STUDY OF BIOLOGICAL AND COMERCIALLY IMPORTANT ORGANIC COMPOUNDS

SUBMITTED TO

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BY

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UNDER THE GUIDANCE OF

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CERTIFICATE BY GUIDE

This is to certify that this report for Dissertation-II is a bonafide work done by Rohit Kumar Khan in partial fulfillment of the requirement for the Degree of Master of Science (Chemistry).

Date:
Place:

Supervisor

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Lovely Professional University

Acknowledgement

“It is not possible to prepare a project report without the assistance and encouragement of the other people. This one is certainly no exception”.

On the very outset of this report, I would like to extend my sincere and heartfelt obligation toward all the personages who helped me in the Endeavour without their active guidance, help, cooperation and encouragement, I would not have made headway in the project.

My profound gratitude and deep regards to my guide Dr. Praveen Kumar Sharma for her exemplary guidance, monitoring and constant encouragement throughout the course of this report. The blessing, help and guidance given by her time to time shall carry me a long way in the journey of life on which I am about to embark.

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My acknowledgement also goes to my department and to my Head of School Dr. Ramesh Chand Thakur, thanks for providing a wonderful environment and opportunity to do this project. Lastly, much gratitude to my parents whose valuable ideas, encouragements, and prayers give me strength and fruitful results in my life.

Thanking you

Rohit Kumar Khan

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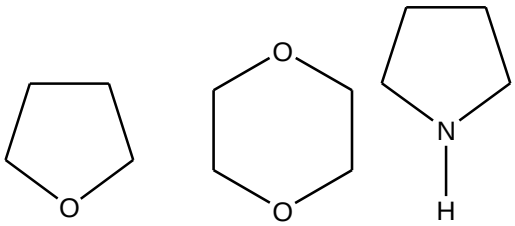
Contents

Introduction

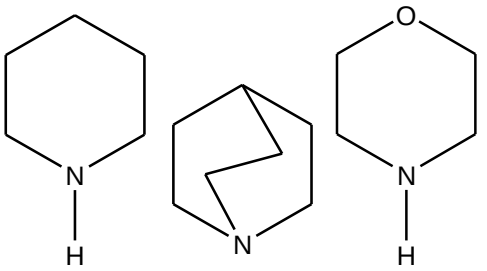
A literature search is a way by which we search different research articles according to our need, which are relevant to our research topic. It includes read, analyses and sort literature in order to understand the concept. Education researches will share information, conduct various literature researches to get papers accordingly and get to know what our previous researchers have achieved. The success of research project depends upon that how you have studied the literature. Therefore it is the most important part of any research project. Literature searching must be effective and it should provide important information collecting activity that whether it is in academia or not. Proper literature search helps in research projects and improvise the research quality. Other than the academic texts, journals are the main source of information related to dissertation or research project and to collect valuable data related to your topic many other sources like internet source, newspaper and images will prove to be equally important and valuable[1-5].

A cyclic organic compound containing all carbon atoms in ring formation is referred to carbocyclic compound. If it least one atom than carbon forms A part of the ring system, heterocyclic compound contain nitrogen, oxygen and sulfur are most common. Some important natural product alkaloids, chlorophyll, vitamins, drug its derivatives of simple five or six-membered nitrogen heterocyclic and it's classified as non-aromatic and aromatic.

Examples of non-aromatic heterocyclic compound are:



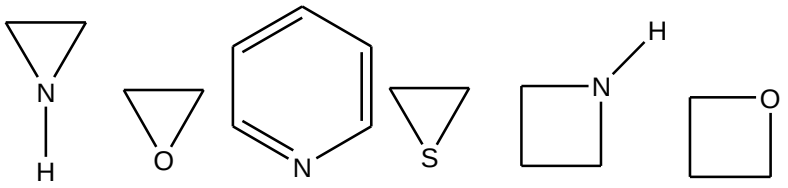
Tetrahydrofuran 1, 4-Dioxane Pyrrolidine



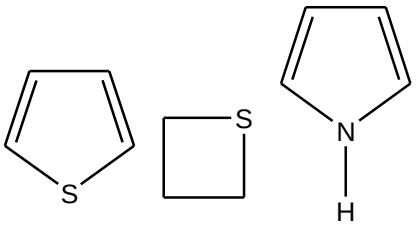
Piperidine Quinuclidine Morpholine

Cyclic compounds having different atoms in a ring at different positions are Heterocyclic compounds. They are same as that of carboxylic compounds having only ring atoms from the same elements. The most commonly available heteroatoms in heterocycles are Nitrogen, Oxygen, and sulfur. Other atoms like phosphorous and selenium has also been observed in heterocyclic ring. Naturally occurring heterocycles are found in biological system of organisms and some of them are pharmacological active, can be used for treatment purpose. In humans, they are found in DNA as Nitrogen containing heterocycles such as adenine, guanine, cytosine and thymine.

Examples of heterocyclic compound:



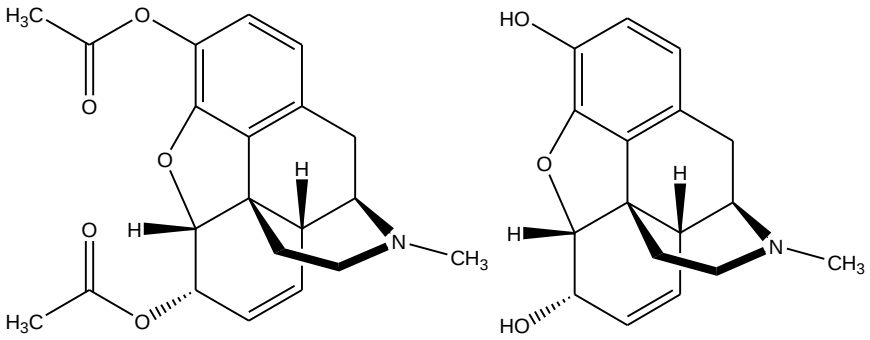
Aziridine Oxirane Pyridine Thiirane Azetidine Oxetane



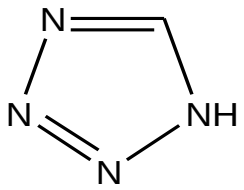
Thiophene Thietane Pyrrole

Biological and commercial important organic compound.

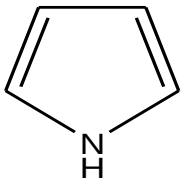
Drugs are the chemical compounds which are used for treatment purpose. Drugs can be extracted from animals and plants. Drugs obtained from natural sources are organic drugs. Man-made drugs are known as synthetic drugs. Some synthetic drugs are synthesized to mimic the drugs obtained from natural sources. Natural occurring drugs are marijuana, heroin, opium, cocaine and many more. But these drugs are not commercial drugs. These drugs should be used in limited amount and overconsumption is harmful for health. Commercial drugs are consumable as they have fewer side effects and are approved by FDA. Commercial drugs for treatment of diabetes are Humulin N, Novolin, Flexpen, Tresiba, Levemir etc. All these drugs are available in market. Heterocyclic compound Tetrazole is used in many drugs which is used as cardiovascular and sometimes as anti-biotic. In tetrazole, there are four nitrogen present in the ring, making it heterocyclic ring. Some drugs like cocaine, morphine, caffeine are used for medication at higher levels. Morphine is used as pain killer but it is illegal in the market because person can become habitual to it. Obatoclax, drug used for leukemia, contain pyrrole ring in its structure and Furfanorex contain Furan ring. Pyrantal drug consist of thiophene ring and is used to prevent intestinal parasites in small animal pets.



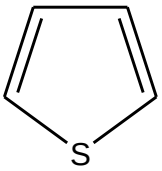
Heroin Morphine



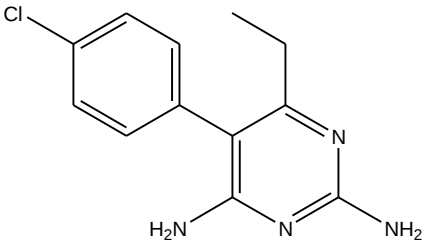
Tetrazole



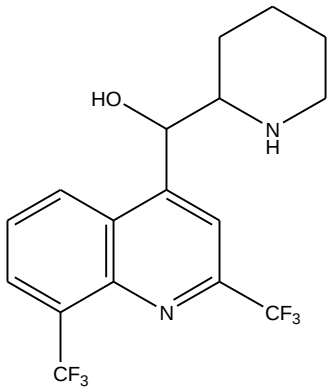
Pyrrole



Thiophene



Pyrimethamine



Mefloquine

Some important biological and commercial important Heterocyclic compounds

1. Ahmed et al synthesized pyranochromene, benzochromene, chromenopyridine and chromenopyrazole by cyclocondensation of benzoylacetate with salicylaldehyde. They sysnthesized these by four methods and evaluated its biological activity against a bacterial species obtained from laboratory of Microbial Biochemistry. Dihydropyranochromene and phenyl-6H-benzochromene showed moderate activity for the tested organism. [6]
2. Bioactivities of a new category of sulfone linked bis(heterocycles)1-aroyl-2-chloroethene used as precursor and made to react with acid and then oxidation and esterification yielded aroylethenesulfonylacetic acid methyl ester. This compound than reacted in the presence of $SnCl_3$, with 2-aminoethanethiol and *n*-butyllithium,in toluene and final product was identified by H-NMR spectroscopic study and product was found to be 2-(aroylethenesulfonylmethyl)-4,5-dihydrothiazole. [7]

3. Oleg A. Rakitin synthesized sulfur containing hetrocycles from simple organic substrate. Author reacted $S_2Cl_2$with *N*-ethyldiisopropylamine, S_2Cl_2 with *N*-ethyldiisopropylamine, S_2Cl_2 with *N*-chloroethyldiisopropylamine then author synthesized bisdithiolothiazineketothiones, bisdithiolothiazinediketones, bis(dithiolyl)amines on reaction with S_2Cl_2. Author also produced fused rings like 1,2,3,4,5-pentathiepins, dichloropyrrolopentathiepin. [8-10]
4. Nataliya P. Belskaya along with workers synthesized hydrazones having carboxamide, thioamide and amidine functions and studied its properties. For the synthesize of hydrazono-amide, -thiomide and –amidines they reacted hydrazine with carbonyl compound due to high nucleophilicity of both hydrazine nitrogen atoms the use of this method is difficult for the preparation of hydrazones bearing carbonyl and other electrophilic substituents. Another method for synthesize of hydrazono-amide, -thiomide and –amidines was copupling of diazonium salts with active methylene compound. Structure analysis ofhydrazono-amide, -thioamide, and –amidine shows that molecules contain a π-system of two double bonds and an NH-fragment that provides the basis for the azohydrazonetautomerism and *Z,E*stereoisomerism. [11]
5. NegarLashgari and his worker gave the review of isatin from the period of 2000 to 2011. They carried out the Synthesis of Monospiropyrrolo/pyrrolizidino-oxindole Ring Systems by condensing isatin with amino acid derivatives. They also done synthesis of Dispiropyrrolo/pyrrolizidino-oxindole Ring Systemsby 1,3-dipolar cycloaddition reaction of azomethineylides with dipolarophiles. [12]
6. Paige J. Monsen with his worker presented review on fluorination of natural products like terpenoids, natural lipid products including aliphatic natural products acetogenins, steroids and polyketides. Fluoride ion behaved as nucleophile and attacked on electrophilic substrate. Alkali metal fluorides and HF-based reagents were used as source of fluoride ion. Fluorination of terpenoids like borneol, camphor was done. For borneol, DAST was used as fluorinating agent and for camphor, NFSI was used. [13]
7. Christian Espinosa-Bustos et al synthesized nitrogen containing heterocyclic compound such as substituted pyrrolo[2,3-d]pyrimidine by Lam-Chan conditions. In first attempt under Lam-Chan conditions, low yield was obtained because DCM was used as solvent and reaction time was 48 h. But when methanol was used as solvent than reaction time was 4 hours and

yield obtained was also high. 1.0 equivalent of Copper acetate, used as catalyst, gave highest yield of 58 %. [14]

8. BalaramanSelvakumar et al synthesized nitrogen and oxygen containing heterocyclic compound having anti-viral activity studied against avian paramyxovirus. Sysnthesize of morpholine derivatives involve eight steps, starting with important commercially accessible 3,3-dimethyl cyclohexanone treating with dimethly carbonate in the presence of THF. All the structures were confirmed by 1H and 13C NMR spectroscopy. [15]
9. MarziehAnjomshoa et al synthesized two important bioactive compounds $[Cu(dimethylbpy)_2Cl]PF_6$ and$[Cu\ (dimethoxybpy)_2](PF_6)_2$. Then they studied their structure activity relationship. Characterization was done with XRD which indicates that compound one have square planner geometry and Compound two, $[Cu(dimethylbpy)_2Cl]PF_6$ have square-pyramidal structure. Both the compound was investigated by absorption and emission spectra for their DNA binding properties[16]
10. A simple and efficient synthesis of some polyfunctionalizedpyrrole derivatives by triphenyl-phosphine-promoted condensation reaction between substituted 2-hydroxyethanones and substituted acetylene-dicarboxylates is described. [17-20]
11. Oleg A Raktin synthesized sulphur nitrogen hetrocycles by various novel stretegies from readily available organic subtrates no. of hetrocycles like 1,2-dithiole 1,2,3,4,5 pentathipins 1,2,3-dithiazoles ,1,4-thiazines has been developed. The simple organic substrate used in this process is S_2Cl_2. S_2Cl_2 is currently used for perchlorination of aromatic system. They also found that organic substrate that contain C-H bond, nitrile and Imino groups can undergo reaction with S_2Cl_2. [21]
12. Jignesh P. Raval along with his worker synthesized different type of *N* (2-methyl-7-aryl-8-cyano-[1,2,4] triazolo [1,5-*a*] pyridin-5-yl) phenothiazines using chalcones of *N* – acetylphenothiazine and found biological active compounds [22]
13. Y. HariBabu et,al synthesized 2-(heterylcarboxamido)-2,3-dihydro-1*H*-1,2,5-oxadiazolo[3,4-c][1,3,2]diazaphosphole- 2-oxides. by the reaction of substituted oxadiazole with various phosphinyl-carboxamides and tested for their Antimicrobial activity and exhibit excellent result as antimicrobial agents. [23]
14. B. Jayashankara and co-workers synthesized bis(isoxazoline) and their derivatives by using aldoximes, which was produced using corresponding aldehydes. Oil of pale yellow colour

was obtained and was identified by NMR spyspectroscoy. Synthesized compounds exhibit antimicrobial activities [24]

15. M. S. Singh et al on reaction of salicylaldehyde with *o*-aminobenzyl alcohol in ethanol obtained *N*-(2-hydroxymethylphenyl)-salicylideneimine. Its structure was confirmed by IR and NMR spectroscopic technique. [25]
16. Mangesh J. Pawarwith his workers synthesized of some new biological active heterocyclic compounds containing thiadiazoles, -selenadiazole, spiro- -thiadiazolines and benzopyrans, as sub-units. spiro[chroman-2,1'-cyclohexan]-4-ones on reaction with semicarbazide hydrochloride converted into semicarbazone derivatives. [26]
17. Anil K. Patel and co-workers treated appropriate 1-[2*H*-1-benzopyran-2-on-3-yl]-3 aryl-prop-2-en-1-ones with 3-coumarinoyl methyl pyridinium salts to obtain Substituted 2,6-di(coumarin-3 yl) pyridines under Kröhnke reaction conditions. Anti-bacterial activity was tested with different microbial strains and treated as antimicrobial agents. [27]
18. A. Aboelmagdet al synthesizedglycoside, hydrazide and hydrazone moieties which have great anti- fungal activity. Two fungi strains *Candida albicans*and *Aspergillusflavus* were taken to study the activity and exhibit magnificent biological activities.[28]
19. Substituted (1*H*-indol- 3-yl) quinoxalines, acid chloride was prepared on reaction of indole based aldehydes with 1,2-phenylenediamine and exhibit biological activity such as antibacterial, antifungal, anticancer, antidepressant. [30]
20. Oľga Caletková et al synthesized Veritriol using ribonolactone. The mainstep during the synthesis is introduction of the methyl group at C-1 and Julia-Kocieńskiolefination with aromatic aldehyde at C-5.Synthesis include 8 steps and yield is also good.Cytotoxicity was observed over leukemia cells, colon cancer cells. It was observed that varitriols, whose configuration was modified, showed significant activity. Whereas, Z isomer was even better than E isomers, observed in the linkage difference. [31]
21. G. M. Giarani et al synthesized five and six membered spiro-fused compounds involving three and four step component reaction of isatin. Isatin is a key component in many of the drugs and building block for anti-malarial, anti-HIV, antimicrobial drugs. For five membered system, ceric ammonium nitrate was treated with 1,4-naphthoquinone and isatin with acetic acid. The plausible mechanism involves the 1,3-dipolar cycloaddition of azomethineylide. The compounds were evaluated for their anti-inflammatory and analgesic activity. [32]

22. Emmanuel O. Olawode et al synthesized cinnamic acids, (E)-styrylthiazoles and the (E)-2-[2-(naphthalen-1-yl)viny]thiazoles, all follow Lipinski rule of 5. Malonic acid was reacted with commercially available aldehydes in pyridine for 1 hour at 90^{O}C. The synthesis of the (E)-2-styrylthiazoles completed via three steps, first by conversion of (E)-cinnamic acid to cinnamamide, than thionation to obtain the thioamide and last condensation with α-halo carbonyl derivatives to give the corresponding thiazoles. [33]
23. Aldo Andreani et al synthesis above said compound in which key intermediate was di-imidazo-[2,1-*b*:1,2-*d*]-[1,3,4]-thiadiazole. The crystal was studied by X-Ray crystallography and by other spectroscopy methods. Studies showed that structure is stable due to formation of hydrogen bonds and stacking interactions. The distance between two rings was found to be 3.61 A. [34]
24. Carme Cantos Llopart and John A. Joule synthesized substituted 1-(2-aminophenyl)-6-ethyl-2,3-dihydro- 1*H* pyrrolizine and6-Ethyl-2,3-dihydro-1-phenyl-1*H*-pyrrolizine. During the route of synthesis, the diels alder cycloaddition is the key step. 9 different methods have been used for the synthesis of bicyclic pyrrol, which can be used in treating pains, malaria. [35]
25. Andrés A. Poeylaut Palena and Ernesto G. Mata converted carbonyl group into thiocarbonyl group in pencillins and cephalosporins. In this work, author used Lawesson's reagent for the reaction to take place. Thionation of cephalosporins was done under the temperature less than 100 using two equivalents of lawesson's reagent and 89% of yield was obtained. Author also found that pencillin was less reactive to lawesson's reagent as compare to cephalosporins. Yield obtained for 6α-methoxy-7-thioxopenicillins was 14%. [36-37]

Aims of search:

- Studying existing critical opinions/theories
- Latest research topics are identified.
- Identifying research methods or models that is potential enough to add quality to your project.

Literature Search: Stages

The steps in quality literature search are as follows:

- Reading and preparation, in background, related to the topic

- Working with title: identifying search topics
- Identify the best resources and search topics
- Searching with different techniques
- Analyzing obtained results

By comparing between to approach (traditional review based or non-research review based)of literature search we can find out which one is good and which one is bad on comparison of its result. One of the processes can be time consuming and other may use less time, so we choose best out of the two processes. Review gives us knowledge about research purpose and non-research purpose.

- In review of research we find out different methods by which a work is carried out. It consist of instrumentations, data collection and analysis methods.
- In review of non-research we try to solve our problems related to subject or any concept.

Literature survey can be of two types

- **Survey of complete data**: It includes data of those files which are based on real works like research work, laboratory work. It is prepared by students as their academic tasks.
- **Conceptual Research**: It consist papers related to theories, ideas and concepts. It is generally published by scholars. These kinds of papers are not proved one. They are just hypothetical papers.
- **Background reading and preparation related to the topic**

Reading different textbooks, topics from encyclopedia etc., and get knowledge for topic which will be helpful in the course of research.

- **Working with title: identifying research terms:**

First of all identify reading material to get an overview of the topic. After initiation it will be become easy for researcher and will allow him for further reading. Identifyingkey terminology related to your topic is very important. Different terms will be included in this up to a wide range, like:

- Authors
- Theories/principles/concepts

- Important research papers
- Key genres

To identify such terms it require some time for thinking about the wording for making it a part of research paper. [3-5]

Purpose of literature survey:

- The overall purpose of literature survey is to discover the knowledge of student.
- It provide student with knowledge of work that had been done in recent time.
- It gives knowledge of certain topic on which student will work in coming time.
- Person will understand how to publish a paper, and is helpful to student when he/she will go for higher studies.

Identify the resources to search

There is not any source that will contain all information which is required forliterature search. However, only limited sources are important that contain information according to your research topic. Further sources of information are required to extend research topic.

Start byusingsearch tab on the internet. It will make access to number of research articles published by other authors. References are important to note down when to learn it from online sources. [5]

Every research article have its own DOI (Digital object identifier) number which can be used for getting full excess to the article or one can also get by paying specific amount.

Scope Of Study

- Will get to know what is heterocyclic.
- Kind of research is going over the different heterocycles in the world.
- How they interact with our biological system.
- Natural and artificial heterocyclic.
- Use of heterocycles in our day to day life.
- To make student familiar with article, and how they are published.

Reading different research articles will let me understand that how to write articles by giving mentions of previous research articles those who have done work over it. Reading article is important, because unless until we don't know which stage others have reached, we can't start. We must be aware of the latest trend in the provided topic. [29]

After reading and analyzing several research articles, I have found that heterocyclic compounds containing oxygen, sulfur, nitrogen can be used in treatment of many bacterial, fungal diseases as they show pharmacological activities. These compounds can act as drug or can be used as a part of the drug. By preparing their derivatives, different drugs are being produced.

Work plan/methodology

It is of two types:

a) Recognition of commercially important heterocyclic compounds.

b) Assessment of biological important heterocycles.

Research Methodology of biological activity of heterocyclic compounds

Many of the heterocyclic compounds used for treatment of tumors, cancer cells, tuberculosis, pain, fungal disease, infections, are the constituent of different drugs. Literature survey will tell us the important heterocycles used in different drugs. Their biological activity will be tested and discussed in the next stage of project.

Antimicrobial Activities

Drugs used to kill microbes or to stop their growth are called anti-microbial drugs. Skin diseases are mainly caused by the microbes present on the skin. Microbial agents kill the microbes whereas bacteriostatic agents retards the growth of the microbes [38, 39].

Material, Chemicals and Instrumentation Required

Potato-dextrose agar + Broth

Nutrient Agar + Broth

Agar-Agar

Ethanol

Bacteria

Fungi

Petri plates

Para film foil

Graduated pipettes

Hot Air oven

Autoclave

Laminar

Incubation

Procedure

The bacterial inoculums repair to definite concentration will be inoculated on to the total face of a plate through a sterile cotton-tipped pad to form an even lawn. The above components will be dissolved and sterilized in an autoclave at 121 oC for fifteen minutes at 15lbs pressure. The sterilized medium release into different sterilized Petra-plates in laminar and endorsed to solidify. The paper disks saturate with diluted sample compound solution placed on the surface of each nutrient agar plate using a sterile pair of tongs. Plates will aerobically incubated and the diameter of zone inhibition observed by a calliper. Based on inhibition zone and the results will be assigned to three categories, resistant susceptible or intermediate. Bigger the inhibition zone, more susceptible is the microorganism to the antimicrobial compound.Cultures having 10^5CFU/mL will be used against each concentration levels. The saturated disks should be positioned on the medium correctly spaced separately, and the plates incubated at 37 ^{o}C for 24 h and 28^{o}C for fungal species [40].

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