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SYNTHESIS OF SOME NEW SCHIFF'S BASES OF QUINOXALINE-2(1H)-ONE AS POTENT ANTI-INFLAMMATORY AGENTS

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ABSTRACT

In the present investigation, A series Novel Schiff's bases 3-[substituted (phenyl methylidene) amino} ethyl) amino] quinoxalin-2(1H)-one have been synthesized. Final derivatives were screened for their *in-vivo* anti inflammatory activity. All the compounds were characterized by IR and ¹H NMR spectroscopic data. This activity was carried out by using carrageenan- induced paws Model is utilized for this study.

Compound (IIIe) Showed maximum anti inflammatory activity, While compound (III f) showed slight anti-inflammatory activity at both dose when compared with standard drug. The time period for greatest % of inhibition is considered as peak time. It was observed that peak time for compounds was at 3 hr that means % inhibition was maximum at 3 hr. Only two compound i.e. compound IIIe, III d cross value ≥ 50 % inhibition.

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Key Words

Quinoxaline, Phillips condensation, Schiff's bases, aromatic aldehydes, Anti-inflammatory.

INTRODUCTION

Heterocyclic compounds represent an important class of biological active molecules. Specifically those containing quinoxaline derivatives have evoked considerable attention in recent years as these are endowed. Quinoxalines are a versatile class of nitrogen containing heterocyclic compounds and they constitute useful intermediates in organic synthesis. Quinoxaline, also called a benzopyrazine, in organic chemistry, is a heterocyclic compound containing a ring complex made up of a benzene ring and a pyrazine ring and they are isomeric with cinnolones, phthalazines and quinazolines¹. There are a number of processes available to generate quinoxaline but generally, they are synthesized by the condensation of 1, 2-dicarbonyls with 1,2 diamines in presence of suitable catalyst using various solvent systems.

They possess well known biological activities including AMPA/GlyN receptor antagonis², antihistaminic agents³, anti-trypanosomal activity⁴, anti-herps⁵, antiplasmodial activity⁶, Ca uptake/ Release inhibitor⁷, inhibit vascular smooth muscle cell proliferation⁸. Quinoxaline derivatives constitute the basis of many insecticides, fungicides, herbicides, as well as being important in human health and as receptor antagonists. Although rarely described in nature, synthetic quinoxaline moiety is a part of number of antibiotics such as echinomycin, levomycin and actinomycin which are known to inhibit the growth of Gram-positive bacteria and also active against various transplantable tumours.^{9,10} In addition, quinoxaline derivatives are reported for their application in dyes, efficient electroluminescent materials, organic semiconductors and DNA cleaving agents¹¹. These are useful as intermediates for many target molecules in organic synthesis and also as synthons.

Numerous methods are available for the synthesis of quinoxaline derivatives which Extensive researches have generated numerous synthetic approaches for the construction of the skeleton of such heterocycles. Among these methods, the most widely used one relies on the condensation of aryl-1,2-diamines with aryl ketones, usually α -dicarbonyl compounds or their equivalents¹². Recent

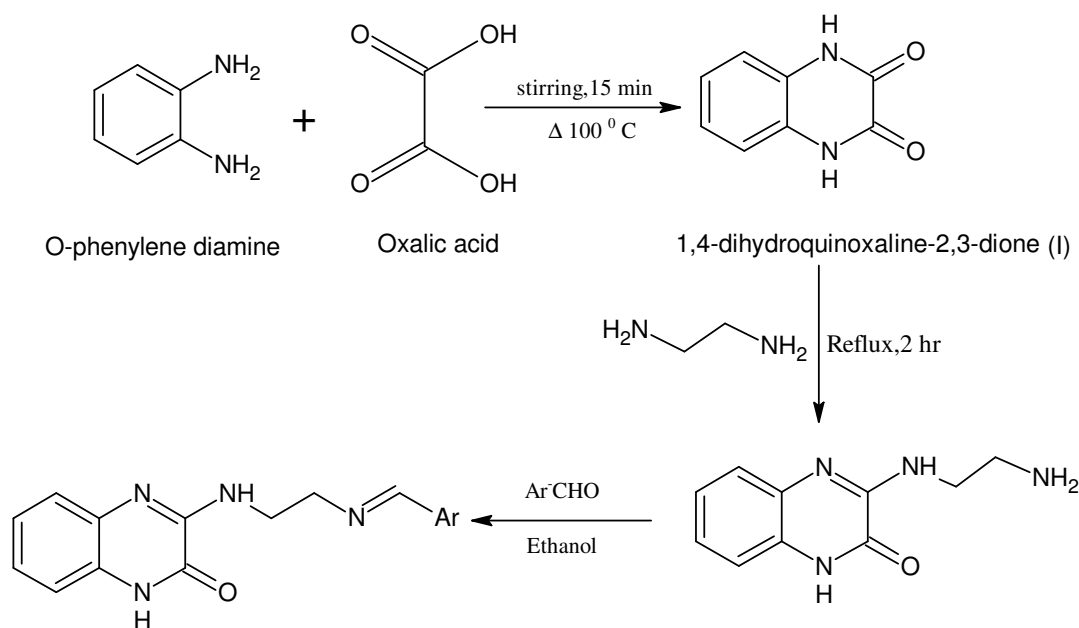
improvements on these conditions were reported via solid-phase¹³, oxidative coupling of epoxides with ene-1,2-diamines¹⁴. Improved methods have been reported via a condensation process catalyzed by CAN¹⁵, molecular iodine as a catalyst¹⁶, manganese octahedral molecular sieves¹⁷, task-specific ionic liquid¹⁸, from PEG-400¹⁹, from IBX²⁰, from PbO²¹, from ZrO₂²², from galactose²³. Recently, a number of catalysts have been reported for the synthesis of quinoxalines. Considering the significant applications in the fields of medicinal, industrial and synthetic organic chemistry, there has been tremendous interest in developing efficient methods for the synthesis of quinoxalines.

EXPERIMENTAL:

MATERIALS AND METHOD:

All chemicals and solvents were procured from commercial sources, and were used without any additional purification. The chemicals were purchased From Sigma-Aldrich, Fine Chemicals and Merck Pvt. Ltd. (India), Laboratory (Pune), Research Lab (Poona), Loba chemicals Pvt. Ltd. (Mumbai) etc. The melting points of the compounds were determined on a VMP-I electric melting point apparatus and the values were uncorrected. Thin layer chromatography was used to assess the course of reactions and the purity of the intermediates and final compounds, giving a single spot on TLC plate (Silica gel G), using various solvent systems. Visualization of the compounds on chromatographic plates was done by exposure to iodine vapors. The ¹H NMR spectra were recorded using TMS as the internal standard and with CDCl₃ as the solvents; the chemical shifts are reported in ppm. Infra red (IR) spectra of the intermediates and final compounds were recorded on Jasco FTIR-410 spectrophotometer using KBr pellet method the frequencies are expressed in cm⁻¹.

Scheme 1



Schiff's bases of substituted quinoxaline 2(1H)-one (III)a-f

3-[(2-aminoethyl)amino]quinoxalin-2(1H)-one (II)

General procedure for synthesis of schiff's bases of quinoxalines:

Synthesis of 1,4-dihydroquinoxaline-2,3-dione (I)

A solution of oxalic acid dihydrate (0.238mole, 30g) in H₂O (100ml) was heated to 100 °C and conc.HCl 4.5 ml was added, followed by O-phenyldiamine (0.204 mole, 22g) with stirring ,temperature was maintained at 100 °C for 20 min. the mixture cooled by addition of ice. The precipitate was formed and washed with water. Product was recrystallized from ethanol.

Synthesis of 3-[(2-aminoethyl)amino]-3,4-dihydroquinoxalin-2(1H)-one (II)

A mixture of the quinoxalindione (I) (0.062mole, 10.04g), ethylene diamine (1mole, 50ml,) , and water (50ml) was heated under reflux for 2 hr, then cooled to room temperature, the precipitate was filtered, washed with water and crystallized from 2-butanol.

Synthesis of 3-[(2-[(E)-(substituted phenyl)methylidene] amino} ethyl) amino]quinoxalin-2(1H)-one (Schiff's bases) (IIIa-f)

In this step, compound 3-[(2 amino ethyl) amino] quinoxalin-2(1H)-one (II) and the corresponding aromatic aldehydes (0.01 mole of each) in ethanol as solvent (20ml) was refluxed for 5hr. Upon cooling the

precipitate was obtained, filtered, dried and crystallized from ethanol.

Physical and spectral data of synthesized compounds

1,4-dihydroquinoxaline-2,3-dione (I)

m.p. = 300 °C, molecular formula (C₈H₆N₂O₂)

IR:3404,3176,3113,1682,1618,1522,1499,1426,1383,755,744; ¹H-NMR (CDCl₃), δ ppm 8.003(s, 2H, NH), 6.978(t, 2H, CH), 6.715 (d,2H, CH)

3-[(2-aminoethyl) amino] quinoxalin-2(1H)-one (II)

m.p. = 262 °C, molecular formula (C₁₀H₁₂N₄O)

IR:3484,3374,3098,2968,2928,1608,1513,1494,1435,820,746;¹HNMR(CDCl₃):,δppm7.711(d,2H,CH),7.590(t,2H,ArH),2.268(q,2H,CH₂),2.747(t,2H,CH₂),8.131(s,2H,NHCO),3.631(s,1H,NH),5.929(s,2H,NH₂)

(3-[(2-[(E)-phenylmethylidene] amino} ethyl) amino] quinoxalin-2(1H)-one (IIIa)

m.p. =222^oC, molecular formula (C₁₇H₁₆ N₄O);

IR:3429,3037,2924,1655,1617,1570,1458,1418,1384,1346,839,751; ¹H-NMR (CDCl₃):, δ ppm: 7.962 (t, 2H, Ar-H), 7.737 (d, 2H, Ar-H), δ 9.953 (s, 1H, CH=N), δ 3.759 (s, 1H, NH), 8.622(s,1H,NHCO),2.282 (q, 2H, CH₂), 2.523 (t, 2H, CH₂), 6.155-7.179 (m, 5H, Ar-H)

3-[(2-[(E)-(3-nitrophenyl) methylidene] amino} ethyl) amino] quinoxalin-2(1H)-one (IIIb)

m.p. = 247^oC, molecular formula (C₁₇H₁₅ N₅O₃);
IR:3403,3048,3083,2984,1679,1615,1563,1312,1471,14
26,1384,807,752;¹H-NMR (CDCl₃):, δ ppm 7.764 (t, 2H,
Ar-H), 6.690(d, 2H, Ar-H), δ 9.977 (s, 1H, CH=N), δ 3.890
(s, 1H, NH), 8.564(s,1H,NHCO),2.548 (q, 2H, CH₂), 3.036
(t, 2H, CH₂), 8.397 (s,1H,Ar-H), 7.89-8.101 (d,2H,Ar-
H).7.892 (t,1H, Ar-H)

3-[(2-[(E)-(2-nitrophenyl) methylidene] amino) ethyl]
amino] quinoxalin-2(1H)-one (IIIc)

m.p. = 232^oC C, molecular formula (C₁₇H₁₅ N₅O₃);
IR:3434,3011,2899,1675,1567,1506,1384,1430,1470,13
56,1301,756,742; ¹H-NMR (CDCl₃):, δ ppm; 7.361 (t, 2H,
Ar-H), 7.290(d, 2H, Ar-H), δ 9.922 (s, 1H, CH=N), δ 3.774
(s, 1H, NH), 8.426(s,1H,NHCO),2.348 (q, 2H, CH₂), 2.136
(t, 2H, CH₂), 7.654-8.197 (d, 5H, Ar-H)

3-[(2-[(E)-(2-hydroxyphenyl) methylidene] amino) ethyl]
amino] quinoxalin-2(1H)-one (III d)

m.p. = 138^oC, molecular formula (C₁₇H₁₆N₄O₂);
IR:3469,3414,3057,2924,2853,1686,1617,1575,1461,14
13,1384,1343,815,745;¹H-NMR (CDCl₃):, δ ppm; 7.380 (t,
2H, Ar-H), 7.095(d, 2H, Ar-H), δ 10.722 (s, 1H, CH=N), δ
3.741 (s, 1H, NH), 8.185 (s,1H,NHCO),2.369 (q, 2H, CH₂),
2.570 (t, 2H, CH₂),11.562(s,2H,OH), 6.668-6.843(d,5H,
Ar-H

3-[(2-[(E)-(4-methoxyphenyl)methylidene] amino)
ethyl amino] quinoxaline-2(1H)-one (IIIe)

m.p. = 273^oC C, molecular formula (C₁₈H₈N₄O₂);
IR:3484,3417,3066,2981,2924,1512,1495,1420,1384,13
42,1246,1162,820,746;H-NMR(CDCl₃) δ ppm; 7.982 (t,
2H, Ar-H), 7.645(d, 2H, Ar-H), δ 10.474 (s, 1H, CH=N), δ
3.832 (s, 1H, NH), 8.943 (s,1H,NHCO),2.378 (q, 2H, CH₂),
2.870 (t, 2H, CH₂),3.616(s,3H,CH₃O), 6.798-6.864(d,4H,
Ar-H)

3-[(2-[(1E, 2E)-3-phenylprop-2-en-1-ylidene] amino)
ethyl amino]quinoxalin-2(1H)-one (III f)

m.p. = 258^oC, molecular formula (C₁₉H₁₈N₄O);
IR:3448,3417,3067,2923,1699,1610,1586,1456,1586,14
56,1427,1383,1315,739,780;H-NMR(CDCl₃) δ ppm ; 7778
(t, 2H, Ar-H), 7.678(d, 2H, Ar-H), δ 10.694 (s, 1H, CH=N),
δ 3.446 (s, 1H, NH), 9.065 (s,1H,NHCO),2.291 (q, 2H,
CH₂), 2.509 (t, 2H, CH₂),6.845(d,1H,Ar-H),7.074(t,1H,Ar-
H),7.310-7.549(m,2H, Ar-H),7.742-7.254(d,2H, Ar-H)

Pharmacological evaluation:

Animals for Experiments:

Adult Albino wistar rats (120-260 gm) were procured from Animal House of Appasaheb Birnale College of Pharmacy, Sangli, Maharashtra. These animals were maintained under standard condition and provided pelleted diet and sterile water ad libitum and kept in 12-12 hrs light-dark cycle. All the Animal's experiments were performed by following the approval of study protocols by the Institutional Animal Ethical Committee.

Anti-inflammatory activity:

Animals were divided into eight groups, out of which six groups are of tests animals, one group each of standard and control. (n=6) starved overnight with water ad libitum prior to the day of experiment. The control group has given vehicle orally, while other group given test drug and standard drug respectively. All the compounds were dissolved in DMSO to get concentration of 10 mg/kg and 20 mg/kg. Diclofenac sodium was dissolved in DMSO to get concentration of 5 mg/kg; this was used as a standard for determination of anti inflammatory activity. Left paw was marked with ink at the level of lateral malleolus; basal paw volume was measured plethysmographically by volume displacement method using Plethysmometer (UGO Basile 7140) by immersing the paw till the level of lateral malleolus. The animals were given drug treatment. One hour after dosing, the rats are challenged by a subcutaneous injection of 0.1ml of 1% solution of carrageenan into the sub-plantar side of the left hind paw. The paw volume was measured again at 1, 2, 3, 4 & 5 hours after challenge. The increase in paw volume was calculated as percentage compared with the basal volume. The difference of average values between treated animals and control group is calculated for each time interval and evaluated statistically. The percent Inhibition was calculated using the formula as follows.

$$\% \text{ edema inhibition} = [1 - (V_t / V_c)] \times 100$$

Where, V_t and V_c are edema volume in the drug treated and control groups respectively. Observations were taken as a Percentage of Inhibition (%) of paw volume and recorded in Table No. 3

Table No.1 List of aromatic aldehyde used.

Compound No.	Aromatic aldehyde
III a	C ₆ H ₅ .CHO
III b	3 NO ₂ -C ₆ H ₄ .CHO
III c	2 NO ₂ -C ₆ H ₄ .CHO
III d	2 OH-C ₆ H ₄ CHO
III e	CH ₃ O-C ₆ H ₄ CHO
III f	C ₆ H ₅ .CH ₂ CH=CH CHO

Table No.2 Physicochemical data for the compound III a-f

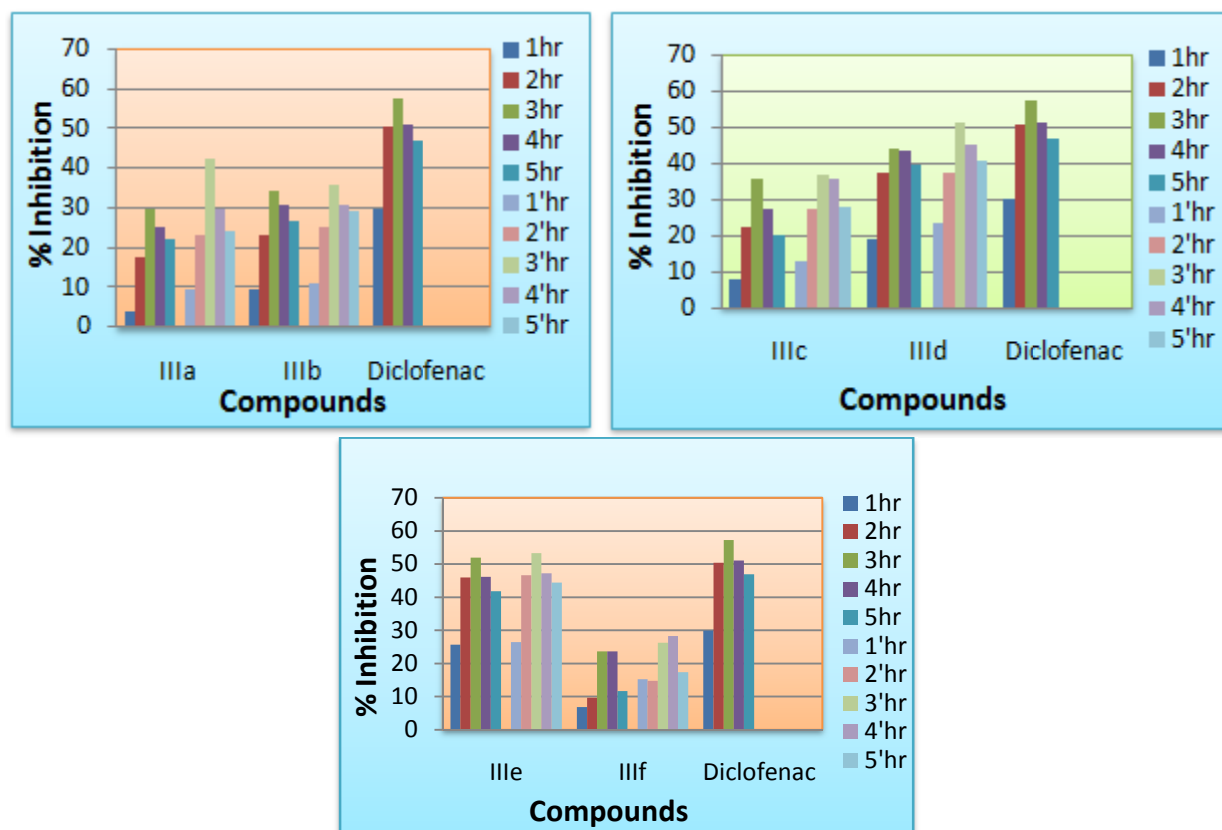
Compound No.	Molecular Formula	M.P	%	*R _f value
			Yield	
III a	C ₁₇ H ₁₆ N ₄ O	222 ⁰ C	64	0.77
III b	C ₁₇ H ₁₅ N ₅ O ₃	247 ⁰ C	59	0.83
III c	C ₁₇ H ₁₅ N ₅ O ₃	232 ⁰ C	62	0.89
III d	C ₁₇ H ₁₆ N ₄ O ₂	138 ⁰ C	67	0.87
III e	C ₁₈ H ₈ N ₄ O ₂	273 ⁰ C	54	0.64
III f	C ₁₉ H ₁₈ N ₄ O	258 ⁰ C	71	0.51

Table No 3. Percentage of Inhibitions (%) of paw volume of rats

Compound	Conc. of Test Compound (mg/kg)	Percentage of Inhibition (%)				
		1 hr	2 hr	3 hr	4 hr	5 hr
Standard	5	29.41	50.37	57.23	51.09	46.43
IIIa	10	4.27	17.77	29.60	25.27	21.93
	20	9.40	22.46	42.5	29.67	23.97
IIIb	10	9.40	22.96	34.21	30.76	26.53
	20	11.11	25.18	35.52	30.96	29.08
IIIc	10	7.69	22.22	35.52	27.47	19.89
	20	12.82	27.40	36.84	38.57	27.55

III d	10	18.80	37.03	44.07	43.40	39.28
	20	23.07	37.03	51.31	45.05	40.30
III e	10	25.64	45.92	51.97	46.15	41.83
	20	26.494	46.66	53.28	47.25	44.38
III f	10	6.83	9.62	23.68	23.62	11.73
	20	15.21	14.01	26.31	28.27	17.34

Figure No.1 Graph showing % Inhibition of Test compounds



Where, *1, 2, 3, 4, 5 hr Dose of test compound at 10 mg/kg

*1' 2', 3', 4', 5' hr Dose of test compound at 20 mg/kg

RESULTS AND DISCUSSION:

In the current research work, we aimed to synthesize some novel Schiff's bases of quinoxalines. The aforementioned compounds were prepared according to the synthetic process illustrated in scheme 1. The structural elucidation of the synthesized compounds was carried out with the help of IR spectroscopy and ^1H

NMR spectroscopy. Screening of the in vivo anti-inflammatory activity of the novel Schiff's bases of 3-[[2-((E)-[substituted] phenyl) methylidene] amino] ethyl] amino} quinoxalin-2(1H)-one Allowed us to identify interesting anti-inflammatory candidates based on their potency, making them valid new leads for synthesizing new compounds that might improve the

previously methods of synthesis. This activity was carried out by using carrageenan induced paws Model is utilized for this study. In the carrageenan induced paws, the test and standards drug produced significant percent of decrease in paws edema volume as compared to the control.

Compound (IIIe) Showed maximum anti inflammatory activity, Percentage of Inhibition 53.28%, at both dose when compared with standard drug while compound (IIIb) possesses moderate activity at dose 20 mg/kg Percentage of Inhibition 35.52%. Compound (IIIc) showed slight anti inflammatory activity at both dose when compared with standard drug, Percentage of Inhibition 26.31%. The time period for greatest % of inhibition is considered as peak time. It was observed that peak time for compounds was at 3 hr that means % inhibition was maximum at 3 hr. Only two compound i.e. compound IIIe, IIIc cross value \geq 50 % inhibition.

Carrageenan induced paw edema is a biphasic response. The first phase was mediated through the release of Histamine, serotonin & Kinin, where as the second phase is related to the release of prostaglandin. The synthesized compounds produced significant inhibition of Carrageenan induced paw edema.

STATISTICAL ANALYSIS:

Statistical analysis of the differences observed between control and treated groups were carried out using ANOVA. P value <0.005 was considered significant. Dennett's post ANOVA has been done.

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