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ECO-FRIENDLY PREPARATION OF DIFFERENT QUINOXALINE ANALOGUES AND THEIR ANTI-DIABETIC EVALUATION

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ABSTRACT

In an effort to develop newer quinoxaline derivatives synthesized by green synthetic techniques and perform *in vitro* and *in vivo* evaluation for potent anti-microbial and anti-diabetic activities respectively. To synthesize few newer quinoxaline derivatives and the synthesized quinoxaline derivatives having antibacterial and anti-diabetic properties. When compared to all the synthesized derivatives, QX2, and QX3 have a greater anti-microbial and anti-diabetic activities, further characterization of derivatives was done by determining their melting point, Retention factor from thin layer chromatography and spectroscopic studies. This research article highlights the outcomes of quinoxaline derivatives by performing anti-diabetic activity. This has shown a positive potency for some derivatives by assessing the microbial and pharmacological activities by comparing them with standard marketed drugs.

Keywords: Quinoxaline, Anti-diabetic, Anti-microbial, Alloxan, Green Synthesis

INTRODUCTION:

One of the most important heterocyclic scaffolds is the quinoxaline nucleus. Quinoxaline can be found as a biologically active chemical, whereas antibiotics such as Levomycin, Actinoleutin and Echinomycin, are known to be efficacious against various transplantable tumours **[1]**. Therapeutic applications in pharmaceutical research include properties like anti-cancer **[2-4]**, anti-inflammatory **[5]**, anti-viral **[6, 7]**, anti-diabetic **[8, 9]**, anti-depressant **[10]**, anti-helminthic **[11]**, anti-tuberculosis **[12]**, anti-bacterial **[13, 14]** and anti-protozoal **[15, 16]**. Apart from that, they have several

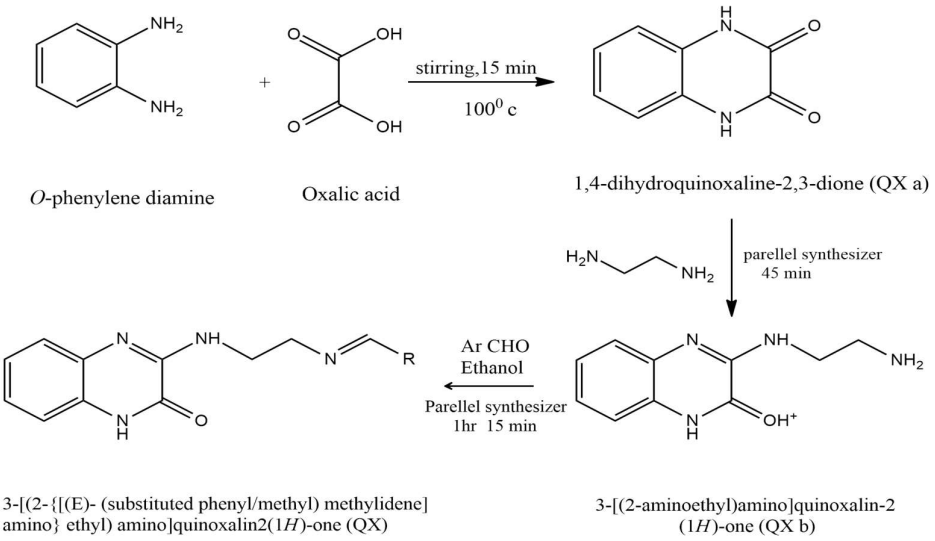
applications in various fields of industries including agriculture **[17]**, Fluorescent materials **[18]**, Dyes **[19]**, Electroluminescent materials **[20]**, organic semiconductors **[21]**, organic light emitting devices **[22]** and medicinal chemistry. Beyond that, quinoxalines are also utilised as herbicides, insecticides and fungicides in agriculture **[17]**. As a result of the wide range of practical uses for quinoxalines, scientists place a high value on traditional synthesis methods. The alteration, as well as novel ways of synthesizing quinoxalines in order to ensure the availability of more functionalized quinoxalines.

Diabetes mellitus is a group of chronic metabolic diseases with various etiologies that are characterised by hyperglycaemia and abnormalities in protein, lipid, and carbohydrate metabolism as a result of a partial or complete lack of insulin. Diabetes can be classified into three types: Type-1 diabetes mellitus is an auto-immune illness in which the body's immune system assaults the pancreas, stopping it from generating insulin **[23]**. Type-2 diabetes mellitus can be distinguished by insulin resistance or a deficiency in insulin production **[24]**. Biguanides like Metformin, Sulfonylureas like Glimepiride and Glipizide, Meglitinides like Repaglinide and Nate glinide, and Thiazolidines like Pioglitazone and Rosiglitazone are some of the anti-diabetic medications now in use **[25]**.

EXPERIMENTAL SECTION

All chemicals and solvents were purchased and procured commercially and utilised without further purification. Thin layer chromatography (TLC) was used to monitor the reactions on grade 60 F_{254} silica gel plates. All melting points were measured in an "AMTECH" melting point apparatus, and accurate derivative results are provided. The infrared spectra of the synthesised compounds were acquired using a BROOKER-ALPHA spectrophotometer by the potassium bromide pellet technique. The 1^{H} NMR & ^{13}C NMR spectra were recorded on a BROOKER AC 100 MHZ spectrophotometer, using TMS as the internal standard and $CDCl_3$ as the solvents; chemical shifts are reported in parts per million relatives to tetramethyl silane (1%) as an internal standard.

SCHEME:



GENERAL PROCEDURE FOR SYNTHESIS:

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

A solution of oxalic acid dihydrate (0.238mole, 30g) in H_2O (100ml) was heated to 100^0C, then 4.5 ml of Conc. HCl was added, followed by *O*-phenylenediamine (0.204 moles, 22g) with stirring, and the temperature was kept at 100^0C for 20 minutes. The mixture was chilled by adding ice. Water was used to wash the precipitate and Ethanol for recrystallization.

Synthesis of 3-[(2-aminoethyl) amino] quinoxaline-2(1*H*)-one (QX b)

A mixture of quinoxalinedione (QX a) (0.0602mole,10.04g), ethylene diamine (1mole, 50 ml), and water (50ml) was heated in a parallel synthesiser for 45 minutes, cooled to room temperature, and the precipitate was filtered, washed with water, and crystallised from 2-butanol.

Synthesis of 3-[(2-{[(E)-substituted (phenyl)methylidene] amino} ethyl) amino] quinoxaline-2(1*H*)-one (QX): A parallel synthesised mixture of 3-[(2-aminoethyl) amino] quinoxaline-2(1*H*)-one (QX b) and the corresponding aromatic aldehyde (0.01 mole of each) in ethanol as solvent (20ml). The precipitate was collected, filtered, dried, and crystallised from ethanol after cooling.

Table 1: The physical properties of synthesized quinoxaline derivatives

Compounds	Molecular formula	M.W	M.P(^{0}C)	% Yield	R_f
QX a	$C_6H_2N_2O_2$	134.6	300^{0}C	90.12%	0.65
QX b	$C_{10}H_{12}N_4O$	204.3	262^{0}C	83.19%	0.52
QX 1	$C_{19}H_{21}N_5O$	335.1	177^{0}C	85.7%	0.86
QX 2	$C_{17}H_{16}N_4O_2$	308.3	222^{0}C	80.6%	0.76
QX 3	$C_{17}H_{15}ClN_4O$	326.7	232^{0}C	84.22%	0.89
QX 4	$C_{20}H_{22}N_4O_4$	382.4	186^{0}C	89.15%	0.66
QX 5	$C_{12}H_{14}N_4O$	230.2	276^{0}C	80.85%	0.60
QX 6	$C_{19}H_{20}N_4O_3$	352.3	238^{0}C	86%	0.46

1. **3-{2-[(4-Dimethylamino-benzylidine)-amino]-ethylamino}-ethyl}-1*H*-quinoxalin-2-one (QX 1)** : M.W: 335.1; M.P (^{0}C): 177; molecular formula ($C_{19}H_{21}N_5O$); IR: N-H (3317.08); C-H (2357.47); C=O (1684.65); C-N (1241.17); C=C (750.70)^{1}HNMR; CH aromatic (7.076,7.084,7.131,7.139); CH benzylidene (6.730,6.709,7.502,7.526,7.548); CH_3 (2.526,2.784); CH_2(3.483,3.742); NH amide (3.003); NH sec amine (8.142) ;^{13}C NMR: CH aromatic (7.157,7.149,7.448,7.467); CH benzylidene (8.019,7.999,7.574,7.593,7.612.); NH (8.581); CH_2 (3.624,3.950); Elemental analysis: C,66.22; H,5.23; N,18.17; O,10.38.
2. **3-{2-[(2-cholro-benzylidine)-amino]-ethylamino}-1*H*-quinoxalin-2-one (QX 2):** M.W:308.3; M.P(^{0}C): 222^{0}C; Molecular formula: $C_{17}H_{16}N_4O_2$; IR:C-Cl (861.32; C-O (1258.10); C-N (1018.63); O-H (1383.88); C-H (1678.58); O-H (2925.69) H NMR: CH:(7.0,7.2,7.6,7.2); CH benzylidene:(8.11,7.30,7.23,7.17,7.56); CH_2:(3.01,3.81); NH amine (2.0); NH sec amine (8.0). C NMR: CH:(125.4,127.2,121.7,122.2); CH benzylidene (128.5); C benzene (131.7,140.9); CH_2 (54.7,43.7); C imine (163); C imide (161); C,62.48; H,4.63; Cl,10.85; N,17.15; O,4.90.
3. **3-{2-[(3,4,5-Trimethoxy-benzylidine)-amino]-ethylamino}-1*H*-quinoxalin-2-one (QX 3):** M.W**:**326.7; M.P(^{0}C): 232^{0}C; Molecular formula: $C_{17}H_{15}ClN_4O$; IR: O-H (2961.50); C=O (1681.21); N-H (1590.42); C-O (1132.88); C-N (1236.41); C-H (749.57,704.50).H NMR:CH (7.6,7.2,7.0,7.2); CH benzylidene (6.58,6.58,8.11); CH_2 (3.81,3.01); CH_3 (3.73); NH amine (2.0); NH sec-amine (8.0). C NMR: CH (121.7,127.2,125.4,122.2); CH benzylidene (136.6,107.9,107.9,163.7); CH_2 (54.7,43.7); C-O (148.7,135.5,148.7). Elemental analysis: C,62.82; H,5.80; N,14.65; O,16.74.
4. **3-(2-Ethylideneamino-ethylamino)-1*H*-quinoxalin-2-one (QX 4):** M.W: 382.4; M.P(^{0}C): 186^{0}C; Molecular formula: $C_{12}H_{14}N_4O$; IR: C=O (1683.13); O-H (1392.98); C-N (1243.77); C-H (1513.67); C=C (749.98).H NMR: CH (7.6,7.2,7.0,7.2); NH amine (2.0); NH sec-amine (8.0); CH_3 (0.9), CH_2 (1.6,2.7). C NMR: CH (121.7,127.2,125.4,122.2); CH_2

(54.7,43.7); CH_3 (12.4); CH imine (163.7); C amine (161,163): Elemental analysis: C,62.59; H,6.13; N,24.33; O,6.95.

5. **3-{2-[(3,4-Dimethoxy-benzylidine)-amino]-ethylamino}-1*H*-quinoxalin-2-one (QX 5)** M.W: 230.2; M.P(^{0}C): 276^{0}C; Molecular formula: $C_{19}H_{20}N_4O_3$; IR: O-H (3045.10); C=O (1679.17); C-H (1385.72); C-H (856.81) [1,3 disubstituted]. H NMR: CH (7.6,7.2,7.0,7.2); CH benzylidene (7.02,7.07,6.69,8.11); CH_2 (3.81,3.01); CH_3 (3.73); NH amine (2.0); NH sec-amine (8.0). C NMR: CH (121.7,127.2,125.4,122.2); CH_2 (54.7,43.7); C imine (163); C imide (161); CH benzylidene (130.6,122.3,125.4,122.2); C-O (149.9, 147.7); O-C (56.3): Elemental analysis:64.76; H,5.72; N,15.90; O,13.62.
6. **3-{2-[(4-Hydroxy-benzylidine) -amino]-methylamino}-1*H*-quinoxalin-2-one (QX 6)** M.W: 352.3; M.P(^{0}C): 238^{0}C; Molecular formula: $C_{19}H_{20}N_4O_3$; IR: C=O (1686.46); O-H (3046.15); C-H (1394.14); C=C (753.25). H NMR: CH benzene (7.081,7.088,7.130,7.138), CH benzylidene (6.794,6.808,7.517,7.538,8.197); CH_2 (3.501,3.765); NH (2.508) O-H (5.0): ^{13}C NMR:CH aromatic (115.11-125.66); CH imine (155.12); CH_2 ethylenediamine (40.08,40.29); Elemental analysis: C,66.22; H,5.23; N,18.17; O,10.38.

PHARMACOLOGICAL EVALUATION:

ANTI-DIABETIC ACTIVITY:

Normal healthy Wister rats (200g) of either sex were used in the present study. The experimental protocol was priorly approved by the Institutional Animal Ethics Committee of Chalapathi Institute of pharmaceutical sciences (Approval No.19/IAEC/CLPT/2022-23); dated 27/01/2023. Before the trial began, the animals were given 72 hours of time for acclimatization to the lab environment. Before starting the experiment, the animals were separated into seven groups, each of which had four animals on or before 12 hours of light and dark cycles separation must be done. These groups were kept under their respective controlled temperature conditions for 30 days. Prior to the experimentation, the animals were fasted for 18 hours with denied food and water access.

Induction of diabetes: After fasting, rats were given an intraperitoneal injection of 160 mg/kg of alloxan monohydrate diluted in sterile saline to induce hyperglycaemia. Following an hour of alloxan administration, the animals were followed

for the estimation of fasting blood glucose levels and started given regular pellets and unlimited access to water. Diabetic rats were defined as those with fasting blood glucose levels greater than 200mg/dl and were chosen for investigation **[26, 27]**.

Blood Glucose Estimation: Blood collected from the tip of the tail, and blood glucose levels were calculated using a glucometer (Jan Aushadhi) using the strip method on 0,7,14,21 days of the experiment.

Anti-Microbial Activity: By using the Disc diffusion technique, all synthesized derivatives and common medications have been tested for their *in vitro* anti-microbial activity against four bacterial strains, including two gram-positive strains and two gram-negative strains. It included *Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli*, and compared activity with standard marketed drugs like ampicillin.

Preparation of Discs:

The Whatman filter paper was punched to create paper discs. Then discs were submerged in DMSO-based solutions with synthesized drug concentrations of 50 and 500 µg/ml, respectively. After preparing the discs, they were dipped in ampicillin standards (50µg/ml and 500µg/ml in DMSO). The discs were then removed from the liquids using sterile forceps and placed individually on Petri dishes with the solid medium. To achieve optimal dispersion, the Petri plates were placed in a hot air oven for 5-10 minutes after being removed. The infected plates were incubated at 37^0C for 24 hrs to 48 hrs, depending on whether they had been injected with bacteria or fungi. Zones of inhibition were identified on Petri plates which (in millimetres) were reported **[28]**.

RESULTS AND DISCUSSION

Anti-Diabetic Activity: Apart from streptozotocin, alloxan is a commonly utilised drug for the production of diabetes mellitus. Alloxan is toxic to pancreatic beta cells. Alloxan can cause hyperglycaemia by destroying ß-cells in the islets of Langerhans. Insulin insufficiency causes metabolic changes in animals such as increased blood glucose, cholesterol, alkaline phosphate levels, and transaminases. Alloxan (160mg/kg intraperitoneal.) caused an increase in fasting blood glucose levels, which was sustained over a 21-day period of daily treatment with the standard and test derivatives, resulting in a drop in blood sugar levels. The disruption of the pancreas in alloxan-treated diabetic control rats and cell regeneration by glibenclamide were documented in multiple investigations. It has been discovered that QX 2 and QX 3 are more effective during the first 21 days of treatment and have a similar therapeutic result as that of standard, Glibenclamide (5mg/kg).

Table 2: Data regarding diabetes

Days	control	Diabetic control	standard	QX 1	QX 2	QX 3	QX 4
0	100±0.91	345±0.95	331±1.29	331±0.86	324±1.04	333±1.10	343±1.58
7	103±0.47	359±0.64	261±0.85	276±0.81	277±0.85	274±1.37	283±1.10
14	105±0.47	372±1.47	143±1.08	234±1.10	225±1.08	207±1.29	233±1.88
21	107±1.04	381±0.62	122±0.47	155±1.10	135±0.85	147±1.25	165±1.08

Table 3: Anti-microbial activity presented as a zone of inhibition (mm)

Compound	Conc. of test compound(µg/ml)	Zone of inhibition (mm)			
		Bacillus subtilis	*Staphylococcus aureus*	*Pseudomonas aerogenosa*	*Escherichia coli*
Ampicillin	500	23	14	24.7	13.9
	50	16.5	11	18.3	12.1
QX 1	500	10.1	7.3	15.7	8.3
	50	7.3	4.9	12.3	7.7
QX 2	500	14.7	9.6	25.9	10.8
	50	13	7.4	13.5	9.5
QX 3	500	18.3	9.2	13.2	11.3
	50	12.6	6.9	12.2	10.3
QX 4	500	18.1	8.8	16.9	9.6
	50	12.4	5.4	10.9	7.7
QX 5	500	12.4	8.5	13.1	9.2
	50	12.2	5.3	12.7	8.5
QX 6	500	12.4	8.1	12.5	8.9
	50	8.1	5.6	11.3	7.1

Statistical Analysis: All values were expressed as the standard error of the mean. Statistical significance was made by using two-way ANOVA multiple comparison tests using Graph pad Prism 4.0 software

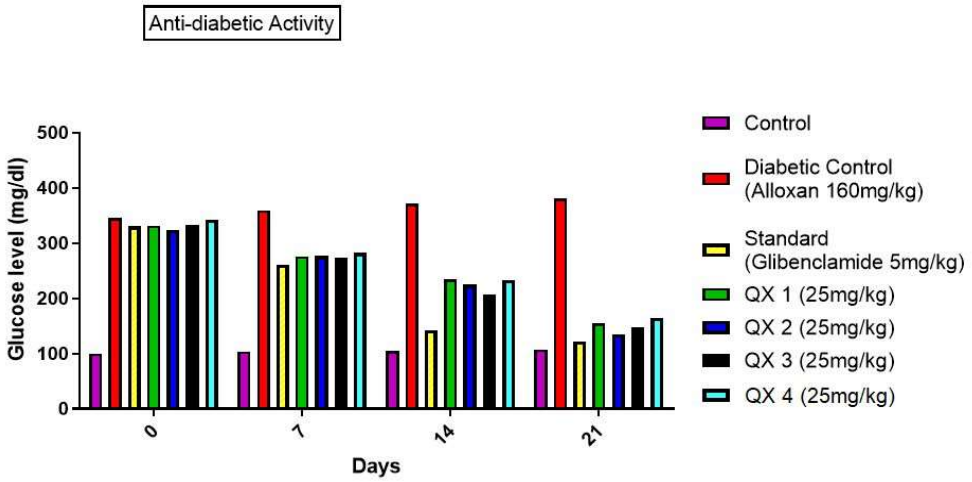


Figure 1: Anti-diabetic activity of synthesized quinoxaline derivatives

The screening of the 3-[2-((E)-[Substituted)phenyl] methylidene amino) quinoxaline-2(1*H*)-one (QX) derivatives, allowed us to find interesting anti-microbial compounds based on their potency, making it possible to develop novel anti-microbial agents. They are valid new leads for synthesizing novel chemicals, which may improve earlier methods of synthesis.

Different types of aldehydes were utilized in this approach and the physicochemical parameters of the synthesized derivatives are summarised in **Tables 1 and 2** respectively. The ambient circumstances,

very good yields, fast reaction times, and use of an inexpensive, easily available material are some of the key advantages of this technique. Simple workup technique, no volatile or toxic solvents no metal catalysts. All derivatives were tested for the zone of inhibition by comparing them to the standard at two different concentrations (50µg/ml and 500µg/ml). *Bacillus subtilis, Pseudomonas aeruginosa staphylococcus aureus, and Escherichia coli* were studied. It can be concluded that QX 2 and QX 3 have displayed maximum activity against all bacteria utilized and also maximum responses for QX 4 towards *Bacillus subtilis and Pseudomonas aeruginosa*. QX 5 for *Escherichia coli and* QX 6 for *Staphylococcus aureus* showed their maximum responses.

CONCLUSION: It can be concluded from the present investigation that synthesized Quinoxaline derivatives have shown excellence in their activities such as anti-bacterial and anti-diabetic. In that mainly we spotted QX 2 and QX 3 can show their maximum activities when there are compared to reference/ standard marketed drugs activities for both anti-bacterial and anti-diabetic.

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