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SYNTHESIS AND BIOLOGICAL EVALUTION OF NEWER DERIVATIVES OF QUINOXALINES

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ABSTRACT

Naturally occurring compounds contain quinoxaline ring and proven to have several biological activities. Quinoxaline is also known as benzopyrazine. Quinoxalines containing both benzene and pyrazine ring. Cyclization of o-phenylinediamine was carried out with ethyl pyruvate in presence of n-butanol. The product obtain was recrystalized from ethanol. Then chlorination reaction was carried out by using $POCl_3$. Then reacted with salicyladehyde in acetonitrile to obtained intermediate compounds. The intermediate product was reacted with different anilines to obtain title compound, viz., SSB-QMNA, SSB-QXPAP, SSB-QXPMA, SSB-QXOMA, and SSB-QXPNA. These compounds were tested for antibacterial activity against ***E. coli*** (gram negative) and ***Staphylococcus aureus*** (gram positive) using cup plate method. Compounds showed significant activity at concentration of 500µ/ml and 750µ/ml, Chloramphenicol was used as reference standard drugs. The compounds were analyzed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectrum.

KEYWORDS: o-phenylinediamine, Ethyl pyruvate, n-butanol, $POCl_3$, Acetonitrile, Salicyladehyde, Ethanol, Aniline derivatives and Antibacterial activity.

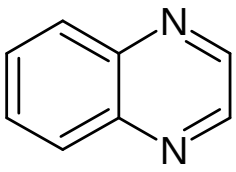
INTRODUCTION

In recent times medicines are the product of restless attempts made by human society. Beginning of new medicines is preparation of various chemical molecules with higher

activity. Since production of a new moiety is very complex process, derivation of these existing molecules was created to form new compounds with higher therapeutic value.[1]

This process has the advantages in decreasing the toxicity as well as enhancing the strength of the parent moiety. The new drug design and development based on the various physiochemical properties. As a result, majority of the drugs in daily use derivative of the parent molecules, whether it is β-lactam antibiotics (Penicillin G, Penicillin V, and Ampicillin) irreversible proton pump Omeprazole, Lansoprazole, Rabeprazole), or CNS drugs such as Benzodiazepines derivatives (Diazepam, Clonazepam etc.)

Commonly drugs sources are available in different form of animals, plant, microbial and mineral sources. These drugs available cannot be consumed directly by human beings because of their increased toxicity levels. Therefore, in order to make these drugs suitable for human consumption they need to be modified by forming derivatives of these existing drugs. These derivatives form an important part in enhancing the action of drugs.



Quinoxaline known as benzopyrazine, in organic chemistry, it made up of a benzene and pyrazine ring. The other isomeric moiety is napthyridines with quinazoleline, phthalazine and cinnoline are the colorless oil that melts room temperature only. The parent moiety mainly used as dyes, pharmaceuticals and antibiotics such as olaquindox, levomycin and actinoleutin etc.

Properties

Chemical formula : $C_6H_8N_2$

Molar mass : $130.15 g.mol^{-1}$

Melting point : 29-32°C

Boling point : 220-223°C

Quinoxaline and their derivatives incorporated the functional groups which are important biological agents and a major research activity has been focused on this dissertation. Different methods have been synthesis of quinoxaline moiety. Number of quinoxalines has

been significant biological activity in research work. They have different pharmacological effects, such as antimicrobial, antimycobacterial, antifungal, antiviral, anti-protozoal, anti-malarial, antioxidant, anti-inflammatory, anticonvulsant, antidepressant and anticancer activity. They have some potent receptor in selective biological activity like AMPA receptor antagonist activity. Qinoxaline 1,4-di-N-oxides seen to be the most often studied quinoxaline type compounds. As a result, a great number of such quinoxalines by, using different synthetic methods for their preparation have been described in the literature. The current review provides a close view to quinoxaline synthesis and its biological activities all along the collection of recent patents on quinoxaline.[2-3]

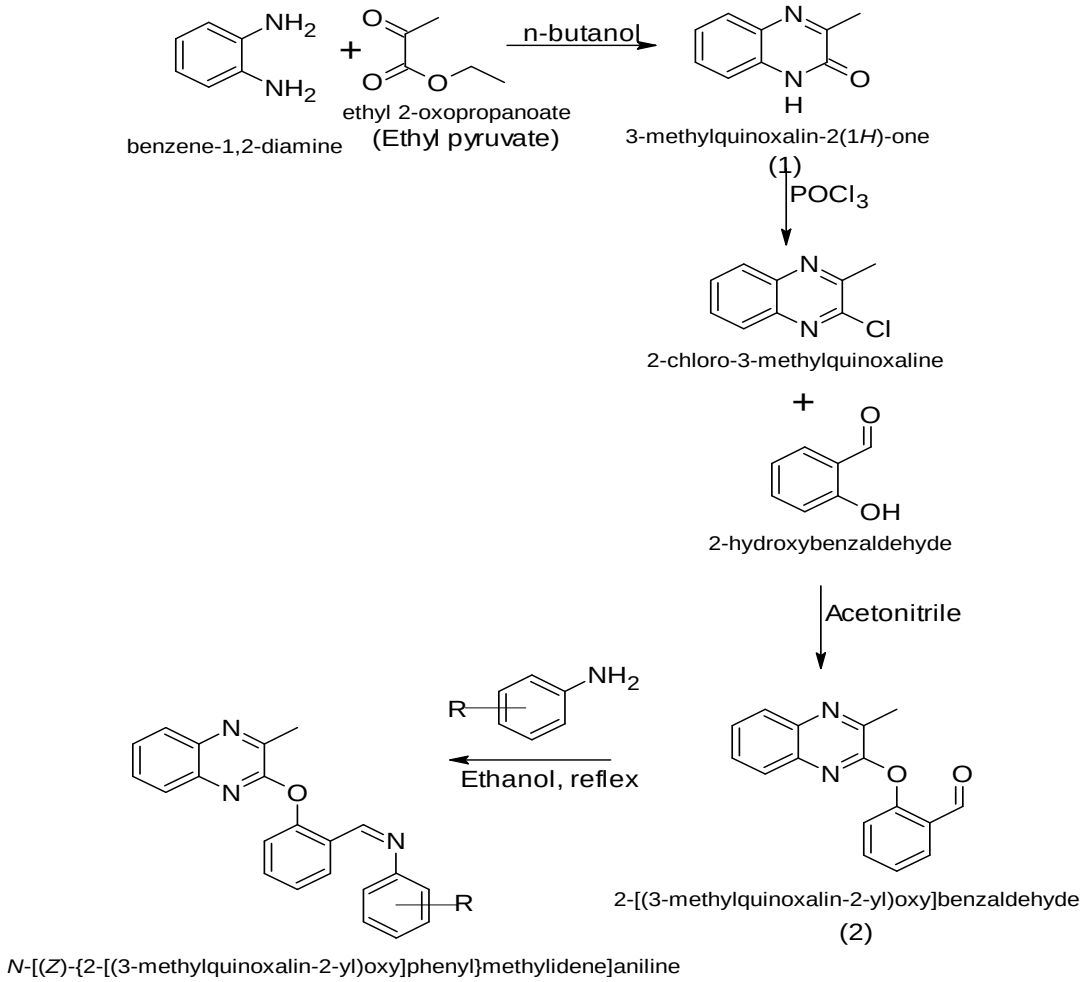
Quinoxaline derivatives are a group of substances possessing a broad spectrum of pharmacological activities, such as antibacterial, antiviral, anticancer, ant fungicidal, anti helmintic, and insecticidal. Since a strong interest in the biological activities linked with these compounds, the synthesis of new quinoxaline derivatives has been performed by our group 2-5. Some of these derivatives showed fine in vitro anticancer activity as well as proficient cytotoxicity against hypoxic cells in solid tumors.[4-13]

As indicated by the approximate costs of cancer in 2007 of $226.8 billion[14], and by the 7.6 million cancer world-wide deaths (13% of all deaths) in 2008, cancer is evidently a major concern. The need for useful treatment and new anticancer agents is of chief importance.[15]

The earlier reported on the biological activities of hydrazone derivatives of a number of different hetero aromatic compounds.[16-23] Now we wish to report the evaluation of the anti-cancer activities of a series of hydrazones-quinoxaline derivatives.

Quinoxaline compounds have an extensive range of uses, mainly as biologically active compounds, but also as dyestuffs.[24-34] The biological activities of hydrazone derivatives of hetero aromatic compounds have also been well reported[35-44], with anticancer activities being of significant interest.

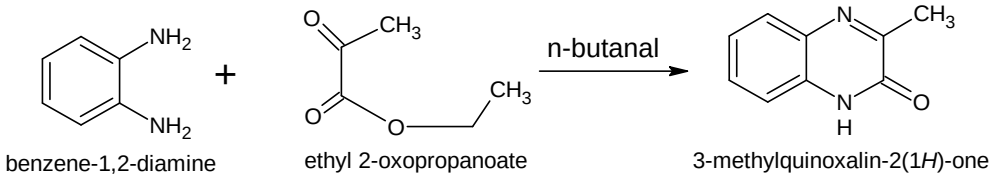
MATERIAL AND METHODS: Scheme



Theoretical: Heterocyclic compounds containing nitrogen possess potential biological and pharmacological activities. Quinoxaline moiety consists a significant group of heterocyclic compounds having different pharmacological activities, viz, Anticancer, anti allergic, antibacterial, fungicidal, anti-malarial agents, Anti-oxidant, Anti-tuberculosis, Anticonvulsant agents, Anti-inflammatory.

Experimental

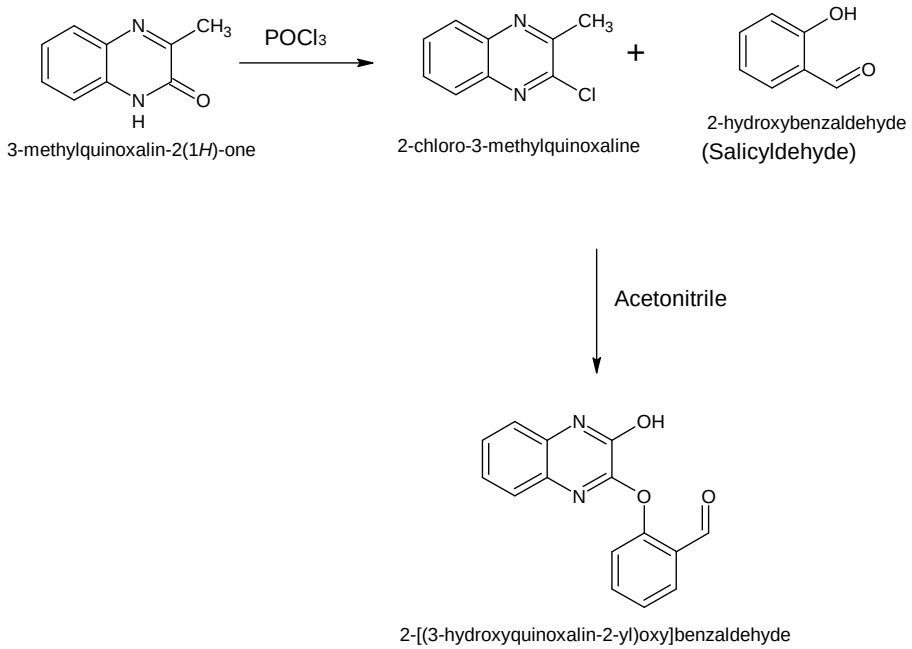
Reaction: Compound SSB1



Chemicals: Orthophenyldiamine (OPD)**,** Ethyl Pyruvate**,** n-Butanol, Ethanol.

Procedure: Benzene-1, 2-diamine (*o*-phenyldiamine) (OPD) (10.8gm, 0.10mol) was dissolving in n-butanol (300ml) with warming. Ethyl 2-oxopropanoate (ethyl pyruvate) (11.6gm, 15ml, 0.10M) was dissolved separately in n-butanol (100ml) and added to the previous solution with constant shaking. The mixture was place aside for 30 min. and then it was heated for 1 hr on water bath. Then cool to room temperature, the needle shape crystals were obtained and filtered, washed with n-hexane and purify by recrystallization from ethanol to yield pale brown, light weight, needle shaped crystals of 2-hydroxy-3-methylquinoxaline. Physical data presented in table No. 1

Reaction: CompoundSSB2



3-methylquinoxalin-2(1*H*)-one

2-chloro-3-methylquinoxaline

2-hydroxybenzaldehyde (Salicyldehyde)

2-[(3-hydroxyquinoxalin-2-yl)oxy]benzaldehyde

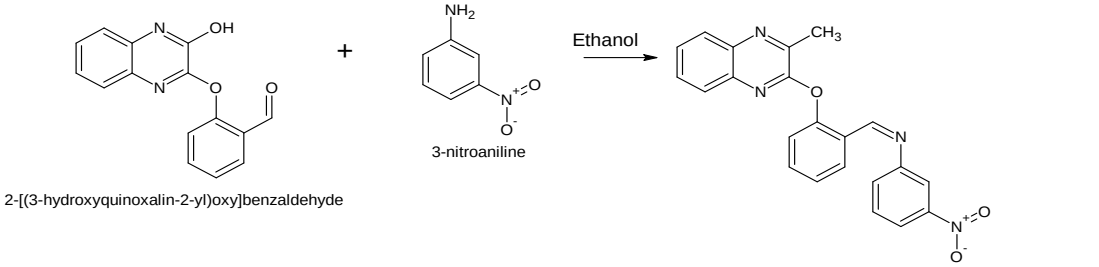
Chemicals: 3-methylquinoxalin-2(1H)-one, $POCl_3$, Salicylaldehyde, Acetonitrile, Ethyl acetate.

Procedure: 3-methylquinoxalin-2(1*H*)-one (16.0 gm, 0.10mol) was taken in 250ml RBF. $POCl_3$ (60ml) was added drop by drop with constant stirring more than1 hrs. After keep the reaction refluxing for 2hrs. Process of the reaction was monitored by TLC method by using of Methanol: Chloroform (1:9).

Then Salicyladehyde (2-hydroxybenzaldehyde) (1.9 ml) and acetonitrile (50ml) was refluxed for 60 minutes. This hot solution was added to above reaction mixture drop wise. After complete adding, the temperature of reaction solution was increased and refluxed. Process of the reaction was monitored by TLC method by using of Methanol: Chloroform (1:9). The

reaction cooled to room temperature. Reaction mixture been added with Ethyl acetate (30ml) layer and water (150 ml). Ethyl acetate layer was collected and distilled out (30hrs). A physical property is show table No. 01.

Reaction: Compound SSB-QXMNA

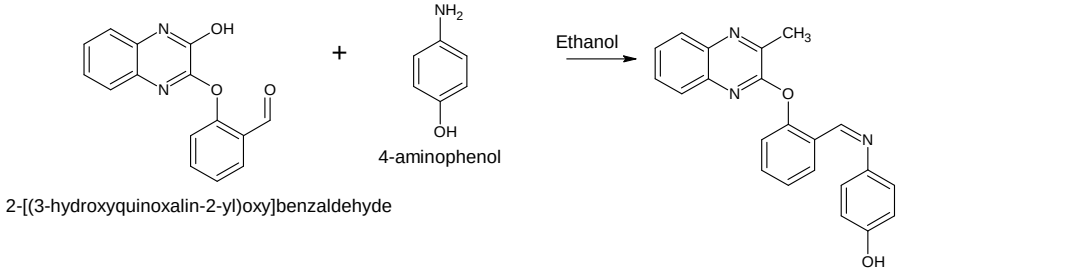


2-[(3-hydroxyquinoxalin-2-yl)oxy]benzaldehyde + 3-nitroaniline → *N*-[(*Z*)-{2-[(3-methylquinoxalin-2-yl)oxy]phenyl}methylidene]-3-nitroaniline

Chemical: 2-[(3-hydroxyquinoxalin-2-yl) oxy] benzaldehyde, Ethanol, m-Nitro aniline.z

Procedure: 2-[(3-hydroxyquinoxalin-2-yl) oxy] benzaldehyde (compound 2) 3gm, (0.011 mol) and 20 ml of ethanol added and stirred. m-Nitro aniline3.59ml, (0.022mol.) was dissolved in ethanol 10 ml and added the reaction mixture. Temperature of the reaction solution was increases to reflux. The process of the reaction mixture was monitored by TLC method by using Ethyl acetate: n-Hexane (1:1). After end of reaction, acidify with dil. Hydrochloric acid and extract with ethyl acetate. Aqueous layer was collected and basified with sodium carbonate until pH 8 and then extracted with ethyl acetate. Ethyl acetate layer is collected by using separating funnel and distilled.

Reaction: Compound SSB-QXPAP



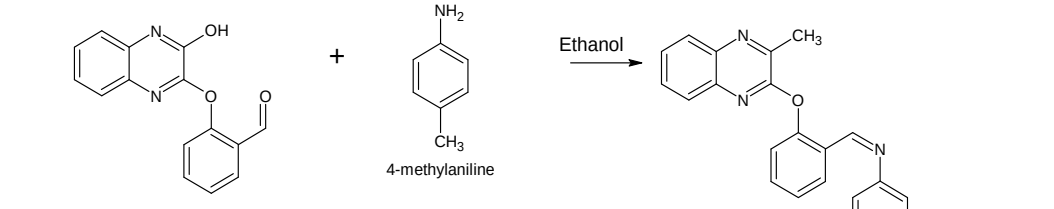
2-[(3-hydroxyquinoxalin-2-yl)oxy]benzaldehyde + 4-aminophenol → 4-[(*Z*)-({2-[(3-methylquinoxalin-2-yl)oxy]phenyl}methylidene)amino]phenol

Chemicals: 2-[(3-hydroxyquinoxalin-2-yl) oxy] benzaldehyde, Ethanol, p-amino phenol.

Procedure: 2-[(3-hydroxyquinoxalin-2-yl)oxy] benzaldehyde (Compound SSB2) 3gm, (0.011 mol.) and 20 ml of ethanol added and stirred. P-amino phenol 2.89ml, (0.022 mol.) was dissolved in ethanol 10 ml and addition to the reaction mixture. Temperature of the

reaction solution was increases to reflux. The process of the reaction mixture was monitor by TLC method by using of Ethyl acetate: n-Hexane (1:1). After end of the reaction, acidify with dil. HCl and isolate with ethyl acetate. Aqueous layer was collected and basified with sodium carbonate until pH 8 and then extracted with ethyl acetate. Ethyl acetate layers collected by using separating funnel and distilled.

Reaction: Compound SSB-QXPMA



2-[(3-hydroxyquinoxalin-2-yl)oxy]benzaldehyde

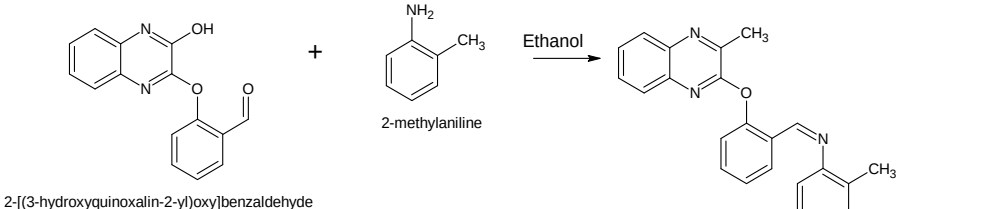
4-methylaniline

4-methyl-*N*-[(*Z*)-{2-[(3-methylquinoxalin-2-yl)oxy]phenyl}methylidene]aniline

Chemicals: 2-[(3-hydroxyquinoxalin-2-yl) oxy] benzaldehyde, Ethanol, 4-Methyl aniline.

Procedure: 2-[(3-hydroxyquinoxalin-2-yl) oxy] benzaldehyde (Compound SSB2) 3gm, (0.011 mol.) and 20 ml of ethanol added and stirred. 4-methyl aniline 2.35ml (0.022 M) was dissolved in ethanol 10 ml and addition to the reaction mixture. Temperature of the reaction mixture solution was increases to reflux. The process of the reaction mixture was monitored by TLC method by using of Ethyl acetate: n-Hexane (1:1). After end of the reaction, acidify with dil. HCl and isolate with ethyl acetate. Aqueous layer was collected and basified with sodium carbonate until pH 8 and then extracted with ethyl acetate. Ethyl acetate layer is collected by using separating funnel and distilled.

Reaction: Compound SSB-QXOMA



2-[(3-hydroxyquinoxalin-2-yl)oxy]benzaldehyde

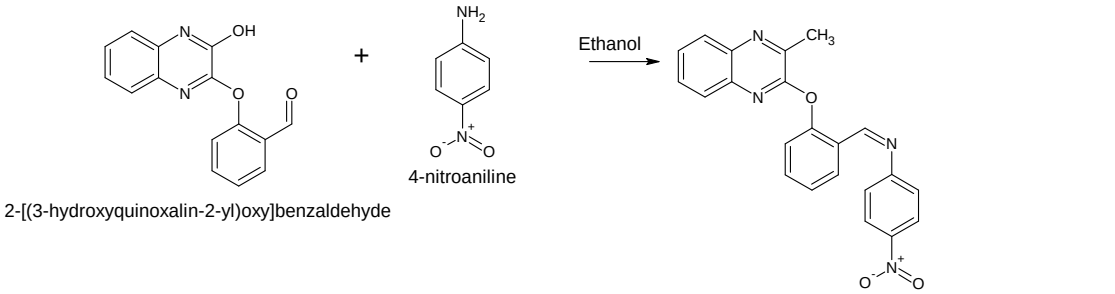
2-methylaniline

2-methyl-*N*-[(*Z*)-{2-[(3-methylquinoxalin-2-yl)oxy]phenyl}methylidene]aniline

Chemicals: 2-[(3-hydroxyquinoxalin-2-yl) oxy] benzaldehyde, Ethanol, 2-Methyl aniline.

Procedure: 2-[(3-hydroxyquinoxalin-2-yl) oxy] benzaldehyde (Compound SSB2)3gm, (0.011 mol.) and 20 ml of ethanol added and stirred. 2-methyl aniline 2.59ml (0.022 mol.) was dissolved in ethanol 10 ml and addition to the reaction mixture. Temperature of the reaction mixture was increases to reflux. The process of the reaction mixture was monitored by TLC method by using of Ethyl acetate: n-Hexane (1:1). After end of the reaction, acidify with dil. HCl and isolate with ethyl acetate. Aqueous layer was collected and basified with sodium carbonate until pH 8 and then extracting with ethyl acetate. Ethyl acetate layer is collected by using separating funnel and distilled.

Reaction: Compound SSB-QXPNA



2-[(3-hydroxyquinoxalin-2-yl)oxy]benzaldehyde

4-nitroaniline

(*Z*)-1-{2-[(3-methylquinoxalin-2-yl)oxy]phenyl}-*N*-(4-nitrophenyl)methanimine

Chemical: 2-[(3-hydroxyquinoxalin-2-yl) oxy] benzaldehyde, Ethanol, p-Nitro aniline.

Procedure: 2-[(3-hydroxyquinoxalin-2-yl) oxy] benzaldehyde (Compound SSB2) 3gm, 0.011 mol.) And 20 ml of ethanol added and stirred. P-nitro aniline 2.59gm, (0.022 mol.) was dissolved in ethanol 10 ml and addition to the reaction mixture. Temperature of the reaction mixture was increases and reflex. The process of the reaction mixture was monitored by TLC method by using of Ethyl acetate: n-Hexane (1:1). After end of the reaction, acidify with dil. HCl and isolate with ethyl acetate. Aqueous layer was collected and basified with sodium carbonate until pH 8 and then extracted with ethyl acetate. Ethyl acetate layer is collected by using separating funnel and distilled.

Identification and Characterization

Introduction: The confirmation of the prepared compound can be done by using below procedure to ascertain that all synthesized chemical moiety had changed chemical nature than the potent compound.

The identification can be carried out by

- Melting point.

- Thin layer chromatography
- Infrared spectroscopy (IR)
- Nuclear magnetic resonance (NMR)
- Mass spectroscopy (MS)

Melting point determination: Melting point determination is one of the measure procedures to confirm the purity of the given compound. It can be determined by open capillary tube method. The purity of the compound should not be assumed but it should be observed if any changes in the melting point. There is a small change in the melting point of the compound when the compound is recrystellized.

The compound was filled in the capillary tube and was kept in the Thieles tube and checked the MP.

Thin layer Chromatography: Thin layer chromatography is used to confirm the development of the new compound and also to determine the impurity of the given compound. The TLC provides information about the Rf values which is the characteristic of all of the synthesized drug. Using readymade Aluminium silicon coated plates by current work, purchasing mark company products.

Application of sample: It done by taking the solution of the parent compound and its derivative in capillary tubes. The spot are made on the plates 2cm from the base so that solvent should not merge the spot. After spotting is done the plates are then transferred to the chamber containing the solvent for the development. The chamber should be kept closed. After the development the slide is taken out dried at room temperature.

Detection of sample: The spot can be observed and detected by observing it in the UV chamber, if fluorescent spot is are not detected in UV chamber they can be detected by using iodine vapors.

$$Rf = \frac{Distance\ travelled\ by\ solute}{Distance\ Travelle\ by\ solvent}$$

In every case different sample possesses a different point on the slide. That point can be determined by the distance travelled by the solvents. This ensures that the both spots are different from each other. Based on the spot the compounds can be differentiated from the

other. If the compound shows only one single spot that confirms the compound is pure and free from any impurities.

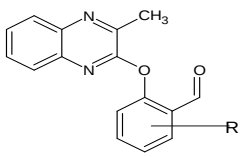
Spectral studies

IR Spectra: Every compound absorbs a different wavelength based on the vibration the compound can be detected. The peaks in the results give a rough idea about the probability of the structure. The IR ranges from 400-4000 cm^{-1}. The synthesized compounds are tested in our instrumental analysis lab, by using SHIMADZU FTIR software at BLDEA's SSM College of pharmacy and research centre. Vijayapur, Karnataka.

NMR spectra: NMR spectroscopy is the study of spin changes at the nuclear level when radiofrequency energy is absorbed in the presence of magnetic field. When the energy radiofrequency is applied, absorption of energy occurs and a NMR signal is recorded. Because of the absorption of energy, the nucleus moves from ground state to excited state, this results in spin reversal or antiparallel orientation. The NMR ranges from 0-14δ.[69] Synthesized compound are checked by Bruker software at in Sholapur University, Solapur, Maharashtra.

Mass spectrum: Mass or molecular weight of a compound can be found in mass spectroscopy. Not only determination of mass, but the technique can be used for structure elucidation, quantitative analysis and even advanced studies could be done by using mass spectrum of a compound. Mass spectrum conversion of neutral molecule into a charged molecule, preferably to a positively charged molecule. And separation of the positively charged fragments formed, based on their masses, by using electrical or magnetic field or both.[69] Synthesized compound are checked in AnSys Research Laboratories, Gota, Ahmedabad-Gujarat-382481. India.

Physical data of the synthesized compounds



Biological evaluation

Antibacterial Activity

The Agar Diffusion Method: The antibacterial action of the synthesized compound was studied, significantly against two different strains of bacteria gram positive and gram negative by the agar diffusion technique.

Commonly antibacterial action of a drug is expressed in the terms of its capability to stop the growth of bacteria in nutrient broth or agar, bacterial inhibition can be find out by two methods: one is the serial dilution method and the other is diffusion method.

The exact method adopted in the current examination is cup plate method involving cups of standard diameter of the nutrient agar medium and contain standard bacterium inoculums. The test compounds were introduced into the cup and diameter of the zones of inhibition is calculated.

All test compounds is evaluate for antibacterial action against s*taphylococcus aureus* (gram +ve) *Escherichia coli* (gram –ve), follow the agar diffusion method of assay.

The bacteria organisms are sub-cultured by nutrient agar medium. The tube contain sterilized medium are inoculated with particular bacterial strain. After incubation at 37 ± 1^0C for 24 hrs. And store in a refrigerator. The stock culture is maintained. Bacterial inoculums is prepare by transfer a loop full of stock culture to nutrient broth (100ml) in a clean and antiseptic conical flask (250ml) are incubated at 37 ± 1^0C for 18 hrs. Before the conducting tests solution of the test drug is prepared by dissolving 1500mcg of compound in 10ml (1500mcg/ml) of methanol. From stock solution, 0.5ml & 0.33ml of solution are taken by using of micropipette 750mcg/ml and 500mcg/ml respectively.

Take a 250 ml conical flask, nutrient agar (5.6gm) is dissolved in 200 ml of distilled water, mixed properly complete the soluble nutrient agar medium, pack the conical flask neck with help of sterile cotton, aluminum paper, and brown paper. The nutrient agar mixture was sterilized by autoclaving at 15 lbs for 30 min. at 121^0C. The Petri-plates are sterilized in hot air oven at 150^0C, for an hour. Into each sterilized Petri-plate about 50ml each of molten nutrient agar media pour by taking care of aseptic condition. The plates were keeping at room temperature to allow to stand for solidification. In each plate, four cups of 6mm diameter are made with a sterile borer. Then, 0.5ml and 0.33ml of the test solution was added to the cups,

aseptically and labeled accordingly. The plates are set aside undisturbed for at least 2 hrs. at room temperature to allow diffusion of the drug solution properly, into the nutrient agar medium. The media containing plates are keeping at 37 ± 1^0C for 24 hrs. After incubation calculated the diameter of the zone of inhibition surrounding each of the cups are measured by using 'antibiotic zone reader'. Simultaneously, maintained employing 0.5ml of methanol to observe the solvent effects. Standard drug are using chloramphenicol 100mcg/ml.

RESULTS: Results for the anti-bacterial activity are given in the table no. 3.

RESULTS AND DISCUSSION

Synthetic Methods: All targeted compounds were prepared in good yield, ranging from 46% to 66%, using available laboratory facilities. All compounds found to be pure when analyzed through TLC and Melting point determination.

Spectral analysis: The synthesized compounds are analyzed by, IR, NMR and Mass spectroscopy. All compounds are in agreement with reference values. Silverstein and Chatawal books were used as references.

Anti bacterial activity: The antibacterial activity study was carried out for all synthesized compounds using Gram +ve and Gram –ve bacterial strains. The study was carried out in our microbiology laboratory. The results are presented in table No. 3.

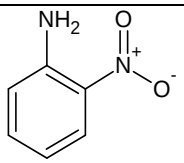
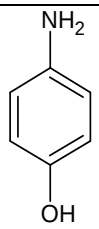
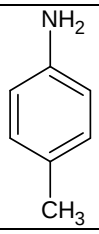
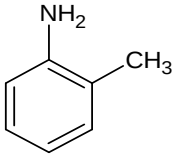
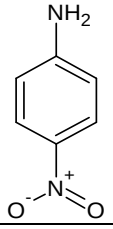
The synthesized compound, viz., SSB-QXMNA, SSB-QXPAP,SSB-QXPMA,SSB-QXOMA and SSB-QXPNA were screen against *E. coli* (gram -ve) and *Staph. Aureus* (gram +ve) for testing antibacterial action at lower (500mcg/ml) and higher (750 mcg/ml) concentration. Among the synthesized compounds. SSB-QXMNA, SSB-QXPMA and SSB-QXPNA showed effective inhibition of growth against ***Escherichia coli*** and SSB-QXMNA, SSB-QXPAP and SSB-QXPNA showed significant effects against ***Staphylococcus aureus*** when compare to standard drugs Chloramphenicol which shown zone of inhibition 22 mm and 12 mm against *E. coli* and *S. aureus* respectively. Some compounds shown significant zone of inhibition as compared to the standard drug.

Table No. 01: Physiochemical properties of compound SSB1 and SSB2.

Sr. No	Comp. Code	Mol. formula	Mol. Wt.	%Yield	MP (^{o}C)	Rf value
01	Comp.SSB1	$C_9H_8N_2O$	160	91.17%	246-248 ^{o}C	0.81
02	Comp.SSB2	$C_{16}H_{12}N_2O_2$	264	84.92%	70-72 ^{o}C	0.71

- TLC Solvent & ratio, Methanol:Chloroform 9:1
- Recrystallisation solvent is used ethanol

Table No. 2: Physiochemical properties of compounds quinoxaline derivatives.

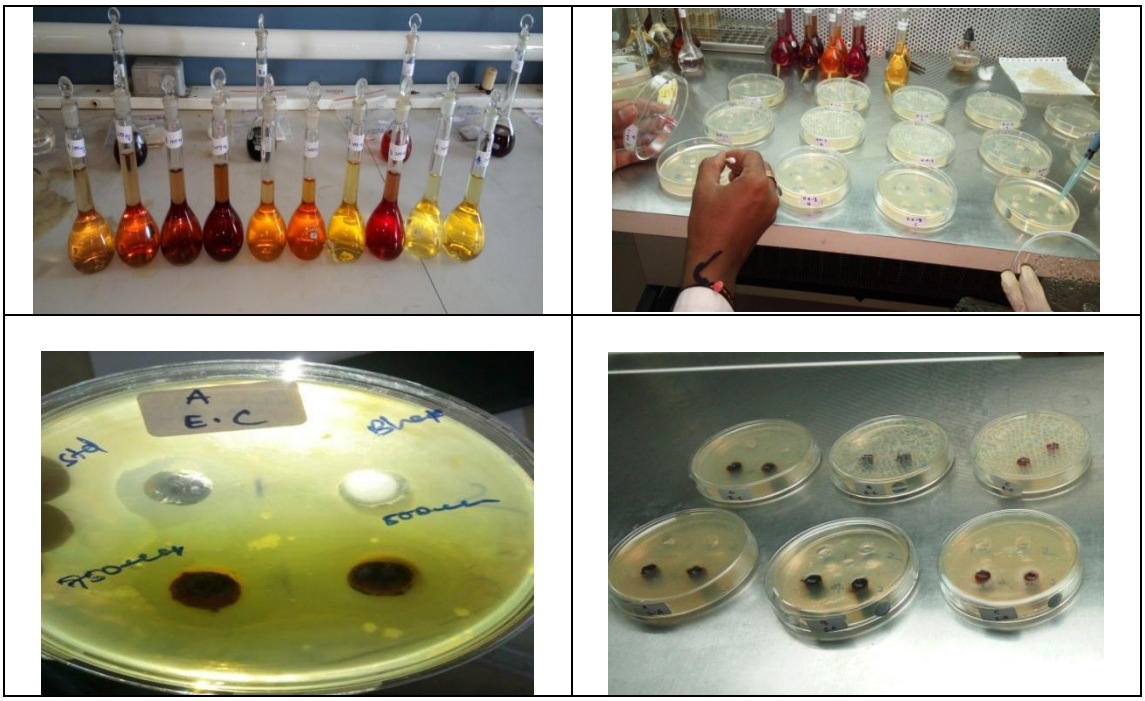
Sl No	Comp. code	R	Mol.formula	Mol. Wt.	% Yield	MP (^{o}C)	Rf value
01	SSB-QXMNA		$C_{22}H_{18}N_4O_3$	384	57.14 %	114-116	0.98
02	SSB-QXPAP		$C_{22}H_{19}N_3O_2$	355	66.03 %	80-82	0.97
03	SSB-QXPMA		$C_{23}H_{21}N_3O$	353	46.64 %	108-110	0.11
04	SSB-QXOMA		$C_{23}H_{21}N_3O$	353	55.15 %	159-160	0.85
05	SSB-QXPNA		$C_{22}H_{18}N_4O_3$	384	63.67 %	120-122	0.90

- TLC Solvent & ratio, Ethyl acetate : n-hexane 1:1
- Recrystallisation solvent is Methanol.

Table No. 03: Antibacterial Activity of synthesized compounds by cup plate method.

Sl. No.	Compound Code	*Escherichia coli (gram -ve)*		*Staphylococcus aureus (gram +ve)*	
		Concentration of drugs (µg /ml)		Concentration of drugs (µg /ml)	
		500	750	500	750
		Mean zone of Inhibition (mm)		Mean zone of Inhibition (mm)	
1	SSB-QXMNA	23	25	17	21
2	SSB-QXPAP	15	16	31	24
3	SSB-QXPMA	24	29	14	17
4	SSB-QXOMA	17	19	15	19
5	SSB-QXPNA	22	27	22	21
Std	Chloramphenicol (100 mcg/ml)	22		12	

Photos



SUMMARY AND CONCLUSION

SUMMARY: The new compounds SSB-QXMNA, SSB-QXPAP, SSBQXPMA, SSB-QXOMA and SSB-QXPNA are synthesize all the compounds are analyzed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral studies.

The synthesized compounds are tested for antibacterial activity using cup plate technique. Tested compounds exhibited significant antibacterial activity when compared to standard drug chloramphenicol. Some drugs showed significant antibacterial activity.

This thesis constitutes as specified here under: The aim of the objectives of the present work on quinoxalines has been specifically outlined. The present survey of literature has been prepared on various synthetic routes of quinoxalines and their derivative of different biological and pharmacological interest. It has been followed by a need for the present work and to study their antibacterial attempt has been made as follows.

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REFERENCES

1. Shaik. A, Shaik M. A review Synthesis, Biological evaluation and Structural activity relationship of Quinoxalinederivatives. IJPT; 2016; 8(4): 4947-63.
2. https://en.wikipedia.org/wiki/Quinoxaline.
3. Achal M, Takesh K N, Reman L S. A Review on Quinoxaline-Pharmacophore And Derivatives With Diverse Biological Properties. World J Pharma. and Pharm. SC., 2013; 2(6): 6486-506.
4. Porter, A. E. A. In Comprehensive Heterocyclic Chemistry; Pergamum: New York, 1984; 157-97.
5. Zarranz, B, Jaso, A., Aldana, I., Monge, A, Maurel S, Deharo E. Jullian V, SauvainM. Synthesis and antimalarial activity of new 3-arylquinoxaline-2-carbonitrile derivatives. Arzneim.-Forsch, 2005; 55: 754-61.
6. Lima, L. M, Zarranz, B, Marin, A, Solano B, Vicente E, Silanes S. P, Aldana, MongeA, Comparative use of solvent-free KFAl2O3 and K2CO3 in acetone in the synthesis of quinoxaline 1,4- dioxide derivatives designed as antimalarial drug candidates. J. Heterocycl. Chem., 2005; 42: 1381-85.
7. Jaso, A., Zarranz, B, Aldana, I, Monge. Synthesis of new quinoxaline-2-carboxylate 1, 4-dioxide derivatives as anti-Mycobacterium tuberculosis agents. J. Med. Chem., 2005; 48: 2019-25.
8. Aguirre G, Cerecetto H, Di Maio R, Gonzalez M, Alfaro. M. E. M, Jaso A, Zarranz, B, Ortega M A, Aldana I, Monge. Quinoxaline NN′-dioxide derivatives and related compounds as growth inhibitors of Trypanosome cruzi. Structure-activity relationships. Bio.org. Med. Chem. Let., 2004; 14: 3835-39.
9. Monge, APalop, J. A, Lopez de Cerain, A. L, Senador V, Martinez-Crespo, F. J. Sainz. Y, Narro S, Garcia E, de Miguel C, Gonzalez M, Hamilton E, Barker A. J, Clarke E. D, Greenhow D. T. Hypoxia-selective agents derived from quinoxaline 1,4-di-N-oxides. J. Med. Chem., 199; 38: 1786-92.
10. Azqueta, A, Pachon, G, Cascante, M, Creppy E. E, Monge A, de Cerain A. L. Selective toxicity of a quinoxaline 1,4-di-N-oxide derivative in human tumour cell lines. Arzneim.-Forsch, 2005; 55: 177-82.
11. Ortega M. A, Morancho M. J, Martinez-Crespo F. J, Sainz Y, Montoya M. E, de Cerain A. L, MongeA. New quinoxalinecarbonitrile 1, 4-di-N-oxide derivatives as hypoxic-cytotoxic agents. Eur. J. Med. Chem., 2000; 35: 21-30.

12. Monge A, Palop J. A, Gonzalez M, Martinez-Crespo F. J, Lopez C A. L, Sainz Y, Narro S, Barker A. J, Hamilton E. New hypoxia-selective cytotoxins derived from quinoxaline 1, 4- dioxides. J. Heterocycl. Chem., 1995; 32: 1213-17.
13. Zarranz B, Jaso A, Aldana I., Monge A. Synthesis and anticancer activity evaluation of new 2-alkylcarbonyl and 2-benzoyl-3-trifluoromethyl-quinoxaline 1, 4-di-N-oxide derivatives. Bio.org. Med. Chem., 2004; 12: 3711-21.
14. American Cancer Society, http://www.cancer.org/ (accessedmay 2013).
15. Word World Health Organization, http://www.who.int/gho/ncd/ mortality morbidity/cancer/en/index.html (accessed May 2013).
16. Carvalho S. A, Silva E. F, Lourenco M. C. S, Souza M. V. N, Fraga, C. A. M. Let. Drug Des. Disc., 2010; 7: 606.
17. Ferreira M. L, Candea A. L. P, Henrique M. G. M. O, Kaiser C. R, Lima C. H. S, Souza M. V. N. Let. Drug Des. Disc., 2010; 274.
18. Howie R. A, Souza M. V. N, Ferreira M. L, Kaiser C. R, Wardell J. L, Wardell S. M. S. V. Z. Kristall.ogr., 2010; 225: 440.
19. Ferreira M. L, Goncalves S. S. B, Cardoso L. N. F, Kaiser C. R, Candea A. L. P, Henrique's M. G. M. O. Scientific World Journal, 2010; 10: 1347.
20. Vergara F. M. F, Lima C. H. S, Henrique's M. G. M. O, Candea A. L. P, Lourenco M. C. S, Ferreira M. L. Eur. J. Med. Chem., 2009; 44: 4954.
21. Candea A. L. P, Ferreira M. L, Pais K. C, Cardoso L. N. F, Kaiser C. R, Henrique's M. G. M. O. Bio.org. Med. Chem. Let., 2009; 19: 6272.
22. Lourenco M. C. S, Ferreira M. L, Souza M. V. N, Peralta M. A, Vasconcelos T. R. A, Henrique's M. G. M. O. Eur. J. Med. Chem., 2008; 43: 1344.
23. Souza M. V. N, Bispo M. L. F, Alcantara C. C, Wardell S. M. S. V, Wardell J. L. Z. Kristall.ogr. 2013; 228 & 232.
24. Coimbra E. S, Antinarelli L. M. R, Silva A. D, Bispo M. L. F, Kaiser C. R, Souza M. V. N. Chem. Biol. Drug Des., 2013; 81: 658.
25. González M, Cerecetto H. Exp. Opin. Ther. Pat., 2012; 22: 1289.
26. Patidar A. K, Jeyakandan M, Mobiya A. K, SelvamG. Int. J. Pharm. Tech Res., 2011; 3: 386.
27. Kumar A, Verma A, Chawla G, Vaishali. Int. J. Chem. Tech Res., 2009; 1: 1177.
28. Suresh M, Lavanya P, Sudhakar D, Vasu K, RaoC. V. J. Chem. Pharm. Res., 2010; 2: 497.
29. Noolvi M. N, Patel H. M, Bhardwaj V, Chauhan A. Eur. J. Med. Chem. 2011; 46, 2327.

30. Rajurkar R. M, Agrawal V. A, Thonte S. S, Ingale R. G. Pharmacophore, 2010; 1: 65.
31. Hassam S. Y. Molecules, 2013; 18: 2683.
32. Mielcke T. R, Mascarello A, Fillipi-Chiela E, Zanin R. F, Lenz G, Leal P. C. Eur. J. Med. Chem., 2012; 48: 255.
33. Mamedov V. A, Zhukova N. A. In Prog. Heterocycl. Chem, Eds. Gribble G. W. Joule. J. A. Kasan., 2012; 24(2): 55–88.
34. Wu P, Su Y, Liu X., Yan J, Ye Y, Zhang L. Med. Chem. Comm., 2012; 3: 659.
35. Wei Q, Zhang D, Yao A, Mai L, Zhang Z, Zhou., 2012; 7(5): 2199.
36. Fraga C. A. M, Barreiro. E. J. Cur. Med. Chem., 2006; 13: 167.
37. Rollas S, Küçükgüzel S. G. Molecules, 2007; 12: 1910.
38. Terzioglu N, Gürsoy A. Eur. J. Med. Chem., 2003; 38: 781.
39. Patil B R, Machakanur S. S, Hunoor R S, Badiger D. S, Gudasi K B, Derbligh S. W. A. Pharm. Chemical., 2011; 3: 377.
40. Zhao Y, Hui Z. Y, Wang D, Zhu L, Fang J. H, Zhao X. D. Chem. Pharm. Bull. (Tokyo), 2010; 58: 1324.
41. Hari N. S, Moorthy N, Cerqueira N S, Ramos M. J,Fernandes P. A. Med. Chem. Res., 2012; 12: 133.
42. Zulkepli N. A, Rou K. V. K, Sulaiman W. N. H. W, Salhin A, Saad B, Seeni A. Asian Pac. J. Cancer Prev., 2011; 12: 259.
43. Wardakhan W. W, El-Sayed N. N. R, Mohareb M.Acta. Pharm., 2013; 63: 45.
44. Li J. Z, Li L, Kim J. H, Cui B. C, Wang J. J, Shim Y K. J.Porphyr. Phthalocyanines, 2011; 15: 264.
45. FarghalyT A, Abdallah Z. A. S. Arki.voc, 2008; 295.
46. Gomes L R, Low J. N, Rodrigues A. S. M. C, Wardell J. L, Souza M. V. N, Nogueira T. C. M., Pinheiro A. C. Acta. Crystall. Ogr. Sect. C, 2013; 69: 549.
47. Achal M, Takesh K M, Reman L S. A Review On Quinoxaline-Pharmacophore And Derivatives With Diverse Biological Properties, W J Pharm. and Pharm. SC., 2013; 2(6): 6486-506.
48. Ashutosh K P, Jeyakandan M, Ashok K M, G Selvam. International Journal of Pharma.tech Res. CODEN (USA), 3: 386-92.
49. Mohammad R I and Zahra H. ARKIVOC, 2008; 280-287.
50. Diego M R, Juan J C, Autino J Nancy Quaranta, Patricia G. V azquez, and Gustavo P. R. The Scient. W J Volume, Article ID 174784. 2012.
51. Jing-Jun ,Chao L, Tao G, Xin Z, Ma and H J H. ISSN 1011-3924, 2011

52. Pranita M, Devaanshi J and Rupen J; ISSN 2348-7968, 2014.
53. Hossein R, Farshid M, Kioumars A. J Braz. Chem. Soc., 2007; 18(2): 297-303.
54. SmdNoorulla. Screenivasulu. 2011; ISSN; 2229-3701.
55. Reza S, Neda N, Shohree T and Shririn H. Oriental j chem., 2012; 28: 687-701.
56. Saifina D F, Trymbake and Mahendra S.K Design, Synthesis and Antimicrobial activity of Amide-Linked Quinoxaline Derivates, Int. J. Appl. Chem., 2017; 13(3): 433-51.
57. Hebat-Allah S. Abbas, Aisha R. M, Al-Marhabi and Yousry A. A. Design, Synthesis And Biological Evaluation Of 2,3-Disubstituted And Fused Quinoxalines As Potential Anticancer And Antimicrobial Agents, ISSN 0001-6837 Polish Pharm. Soc., Acta Poloniae Pharm. D Res., 2017; 74(2): 445-58.
58. Asif H and Diwakar M, Recent Advances In Pharmacological Activities Of Quinoxaline Derivatives.2011; J. Pharm. Res., 4(3): 924-29.
59. Available online through http://jprsolutions.info
60. Essassi E M, Ahoya A. C, Daouda B, Bouhfid R, Hançali A, Bousmina M, Zerzouf A, and Aouad R E. Synthesis and antibacterial activity of new spiro[thiadiazolinequinoxaline] derivatives, General Papers, ARKIVOC, 2011; 2: 217-226.
61. Dharmchand P S, Sanjay K D, Syed R H and Ram G S, Synthesis and Antimicrobial Activity of Some New Quinoxaline Derivatives, ISSN 1424-8247, Pharmaceuticals, 2010; 3: 2416-25.
62. Gayathri R, Jubie S, Suresh S, Thirumurthy R, Md. Moklesur, Rahman S. In vitro anthelmintic and antimicrobial activity of novel series of quinoxaline- 2, 3-dione -6-sulphonyl Benzimidazole (s), J Chem. Pharm. Sci., 2015; 8(4): 656-60.
63. Abdelghany A E, Rezk A, Mohamed F Z, Synthesis and biological evaluation of some novel quinoxaline derivatives as anticonvulsant agents, © ECV · Editio Cantor Verlag, Aulendorf (Germany, Arzneimittelforschung, 2011; 61(7): 379–81.
64. Marcus V. N, Souza D, Felipe A. R, Rodrigues I S, Bomfim, Bruno C, Cavalcanti, Claudia Ó, Pessoa J L, Wardell S, Wardell M, Alessandra C P, Carlos R K, Thais C. M, Nogueira, J N. L and Ligia R. G. Design, synthesis and biological evaluation of (E)-2-(2-arylhydrazinyl)quinoxalines, a promising and potent new class of anticancer agents, Bio.org. Med. Chem. Lett., 2014; 24: 934–39.
65. Abbas H S, Aisha R.M, Al-Marhabi and yousry A. Design, synthesis and Biological Evaluation of 2,3- di substituted And Fused Quinoxalines as Potential Anticancer Agents, ActyaPoloniaePharma. Drug. Res., 2017; 16(3); 953-65.

66. Soliman D H, Abdel S and Amad S H. Design, Synthesis and Evaluation of 1,2,2 Diazaphosphorin [4,5- b] Quinoxaline-5,10-di-n-oxide derivates as Novel VEGFR-2 and SRC Kinase Inhibitors in the Treatment of Prostate Cancer, The open Conference. Proceedings J, 2013; 4: 77-86.
67. Usha Rani U, Sivappa N P, Sukanya G, Sri Datha P, Pramod K S, Venkata R V, Synthesis and Biological Evaluation of Isatin incorporated Quinoxalines as Anti-Tubercular Agents, ISSN 0976 – 044X, Int. J. Pharm. Sci. Rev. Res., 2017; 47(2): 67-70.
68. Mery S V, Silvia B, Pérez-Silanesa B, Enrique T, and Elsa M V, Design and synthesis of novel quinoxaline derivatives as potential candidates for treatment of multidrug-resistant and latent tuberculosis, Bioorg Med Chem. Let., 2016; 26(9): 2188–93.
69. Ravi Sankar S, Text book of pharmaceutical analysis, IIIrd edition, 2011; 6.1-6.5, 8.1-8.4.