General Introduction

Heterocyclic chemistry is a very popular branch of organic chemistry in which studies of various synthesis routes of those compounds in which one or more carbon atoms in the cycle are substituted by hetero atoms like nitrogen, oxygen, sulfur or selenium. The displacement of those heteroatoms in place of carbon atom may increase its biological, physical properties significantly. According to IUPAC (International Union of Pure and Applied Chemistry), the heterocyclic compounds are “cyclic compounds that have at least one different hetero atoms (N, O, S, or Se) as a membered of cyclic ring”.¹ A survey of literature confirmed that HETEROCYCLES have been increasingly important not only in the field of medicinal world but also in the agriculture, physical sciences, and material sciences.

There are so many natural products like vitamins, alkaloids, terpenoids, polyketides, amino acids, peptides, carbohydrates, and nucleic acids and bases contain a number of diversified heterocyclic compounds. They are used as drug in biochemical reactions occurs in living organisms. The structures of some vitamins that contain heterocycles in their nucleus are shown in figure: 1.

Besides this, the huge class of drug molecules contains various heterocycles, because some drugs show its bioactivity only due to the presence of such heterocycles.

Anastrozole contains triazole ring and active substituent like cyano group in its core side (see structure in fig. 2), which is an aromatase-inhibiting drug approved for the treatment of breast cancer after surgery and for metastasis in both pre and post-menopausal women. The severity of breast cancer is increased by estrogen, as sex hormones cause hyperplasia, and differentiation at estrogen receptor sites.²
Anastrozole works by inhibiting the synthesis of estrogen. Another type of drug having an indole as a heterocyclic nucleus is sumatriptan, which is used for the treatment of a migraine and cluster headaches. The synthetic androgenic steroid danazol also possesses an isoxazole ring. Acetazolamide, also known as its trade name Diamox. It is also used to treat glaucoma, epilepsy, altitude sickness, periodic paralysis, idiopathic intracranial hypertension, and heart failure. Some piperidine and pyrimidine derivatives also possess antidepressant activity.

![Heterocycles Diagram](image)

**Figure 2:** structure of heterocycles contains drugs

A **medicinal chemist** is a skilled chemist who mainly focuses on drug discovery and development. They synthesize new drugs and improve the synthetic method of existing drugs. The medicinal chemist likes both biology and chemistry, and uses them to help in treatment of diseases and health-related issues. In the present studies, we have try to improve and invent new molecules useful in treatment of diseases with minimum toxic effect and maximum pharmacologic effect.

**Drug discovery** is not a single process but it is a sequence of number of processes, that means after synthesis, the work is not over yet, but it may overcome with some defect like toxicity and some undesired human behaviours, at such a time chemist was try to resolve that problem by making changes in the structure pattern of the molecules. The starting step of the drug discovery is to identify the target and based on this the ligand was synthesized. Then validate the target by various parameters. Followed by a screening of all synthesized ligands with the same target and get lead compounds whose effectiveness are maximum. The lead optimization followed by preclinical and clinical evaluation, after the success in above steps the molecule was synthesized.
The drugs which are being presently used for curing human disorder mainly involve several natural products having complex structures. These are derived from terrestrial micro-organisms, plants, and animals. The synthetic analogs of the above or other synthetic compounds that are totally non-natural also serve as drugs. The heterocyclic chemistry involves both natural and synthetic compounds. They are aromatic or may be aliphatic in nature.

The range of heterocyclic compounds is bigger, their chemistry is complex and synthesizing them requires great skill as well as certain specific conditions. Among a large number of heterocycles found in nature nitrogen-containing heterocycles are found in most abundant than those containing oxygen or sulfur having in their wide distribution in a nucleic acid instance and involvement in almost every physiological process of plants and animals.

The review of the literature shows that the scope of research in some nitrogen-containing heterocyclic compounds like imidazo pyrimidine, dihydropyridine (DHP) substituted quinolone derivatives and pyridine substituted pyrazole derivatives, some oxygen-containing heterocyclic compounds like benzofuran and sulfur-containing heterocyclic compounds like tetrahydro benzothiazole, thiazolidinediones are still possible. There are so many synthetic methods are already reported but we have try to approach via shortest as well as economical path with respect to reduce hazardous chemical uses, less solvent uses, less time-consuming processes and produced new compounds which have probability towards bioactivity was maximum by changing substituent groups. A short information regarding all studied heterocycles that we have describes in our research work.

1. Benzothiazole shows a wide range of biological properties like antimicrobial, anti-tubercular, antitumor, antimalarial, anticonvulsant, anthelmintic, analgesic and anti-inflammatory activity. Recent research on 4,5,6,7-Tetrahydrobenzo[1,2-d]thiazole reveals that it is used as DNA gyrase inhibitors(see structure in fig. 3).\(^7\) Bacterial DNA gyrase are essential enzymes that control the topological state of DNA during replication and validated antibacterial drug targets. Due to such wide range of activity, we have synthesized some new heterocyclic compounds containing tetrahydro
benzothiazole nucleus and triazole core ring and evaluate them with anti-microbacterial activity. Some of the synthesized compounds showed moderate to good activity.

Figure 3: DNA gyrase inhibitor

2. Aryl propionic acid derivatives are the well-known class of non-steroidal anti-inflammatory drugs (NSAIDs) (figure: 4) like ibuprofen, dexibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin and loxoprofen.

Figure 4: Designing of the molecule

Here we have designed the molecule in such a way that it is containing aryl propionic acid part and heterocyclic ring (fig. 4). The propionic acid has a broad biological activity and addition to it heterocycles, increased the amount of activity. Moreover, due to an asymmetric carbon (chiral carbon), the two enantiomer are formed during synthesis.

3. Thiazolidinedione’s is a five-membered heterocycle having a sulfur and nitrogen on the first and third position of ring respectively and two carbonyl group on second and fourth position and remaining member is methylene group. The 2,4-thiazolidinedione derivatives possess an important class of heterocyclic compounds for which numerous biological properties such as antibacterial and antifungal, antiviral, antitumor and anti-diabetic etc. have been reported. The first ever pharmacological evaluation, that is, anti-TB activity of any thiazolidinediones(TZD) derivative was reported by an italian scientist ‘Vistentini’ in 1954. This small heterocycle have a used in so many receptors based drug among one is for diabetes, it is used as peroxisome proliferator-activated receptor gamma (PPAR-γ or PPARG) and protein-tyrosine
phosphatase 1B receptors, for cancer the receptor such as phosphatidylinositol-4,5-bisphosphate 3-kinase and mitogen-activated protein kinases (MAPKs) was used by thiazolidinediones.\textsuperscript{11}

In present studies, we have synthesized some new thiazolidinedione derivatives which substituted on methylene carbon hydrogen and another substituent on nitrogen (fig. 5). The targeted molecules were prepared by using microwave-assisted Suzuki-miyaura carbon-carbon cross-coupling reaction.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{General structure of molecules}
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4. Nitrogen-containing heterocyclic compounds are key building blocks used to develop compounds of biological or medicinal interest to chemists. A vast number of nitrogen-containing heterocyclic building blocks have applications in pharmaceutical research, agriculture science and drug discovery. Most of the organic compounds containing heterocyclic compounds show better biological activity than non-nitrogen compounds.

One of the nitrogen-containing heterocycles are \textit{imidazo[1,2-a]pyridine}, in short, \textit{imidazopyridine}. The imidazole moiety fused with the pyridine ring, is an important biologically active nitrogen-containing heterocycle. Imidazopyridine derivatives showed a wide range of biological activities such as antifungal, anti-inflammatory, antitumor, antiviral, antibacterial, antiprotozoal, antipyretic, analgesic, antiapoptotic, hypnoselective and anxioselective activities,\textsuperscript{12-17} The fig.6 shows the structures of some potent active drug containing imidazopyridine nucleus.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Imidazopyridine ring contains drugs}
\end{figure}

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5. Pyridine containing heterocyclic compounds are popular due to its interesting biological activity and also for the synthon in many chemical reaction. In present...
studies, we have synthesized pyridine as well as it’s reduce form containing derivatives.

![Pyridine and 1,4-dihydropyridine](image)

We have synthesized dihydropyridine and 2-quinolone. They both coupled and prepared new heterocyclic derivatives.

![Amlodipine (CCB) and Felodipine (CCB)](image)

**Figure 7: Structure of DHP having a CCB (Calcium channel blockers) activity**

1,4-dihydropyridine also known as DHP shows various biological activity like its class of calcium channel blockers inhibits the Ca\(^{2+}\) influx represents a major therapeutic advance in the treatment of cardiovascular diseases, such as hypertension, angina pectoris, and other spastic smooth muscle diseases.\(^{18}\) The **fig.7** shows the structure of some dihydropyrimidine containing calcium channel blockers.

6. Pyrazole is an important class of five members of heterocyclic compounds with two adjacent nitrogen, in our case one nitrogen is substituted by phenyl ring. Pyrazolo derivatives are shown numerous biological activities like antimicrobial,\(^{19}\) antibacterial, antifungal,\(^{20,21}\) anti-tubercular, anti-inflammatory, anticonvulsant, anticancer, anti-viral, angiotensin-converting enzyme (ACE) inhibitory, neuroprotective, cholecystokinin-1 receptor antagonist, and estrogen receptor (ER) ligand activity.\(^{22}\) Due to such a wide range of biological activity of pyrazole and pyridine heterocycles, we have synthesized some new derivatives which possess pyrazole and pyridine nucleus.

**Aims and objectives:**

Taking in view the significance of heterocyclic compounds, we have undertaken the preparation of heterocycles having a tetrahydro benzothiazole,
benzofuran, thiazolidinediones, imidazopyrimidine, dihydropyridine substituted quinolone and pyridine substituted pyrazole nucleus. During the designing of all molecules, we have taken care of substituent i.e. position of substituent on heterocyclic framework. The objective of the present study is to develop rapid, operationally simple and environmentally benign methodologies for the synthesis of proposed heterocycles. Hence we have focused on following points.

- Overview of a literature survey on the biological activities and synthesis of nitrogen, oxygen and sulfur based heterocyclic compounds.
- To develop an efficient, operationally simple, environmentally benign for the synthesis tetrahydro benzothiazole and its characterization and antimicrobial evaluation.
- To study the in-vivo anti-diabetic activity of some new aryl propionic acid derivative having a benzofuran nucleus.
- To synthesize of fused heterocyclic ring system like imidazo[1,2-a]pyridine and evaluate them for anti-microbial activity and fluorescence properties.
- To synthesize dihydropyridine (DHP) substituted quinolone derivative and characterized and evaluate their biological activities.
- To study the microwave-assisted carbon-carbon coupling reaction like Suzuki-miyaura and sonogashira.
- To characterize all the synthesized compounds for structure elucidation using various spectroscopic techniques like IR, \(^1\)H and \(^{13}\)C NMR and mass spectral studies.
- To grow a single crystal of the synthesized compounds and study their X-ray crystallography for the establishment of the structure.
- To study optical activity study of some synthesized compounds like UV and fluorescence.
- To monitor the reaction and check the purity of all synthesized compounds using thin layer chromatography, and purify the compounds by column chromatography and re-crystallization techniques.

REFERENCES:
(2) Mauras, N.; Bishop, K.; Merinbaum, D.; Emeribe, U.; Agbo, F.; Lowe, E. J.


(6) Smith, S. V; Friedman, D. I. Headache J. Head Face Pain 2017, 57 (8), 1303.


