A SYNOPSIS OF THE THESIS
TO BE SUBMITTED TO THE
INSTITUTE OF CHEMICAL TECHNOLOGY
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY IN SCIENCE
WITH SPECIALIZATION IN
ORGANIC CHEMISTRY

TITLE OF THE THESIS : Development and Application of New Methodologies for Synthesis of Bioactive Molecules

NAME OF THE CANDIDATE : Harshal Madhukar Bachhav

NAME AND DESIGNATION OF THE RESEARCH GUIDE : Dr. V. N. Telvekar
Lecturer in Pharmaceutical Chemistry,
Institute of Chemical Technology

PLACE OF THE RESEARCH : Department of Pharmaceutical Sciences and Technology,
(Institute of Chemical Technology)
Matunga, Mumbai- 400 019


DATE OF SUBMISSION OF THE SYNOPSIS :

SIGNATURE OF THE CANDIDATE : (Harshal Madhukar Bachhav)

SIGNATURE OF THE GUIDE : (Dr. V. N. Telvekar)
Chapter 1: Development of Process chemistry of Indole

Indole is the commonly used name for the benzopyrrole ring system,\(^1,^2\) consisting of a benzene ring fused to the 2,3-position of a pyrrole ring. The indole ring system is found in many natural products, pharmaceutical agents and polymer. The interest and development in indole chemistry started in mid-nineteenth century, with intensive studies of indigo, a violet-blue dye from India, originally derived from \textit{Indigofera species}. Perhaps the most widely used route is the Fischer indole synthesis,\(^3\) which also can be used on a large scale, e.g., for production of the stabilizer 2-phenlindole in manufacture of PVC.\(^4,^5\)

The indole ring system is one of the most prevalent structural motifs found in biologically active compounds of both natural and synthetic origin. For example, the neurotransmitter serotonin (5-HT), the semisynthetic hallucinogen lysergic acid diethylamide (LSD), and the alkaloid strychnine, as well as the pharmaceuticals ondansetron (zofran),\(^6\) sumatriptan (imigran),\(^7\) or tadalafil (cialis),\(^8\) are indole derivatives. Among various indole derivatives, indole 3-acetic acid display diverse biological as well as pharmacological activities and are useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome. Thus, the development of high-throughput methods for the synthesis of indole and indole 3-acetic acid remains a topic of paramount importance in view of their versatile biological and pharmacological activities.

\textbf{Scheme 1}
Chapter 2: A Novel Application of (Diacetoxyiodo)benzene for Carbon–Carbon Cleavage of Aryl Diamines and Synthesis of Quinones

(Diacetoxyiodo)benzene is a hypervalent iodine reagent which is readily available and frequently used in several oxidative transformation.\textsuperscript{9,10} During the course of our studies, we found that treatment of (diacetoxyiodo)benzene to 1,2-diaminobenzene in acetone resulted into formation of cis, cis-muconitrile\textsuperscript{11} by oxidative cleavage of carbon-carbon bond. It was interesting to know that under these reaction conditions 1,3-diaminobenzene was unaffected while 1,4-diaminobenzene showed unexpected results by formation of benzoquinone rather than expected fumaronitrile and provided an interesting route to quinones.\textsuperscript{12} The advantages of this protocol are shorter reaction times and mild reaction conditions to obtain moderate to good yields. And successfully applied this method for the synthesis of muconic acid, adipic acid and quinones as well as its derivatives.
**Application: Application of Muconitrile (Section I)**

a) Synthesis of Muconic acid.

![Chemical Reaction](attachment:muconitrile.png)

Application of muconic acid in the Total Synthesis of Deoxyjirinomycin.

![Chemical Reaction](attachment:deoxyjirinomycin.png)

b) Synthesis of adipic acid.

![Chemical Reaction](attachment:adipic_acid.png)

Applications of adipic acid

![Chemical Structures](attachment:applications.png)
Chapter 3: Efficient Synthesis of Bis(4-dimethaminophenyl) arylmethanes and Bis(4-dimethaminophenyl)alkanes using Iodine Reagent.

Diaminotriphenylmethane (DTM) compounds have received considerable attention because of their applications in various displays such as in the biological and analytical fields where these compounds are used as dyes for detection of hydrogen peroxide in medical diagnostic kits and biotechnology process control.\textsuperscript{13} Where as in the medicinal field these compounds are used as antifungal\textsuperscript{14} anti-tubercular,\textsuperscript{15} anti-infective, and anti-
microbial agents.\(^{16}\) Different methods have been reported for the preparation of the 4,4’-diaminotriphenylmethane compounds such as from 4,4’-diaminodiphenylmethanes and amines, by condensation of amines and anilines in acid medium, using zeolites, metal catalyst or clay-mediated by microwave.\(^{17}\) Most of these protocols, however, suffer from drawbacks, such as long reaction times and use of corrosive acids or toxic metallic compounds that result in generation of waste streams, complicated workup procedures, by-products and consequently, low yields. Thus despite of the availability of variety of well known methods, the development of new general synthetic protocols for DTM is still an active field.

A first novel synthetic utility of NaICl\(_2\) for preparation of bis(4-dimethaminophenyl)arylmethanes and bis(4-dimethaminophenyl)alkanes is described. In the presence of aqueous solution of NaICl\(_2\), the reaction of arenes with aromatic aldehydes gives corresponding triarylmethane derivatives regioselectively, in moderate to good yields. The method is also useful for the preparation of diarylalkane derivatives by using aliphatic aldehydes.
Chapter 4: Efficient Protocol for the Synthesis of Quinoxaline, Benzoxazole and Benzimidazole Derivatives Using Glycerol as Green Solvent.

Solvents are used daily in numerous industrial processes as reaction medium, in separation procedures, and as diluters. As solvents are responsible for a large part of the waste and pollution generated by chemical processes, a key factor to enabling a sustainable chemical process is solvent selection. Due to environmental concerns, safety considerations, reduction of costs, and the simplicity of the process, reactions using green solvents have drawn great attention in recent years.

The quinoxaline, benzoxazoles and benzimidazole, scaffold can be found in a number of biologically active compounds especially anti-viral, anti-bacterial, anti-inflammatory, anti-protozoal, anti-cancer (colon cancer therapies), anti-depressant, anti-HIV, and as kinase inhibitors. They are also used in the agricultural field as fungicides, herbicides, and insecticides. Quinoxaline moieties are present in the structure of various antibiotics such as echinomycin, levomycin and actinoleutin, which are known to inhibit the growth of gram positive bacteria and they are active against various transplantable tumors.

Scheme 1

Scheme 2
A straightforward, efficient, and more sustainable catalyst free method has been developed for the synthesis of quinoxaline, benzoazole and benzimidazole ring system in glycerol to achieve yields that were comparable to, or better than, those in conventional media. It is noteworthy that the reaction was exclusively carried out in glycerol:water system, rendering the methodology highly valuable from both environmental and economical points of view.

**Chapter 5: Synthesis of 2-aminobenzthiazole.**

The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry. These structures represent a class of molecules capable of binding to multiple receptors with high affinity. The exploitation of these molecules enables the medicinal chemist to rapidly discover biologically active compounds across a wide range of therapeutic areas on a reasonable time scale. 2-Arylbenzothiazoles are an important class of bicyclic privileged substructures owing to their potent utility as imaging agents for β-amyloid, antitumor agents, calcium channel antagonists, antituberculotics, antiparasitics, chemiluminescent agents, and also as photosensitizers.\(^{22-24}\) Two common approaches are applied for the construction of 2-substituted benzothiazoles. The first approach used various oxidants, including Jacobson’s and Hugershoff’s methods via oxidative cyclization of thiobenzanilides.\(^{25}\) However, using stoichiometric or excess amounts of toxic reagents, such as bromine or metals, is a major
drawback of these methods, and low functional group tolerance also have disadvantages. Synthesized via palladium- or copper-catalyzed cyclization of ortho-halobenzo-thioureas\textsuperscript{26} or directly functionalized aromatic C-H bonds to construct C-S bonds,\textsuperscript{27} provided another access to benzothiazoles. However, these reactions still require large amount of catalyst (typically 1 mol % to 20 mol %) to promote the transformation efficiently. Very recently, the intramolecular nucleophilic aromatic substitution of \textit{o}-halothiobenzanilides (INASOB) promoted by a base was reported by some groups.\textsuperscript{28} However, these catalyst-free methods could produce the 2-(alkyl)arylbenzothiazoles only. So there is an urgent need to develop less expensive and easily available catalyst systems for these important heterocycles.

So, we have developed an efficient method for synthesis of 2-aminobenzthhizole.

**Scheme: 1**

**Application:**

a) **Synthesis of Luciferine**

b) **Synthesis of Riluzol (Drug)**
References:


