CHAPTER-1

INTRODUCTION
1.0.0 GENERAL INTRODUCTION:

Heterocyclic compound with one or multiple hetero atoms is found abundant in nature, almost all the metabolic processes are perform with the help of one or multiple heterocyclic compound. Heterocyclic shape extreme in biggest of classical division of medicinal drug chemistry.

One or more remarkable structural feature likely to heterocyclic, which keep on to demoralized to benefits by the drug industry, lies in their ability to patent substituent approximately a nucleus gallows in defined three (3), dimensional representations. Among or with the various heterocyclic compounds, Nitrogen heterocyclic compounds are the most prevalent.

To consideration overall study evaluate various or different heterocyclic molecule as a possible antagonist like “Piper dine”, or “Purine”

To construct the desired moiety different other biological active moieties have also been used like amino acids or derivatives etc. Backbone construction is possible target moiety Carbohydrazide linkage.

Natural has total twenty three protéinogenic amino acids; the present study has also tried to explore biological activity of moieties bearing novel moieties bearing photogenic and non-photogenic amino acid residue.

The anticancer antibacterial, antiviral, anti-inflammatory, analgesic, anticancer, and respiratory analeptic activities.

Carbohydrazide is a pharmacologically active compounds. Present in metabolic system. Nearly all known enzymes are proteins, which are Carbohydrazide important role in enzymatic catalyst with polymer compounds.
Carbohydrazide of amino acid are of particular interest to researchers as it shows wide range of pharmacological activities like antibacterial, anticancer, anti-inflammatory, anti HIV etc.

For this purpose we have used Carbohydrazide as main coupling entity for developing different derivatives of heterocyclic compounds.

Bicyclical aromatic heterocyclic compound such as Purine quinazolines, indoles, benzimidazoles are well-known well represented in chemical compound libraries.

Another biologically important back bone of drug design is Piper dine. Piper dine and its derivatives are of great significance due to their major roles in biological system, as proton acceptor with donor, coordination system legends and the base of charge-transfer processes.

Piperdine is anticonvulsant, anti-Parkinson and oxidize inhibitory activity. Piper dine is back bone of many existing generic drugs.

Derivatives of Piper dine have exhibited various pharmacological activities against various pathogens, for example

- antibacterial,
- antifungal,
- antiprotozoal and
- anthelmintic.

Due to this reason Piper dine remains a primary target of drug design. Taking inspiration from this present study explores different derivatives of Piper dine for their biological activity.

**Another important structural residue of heterocyclic nature is Pipyridine.**

Pipyridine is six member ring with Nitrogen heteroatom, Numerous natural alkaloids have the piper dine structural motif. Its effect with different compounds like

- raloxifene,
- monoxide,
- resperidone. The piper dine structure is found in the pharmaceuticals like toxin solenopsin.

Piper dine is also commonly used in heterocyclic compound in medicinal used. In this section, a detail literature survey of nitrogen containing heterocyclic Purine and their evaluation of therapeutics category and various route of synthesis is described.

In early 1935, possibility of using Purine derivatives as chemotherapeutic agents was investigated.
Target various enzymes involved in different diseases and cellular processes, most notably the kinase family. Its known as Hsp90, antineoplastic, antitumor and antiviral antitubercular, antiulcer, antimicrobial, as potent inhibitors of properties.

Heterocyclic compounds are the most important part of human being. It would not be inflated to state that the very existence of human life being is dependent on existence of heterocyclic compounds. This very fact could not be denied as every live species on this earth uses heterocyclic compound in its metabolic system.

Almost all metabolic system known, whether in human being or otherwise is having interest heterocyclic compound in different stages.

Not only nature uses heterocyclic compounds for performing various metabolic activities, even researcher in the field of drug design as well as other fields like

• perfumery,
• pesticides,
• cosmetics, etc

Are very much dependent on Heterocyclic compounds to achieve materials of desired properties. This is marked from the fact that majority of the drugs currently being marketed are heterocyclic compounds.

On the basis of literature available data heterocyclic chemistry began in 18th century along with development of organic chemistry, since than it has remained main heart of research for different application and this lead to the fact that more than half of the total novel compounds synthesized in organic chemistry is heterocyclic compounds.

Heterocyclic compounds provide a very high structural diversity and hence proved as important class of cost-effective interest particularly as therapeutic agents for almost all elements.

**DEFINITION: HETEROCYCLIC COMPOUNDS:**

“Heterocyclic compounds or molecules are cyclic organic compounds having at least single atom other than carbon and hydrogen such as Boron, Nitrogen, Sulphur, Oxygen, Phosphorous, Silicon, and Selenium which is known as hetero atom for the system and hence it is so call “Heterocyclic” compounds.

The most common hetero atoms are Sulphur, Nitrogen, Oxygen. In heterocyclic compound one of the carbon atoms belonging to cycle is replace by at least single hetero atom. In addition to this, these compounds at times have erstwhile structural part also such
as extra ring structure with or without hetero atom and straight or branched chain as substituent at different position of the cyclic structure.

The heterocyclic ring is either non-aromatic aromatic in nature and is mostly stable in nature, i.e. generally does not polymerized

- hydrolyzed,
- reduced,
- oxidized,
- or undergo various other conversion reaction under normal condition.

The heterocyclic compounds with one hetero atom are relatively more reactive and generally used a number of places as intermediates to prepare greater structural back bones.

Though the fact three or four member heterocyclic compound are very reactive, they are used as an intermediate to take advantage of their very high reactivity, not only this they are also found in some of the heterocyclic compound of medical interest.

Out of these 3, 4 member heterocyclic compounds Oxidant and Aziridine are more frequently found or used as a substrate in the field of drugs discovery.

Six member heterocyclic compounds with one or more hetero atom and frequently observed as being used by medicinal scientist are

- Pyrazine,
- pyrimidine,
- Piperidine Piperazine,
- Morph line and
- Dioxin.”
Generally, found four member heterocyclic compounds are Onetime, 2H-Oxete, Thirteen, 2H-Thietene, Azetidine and Arête etc.

Along with these Oceans and Azetidines are frequently used for drug application for optimizing biological as well as physicochemical property.

Five and six member heterocyclic compounds are used in medicinal chemistry more frequently than other ring sizes.

This heterocyclic compounds also used commonly used by in final drug compound.

Unsaturated five or six member heterocyclic compounds are more stable due to presence of aromatic region or aromatization.

Most frequently found five member heterocyclic compounds with single, hetero atom. For example,

Pyrrole,
Pyrrolidine,
Furan,
Tetrahydrofuran,
Theteahydrothiophene and
Thiophene etc.
Saturated one hetero atom five member heterocyclic compounds, out of these Pyrrolidines, Tetrahydrofurans and Oxazolidines are most frequently found in medicinal chemistry.

Five members heterocyclic compounds with two hetero atoms are generally, found in nature as well as in drug compounds. Some of the frequently found structures are

- Pyrazole,
- Imidazo,
- Oxazole,
- Isoxazole,
- Thiazole,
- Isothiazole,
- Pyrazolidine,
✓ Imidazolidine,
✓ Oxazolidine,
✓ Isoxazolidine,
✓ Thiazolidine
✓ and Isothiazolidine.

Un-saturated two hetero atom 5 member heterocyclic compounds, out of which Pyrazole, Imidazo and Oxazole are found in new drug discovery more often than other compound.

Saturated two hetero atom five member heterocyclic compounds commonly found are

• Pyrazolidine,
• Imidazolidine,
• Oxazolidine,
• Isothiazolidine,
• Thiazolidine and
• Isoxazolidine.
Apart from this, there exists five member heterocyclic compounds with three or four hetero atoms observed in drug design, ex. Are Triazole, Ox diazole and Tetrazole.

Six member heterocyclic compounds with one or more hetero atom and frequently observed as being used by medicinal scientist are Pyridine, Pyridine, pyrimidine, Piperidine Piperazin, Morph line and Dioxin.
“IMPORTANCE OF HETROCYCLIC COMPOUNDS IN DRUG DEVELOPMENT”:

**Concept:** The goal of heterocyclic compound is to synthesized different design of drugs minimize the side effects to human body’s.

The sound knowledge of organic chemist having two last century, about heterocyclic compound is continuously improved with different specifications. Heterocyclic compounds were recognised by organic chemists almost two century ago after discovery of naturally occurring alkaloids such as morphine and quinine.

After that was established in various fields of biochemistry and physiology, to name major few of them are photosynthesis, amino acids, DNA bases, Vitamins, Neurone-transmission etc.

**Meaning and nature of Heterocyclic compound:**

In simple language, the atoms of carbon and at least one other element is made up in ring system is known as heterocyclic.”

Heterocyclic compound nature is to achieve a required modification of drug design or development of drug.

**Application of Heterocyclic compounds:**

- Fungicide
- Agrochemical
- Pharmaceutical
- Medicinal chemistry
- Chemical
- Organic Chemistry
- General chemistry
- Polymer chemistry
- Natural and synthetic chemistry
- Textile
- Veterinary products

In other hand more many application of heterocyclic compounds, structures is more groups of structures that have overall similarities of physical properties of aromatic compounds, some little bit difference with in groups like in
acidity,
basicity,
dipole moment,
pKa value,
polarity difference.

Another important feature of heterocyclic compound is to incorporate the functional group or amino group also apart of aromatic ring system itself. It means that the structures are particularly to providing the functional group.

Drug product above conditions fallowed by only below parameters.
A. Confirmation from laboratory testing and assays on dry basis that the drug products meet all specific standards of
   Identity of drug product,
   Strength of drug product,
   Quality of drug product,
   Purity of drug product,
B. Confirmation from inspection drug products in classified area and their associated with packaging area,

All drug products how to control in laboratory so below details are mentioned..
a) The organization of some qualifications, principles, part, as well as should be drafted by the suitable managerial unit,
Check all documents should be thoroughly with desired specification to concern person.

(4) The calibration is a also part of good manufacturing system of drug substance, Below are the lists of functional group in heterocyclic compounds:

<table>
<thead>
<tr>
<th>Sr. No’s</th>
<th>Name of functional group</th>
<th>pKa value,</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alcohol</td>
<td>15-19</td>
</tr>
<tr>
<td>2</td>
<td>Ether</td>
<td>-2 to -3</td>
</tr>
<tr>
<td>3</td>
<td>Alkynes</td>
<td>~25</td>
</tr>
<tr>
<td>4</td>
<td>Epoxies</td>
<td>~11</td>
</tr>
<tr>
<td>5</td>
<td>Ketene</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>Amine</td>
<td>38-40</td>
</tr>
<tr>
<td>7</td>
<td>Nitride</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>Aldehyde</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>Ester</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>Amide</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>Thiol</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>Carboxylic acid</td>
<td>4-5</td>
</tr>
<tr>
<td>13</td>
<td>Acid anhydride</td>
<td>4.75 (not sure)</td>
</tr>
<tr>
<td>14</td>
<td>Aryl halide</td>
<td>~16</td>
</tr>
</tbody>
</table>

Polarity difference.

Amide> Acid> Alcohol> Ketone ~ Aldehyde> Amine> Ester> Ether> Alkane.

**Scientist applied following contents during development of drug.**

- To apply science behind the molecule and concept behind managing the Therapeutic Area for effective customer influencing
- To see & expand key judgment best to boost product usage,
- Reviewing & approval of all analytical data & COA of raw material, packing material, in-process, intermediate and finished product.
• Review of purified and potable water report.
• COA preparation of finished product samples
• Reviewing of stability sample analysis.
• SCM activity approval of RM,PM.
• Preparation of master calibration scheduled and planning of the calibration of the QC instruments and review of this instrument calibration record.
• Trouble shooting of the QC instrument
• Handling of change controls.oos, incidents and deviations
• Conduction the training of QC Analysts
• Actively involved related to Laboratory information management systems.
• HPLC/GC Column Management.
• Working Standard and reference standard Management.
• Handling of internal audits, customer audit and conducting of GMP training programmer.
Chlorophyll, one of the major element of photosynthesis, exists in nature has five member unsaturated nitrogen heterocyclic atoms.

This is the basis of sustaining life of all plants and other live species which are dependent on plant to fulfil their requirement of carbohydrate.

Apart from these main elements of metabolic processes, many other molecule involved in metabolic system are heterocyclic compounds, for examples amino acids like Histamine, and Proline contains heterocyclic compounds.
Other physiological and biochemical process like neuron-transmission and modulation uses various heterocyclic compounds in their processes. Some of them are Histamine, Serotonin, Melatonin and Tryptamine.

![Chemical structures of Histamine, Serotonin, Tryptamine, and Melatonin](image)

On the basis of above data, nature extensively dependent on use of heterocyclic compounds for performing its metabolic process researcher always remained inclined to explore moieties having structural similarity with the one exists in biological system not only that the intrinsic structural versatility.
Ability to newly modify physical and chemical properties of heterocyclic compounds by derivatization have poised them as important cornerstone in drug invent.

In other hand marketed drugs, numerous other heterocyclic compounds are being investigated for their various activities against various ailments.

Drugs of all categories are having heterocyclic compounds as members, not only that numerous.”

Others are being investigated for better activity, lower toxicity or various desired physicochemical properties.

Heterocyclic compounds have enormous potential as most of the lead structure in the drug design and also finding to intermediate of organic synthesis.

Heterocyclic structure is most common part of drug being marketed today or being investigated for various existing as well as many non-curable ailments, highlighting its central role in the modern drug design.

This is also due to the fact that heterocyclic compounds could be manipulated for its polarity and hydrogen bonding, physicochemical properties, which are very vital for improvement of pharmacological, pharmacokinetic and toxicological property of potential drug candidates.
“SALT FORMATION IN DRUG DESIGN DEPENDS ON BELOW MENTION FACTORS”:

- Higher activity of drugs
  - Its beneficial of patient to minimize the side effects.

- Lower toxicity of drugs
  - Its useful to avoid the less toxicity of final drug.

- Solubility of drug in water
  - Its useful of to easily digest with patient.

- Novel moieties
  - Innovative idea is define novel drug synthesis.

- Physicochemical properties
  - Its helpful to prepare drug molecule.

- More stability of drug
  - Its generally useful longer time compound is stable and design the self life period of drug.

- Bioavailability
  - Biological study is completely in this section.

  Solubility of drug in water is one of the key physicochemical property of drug and this is evident from the fact that almost half the drugs being administered today is in their salt forms as solubility of salts are better compared to their free amines or carboxylic acids.

  Solubility of drugs has direct impact on drugs bioavailability and hence salt formation has become one of the significant aspects in drug development.

  Drug candidate having some of the undesired features are sometimes overcome by applying this simple technique of salt formation.

NEED OF NOVEL DRUGS:

“ The total pharmaceutical industry today is faced with the challenge of increasing resistance of pathogen against existing drugs as well as its toxicity and side effects. To overcome these problems, its need of the hour to develop a new drug with higher activity and lesser toxicity or side effects.

Various factors play a role while targeting a moiety as a possible new drugs, the most crucial being a base moiety i.e. skeleton of the molecule.
As already stated earlier researcher has time and again remained dependent on nature to take clues for developing new drugs, moieties structurally similar to compounds exists in metabolic system are preferred and then engineered for desired Pharmacophore.

Taking the same path study carried out in this research also mainly based on compounds existing in nature, i.e. Heterocyclic compounds. Almost all the compounds we know as synthetic drugs such as

- diazepam,
- barbiturates,
- Antipyrine,
- Caporal and methotrexate are also heterocyclic.

Among the various heterocyclic compounds, Nitrogen heterocyclic compounds are the most prevalent. In addition to this Sulphur heterocyclic is also a significant member of metabolic system.

Taking this fact into consideration this study evaluate various heterocyclic base moieties as a possible antagonist like

- “Imidazo”,
- “Thiazole”,
- Piperidine"
- Thioimidazole and their salts.

To construct the desired moiety various other biological active moieties have also been used, like derivatives of amino acid and phthalimide. The backbone construction of the possible target moiety is attained mainly by carboxamide linkage.”

**BELOW ARE THE STRUCTURAL MOIETIES USED IN THIS STUDY ARE FURTHER EXPLAINED IN DETAILS IN FOLLOWING PART OF THIS CHAPTER:**

### AMINO ACIDS:

All 23 amino acids are important role in medicinal chemistry. It's very helpful to design the drug substance and because of amino acid

Its very stable during preparation of final drug substance. All amino acid related moities are more stable in drug compound.

Amino acids were discovered in beginning of 19th (nineteenth) century, with discovery of first amino acid asparagines by French chemist,
While the last common amino acid was discovered by William Cumming Rose in 1935.

Amino acids are biologically important compound, containing

- Carboxylic acid and
- Amine functionality.

Other side, two functional group it contains a side chain specific to a particular amino acid, except glycine where no side chain is present.

All amino acid are chiral compound except glucose for which absence of side chain renders it as archival compound.

As many as five hundred amino acids are known and are classified in several different ways. The well known classifications are based on,

- Core structural functional groups, i.e. alpha, beta, gamma or delta amino acids.
- Type of side chain, i.e. Aliphatic, acyclic, aromatic etc.
- Property of amino acid, i.e. Polar, non-polar.
- Although numerous amino acids there are six main based on their structure and chemical characteristic of side chain.

**TABLE 1.0 : Class of Amino acids**

**Different Class of Amino acid**

Aliphatic

Hydroxyl or Sulphur/Selenium containing

“Among this amino acid bearing amine and carboxylic group on the same carbon is alpha (α) amino acids, with un-ionised generic formula as given below”

\[
\begin{array}{c}
R \\
\text{H}_2\text{N} \\
\text{O} \\
\text{OH}
\end{array}
\]

\(\alpha\)-Amino acid
Amino acids are second largest component of human muscle, tissues and cells, the first being water.

Many important biological processes involve amino acids, like biosynthesis, neurotransmitter transport.

Generally the term “amino acid” referred to photogenic (protein building block) alpha amino acid. There are 23 (twenty three) photogenic amino acids.

Out of these 20(twenty) AA are referred as “Standard amino acid”. All these are mainly L-amino acids while occurrence of D-amino acids are rare. In general other amino acids are termed as un-natural amino acids or non-proteogenic amino acids which includes all D Isomer of proteogenic amino acids.

Structure of Natural Amino acids are given below. All the amino acid where configuration is not mentioned are L-amino acids.
Chemically, Purine in which imidazole ring at 4 and 5 positions, is fused with bond of pyrimidine.

It would not be too perfect to state that life on this planet is totally dependent on two compounds based on the Purine nucleus.

Guanine and adenine are in fact substituted Purine. Additionally as nucleosides and nucleotides they act as hormones.

The interconversion of mono-di and triphosphate esters of nucleosides is at the heart of Energy-transfer in various metabolic systems and is also involved in intracellular signalling.

These central biological importances together with medicinal chemist’s search for antifungal agent have resulted in a rapid expansion of Purine chemistry in recent years.

Some major Purine are uric acid, adenine, guanine, hypoxanthine, xanthenes, the bromine, caffeine, uric acid and is guanine.

The first pure Purine was found from **Uric acid (2)** which was isolated from kidney stones in 1776 but its structure was confirmed one hundred year later by Medicus and the chemistry of Purine flourished from 1906 onwards until today.

The biological study, in synthesis of Trisubstituted Purine derivatives was an interesting objective.

Purine derivative having structural variations at its 2, 6 and 9-position is of great interest in medicinal chemistry.

It has broad biomedical value as therapeutics. Several types of cell cycle dependent kinas (CDK) inhibitors e.g. Olomoucine,
• Olomoucine-II,
• Roscovitine,
• Bohemian,
• Purvalanol.

2, 6, 9-trisubstituted Purine derivatives, Myoseverin act as microtubule assembly. Trisubstituted Purine family currently being explored as an novel anticancer drugs,

as protein A mimetic for the treatment of autoimmune diseases, as inhibitors of P38 mutagen-activated protein kinas, as potent Hsp90 inhibitor, as potent stat3 binding inhibitor,

• Antitumor,
• Sulfotransferase,
• Inhibitors of phosphodiesterase 7 (PDE7)
• Adenosine receptor antagonists.

The inhibitory activity of Purine derivatives varied depending on the C2 substituent.

\[
\begin{align*}
\text{Arginine (Arg)} & \\
\text{Lysine (Lys)} & \\
\text{Histidine (His)} & 
\end{align*}
\]

The objective of research is to design other Trisubstituted Purine.

Definitely amino acid derivatives is the prominent functionalized substituent of high biological application, anti tuberculosis, anti-inflammatory/analgesic, anti-HIV-1, anticancer, respiratory analeptic and anti-anoxic activity. So we have been synthesized Trisubstituted Purine coupled along with amino acid derivatives.

The diseases caused by organisms the community. Infections caused by these organisms build a grave. A number of novel Trisubstituted Purine coupled with amino acid derivatives with several structural variations and containing various other biologically important scaffolds through various reaction intermediates like
- N-Phthaloyl
- Purine derivatives.

using diverse spectroscopic techniques.

Antimicrobial activity of the synthesized compounds revealed that some of the synthesized compounds are moderate to highly active against the selected pathogens.

Chemically, Purine is a imidazole ring at 4 and 5 positions is fused with d bond of pyrimidine. Chemical name is imidazole (4, 5-d) pyrimidine.

The structure of Purine (Fig. 1.1) is that of a cyclohexane (pyrimidine group) and cyclopentane (imidazole group) attached to one another, the nitrogen atoms are at positions 1,3,7,9.

![Fig. 1.1](image)

Purine exits in four possible tautomeric forms (Fig. 1.2), namely 1H, 3H, 7H-purine and 9H-purine [4]. 7H Purine is crystalline and 7H and 9H are present in equal amounts in solution but in the solid state 7H-form is dominant [4-5].

![Fig.](image)
Some notable Purine are (Fig. 1.3) adenine (7), guanine (8), hypoxanthine (9), xanthenes (10), the bromine (11), caffeine (12), uric acid (13) and is guanine (14).

In this section, a detail literature survey of nitrogen containing heterocyclic Purine and their evaluation of therapeutics category and various route of synthesis is described.
1.1.1 **General method for synthesis of Purine:**

Purine itself has not been found in nature, but wide varieties of substituted Purine derivatives have been isolated from natural sources.

In 1899 Fischer E., first synthesized pure Purine from uric acid (Fig. 1.4). In this process, uric acid (13), was reacted with PCl₅ to get 2, 6, 8-trichloropurine 15, to 2, 6-di-iodo derivative (16) with HI and PH₄I. Product was reduced to Purine 2 using zinc-dust or powder.

![Fig. 1.4](image1.png)

Wilhelm Traubel (17) in 1900 reported a versatile synthesis of Purine from other precursors 4, 5-diaminopyrimidine (17) and with formic acid or chlorocarbonic ester or by carbonyl condensation,

while in 1906 Oskar Islay reported the synthesis of Purine by cyclization of 4, 5-diaminopyrimidine (17) with anhydrous formic acid in the carbon monoxide atmosphere. It is still the most important method of preparing Purine from other precursors (Fig. 1.5).

![Fig. 1.5](image2.png)

Broderick H reported the synthesis of Purine reaction with triethyl (formylamino) methane (18) with phthalimidacetonitrile 19 at high temperature (Fig. 1.6) and reaction of form amide (20) with aminoacetonitrile (21) (Fig. 1.7).

![Fig. 1.6](image3.png)
Yamada and Okamoto reported synthesis of Purine in better yield when form amide 22 is heated in an open vessel at 160-200°C for 28 hours.

1.1.2 Importance of Purine derivatives:

Purine derivatives have great significance as In early 1935, possibility of using Purine derivatives as chemotherapeutic agents was investigated. In medicinal useful molecules having various biological activities. Purine derivatives used target various enzymes involved in different diseases and cellular processes, most notably the kinas family. It’s known as ant Tubercular, Antiulcer, Antimicrobial, Antineoplastic, Antitumor and Antiviral properties.

The chemotherapeutic uses of Purine and purine analogues have prompted tremendous efforts towards their synthesis, both in the pharmaceutical industry as well as academia.

Substituted Purine This central biological importance of Purine chemistry in recent years. Aspargine
Glutamic acid

![Glutamic acid structure](image1)

Glutamine

![Glutamine structure](image2)

1. Serine

![Serine structure](image3)

2. Threonine

![Threonine structure](image4)

3. Cysteine

![Cysteine structure](image5)

4. Selenocysteine

![Selenocysteine structure](image6)
Here, main focus on the methods for coupling of Purine with amino acid derivatives, which provides convenient access to substituted Purine derivatives with applications in drug discovery and chemical biology.

The Structures of drugs containing Purine moiety are shown below (Fig.1.9)

Synthesis of purines derivatives is very useful in fallowing drugs and that are used as a human being with controlled drug substance like that end used of final products.
Drug was selected on the basis of their biological activity and cost effective as well as less side effects of patients.

Generally below listed deriv. of purin used in pharma industry. Subsequent polymorph also prepared into derivatives of purine molecules.
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drug</th>
<th>Application</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abacavir</td>
<td>Reverse transcriptase inhibitor (NRTI) used to treat HIV and AIDS</td>
<td><img src="image" alt="Abacavir structure" /></td>
</tr>
<tr>
<td>2</td>
<td>Arprinocid</td>
<td>Coccidiostat used in veterinary medicine</td>
<td><img src="image" alt="Arprinocid structure" /></td>
</tr>
<tr>
<td>3</td>
<td>Azathioprine</td>
<td>Used in organ transplantation and autoimmune disease</td>
<td><img src="image" alt="Azathioprine structure" /></td>
</tr>
<tr>
<td>4</td>
<td>Cladribine</td>
<td>Drug used to treat hairy cell leukaemia</td>
<td><img src="image" alt="Cladribine structure" /></td>
</tr>
<tr>
<td>5</td>
<td>Clofarabine</td>
<td>Drug used for acute lymphoblastic leukaemia (ALL)</td>
<td><img src="image" alt="Clofarabine structure" /></td>
</tr>
<tr>
<td>6</td>
<td>Famciclovir</td>
<td>Herpes Antiviral</td>
<td><img src="image" alt="Famciclovir structure" /></td>
</tr>
</tbody>
</table>
Many non photogenic amino acids also plays critical role in metabolic system. Like gamma-amino butyric acid (GABA) as neurotransmitters, carnation in lipid transport. Structure of some of the major un-natural amino acids are as following.

**Fig.1.9:** Structure of drug containing Purine moiety
1. Beta-alanine

\[
\text{H}_2\text{N}\text{CH}_2\text{CH}_2\text{OH}
\]

2. Gama-Aminobutyric acid (GABA)

\[
\text{H}_2\text{N}\text{CH}_2\text{CH}_2\text{COOH}
\]

3. 4-Amino benzoic acid (PABA)

\[
\text{COOH} \\
\text{NH}_2 \\
\text{\text{C}_6H_4}
\]

4. Amino is butyric acid

\[
\text{H}_2\text{N}\text{CH}_2\text{CH}_2\text{COOH}
\]

5. Dehydroalanine

\[
\text{H}_2\text{C}_3\text{NH}_2\text{COOH}
\]

6. L-DOPA

\[
\text{OH} \\
\text{\text{C}_6H_4} \\
\text{\text{NH}_2} \\
\text{OH}
\]

7. Ornithine

\[
\text{H}_2\text{N}\text{\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}}
\]
Out of these proteogenic amino acids, nine amino acids are essential amino acids as these amino acids are not created by human body and hence to be supplied from outside mainly as a part of food.

The following list of essential amino acids is different for different species.

**TABLE NO 1.2 : Essential and Nonessential amino acids (All above mention)**

<table>
<thead>
<tr>
<th>Essential</th>
<th>Nonessential</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.Histidine</td>
<td>6.Isoleucine</td>
</tr>
<tr>
<td>2.Leucine</td>
<td>7.Lysine</td>
</tr>
<tr>
<td>3.Methionine</td>
<td>8.Phenylalanine</td>
</tr>
<tr>
<td>4.Threonine</td>
<td>9.Tryptophan</td>
</tr>
<tr>
<td>5.Valine</td>
<td></td>
</tr>
</tbody>
</table>
Nonessential
1. Alanine
2. Asparagine
3. Cysteine
4. Glutamine
5. Proline
6. Arginine
7. Aspartic acid
8. Glutamic acid
9. Glycine
10. Selenocysteine
11. Tyrosine

Apart from production of drugs. The other important uses apart from these are chiral synthesis, as Chiral building blocks for various chemicals as they are available in enantiomeric pure form and production of biodegradable plastics.”
DRUGS CONTAIN AMINO ACID RESIDUE:

Some of the well known drugs containing amino acid residue are listed below as examples to highlight the importance of amino acid residue in drug molecules.

Imidazo, as already a very versatile base moiety in modern drug design was first synthesized by scientist in 1858, prior to that in 1840s. It was originally named as Glyoxalin.

Many natural products contains imidazole ring, especially alkaloids. molecules like Histamine, Histamine, Many natural and synthetic drugs contain an imidazole ring. Imidazole when fused with pyrimidine ring results in Purine, Three carbon two nitrogen ring. both the tautomers are equivalent when not substituted or substituted with same group on position three and four position. But if give rise to different compounds when position three and four are having different substituent’s, mostly when part of polycyclic ring structure.

Imidazo ring is a highly polar in nature, Its Very soluble in water. By virtue of sextet of π-electrons, pair of lone pair and one electron each from remaining three carbons and one nitrogen contributes to the sextet of electrons responsible for aromaticity. It also exhibit resonance, the resonance structure are shown as below.

![Imidazo Structure](image)

Imidazo as well as a base depending on medium in which it is being present.
It has pKa value 14.5, making very weak acid, i. e. The basis site in imidazole is N-3. Protonated imidazol,

**BIOLOGICAL SIGNIFICANCE OF IMIDAZOLE**
The high therapeutic properties have been encouraging medicinal chemists to developed many important biological molecules.

The most known to organic chemist is the amino acid histamine, possesses imidazole side-chain, which is very important molecule of metabolic system and carries oxygen from lungs to various part of body to perform metabolic activity of generating energy.

Histamine on decarboxylation results in histamine, another important molecule of metabolic system.
Histamine can cause urticaria (hives), when produced during allergic reaction. The relationship between histamine and histamine in biological system is shown below:

![Histamine Reaction Diagram](image)

Large resulting in displacement of His-tag from nickel co-ordination. Its useful application of synthetic imidazoles.

**PHARMACEUTICAL APPLICATION OF IMIDAZOLE:**
This interesting group of heterocyclic compound has diverse biological activities such as
- Antimicrobial,
- Anticancer,
- Analgesic,
- Anti-inflammatory,
- Antiviral,
- Anthelmintic,
- Anticonvulsant,

**OTHER NON-PHARMA / INDUSTRIAL APPLICATIONS**
Imidazo is being as conductivity test of the Imidazo derivatives are part of. Imidazo derivatives can also be found in various photography and electronics applications.
IMPORTANCE OF IMIDAZOLE IN LIFE
Imidazo are well-known base moiety and found in variety of medicinal agents Literature survey shows that derivative of Imidazo show pharmacological activity such as
1. Anticancer
2. Ant tubercular
3. Antifungal
4. Anti-HIV
5. Anti conversant
6. Muscle relaxant
7. Anti-inflammatory
8. Anti-viral
9. Anthelmintic
10. Anticonvulsant
11. Antiulcer
   Anti-allergic
DRUGS BASED ON IMIDAZOLE

As Imidazole derivatives remained the prime interest of researcher for almost two century, it resulted in various drug molecules.

Many Imidazo derivatives are existing drugs being marketed today for various ailments. Some of the representative examples are,

(Ketoconazole)

(Cimetidine)

Losartan
Decarbazine (anticancer)

Metonidazole (antibacterial)

These examples further highlights the importance and rational to use imidazole moieties as possible target as drug molecules.

**THIAZOLE**
Thiazole, also referred as 1, 3-thiazole is heterocyclic aromatic compound having two hetero-atom sulphur and nitrogen. Thiazole is also referred in general term for family of thiazol containing derivatives. The well known existence of thiazole in nature is Vitamin B1 and Penicillin.
Thiazoles are sub-members of azoles family. Pi-current density of thiazole is such that electrophilic substitution takes place on C5 carbon and nucleophilic substitution takes place on C2 carbon.

Apart from Vitamin B1 and Penicillin, other well known natural existence of thiazole compound is epothilone, drug used for cancer and the fire fly chemical luciferin, light emitting chemical found in organisms generating bioluminescence.

Approximately forty alkaloids are known to have thiazole rings structure, for examples
- antibiotic coumermycine and
- acidomyicine,
- Anthelmintic micothiazole,
- Macroyclic alkaloids tantazole,
- Sisomycine to name some of them.

Thiazoles are used as non-steroidal anti-inflammatory drug Meloxicam. Other then medicinal importance, thiazoles are also used in dyes and fungicides like Thifluzamide, Tricyclazole and Thiabendazole as various agricultural pest control.

Thiazoles often used as fused with benzene ring, called benzothiazoles.

Examples of drugs containing benzothiazoles are riluzole and pramipexole. Some of the other occurrence of Benzothiazole subunit are anthraquinone dyes, like
- Algol Yellow GC,
- Algol Yellow 8,
- Indanthren Rubine B,
- Indanthrene Blue CLB,
- Indanthrene Blue CLG etc.
Over the years researchers have noticed interesting biological activities of thiazole derivatives. Thiazole core unit were found to show interesting biological activities such as

- Anti-anoxic,
- Allosteric
- Enhancer of adenosine A1 receptors,
- Mycobacterium tuberculosis methionine amino peptidases,
- Anti-helicobacter pylori (H-pylori) agent and
- Adenosine A2B receptor antagonist.

The importance of thiazole moiety is also evident from the fact that it is

- Ritonavir
- Abafungin and
- Bleomycin
- Tiazofurin

Thiazole derivatives displays, an anti retroviral drug Ritonavir, and antimicrobial drug Sulfathiazole.

An antifungal drug Abafugin,

an antineoplastic drug Tiazofurin.

Modification of thiazole ring has been proving a highly effective of improving potency and reducing toxicity.

In our endeavour to develop new routes to diversely substituted Imidazo-thiazole we have explored relatively unexplored Imidazo-thiazole scaffolds. Several novel derivatives of Imidazo-thiazole were prepared.
**PIPERIDINE:**

Piperidine is six member organic nitrogen heterocyclic. The name Piperidine comes from Latin word Piper means pepper. It is widely used building block in the field of pharmaceutical as well as other area of chemical application.

Piperidine has been obtained from black pepper. Piperidine motif is part of several natural alkaloids, like Pipeline responsible for spicy taste of pepper. Fire ant toxin solenopsin which inhibits angiogenesis.

Anabasine of the tree Tobacco which is used as Lobe line of Indian tobacco, which is used for the treatment of drug addiction such as addiction to alcohol, cocaine and amphetamines.

Piperidine derivatives are very common of pharmaceutical as well as fine chemicals. Several compound of medicinal application contains Piperidine motieff, some of the examples are
• Nootropics
• pipradrol and desoxypipradrol.
• Vasodilators.
• Narcoleptics (Antipsychotics).
• risperidone,
• thioridazine,
• haloperidol,
• droperidol
• and mesoridazine
• Opioids.
• Pethidine (Meperidine) and lope amide
• Psychochemical compounds.
• N-methyl-3-piperidyl benzoate (JB-336).
  So piperidine is yet another important structural residue of heterocyclic nature.
  Piperidine is also commonly used in chemical degradation reactions, such as the sequencing of DNAs.

CARBOHYDRAZIDE :
Carbohydrazide, also known as amide of carboxylic acid is another common feature pharmacologically active compounds, General structure of Carbohydrazide is as below.

\[
\text{H}_2\text{N}\text{NH}\text{NH}_2\text{NH}_2\text{NH}_2\text{O}
\]

Carbohydrazide are mainly prepared by coupling of carboxylic acid with amino acids. Many state-of-the-science methodologies are available in literature for preparation of carboxamide.
Carbohydrazide or in other words amide, Nearly all known enzymes are protein
1. Antifungal,
2. Antiviral,
3. Anti-inflammatory-analgesic,
4. Anti-tuberculosis,
5. Anticancer,
Respiratory analeptic activities and Carboxamide of amino acid are of particular interest to researchers as it shows wide range of pharmacological activities like antibacterial, anticancer, anti-inflammatory, anti HIV etc.

For very purpose we have used in our study carboxamide as main coupling entity for developing different derivatives of heterocyclic compounds.

**PHTHALIMIDE**
Phthalimide is organic compound derived mainly from phthalic anhydride. Used mainly as precursor to other organic compounds.

![Phthalimide](image)

Phthalimide is precursor to some well known compound of commercial interest are anthranilic acid and saccharin.

Below are the two phthalimide moieties structure for reference.

![Saccharin](image)

![Anthranilic acid](image)
Phthalimide though not found in natural products, has gained importance in drug development as a building block for pharmaceutical as well as other products of commercial interest. Some other synthetically equivalent starting material to phthalimide used in pharmaceutical chemistry to get desired target structure or for ease of synthesis are phthalic acid, Mono or di-ester of phthalic acid and phthalic anhydride.

**AMMONIUM CARBOXYLATE/ CARBOHYDRAZIDE SALTS**

Drugs marketed today if assessed reveals that more than half of the drugs are administered in the form of salts, also termed as pharmaceutical salts. These are ionisable drugs those have been combined with counter ions to form Pharmaceutical salts. Salt formation is achieved by neutralization of parent drug molecule with an acid or base.

Today’s need to develop drugs with more potency and lower toxicity or side effect as well as development of drugs for un-curable ailments has pushed researcher to explore more complex scaffold or scaffolds which are relatively un-explored till now for potential drug candidates.

As researcher tries to discover newer drugs for non-curable ailments as well as drugs with higher activity and lower toxicity, novel moieties are being discovered and tried for their biological activity.

These attempts have many times resulted in the drug candidates with very limited physicochemical property favourable for a potential drug. Solubility of the drug is one of the prominent properties for drug candidates.

Solubility of drug particularly in water is one of the key physicochemical property of drug and this is evident from the fact that almost half the drugs being administered today is in their salt forms, as solubility of salts are better compared to their free amines or carboxylic acids.

Solubility of drug has direct impact on drugs bioavailability and hence salt formation has become one of the significant aspects in drug development.

Researcher has applied several strategies to overcome several physicochemical limitations of drug candidates,

1. One of the commonly applied one is derivatization of the scaffold,
2. Apart from this the other common strategy applied to overcome physicochemical constraints of drug candidate is salt formation.
Drug candidate having some undesired features are also overcome by applying this simple technique of salt formation.

Converting a drug candidate into its salt may change several key properties to its optimal level,

Some of the anticipated changes are higher chemical stability,

Better administratibility as well as manipulate drug candidates other pharmacokinetic profile.

For these reasons salt formation or salt selection of drug candidate has become a common practice during drug developments, and in many cases the salt of the parent molecule has displayed preferential properties necessary for potential drug molecule.

As a result more and more drugs are produced in salt form, not only that more than one salt forms of a single parent molecules are being explored as potential drugs candidates and as a result many drugs are found administered in their multiple salt forms.

However examples are also found where different salt of parent drug molecule in not therapeutically equivalent.

Literature reveals that amine drugs are mostly applied as hydrochloride salt, apart from that other salts applied are

- Sulphate,
- Oxalate,
- Acetate etc.

Whereas carboxylic acid drugs are applied as sodium, potassium, calcium and ammonium as well as quaternary ammonium salt of various organic bases like

- Ammonia,
- Morph line,
- Lysine ,
- Môn ethanolamine,
- Illumine,
- Benzyl amine,
- Diethyl amine etc.
Some of the drugs marketed in their salt forms. Below are the mention here some examples of API with their role.

1. Atorvastatin calcium a lipid lowering agent,
2. Clorazepate dipotassium a tranquilizer,
3. Montelukast sodium a leukotriene receptor antagonist (LTRA).

Drugs being administered as their ammonium salt are Ammonium salt of Acetoxolone an ant-ulcerative and Flugenamic acid an anti-inflammatory drug, and quaternary ammonium salts are Morph line salt of

Following are the examples of quaternary ammonium salts.

a. Acediasulfone an antibacterial drug,
   b. Lysine salt of Clonixin an analgesic,
   c. Diethylamide salt of Diclofenac,
   d. Anti-inflammatory drug,
   e. Illumine salt of Flunixin,
   f. Anti-inflammatory drug,

CONCEPT OF SALTFORMATION
When a parent drug candidate counter ion results in formation of salt, in several cases simultaneously resulting in the crystallization of the desired pharmaceutical salt.

“TO LEAD OF SALT FORMATION IN DRUG DESIGN:
Salt of drug candidates may have not only that the selection of counter ions used also affects the pharmaceutical properties of drug and could render significant advantage towards its production and formulation. Some of the key advantages of salt formation are listed as below.

- Improved efficacy.
- Enhanced permeability.
- Optimized solubility and dissolution.
- Controlled release.
- Target specific delivery.
- Improved thermal stability.
- Improved photo stability.
- Improved hydrolytic property.
Lower hygroscopicity.
Better taste (Improved patient acceptability).
Reduced pain during administration (Injection).
Optimum melting (Resulting in ease of handling and formulation).
Ease of purification, handling and processing.
Improved compressibility.
Extended “IP rights.

CRITERIA USED FOR SELECTION OF PHARMACEUTICAL DRUG
There are certain criteria observed during selection of salt against its parent as potential drug candidate.
1. Solubility in water at various pH values.
2. Degree of crystallinity.
3. Lower hygroscopicity.
4. Optimal chemical and solid state stability.
   A deficiency in any of the above criteria reduces the chance of drug candidate being consider for further development.
In addition of the above criteria certain other factors which influences the selection of pharmaceutical salt as potential drug candidate are

1. Polymorphic variability (i.e. Reduced number or absence of polymorphic form).
2. Ease of synthesis and formulation.
   In addition to these some other factors considered during selection of salt based on their intended application are,
1. Acidity or basicity of parent drug and counter ion.
2. Route of administration.
3. Intended dosage form.
Due to their anticipated pharmacological profile, hydrochloride and maleate salts are preferred in solid dosage forms while hydrochloride and maleate are preferred for solution dose or injectable.

Relatively large insoluble counter ions like ebonite etiolate and tosylate are preferred for formulation of suspension. The free base is preferred as suppositories formulation.

Selection of large counter ion like tosylate may further complicate formulation process with high dosage while the same is acceptable with low dose formulations.

Hydrochloride and sodium salt are preferred for immediate release of drugs while slow release is administered preferably with relatively large of insoluble counter ions.

Sodium salts are not preferred for anti-hypertensive and anti-diabetic drugs due to restricted intake of sodium.

Regulatory restrictions or expectations also need to be applied when counter ions with known route cause of drug substance. Sometimes use of certain salt forms are restricted.

The preparation of stable salt may not be feasible due to low acidity or basicity of parent compounds or for other reasons like sterically hindered salt forming site or resulting salt may have some undesired characteristics compared to parent drug candidate.

The key development projects assigned to the formulation development, overall all phases of the projects from formulation development to requirement of registration and commercially launching. Capability of strong management to achieve the target.

End to end responsible for developing products developed to the industry. To fulfilled the customer requirements.

Accountability for projects deliverables, contract negotiation, and management of budget is also considerations in this section.

Interface all pharmaceutical projects like API or formulations starting with scope definition, formulation development, bioequivalence study, process design, study of stability tech transfer facility, validation batches of API and final drug. Build up of regulatory requirements or submission as their formats.
Elemental impurities also studied in final drug substance.
Possibilities of elemental impurities are mention below during preparation of drug substance.

➤ From raw materials to consumed during process.
➤ From equipment facility to make final API.
➤ Some time in drying oven its come from vacuum.
➤ During analysis its may contaminated.
➤ During product isolation.
➤ During more time holding final product.
➤ Chemist was used during processing ornamentals, some time he may forget.
➤ From excipients elemental impurities may contaminated.
➤ Material scrapping its should may contaminated.

Above possibility to avoid final drug substance IS analysis by all elemental impurities by daily dose concentrations.

Genotoxic impurities also most important part to control the final API. Fallowing precaution is to be taken to avid the genotoxic impurities.

• To avoid the carcinogenic material during processing.
• To avoid the genotoxic or carcinogenic reagent during manufacturing.
• To avoid the ligand moiety during route selection.
• To avoid amine and chloro compounds during process.
• To avoid aldehyde or ketone solvents with acidic conditions.
• Complete control to API.

Acetaminophen → Hydrolysis → 4-Aminophenol

1. Information about drug substance
2. Literature and patent references
3. Synthetic scheme
4. List of Raw materials
5. Process flow diagram
6. Laboratory procedures of synthesis
   a. Step 1 : Aldol Condensation
   b. Step 2 : Hydrogenation
c. Step 3: Crystallization

d. Preparation of key raw material

e. Synthetic scheme

f. List of raw materials

g. Process flow charts

h. Laboratory procedure of synthesis

7. List of critical parameters

8. Scale up recommendation(s).

9. Purification methods for the crude product (Reprocessing)

10. Impurity profile

a. Impurity 1:

b. 2:

c. 3

d. 4:

e. 5:

f. 6:

11. List of used solvents

12. Product description

a. Polymorphism,

b. Isomerism,

c. Solubility,

d. Characterization IR, NMR, MS, DSC, XRPD

13. Packaging and storage


15. Analytical methods for IPC, raw material, intermediate and final product.

MSDS: Intermediates and Key raw materials
1. **Scale up recommendation**

   **Examples:**

   a. **Stage 1 : Aldol condensation**
      
      The stage is envisaged to be having no much effect of scale on product quality, and hence except the effect of extended time requirement for the operations, no other specific recommendations are expected.

   b. **Stage 2 : Hydrogenation**
      
      The hydrogenation step involves reduction using hydrogen gas at low pressure and temperature. Though the reaction is expected to be smooth with hydrogen bubbling with longer reaction time, on higher scale flow of hydrogen needs to be adjusted by carrying out reaction.

   c. **Stage 3 : Crystallization**
      
      Carrying out crystallization at higher scale will need efficient stirring as the mass is heterogeneous in nature else the formation of product of desired physical property may take longer time then expected.

**DISADVANTAGES OF SALT FORMATION**

Though there are several advantages associated with salt formation, there are some disadvantages if due care is not taken in selection and approach in salt selection.

1. Requirement of higher dose size, as percentage of actual active drug content decreases.
2. Requirement of higher volume may lead to problems in tableting, or capsule filling.
3. Resulting in variation in pharmaceutical property of drug inconsistent of polymorph.
4. Reduced dissolution rate for HCl salt in gastric fluid due to precipitation of free acid of base.
5. Corrosiveness of salts resulting in tableting problems.
7. Requirement of additional synthetic steps during synthesis of medicinal compound.
8. Physical changes of drug substances.
9. Kinetic energy of drug compounds.
10. Effect of temperature i.e. melting range of drug molecules.
11. The rates of chemical reactions.
12. Concentration variations.
13. Particle size
14. Dissociation constant
15. Dielectric constant
16. Partition coefficient
17. Hydrochloride impurities related to API
18. Different pH like acidic or basic
19. Hygroscopic nature of product
20. Water effect
21. Isotropic effect
22. Derivatized method
23. Capacity of water absorption
24. Granules of molecule.

**ANALYSIS OF SALTS**

Once the pharmaceutical salt is formed it requires to be assessed for its identity, quality and phase homogeneity.

Several methods are employed for assessing formation and quality of pharmaceutical salt. Some of the prominent methods applied are described below.

1. Elemental analysis: Applied for evaluating formation salt as well as confirming their stoichiometry.
2. FTIR Spectroscopy: Proving identity of salt form and gives insight in formation of salt and their site of salt formation when more than one site is available for salt formation.
3. Differential scanning calorimetry and
4. Thermal gravimetric analysis and provides crystallinity.
5. Particle size analyzer: Analyse for particle size distribution.
7. Single crystal PXRD: Analysis of Polymorphic structure
8. and crystallographic information.
9. In vitro Dissolution study: Analysis of intrinsic dissolution rate at different pH.
10. Saturated salt solution: Analysis of hygroscopicity at different relative humidity.
13. Thermo-Gravimetric mass spectroscopy:
Elaboration of degradation mechanism and identification of solvates.

14. Thermo-Gravimetric infra-red spectroscopy:
   Thermal decomposition and kinetics of decomposition.

15. High performance liquid chromatography:
   Salt formation, stoichiometry, purity and polarity.

16. Nuclear Magnetic Resonant:
   Salt formation,
   Stoichiometry and
   purity.

**SELECTION OF SALT**

Different salts of drug candidates are biopharmaceutical properties to select most suitable salt for given application. The properties which generally assessed apart from drugs specific property are as below.

Due to their anticipated pharmacological profile, hydrochloride and maleate salts are preferred in solid dosage forms while hydrochloride and mesylate are preferred for solution dose or injectable.

Relatively large insoluble counter ions like

- Embonate,
- Esteolate and
- Tosylate

are preferred for formulation of suspension. The free base are preferred as suppositories formulation.

Selection of large counter ion like tosylate may further complicate formulation process with high dosage while the same is satisfactory with low dose formulations.

Hydrochloride and sodium salt are ideal for instant release of drugs while slow release is administered preferably with reasonably large of insoluble counter ions. Sodium salts are not chosen for anti-hypertensive and anti-diabetic drugs due to restricted intake of sodium.

Regulatory limits also requirements to be applied when the selected salt form have potential poor safety implications as well as for counter ions. Sometimes use of certain salt forms are restricted Hydrochloride form.

Tosylate form

Tartarate form
CRYSTALLINITY
Crystalline is one of the key and the first property of the salt being evaluated. The salt should be more crystalline compared to parent compound so that it could be more stable during
✓ handling and
✓ transportation,
✓ as crystalline nature is generally more stable in comparison to any other forms.

Seeking challenging assignment in the field of R & D wherein we can contribute substantially toward the development of innovative and technologically advanced process of
✓ API,
✓ Intermediates,
✓ speciality chemicals,
✓ Purine derivatives, etc.

A skilled and result oriented professional in research ore activities like
basic research,
development of non infringing,
cost effective
and safe processes for APIs,
fine chemicals,
speciality chemicals,
agrochemicals etc.

HYGROSCOPICITY AND SOLUBILITY
Once the salt have shown acceptable crystalline it is evaluated for hygroscopic nature. Hygroscopicity of the salt form should be such that, specifically conditions described by ICH guidelines for stability study of the drugs substance and drug product.
The salt form found suitable in this condition is then evaluated for their solubility at various pH conditions.
**STABILITY**

If hygroscopicity of the salt form is acceptable then it is tested for their physicochemical and chemical stability which also includes

- Thermal and
- Photochemical stability,
- Polymorphic stability

its compatibility with probable excipients based on route of administration.

In stability different condition are available in pharmaceutical drug substance.

Below are the following conditions applicable for drug molecule.

- At 25 to 30°C
- At 40±2°C
- At 2 to 8°C

**POLYMORPHIC CHARACTERIZATION**

Salt with acceptable stability is evaluated for possible changes of properties due to change of polymorphs.

Salts with less number of polymorphs are more suitable as their physical properties are predictable during operations due to presence of single polymorph.

Polymorph is also depends on following parameters on laboratory scale and manufacturing scale.

- Stirring pattern
- Mixture of solvents
- Temperature
- Particle size of material
- Solubility
- Melting range
PROCESS CONTROL AND FEASIBILITY STUDY

Salt from which has acceptable polymorphism is tested for process ability, economic feasibility and process control for better handling during manufacturing and formulation. An best possible point from the wet granulation DOE was select from the data available and was produced repeatedly to study drying.

Drying was controlled using a hybrid method that combine first principles

- modeling with empirical measurements,
- process models,
- and real time data management.

**Summary of Drying Granules Specs**

- Residual moisture allows for more efficient drying times and higher mass yield.
- Residual moisture results in larger particles, but wider PS distributions.
- Residual moisture results in poorer flow properties.
- The EEF factor does not have a clear relationship with flow properties.
  Higher bulk densities show better flow properties.
- High temperature drying does not result in more professional drying, but it does show increases in lactam formation.
- A trade off must made for the End Moisture Target
  Residual moisture in the granules results in poorer flow properties, but also results in harder tablets

Pharmaceutical Development & Product Lifecycle

Products Design & Development:

- Initial Scoping
- Product Characterization
- Product Optimization

**Classification of impurities**

1. Organic impurities
2. Inorganic impurities
3. Residual solvents
Mass Balance Example.

\[
\begin{array}{c}
\text{Stage 1} \\
A \\
\text{Th. Yield (0.X w/w)} \\
\text{Ach. Yield} \\
\text{Stage 2} \\
B \\
\text{Th. Yield (0.X w/w)} \\
\text{Ach. Yield} \\
\text{Stage 3} \\
C \\
D \\
\text{Stage 4} \\
E
\end{array}
\]

**PHARMACODYNAMIC EVALUATION**

The salt which satisfy all the above property along with specification for its onset and duration of activity as well as pharmacological safety of the salt.

**CLINICAL TRIALS**

The salt which has acceptable properties as described above is then subjected to extensive long term (Temperature 25±2°C) toxicological study.

**PATENTABILITY**

Patentability is another aspects which plays a major role in salt selection, as salt with superior properties could be patented leading to a major economical benefit to the researcher.

Salt of a existing drug at times have better properties due to its crystalline nature and sometimes may result in its novel polymorphic form.

Salt of parent compound or newer salt of a existing drug may give advantage of newer route of administration which could be difficult with existing drug form due to its limited physicochemical properties.

One of the well known examples being diclofenac sodium earlier marketed by Ciba-Geigy as Voltaire, before the patent for Voltaire expires diclofenac diethylamide with superior skin penetration property was discovered and patented, which was more suitable for topical administration.
The decision to use a drug candidate as salt or free base or acid depends on various other merits such as pharmaceutical merits and commercial merits of these forms.

If the free base of acid are water soluble having high melting point then use of salt form generally may not give any substantial advantage.

Though various advantages associated with salt form against their free acid or base, preparation of salt is not always easy or even feasible sometimes.

The salt formed may have lower stability in its salt form compared to free drug. In such cases it would be more advisable to proceed with free acid or base.

The selection of parent compound of its salt sometimes may not be the ideal one from researchers point of view but it would be the most suited one as it has to satisfy various parameters during the process of drug development.

So at times selection or sacrifice of certain property for fulfilment of other more desired properties for the final application of the drug molecule.

In this study we have investigated biological application of ammonium salt of “1-[2-(2-tert-butylcarbamoyl-Benzoylamino)-Alkyl-Acyl]-Piperidine-4-CarboxylicAcid” derivatives.

The parent methyl ester derivatives 1-[2-(2-tert-butylcarbamoyl-Benzoylamino)-Alkyl-Acyl]-Piperidine-4-CarboxylicAcid have already demonstrated its biological potential as antibacterial and anti fungal agents.

**AIM OF THIS STUDY**

Considering all these important aspects of drug design, this study is aimed at developing novel potential drug candidates for various ailments with one or more of the above structural moieties.

The objective of this study is to lead a path for development of drug with better activity and lower toxicity as well as with enhanced desired physicochemical property.

Suitable of all activity of drug.
SAFETY INSTRUCTIONS FOR HIGH POTENT DRUG SUBSTANCES
All manufacturing chemists, analytical chemists and process development scientists must receive training for handling hazardous drug substances / cytotoxic drug substances safety, cleaning techniques for spills and using all equipments and personnel protective equipments (PPE) properly.

There must be established work practice related to both drug manipulation techniques and to general hygiene practice. Work place procedure must be developed for using and maintaining all equipments that functions to reduce hazardous exposure.

Work safe occupational health and safety regulation 6.52 states ,the manufacturing workers, who prepare or handling hazardous drug substances, including the name of the drug handled and when practicable, the number must be maintained for the duration of employment plus 10 years.

Acute exposures as a result of spill or other accident must be immediately reported to the manufacturing head / production head and occupational health and safety manager.

Potential hazard for workers and staff exposure:
Manufacturing chemists, workers, analytical chemists and process development scientists may be exposed to a drug substance throughout its life cycle from,
Manufacturing, development of process,
physical operation,
packing operation,
distribution and transportation.

Formal Experimental Design:
Its depends on quality and out-put of product.

Manufacturing process of API and formulated molecule.

Manufacturing of each batch prepared and issued to the manufacturing or production team. In manufacturing batch record mention details process of particular product and this record is varies organization.
Manufacturing having details of process and anyone having knowledge of operating, equipments can manufacture the product with the help of MBMR. (Master batch manufacturing records).

The production team is involved in batch manufacturing records carries out the process as per directions issued of MBMR. The readings and findings during the manufacturing process are entered into the MBMR and person signed or supervising the manufacturing at the completion of the batch.

The entries made in MBMR and signed or review by key personnel of manufacturing and quality assurance departments and further approved by senior level management. Only thereafter can the product manufactured be used consumption.

At the end of manufacturing process the authorized persons having signature logs and declared to the effect that product/batch was manufactured using the process/technology which was otherwise given by research and development scientist. Distillation app.

Quality:
Its desired or requirement drug properties, process fulfils requirements. Entire manufacturing process is depend with all operational details as well as operational parameters. The enable the product to be manufactured using technology, process or other quality parameters such as

- HPLC,
1.2.0 PROBLEM ON HAND

Researcher around the humanity is always in search for new drugs. There are many reasons for search of new drugs. The prime reason is the pathogen being targeted by a drug develops resistance to drug over a period of time.

So after a period of time a drug loses its activity adjacent to particular pathogens.

One of the other prime reason for developing drugs are rise of new ailments, due to various known and unknown factor various new ailments comes in to existence which needs to be cured. So in order to cure these new ailments drugs effective against these pathogen is being invested.

Apart from these two primary reasons, there are some other reasons for which drugs are being investigated, for example to minimize the side effect of existing drugs, which remained one of the key drivers for researcher to look for new drugs for existing ailments.
Apart from these reasons there are several other factors which compels researcher to develop new drugs such as

- **Economical reason**: Drugs which are not economical in availability to general population need to be replaced by newer economical drugs.
- **Patent rights**: Drugs covered under patent are not available to use and hence other substitute for same ailments are sought.
- **Drugs regime issue**: Some of the example where drug regime compel researcher to develop new drugs are dose size, very big dose size as well as very potent drugs with very low dose size pose problem in easy drug regime.
• **Drugs palatability:** Drugs palatability, such as test also drives researcher to develop newer alternative drugs for various ailments.

• **Physiological constraints:** Certain physiological constraints such as assimilation of drugs in metabolic system results in un-desired biological availability of drug and in order to overcome these problem also research develop new drugs.

These are the few indicative factors listed to highlight the importance of and justification for new drug development.

From the above factors it is quite evidence that there are always a need for development newer drugs with better pharmacological merits.

In order to contribute in these endeavours of developing new drugs, this study is aimed towards developing new biologically active moieties which would lead to or put a path for successful drug candidates.

### 1.3.0 RESEARCH OBJECTIVE

“Taking the various factors of drug design in to account and looking at importance and applicability of heterocyclic compounds, we undertook the synthesis of novel heterocyclic having base moiety

- phthalimide,
- Piperidine,
- Imidazo,
- thiazole as well as Imidazo-thiazole moieties bearing various substituent’s”.

The compounds formed during this study was characterized using various spectroscopic methods Such as

- Infrared Spectroscopy (IR),
- Mass spectroscopy (MS)
- Nuclear Magnetic Spectroscopy (NMR).
- Thin layer chromatography (TLC)
- Elemental analysis (CHN)
- Raman spectroscopy
- Diffraction chromatography (DSC)
- Melting point (m.p.)

Generally during research work we used easily available techniques like M.P.,
The compounds synthesised were evaluated for their biological activity, particularly for antibacterial and antifungal activity. The activity results were compared with an existing drugs as reference standard. More reliable and consistent processes (& product) Less failures, less reworks, less recalls Flexibility w.r.t. scale and equipment Better / faster Quality Systems Process Enhancement Opportunities

**The objective of this research work is summarized as below.**

- To synthesize various Piperidine, Phthalimide, Imidazole, Imidazo-thiazole derivatives and salt of ammonium carboxyl ate salts.
- To characterized compounds prepared using analytical technique, like Melting point, IR, 1H NMR, MASS and other relevant techniques.
- To study biological evaluation for -antibacterial, -antiviral, -antifungal activity using suitable method and suitable reference standard.
- To study of stability of compounds with different conditions or temperature.
- To discover relative risk levels at the beginning of product development
- To prioritize incomplete development resources
- To document the decision production process throughout development
- To review the needs of additional studies for scale up and technology transfer
- To identify correct specifications, cpp and manufacturing controls
- To cut variability of critical quality attributes
API process. Analytical technology includes following points.
sensible measurements during processing
important quality and performance attributes
rare and in-process materials
At-line, on-line or in-line measurements
Founded on “Process Understanding”
Opportunities for improvement

1.4.0 SCOPE OF RESEARCH WORK

“Based on the work carried out and observation made during this study we have to make following recommendation for future work.”

For all the moieties synthesised, other amino acid (proteogenic as well as non-proteogenic) derivatives could be prepared, characterized and their biological activity could be evaluated for achieving better biological activity.

Synthesised here is tested for antibacterial and antifungal activity in this study, these compounds can also be evaluated for other bacterial and fungal pathogens than the one used in this study.
✓ These compounds could also be evaluated for other biological activities like anti-cancer,
✓ antihypertensive,
✓ antithrombotic as well as treatment of
✓ allergies,
✓ hypertension,
✓ inflammation,
✓ HIV infections etc. as several other biologically active compounds having similar moieties studied here exhibits these activity.

Below is the list of research conditions required for research scientist in pharmaceutical industries.
✓ Possess sound knowledge of chemistry including various unit chemical processes.
✓ Exposure with cross functional teams in generic companies Can play important role in vertical Integration product development.
✓ Undergone training in polymorphism and crystallization.
✓ Expertize in Chiral chemistry especially in biotransformations using enzymes.
✓ Patent evaluation, claim interpretation and design strategy to make the process non-infringing.
✓ Exposure to various Intellectual Property issues related to infringement.
✓ Proficient in managing R&D overall activities including resource planning, budgeting, inter-departmental co-ordination, audit, compliance and GLP/ GMP inspections, developing SOPs and control procedures.
✓ Well versed with regulated market requirements including QbD for filing of Drug Master File.
✓ Efficient project implementations through micro planning and timeline monitoring.
✓ Team Development & Management through excellent Leadership skills.
✓ Excellent communication and presentation skills.

**API Research Development includes below listed points.**

- Project initiation, patent evaluation, design & development of route of synthesis.
- Process Development of APIs from lab scale to pilot plant scale.
- Documentation including Process Development Reports (PDR) and Technology Transfer Documents (TTD), DMF submission.
- Recruitment, Training and Orientation of research team.

**Highlights:**

- Built team and streamlined the project activities.
- Initiated and executed Para IV product on top priority for external customer.
- Filed DMFs for vertical Integration products for USA.
- Project selection, planning and execution.
- Process Development of APIs, intermediates from lab scale to plant scale.
- Documentation including Process Development Reports (PDR) and Technology Transfer Protocols.
- Process improvements in existing products towards safety and cost effectiveness.
- Defining project activity, timelines and monitor the project progress.
- Process optimization on laboratory and kilo scale.
- Budgeting of individual projects and Development Centre.
- Sourcing of key raw materials and intermediates.
- Drafting of patent applications in consultation with patent attorney.
- Interpretation of Route of Synthesis for non-infringement issues.
• Patent evaluation, claim interpretation and design strategy to make the process non-infringing.
• Coordinate in the development and manufacture of Active Pharmaceutical Ingredients through partner companies. Audited many Indian suppliers for ROS evaluation.
• Managing technical issues (stability, impurity profile etc) to assemble the data for regulatory submissions relating to Active Pharmaceutical Ingredients.
• Sourcing of Active Pharmaceutical Ingredients suitable for US and European markets.
• Process development (safe and cost effective) for generic products.
• Trouble-shooting various problems that arise in the production department.
• Documentation including Process Manuals, Standard Operating Procedures and Drug Master Files (process part & impurity profile only).
• Coordinate to identify the potential suppliers for intermediates and bulk drugs.
• Coordinate to identify partners for contract manufacturing and contract research projects
• Developed processes for various generic molecules
• Initiated and executed a NCE intermediate contract research project in India with a leading company
• Contributed in identifying potential suppliers for intermediates and bulk drugs Set up a process development laboratory and pilot plant.
• Literature search, design of experiments, synthesis, isolation and characterization of new molecules.
• Various projects including APIs, Agrochemicals, and Surfactants.
• Use of enzymes (lipases) in kinetic resolutions of various secondary alcohols.
Example for API Impurities

a. **Imp 1**: De-benzyl impurity

Structure:

![Structure of Imp 1](image)

Name: 5,6-dimethoxy-2-((piperidin-4-ylmethyl)-2,3-dihydro-1H-inden-1-one hydrochloride

(In USP Draft 2, Impurity 1: 2,3-Dihydro-5,6-dimethoxy-2-(4-piperidinyl)methylindan-1-one hydrochloride)

**Str.**:

![Structure of Imp 1](image)

5,6-dimethoxy-2-((pyridin-4-ylmethyl)-2,3-dihydro-1H-inden-1-one (In USP Draft 2, Impurity 2: 5,5,6-Dimethoxy-2-(4-pyridyl)methylindan-1-one)

![Structure of Imp 1](image)

1,1-Dimethoxy-2-4-[(5,6-dimethoxy-1-oxo-2,3-dihydro-1H-yl)inden-2-yl)methyl] piperidinum bromide.

Name: 1-Benzyl-4-[(5,6-dimethoxy-1H-yl)inden-2-yl)methyl] piperidine
hydrochloride.

Name: 1-Benzyl-4-[(5, 6-dimethoxy-2,3-dihydro-1\(H\)-inden-2-yl)methyl] piperidine hydrochloride

b. Alcohol imp. (Not reported in USP)

Sulfamate and Sulphate from Topiramate Extended release Capsules:
Chromatographic Conditions:
Column: Ion-Pac AS11-HC (4.3*250mm) and IonPac AG11-HC (4**50mm)
Eluent: KOH Concentration Gradient (Eluent Generator)
Flow Rate: 1.2 to 1.3 mL/min to 1.3
Injection Volume: 25µL
Suppressor: ASRS 300 4mmSuppressor with recycle Mode
Suppressor Current: 130mA
Diluent: Water
Standard Concentration: 5ppm of each Sulfamate and Sulphate
API Preparation: 6mg/mL
Placebo Preparation: 200mg/50mL --- sonicated for 20mins (observed particles are settled down in flask).
Sample Preparation: 300mg/50mL --- sonicated for 20mins (observed particles are settled down in flask).
7 Anions and Sulfamate Standard mix:
Six replicated injections of Mix Standard Sulfamate and Sulphate (5ppm)

Three replicated injections of API:
Three replicated injections of Placebo:

Overlay Chromatogram of Blank, Standard and API, Placebo:

Overlay Chromatogram of Placebo and Sample Passed through On Guard RP and 0.22µ PVDF filter:
Connected CRD 200 to remove Carbonate: Overlay Chromatogram of Mix Standard and Placebo, Sample (Initial Standard shown bit noisy because of stabilization).