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Sulfonamido Quinoxalines - Search for Anti-inflammatory Agents

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Abstract
A set of ten new 2, 3 diphenyl-7-sulfonamide quinaxoline derivatives were synthesized and screened for anti-inflammatory activity by carrageenan induced rat paw edema method by using Digital Plethysmometer (UGO Basile 7140).Test derivatives L1, L2, L5 were shown activity with percent inhibition ranging from 2.25% to 22.95% and compare with reference standard diclofenac sodium (10 mg/kg). a substituted quinoxalines derivative gives potent activity than plane quinoxaline derivatives.

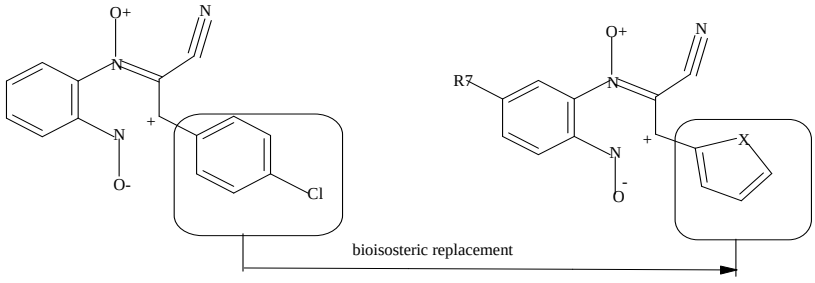
Keywords: *Sulfonamides quinoxalines, anti-inflammatory, carrageenan, digital Plethysmometer.*

Introduction

Quinoxalines are becoming the attractive target of extensive research due to its. 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 possess significant antimicrobial potential against bacteria, fungi, and mycobacterium[1]. Antimicrobial agent shows activity against bacteria, fungi, mycobacterium species, called antibacterial, antifungal, antitubercular activity respectively. There are various quinoxaline derivatives showing antimicrobial activity[2]. 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[2]. The present study aims to synthesis and characterization of various N-substituted sulfonamide derivatives of quinoxaline, conformation derivatives and determination of anti-inflammatory activity.

Pharmacophore and synthesis of test of series[3]

A group of potent antimicrobial sulfonamides were selected for pharmacophoric studies. A two point pharmacophore is generated where in heteroaromatic center separated from H-bonding acceptor/donor group was found to be essential for activity.



Series A (1-6): X=O
Series B (7-12): X=S

R7= H(1,7);F(2,8);Cl(3,9);CH_3(4,10);CF_3(5,11); OCH_3(6,12)

The substituted sulfonamide quinoxalines were synthesized using 2, 3-diphenylquinoxaline 7-sulfonylchloride as an important intermediate which was synthesized by reported method in which was achieved by treating of 2, 3 diphenylquinoxaline 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. Various different organic amines were treated at different reaction condition to give the series of 7-sulfonamide derivatives of 2, 3-diphenylquinoxaline.

1. Experimental Protocols

1.1. Synthesis

Progress of all reaction is monitored by thin-layer chromatography using Merck precoated silica GF 254.Compounds were puried by Column Chromatography using silica gel 60 from Merck. Melting points were recorded on electrically heated melting point apparatus. All intermediates are characterized by infrared spectroscopy (KBr disc method) on JASCO FT/IR 5300.The ^{1}H NMR spectrum was recorded on varian-VXR-300S at 300 MHz. Mass spectroscopy data.

1.1a. Synthesis of 2, 3-diphenylquinoxaline 7-sulfonylchloride (L) {Scheme: 1}

2, 3 diphenylquinoxaline (0.01 moles, 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. Yield: 76%, m.p.-128^{0}C; IR (KBr) cm^{-1} 1622, 770, 1558, 3057, 1173, 1348, 597; ^{1}H NMR (CDCl3) δ ppm: 7.35, 7.28, 7.24; m/z: 385, 157, 283[1].

1.1b. Synthesis of sulfonamide derivatives of quinoxaline {Scheme: 2}

3.1b.i. Synthesis of 2, 3-Diphenyl -7-sulfonamido quinoxaline (L1)

2, 3-diphenylquinoxaline -7-sulfonylchloride 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. Yield: 64%, m.p.-194^{0}C; IR (KBr) cm^{-1} 1674, 1584, 3088, 1173, 3423, 1384.

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

2, 3-diphenylquinoxaline -7-sulfonylchloride (1mmol) and aniline (1mmol) was taken in round bottom flask and dissolved in 10ml methanol to the clear solution 2-3 drops of pyridine was added and then subjected to microwave irradiation (300 W,15 min). On completion of reaction the solvent was distilled off and crude product was washed with diethyl ether to get final product. Yield: 71%, m.p.-95^{0}C; IR (KBr) cm^{-1} 1497, 1157, 1348, 3056, 771^{5}; m/z: 483, 344, 378, 289, 405.

1.1b.ii. Synthesis of 2, 3-Diphenyl-7-(2-nitro-N-phenyl)-sulfonamido quinoxaline (L3)

O-nitroaniline (1gm) was refluxed with 2, 3-diphenylquinoxaline-7-sulfonylchloride (2gm) 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. Yield: 68 %, m.p.-70^{O}C; IR (KBr) cm^{-1} 1506, 1174, 1345, 3345, 1506, 770; m/z: 483, 344, 378, 289, 405.

1.1b.iii. Synthesis of 2, 3-Diphenyl-7-(2-hydroxyl-N-phenyl)-sulfonamido quinoxaline (L4)

2-aminophenol (1gm) and 2, 3-diphenylquinoxaline-7-sulfonylchloride (2gm) 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. Yield-79%, m.p.-120^{0}C; IR (KBr) cm^{-1} 1506, 1174, 1345, 3345, 1506, 770.

1.1b.iv. Synthesis of 2, 3-Diphenyl-7-(N-acetyl)-sulfonamido quinoxaline (L5)

Acetamide(1gm) and 2, 3-diphenylquinoxaline-7-sulfonylchloride (2gm) 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. Yield: 82%, m.p.-104^{0}C; IR (KBr) cm^{-1} 1580, 1175, 1348, 3346, 1661, 2924, 771.

1.1b.v. Synthesis of 2, 3-Diphenyl-7-thiosemicarbazide sulfonamido quinoxaline (L6)

Thiosemicarbazide (1gm) and 2, 3-diphenylquinoxaline-7- sulfonylchoride (2gm) and 5ml of pyridine and 5ml of methanol was stirred in microwave for 20min at 300W. Solvent was distilled off and recrystalized by diethyl ether. Yield: 75%, m.p.-110^{0}C; IR (KBr) cm^{-1} 1588, 1158, 1352, 3261, 1236, 3000, 767.

1.1b.vi. Synthesis of 2, 3-Diphenyl-7-(N-diphenyl)-sulfonamido quinoxaline (L7)

2, 3-diphenylquinoxaline-7- sulfonylchoride (2gm) was dissolved in 20ml dry DMF followed by addition of diphenyl amine (1gm) 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. Yield**:** 59%, m.p.-160^{0}C; IR (KBr) cm^{-1} 1600, 1172, 1322, 3383, 798.

1.1b.vii. Synthesis of 2, 3-Diphenyl-7-sulfonyl azido quinoxaline (L8)

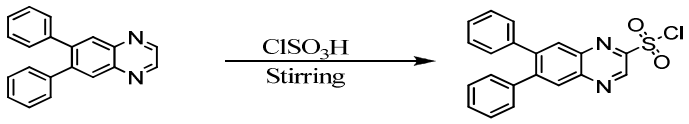
2, 3-diphenylquinoxaline-7-sulfonylchloride (2gm) was dissolved in 25ml acetone and sodium azide (1gm) in minimum amount of water was added in drop with continuous stirring .The mixture was stirring at room temperature for 8hrs.Acetone was removed under reduced pressure followed by addition of water gave crude crystals which was recrystalized from ethanol. Yield: 73%, m.p.-230^{0}C; IR (KBr) cm^{-1} 1561, 1194, 1341, 2124, 798[6].

1.1b.viii. Synthesis of 2, 3-Diphenyl-7-(2- chloro-N-benzyl)-sulfonamido quinoxaline (L9)

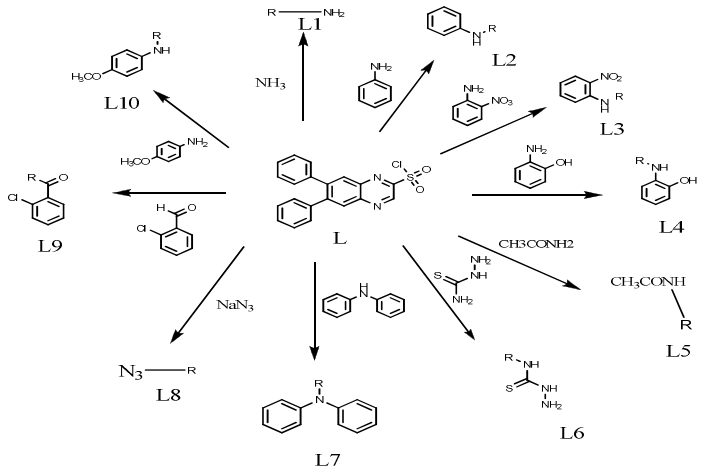
2, 3-Diphenyl-7-sulfonamido quinoxaline (2gm; 0.01moles) and o-chloro benzaldehyde (1gm; 0.01moles) was refluxed with 25ml of ethanol and 1 to 2 drops of glacial acetic acid was added. This reaction takes 4hrs for completion. Crude product was recrystalized from ethanol. Yield: 81%, m.p.-110^{0}C; IR (KBr) cm^{-1} 1592, 1151, 1347, 1664, 2924, 2853, 697[7]; ^{1}H NMR (CDCl3) δ ppm: 8.22, 7.28, 2.28.

3.1b.ix. Synthesis of 2, 3-Diphenyl-7-(4-methoxy-N-phenyl)-sulfonamido quinoxaline (L10)

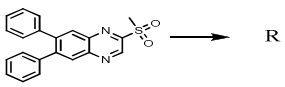
Anisidine (1gm) and 2, 3-diphenylquinoxaline-7-sulfonylchoride (2gm) and 5ml. of pyridine were refluxed for 3hrs. Then reaction mixture was poured into 10ml of cold water and stirred until the product crystallized then product was filtered and recrystalized by ethanol. Yield: 85%, m.p.-120^0 C; IR (KBr) cm^{-1} 1561, 1144, 1334, 3058, 2853, 2920.



Scheme 1: Scheme for synthesis of parent compound (L)



Scheme 2: Synthetic route for the preparation of the target compounds **L1-L10**



2. Results and Discussion

2.1. Anti-inflammatory Screening:

2.1à. Materials/Requirement:

2.1a.i. Selection of experimental animals: Healthy wistar albino rats of either sex weighing between 100-150g were used for the evaluation of anti-inflammatory activity.
2.1a.ii. Laboratory conditions: The rats were housed comfortably in a group of six in a single clean plastic cage with a metal frame lid on its top. They were housed under standard environmental conditions of temperature (24± 2^0C) and relative humidity of 30-70%.
Food and water: All animals had free access to water and standard pelletized laboratory animal diet *ad libitum*.
2.1a.iii. Bedding: In the present study, animals were provided with clean paddy husk bedding. Bedding was changed every alternate day to maintain proper hygienic condition.
Instrument: Digital Plethysmometer (UGO Basile 7140).
2.1a.iv. Inflammation inducer: Carrageenan solution (1% w/v) in distilled water, Standard drug used Diclofenac sodium (10mg/kg).
2.1a.v. Test Compounds: Suspension of compounds (25mg/kg) using 1% w/v solution of acacia as suspending agent.
2.1a.vi. Apparatus: Feeding needles (for oral dosing), Syringes (2ml, 5ml), tuberculin syringe, 24 no. needles, sample tubes (to prepare suspension of test compounds).

2.2. Synthesized compounds were subjected to testing for anti-inflammatory activity[8] in albino rats employing the carrageenan induced rat paw edema test using Plethysmometer (UGO Basile 7140). The compounds were injected orally to the wistar albino rats. Percentage reduction in the inflammation (i.e. reduction in the hind paw edema volume of the animals) at different time interval after administration of carrageenan was recorded, and test compounds (25mg/kg body weight) were compared with that of the animals administrated with carrageenan using the reference standard Diclofenac sodium (10mg/kg body weight).

Data was expressed as Mean Paw Volume ± SEM and analyzed by One-Way ANOVA followed by Dunnett's Test to determine the significance of the difference between the control group and group treated with test compounds. All the statistical calculations were carried out using Graph Pad InStat 3 Statistical Software. The result for anti-inflammatory activity was shown as follows.

Table 1: Mean paw volume and % inhibition of compounds after 30 min

Compounds	Mean Paw Volume (ml) ± SEM	% Inhibition of Edema
Control	0.99 ±0.040	....
L1	0.96 ±0.058	4.04
L2	0.96 ±0.052	3.82
L5	0.98 ±0.021	1.17
Diclofenac sodium	0.85 ±0.0085	15.15

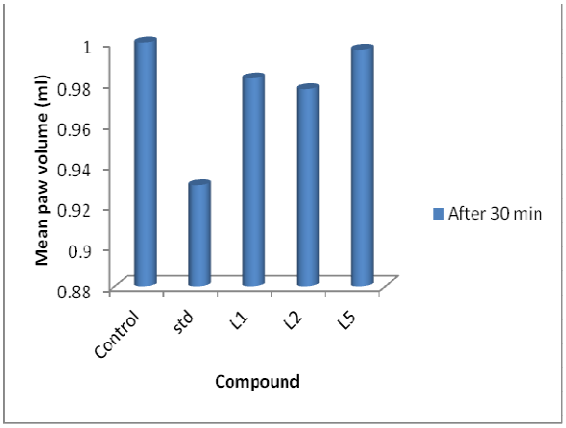


Figure 1: Mean Paw Volume vs. Compound after 30 min.

Table 2: Mean paw volume and % inhibition of compounds after 1hr.

Compounds	Mean Paw Volume (ml) ± SEM	% Inhibition of Edema
Control	1.0 ± 0.063	---
L1	0.98 ±0.032	1.12
L2	0.97 ±0.028	2.25
L5	0.99 ±0.031	0.35
Diclofenac sodium	0.93 ±0.029	7.78

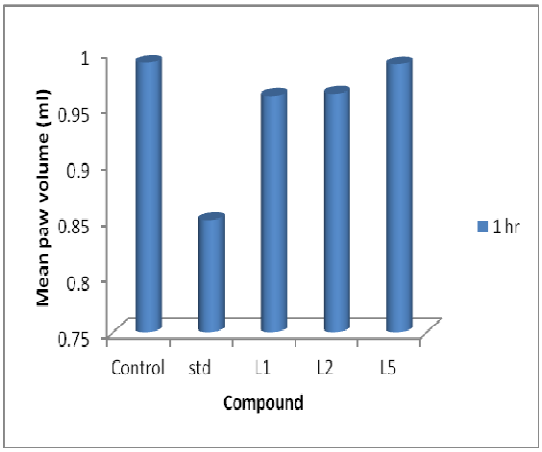


Figure 2: Mean Paw Volume vs. Compound after 1hr.

Table 3: Mean paw volume and % inhibition of compounds after 2 hr

Compounds	Mean Paw Volume (ml) ± SEM	% Inhibition of Edema
Control	1.0 ±0.058	....
L1	0.87 ±0.021	12.77
L2	0.91 ±0.026	8.66
L5	0.90 ±0.054	9.90
Diclofenac sodium	0.78 ±0.010	21.5

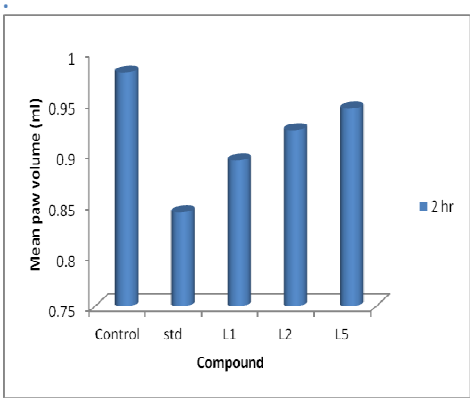


Figure 3: Mean Paw Volume vs. Compound after 2hr

Table 4: Mean paw volume and % inhibition of compounds after 3 hr.

Compounds	Mean Paw Volume (ml) ± SEM	% Inhibition of Edema
Control	0.98 ±0.068	.....
L1	0.89 ±0.014	10.86
L2	0.92 ±0.029	7.84
L5	0.94 ±0.054	5.66
Diclofenac sodium	0.84 ±0.0085	16.06

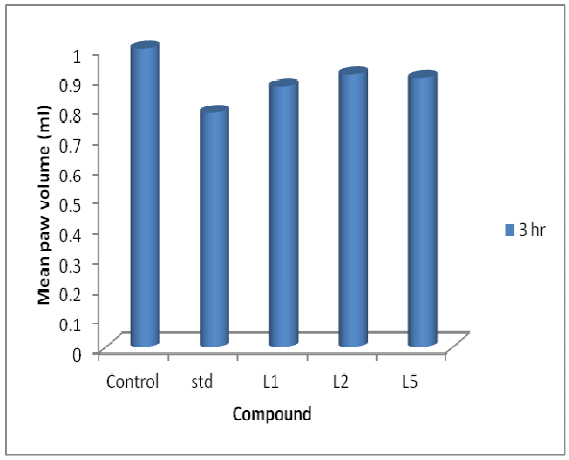


Figure 4: Mean Paw Volume vs. Compound after 3 hr.

Table 5: Mean paw volume and % inhibition of compounds after 6 hr.

Compounds	Mean Paw Volume (ml) ± SEM	% Inhibition of Edema
Control	0.98 ±0.074	.....
L1	0.81 ±0.027	19.15
L2	0.92 ±0.015	8.16
L5	0.82 ±0.021	17.90
Diclofenac sodium	0.77 ±0.006	22.95

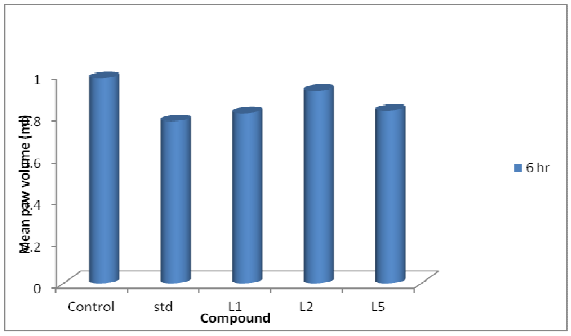


Figure 6: Mean Paw Volume vs. Compound after 6hr.

Table 6: Mean paw volume and % inhibition of compounds after 24 hr.

Compounds	Mean Paw Volume (ml) ± SEM	% Inhibition of Edema
Control	0.99 ±0.056	....
L1	0.80 ±0.026	19.98
L2	0.89 ±0.012	10.75
L5	0.81 ±0.017	19.07
Diclofenac sodium	0.79 ±0.012	21.21

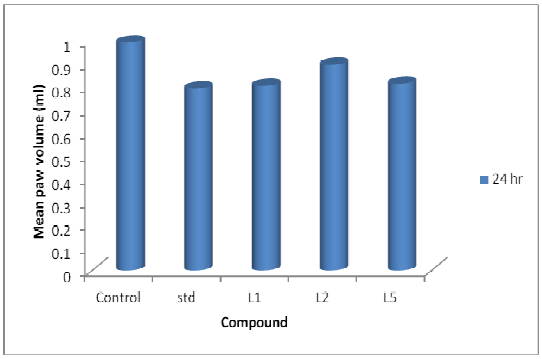


Figure 6: Mean Paw Volume vs. Compound after 24 hr.

"Cite this article"

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