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SYNTHESIS OF UNIQUE QUINOXALINE COMPOUNDS AND THEIR ANALGESIC ACTIVITY

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ABSTRACT

In an approach to develop potent analgesic agents, we synthesized few of newer quinoxaline derivatives through green synthesis. Final derivatives were screened for their *in-vitro* and *in-vivo* anti-bacterial and analgesic activities on different bacterial species like *Bacillus subtilis, Staphylococcus epidermititis, Pseudomonas vulgaris, Pseudomonas aeruginosa* and animals like Swiss albino mice. All the compounds were characterized by IR and H^1 NMR spectroscopic data. By performing the above screening procedures, all the synthesized quinoxaline derivatives are unique compounds that show good responses for both anti-bacterial and analgesic activities. In that, the compounds QX2 and QX3 have shown maximum response for both activities when compared to standard drugs like Ampicillin and Pentazocine.

Keywords: Quinoxaline, Anti-bacterial, Green-synthesizer, Analgesic

INTRODUCTION

Quinoxaline compounds have a wide range of activities including antibacterial **[1 -2]**, antifungal **[3-4]**, anti-tubercular **[5]** analgesic **[6]** and anti-inflammatory **[7]**, anti-oxidant **[8-9]**, anti-diabetic **[10]**, anticonvulsant **[11-13]**, anti-hypertensive **[14-15]**, antiviral **[16-17]** anti-HIV **[18]** anti-cancer activities **[19-20]**. In addition, they have a number of uses in numerous industrial sectors, such as agriculture, fluorescent materials, dyes **[21]**, electroluminescent materials, organic semi-conductors **[22]**, and organic light-emitting apparatuses **[23]**. In addition, quinoxalines are used in agriculture as fungicides, insecticides, and herbicides. Quinoxalines

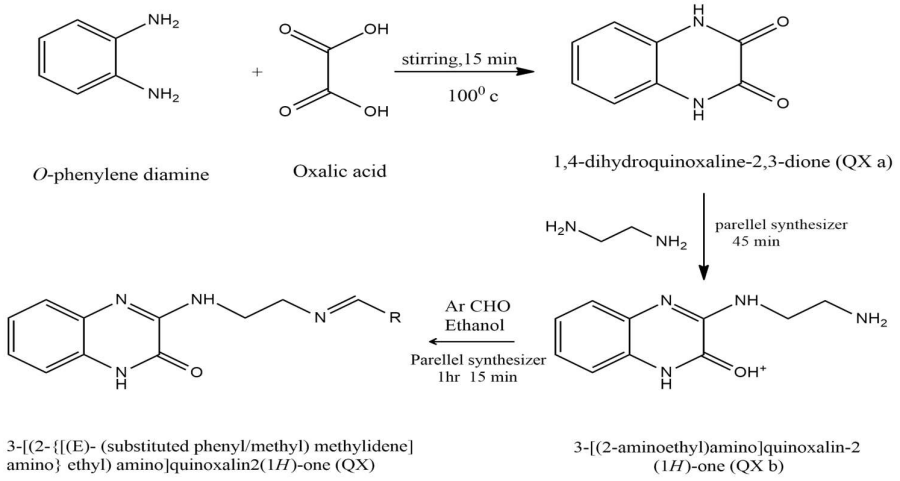
have a wide range of practical applications, thus scientists place a high emphasis on conventional synthesis techniques. Quinoxalines must be altered and produced in unique ways to assure the availability of more functionalized quinoxalines.

Analgesics are drugs that relieve pain by acting on the central nervous system or on a peripheral pain mechanism, without significantly altering consciousness **[24]**. Analgesics are broadly divided into two groups. They are opioid and non-opioid analgesics. Opioid analgesics act on central nervous system and are more potent. Examples: Morphine, whereas non-opioid analgesics act on peripheral nervous system and are less potent **[25]**. Examples: NSAID's. In this, we have synthesized newer quinoxaline derivatives and evaluated for anti-bacterial and analgesic activity.

EXPERIMENTAL SECTION

All of the chemicals as well as the solvents used in the experiment were made by companies like Lobra Chemicals Pvt. Ltd., Mylochem Pvt. Ltd., and Ayra Chemicals Pvt. Ltd. and were obtained from the Delta Scientific Company. Thin layer chromatography (TLC) was used to monitor the reaction on gel glass plates. By using the Thiele tube method, the melting points of several derivatives were determined. (jsgw). Using the potassium bromide pellet approach, the infrared spectra of the synthesized derivatives have been recorded using a JASCO-FTIR 8400 spectrophotometer. The chemical shifts are provided in ppm (δ), and the 1H-NMR spectra were obtained using a Bruker 400 Ultra shield instrument (300 MHz), TMS as the internal standard, and CDCl3 as the solvent. Chemical shifts are expressed in parts per million (δ) with respect to the internal standard, tetramethylsilane (1%) in this case. (CDRI, Lucknow, India).

SCHEME FOR SYNTHESIS:-



Steps involved in the synthesis of quinoxaline derivatives: -

1. Synthesis of 1,4-dihydroquinoxaline-2,3-dione.
2. Synthesis of 3-[(2-aminoethyl) amino] quinoxaline-2(1*H*)-one.
3. Synthesis of Quinoxaline containing aldehyde derivatives.

Procedure: -

1) Synthesis of 1,4-dihydroquinoxaline-2,3-dione:

Oxalic acid dihydrate of (0.238moles) 30g is weighed and dissolved in 100ml of water and heated to 100^0C.To this add conc. HCl of 4.5ml was added followed by the addition of o-phenylene diamine of (0.204 moles) 22g upon stirring by maintaining the temperature at 100^0C for 20min.The mixture was then placed on ice-bath and cooled by the addition of ice. The precipitate was formed upon constant stirring & it is collected and washed with water.

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

To the first step product, ethylene diamine of (1mole) 50ml was added and followed by 50ml of distilled water and synthesized through parallel synthesizer for 45min , then the mixture was cooled to room temperature . The formed precipitate was filtered and washed with water.

3) Quinoxaline containing aldehyde derivatives:

To the second step product add the corresponding aromatic aldehyde (T_1-T_7), (0.01 mole of each) and ethanol as solvent of 20ml and was kept in parallel synthesized for 1hr 15min. The mixture was cooled to room temperature and the product was filtered and dried **[26]**.

Table 1: List of aromatic aldehydes used

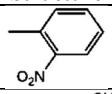
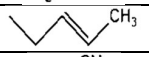
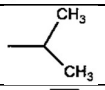
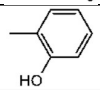
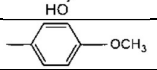
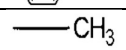
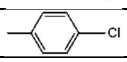
Compounds	Structure	Aromatic aldehyde & Ketone
QX1		2- Nitro benzaldehyde
QX2		Crotonaldehyde
QX3		Ethyl methyl ketone
QX4		Salicylaldehyde
QX5		Anisaldehyde
QX6		Formaldehyde
QX7		p- chloro benzaldehyde

Table 2: Physical properties of compounds

Compound Code	Mol. Formula	Mol. wt.	m.p.	R_f	Percentage yield	Solubility	color
QX1	$C_{17}H_{15}N_5O_3$	337.3	232	0.89	90.52	DMSO	Solid/white
QX2	$C_{15}H_{18}N_4O$	270.3	226	0.76	89.23	DMSO	Solid/white
QX3	$C_{14}H_{20}N_4$	244.3	247	0.56	95.2	DMSO	Solid/white
QX4	$C_{17}H_{16}N_4O_2$	308.3	222	0.76	90.77	DMSO	Solid/yellow
QX5	$C_{18}H_{18}N_4O_2$	322.3	190	0.82	89.15	DMSO	Solid/white
QX6	$C_{11}H_{12}N_4O$	216.2	262	0.54	81.38	DMSO	Solid/white
QX7	$C_{17}H_{15}ON_4Cl$	326.7	300	0.85	80	DMSO	Solid/white

Physical and Spectral data of synthesized compounds:-

1. **3-{2-[(2-Nitro-benzylidene)-amino}-1*H*-quinoxalin-2-one (QX1):**

M.W: 337.32; M.P(^{0}C): 232; Molecular formula: $C_{17}H_{15}N_5O_3$. Elemental analysis: C, 60.53; H, 4.48; N, 20.76; O, 14.23. IR (KBr, v, cm^{-1}): C=O (1684.20); O-H (3044.83); C-H (748.12); N-O (1514.86); O-H (1337.57); C-N (1244.91); C=C (699.30); ^{1}H 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); ^{13}CNMR: CH (115.12, 131.80), N=C (155.14), CH_2 (45.62, 72.16).

2. **(2-Pent-3-enylideneamino-ethylamino)-1*H*-quinoxalin-2-one (QX2):**

M.W: 270.33; M.P(^{0}C): 226; Molecular formula: $C_{15}H_{18}N_4O$. Elemental analysis: C, 66.64; H, 6.71; N, 20.73; O, 5.92. IR (KBr, v, cm^{-1}): O-H (3046.13); C=O (1682.53); CH (1387.58); C=C (856.76); CH (2777.57) ^{1}H NMR: CH aromatic (7.076, 7,084, 7.131, 7.139), CH benzylidene (6.730, 6.709, 7.502, 7.526, 7.548), CH_3 methyl (2.526, 2.784), CH_2 (3.483, 3.742). ^{13}C NMR: CH (7.077, 7.137), CH_2 (2.506), CH aromatic (111.52, 129.02), CH imine (155.17), N-C (39.68, 39.89, 40.10, 40.31).

3. ***N*-(3,4-Dihydro-quinoxalin-2-yl)-*N*'-isobutylidene-ethane-1,2-diamine (QX3):**

M.W: 244.34; M.P(^{0}C): 247^{0}C; Molecular formula: $C_{14}H_{20}N_4$. Elemental analysis: C ,68.82; H, 8.25; N, 22.93. IR (KBr, v, cm^{-1}): N-H (3317.29), C=O (1685.35), C-H (748.86), C=C (1598.53), O-H (3086.76), C-N (1236.41), O-H (1397.49); ^{1}H NMR: CH (7.6, 7.2, 7.0, 7.2), NH amine (2.0), NH sec amine (8.0), CH_2 (1.6,2.7), CH_3 (0.9); ^{13}C NMR: CH (121.7, 127.2, 125.4, 122.2), CH_2 (55.4, 43.7), CH_3 (18.7), C benzene (140.9, 131.7), C amide (161), C amide (163).

4. **3-{2-[(2-Hydroxy-benzylidene) amino}-1*H*-quinoxalin-2-one (QX4):**

M.W: 308.33; M.P(^{0}C): 222^{0}C; Molecular formula: $C_{17}H_{16}N_4O_2$. Elemental analysis: C, 66.22; H, 5.23; N, 18.17; O, 10.38. IR (KBr, v, cm^{-1}): O-H (3046.37), C=O (1682.84), CH (1391.10), CO (1285.86), C=C (854.84), CH (748.97); ^{1}H NMR: CH (7.6, 7.2, 7.0, 7.2), CH_2 (3.01, 3.81), CH benzylidine (8.11, 7.45, 6.85, 7.12, 6.76), OH (5.0), NH amine (2.0), NH sec amine (8.0); ^{13}C NMR: CH (121.7, 127.2, 125.4, 122.2), C amide (161), C imine (163), C benzene (131.7, 140.3), CH_2 (43.7, 54.7), CH benzylidene (163.7, 124.5, 130.4, 121.2, 132.2, 115.8, 157.8).

5. **3-(2-Ethylideneamino-ethylamino)-1*H*-quinoxalin-2-one (QX5):**

M.W: 230.26; M.P(^{0}C): 276^{0}C; Molecular formula: $C_{12}H_{14}N_4O$. Elemental analysis: C, 62.59; H, 6.13; N, 24.33; O, 6.95. IR (KBr, v, cm^{-1}): C=O (1683.13); O-H (1392.98); C-N (1243.77); C-H (1513.67); C=C (749.98); ^{1}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). ^{13}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).

6. **3-(2-Methyleneamino-ethylamino)-1*H*-quinoxalin-2-one (QX6):**

M.W: 216.24; M.P(^{0}C): 262^{0}C; Molecular formula: $C_{11}H_{12}N_4O$. Elemental analysis: C, 61.10; H, 5.59; N, 25.91; O, 7.40. IR (KBr, v, cm^{-1}): C=O (1679.97), C-H (1383.73), C-H (1474.37) alkane, C-H (3045.28, 2874.83), C=C (833.70); ^{1}H NMR: CH_2 (2.7, 2.0), CH (7.6, 7.2, 7.0, 7.2), NH amine (2.0), NH sec amine (8.0); ^{13}C NMR: CH (121.7, 127.2, 125.4, 122.2), C benzene (131.7, 140.9), C amide (161), CH_2 (55.3, 43.4), N=C (162.8).

7. **3-{2-[(4-Chloro-benzylidene)-amino]-ethylamino}-1*H*-quinoxalin-2-one (QX7):**

M.W: 326.78; M.P(^{0}C): 300^{0}C; Molecular formula: $C_{17}H_{15}ON_4Cl$. Elemental analysis: C, 62.48; H, 4.63; Cl, 10.85; N, 17.15; O, 4.90. IR (KBr, v, cm^{-1}): C=O (1680.39), O-H (3045.02), C-H (1385.12), C-Cl (856.65). ^{1}H NMR: CH (7.6, 7.2, 7.0, 7.2), CH_2 (3.01, 3.81), CH benzylidene (8.11, 7.56, 7.30, 7.30, 7.56), NH amine (2.0), NH sec amine (8.0); ^{13}C NMR: CH (121.7, 127.2, 125.4, 122.2), CH_2 (43.7, 54.7), CH benzylidene (163.7, 135.4, 130.4, 129.0, 136.1, 129.0, 130.4), C amide (161), C imine (163).

BIOLOGICAL EVALUATION

ANTI-BACTERIAL ACTIVITY:

The antibacterial activity of synthesized newer quinoxaline derivatives was assessed. The disc-plate technique with a nutrient agar medium was used to evaluate the microorganisms. *Bacillus subtilis* and *Pseudomonas aeruginosa* bacterial strains were used for the study. A bacterial culture was injected into newly produced nutrient agar. After being put on a Petri plate, the infected medium was allowed to harden at low temperatures for 15 minutes. Test solutions containing 50µg/ml and 500µg/ml discs were introduced after the medium gets harder and kept for the growth of organisms. Ampicillin(50µg/ml,500µg/ml) was employed as the standard. The plates were incubated for 24 hours at 37°C, and the results were noted. Using a digital zone reader (mm), the zone of microbial growth inhibition caused by the test drugs was quantified.

ANALGESIC ACTIVITY:

Experimentation on animals:

Using Swiss albino mice weighing 20 to 25g, pharmacological studies were carried out**.** The animals were housed in polyacrylic cages at standard temperatures (25± 2^0C) and relative humidity (40–70%) with 12-hour cycles of darkness and light. The mice were supplied standard laboratory food and water at their discretion. The mice were used in the laboratory environment for 1 day before the experiment. Animals were denied access to food for the duration of the trial.

IAEC approval:

The pharmacological evaluation of quinoxaline derivatives for various screening methods has been approved (approval No:19/IAEC/CLPT/2022-2023) by the Institutional Animal Ethics Committee (IAEC) of Chalapathi Institute of Pharmaceutical Sciences, Guntur, India (Reg.No.: 1048/PO/Re/S/07/CPCSEA).

Eddy's hot plate method:

Eddy's hot plate technique was used to investigate the analgesic potency of quinoxaline derivatives. It was kept at 55^0C with a 0.2^0C accuracy. The animals licked their limbs, indicating their jumping. These mice were treated as a control group with saline, a standard group with pentazocine 10 mg\kg, and four test groups were treated with synthesized quinoxaline derivatives subcutaneously. Mice were put on the hot plate 1 h after dosing group-specific drugs and the time was monitored by a stopwatch before either licking or jumping occurred. The latency period was reported after subcutaneous administration of group-specific drugs, for 0, 5, 15, 30, and 60 min.

RESULTS AND DISCUSSION:

ANTI-BACTERIAL ACTIVITY: (Table 3)

ANALGESIC ACTIVITY: (Figure 1)

We were able to identify intriguing anti-microbial compounds based on their efficacy through the screening of the 3-[2-((E)-[Substituted]phenyl]methylidene amino] quinoxaline-2(1H)-one derivatives, allowing us to create new anti-microbial drugs. They are reliable fresh leads for making unique chemicals, which could advance earlier synthetic techniques.

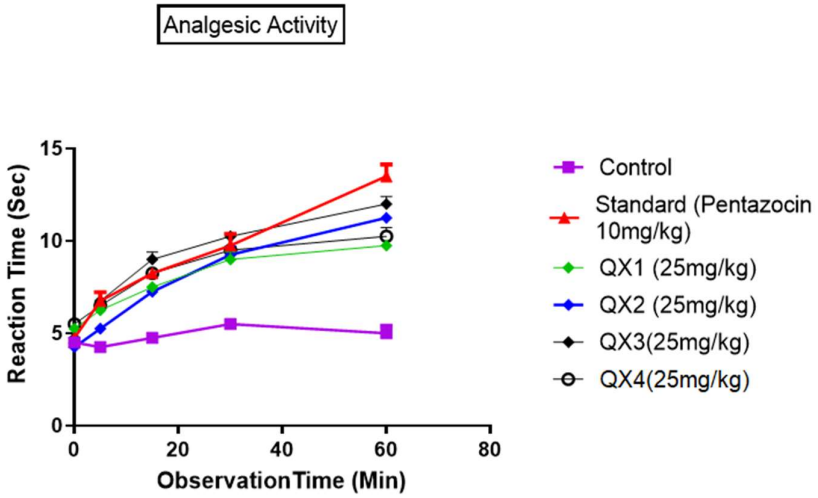
This method used a variety of aldehydes, and **Table 3 and Figure 1** show anti- microbial screening and analgesic activity was mentioned. The ambient conditions, excellent yields, quick reaction times, and use of a cheap, widely accessible material are some of the technique's main benefits. Simple workup method; absence of metal catalysts or poisonous or volatile solvents.

In the above anti-bacterial screening by using zone of inhitibition(mm) for gram+ve and gram-ve organisms like *B.subtilis, S.epidermititis and P.vulgaris, P.aeruginosa* were done by taking concentration of 50µg and 500µg/ml solutions. The solvent used for dilutions is DMSO. The compounds QX1, QX6 for *Bacillus subtilis and Pseudomonas aeruginosa* and QX4 for *Staphylococcus epidermititis*, QX2, QX3 for *Pseudomonas vulgaris* have shown maximum responses.

After performing of anti-bacterial screening we have proceeded to animal studies. In that we performed analgesic activity, it is observed that the compounds QX2 and QX6 have shown maximum activity.

Table 3: Zone of inhibition of synthesized compounds

Compound	Conc of Test Compound(ug/ml)	Zone of Inhibition (diameter in mm)			
		B.Subtilis	*S. epidermidis*	*P.vulgaris*	*P.aerogenosa*
Ampicillin	500	23	13	12	24.7
	50	16.5	10	9	18.3
QX1	500	17.1	7.5	8	17.1
	50	11.8	6.8	7	11.8
QX2	500	15	9.2	11	15
	50	11.3	5.4	8	11.3
QX3	500	12.5	9.1	9	12.5
	50	12.5	7.3	7	12.5
QX4	500	13.9	9.5	8	13.9
	50	11.7	6.4	6	11.7
QX5	500	16.9	7.2	9	16.9
	50	4.2	6.3	6	3.5
QX6	500	16.4	8.1	7	16.9
	50	14.7	9.7	6	14.7
QX7	500	15.6	7.6	8	15.6
	50	15	6.9	7	15



QX1	2-Nitro Benzaldehyde
QX2	Ethyl Methyl Ketone
QX3	Anisaldehyde
QX4	Crotanaldehyde

Figure 1

CONCLUSION:

The quinoxaline compounds have a wide range of activities. By the above tests we conclude that the compounds QX2 and QX6 have shown better maximum response for both anti-bacterial screening and analgesic activity.

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