Chapter-3

3.1. Synthesis and Characterization of Naphthelene based Quinoxalines

3.1.1. General introduction of quinoxalines

Heterocycles constitute an important class of organic compounds that are identified by the feature that some of the atoms in their molecules are joined in rings containing at least one atom of an element other than carbon. The most common and naturally occurring heterocycles include those having either five or six member rings containing N, O and S. The heterocyclic compounds having lesser common atoms such as phosphorus, tin, boron, silicon, bromine, etc. have been much investigated in recent years. The heterocyclic compounds having five or six atoms in the ring are the most important [Mansuri, M. et al., 2012]. These molecules have lot of applications not only in our daily life, but also in the formation of life. For example, many heterocyclic derivatives such as papaverine, theobromine, theophylline, atropine, procaine, codeine, reserpine, morphine etc are used as life-saving drugs and all these are natural drugs. On the other hand, diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyritic, captopril, methotrexate, etc. are synthetic drugs [Chin, Y. M. et al., 2006]. They also constitute the core unit of several antibiotics, vitamin, hallucinogens, pesticides, dyes, pigments, plastics and cosmetics etc [Joule, J. A. et al., 2001].
The understanding of drug design and developments of the synthetic drugs needs the knowledge of physicochemical properties of chemicals compounds used to develop new pharmacologically active compounds. These normally include but not limited to biological activities, mechanism of actions, metabolism and possible biological activities of the metabolites and importance of stereochemistry for molecules for new drug design. On the other hand, nucleic acids contain five or six member heterocycles. For example, furan is the basic unit of the sugar part of DNA and RNA while Adenine, guanine, cytosine, thymine and uracil are the four or five bases that are vital constituents in DNA and RNA. Though a transition metal catalyst usually relies on homogeneous catalysis, its use has been restricted due to the following disadvantages.

- Difficulties to separate and recover the catalyst from the reaction mixture
- Usualy no reusability of the catalyst
- Chance of metal contamination with the end product
- Significantly in large-scale reaction it often leads to the generation of huge metal-waste to the environment
- Causing environmental pollution due to improper disposal.

In order to overcome these problems, various solid heterogeneous supports have been used to immobilize the metal and these are known as heterogeneous supported metal catalyst. These catalysts can easily be recovered from the reaction mixture due to their heterogeneity. Also, the possibility of
metal contamination with the end product and the formation of metal waste to the environment are very less as the metal remains bounded firmly on the surface of the solid support even after several reactions. Hence, heterogeneous supported metal catalysis has received considerable attention in recent times.

In this chapter, heterogeneous supported metal catalyzed synthesis of various bioactive five and six member heterocycles will be discussed. N-containing heterocycles occupy a major space in the domain of heterocyclic compounds. These molecules are found in various natural products and they possess significant biological activities. Various N-containing heterocycles such as indole, triazole, oxindole, quinilone, quinazoline and quinoxaline have been vastly synthesized [Djakovitch, L .et al., 2011].

3.1.2. Commercial Available Drugs

They are the key building blocks in the preparation of dyes, electroluminescent material, organic semiconductors, cavitands and dehydroannulenes. Quinoxalines act as potential rigid subunits in macrocyclic receptors [Mizuno, et al., 2002, Elwahy, et al., 2000] for the recognition of molecules and chemically controllable switches [Crossley, Jhonston, et al., 2002]. Pyridazine and phthalazine derivatives are found in skeleton of some commercially available drugs. For instance, apresoline contains hydralazine as a pyridazine derivative that is used to treat hypertension for pregnant [Vigil-De Gracia, P. et al., 2006].
Agents involved in this category include sedatives, hypnotic, anticonvulsants, anxiolytic agents, pyrimidine anaesthetics etc. Large variety of barbiturates is used as CNS active agents and is classified as short, intermediate and long acting depending upon duration of action. Risoperidone is an antipsychotic drug, which is a structural hybrid of butyrophenone and can be used as anxiolytic, antidepressant and anti parkinsonian drug. A pyrimidine analogue, thimylal is a short acting general anaesthetic drug. [Wang, S. Q. et al., 2004, Jain, K. et al., 2006, Rahaman, S. A. et al., 2009, Rashad, A. E, et al., 2010 ].

3.1.3. Biological Importance of Heterocyclic Compounds

In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. The presence of a pyrimidine base in thymine, cytosine and uracil, which are the essential building blocks of nucleic acids, DNA and RNA is one of the possible reasons for their activities [Amir, M. et al., 2007] Vitamins are essential for body. Pyrimidine ring is found in vitamins like riboflavin, thiamine and folic acid.

Pyrimidine nucleus is also present in barbituric acid and its several derivatives e.g. Veranal) which are used as hypnotics. In addition to this, pyrimidine nucleus is also found in alloxan, which is known for its diabetogenic action in a number of animals. Medicinal importance of Pyrimidine derivatives have been very well known for their therapeutic
applications. Many pyrimidine derivatives have been developed as chemotherapeutic agents and are widely used. Antimicrobial activity microbes are causative agents for various types of disease like pneumonia, amoebiasis, typhoid, malaria, common cough and cold various infections and some severe diseases like tuberculosis, influenza, syphilis and AIDS as well. Various approaches were made to check the role of pyrimidine moiety as antimicrobial agent from the discovery of molecule to the present scenario. Hitchings, in 1948, made an important observation that a large number of 2, 4 di amino pyrimidines and some 2-amino-4 hydroxy pyrimidines are antagonists of folic acid. These pyrimidines were than eventually proved as inhibitors of the enzyme dihydrofolate reductase (DHFR). Amongst the 2,4-diaminopyrimidine drugs, pyrimethamine is a selective inhibitor of the DHFR of malarial plasmodia. Trimethoprim, an antibacterial drug is also a selective inhibitor and selectively inhibits bacterial DHFR. Brodimoprim is also found to be an effective antibacterial compound. Pyrimidine also shows antifungal properties. Flucytosine is a fluorinated pyrimidine used as nucleosidal anti fungal agent for the treatment of serious systemic infections caused by susceptible strains of candida and Cryptococcus [Padamshari, B. et al., 2002, Naik, T. et al., 2007, Mishra, R. et al., 2004].

Analgesic and anti-inflammatory activity Pyrimidine has a remarkable pharmacological efficiency and therefore an intensive research has been focused on anti-inflammatory activity of pyrimidine nucleus. New forms of
thiamine are lipid-soluble like acetiamine, bentiamine etc, having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism especially in the treatment of long-standing insulin-dependent diabetes mellitus. Acetiamine bentiamine afloqualone has been evaluated as a successful anti-inflammatory agent with lower back pain patients. A condensed pyrimidin-2-one derivative, proquazone, has been reported to exhibit good NSAID potential [Ishwaarsinh, R. S. et al., 2000, Belema, M. et al., 2003].

3.1.4. Anti Cancer Activity

Methyl (4-(substituted 2-quinoxalinyloxy) phenyl acetates and ethyl N-f(4-(substituted 2-quinoxalinyloxy) phenyl acetyl glutamate analogs of methotrexate and evaluated for in vitro anti cancer activity bio-isosteric replacement of pteridine ring with 6(7)-trifluoromethyl quinoxaline affords a good substrate for the classical antifolate analogs and bioisosteric replacement of 2-NH group with an oxygen that in some cases was of relevance in anticancer activity. Quinoxaline bearing a 2-(4-substituted phenoxy) substituent was endowed with potent antitumor activity [Gupta, R. R. et al., 1998, Joule, J. et al., 2000].

3.1.5. Biological activities Substituted phtahlazines

The diverse biological activities of various functional derivatives of substituted phtahlazines are well known. Some of the phtahlazines derivatives
have found application in clinical medicine due to their pronounced antipyretic, analgesic and cardiovascular activity while others have shown interesting vasodialator and antihypertensive properties [Yamaguchi, M. et al., 1993, Demirayak, S. et al., 2004].

Phthalazines bearing a substitution represent key intermediates in the synthesis of various compounds with highly interesting pharmacological properties. Phthalazines has been found to be a selective PDE inhibitor or the thromboxane synthetase inhibitor and bronchodilator. The phthalazine nucleus has been proved to be a versatile system in medicinal chemistry. Moreover a number of established drug molecules [Napoletano, M. et al., 2001]. The development of new and efficient methodologies for the synthesis of such potentially bioactive phthalazine derivatives is important. Therefore, functionalization of the nucleus continues to be of synthetic interest. In general, most of the structural modifications of the parent system have been carried out in order to optimize the biological activity of diazines-derived drug [Abdel-Khalik, M. M. et al., 2001, Haack, T. et al., 2005].

Many heterocyclic compounds derived from synthetic as well as natural sources, commonly in practice contain one or more nitrogen in the heterocyclic ring system. Diazines (1,2 / 1,3 /1, 4-diazines) are important heterocyclic rings. Recently, much attention has been focused on diazine derivatives for their broad spectrum biological activities. Various structural modifications were carried out in diazines ring systems. These structural

3.1.6. Psychological Disorders

Psychological disorders are occurring in an individual and to cause distress or disability. The mental disorders have changed over time. Mental disorders can vary, may included dissociative disorders, mood disorders, anxiety, psychosis, eating disorders, developmental disorders, personality disorders, ambulatory disorders and many other. Mental disorders have been found to be common, with over a third of people at some point in their life. The central nervous system (CNS) is functionality far more complex than any other system in the body so the drugs that act at CNS, it is difficult to understand its mechanism clearly. Nearly all the molecules entering the brain have to pass through the endothelial cell membranes, through the blood brain barrier (BBB). It is more difficult for polar molecules to enter the brain unless they are actively transported. This factor must be taken when designing drugs to target the brain. The lipid solubility increases the drug easily cross BBB and gives its response. The BBB also contains enzymes that protect the brain. Thus, this factor must be taken when designing drugs to target the brain. Piperazine has chemical similarity with piperidine and readily absorbs water and carbon dioxide from the air. Various piperazine derivatives occur
naturally. Piperazine exists as deliquescent crystals with a salin taste. The Piperazine is a broad class of chemical compounds with important biological activities [Tripathi, K. et al., 2003, Thomas, G. et al., 2004].

Most of these compounds can be classified as either phenyl/benzyl-piperazines, diphenylmethyl piperazines (benzhydrylpiperazines), pyridinyl-piperazines, pyrimidinylpiperazines or tricyclics (piperazine ring attached to the heterocyclic ring via a side chain). Pipofezine (Azafen or Azaphen) is a tricyclic antidepressant (TCA) used as anti-depressant. Pipofezine is act as a potent reuptake inhibitor of serotonin. It also has sedative as well as antihistamine activity. Quinoxaline is nitrogen containing six members heterocyclic, in which two nitrogen atoms are based on pyrazine so called as benzopyrazine. Quinoxaline have become attractive target of extensive research due to its inherent properties and therapeutic uses. Quinoxaline finds many pharmacological activities like antimicrobial, anti-tuberculer, anti-inflammatory, anti-hyperglycemic, antitumor etc. Heterocyclic compounds are very widely distributed in nature and are particularly important because of the wide variety of physiological activities associated with this class of substances. Several of the important compounds contain heterocyclic rings, e.g. mostly the members of vitamin B-complex, alkaloids, antibiotics, chlorophyll, other plants pigments, amino acids, dyes, drugs, enzymes, the genetic material, DNA etc [Rajurkar, R. et al., 2010].
They bind to physiological targets or receptors, producing many possible mechanisms of actions. Diazines are inexpensive and easily synthesized and therefore have been examined as different biological activities. A slight variation in the substitution pattern on the diazines nucleus often causes a marked difference in activities and therefore diazines with various substituent are being synthesized and tested for activities in search of better medicinal agents and great interest has arisen in the design and synthesis of new diazines compounds to explore their potent activities against various diseases or disorders. The diazines nucleus, which has a useful structure for further molecular exploration for the development of new derivatives with different biological activities, has received much attention in recent years. [Bitter, I. et al., 2004, Johnson, R. et al., 2004, Aleeva, G. et al., 2009, Kakui, N.et al., 2009, Elmore, C. et al., 2009, Aleeva, G. et al., 2009, Maki, N. et al., 2010 Costas, T. et al., 2010, Arya, A. et al., 2011].

3.1.7. Bio Products Containing Heterocyclic Compounds

The majority of essential bio products contain at least one heterocyclic subunit with in their structures and therefore heterocyclic chemistry is essential part of the pharmaceutical industry. A wide variety of receptors have precious biological activity due to their rigid structures and functional heterocyclic generally possess drug-like belongings. In order to further explored chemical space available for pharmaceutical applications, there is a continued demand for the development of new diazine heterocyclic core
scaffolds that have novel structures and bear functionality and subsequent hit-to-lead medicinal chemistry development. These six member saturated moiety containing nitrogen atoms can be explore to synthesize many of its analogous which can be effectively and successfully exploit to obtained the new molecule which shows better biological response as to treat psychological and neurological disorders. Since the prevalence of mental health problems, particularly psychosis, schizophrenia, depression and anxiety, in the general population is around one in six people and around 40% of people with mental health problems will have symptoms of both anxiety and depression. Drug acting on the CNS include the centrally acting analgesics, anti-epileptics and anti Parkinson agents, as well as those for psychiatric disorders. Based on the literature it may be concluded that six member saturated nitrogen containing rings are important and it throws attention to set the mind of researchers to carry out the work for developing its various analogous used in neurological and psychological disorders which can ultimately beneficial for humans beings . [Smith, M. B. et al., 2001, Beale, J. M. et al., 2004, Kim, W. et al., 2006, Padavala, A. B. et al., 2010, Pai, N. et al., 2010, Rao, G. K. et al., 2010, Singh, M. et al., 2010, Patrick, L. G. et al., 2013].

Pyridazine derivatives have different functionalities in their structures. For example, pyridate has thiocarbonate composition, credazine 8 comprises the ether linkage and pyridafol consists of alcohol unit. Pyridazinones hold
considerable interest relative to the preparation of organic intermediates and physiologically active compounds [Hovakimyan, S. et al., 2004].

3.2. Literature survey

3.2.1. Discovery

Synthesis of quinoxaline derivatives has attracted a great deal of attention in view of their potent pharmacological activities [Ogita, K, et al., 1990]. Approximately 1% of the world’s population is affected by epilepsy [Walker, M. C. et al., 1996]. Therefore, investigation of new anticonvulsant is still a challenge. Most of the currently used anticonvulsant drugs are associated with adverse effects, such as sedation, ataxia and weight loss or weight gain. Rare adverse effects can be life threatening such as aplastic anemia [Bourgeois, B. F. et al., 1998].

His development of safer and more effective new anticonvulsant drugs is necessary. It was reported that, the majority of anticonvulsant agents mediate their effect through their action either by activation of the \( \gamma \)-aminobutyric acid (GABA) receptor or by inhibition of the glutamate receptor. Glutamate receptors are classified into two main subtypes, N-methyl-d-aspartate (NMDA) and \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor. [Rogawski, M. A. et al., 2006] In fact, NMDA receptor antagonists may produce schizophrenia like symptoms, perceptual alterations and memory impairment AMPA receptor antagonists
have no such psychoactive properties [Rutecki, P. A. et al., 2002]. On the other hand, from the literature survey it was found that many quinoxaline derivatives showed anticonvulsant activity [Jackson, P. F. et al., 1991, McQuaid, L. A. et al., 1992].

3.2.2. History and Background

Quinoxaline is also called as benzopyrazine. It is heterocyclic compound containing benzene ring and pyrazine ring. Pyrazine are stable, colorless compound which are soluble in water. Unlike pyridine, they are expensive, not readily available and so are seldom used as starting material for synthesis of their derivative. Diazines are fused to benzene ring to form quinoxaline. The pyrazine ring system is found in the fungal metabolite aspergillic acid and in dihydro form in luciferin of several bettles including the fire fly is responsible for the chemiluminescence of this ostracod. Methoxy pyrazine are very important component of aroma of many fruits and vegetable such as Peas and Capsicum peppers and also of wines [Gupta, R. R. et al.1998, Patidar, A. K. et al., 2011].

The biological safety profile of sugar conjugates derived from natural and synthetic agents [Ramalingam, P. et al., 2010, Calvaresi, E. C. et al., 2013, Luginina, J. et al., 2013] and in continuation with our earlier studies on quinoxaline, herein we report some saccharide (sugar) linked quinoxaline. In this work, the hydrazino intermediate was preferred to achieve sugar
conjugates in order to mimic the structural resemblance to nucleosides and other active hydrazide drugs [Ganapaty, S. et. al., 2008, Peraman, R. et al., 2015].

3.2.3. Structural Features of Quinoxalines

Benzene fused with N,N-containing hetero aromatics are important substructures found in numerous natural or synthetic alkaloids. The diversity of the structures encountered as well as their biological and pharmaceutical relevance, has motivated research aimed at the development of new economical, efficient and selective synthetic strategies to access these compounds. A diverse array of benzo fused N,N-containing six heterocycles [Balaban, A. T.et al., 2004, Cordeu, L.et al., 2007].

3.2.4. Synthesis and Advancements of Quinoxalines

Quinoxalines are synthesized from alkyl or aromatic alkynes using PdCl₂/CuCl₂ catalyst at room temperature are refluxing with 14-20 hours than yield 75-80% [Chandrasekhar, S. et al., 2010].

Synthesis of quinoxalines is relies on condensation of aromatic 1,2 diamine with 1,2 diketones in refluxing suitable solvent for 2-12 hours for example the condensation of o-phenylene diamine with aryl diketones yields ranging from 34-85% depending on specific condition [Brown, D. J. et al., 2004].
Quinoxalines are synthesized in the microwave assisted condensation was carried out between alpha diketones with various 1,2 diamines with yield was 65-96% [Farshid Mohsenzadesh, et al., 2007].

Synthesis of biologically active heterocyclic compounds and the use of green chemistry techniques in organic synthesis, herein we report a simple and efficient method for the synthesis of quinoxaline derivatives using heteropolyacids $\text{HPMo}_{11}\text{VFeO}_{40}$ and $\text{H}_2\text{PMo}_{11}\text{VCuO}_{40}$ as catalysts at room temperature and catalyst can be recycled. If aromatic 1,2 diamines having electron donating groups favour for the product formation. Where as, diamines having electron withdrawing groups slightly lower the yield of reaction [Diego M. Ruiz, et al., 2012].

One-pot procedure for the synthesis of quinoxalines directly from readily available and low cost β-diketones/β-ketoesters and o-phenylenediamines The in situ preparation of α halo β-ketone α-halo-β-ketoester as the main reactant reduces the steps and time involved in the reaction strategy. The advantages of the present protocol are the shorter reaction pathway and the use of aqueous medium for the conduct of the reaction with yield 78-85% [Anil Kumar, B. S. P. et al., 2011].

An efficient synthesis of quinoxalines from α-halo β-ketoesters using ionic liquid as reaction medium in the absence of catalyst. To the best of our knowledge this is the first report for the one-pot synthesis of quinoxalines.
Thus, the reaction of aromatic diamines with α-halo-β ketoesters in ionic liquid [bmim]BF$_4$ at room temperature gave the expected quinoxalines in high yield (93%). The electronic effect of substituents on 1,2-diamine was studied as follows.

Quinoxalines are synthesized from a series of alkynes with different substituents on the aromatic ring were examined. To our delight, aromatic alkynes bearing both electron rich and electron-poor functional groups were oxidized to the corresponding aromatic 1,2-diketones in moderate to excellent yields. Which is coupled with aromatic 1,2 diamines to formation of quinoxalines in the presence of Ruthenium catalyst under room temperature for 12 hours with yield was 59-78% obtained [Yuan Xu, et al., 2013].

Quinoxalines are synthesized from two step process first step ketones into α-hydroxylimino ketones by oximation employing chlorotrimethylsilane and isoamyl nitrile or sodium nitrite and Conc HCl, after making some changing in the reaction condition. The α-hydroxylimino ketones is condensed with aryl 1,2 diamines under microwave irradiation, time consuming 3-9 minutes with yield 64-85% [Padmavathy, K. et al., 2011]

3.2.5. Biological Activity of Quinoxalines

The study of quinoxaline and its derivatives has become a subject of interest in recent years due to their wide variety of biological activities as well as therapeutic applications. Since they are rare in nature, synthetic
quinoxalines are included in various antibiotics such as echinomycin, levomycin and actinomycin, well-known to inhibit the growth of Gram-positive bacteria and are also active against transplant tumors [Khan, S. A. et al., 2006, Patidar, A. et al., 2011] Echinomycin, for example have quinoxalinyl moiety in their structure and also some known drugs, like Brimonidins, alleviates glaucoma symptoms [Deepika, Y. et al., 2011].

The vast scope of synthesized quinoxaline and derivatives potential is well referenced and published in a wide range of scientific journals. Scientific data concerning the potential relevance of quinoxaline and derivatives in the literature were analyzed.

### 3.2.6. Antimicrobial Activity

The antimicrobial resistance is a serious threat to global public health, as a result of the widely disseminated and careless use of antimicrobials [Ferraz, R. et al., 2012] and demands a continuous effort in order to seek for better antimicrobial agents, effective against resistant pathogenic microorganisms [Patidar, A. et al., 2011, Vieira, M. et al., 2014]. There are a wide range of quinoxaline derivatives with antimicrobial activity documented [Vieira, M. et al., 2014].

### 3.2.7. Antibacterial Activity

Another arrangement of 8-chloro-1,4-substituted[1,2,4]triazolo[4,3-a]quinoxaline subordinates, being the substituents was incorporated and
screened for antimicrobial and cell reinforcement exercises [Suresh, M. et al., 2010]. The antibacterial activity was screened against Gram-positive *Staphylococcus aureus* and *Bacillus subtilis* and Gramnegative *Proteus vulgaris* and *Klebsiella pneumoniae*, using chloramphenicol as reference drug [Ammar, et al., 2002, Asif Husain, M. D. et al., 2011] have synthesized thieno [2,3-d] pyrimidines and pyrrolo [3,4-b] quinoxalines which antibacterial activity was tested against *S. aureus* and *Escherichia coli*.

### 3.2.8. Antitubercular Activity

Mycobacterium is a specific bacterium that is in charge of an infectious malady, a disease called *Tuberculosis* (TB), created by *Mycobacterium tuberculosis*. This illness has a high rate of mortality on the planet. Around 3 million individuals bite the dust each year from TB and 8 million new cases are evaluated every year, which 95% of them happen in creating nations [Harries, A. D. et al., 2002]. The therapy used in these days to fight TB consists in the administration of one of three drugs (isoniazid, rifampin or pyrazinamide) for 2 months, followed by 4 months of follow-up therapy with isoniazid and rifampin. However, due to the arising of multidrug resistant (MDR) TB it is required the development of new therapeutic agents, with a unique mechanism of action, able to treat MDR forms of the disease [Palomino, J. C. et al., 2013] possess *M. tuberculosis* growth inhibition values from 99 to 100% [Jaso, A. et al., 2003, Asif Husain, D. M. et al., 2011]. However, it is observed that the lack of the two N-oxide groups lead to the
loss of the antimycobacterial activity [Jaso, A. et al., 2003, Badaw, M. et al., 2010]. Some novel dense bridgehead nitrogen heterocycles of quinoxalines have been combined and movement against \textit{M. Tuberculosis} H 37 Rv species was obtained [Patidar, A. et al., 2011, Asif Husain, M. D. et al., 2011, Enrique Torres, E. et al., 2011]. The compound 3-methyl-2-phenylthioquinoxaline-1,4-dioxide for the most part introduced a decent movement against \textit{M. tuberculosis} in the preparatory \textit{in vitro} assessment and displayed Minimum Inhibitory Concentration (MIC) in the vicinity of 0.39 and 0.78mg/mL (rifampicin MIC $\frac{1}{4}$ 0.25mg/mL) [Carta, A. et al., 2002]. The MIC is defined as the most minimal concentration of an antimicrobial that restrains the obvious development of a microorganism after over night brooding. The scope of anti-microbial fixations utilized for deciding MICs is all around acknowledged to be in multiplying weakening strides all over from 1 mg/L as fundamental [Andrews, J. M. et al., 2001]. Another class of hostile to infective operators against MDR \textit{M. tuberculosis}, with no cytotoxicity detailed was introduced and incorporates 3-methyl - 9-substituted - 6-oxo - 6,9- dihydro-3H-(1,2,3)- triazolo [4,5-h] quinolone carboxylic acids and their ester [Antonio Carta, M. et al., 2007].

Several studies have been described, concerning synthesis and biological activity of a large amount of quinoxalines and 1,4-di-N-oxide quinoxaline derivatives, where compounds such as 7-chloro-3-(p-substituted)-phenylaminoquinoxaline-2-carbonitrile-1,4-di-N-oxide, 6,7-dichloro-2-
ethoxycarbonyl-3-methylquinoxaline-1,4-di-N-oxide and 3-acetamide-6,7-dichloroquinoxaline-2-carbonitrile-1,4-di-N-oxide derivatives have been shown to be synthesized and evaluated for enzyme activity, and was found to be a very potent inhibitor for both HIV-1 RT activity and HIV-1 replication in tissue cultures. Although, like some other nonnucleoside RT inhibitors, this compound was not effective against human immune deficiency virus type 2 (HIV-2 RT [Asif Husain, M. D. et al., 2011].

Vitro fluorescence polarization measure exhibited that a library of quinoxaline subordinates, arranged to target non basic protein 1 of influenza A (NS1A), upset the dsRNAeNS1A communication to fluctuating degrees, which prompt the improvement of hostile to influenza drugs [Lei You, E. J. et al., 2011]. In this review, examiners have arranged a library in light of 2, 3-difuryl-4 quinoxaline-R-metal carboxamide subsidiaries, with 2-furyl bunches at position 2 and 3 and phenyl amass in position 6 through an amide linker. These mixes don't hinder NS1AedsRNA connections by meddling with dsRNA however by the official to NS1A dsRNA-restricting space itself. Additionally, the compound could restrain influenza an infection development [Lei You, E. J. et al., 2011].

3.2.9. Antifungal Activity

Commonness of parasitic maladies has expanded significantly in the previous 50 years. Contagious illnesses show themselves in an unexpected
way, incorporating mycoses in the skin, hair, nails, additionally as systemic mycoses, being the last one an issue of incredible medicinal worry because of the expansion in the safe traded off patient populace [Dorr, P. et al., 2007]. A standout amongst the most widely recognized contagious diseases is candidiasis, brought about by Candida albicans, a diploid parasite that becomes both as yeast and filamentous cells [Ryan, K. J. et al., 1996]. This fungus can also develop resistance to antimycotic drugs that already exist in the market [Leah, E. et al., 2002], being important a constant search for new drugs and treatments. Thieno [2,3-d] pyrimidines and pyrrolo [3,4-b] quinoxalines were synthesized and tested against C. albicans and presented antifungal activity [Ammar, Y. A. et al., 2002, Patidar, A. et al., 2011]. Specialists additionally revealed some 2-sulphonyl quinoxalines and 3-[(alkylthio) methyl] quinoxaline-1-oxide subsidiaries as mixes with high antifungal movement [Carta, A. et al., 2002] and also pyrazolo quinoxalines which were observed to be active against fungal infections [ Deepika, Y. et al., 2011].

3. 2.10. Antiprotozoan Activity

Antiamoebic activity Entamoeba histolytica is a protozoan responsible for the amoebiasis infection [Shadab Miyan Siddiqui, A. S. et al., 2012], causing amoebic colitis, brain and liver abscess, being an important leading cause of death worldwide. The traditional treatment used is based in anti-amoebic compounds such as nitroimidazoles, but not always effective, raising
the possibility of drug resistance, leading to the search of new compounds able to fight the infection successfully [Mohammad Abid, A. A. et al., 2006]. Some 1-thiazole [4,5-b] quinoxaline-2-yl]-3-Phenyl -2- pyrazolines derivatives produced were found to be a potent inhibitor of HM1: IMSS strain of \( E. \) histolytica, where the presence of 3-bromo or 3-chloro substituents on the phenyl ring and 4-methyl group on the pyrazoline ring affected antiamoebic activity to a great extent [Mohammad Abid, A. A. et al., 2006]. 2-Cyano-3-(4-phenylpiperazine-1-carboxamido) quinoxaline 1,4-dioxide derivatives have also presented activity against Leishmania, but were not effective against Plasmodium [Barea, C. et al., 2012]. In such study metronidazole was used as the reference drug and had a 50% inhibitory concentration of IC 50 1.69, 1.82m M and Bromo, chloro, methyl substitution on pyrazoline ring, showed great effectiveness, being the most actives, presenting IC 50 1.45m M and IC 50 0.72 m M, respectively [Mohammad Abid, A. A. et al., 2006].

### 3.2.11. Antiviral activity

Infections are little irresistible specialists that recreate just inside the living cells of a creature and can contaminate a wide range of life forms, from creatures and plants to microorganisms [Koonin, K. V. et al., 2006]. Viruses such as Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) belong to the Herpesviridae family, are double stranded DNA [Iou-Jiun Kang, L. W. et al., 2011]. Also, share high homology in genome structure and DNA
arrangement. These infections can bring about different ailments states from asymptomatic contamination to fulminant spread ailments, including labials herpes, keratitis (cornea inflammation), genital herpes and encephalitis. There are a wide number of medications for treatment of HSV infections like acyclovir, ganciclovir, penciclovir, valaciclovir (changed over to acyclovir) and famciclovir (changed over to penciclovir) [Balfour, H. H. et al., 1999, Iou-Jiun Kang, L. W. et al., 2011] being acyclovir the most common drug used. However, there are drug-resistant strains of HSV emerging and increasing [Field, A. K. et al., 1994, Iou-Jiun Kang, L. W. et al., 2011, ], leading to the search of new antiviral drugs. Quinoxalines have a variable antiviral activity, suggesting that their activity depends on specific substitution patterns. Novel series of al 6H-indolo-[2,3-b] quinoxalines were synthesized and evaluated for antiherpes virus activity and the compound 2,3-dimethyl (dimethylaminoethyl)-6H-indolo-[2,3-b] quinoxaline had the major antiviral activity. This specific compound was tested for its antiviral effect and action mechanism, showing the capacity to inhibit replication of HSV-1, cytomegalo virus and varicellaezoster virus in tissue culture, in concentrations of 1.5m M, depending on the virus amount and cell type used in the assay. Also the compound 2,3-dimethyl-6-(dimethyl aminoethyl)-6H-indolo-(2,3-b) quinoxaline presented high activity against HSV and derivatives with 6-(2-dimethylaminoethyl) side chain, due to their DNA binding properties, showed an improved biological activity [Deepika, Y. et al., 2011].
There is likewise reference to IndQloquinoxalines (2,3-dimethyl-6-(dimethylaminoethyl)-6H-indolo [2,3-b] - quinoxaline) with ability to inactivate virions in high fixations (around 300m M) and abatement the amalgamation of viral DNA and protein at lower focuses (around 3m M) [Asif Husain, D. M. et al., 2011]. Concerning human immunodeficiency virus type 1 (HIV-1), which is the agent causative of acquired immunodeficiency syndrome (AIDS) [Amy, L. et al., 2011] there are a wide number of clinical drugs used to fight the disease, such as non-nucleoside reverse transcriptase (RT) inhibitors, which interact with a specific allosteric non-substrate binding site on HIV-1 RT [Patidar, A. et al., 2011]. Compound 6-chloro-3, 3-dimethyl-4-isopropenyloxycarbonyl-3,4-dihydroquinoxalin-2-[1H]-thione.

3.2.12. Antiparasitic Activity

Leishmaniasis is a parasitic disease cause by protozoan of the genus Leishmania in tropical and sub-tropical areas of the World and despite all efforts to fight this disease about 1-2 million new cases are registered every year [Croft, S. L. et al., 2003, Asif Husain, D. M. et al., 2011]. Most of the drugs available against leishmaniasis are expensive and require a long treatment and are becoming more and more ineffective [Carlos Barea, A. P. et al., 2011]. Malaria is also a tropical parasitic disease, caused by Plasmodium falciparum, leading to over a million deaths annually, and rising, probably due to a resistance increasing, requiring the development of cheaper and more effective drugs [Esther Vicente, S. et al., 2010, Carlos Barea, A. P. et al.,
Recently, 14 new 3-amino-1,4-di-N-oxide quinoxaline-2- carbonitrile derivatives were synthesized. These compounds were evaluated for their in vitro anti-malarial and antileishmanial activity.

3.2.13. Diabetes

Diabetes Mellitus is a disease caused by the dysfunction of glucose homeostasis, in which glucose levels appear abnormal with tendency to hyperglycemia. Diabetes type 1 is insulin dependent and requires a daily subcutaneous injection of insulin, while diabetes type 2 is non-insulin dependent and can be treated with several drugs such as sulfonyl ureas, nateglinide and biguanides, among others [De, M. 2001, Naveen Kulkarni, V. K. et al., 2012]. However these treatments have limited efficacy, tolerability and could cause severe side effects. In this regard, new transition metal complexes of quinoxaline ethiosemicarbazone ligands L$_1$H$_2$ and L$_2$H$_2$ were prepared. The ligands were explored with copper and zinc complexes in diabetes induced Wister rats. The compounds [ZnL$_1$(H$_2$O)] and L$_2$H$_2$ have showed prominent reduction in blood glucose level and the complexes [CuL$_1$(H$_2$O)], [ZnL$_1$(H$_2$O)] and [CuL$_2$(H$_2$O)] have exhibited good activity in oral glucose tolerance test (OGTT) and showed low toxicity [Naveen Kulkarni, V. K. et al., 2012]. Also (N-arylcarbamoyl and N-aryl thiocarbamoyl)hydrazine-quinoxalin-2-(1H) have been reported as mild hypoglycaemic agents [ Deepika, Y. et al., 2011].
steroidal anti-inflammatory drugs (NSAIDs) are widely used in therapeutics, generally for the treatment of the pain and inflammation. Nevertheless its long-term usage can lead to significant side effects like gastrointestinal lesions, bleeding and nephrotoxicity. Due to the reasons mentioned it is important the discovery of new safer anti-inflammatory drugs [Abu-Hashem, A. A. et al., 2010, Kim Peterson, M. M. et al., 2010]. Quinoxaline 1,4-di-N-oxide derivatives such as 4-(7-fluoro-3-methyl-quinoxalin-2-yl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamine and 2,6,7-trimethyl -3-[5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-1H-pyrazol-3-yl]-quinoxaline, showed an in vivo anti-inflammatory effect, higher than one reference drug, IMA (indomethacin) and in vitro decreasing values of LOX (lipoxygenase). LOX is an enzyme essential to arachidonic acid (AA) metabolism, which leads to the formation of leukotrienes, a type of proinflammatory mediator involved in processes like fever, asthma and cardiovascular disease [Asuncion Burguete, E. P. et al., 2011]. It was demonstrated that the incorporation of pyrimidine, thiazolopyrimidine, pyrazolopyridine, pyridopyridine, p-chlorophenyl, p-methoxyphenyl or pyridine nucleus to quinoxaline moiety cause significant anti-inflammatory activity and also analgesic [Abu-Hashem, A. A. et al., 2010]. 4-Alkoxy 6,9dichloro [1,2,4]triazolo [4,3-a] quinoxalines were also synthesized and anti-inflammatory activity was tested as inhibitors of the pro-inflammatory cytokines TNF-a and IL-6 [Guirado, Lopez Sanchez, A. et al., 2012]. Results revealed efficiency in both cytokines was demonstrated.
3.2.14. Cancer

Quinoxaline nucleuses exhibit potential anticancer activity, which makes them an important basis for the anticancer drugs [Asif Husain, D. M. et al., 2011]. A new series of 2-alkylcarbonyl and 2-benzoyl-3-trifluoromethyl quinoxaline-1,4-di-N-oxide derivatives was synthesized and evaluated for in vitro antitumor activity against a 3-cell line panel (MCF7 (breast), NCIH 460 (lung) and SF-268 (CNS)), and then evaluated in full panel of 60 human tumor cell lines, derived from nine cancer cell types. Anticancer activity depends on the substituents in the carbonyl group, increasing the activity in the order, ethyl < isopropyl < tert-butyl < phenyl-ones. Among these the compounds 2-(3-methylbut-1-en-2-yl)-3(trifluoromethyl) quinoxaline-1,4-di-N-oxide, 2-benzoyl-6,7-dichloro-3-trifluoromethyl quinoxaline 1,4-di-N-oxide, their difluorinated analogs (6,7-difluoro-2-isobutyryl-3-trifluoro methyl quinoxaline 1,4-di-N-oxide and 2-benzoyl-6,7-difluoro-3-trifluoromethyl quinoxaline 1,4-di-N-oxide) and 2-(2,2-dimethylpropanoyl)-3-trifluoromethyl-quinoxaline 1,4-di-N-oxide (Compound 5) were the most active, with higher anticancer activity with mean GI 50 (Growth Inhibition) values of 1.02, 0.42, 0.52, 0.15, and 0.49 mM, respectively [Belen Zarranz, A. J. et al., 2004, Asif Husain, D. M. et al., 2011].

3.2.15. Glaucoma

Glaucoma is the assignment to allude the illnesses that influence the optic nerve, including the loss of retinal ganglion cells in a trademark
example of optic neuropathy and unearthings of the nerve head [Quigley, H. A. et al., 2011] Just about 67 million individuals worldwide are influenced by glaucoma, staying one of the reasons for irreversible visual deficiency, in charge of 8% of visual impairment after water fall [Organization, W. H., WHO, 2010]. Alphagan (Brimonidin) is a moderately particular alpha-2 adrenergic receptor agonist and its piece comprises in (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)- 6-quinoxaline. This medication fills in as an antiglaucoma specialist, because of its energy to diminish the intraocular weight, reducing the side effects of glaucoma [Deepika, Y. et al., 2011, Asif Husain, D. M. et al., 2011].

3.2.16. Atherosclerosis

Atherosclerosis is in charge of half of all mortality in the USA, Europe and Japan, is the key reason for heart assault, stroke and gangrene of the furthest points [Ross, R. et al., 1993]. After course harm, unusual expansion and relocation of vascular smooth cells (SMCs) into the intimal layer of the blood vessel divider happens, multiplying and orchestrating extracellular network segments, assuming a critical part in coronary vein atherosclerosis and restenosis after an angioplasty [Sung-Yu Hongb, K. H. C. et al., 2004]. A progression of 6-arylamino-2, 3-bis (pyridin-2-yl)- 7-choloro quinoxaline-5, 8-diones were combined and screened for their inhibitory action on rodent aortic smooth muscle cell (RAoSMC) multiplication. Conceivable substituents of this compound are spoken to (Inhibition Concentration)
qualities were resolved and contrasted with the positive control mycophenolic corrosive (MPA) and the greater part of the mixes demonstrated great movement and the quinoxaline-5,8-diones were found as strong antiproliferative operators [Chung, H. et al., 2005, Deepika, Y. et al., 2011, Asif Husain, D. M. et al., 2011]. Quinoxaline derivatives were also tested as specific inhibitors for cancer cells survival, by inhibition of transglutaminase.

3.3. Reaction Scheme

Table 9: Reaction Scheme of quinoxalines

<table>
<thead>
<tr>
<th>2, 3 Diaminonaphthalene</th>
<th>Benzils</th>
<th>Quinoxaline</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Reaction Scheme 1" /></td>
<td><img src="image2" alt="Reaction Scheme 2" /></td>
<td><img src="image3" alt="Reaction Scheme 3" /></td>
</tr>
<tr>
<td><img src="image4" alt="Reaction Scheme 4" /></td>
<td><img src="image5" alt="Reaction Scheme 5" /></td>
<td><img src="image6" alt="Reaction Scheme 6" /></td>
</tr>
<tr>
<td><img src="image7" alt="Reaction Scheme 7" /></td>
<td><img src="image8" alt="Reaction Scheme 8" /></td>
<td><img src="image9" alt="Reaction Scheme 9" /></td>
</tr>
</tbody>
</table>
3.4. Materials and Methods

Both 2,3-diaminonapthalene (99.9%), 1,2-diketones (99.8%) were obtained from Sigma-Aldrich, India and were used as such without further purification. 1,2-diketone was used in three different forms namely, unsubstituted Benzil, 4,4’-dimethylBenzil and 4,4’-difluroBenzil for the purpose of finding the substituent effect. CTAB was used as the cationic surfactant. A mixture of 1M HCl and Ethanol was used as the solvent. After completion of the reaction (which was completely monitored by TLC), the synthesized product was precipitated by using Ethanol. Surfactant (CTAB) was left in the solvent without further actions.

3.4.1. Melting point

Melting points were determined using a capillary in a melting point apparatus (Toshiba) and are noted as such. Formation of compounds was checked by TLC on silica gel 60F_{254} plates.

3.4.2. FT-IR Spectroscopy

FT-IR is the most important tool for determine the various functional group and the possible chemical structure. The FTIR Spectra were recorded on a Perkin Elmer Spectrum1 FT-IR instrument with a typical resolution of 1.0 cm\(^{-1}\) using the KBr disc in the range of 4000-400 cm\(^{-1}\).
3.4.3. $^1$H NMR and $^{13}$C NMR Spectroscopy

The proton $^1$HNMR and $^{13}$C NMR spectra were measured on a Bruker Advance III instrument (400 and 150 MHz, respectively) using a solvent signal as the reference. The units of Chemical shifts ($\delta$) are given in ppm and coupling constants ($J$) in Hz. Assignments of signals in $^{13}$C NMR spectra were made on the basis of the HMQC experiments.

3.4.4. Mass Spectroscopy

Mass studies were performed on LC-MS system equipped with Agilent 1100 series, (LC/MSD detector and 1000 Series Agilent HPLC pump, positive mode API-ES). Mass spectral studies reveal the molecular weight of the compound.

3.4.5. Experimental Section

3.4.5.1. General procedure for synthesis of quinoxaline derivatives

In a 100 ml beaker, 2 mmol of Benzil, 2 mmol of CTAB were added to 10 ml Ethanol and placed on a magnetic stirrer cum temperature bath at stirring speed of 750 rpm at 35 °C. 10 ml of 2, 3-diaminonapthalene in 1M HCl was added in-situ to this reaction mixture drop by drop. A pale brown coloured precipitate was obtained after 10 minutes. The precipitate was filtered using Whatmann 40 filter paper and subsequently dried under shadow. The precipitate was re-crystallized with Ethanol. This re-crystallized
yield was used for further characterization. The structure of the resulting compound was as shown in the figure 20.

![Figure 20. Structure of 2, 3-Diphenyl benzo(g)quinoxaline](image)

[X = H or -M or +M group]

### 3.4.5.2. Synthesis of 2, 3-diphenylbenzo[g]quinoxaline

![Figure 21. Structure of 2, 3-diphenylbenzo[g]quinoxaline](image)

In a 100 ml beaker, 2 mmol of Benzil, 2 mmol of CTAB were added to 10 ml Ethanol and placed on a magnetic stirrer cum temperature bath at stirring speed of 750 rpm at 35°C. 2 mmol 2,3-diaminonaphthalene in 1M HCl
was added in-situ to this reaction mixture drop by drop. A brown coloured precipitate was obtained after 10 minutes. The precipitate was filtered using Whatmann 40 filter paper and dried under shadow. The precipitate was re-crystallized with Ethanol. This re-crystallized yield was used for further characterization.

### 3.4.5.3. Synthesis of 2, 3-bis(4-methylphenyl)benzo[g]quinoxaline

![Structure of 2, 3-bis(4-methylphenyl)benzo[g]quinoxaline](image)

**Figure 22. Structure of 2, 3-bis(4-methylphenyl)benzo[g]quinoxaline**

In a 100 ml beaker, 2 mmol of dimethyl benzil, 2 mmol of CTAB were added to 10 ml ethanol and placed on a magnetic stirrer cum temperature bath at stirring speed of 750 rpm at 35°C. 2 mmol 2,3-diaminonapthalene in 1M HCl was added in-situ to this reaction mixture drop by drop. A brown coloured precipitate was obtained after 10 minutes. The precipitate was filtered using Whatmann 40 filter paper and dried under shadow. The precipitate was re-crystallized with Ethanol. This re-crystallized yield was used for further characterization.
3.4.5.4. Synthesis of 2, 3-bis (4-fluorophenyl)benzo[g]quinoxaline

![Figure 23. Structure of 2, 3-bis(4-fluorophenyl)benzo[g]quinoxaline](image)

In a 100 ml beaker, 2 mmol of dimethyl benzil, 2 mmol of CTAB were added to 10 ml Ethanol and placed on a magnetic stirrer cum temperature bath at stirring speed of 750 rpm at 35°C. 2 mmol 2, 3-diaminonaphthalene in 1M HCl was added in-situ to this reaction mixture drop by drop. A brown coloured precipitate was obtained after 10 minutes. The precipitate was filtered using Whatmann 40 filter paper and dried under shadow. The precipitate was re-crystallized with Ethanol. This re-crystallized yield was used for further characterization.
Table 10: CTAB Catalyst are used to Synthesis Naphthalene based quinoxalines

<table>
<thead>
<tr>
<th>compound</th>
<th>Structure</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Melting Point (indegrees) (reported)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td><img src="image" alt="Structure 3a" /></td>
<td>5</td>
<td>95</td>
<td>120</td>
</tr>
<tr>
<td>3b</td>
<td><img src="image" alt="Structure 3b" /></td>
<td>8</td>
<td>92</td>
<td>126</td>
</tr>
<tr>
<td>3c</td>
<td><img src="image" alt="Structure 3c" /></td>
<td>4</td>
<td>97</td>
<td>129</td>
</tr>
</tbody>
</table>

3.5. Results and discussion

The reaction of 2,3 diamino naphthalene with aromatic 1,2 diketones (3a,3b and 3c) in the presence of CTAB surfactant and polymer supported sulphonilic acid catalyst is discussed experimental section. The compound
formed is pale brown solid and are stable at room temperature. They are insoluble in water but soluble in ethanol. The results and the detailed spectral interpretation as follows.

Table 11. Comparison of polymer Supported Sulphanilic acid and CTAB catalyst for Synthesis of naphthalene based quinoxalines

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Compound</th>
<th>Polymer Supported Sulphanilic acid</th>
<th>CTAB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (min)</td>
<td>Percentage of yield</td>
</tr>
<tr>
<td>1</td>
<td>Nap Ben</td>
<td>56</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>Nap Ben-Me</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>Nap Ben-F</td>
<td>46</td>
<td>78</td>
</tr>
</tbody>
</table>

- Nap Ben- 2, 3-diphenylbenzo[g]quinoxaline
- Nap Ben-Me- 2, 3-bis(4-fluorophenyl)benzo[g]quinoxaline
- Nap Ben-F- 2,3-bis(4-methylphenyl) benzo[g]quinoxaline

3.5.1. FT- Infrared Spectra of compound 2, 3-diphenylbenzo[g]quinoxaline

The IR (KBr) spectral dates of compound 2, 3-diphenylbenzo[g]quinoxaline were recorded. Many bands were observed in the in the IR spectrum, among these there are three significant bands noticed, those are occurred at

148
i) Heterocyclic -C=N & -C=C- str. = 1595.13 cm\(^{-1}\),

ii) Aromatic –CH str. = 3061.03 cm\(^{-1}\),

iii) Aromatic –C=C- str. = 1666.50 cm\(^{-1}\),

iv) Aromatic –C-C- str. = 1517.98 cm\(^{-1}\),

v) Aromatic –C-N- str. = 1325.10 cm\(^{-1}\)

3.5.2. \(^1\)H-NMR Spectral data of Compound 2,3-diphenylbenzo( g) quinoxaline

The \(^1\)H-NMR was recorded from Brukar spectrophotometer, using DMSO-d6 is an internal standard, the spectral data of the compound 2,3-diphenylbenzo( g) quinoxaline shown in the desending manner the peak was observed at \(^1\)H NMR : (400 MHz, DMSO):

i) \(\delta = 7.4\) (multiplet, aromatic, 4H)

ii) \(\delta = 7.8\) (multiplet, aromatic, 5H)

iii) \(\delta = 8.4\) (aromatic, 2H)

iv) \(\delta = 8.6\) (aromatic, 2H)

3.5.3. \(^{13}\)C-NMR Spectral data of Compound 2,3-diphenylbenzo( g) quinoxaline

The \(^{13}\)C-NMR spectrum was recorded using DMSO-d6 is a standard, the spectral data of the compound 2,3-diphenylbenzo[g] quinoxaline is interpreted as in the following manner. The peaks at \(\delta 194.79, 135.50\) is due
heterocyclic carbon. The peaks were observed δ 132.25, 129.66, 129.56, 129.48, 128.39, 128.01, 127.11 is due aromatic carbon. The peaks δ 40.18, 39.97, 39.76, 39.55, 39.34, 39.14, 38.93 is due methylene carbon.

3.5.4. FT-IR Spectral data of the Compound 2, 3-bis (4-methylphenyl) benzo[g] quinoxaline

The IR (KBr) spectral dates of compound 2, 3-diphenylbenzo[g] quinoxaline were recorded. Many bands were observed in the in the IR spectrum, among these there are three significant bands noticed, those are occurred at

i) Heterocyclic -C=N stretching & -C=C- streaching 1595.13 cm⁻¹,

ii) aromatic –C-H stretching 3047.53 cm⁻¹

iii) aromatic –C-C- stretching 1429.25 cm⁻¹

iv) aromatic –C-N- streaching 1313.52 cm⁻¹

v) –C-H- streching in CH₃ 2922.16 cm⁻¹

vi) In-plane bending of –C-H- in CH₃ = 1037.70 cm⁻¹

vii) Out of plane bending of –C-H- in CH₃ = 736.81 cm⁻¹

3.5.5. ¹H-NMR spectral data of the Compound 2, 3-bis (4-methylphenyl) benzo[g]quinoxaline

The ¹H-NMR were recorded from Brukar spectrophotometer, using DMSO-d₆ is an internal standard, the spectral data of the compound
quinoxaline shown in the descending manner the peak was observed at 2, 3-bis(4-methylphenyl) benzo[g] quinoxaline.

i) $\delta = 7.3$ (multiplet, aromatic, 4H)

ii) $\delta = 7.8$ (multiplet, aromatic, 6H)

iii) $\delta = 8.4$ (multiplet, aromatic, 2H)

iv) $\delta = 8.6$ (multiplet, aromatic, 4H) and v) $\delta = 2.4$ (singlet, methyl, 3H)

### 3.5.6. $^{13}$C-NMR spectral data of the Compound 2, 3-bis(4-methylphenyl) benzo[g] quinoxaline

The $^{13}$C-NMR spectrum were recorded using DMSO-d6 is a standard, the spectral data of the compound 2, 3-diphenylbenzo[g]quinoxaline is interpreted as in the following manner. The peaks at $\delta$ 194.60, 146.44 is due to heterocyclic carbon. The peaks were observed $\delta$ 130.03, 129.95, 129.59 is due to aromatic carbon. The peaks $\delta$ 40.18, 39.97, 39.76, 39.55, 39.34, 39.13, 38.92, 21.41 is due to methyl carbon.

### 3.5.7. IR Spectral data of the Compound 2, 3-bis(4-fluorophenyl) benzo[g] quinoxaline

The IR (KBr) spectral dates of compound 2, 3-diphenylbenzo[g] quinoxaline were recorded. Many bands were observed in the in the IR spectrum, among these there are three significant bands noticed, those occurred at
i) Heterocyclic -C=N & -C=C- stretching. = 1597.06 cm$^{-1}$, 
ii) aromatic –C-H stretching 3074.53 cm$^{-1}$, 
iii) aromatic –C=C- stretching. 1666.50 cm$^{-1}$, 
iv) aromatic –C-C- stretching 1506.41 cm$^{-1}$, 
v) aromatic –C-N stretching 1317.38 cm$^{-1}$, 
vi) C-F bond stretching 1101.35 cm$^{-1}$

3.5.8. $^1$H-NMR spectral data of the Compound 2, 3-bis(4-fluorophenyl) benzo[g] quinoxaline

The $^1$H-NMR were recorded from Brukar spectrophotometer, using DMSO-d$_6$ is an internal standard, the spectral data of the compound quinoxaline shown in the desending manner the peak was observed at 2, 3-bis(4-methylphenyl)benzo[g]quinoxaline.

i) $\delta = 7.4$ (multiplet, aromatic, 4H) 
ii) $\delta = 7.8$ (multiplet, aromatic, 2H) 
iii) $\delta = 8.4$ (multiplet, aromatic, 2H) 
iv) $\delta = 8.6$ (multiplet, aromatic, 4H)

3.5.9. $^{13}$C-NMR spectral data of the Compound 2, 3-bis(4-fluorophenyl) benzo[g] quinoxaline

The $^{13}$C-NMR spectrum were recorded using DMSO-d$_6$ is a standard, the spectral data of the compound 2, 3-diphenylbenzo[g]quinoxaline is
interpreted as in the following manner. The peaks at \( \delta \) 192.60, 167.51, 164.97 is due to heterocyclic carbon. The peaks were observed \( \delta \) 133.06, 132.96, 128.99, 128.97, 116.86, 116.64 is due to aromatic carbon. The peaks \( \delta \) 40.11, 39.91, 39.70, 39.49, 39.28, 39.07, 38.86 are due methylene carbon.

Condensation of 2, 3-diaminonaphthalene with benzil was employed as the key reaction. The effect of para substituent present on was verified by varying different types of groups (such as electron donating and electron withdrawing) and the corresponding results are listed in table 1. From the results, the electron withdrawing substituent such as -Fluro, yield (Scheme III) was better than the electron donating groups such as -Methyl, (Scheme II). The electron-donating substituents enhance the rate of reaction and gave the corresponding products in good yield. It was interesting to note that the presence of methyl group at fourth position of 1,2-phenylenediamine gave two isomeric products. This phenomenon was not observed in the case of electron-withdrawing substituents. This fact may be attributed to the electron-donating nature of methyl group which may favour to increase the nucleophilic character of amine group. It was noticed that electron-withdrawing substituents suppress the reaction [Meshram, H. M. et al., 2010].
Practical method for the synthesis of 2-substituted benzothiazoles was carried out using the condensation of 2-aminothiophenol with aldehyde catalysed by CTAB in water [Xiao-Liang Yang, et al., 2010]. One step synthesis of micro/mesoporous material by adopting the dual templates consisting of the conventional cationic surfactant CTAB [Jun Hu, et al., 2011] was achieved.

**Table 12: Effect of Solvent for Synthesis of naphthalene based quinoxalines**

<table>
<thead>
<tr>
<th>S.no</th>
<th>Solvent</th>
<th>CTAB (mmol)</th>
<th>% Yield</th>
<th>Time in minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethanol/HCl</td>
<td>2</td>
<td>&gt;93</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Methanol/HCl</td>
<td>2</td>
<td>&gt;89</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>H₂O/HCl</td>
<td>2</td>
<td>&gt;80</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>2</td>
<td>&gt;96</td>
<td>9</td>
</tr>
</tbody>
</table>

**Table 13: Effect of temperature on yield of quinoxalines**

<table>
<thead>
<tr>
<th>S.no</th>
<th>Compound</th>
<th>CTAB (mmol)</th>
<th>% Yield at room temperature</th>
<th>%Yield at 35°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nap Ben</td>
<td>2</td>
<td>86</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Nap Ben-Me</td>
<td>2</td>
<td>85</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>Nap Ben-F</td>
<td>2</td>
<td>90</td>
<td>97</td>
</tr>
</tbody>
</table>

➢ **Nap Ben-** 2, 3-diphenylbenzo[g]quinoxaline

➢ **Nap Ben-Me-** 2, 3-bis(4-fluorophenyl)benzo[g]quinoxaline

➢ **Nap Ben-F-** 2,3-bis(4-methylphenyl) benzol[g]quinoxaline
3.6. Conclusion

Naphthalene based Quinoxalines were successfully synthesized with greater yield (96%) and shorter duration (5 min) using CTAB as the surfactant. The synthesis in the absence of cationic surfactant resulted in poor yield and time consuming (35% and 90 min). The solubility of this compound in ethanol, suggests that this product can be used as a challenging drug for the pathogens. The synthesis of Naphthalene based quinoxaline by this method produced no harmful emissions.
Figure 24. FT-IR Spectrum of 2, 3-diphenylbenzo[g]quinoxaline (3a)
Figure 25. $^1$H NMR Spectrum of 2, 3-diphenylbenzo[g]quinoxaline (3a)
Figure 26. $^{13}$C NMR Spectrum of 2, 3-diphenylbenzo[g]quinoxaline (3a)
Observation:

1) m/z-333(M+1) & 374(M+1)+41) is observed.

Figure 27. Mass Spectrum of 2, 3-diphenylbenzo[g]quinoxaline (3a)
Figure 28. FT-IR Spectrum of 2, 3-bis(4-methylphenyl) benzo[\(g\)] quinoxalines (3b)
Figure 29. $^1$HNMR Spectrum of 2, 3-bis(4-methylphenyl)benzo[g]quinoxaline (3b)
Figure 30. $^{13}$CNMR Spectrum of 2, 3-bis(4-methylphenyl)benzo[g]quinoxaline (3b)
Figure 31. Mass Spectrum of 2, 3-bis(4-methylphenyl)benzo[g] quinoxaline (3b)
Figure 3.2. FT-IR Spectrum of 2, 3-bis(4-fluorophenyl)benzo[g] quinoxaline (3c)
Figure 33. $^1$H NMR Spectrum of 2, 3-bis(4-fluorophenyl)benzo[g]quinoxaline (3c)
Figure 34. $^{13}$C NMR Spectrum of 2, 3-bis(4-fluorophenyl)benzo[g]
quinoxaline (3c)
Figure 35. Mass Spectrum of 2, 3-bis(4-fluorophenyl)benzo[g]quinoxaline (3c)

Observation:

1) \text{m/z-369(M+1)} \text{ is observed.}