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SYNTHESIS, CHEMICAL CHARACTERIZATION AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF SOME NOVEL QUINOXALINES

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Keywords:

Quinoxaline, Piperazine, Schiff base, Spectra, Ciprofloxacin Antibacterial activity, Antifungal activity, Disc diffusion

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ABSTRACT: Substituted quinoxaline has received considerable attention during the last few years as they are endowed with various biological activities and have a wide range of therapeutic properties. Piperazine has proven its worth in numerous clinically active drugs broader areas of therapeutic index. Hence, biologically important quinoxaline derivatives containing a piperazine moiety and Schiff base scaffolds were prepared. The structures of the synthesized compounds were characterised by elemental analysis, IR, NMR, and Mass spectra. All the prepared derivatives were screened for antibacterial and antifungal activity by disc diffusion method using nutrient agar media against *Bacillus subtilis*, *Bacillus pumilus*, *Escherichia coli* and *Pseudomonas aeruginosa*, & potato dextrose agar medium for activity against *Aspergillus niger* and *Candida albicans* using ciprofloxacin as a standard for antibacterial and clotrimazole as a standard for antifungal activity respectively. Fluoro and trimethoxy-containing derivatives have shown promising activity against gram–ve bacteria *P. aeruginosa.* Some compounds have shown moderate antifungal and antibacterial activity.

INTRODUCTION: Quinoxaline derivatives are an important class of heterocyclic compounds, formed by replacing carbon atoms in naphthalene ring with an N atom. Quinoxaline consists of two rings, one aromatic benzene ring, and another heterocyclic aromatic pyrazine ring because of which this is also called benzopyrazine. It is recognized as a bioisoster of quinoline, naphthalene and benzothiophene. Quinoxaline has occupied an enormous focus against biologically important broad-spectrum bacteria, fungi, viruses, leishmania, tuberculosis, malaria, cancer, depression, and neurological activities.

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The pharmacophore of quinoxaline acts as a forerunner for the congregation of a number of new chemical entities for diverse applications [1]. Bicyclic quinoxaline desipeptide antibiotics such as echinomycin, triostin C, and triostin A are the agents that have been reported to have activity against gram-positive bacteria and certain tumours to inhibit RNA synthesis [2, 3].

Morbidity and mortality due to enteric bacterial infections remain important health problems worldwide, mainly in developing countries and regions such as the Indian sub-dominant part of South America. Toxicity and drug resistance also play an important role in treatment failure.

There is an urgent need for the development of new antibacterial agents. The study of quinoxaline has become much interest in recent years on account of its antibacterial, antifungal, antiviral, anticancer, antidepressant, and anti-inflammatory activities.

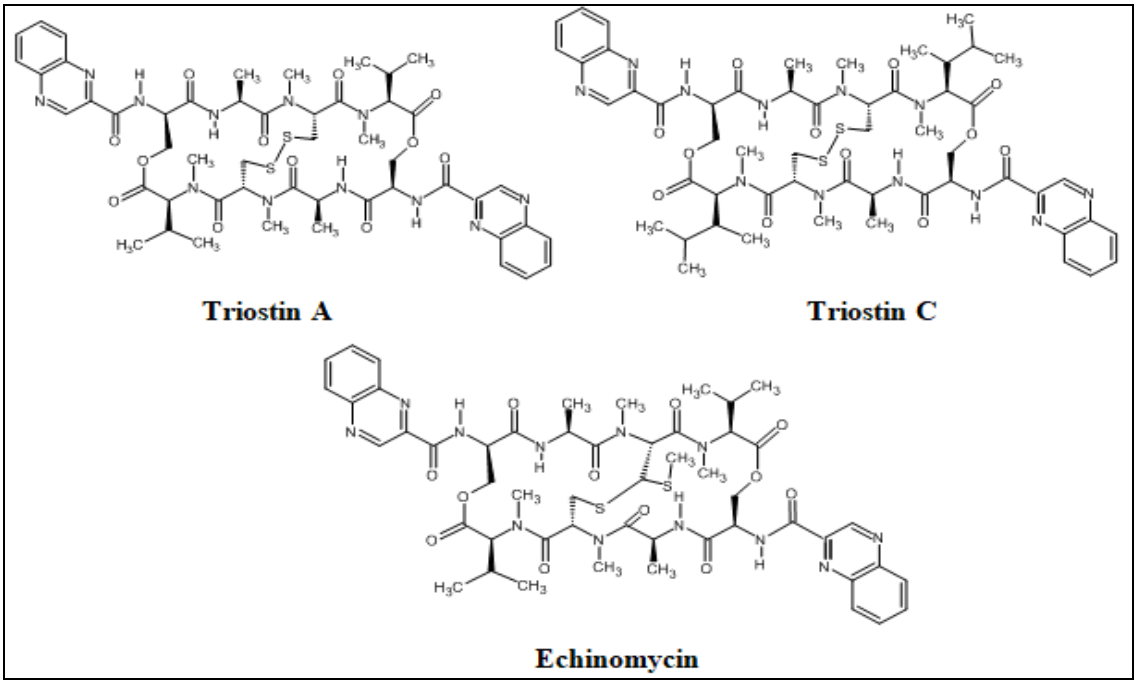
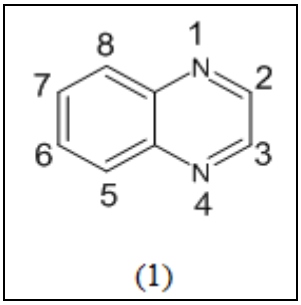


FIG. 1: QUINOXALINE-CONTAINING ANTIBIOTICS

Quinoxaline: Quinoxaline is commonly called 1, 4-diazanaphthalene, or benzopyrine (1). Quinoxaline analogues are heterocycles where N replaces some carbon atoms in the ring of naphthalene [1]. The approved numbering of the ring atom is shown below.



(1)

Quinoxaline and its derivatives are mostly of synthetic origin, and some are known to possess antibacterial activities. Quinoxaline has also been used in reactive dyes and pigments, azo dyes, and fluorescein dyes, and it also forms a part of certain antibiotics. Quinoxaline is a low melting solid m.p. 29-30 ^{o}C and is miscible with water. It is weakly basic (pKa 0.56) and thus considerably weaker base than the isomeric diazonapthalenes namely cinnoline (pKa 2.42), phthalazine (pKa 3.47) or quinazoline (pKa1.95) [3, 4]. Nitrogen consisting heterocycle quinoxaline is a weekly basic bi-cyclic compound made up of benzene and pyrazine. It is also termed diazanaphthalene. Naphthyridines such as quinazoline, phthalazine, and cinnoline are isomeric forms of quinoxaline. It has various activities demonstrated by its presence in biologically important antibiotics such as levomycin, actinoleutin, and echinomycin, which are useful in several transplantable tumours. It possesses industrial applications such as dyes, agricultural and medicinal chemistry also wide spectrum of biological activities like anticancer, anti-inflammatory, antiviral [20], antidiabetic, anti-depressant, anthelmintic, antituberculosis, antimicrobial [19] and antiprotozoal [17].

Similarly, the quinoxaline-containing drug varenicline is clinically used in the treatment of nicotine addiction. Recently the presence of quinoxaline was justified as promising drug-like properties in synthesized compounds as anticholinesterase inhibitors [21]. Similarly, compounds carrying quinoxaline moiety were potent HIV Reverse transcriptase inhibitors, for example, S-2720 [20]. Quinoxaline can be formed by condensing ortho-diamines with 1,2-diketones. It also results when glyoxal is condensed with 1,2-diaminobenzene [17, 22].

The quinoxaline antibiotics are agents of bicyclic depsipeptide antibiotics that have been reported to inhibit RNA synthesis against gram-positive bacteria and certain tumours. These antibiotics consists of two classes one containing two equal parts of despeptide ring made up of cross-bridge

with sulfur which connects these two equal parts and despeptide ring and another class known as quinomycin, which includes thio-acetal cross-bridge for ex. echinomycin and triostin antibiotics having disulfide-bridge at similar location [3, 4]. 2-Hydroxy-but not 2-amino quinoxaline exist in tautomeric forms (2).

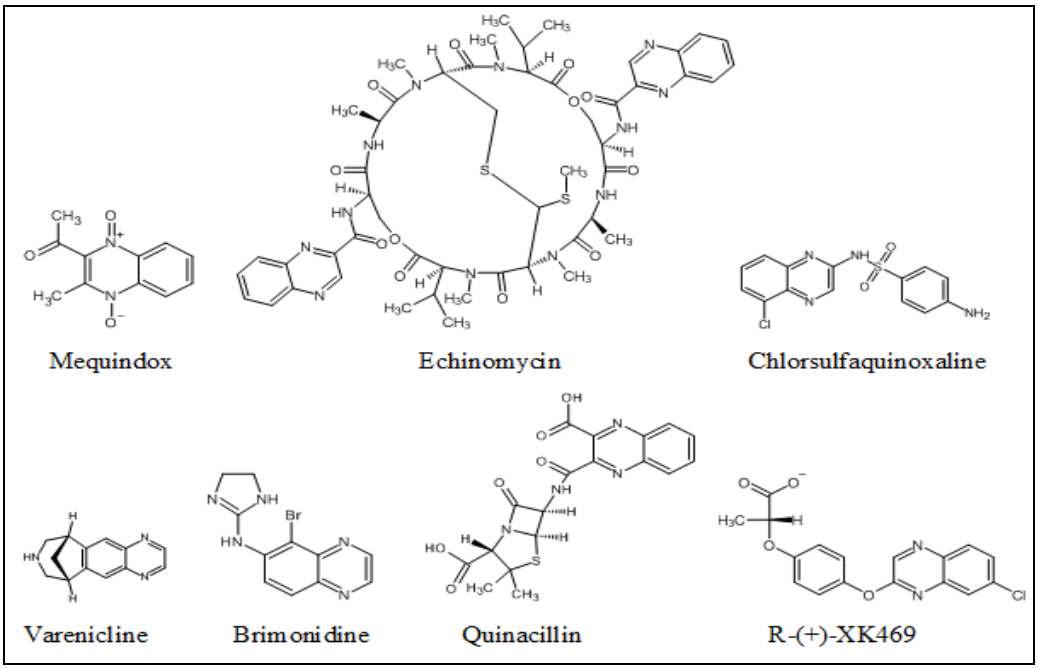
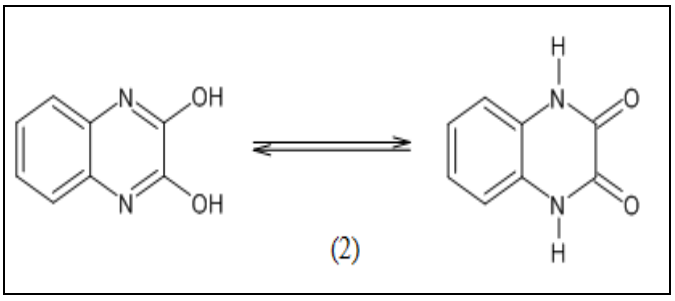
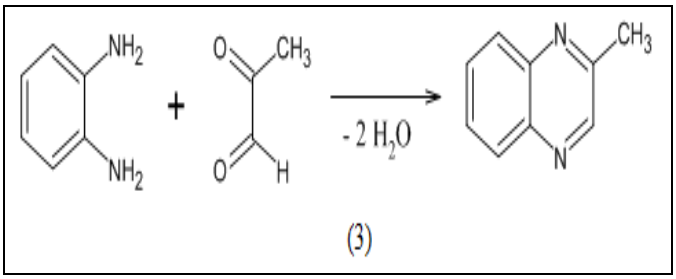


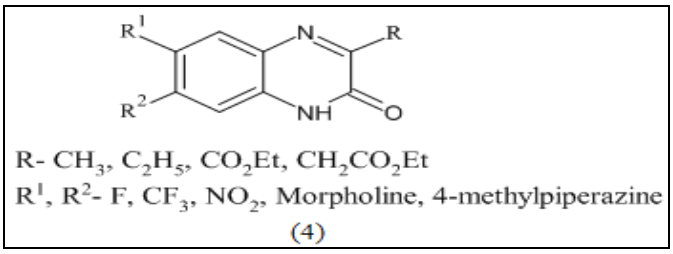
FIG. 2: QUINOXALINE-CONTAINING DRUGS



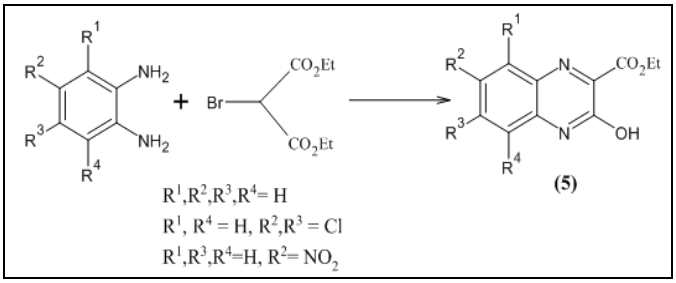
Quinoxaline itself is prepared by the reaction of o-phenylenediamine and glyoxal [5, 22]. Similarly, 2-methyl quinoxaline has been prepared by the reaction of o- phenylene diamine and pyruvaldehyde [6, 22].



The synthesis of 3, 6, 7-substituted-quinoxalin-2-ones and the synthesized compounds were evaluated for antimicrobial and anticancer activity (4) [7].

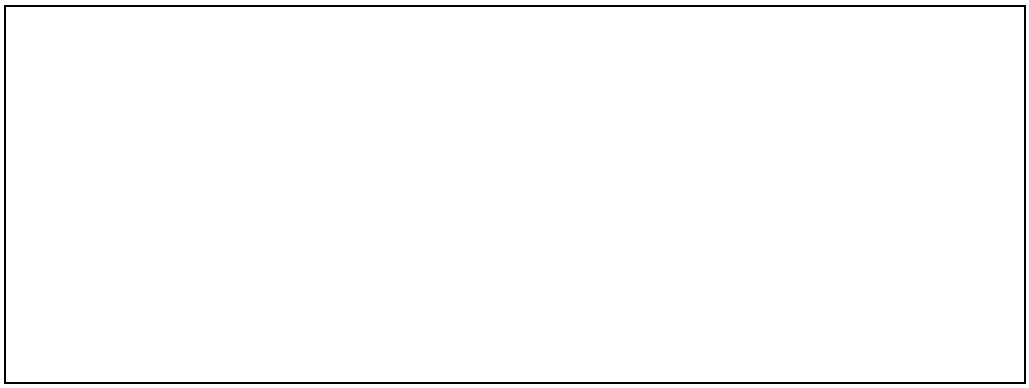


Substituted ethyl 3 – hydroxyquinoxaline – 2 - carboxylates were synthesized by one-pot catalyst-free condensation of aryl-1,2-diamines and diethyl bromomalonate (5) [8].

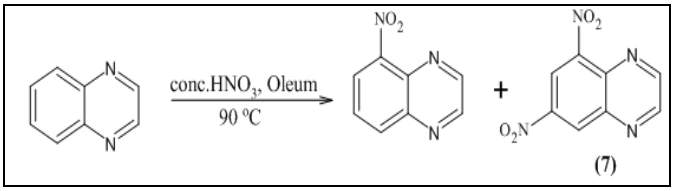


Compounds containing 1, 2, 3, -tricarbonyl functionality have been used in the synthesis of a variety of heterocyclic derivatives [9]. The tricarbonyl group-containing compounds can be prepared by treating 3-keto ester with *p*-nitro sulphonyl peroxide, to give 2-(p- nitro phenyl)-

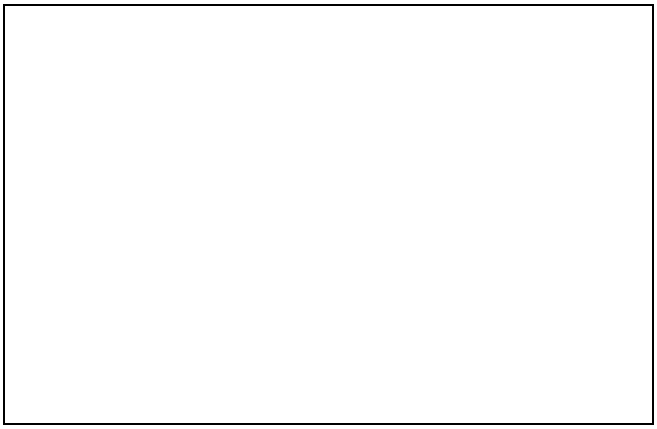
sulfonyl) oxy)-3-keto esters [10]. Treatment of the resulting 2-(nosyloxy)-3-ketoesters with triethyl amine (TEA) in benzene at room temperature results in *vic* tricarbonyl compound. The tricarbonyl compound can be trapped *in situ* with *o*-phenylenediamine to give quinoxaline derivatives (6).



Quinoxaline forms a salt with acids. Nitration occurs only under forcing conditions (Conc. HNO_3, Oleum) to give 5-nitroquinoxaline (1.5%) and 5,7-dinitroquinoxaline (7).

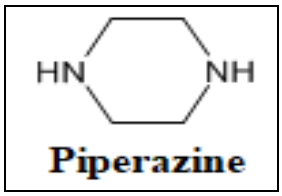


Oxidation of quinoxaline results in the formation of the product depending upon the nature of the oxidizing agent employed. With alkaline potassium permagnate pyrazine-2, 3-dicarboxylic acid is formed, while with per acid, quinoxaline *di*-N-oxide results. 2-methylquinoxaline on selenium dioxide oxidation affords quinoxaline 2-carboxaldehyde (8) [11].



Alkyl radicals produced from acyl peroxide or alkyl hydroperoxide give high yields of 2-Substituted alkyl derivatives. Reduction (Na / C_2H_5OH) of quinoxaline gives a 1,2,3,4-tetrahydro derivatives.

Piperazine: Piperazine is a heterocyclic nucleus consists of a six-membered ring containing two opposing nitrogen atoms. Piperazine exists as small alkaline deliquescent crystals with a saline taste. Piperazines are a broad class of chemical compounds with important pharmacological properties, containing a core piperazine functional group.



Piperazines were originally named because of their chemical similarity with piperidine, a constituent of piperine in the black pepper plant (*Piper nigrum*). However, it is important to note that piperazines are not derived from plants in the *Piper* genus.

Nitrogen heterocycles form an important part of the structure of many phytochemicals and drugs. Piperazine is a six-membered N-heterocycle structurally consisting of N-4 nitrogen which acts as basic amine, while N-1 nitrogen used for introducing hydrogen acceptor. Their interaction with receptor N1- nitrogen is useful in improving water solubility and bioavailability. With the help of both nitrogen, it improves the pharmacological and pharmacokinetic profile of the medicinal compounds [12, 23].

Piperazine was first introduced as an anthelmintic in 1953. A large number of piperazine compounds have anthelmintic action. Their mode of action generally paralyzes parasites, allowing the host body to remove or expel the invading organism easily. This action is mediated by its agonist effects upon the inhibitory GABA (Gamma amino butyric acid) receptor. Its selectivity for helminths is because vertebrates only use GABA in the CNS and the helminths' GABA receptor is a different isoform to the vertebrate's one. Piperazine hydrate and piperazine citrate are the main anthelminthic piperazines. These drugs are often referred to simply as "piperazine" which may cause confusion between the specific anthelmintic drugs and the entire class of piperazine- containing compounds. Piperazines are also used in the manufacture of plastics, resins, pesticides, brake fluid and other industrial materials. Piperazines, especially BZP and TFMPP have become popular substitutes in the club scene for MDMA (although they are more like amphetamines). Piperazine is also a fluid used for CO_2 and H_2S scrubbing in association with MDEA [13-15].

It is an elite structural motif for many biologically active molecules imparting diverse pharmacological activities like anthelminthic (piperazine citrate), anti-allergic (cetrizine), anti-emetic (meclizine), anxiolytic (buspirone), antipsychotic (trifluperazine, clozapine), antidepressant (Trazadone, Amoxapine), in erectile dysfunction treatment (sildenafil) [12, 23], antimycobacterial (Ciprofloxacin, Norfloxacin) [24], promising Scaffold with Analgesic and Anti-inflammatory Potential [25].

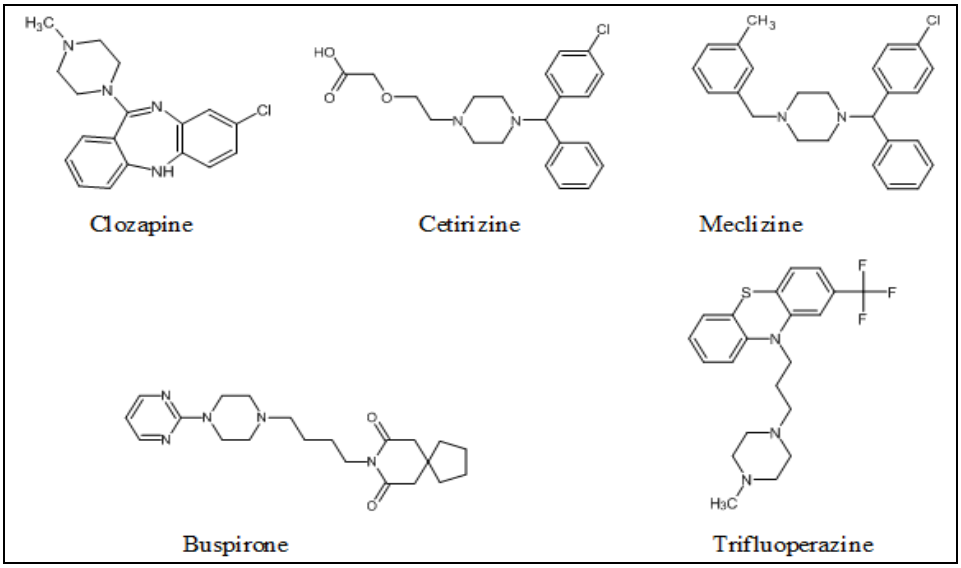


FIG. 3: PIPERAZINE-CONTAINING DRUGS

MATERIALS AND METHODS: All the chemicals are analytical grade and were purified by the established methods. Melting points were determined by using Toshniwal apparatus in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel G plates using chloroform: ethyl acetate (7:3) as solvent system and UV lamp used as a visualizing agent.

IR spectra were recorded using KBr pellets on a Shimadzu 8000 series spectrophotometer. ^{1}H-NMR spectra on a Varian EM-200, Avance 200 MHz spectrophotometer using DMSO-d_6 as solvent and TMS as internal standard (chemical shift values expressed in δ ppm). Mass spectra were recorded by LC-MS method on a Shimadzu 2010A series spectrometry.

Procedure for the Preparation of 1,4-Dihydroquinoxaline-2,3-dione (1): Into a clean, dry, round bottom flask, introduced o-phenylene diamine (0.1 mol) and diethyl oxalate (0.1 mol) and the contents were refluxed for 1 h. Cooled and the separated solid was collected by filtration, washed with 25 ml ether, and dried. The obtained 2,3-dihydroxy quinoxaline was recrystallized from DMF, the yield was 90 %, and the melting point was 360 °C.

^{1}H –NMR: 11.8-12.0 δ (2H, s, NH), 7.0-7.2 δ (4H, dd, Ar-H).

Procedure for the Preparation of 2, 3-dichloro Quinoxaline (2): In a clean, dry, round bottom flask, introduced 1,4-dihydro quinoxaline-2,3-dione (0.01 mol) **(1),** phosphorous oxychloride (0.04 mol) and DMF (1 ml). The content was refluxed for 90 min resulting solution being cooled to room temperature, and then the solution was poured into crushed ice with constant stirring with the glass rod. The solid thus separated was collected by filtration, washed with 25 ml of water, and dried. The obtained 2,3-dichloro quinoxaline was recrystallized from a solution of chloroform and *n*-hexane, the yield was 85 %, and the melting point was 150 °C (2).

IR: 3042, 3001cm^{-1} (Ar-CH-Str).

^{1}H NMR: 7.7-8.1 δ (4H, m, Ar-H).

Procedure for the Preparation of 3-chloro-2-Hydrazino Quinoxaline (3): In to a clean dry round bottom flask, introduced 2,3-dichloro quinoxaline (0.01 mol) (2), hydrazine hydrate (0.01 mol) and methanol (25 ml). The contents of the flask were refluxed for 30 min. Cooled and separated solid was collected by filtration, washed with 25 ml water, and dried. The obtained 3-chloro-2-hydrazino quinoxaline was recrystallized from methanol, the yield was 75 %, and the melting point was 180 °C.

IR: 3385 cm^{-1} (NH_2 Str), 3266, 3236 cm^{-1} (NH Str), 3051 cm^{-1} (Ar-CH Str).

^{1}H NMR: 7.2-7.8 δ (4H, m, Ar-H), 6.7-6.8 δ (1H, s, 1H of NH of NH-NH_2), 4.1-4.2 δ (2H, s, 2H of NH_2 of NH-NH_2).

Mass: Molecular weight of the compound is 194 and molecular ion peak was appeared at 195 as M^{+1}.

Preparation of 2-[2-benzylidenehydrazinyl]-3-Chloroquinoxaline (4A): In to a clean dry round bottom flask introduced 3-chloro-2-hydrazino quinoxaline (0.01 mol) (3), benzaldehyde (0.01 mol), ethanol (25 ml) and glacial acetic acid (1 ml) and the mixture was refluxed for 3 h, cooled and separated solid was collected by filtration and washed with water and dried. The obtained 2-[2-benzylidenehydrazinyl]-3-chloroquinoxaline **(4A)** was recrystallized by using aq. ethanol, the yield was 55 % and the melting point was 270 °C. The other Schiff's bases of this series **(4B-J)** were prepared by using similar procedure and the data was given in the **Table 1**.

4g) IR: 3068 cm^{-1} (NH Str), 2931, 2837 cm^{-1} (Ar-CH Str), 1604 cm^{-1} (HC=N- Str), 867, 756 cm^{-1} (Disubstituted benzene).

^{1}H NMR: 12.20 δ (1H, s, H of NH-N=), 8.70-8.80 δ (1H, s, CH=N), 6.90- 8.60 δ (8H, m, Ar- H), 3.80-3.90 δ (3H, s, OCH_3).

Mass: Molecular weight of the compound is 312 and molecular ion peak was appeared at 311 as M^{-1}.

4i) IR: 3253 cm^{-1} (NH Str), 3068, 3050 cm^{-1} (Ar-CH Str).

^{1}H NMR: 8.15-8.20 δ (1H, s, H of NH-N=), 8.10-8.15 δ (1H, s, H of -N= CH-), 6.90-7.80 δ (8H, m, Ar-H).

Mass: Molecular weight of the compound is 300, and the molecular ion peak was appeared at 301 as M^{+1}.

Preparation of 2-[2-(4-fluorobenzylidene) hydrazinyl]-3-(piperazin-1yl) quinoxaline (5a): In a clean dry round bottom flask introduced 2-chloro-3-[4-(fluorobenzylidene) hydrazinyl] quinoxaline (**4I)** (0.01 mol), piperazine (0.01 mol) in 25 ml ethanol and 5 ml triethylamine and the mixture was refluxed for 6 h, cooled and separated solid was collected by filtration and dried. The obtained 2-[2-(4-fluorobenzylidene) hydrazinyl]-3-(piperazin-1yl) quinoxaline **(5A)** was recrystallized by using methanol, the yield was 40% and melting point was 270 ^{o}C. A similar procedure prepared the other compounds of this series, i.e. (5B-G), and data were given in **Table 2**.

IR: 3273 cm^{-1} (NH Str), 2849 cm^{-1} (Ar-CH Str), 2723, 2608 cm^{-1} (CH_2 Str).

^{1}H NMR: 10.9 δ (1H, s, 1H of NH), 8.5-8.6 δ (1H, s, 1H of CH=N), 7.0-8.2 δ (8H, m, Ar-H), 4.3-4.4 δ (1H, s, 1H of NH), 3.8-4.0 δ (4H, s, 4H of piperazine), 3.1-3.2 δ (4H, s, 4H of piperazine).

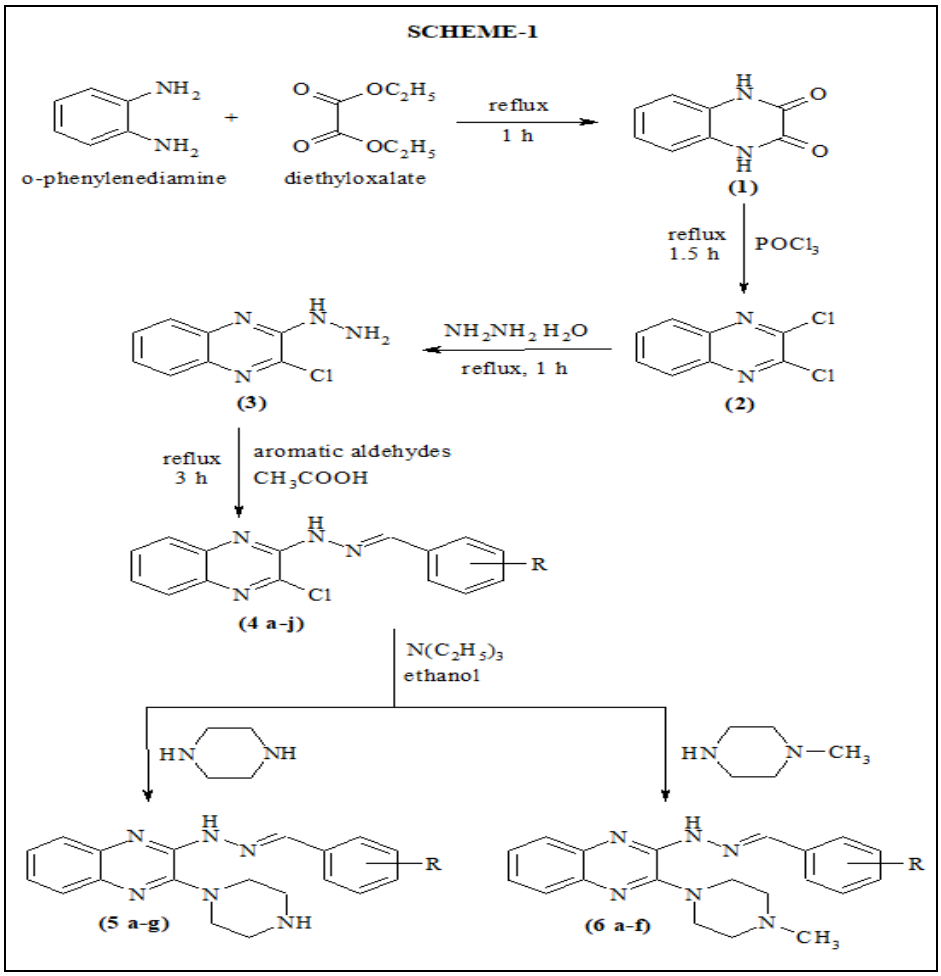
Mass: Molecular weight of the compound is 350, and the molecular ion peak appeared at 351 as M^{+1}.

Preparation of 2-[2(3-nitrobenzylidene) hydrazinyl]-3-(4-methyl Piperazin-1-yl) Quinoxaline (6E): In a clean dry round bottom flask introduced 2-chloro-3-[2-(3-nitrobenzylidene) hydrazinyl] quinoxaline (**4D)** (0.01 mol), N-methyl piperazine (0.01 mol) in 25 ml ethanol and 5 ml triethylamine. The mixture was refluxed for 6 h, cooled, and separated solid was collected by filtration and dried. The obtained 2-[2-(4-fluorobenzylidene) hydrazinyl]-3-(4-methyl piperazin-1-yl) quinoxaline **(6E)** was recrystallized by using methanol, the yield was 42 %, and melting point was 250 ^{o}C. The other derivatives of this series **(6A-D** and **F)** were prepared by a similar procedure, and the data was given in **Table 2**.

IR: 3319 cm^{-1} (NH – Str), 2973, 2850 cm^{-1} (Ar-CH-Str).

^{1}H NMR: 11.1 δ (1H, s, 1H of NH), 8.8 δ (1H, s, 1H of CH=N), 7.0-8.2 δ (8H, m, 8H of Ar-H), 3.8-4.2 δ (4H, dd, 4H of N-$(CH_2)_2$), 3.3-3.4 δ (2H, d, 2H of N-CH_2), 2.1-2.3 δ (2H, d, 2H of N-CH_2), 1.08 δ (3H, s, 3H of CH_3).

Mass: Molecular weight of the compound is 391, and the molecular ion peak appeared at 392 as M^{+1}.



Biological Evaluation:

Antibacterial And Antifungal Activity: The compounds synthesized during the present investigation were screened for their antibacterial activity. The antibacterial tests were conducted on four common microorganisms: *Bacillus subtilis*, *Bacillus pumilus*, *Escherichia coli* and *Pseudomonas aeruginosa*, which are the representative types of gram-positive and gram-negative organisms, respectively. The antibacterial activity of the compounds was assessed by disc diffusion [16]. The antifungal activity of all compounds was determined on potato dextrose agar medium against *Aspergillus niger* and *Candida albicans*, Clotrimazole 100 µg/ml was used as a standard, and DMF was used as control. The sterile

molten potato dextrose medium was cooled to 45 ^{o}C and inoculated with test organisms and; mixed the contents thoroughly, and poured into the sterile Petri dishes under aseptic conditions. All the inoculated Petri dishes were incubated at 28 ^{o}C for 4 days, and the extent diameter of inhibition was measured as the zone of inhibition in millimeters the results are shown in **Table 3.**

TABLE 1: PHYSICAL CHARACTERIZATION DATA OF SCHIFF'S BASES (4A-4J)

S. no.	Compound Code	R	Molecular Formula	Molecular Weight	Molecular Point (^{o}C)	Yield %
1	4a	H	$C_{15}H_{11}N_4Cl$	283	270-272	55
2	4b	4-OH	$C_{15}H_{11}N_4OCl$	299	276-278	58
3	4c	$N(CH_3)_2$	$C_{17}H_{16}N_5Cl$	326	146-148	55
4	4d	3-NO_2	$C_{15}H_{10}N_5O_2Cl$	328	230-232	52
5	4e	2-NO_2	$C_{15}H_{10}N_5O_2Cl$	328	260-262	51
6	4f	2-Cl	$C_{15}H_{10}N_4Cl_2$	317	270-272	53
7	4g	4-OCH_3	$C_{16}H_{13}N_4OCl$	312	276-278	57
8	4h	3,4-di OCH_3	$C_{17}H_{15}N_4O_2Cl$	343	252-254	60
9	4i	4-F	$C_{15}H_{10}N_4ClF$	300	232-234	50
10	4j	3,4,5-triOCH_3	$C_{18}H_{17}N_4O_3Cl$	373	260-262	53

TABLE 2: CHARACTERIZATION DATA OF THE COMPOUNDS. (5A-5G & 6A-6F)

S. no.	Compound Code	R	Molecular Formula	Molecular Weight	Molecular Point (^{o}C)	Yield %
1	5a	4-F	$C_{19}H_{19}N_6F$	340	270-272	58
2	5b	2-Cl	$C_{19}H_{19}N_6Cl$	367	115-117	54
3	5c	4-OH	$C_{19}H_{20}N_6O$	348	328-330	68
4	5d	3,4-di OCH_3	$C_{21}H_{24}N_6O_2$	392	228-230	50
5	5e	4-$N(CH_3)_2$	$C_{21}H_{25}N_7$	375	220-222	50
6	5f	3,4,5-tri OCH_3	$C_{22}H_{26}N_6O_3$	422	160-162	58
7	5g	3-NO_2	$C_{19}H_{19}N_7O_2$	377	256-258	58
8	6a	H	$C_{20}H_{22}N_6$	346	210-212	42
9	6b	4-$N(CH_3)_2$	$C_{22}H_{27}N_7$	389	250-252	40
10	6c	3,4,5-tri OCH_3	$C_{23}H_{28}N_6O_3$	436	160-162	42
11	6d	4-F	$C_{20}H_{21}N_6F$	364	250-252	44
12	6e	3-NO_2	$C_{20}H_{21}N_7O_2$	391	170-172	50
13	6f	2-Cl	$C_{20}H_{21}N_6Cl$	381	150-152	52

TABLE 3: BIOLOGICAL ACTIVITY OF THE COMPOUNDS

Sample code	Inhibition zone diameter in mm								Sample Code	*A. niger*	*C. albicans*
	B. subtilis		*B. pumilus*		*E. coli*		*P. aeruginosa*				
	50µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg		100 µg/ml	100 µg/ml
5a	7	14	6	12	5	8	4	26	5a	4	8
5b	4	7	4	9	7	10	5	12	5b	6	9
5c	5	12	7	14	6	9	7	11	5c	6	10
5d	4	6	5	10	6	10	8	13	5d	5	9
5e	5	10	5	13	5	11	6	14	5e	7	8
5f	4	9	6	11	4	9	7	12	5f	6	10
5g	6	13	9	18	5	8	5	10	5g	8	11
6a	7	15	4	8	6	8	7	11	6a	7	15
6b	5	10	7	14	5	9	7	10	6b	5	11
6c	4	7	4	9	4	10	6	19	6c	6	11
6d	6	13	6	12	7	11	5	15	6d	4	10
6e	6	13	6	13	6	10	4	10	6e	5	9
6f	9	19	5	10	5	12	7	11	6f	7	8
Ciproflox acin	20	32	20	33	21	30	22	31	Clotrim azole	24	26
DMF	-	-		-	-	-	-	-	DMF	-	-

RESULT AND DISCUSSION: The starting compound quinoxaline-2, 3-diol **(1)** was prepared from o-phenylene diamine and diethyl oxalate upon refluxing for 1 hr in a single step. The quinoxaline-2,3-diol **(1)** was refluxed for 90 min with phosphorous oxy chloride, to furnish 2,3-dichloroquinoxaline **(2)**, further the 2-chloro-3-hydrzinoquinoxaline **(3)** was synthesized by the reaction of 2,3-dichloroquinoxaline **(2)** and hydrazine hydrate in the methanolic medium upon refluxing for 60 min. The different Schiff's bases **(4A-J)** of 2-chloro-3-hydrazinoquinoxaline were obtained by refluxing the appropriate substituted benzaldehyde and 2-chloro-3-hydrazinoquinoxaline **(3)** in acetic acid medium for 3 h. The obtained quinoxaline Schiff's bases **(4A-J)** were further converted into the compounds **(5A-G)** and **(6A-F)** by reacting the Schiff's bases with piperazine and N-methyl piperazine in the presence of triethylamine in ethanolic medium. The synthesized compounds were characterized by their physical and spectral data.

CONCLUSION: During the present work, quinoxaline derivatives were synthesized, and IR, 1HNMR, and MassSpectral Studies established the structures of the compounds. The compounds were screened for antibacterial and antifungal activity using standard procedure; few compounds showed moderate antibacterial and significant antifungal activity against *C.albicans*. The molecular modification may perhaps yield compounds with improved activities. Therefore in search of newer generation antibiotics, it may be worthwhile to take up a detailed study on these types of compounds and explain the molecule to increase the potency.

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