SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF QUINOXALINE SULFONAMIDE

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ABSTRACT

Quinoxaline have become attractive target of extensive research due to its inherent properties and therapeutic uses. Quinoxaline finds many pharmacological activities like antibacterial, antifungal, antituberculer, anti-inflammatory, antihyperglycemic, antitumor etc. The present study includes the synthesis of sulfonamide derivatives of quinoxaline, by addition-elimination mechanism. All derivatives were characterized by TLC, IR, MS, ^{1}HNMR.Quinoxaline sulfonamide derivatives were then subjected to antimicrobial screening against gram positive and gram negative bacteria. The results of antimicrobial susceptibility testing revealed that all sulfonamides derivatives showed more pronounced effect on the inhibition of growth, obtained in terms of MIC, against all the strains used as compared to plane quinoxaline derivatives.

Key words: Quinoxaline, Sulfonamide, Antimicrobial activity, MIC,.

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.

MATERIAL AND METHODS

Apparatus:

The melting points were determined by open capillary method and are uncorrected.
Infrared spectra were recorded on FTIR 8400s Shimadzu using KBr. To confirm the completion of reaction TLC were taken by using silica gel G and ethanol: water(7:1) as mobile phase.MIC detected by photocolourimeter.

Chemicals and Reagents:

Benzyl, o-Phenylene diamine, Chlorosulfonic acid, Aniline, Ethanol, nitro aniline thiosemicarbazide, is from Loba Chem Pvt. Limited, Mumbai. All solvents were distilled before use and dried whenever required.

Scheme of synthesis

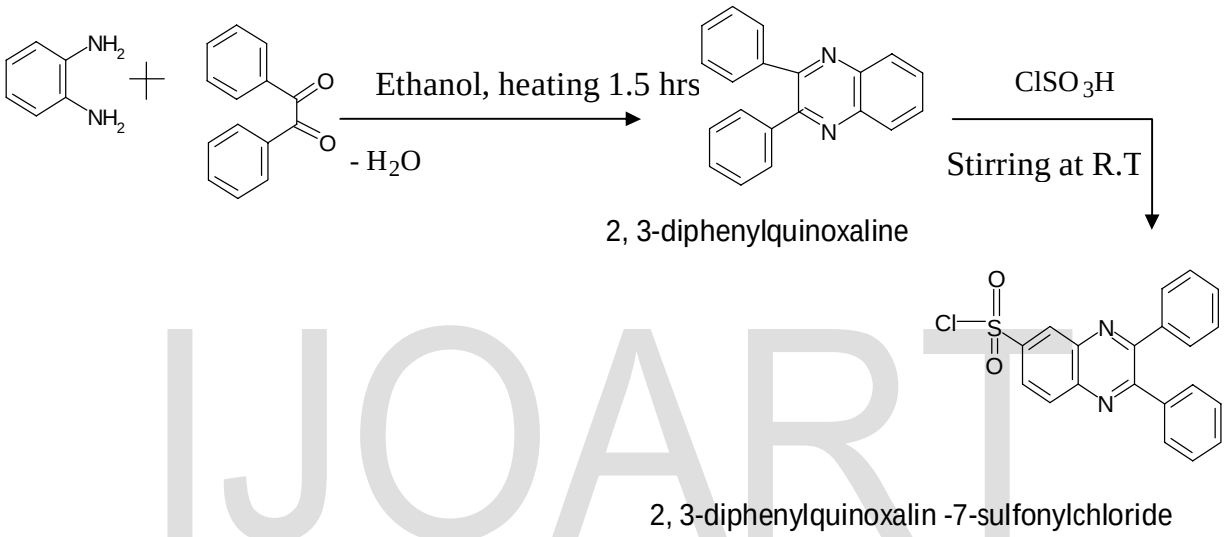

Figure1: Synthesis of 2, 3-diphenylquinoxaline 7-sulfonylchloride (parent compound).

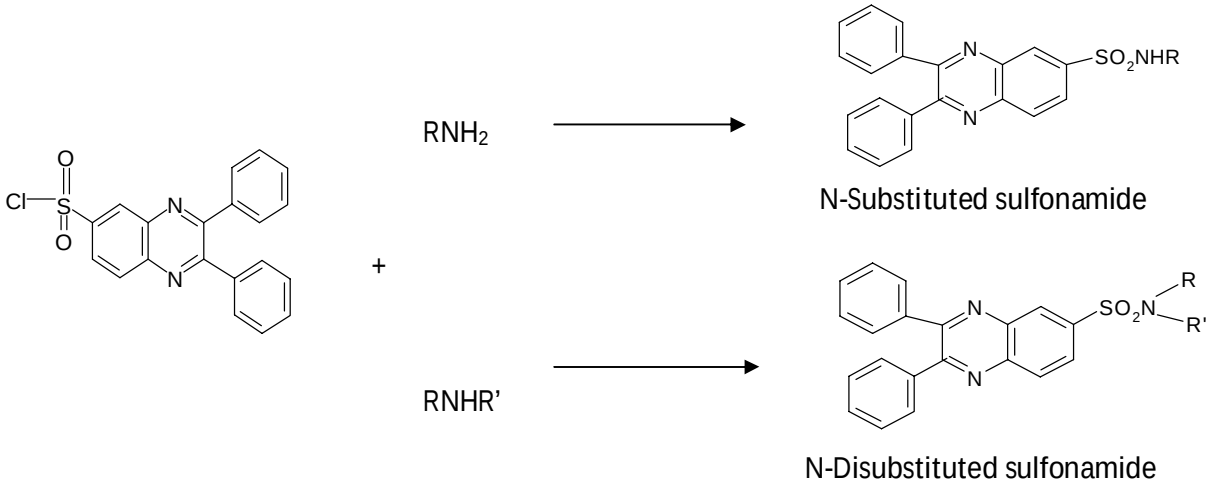

Figure 1: Scheme for synthesis 7-sulfonamide derivatives of 2, 3-diphenylquinoxaline

EXPERIMENTAL METHOD.

Synthesis of parent compound

Synthesis of 2, 3-diphenylquinoxaline 7-sulfonylchloride

0.01 moles of 2, 3 diphenylquinoxaline (2.84g) 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 sulfonylchoride derivative.

Synthesis of sulfonamide derivatives of quinoxaline

Synthesis of 2, 3-Diphenyl, 7-sulfonamido quinoxaline (L1)

Sulfonylchloride quinoxaline derivative was refluxed with 50% (30 ml) NH_3 solution for 1.5 hrs. Then reaction mixture was cooled and poured into water to get sulfonamide derivative of 2, 3-diphenylquinoxaline. The crude product was recrystalized from 90% ethanol.

Synthesis of 2, 3-Diphenyl 7-(N phenyl)-sulfonamido quinoxaline (L2)

A mixture of sulfonyl chloride derivatives of quinoxaline (1mmol) and aniline (1mmol) was taken in round bottom flask and dissolved in 10ml MeOH to the clear solution 2-3 drops of pyridine was added and then subjected to microwave irradiation (300 W,15 min) The progress of reaction was monitored by TLC. On completion of reaction the solvent was distilled off and crude product was washed with diethyl ether to get final product

Synthesis of 2, 3-Diphenyl 7-(2, nitro, N-phenyl)-sulfonamido quinoxaline (L3)

1g of O-nitroaniline was refluxed with 2g of 2, 3-diphenylquinoxaline 7-sulfonylchloride and 5ml. of pyridine for 30 min. Then reaction mixture was poured into 10 ml. cold water and stirred until product crystallized then product was filtered and recrystalized by ethanol. Reaction was monitored by TLC

Synthesis of 2, 3-Diphenyl, 7-(2, hydroxyN-phenyl)-sulfonamido quinoxaline (L4)

1g of 2-aminophenol and 2g of 2, 3-diphenylquinoxaline 7-sulfonylchloride and 5ml of pyridine were refluxed for 3hrs. Then reaction mixture was poured into 10ml. of cold water and stirred until the product crystallized then product was filtered and recrystalized by ethanol. Reaction was monitored by TLC.

Synthesis of 2, 3-Diphenyl, 7-(N-acetyl)-sulfonamido quinoxaline (L5*)*

1g of acetamide and 2g of 2, 3-diphenylquinoxaline 7- sulfonylchloride and 5ml of pyridine was refluxed for 2hrs Then reaction mixture was poured into 10ml. of cold water and stirred until the product crystallized then product was filtered and recrystalized by ethanol. Reaction was monitored by TLC.

Synthesis of 2, 3-Diphenyl, 7-thiosemicarbazide sulfonamido quinoxaline (L6)

1g of thiosemicarbazide and 2g of 2, 3-diphenylquinoxaline, 7- sulfonylchoride and 5ml of pyridine and 5ml of methanol was stirred in microwave for 20min at 300W. Solvent was distilled off. & recrystalized by diethyl ether. Reaction was monitored by TLC.

Synthesis of 2, 3-Diphenyl, 7-(N-diphenyl)-sulfonamido quinoxaline (L7)

2, 3-diphenylquinoxaline, 7- sulfonylchoride 1g was dissolved in 20ml dry DMF followed by addition of diphenyl amine 1.5g and resulting mixture was then poured into water to give precipitate which was recrystalized by ethanol to give pure product. This reaction takes 10hrs.in stirring at room temperature. Reaction was monitored by TLC**.**

Synthesis of 2, 3-Diphenyl, 7-sulfonyl azido quinoxaline (L8)

2, 3-diphenylquinoxaline, 7- sulfonylchloride 1.5g was dissolved in25ml acetone and sodium azide 1.0g in minimum amount of water was added in drop with continuous stirring .The mixture was stirring at room temperature for 8hrs.Acetone was removed under reduced pressure followed by addition of water gave crude crystals which was recrystalized from ethanol.Reaction was monitored by TLC.

Synthesis of 2, 3-Diphenyl, 7-(2, chloro N-benzyl)-sulfonamido quinoxaline (L9)

0.01moles of 2,3-Diphenyl ,7-sulfonamido quinoxaline & 0.01moles O-chloro benzaldehyde was refluxed with 25ml of ethanol and 1to2 drops of glacial acetic acid was added. This reaction takes 4hrs for completion which was monitored by TLC then crude product was recrystalized from ethanol.

Synthesis of 2, 3-Diphenyl, 7-(4, methoxy N-phenyl)-sulfonamido quinoxaline (L10)

1g of anisidine and 2g of 2, 3-diphenylquinoxaline 7- sulfonylchoride and 5ml. of pyridine was refluxed for 3hrs. Then reaction mixture was poured into 10ml. of cold water and stirred until the product crystallized then product was filtered and recrystalized by ethanol.

Table 1: Quinoxaline sulfonamide derivative synthesized by above scheme.

Comp. no	Name of derivative	R	R'
L1	2, 3-Diphenyl ,7-sulfonamido quinoxaline	H	-
L2	2, 3-Diphenyl,7-(N- phenyl)-sulfonamido quinoxaline	C_6H_5	-
L3	2, 3-Diphenyl ,7-(2-nitro,N-phenyl)-sulfonamido quinoxaline	C_6H_5-NO_2	-
L4	2, 3-Diphenyl,7-(2-hydroxyN-phenyl)-sulfonamido quinoxaline	C_6H_5-OH	-
L5	2, 3-Diphenyl,7-(N-acetyl)-sulfonamido quinoxaline	$COCH_3$	-
L6	2, 3-Diphenyl,7-thiosemicarbazide sulfonamido quinoxaline	$CSNHNH_2$	-
L7	2, 3-Diphenyl,7-(N-diphenyl)-sulfonamido quinoxaline	C_6H_5	C_6H_5
L8	2, 3-Diphenyl,7-sulfonyl azido quinoxaline	N_3	-
L9	2, 3-Diphenyl,7-(2-chloro N-benzyl)-sulfonamido quinoxaline	CH-C_6H_5-Cl	-
L10	2, 3-Diphenyl,7-(4-methoxy N-phenyl)-sulfonamido quinoxaline	C_6H_5.OCH_3	-

Table2: Physicochemical properties of synthesized quinoxaline derivatives

Comp. no	M. P. (^{0}C)	Mol. wt	Rf value	Mol. formula	FTIR (cm-1)(7)
L1	194	362	0.39	$C_{12}H_{15}N_3O_2S$	C=N -1673.9, C=C(Aromatic)-1583.62 S=O-1172.56,1383.77 Primary NH_2-3425.35
L2	95	438	0.42	$C_{26}H_{19}O_2N_3S$	C=C(Aromatic)-1496.20 S=O-1156.16, 1347.21 Amine-3055.60 Mono substitute benzene-770.40
L3	70	483	1.2	$C_{26}H_{19}O_4N_4S$	C=C (Aromatic)-1505.86 S=O-1173.30,1345.36 Amine- 3345.36 Mono substitute benzene-770.40 NO_2- 1505.86
L5	105	405	1.7	$C_{22}H_{17}O_3N_3S$	C=C (Aromatic)-1579.06 S=O-1174.97,1347.66 Amine-33.45.36 Mono substitute benzene-770.67,C=O-1660.64
L6	105	495	0.75	$C_{21}H_{17}O_2N_5S_2$	C=C (Aromatic)-1588.22 S=O-1158.4,1353.09 Amine-3260.87, Mono substitute benzene-767.43,C=S -1236.10
L7	160	558	0.25	$C_{32}H_{27}O_2N_3S$	C=C (Aromatic)- 1599.69 S=O – 1171.86, 1321.62 Amine-3382.69, Mono substitute benzene-798.26
L8	230	371	0.44	$C_{20}H_{13}O_2N_2S$	C=C (Aromatic)- 1561.26 S=O – 1193.68, 1340.83 Azide- 2124.45 substitute benzene-798.26
L9	110	]459	0.35	$C_{27}H_{18}O_2N_3S$	C=C (Aromatic)- 1591.94 S=O – 1150.,67, 1346.81 CH aromatic-2923.86 CH aliphatic-2853.31
L10	120	469	0.8	$C_{27}H_{22}O_3N_3S$	C=C (Aromatic)- 1561.15 S=O – 1144, 1333.7 CH aromatic-2853.31CH aliphatic-2920

Antimicrobial Susceptibility Testing

Synthesized quinoxaline derivatives were subjected to antimicrobial susceptibility testing by disk diffusion method against gram positive (*S. aureus, Enterobacteria*) and gram negative bacteria (*E. coli, Proteus vulgaries, Vibrio cholorie*). The results of quinoxaline derivatives in erms of zone of inhibition.

Table 3: Experimental set up for Antimicrobial Susceptibility Testing.

1	Media	Agar-agar, Nutrient broth
2	Test organism	*S. aureus, E. coli, Enterobacteria, P. vulgaris ,v.cholories*
3	Loaded volume of microbial suspension on agar	20 µl
4	Concentration of sample	1000 µg/ml
5	Loaded volume of sample	50 µl
6	Incubation temperature	37℃
7	Incubation period	24 hrs

Table4: Quinoxaline derivatives showing ZOI. against *S. aureus ,Enterobacteria ,V. cholorie E. coli*

Proteus Vulgaris

Zone of inhibition in (mm)

Microorganism	**L4**	**L5**	**L6**	**L7**	**L8**	**L9**	**L10**
S. aureus	19	16	20	22	12	18	08
Enterobacteria	24	02	18	16	10	18	08
V. cholorie	02	06	16	12	14	16	06
E. coli	22	-	12	08	08	16	06
ProteusVulgaris	30	-	16	30	12	16	08

RESULT AND DISCUSION

All the sulfonamides derivatives were confirmed by TLC, IR, MS and ^{1}HNMR. The spectral characterization revealed the formation of sulfonamide derivatives.Melting point was taken by open capillary tube it was found between 70-230^{0c}.FTIR shows the presence of C=C (Aromatic)-1583.62, C=C **(**Aromatic)-1496.20 CH aromatic-2923.86, S=O-1150.67.

All the sulfonamide quinoxaline derivatives were then subjected to antimicrobial susceptibility testing against gram positive (*Enterobacteria, S. aureus*) and gram negative bacteria (*E. coli, P. vulgaries, Vibrio cholorie*). Also, antimicrobial data of quinoxaline derivative were obtained. It was found that sulfonamide quinoxaline has pronounced effect as compared to plane quinoxaline derivative against all the gram positive and gram negative bacteria. The objective of the present study was to synthesize some new 7-sulfonamides of 2, 3 diphenyl quinoxaline which are more potential as antibacterial than parent quinoxalines.1

The plan of work of present study was synthesis of sulfonamides derivatives of quinoxaline and physicochemical and spectral characterization, *in vitro* antimicrobial screening against gram positive and gram negative bacteria. All sulfonamides derivatives of quinoxaline were synthesized on the basis of elimination-addition mechanism.

The reaction was carried out in the presence of base, (pyridine) was used, and all the reaction was refluxed with pyridine on water bath. The reaction time required for each reaction was different it was depends on the amines used. After completion of reaction, reaction mixture was poured into cold water and continuously stirred until product crystallized.

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