses limited application due to their toxic effect. According to conclusion derived in literature survey, it was worthwhile to introduced lipophillic moiety into the 2,3 diphenyl quinoxaline system to make the structure as DNA targeted potent antimicrobial agent the sulfonate have created considerable attention as carrier and lipophillic core in the area of synthetic medicinal chemistry. Based on the observation and in connection with earlier studies (Ganapaty *etal*, 2007), the present work was undertaken synthesize some new phenol & aldehyde derivatives of 2, 3 diphenylquinoxaline 7 sulphonyl chloride which are more potential as antibacterial than parent quinoxalines.

2. MATERIAL AND METHODS:

2.1 Scheme of synthesis



2.2 Derivatives of 2,3-diphenylquinoxaline-7-sulphonyl chloridewithPhenol



2.3 Experimental Procedure:

2.3.1 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.

2.3.2 *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.

2.3.3*Synthesis of Phenyl-2,3-diphenylquinoxaline-7-sulphonate(R2)*

Mix 1 gm of phenol with 2.5ml pyridine & 2 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.

2.3.4Synthesis of 4-hydroxyphenyl-2,3-diphenylquinoxaline-7-sulphonate(R3)

Mix 1.17 gm of quinol with 3ml pyridine & 2.34 gm of sulphonyl chloride derivative &heat on water bath for 55min 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.

4.3.2.4 Synthesis of 4-Chlorophenyl-2,3-diphenylquinoxaline-7-sulphonate(R4)

Mix 1.36 gm of 4-chloro phenol with 3.4ml pyridine & 2.72 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.

2.3.5 Synthesis of Napthalene-1-yl-2,3-diphenylquinoxaline-7-sulphonate(R5)

Mix 1.54gm of 1-naphthol with 3.85ml pyridine & 3.08 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.

2.3.6 Synthesis of Napthalene-2-yl-2,3-diphenylquinoxaline-7-sulphonate (R6)

Mix 1.54 gm of 2-naphthol with 3.85ml pyridine & 3.08 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.

2.4 Physical Properties

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

2.4.1 Melting point

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

2.4.2 Solubility

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

2.4.3 Thin layer chromatography (TLC)

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

2.5 Characterization of Synthesized Compounds:

The identification & characterization of prepared compound were carried out on the basis of spectral data such as Infrared Spectroscopy (IR), Mass Spectrometry (MS), Nuclear Magnetic Resonance Spectroscopy (^{1}HNMR).

3. ANTIMICROBIAL ACTIVITY:

3.1 *Determination of minimum inhibitory concentration*

3.1.1 Tube dilution technique

Preparation of media:

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 forthe remaining test tubes from no. 3 to no. 5 to get the concentration in the range of 250µg/ml to 62.5 µg/ml from 3rd to 5th test tube. From 5th test tube1 ml of solution wasdiscarded so as to get the equal volume in each test tube. Thus, each tube havingconcentration 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: Experimental set up for MIC *(S. aureus)*

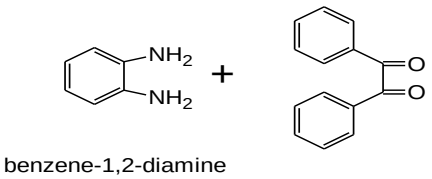
Micro-organism	***S. aureus***
Media	Double strength nutrient broth
Conc. of quinoxaline derivative	1000µg/ml
Loaded volume of media	1 ml
Loaded volume of microbial suspension	20 µl
Incubation temperature	37°C
Incubation period	24 Hrs

4. RESULT AND DISCUSSION:

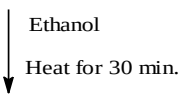
4.1 Raw material characterization

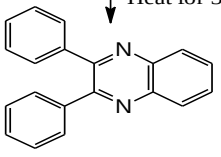
Table 2: Raw material characterization

Sr. no.	Name	Mol. Formula	Mol. Wt.	M.P.	B.P.
1	Benzil	$C_{14}H_{10}O_2$	210.23	93-95	-
2	O- phenylene diamine	$C_6H_8N_2$	108.14	104	-
3	Chlorosulfonic acid	$HClO_3S$	116.52	80	151-152
4	Phenol	C_6H_6O	94.11	-	180-182
5	Resorcinol	$C_6H_6O_2$	110.11	109-111	-
6	Quinol	$C_6H_6O_2$	110.11	170-174	-
7	4-Cl Phenol	C_6H_5OCl	128.5		220-
8	α-Naphthol	$C_{10}H_8O$	144.17	96	288
9	β- Naphthol	$C_{10}H_9O$	144.17	121-123	285-286



benzene-1,2-diamine

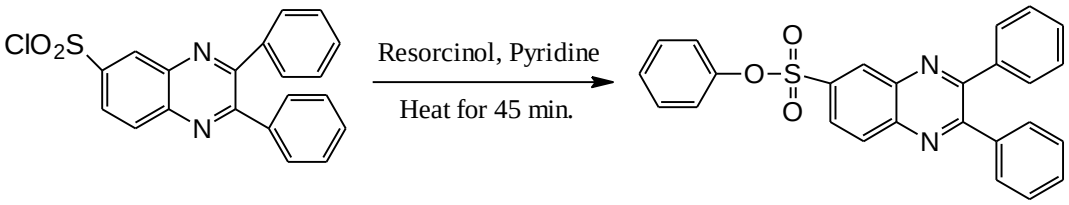




2,3-diphenylquinoxaline

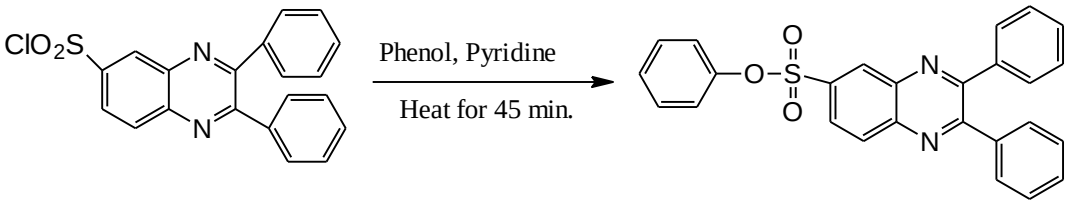
4.2 Synthesis of phenol derivatives of 2,3-diphenylquinoxaline-7-sulphonyl chloride

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



Yield of product: 2.26, Percentage yield: 80%, TLC: Benzene: Methanol(9:1); R_f=0.39

4.2.2. ***Synthesis of Phenyl-2,3-diphenylquinoxaline-7-sulphonate(R2)***

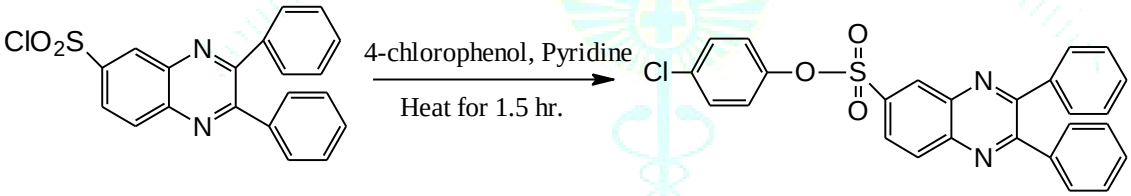


Yield of product: 1.74 , Percentage yield: 75%, TLC: Benzene : Methanol(9:1); R_f=0.42

4.2.3 Synthesis of 4-hydroxyphenyl-2,3-diphenylquinoxaline-7-sulphonate(R3)

Yield of product: 2.20 gm, Percentage yield: 78%, TLC: Benzene: Methanol(9:1); R_f=0.9

4.2.4 Synthesis of 4-Chlorophenyl-2,3-diphenylquinoxaline-7-sulphonate(R4)

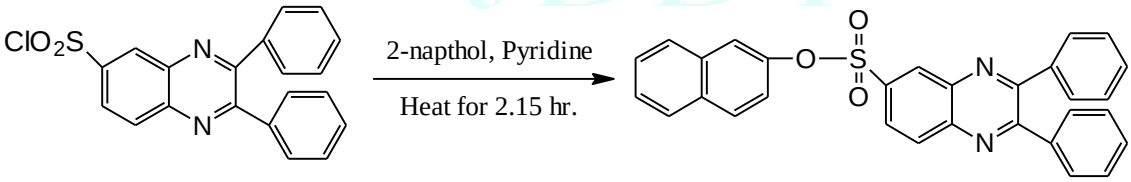


Yield of product: 2.73 gm, Percentage yield: 80%, TLC: Benzene : Methanol(9:1); R_f=0.8

4.2.5 Synthesis of Napthalene-1-yl-2,3-diphenylquinoxaline-7-sulphonate(R5)

Yield of product: 3.11 gm, Percentage yield: 78%, TLC: Benzene : Methanol(9:1); R_f=0.5

4.2.6 Synthesis of Napthalene-2-yl-2,3-diphenylquinoxaline-7-sulphonate (R6)



Yield of product: 3.27 gm, Percentage yield: 82%, TLC: Benzene : Methanol(9:1); R_f=0.7

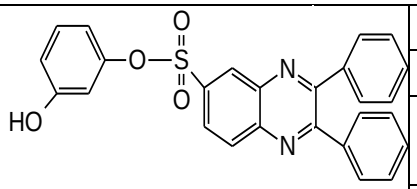
Table 3: QSAR result analysis of synthesized compounds

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_2	5	374.364	-0.2	-0.24	-0.39	-0.22
R_3	5	382.382	-0.17	-0.23	-0.36	-0.11
R_4	5	387.9	-0.19	-0.26	-0.38	-0.27
R_5	5	418.356	-0.2	-0.44	-0.30	-0.32
R_6	5	418.356	-0.17	-0.43	-0.34	-0.21

Table 4: Physicochemical properties of synthesized quinoxaline derivatives

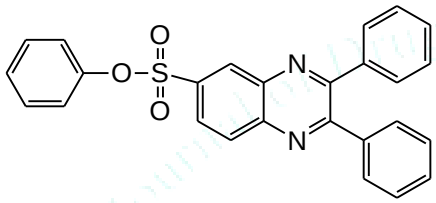
Code no.	M. P. (°C)	Mol. wt	Rf value	Percent yield	Mol. formula
R1	92	460	0.39	80	$C_{26}H_{18}N_2O_4S$
R2	105	443	0.42	75	$C_{26}H_{17}N_2O_3S$
R3	82	460	0.9	78	$C_{26}H_{18}N_2O_4S$
R4	102	478.5	0.8	80	$C_{26}H_{17}N_2O_3SCl$
R5	98	494	0.5	78	$C_{30}H_{20}N_2O_3S$
R6	106	494	0.7	82	$C_{30}H_{20}N_2O_3S$

4.3 FTIR Spectral data of synthesized quinoxaline derivatives



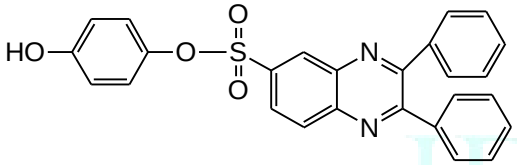
2-hydroxyphenyl-2,3-diphenylquinoxaline-7-sulphonate

Fuctional group	Frequency(cm^{-1})
OH	3500.8
S=O	1132.8(1180-1130) 1330.1 (1370-1300)
Mono sub. Aromatic ring	757.8 (735-770)
CH aromatic	3046.60 (3100-3000)



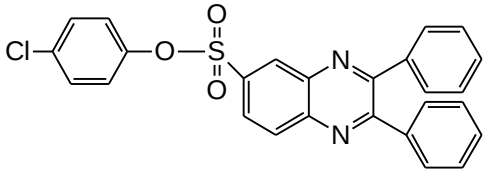
phenyl-2,3-diphenylquinoxaline-7-sulphonate

Fuctional group	Frequency(cm^{-1})
S=O	1132.5(1180-1130) 1339.4 (1370-1300)
C=N	1685.4(1690-1630)
Mono sub. Aromatic ring	757.8 (770-735)
CH aromatic	3045.9 (3100-3000)



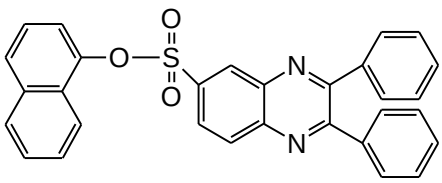
2-4-hydroxyphenyl-2,3-diphenylquinoxaline-7-sulphonate

Fuctional group	Frequency(cm^{-1})
S=O	1132.5(1180-1130) 1334.6 (1370-1300)
OH	3392.3
C=N	1647.3(1690-1620)
CH aromatic	3036.3 (3100-3000)



4-chlorophenyl-2,3-diphenylquinoxaline-7-sulphonate

Fuctional group	Frequency(cm^{-1})
S=O	1137.7(1180-1130) 1339.7(1370-1300)
Cl	690.2(750-500)
Mono sub. Aromatic ring	762.3(770-735)
CH aromatic	3046.6 (3100-3000)



Napthalene-1-yl-2,3-diphenyl-diphenylquinoxaline-7-sulphonate

Fuctional group	Frequency(cm^{-1})
S=O	1137.7(1180-1130) 1339.7(1370-1300)
C=N	1623.6(1690-1620)
Mono sub. Aromatic ring	752.8(770-735)
CH aromatic	3046.6 (3100-3000)

4.5 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 5: 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	-	-
R2	-	-
R3	11	21
R4	-	-
R5	09	18
R6	11	22

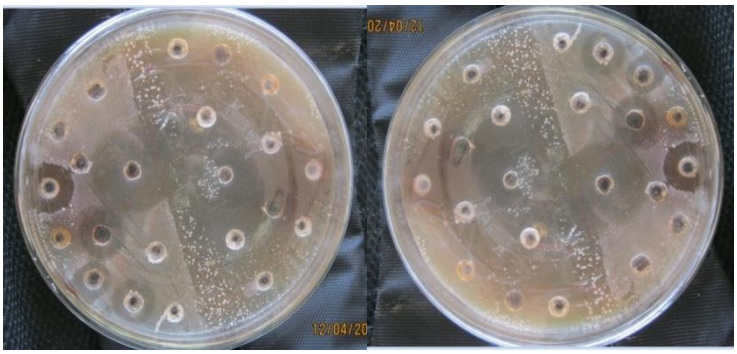
Table 6: Zone of inhibition against *E. coli*

Quinoxaline derivative	Zone of inhibition (mm.) 200 µg. *E.coli*	Zone of inhibition (mm.) 400 µg. *E.coli*
Azithromycin (s)	17	33
R1	-	-
R2	-	-
R3	-	-
R4	-	-
R5	07	13
R6	06	12

The concentration of derivatives used as 200 and 400 microgram initially. When 200 µg concentrations was used R6 shows sensitivity towards *S. aureus* and R6 shows sensitivity towards gram negative *E. coli* organism. When 400 µg used then R3, R5, and R6 shows sensitivity in case of gram positive organism. And in case of gram negative organism R5, R6 shows sensitivity.

The promising results were obtained against *S. aureus*, so quinoxaline derivatives were found to be more sensitive towards gram positive than gram negative organism under the present experimental setup. R3, R5, R6 were slightly sensitive towards *S. aureus*.

Azithromycin is used as Reference drug and a comparative study was done. As compare to reference drug all derivatives shows less sensitivity than S- Standard and R- quinoxaline derivatives respectively.



200 µg/ml strain400 µg/ml strain

Fig 1: Photographs indicating Zone of Inhibition of *S. aureus*&*E. coli*

4.6 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 7: 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
R6	0.797	0.736	0.542	0.204

Table 1 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
R6	0.567	0.473	0.307	0.245

5. CONCLUSION:

The phenol derivatives were synthesized and were confirmed by physicochemical and spectral analysis. 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. The present study was synthesis of derivatives of sulfonyl chloride quinoxaline and physicochemical and spectral characterization, in vitro antimicrobial screening against gram positive and gram negative bacteria. All sulfonyl chloride derivatives of quinoxaline were synthesized on the basis of elimination-addition reaction mechanism. All the derivatives were confirmed by TLC, IR, and ^{1}HNMR. The spectral characterization revealed the formation of sulfonates. The results of pharmacological screenings are satisfactory. 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. QSAR study gives idea about various descriptors of different derivatives and Docking gives idea about having more affinity towards gamma Glutamyltranspeptidase enzyme.

6. REFERNCES:

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