ISBN:978-93-91768-59-1

# Advances in Chemical Science
# Volume I

**Editors**

**Dr. Dhondiram T. Sakhare** **Dr. Rupali A. Gulalkari**

**Dr. Pralhad V. Rege**

Bhumi Publishing

First Edition: 2022

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Bhumi Publishing

2022

*First Edition: 2022*

*ISBN:* **978-93-91768-59-1**




Published by:

Bhumi Publishing,

Nigave Khalasa, Kolhapur 416207, Maharashtra, India

Website: www.bhumipublishing.com

E-mail: bhumipublishing@gmail.com

Book Available online at:

https://www.bhumipublishing.com/books/

# *PREFACE*

*We are delighted to publish our book entitled* ***"Advances in Chemical Science Volume I"****. This book is the compilation of esteemed articles of acknowledged experts in the fields of Chemical Science, and allied areas.*

*This book is published in the hopes of sharing the excitement found in the research and study of chemical science. Chemical science can help us unlock the mysteries of our universe, but beyond that, conquering it can be personally satisfying. We developed this digital book with the goal of helping people achieve that feeling of accomplishment.*

*The articles in the book have been contributed by eminent scientists, academicians. Our special thanks and appreciation goes to experts and research workers whose contributions have enriched this book. We thank our publisher Bhumi Publishing, India for taking pains in bringing out the book.*

*Finally, we will always remain a debtor to all our well-wishers for their blessings, without which this book would not have come into existence.*

***- Editors***

***Advances in Chemical Science Volume I***

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# NUCLEAR MAGNETIC RESONANCE STUDIES OF TI(IV), ZR(IV), CD(II) AND HG(II) COMPLEXES WITH 2-[(1H-INDOL-3-YL METHYLENE) AMINO]-4-METHYL-PHENOL (SCHIFF BASE) LIGAND

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**Abstract:**

2-[(1H-Indol-3-yl methylene) amino]-4-methyl-phenol(AMPIA) was used to synthesize Ti(IV), Zr(IV), Cd(II) and Hg(II) complexes. Metal complexes were characterized by elemental analysis, UV-visible, Infra-red, Nuclear magnetic resonance analysis.

**Keywords:** Nuclear MagneticResonance, (AMPIA), Ti(IV), Zr(IV), Cd(II) and Hg(II) complexes.

**Introduction:**

Indole derivatives and their metal complexes have received much attention due to their wide application in physiology[1] and pharmacology[2]. They constitute an important class of compounds possessing antibacterial[3], anticonvulsant[4] and antihypertensive activity. These observation led to the conception that Schiff bases of indole 3-aldehyde would possess potential antimicrobial properties. Indole and its derivatives are widely used in making perfumes, dyes, agrochemicals and medicines. Schiff bases are usually, synthesized from the condensation of primary amines and active carbonyl group[5].Schiff bases are characterized by the –N=CH- (imines) group which is important for elucidating the mechanism of transamination and racemization reactions in biological systems and are also known to have biological activities such as antimicrobial[6], antifungal[7], antitumor[8] and herbicidal[9-12] activity.Review of literature did not reveal synthesis and characterization to explore the coordination chemistry of transition metal complexes with 2-[(1H-Indol-3-yl methylene) amino]-4-methyl-phenol (Schiff base) ligand.

This has prompted us to synthesize and structural studies of metal complexes involving this newly synthesized ligand. This compound 2-[(1H-Indol-3-yl methylene) amino]-4-methyl-phenol here after referred to as AMPIA is a hetero cyclic ligand having phenolic-OH,

azomethine and secondary amine donor atoms. After observing the structure of ligand it indicates, it have coordination tendency.

**Experimental:**

All chemical and solvents are used AR grade. Metal complexes, are synthesized by adding metal salt solution in appropriate solvent to the solution of the ligand. The pH of reaction mixture is adjusted about 6.9 to 7.2 by adding alcoholic ammonia drop wise. The resulting mixture was refluxed, for five to six hours on water bath and cooled. Precipitate of metal complexes was obtained. It is filtered, washed & dried in vacuum desiccators. Preparation method was given in details in published papers.

**Result and Discussion:**

The $^{1}$HNMR spectrum of the ligand AMPIA (Fig. 2.11) exhibits signals at δ 2.31 (S, 3H) for methyl proton, δ 6.80-8.27 (m, 8H) due to Ar-H, δ 8.96 ppm (S, 1H) for azomethine proton[13], δ 10.1 ppm (S, 1H) NH of Indole ring[14] and δ 12.10 (S, 1H) due to Ar-OH.

In Ti (IV), Zr (IV), Cd (II) and Hg (II) complexes phenolic OH peak at δ 12.10 ppm is disappeared due to attributed deprotonation and involvement in bonding[15].A signal corresponding to azomethine in free ligand, is shifted to down field regions may be attributed to corresponding effect of the nitrogen atoms, which results on deshielding of protons attached to it.

The entire metal complexes (Fig.2,3,4 and 5) signal corresponding to NH of indole ring, is shifted to down field at δ 10.20, δ 10.25, δ 10.28 and δ 10.29 respectively. A new peak observed at δ 2.0 ppm due to coordinated water molecule in only Cd(II) complex[16]. Hence, in AMPIA complexes new bonds may have formed by the involvement of azomethine, -NH group of Indole ring and phenolic oxygen as well as coordinated water.(Fig.1)

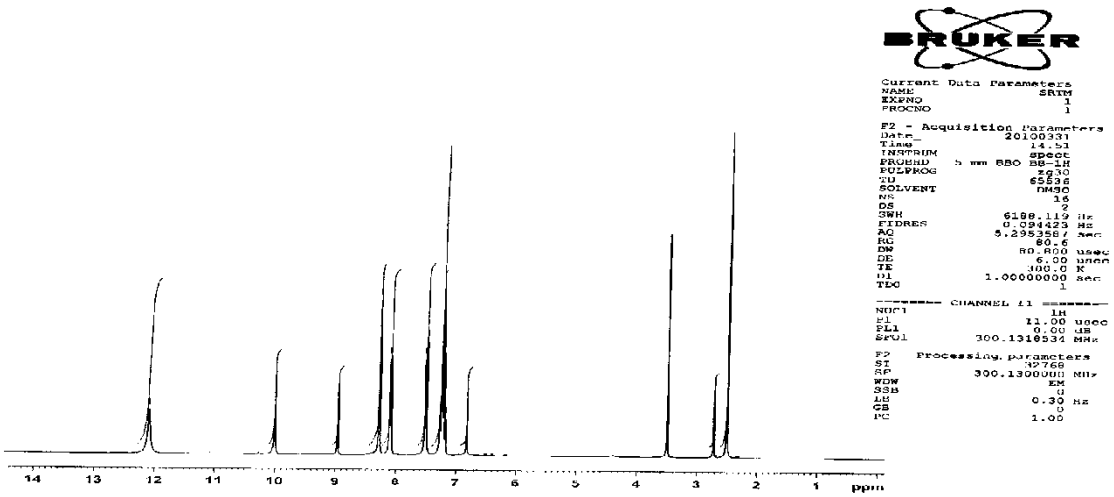


**Figure 1: NMR spectrum of ligand AMPIA**

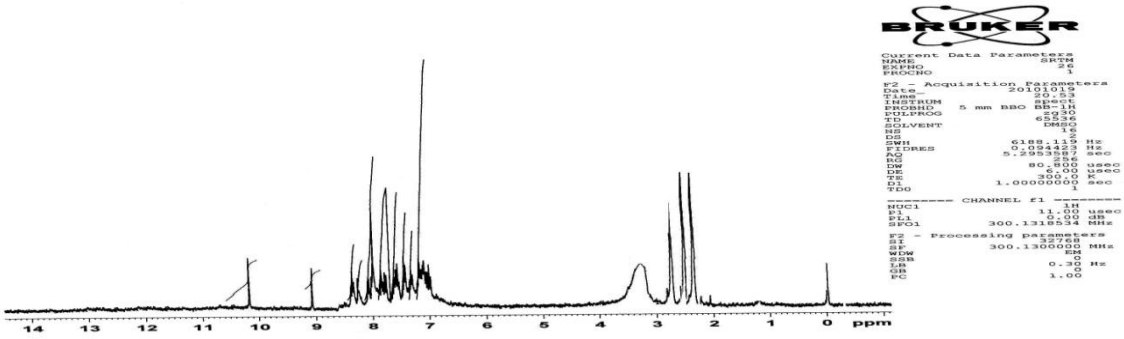


**Figure 2: NMR spectrum of complex $[Ti(AMPIA)_2]Cl_2$**

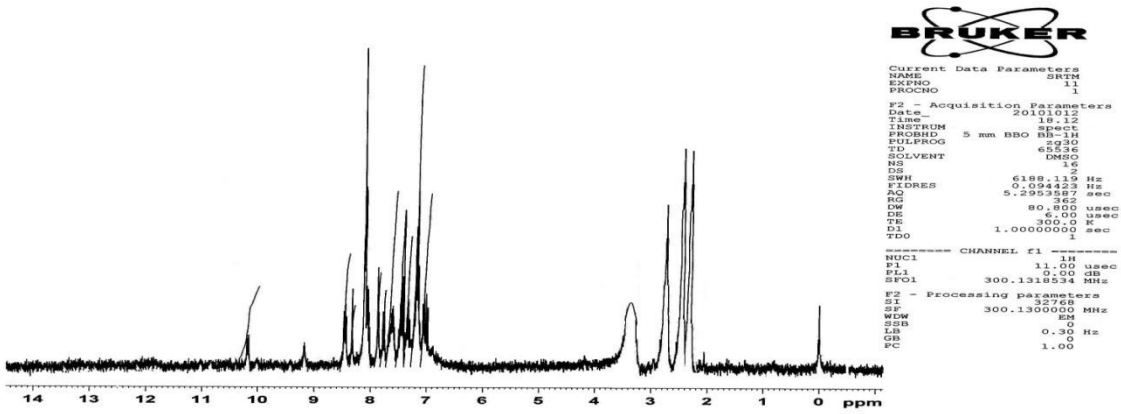


**Figure 3: NMR spectrum of complex $[Zr(AMPIA)_2]Cl_2.H_2O$**

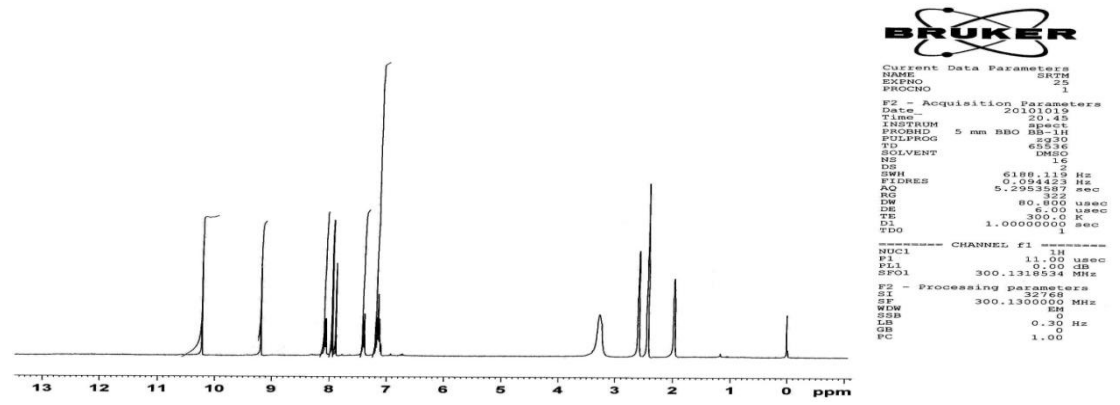


**Figure 4: NMR spectrum of complex $[Cd(AMPIA)H_2O]Cl.H_2O$**

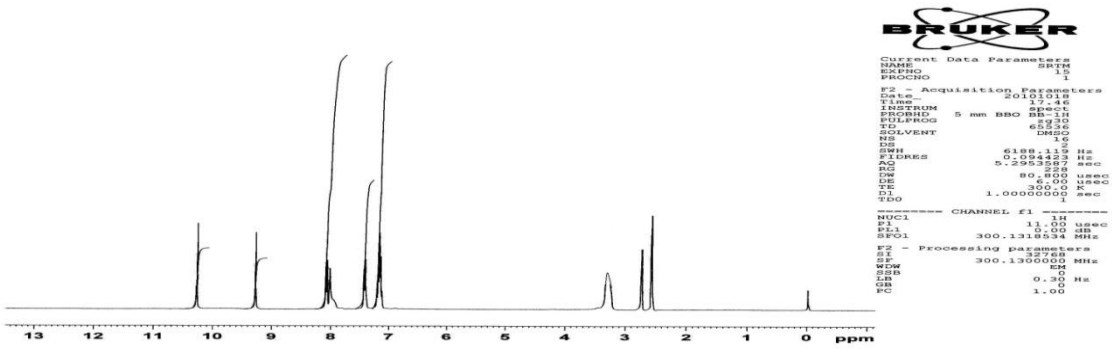


**Figure 5: NMR spectrum of complex $[Hg(AMPIA)Cl]H_2O$**

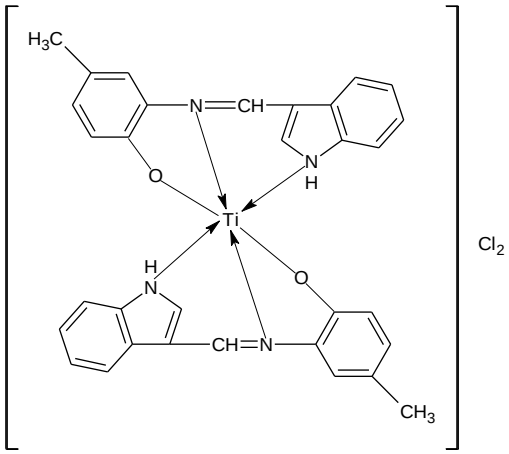


**Figure 2.1: Proposed structure of complex $[Ti(AMPIA)_2]Cl_2Zr\ (AMPIA)_2]Cl_2.H_2O$**

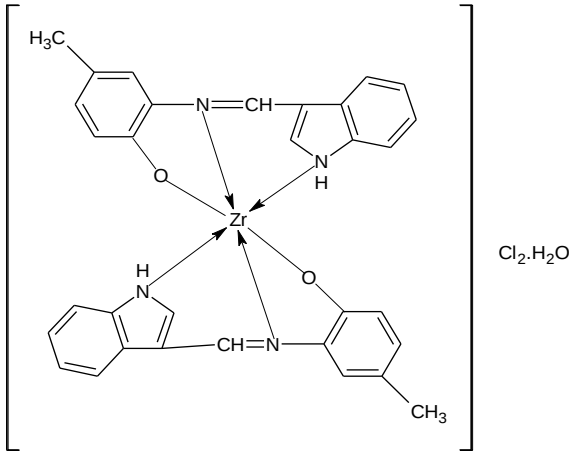


**Figure 2.2: Proposed structure of complex**

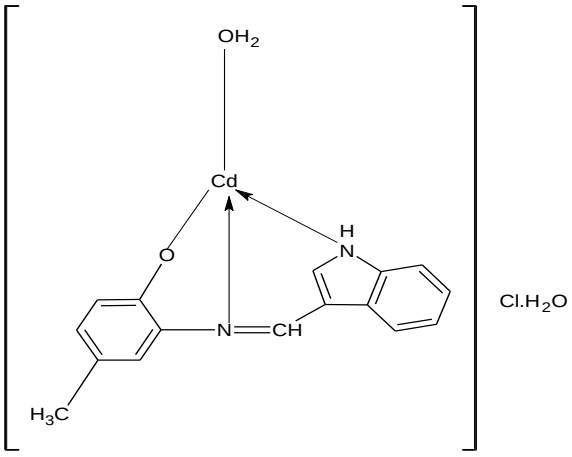


**Figure 2.3: Proposed structure of $[Cd(AMPIA)H_2O]Cl.H_2O$Complex$[Hg(AMPIA)Cl]H_2O$**

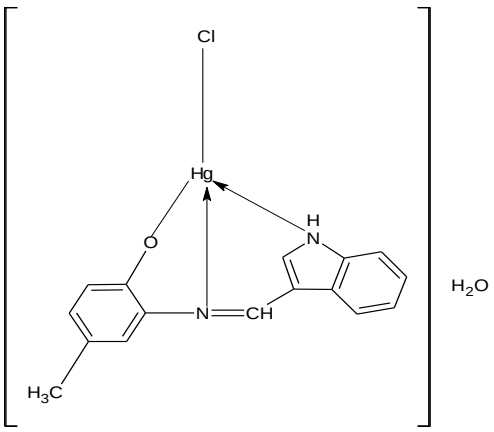


**Figure 2.23: Proposed structure of Complex**

**Conclusion:**

The heterocyclic ligand AMPIA can form metal chelates with transition metal ion viz. Ti(IV), Zr(IV),Cd(II) and Hg(II), coordination number for Ti(IV) and Zr(IV) is found to be six and for Cd(II) and Hg(II) is four . Ligand behaves as uninegative tridentate in nature. $^{1}$H NMR spectra supports involvement of azomethine, -NH group of indole ring and phenolic oxygen in coordination and presence of coordinated water molecule in cadmium complex. Based on elemental analysis, percent of chloride, metal ligand ratio and spectral parameters following structures are proposed, to the synthesized complexes. The proposed structure of Ti(IV), Zr(IV),Cd(II) and Hg(II) complexes are as shown in the following figures.

**Acknowledgements:**

The author would like to thanks the Principal and Head Department of Chemistry, Shri Shivaji College, Parbhani for providing all necessary facilities.

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# BILASTINE- LASTING $H_1$ RECEPTOR ANTAGONIST

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**Abstract:**

Allergen is a substance that triggers allergic inflammatory response. Allergen stimulates histamine receptors by mast cell degranulation, stimulation of H1 receptor produces allergic responses and inflammations produced by histamine. This article put forth bilastine as a frontier drug in the list of anti-histamines; therefore article presents the review of Bilastine.

**Keywords:** Allergy, Histamine, Antihistamine, Bilastine.

## Introduction:

Histamine comes from the words "Histo" which means tissue and "amine" which denotes chemical compounds released from tissue.[1] This amine was released into the bloodstream by white blood cells as part of the immune system's defense against a potential allergen.[2] Mast cells are multifunctional bone marrow-derived tissue-dwelling cells that are the body's most important producers of histamine[3], and they were found in the skin, stomach and intestinal mucosa, liver, lungs, and placenta, as well as blood[1]. Histamine and its receptors ($H_1R$–$H_4R$) play an important role in the progression of allergic disorders like allergic rhinitis, allergic conjunctivitis, and urticaria wheal and flare reactions.[3] Antihistaminic drugs work by specifically inhibiting the production of histamine and hence provide relief from allergic reactions.[4] Antihistamine binds to the histamine receptors (H1-H4) on the cell surface [5], which are physically similar and categorised as G-protein coupled receptors, but differ in tissue distribution and biological effects.[4] $H_1$ receptors were detected on a wide range of cells, including airway cells, vascular smooth muscle, epithelial and endothelial cells, eosinophils, and neutrophils.[6] Antihistamines work by attaching to histamine receptors and counteracting the effects of histamine.

The $H_1$ antihistamine drug act as inverse agonists of histamine[6] were further subdivided into first generation and second generation antihistamine.

- First generation possesses a low degree of selectivity because of its sedating property not suitable for long term treatment, and this class includes Promethazine, Chlorpheniramine, Cyclizine, Cyprohepatidine.
- Second generation exerts high selectivity and inhibits late phase allergic reactions and non sedative which includes Bilastine, Ebastine, Azelastine, Fexofenadine, Loratidine, and this class was recommended as a fine and first line of therapy as per international guidelines.[7]

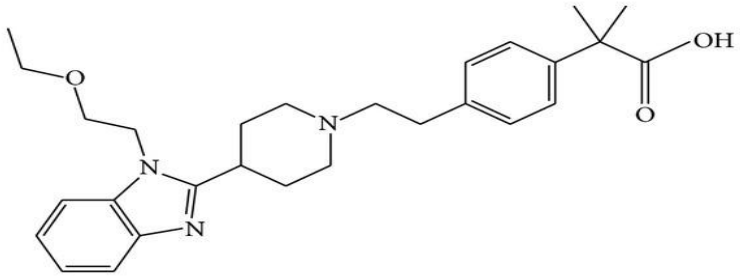
Bilastine was a unique non-sedating antihistamine created for the treatment of allergy issues among the second generation medicines.[8] The review of bilastine, a selective antihistaminic medication, is the focus of this article.

**Description:** [9, 10, 11].

**IUPAC name:**

2-[4-[2-[4-[1-(2-ethoxyethyl) benzimidazol-2-yl] piperidin-1-yl]ethyl]phenyl]-2-methylpropanoic acid.

**Structure:**




**Empirical formula**: $C_{28}H_{37}N_3O_3$.

**Molecular weight**: 463.61 g/mol.

**Appearance**: white to off white crystalline powder.

**Melting point:** 195°-200°c.

**Solubility**: soluble in methylene chloride and chloroform, slightly soluble in methanol, sparingly soluble in 0.1M NaoH, & insoluble in water.

**pKa Value:** 4.15 ± 0.06, when determined by ultraviolet spectrophotometry and 4.18 by HPLC.

**Partition Coefficient (Log p):** 2.3.

**Hygroscopicity:** Bilastine is not hygroscopic tested under ambient temperature (25.1± 0.1°C) and relative humidity (85 % RH) conditions.

**Therapeutic category:** Therapeutic category: Non sedating H1-Antihistamine (second generation), Anti-allergic drug.

**Indications:** Allergic rhinitis, rhinoconjunctivitis and urticaria (pruritus and hives)

**Clinical pharmacology:**

**Mechanism of action:**

Bilastine has a high affinity for histamine H1 receptors (3 and 5 times greater than cetrizine and fexofenadine, respectively), but has no or little effect on receptors for other mediators/amines such as H2, H3, H4, 5-HT2A, Bradykinin B1, Leukotrine D4, N type voltage dependent calcium receptors -1and -2 Adreno receptors, and M1-M5 Muscarinic receptors.

Mast cells degranulate after an allergic reaction, releasing histamine and other chemicals. Bilastine decreases the development of allergy symptoms caused by the release of histamine from mast cells by binding to and blocking activation of the H1 receptors. In-vivo preclinical studies have also revealed a reduction in histamine-induced capillary permeability and micro-vascular leakage, as well as a reduction in histamine-induced bronchospasm.[12]

**Pharmacokinetic and pharmacodynamic properties of Bilastine:**

Bilastine is a second-generation H1 antihistamine that is authorised in Europe for adults and adolescents (over the age of 12) at a dose of 20 mg once daily, and children (6–11 age, with a body mass of at least 20 kg) at a dose of 10 mg once daily, for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria. It also approved in other regulatory agencies for children older than 2 years [13,14]. Bilastine (20 mg tablets) taken once daily is effective in managing the ocular symptoms of allergic rhinoconjunctivitis in clinical trials, with an excellent safety profile and long-term tolerance. Bilastine has also been shown to be effective and safe in treating allergic rhinoconjunctivitis and chronic idiopathic urticaria.[15, 16, 17, 18]

The pharmacokinetics and pharmacodynamics of orally administered bilastine have been studied widely in children[19, 20, 21] and adults[22]. Bilastine is rapidly absorbed after oral administration, reaching peak plasma concentration in 1.3 hours and a mean bioavailability of 60%, with the majority of the drug linked to plasma proteins[22, 23]. Bilastine is not considerably metabolized in the liver, and approximately 95 percent of it is eliminated unchanged in the faeces (66.5%) or urine (28.3%), with a typical elimination half-life of 12–14.5 hours[22, 24].

Over a dose range of 2.5 to 220 mg, pharmacokinetic and pharmacodynamic modeling combined with non-compartmental investigation shows linear kinetics[22]. Bilastine has also been demonstrated to be safe in individuals with renal or hepatic impairment, as well as those aged 65 and up [25, 26]. In vitro, the drug has a lengthy duration of action, which could be due to its high selectivity and affinity for the H1 receptor, which results in a long residence time at the receptor [27, 28]. However, unlike most other second-generation H1 antihistamines, its interaction with H1 receptors in the brain is nearly 0%, implying that brain penetration is low [29, 30].

**Contraindication and precaution:**

This drug contraindicated in hypersensitivity to the active substances or to any of the excipients.

- **Elderly:** No dosage adjustment is required.
- **Children:** Dosage adjustment is required for below 12 years of age.
- **Pregnancy and Lactation:** No or limited amount of data from the use of bilastine in pregnant women and lactating mother. No effects on fertility have been studied in humans. Animal studies did not show negative effects on fertility.
- **Renal impairment:** No dosage adjustment are needed in patients with mild, moderate, or severe renal impairment, if no p-gp inhibitor drug is being concomitantly administered
- **Hepatic impairment:** Not metabolized and is excreted largely unchanged, therefore no dosage adjustment is required in patients with hepatic impairment.

**Drug interactions:**

Bilastine should not be given to patients who concomitantly taking or treated with P-gp inhibitors drug like Cyclosporine, Diltiazem, Erythromycin, Ketoconazole or Ritonavir due to potential for increased plasma bilastine levels and adverse proceedings. Simultaneous ingestion of Bilastine 20mg and Lorazepam 3mg for 8 days did not potentiate the depressant CNS effects of Lorazepam.

**Food interaction:**

Evade grapefruit products or other fruit juices for optimal absorption. Take on an empty stomach, at least two hours prior to or one hour later than eating.

**Adverse effects:**

Most common effects were headaches, somnolence, dizziness, abdominal pain and fatigue reported by patients.

**Storage and stability:**

Store at room temperature in well closed air tight containers and protect from moisture [9, 10].

**Various research studies on Bilastine drug administration:**

**1. Oral route:**

It is the most appropriate and widely utilized route of administration of medications. As a result, it is recommended for solid and liquid dosage forms. Bilastine is now available as a conventional tablet for adults, an orodispersible tablet for children, and an oral solution for children to treat allergic rhinoconjunctivitis and urticaria. It's also referred as per oral (P.O).

Oral tablets for ingestion (20mg):

The tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Taken the tablet when stomach is empty (so one hour before a meal or alternatively, two hours after eating a meal).The tablet should not take tablets with food or with grapefruit juices or any other fruit juices[31.]

Pediatric oral solution and orodispersible tablet (2.5 mg/ml):

For the alleviation of allergic rhino-conjunctivitis symptoms, 4ml of oral solution and 10mg of ODT are used once day (seasonal allergic rhinitis, perennial allergic rhinitis and urticaria)[32].

**2. Sublingual route:**

It is quicker than taking the medicine orally since the drug is inserted under the tongue. It will allow for direct medication release into the systemic circulation, resulting in quicker drug absorption and protection from GI and enzymatic breakdown. Bilastine has a lower bioavailability (61%) due to inadequate absorption and the interplay of a high/low fatty diet. The sublingual approach improves the drug's bioavailability and is a viable alternative to the oral route [33.]

**3. Bilastine transdermal drug delivery:**

It has greater advantages than other routes of drug administration since it provides quick, extended, and stable drug levels. It is a revolutionary methodology that offers more advantages than existing administration methods. It helps to avoid gastrointestinal incompatibility, poor bioavailability, and first-pass metabolism. It also allows you to stop treatment by removing the patch. Whereas oral route absorption is hindered when taken with food and easily absorbed when fasting, transdermal drug delivery of bilastine can achieve optimum bioavailability of the medicine. Antihistamine transdermal medication delivery for allergic rhinitis treatment can also aid to minimize dose frequency and increase patient compliance [34].

**4. Delivery via the ocular route:**

Bilastine ophthalmic formulation is a successful and safe treatment for allergic rhinoconjunctivitis. Its 0.6 percent (6mg/ml) concentration shows the greatest efficacy in lowering signs and symptoms for at least 16 hours after treatment, making it appropriate for once-daily dosing. Topical ocular medicines were well tolerated, and they were favoured because they act faster and had a higher local bioavailability than systemically delivered medications [35, 36].

**Novel drug delivery approaches for allergic disease and innovative treatments:**

NDDS is a technique that is used to improve the efficacy of medicinal drugs, as well as to control and target the drug. In allergic illnesses, many administration methods are used to provide therapeutic agents [37].

| | |
|---|---|
| TOPICAL ROUTE | liposomes, transferosomes, ethosomes, proniosomes, Microemulsion, cyclodextrins, transdermal gel, nanoparticles ,stick. |
| ORAL ROUTE | cyclodextrins, nanoparticles, microparticles, mucoadhesive patches, coated tablets, polymeric matrices, microemulsion, chewing gum, fast disintegrating tablets, orodispersible film, |
| PULMONARY ROUTE | Nanosuspensions, mucoadhesive microspheres or nanoparticles, polymeric micelles ,phospolipid nanomicelles,,stealth liposomes, nanocrystal solid dispersion. |
| PARENTERAL ROUTE | Injectable-Solution, colloidal dispersion, microparticle, released erythrocyte.<br>Implant-solid implant, insitu depot forming system.<br>Infusion devices-osmotic pumps, vapour pressure pump, battery powder pumps. |
| OCULAR ROUTE | Hydrogel, stick, implant, cyclodextrin complexes, miscelles, nanoparticles. |
| NASAL ROUTE | Hydrogel, implant, microemulsion, microspheres. |

**Figure 1: Different routes of drug administration for allergic disorders**

- **Topical delivery:** It refers to drugs that are applied topically to the skin or mucous membranes of the eye, ear, nose, mouth, vaginal canal, and other areas, mostly for local effect. This method of medication delivery ensures a high local concentration of the medicine while avoiding the drug's broad circulation. Absorption into the system circulation, on the other hand, is highly prevalent and can have negative consequences. Systemic absorption is sometimes used for medicinal purposes.
- **Enteral route:** In extreme responses, where a systemic effect is necessary, the most commonly employed method of medication administration is frequently chosen. Within the limits of the physicochemical qualities of the medicine, most drugs taken orally are highly efficiently absorbed into the blood from the GI tract.
- **Pulmonary route/inhalation route:** Inhalation is a typical route for both local and systemic drug administration. When drugs are administered as a gaseous aerosol mist or ultrafine solid particle, the lungs provide a great surface for absorption, resulting in a rapid commencement of action. Another advantage is that plasma concentration may be changed quickly.

- **Parenteral administration:** The injection route, also known as the fastest and second most popular method of administration, is the quickest and second most common method of administration. Introduction of drugs into the body via pathways other than the GI tract; nevertheless, in practice, the word refers to the injection of substances in the form of solution or suspension into the body at various places and depths using a needle and a syringe. The goal is to create rapid systemic effects by injecting the drug material directly into the site of action in order to achieve high drug concentration in the site of action or avoid systemic side effects.
- **Ophthalmic delivery route:** Drugs can be blended with inert ingredients to form a liquid, gel, or ointment that can be applied to the eye. Drugs for the eyes are virtually exclusively employed for their local effects.
- **Nasal method of delivery:** A medicine must be converted into tiny droplets in air before being breathed in and absorbed through the thin mucous membrane that lines the nasal passages (atomized).The medications enter the bloodstream after being absorbed, and drugs taken this way usually work swiftly. The nasal passages are irritated by some of them. Nicotine (for smoking cessation), calcitonin (for osteoporosis), sumatriptan (for migraine headaches), and corticosteroids (for allergies) are all drugs that can be delivered via the nasal route [38, 39, 40.]

**Summary and conclusion:**

- Mast cell degranulation releases histamine, which causes allergic responses.
- An H1-receptor antagonist decreases Allergic inflammatory reactions by blocking histamine's impact.
- Bilastine is a new antihistaminic medication that has been shown to be effective as a selective and long-acting antihistaminic.
- It has been demonstrated to be a safe treatment in patients with hepatic and renal impairment who do not require dose changes.

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# RECENT TRENDS IN DTBP (DI-TERT-BUTYL PEROXIDE) MEDIATED OXIDATIVE CROSS-COUPLING REACTIONS: A CONCISE REVIEW

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**Abstract:**

Modern synthetic chemists are working on developing novel and ecologically friendly processes for the synthesis of C-C and C-heteroatom bonds. This field has lately emerged as a diverse, environmentally friendly, and clean framework for the formation of a protracted synthetic approach. Cross-coupling reactions are a powerful tool in the current scenario of organic synthesis. Oxidative Cross- Coupling reactions are characterised by the production of a new bond between two distinct molecules as well as the loss of a hydrogen atom from each fragment. According to the rapid developments,, Metal-free synthesis has recently received much interest in chemical synthesis as a potent greener protocol for carbon-carbon and carbon-heteroatom scaffolds.

**Keywords:** Cross-Coupling reaction, DTBP, Construction.

## Introduction:

Cross-coupling reactions include the use of a metal catalyst to combine two separate starting compounds, each of which is normally equipped with an activating group. As a result, the two activating groups are lost, and a new covalent connection is formed between the remaining fragments. Organic and organometallic researchers have found cross-coupling processes to be extremely valuable tools for targeted C-C bond coupling (As shown in figure- 1).

Transition-metal-catalyzed coupling reactions, which were first studied in the 1960s as a key topic in organometallic chemistry, have grown substantially over the previous 50 years and are now one of the most practical and direct methods for forming carbon-carbon bonds (Baeten and Maes, 2017; Guo *et al.*, 2017).

Nevertheless, transition-metal-catalyzed coupling reactions confront challenges to some extent, owing to the instinctive drawbacks of the catalytic systems (Shown in Figure 2).

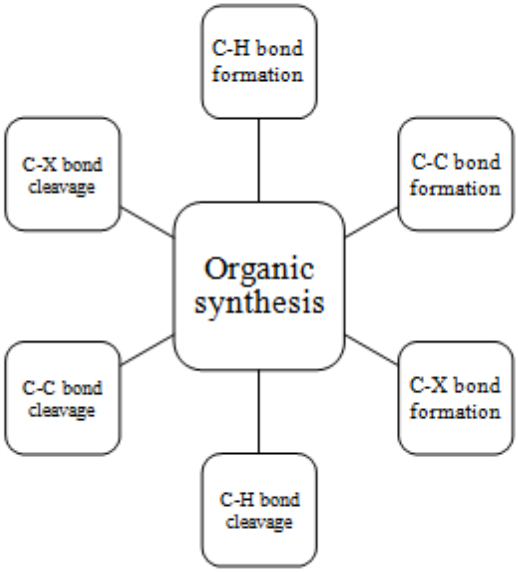



**Figure 1**

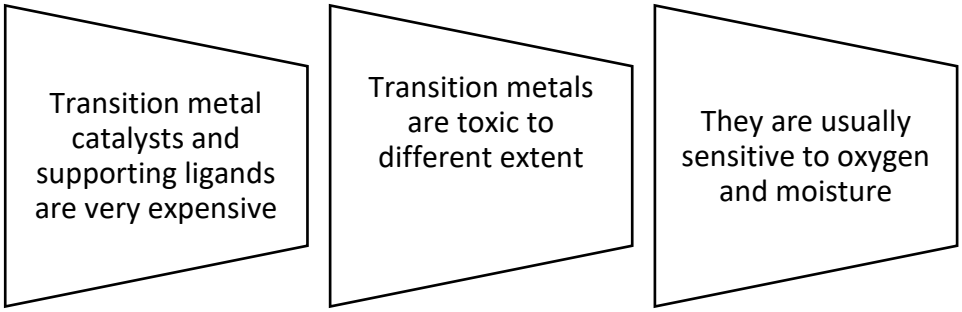



**Figure 2**

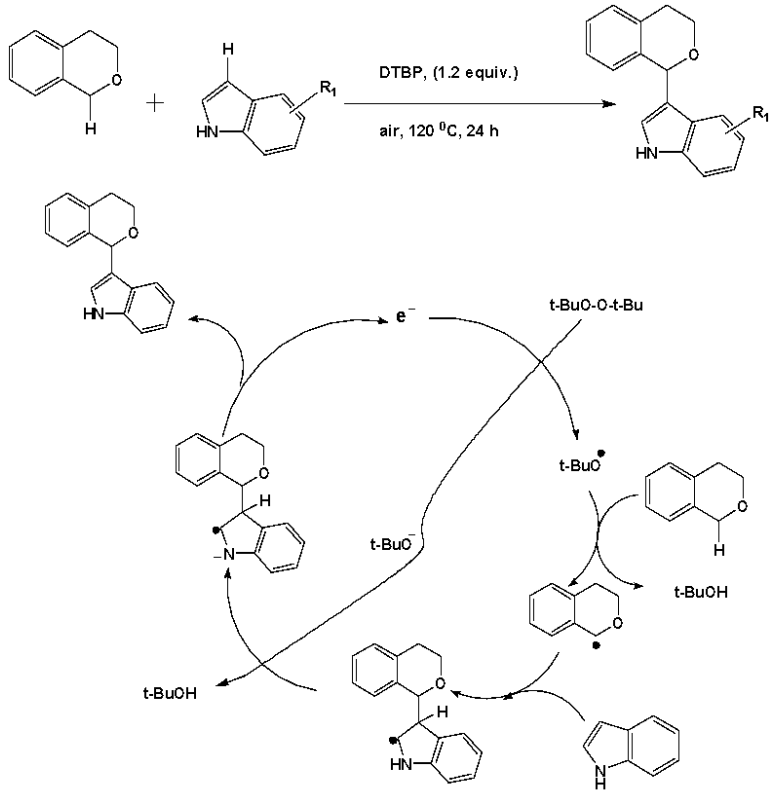
**Transition-Metal-Free Oxidative Coupling Reactions:**

The oxidative coupling reactions between two C−H bonds to form a new carbon−carbon bond are the most attractive and promising. Cross-dehydrogenation coupling (CDC) reactions are oxidative cross-coupling reactions between two distinct C-H bonds. These reactions own high atom economy, and the byproduct is usually the water. Some oxidants exhibit very unique and remarkable features in the oxidative coupling reactions via a totally different pathway. Generally, CDC reactions generate two important intermediates, the nucleophilic anion and the electrophilic cation, in situ via oxidation and single electron transfer (SET) process. Cross-coupling processes for the production of C-C and carbon-heteroatom bonds by direct activation of C–H bonds under cross-dehydrogenative coupling have emerged as a cost-effective and long-term alternative to traditional cross-coupling techniques in the last decade. DTBP and TBHP have recently been

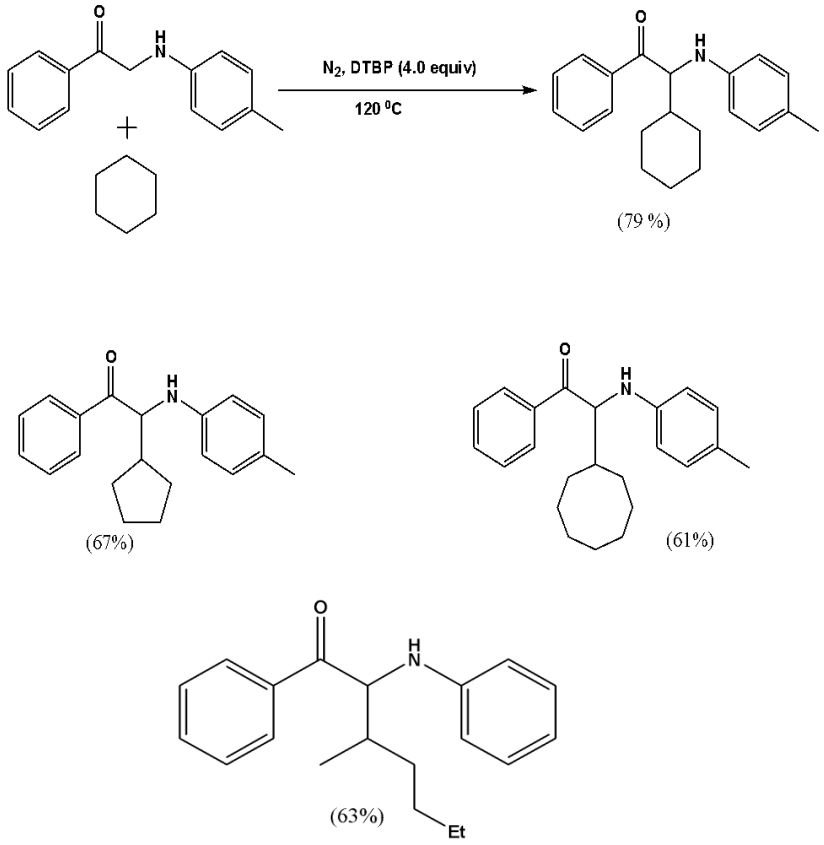
used in a variety of radical processes either in the presence or absence of transition metals for C-C, C-N, and C-S cross-coupling reactions (Nakamura and Yamamoto, 2004; Kim and Li, 2020). Zhang and co-workers (Zhu *et al.,* 2018) have reported the reaction between 3,4-dihydro-1H-2-benzopyran and indole derivatives effectively via a metal-free cross-coupling process (Proposed Mechanism As shown in **scheme-1**).

Peng and co-workers have developed A di-tert butyl peroxide (DTBP)-promoted α-alkylation of α-amino carbonyl compounds by simple alkanes. The reaction was relevent for α-amino ketones and α-amino esters, providing a novel strategy for the α-functionalization of these substrates (Peng *et al.,* 2019). This change involves the radical route. cyclohexane, cyclopentane, cycloheptane, and cyclooctane all worked well, providing the α-alkylation products in good yields (**scheme- 2**). They proposed mechanism is outlined in Scheme 3. In step one, tert-butoxy radical is formed by homolytic cleavage of DTBP. Then tert-butoxy radical abstracts one H of cyclohexane to form cyclohexyl radical. This step is the rate-determining step. In step two, α-amino carbonyl forms imine intermediate. Then, the addition of cyclohexyl radical to substance produces radical intermediate. Finally, intermediate abstracts one H from tBuOH to provide the final product.

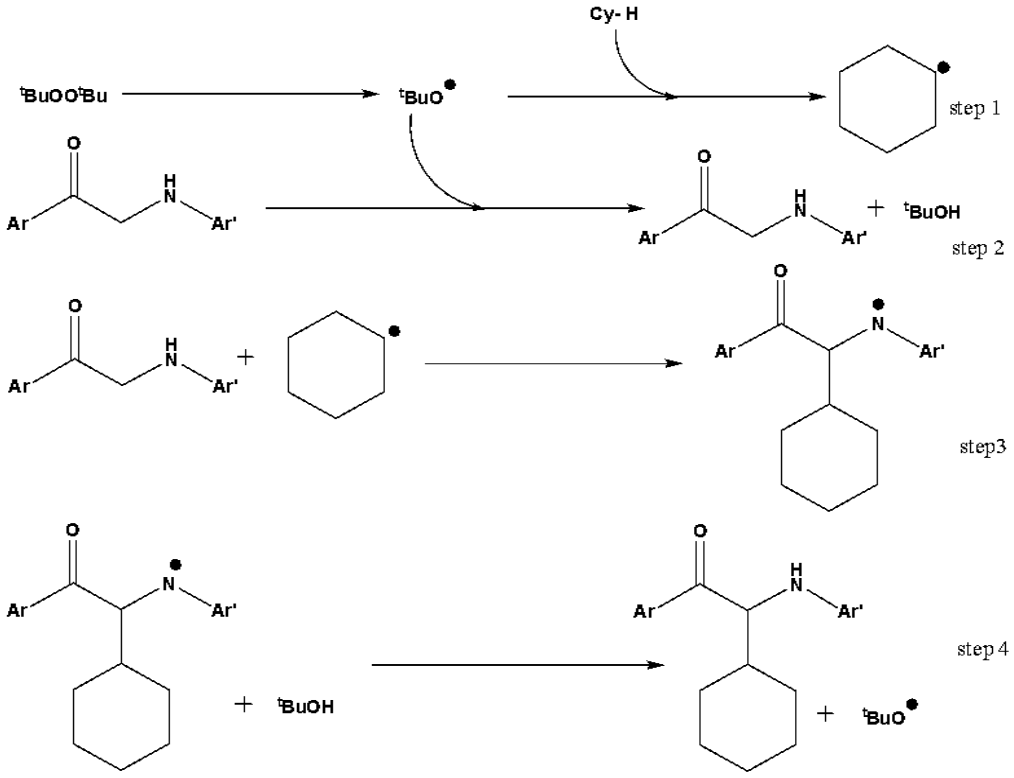
**Scheme 1: Reaction between 3,4-dihydro-1H-2-benzopyran and Indole derivatives**



**Scheme 2: α-alkylation of α-amino carbonyl compounds**

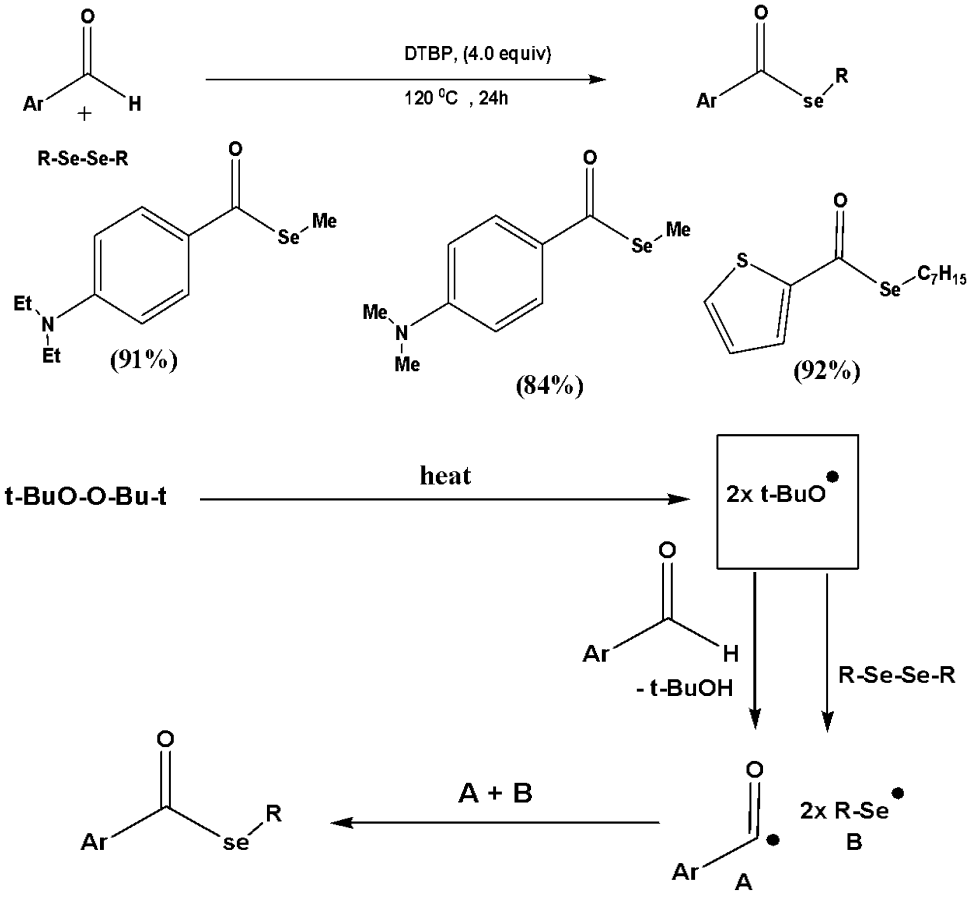



**Scheme 3: Mechanism of α-alkylation of α-amino carbonyl compounds**



Liu and co-workers have been reported the Syntheses of selenoesters through C–H selenation of aldehydes with diselenides under green conditions (Liu *et al.,* 2021). The plausible reaction mechanism is shown in **Scheme 4**.

**Scheme 4: Syntheses of selenoesters through C–H selenation**




**Conclusions and Challenges:**

DTBP promoted reactions have been widely explored during the past several years due to their eco-friendly reaction conditions as well as cost-effectiveness. This chapter provides an updated outcome of this rapidly developing area. New synthetic apporaches and novel reaction conditions that do not compromise product selectivity, energy efficiency, or environmental safety have become major targets in current chemical research. There are still a lot of unknown

synthetic methods, and a number of mechanisms are still being elucidated. Thus, many opportunities and challenges still remain.

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# BIOINORGANIC AND BIOCOORDINATION CHEMISTRY – PRACTICES AND PROSPECTS

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**Abstract:**

Bioinorganic Chemistry has emerged as a new interdisciplinary research area at the interface of classical subjects i.e. inorganic chemistry and biology. It includes the transport, speciation, mineralisation, metal-chelation therapy, diagnostics etc. Bioinorganic chemistry is a rapidly developing field and there is enormous potential for application in medicine, not only for essential elements but also for nonessential and even radioactive elements. Medicinal inorganic chemistry offers real possibilities to pharmaceutical industries, which have traditionally been dominated by organic chemistry alone for the discovery of truly novel drugs with new mechanisms of action. Medicinal inorganic chemistry as discipline has only existed for about last fifty years, since the discovery of the antitumour activity of cis-platin. Biocoordination chemistry has been used in medical sciences in a number of ways. Chelates can be used in the treatment, management and diagnosis of diseases.

**Introduction:**

Since nature has made such extensive use of metal ions in biological systems, the following questions emerge up: Can metal ions be incorporated into drugs? Are coordination compounds potential medicinal agents? Can coordination chemistry be used for medicinal purpose? It is important to note that the first structure-activity relationship evolved by Ehrlich Pau in the first decade of $20^{th}$ century, involved the development of the inorganic compound arsphenamine (salvarsan) for successful treatment of syphilis. Founder of chemotherapy Ehrlich defined it as the use of drugs to injure an invading organism without injury to the host. Recent advances in chelation research have paved the way for targeting "magic-bullets" for chemotherapy, using different strategies and pharmacological manipulation to utilize metal complexes as drugs. Peter Sadler noted some years ago, that most of the elements of periodic table up to and including bismuth have potential uses in design of new drugs and diagnostics agents[1-8].

James Cowan's new molecules, called metal coordination complexes, mimic the activity of natural enzymes that break apart DNA, RNA and proteins in the body. They have tailor-made different complexes to break apart portions of RNA that enables HIV and Hepatitis C virus to function, as well as the ACE enzyme that constricts blood vessels in the body. Moreover, metal ions function as electron deficient/redox centers while most biomolecules are electron rich. Mostly complexes work either in redox chemistry to steal electrons from the bonds holding the target molecules together or hydrolysis to break down the target. Reactivity of metal chelates can be modulated by modifying their redox potential, saturation level of coordination sphere, hydrophilicity and lipophilicity by changing the nature of ligands.

In Bioinorganic chemistry (metallobiochemistry) several creative people are working on biomimetic models, structural models, functional models, replicative models, speculative models etc. Living organisms store and transport transition metals both to provide appropriate concentration of them for use in metalloproteins or cofactors and to protect them against the toxic effects of metal excesses; metalloproteins and metal cofactor are found in plants, animals, and microorganisms. The normal concentration range for each metal in biological system is narrow with both deficiencies and excesses causing pathological changes. Transition metals for which biological storage and transport are significant, are in decreasing abundance as iron, zinc, copper, molybdenum, cobalt, chromium, vanadium and nickel. Although the redox properties of the metals are important in many of the reaction e.g. zinc in the Cu-Zn dismutases. Sometimes equivalent reactions are catalyzed by proteins with different metal centers. Metal ions are required for many critical functions in humans. Scarcity of some metal ions can lead to disease. The ability to recognize, to understand at the molecular level, and to treat diseases caused by inadequate metal-ion function, constitutes an important aspect of medicinal bioinorganic chemistry[9-17].

Metal ions can also induce toxicity in humans; classic examples being heavy metal poisons such as mercury and lead. Even essential metal ions can be toxic when present in excess. Metallic preparations can be toxic, but so can some organic molecules also be, used as drugs. However, at other extreme, certain metals remain toxic in trace amounts, which can enter the body via a variety of routes and often cannot be excreted leading to metal toxicity. There has been recent progress in understanding the coordination chemistry and biochemistry of older metallodrugs including gold antiarthritic, bismuth antiulcer and metal ion mediated neuropharmaceutical and anti-infective drugs. Current areas which exciting clinical potential include manganese superoxide dismutase mimics, vanadium insulin mimics, ruthenium nitric oxide scavengers, lanthanide-based photosensitizers and metal- targeted organic agents. Progress

in medicinal coordination chemistry is equally dependent on understanding of thermodynamics (equilibria and structures) and the kinetics (and mechanisms) of reactions of metal complexes, especially under biological conditions. Understanding the biochemistry and molecular biology of natural detoxification mechanisms, designing and applying ion-specific chelating agents to treat metal overloads, are two components of second major aspects of the new science that is evolving at the interface of bioinorganic chemistry and medicine.

The clinical success of platinum anticancer and gold antiarthritic drugs have changed the attitudes of many who doubted that heavy-metal compounds are notorious for their deleterious effects on human health and would ever play a serious role in chemotherapy. Indeed, we have seen that $Hg^{2+}$, $Pb^{2+}$ and $Cd^{2+}$ are toxic elements. The toxicity is supposed to occur because of metabolic defects that deregulate their control in the cell. An important common theme is selectivity. For a drug to be effective, it must be selectively toxic to diseased tissue while leaving normal tissue alone; or it must selectively kill harmful microorganisms at levels where it fails to deplete helpful ones. There are two general routes to the development of inorganic complexes, and indeed most chemical compounds as drugs. One, illustrated by cis-platin, arises from an empirical observation of biological activity followed by attempts to optimize the clinical efficacy through investigation structure activity relationships (SAR). Knowledge of the molecular mechanism might lead to rational strategy for designing better drugs with incorporated metal ions.

Another approach to drug design may be like- ribonucleotide reductase is required in the first committed step in the biosynthesis of DNA, the conversion of ribo to deoxyribonucleoside diphosphate. The mammalian enzyme contains a binuclear non-hemeiron center required for activity. Compounds that would selectively inhibit this enzyme by destroying this center are potentially useful as antiviral or antitumor agents. Another example is the enzyme reverse transcriptase, encoded by the HIV (AIDS) virus and required for its integration into the genome of the host cell. Compounds like 3'-azidothymidine (AZT) are accepted by the enzyme as substrates but, when added to the terminators than AZT constitutes a rational strategy for developing new anti-AIDS drugs [18-21].

**Metal-chelates in medicine**

Since the discovery of the antitumor activity of cisplatin (cis-$[PtCl_2(NH_3)_2]$; during the 1960s, metal-based drugs have played a major role in anticancer medical treatments. As a matter of fact, a few platinum compounds are today among the most widely used anticancer agents in the clinics. Research in this field is still very active and has been extended, in recent years, to include a conspicuous number of non-platinum metallodrugs. During the last three decades, the

interest of the scientific community working on anticancer metal-based compounds has mostly focused on their interactions with DNA, the commonly accepted "primary" target for platinum compounds. Surprisingly, the reactions of platinum and non-platinum anticancer metallodrugs with proteins have received so far very little attention. Only a few biophysical studies have indeed appeared dealing with the interactions of anticancer metallodrugs with proteins. These studies mostly concerned the two mojor serum proteins, albumin and transferrin as well as metallothioneins, small cysteine-rich intracellular proteins primarily involved in storage and detoxification of soft metal ions. Additional studies were carried out on a few other proteins such as ubiquitin, haemoglobin, myoglobin, cytochrome-C and glutathione-S-transferase, serving in most cases, as model proteins. Thus, metal-chelates in medicine may be considered as for the treatment of metal deficiencies (Dietary supplement); Metals and metal-chelates in chemotherapy (Metallodrugs/ pharmaceuticals, Metallotherapy and Chelation Therapy); Metal ion detoxification, (treatment of metal overload diseases and highly toxic metals) and drugs functioning through interaction with metal ions (drug stabilization and drug detoxification).

Functionalised magnetic nanoparticles are being considered as smart treatment agents, as well as diagnostic tools (Targeting treatment). The idea here is to bind therapeutic drug molecules onto the surface of a nanoparticle, then use a magnetic field gradient to draw tagged particles towards the intended treatment site. Present day drug treatment mechanisms rely on a certain proportion of an injected or orally administered pharmaceutical reaching its intended target. Use of magnetic 'tag and drag' could improve treatment efficacy, while simultaneously reducing administered doses. Researchers are developing Au-coated Fe, Ni and Co-ferromagnetic particles, with diameters of 50-100 nm, for potential drug delivery applications (a nanobiotechnological approach); iron oxide particles are known to be nontoxic and are eventually broken down to form blood hemoglobin. The researchers have shown that magnetofection method works for in-vivo applications. Photodynamic therapy (PDT) involves the treatment of diseased tissues and cells with a photosensitizer and visible light. Most of the clinical interest is focused on cancer, porphyrias, and hematological diseases and various forms of jaundice. Photosensitizers are required which show some selectivity for photodamage to tumor tissue.

Neuropharmacology is another highlight in medicinal inorganic chemistry where roles of Na, K and Ca are well known. Neurochemistry has apparently indicated that Fe and Cu enzymes can control neurotransmitter biosynthetic pathways and millimolar levels of Zn in the hippocampus involved during neurotransmission. Moreover, Mn is abundant in the brain in enzymes such as glutamine synthase and superoxide dismutase. It can be speculated now that the

metal neurochemistry is vital for the prevention of neuronal degradation and perhaps effective for curing the condition such as Parkinson's, Alzheimer's diseases, senile dementia and even Creutzfeldt Jakob disease (CJD). Prion protein believed to be the cause of CJD, is thought to be a copper protein in vivo. These may appear as expected challenges to medicinal inorganic chemistry[22-26].

**Schiff base metal complexes in bioinorganic chemistry**

A large number of Schiff bases and their complexes possess important properties due to their great flexibility and diverse structural aspects e.g. their ability to reversibly bind oxygen, transfer of an amino group and complexing ability towards some toxic metals. The high affinity for the chelation of the Schiff bases towards the transition metal ions is utilized in preparing their solid complexes. Metal complexes of Schiff bases derived from substituted salicylaldehyde and heterocyclic compounds which usually contain nitrogen, sulphur and / or oxygen as ligand atoms are becoming increasingly important as biochemical, analytical, homogenous and heterogeneous catalysis, as pigments and dyes, thermoresistant polymers, magnetic materials, nanoprecursors and antimicrobial agents. 2-amino-4-hydroxy-6-methyl pyrimidine is able to inhibit the synthesis of t-RNA, thus its Schiff-bases may acts as valuable substrates in the synthesis of antitumor chemotherapeutic agents. Schiff base metal complexes of hydrazones have their utility as antiamoebic agents. Isonicotinic acid hydrazide has been one of the most effective anti-tubercular. 2-pyridine carboxaldehyde has been found involved in enzyme reactions as medicine. In the area of bioorganic chemistry interest in Schiff base metal complexes has centered on the role of such complexes in providing synthetic models for the metal containing sites in metalloproteins and metalloenzymes. Most of the major classes of pharmaceutical agents contain examples of metal compounds which are in current clinical use and new areas of application are rapidly emerging. It is well known that N atom play a key role in the coordination of metals at the active sites of numerous metallobiomolecules. The emerging medicinal and biological applications of Schiff bases and their metals chelates are fungicides, insecticides, algaecides, antibacterial, plant growth regulators, enzymatic decarboxylation, catalysis, enzymatic aldolization, antiviral, antibiotic, anesthetic, antituberculosis, antitumor and oxygen carriers in biological system [27-32].

**Synthesis of Schiff base and their metal complexes**

The Schiff base has been synthesized by condensing aldehyde with amine. The reaction mixture was then refluxed on water bath until the product was formed. Schiff base metal complexes have been prepared by mixing the methanolic solution of $M^{II}Cl_2$/ $M^{II}SO_4.nH_2O$ with the Schiff base in 1:1 or 1:2 molar ratio. The resulting mixture was refluxed on water bath for

completion of reaction. A product appears on standing and cooling the above solution. The complexes were filtered off, washed with alcohol and ether, recrystallized thrice and dried under reduced pressure over anhydrous $CaCl_2$. The synthesized Schiff base should be send to characterization[33].

**General Reaction:**

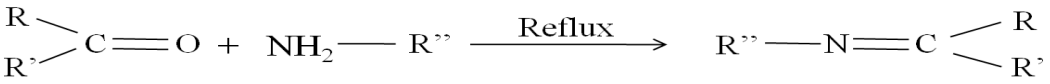


**Figure 1: Scheme for the synthesis of Schiff base ligand**

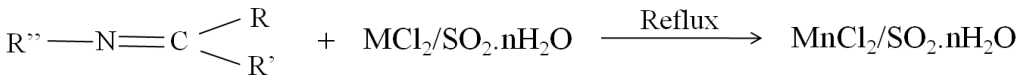


**Figure 2: Scheme for the synthesis of Schiff base metal complex**

**Green Synthesis (Microwave synthesis)**

Microwave synthesis is considered as a "green" technology, principally since many organic reactions can be carried out in solvent-free conditions. Microwave radiation has proved to be highly effective heating source in chemical reactions. Microwaves can accelerate the reaction rate, provide better yields and uniform and selective heating, achieve greater reproducibility of reactions and help in developing cleaner synthetic routes. In this type of synthesis the reaction mixture is irradiated by the microwave oven using 3-4 ml solvent. The reaction was completed in a short time. As a result of microwave –assisted synthesis, it was observed that the reaction was completed in a short time with higher yields compared to the conventional method.

**Characterization**

Schiff-base ligands and their metal complexes / chelates and mixed ligand coordination compounds are preferred to characterized by microanalysis, mass, spectral (UV-Visible, FT-IR, $H^1$-NMR, $C^{13}$-NMR, ESR), magnetic, thermal, electrochemical, XRD studies etc. IR Spectroscopy is most widely used for information about the mode of linkage, presence of functional group, aromatic ring and sites of attachement of ligand to the metal ion. Although the electronic spectra of Metal Complexes with multidenate Schiff base ligands are not in general good indicators of geometry, but they help to support it.

**Electrical Conductivity**

The temperature dependence of the solid state conductivity (σ) of the compounds in their compressed pellet form has been measured at fixed frequency 1KHz in the temperature range 297-413 K. The values of the solid state electrical conductivity of the Schiff base and its complexes increases with increasing temperature and decreases upon cooling over the studied

temperature range indicating their semiconducting behavior. The general behavior of electrical conductivity follows the Arrhenius equation:

$\sigma = \sigma_0 \exp(-Ea/KT)$

Where, Ea is thermal activation energy of conduction, $\sigma_0$ is the conductivity constant and K is the Boltzman constant. The solid state conductivity measurement shows that the plot of log σ vs 1000/T is linear over studied temperature range which indicates their semiconducting nature. For determining the molecular weight of ligand and complexes mass spectral analysis should be done.

**Thermal and Non-Isothermal Kinetic parameters of Schiff Base Metal-Complexes**

In solids, the atoms of reactants are not free to mix with each other but are constrained to oscillate about fixed sites in the lattice and the thermal energy inducing activation vibrational character only. A large number of thermal reactions of coordination compounds have been studied in solid phase but very few systematic studies were performed prior to 1960. At first these studies were focused mainly on the thermal stability and reaction stoichiometry and further the kinetic and thermodynamic studies became common. To find an appropriate kinetic model for a reaction is significant thing. Solid phase reactions include ligand exchange, isomerization of various types, redox reactions and reactions of coordinated ligands. Equations with the thermogravimetric data can be derived for non-reversible reaction so that rate dependent parameters like the rate of reaction, activation energy and order of reaction may be calculated from a single experimental curve. TG studies supported by X-ray, IR and DTA give information about initial, intermediate and final product. High temperature thermal decomposition of transition metal complexes in air or oxygen are being employed for the preparation of oxides and nanomaterials of unique magnetic and catalytic properties.

The thermal behavior of metal complexes shows that the hydrated complexes lose molecules of hydration first; followed by decomposition of ligand molecules in the subsequent steps. The thermal analysis evaluating the thermal stability of the metal complexes study also helps to characterize the metal complexes.

**Non-isothermal degradation Kinetic studies:**

On the basis of thermal decomposition, the Kinetic analysis parameter such as activation energy ($E^*$), pre-exponential factor (Z),entropy of activation ($\Delta G^*$) were calculated by using Piloyan-Novikova, Coats-Redfern and Horowitz-Metzer equations.

**Piloyan-Novikova:** $\mathbf{In[\alpha/T^2] = In(ZR/\beta E^{*)} - E^*/RT}$

**Coats-Redferen:** $\mathbf{In[g(\alpha)/T^2] = In(ZR/\beta E^*) - E^*/RT}$

The high values of activation energies reflect the thermal stability of the complexes. The complexes have negavtive entropy, which indicates that the decomposition reaction proceed with a lower rates than the normal ones. The negative value of entropy also indicates that the activated complexes have a more ordered and more rigid structure than the reactants or intermediates. The negative values of the entropies of activation are compensated by the values of enthalpies of activation, leading to almost the same values for the free energy of activation.

**X-Ray Diffraction study**

X-ray diffraction was performed of metal complexes. The XRD patterns indicate crystalline nature for the complexes. Some of the complexes are nanocrystalline in nature and thus coordination compounds are also being claimed to function as nanoprecursosrs. Thus further creates the basis for exploring the posiibilities of their use in catalysis. X-ray powder diffractogram of the complexes were recorded using Cu Kα as source in the range $5^0$-$90^0$ (2θ).

**ESR studies**

Electronic spin resonance (ESR) spectroscopy is a technique for studying chemical species that have one or more unpaired electrons, such as organic and inorganic free redicals or inorganic complexes possessing transition metal ion. The ESR Spectrum of metal complex ($Cu^{II}$ and $VO^{II}$) provides information on the basis of hyperfine and super hyperfine structures. The geometry and nature of the ligating sites of the Schiff bases and corresponding metal ions can be determined.

**3D molecular Structure: modeling studies of some compounds:**

In the absence of an X-ray crystal structure data, the 3-dimensional structure of the molecules cannot be entirely unambiguous. However, recent major advances in the computational chemistry tools provides an alternative, albeit approximate approach for finding the three dimensional structures of the compounds. Theoretical calculations have paid a considerable attention to the characterization of molecules. Even experimental single crystal data needs theoretical refinements and optimization. The geometry has been optimized by computational method using Gaussian 03W software. Minimization of energy was repeated several times to find the global minimum. The theoretical physical parameters such as bond lengths and bond angles were calculated. The most stable structure among the possible ones is judged as the probable structure.

**Acoustic Studies of some metal complexes in solution:**

Ultrasonic is a potential technique to probe and explore the interaction phenomenon in solution. Due to complexities in structure and nature of biopolymers and biomacromolecules, direct experimental studies are not feasible. Hence ultrasonic, viscometric and volumetric

measurements of simple biomolecules studied under biomimetic conditions have been the indirect way to investigate the physiological and biochemical behavior of molecular systems and effect of electrolytes of them. Acoustics properties of many organic, inorganic and biological compounds in different solvents have been studied.

**Bioinorganic Applications**

**Antimicrobial activities:**

The synthesized compounds have been screened for their antimicrobial activity by well diffusion method techniques against some bacterial strain vz. Bacillus cereus, Staphylococcus aureus, Escherichia coli Pesudomonas aeruginosa and fungi viz. aspergillus niger, Aspergillus fumigates, Fusarium oxysporium and Candida albicans. Etc. Generally the metal complexes are more active than their respective ligands. This can be explained on the basis of Overtone's concept and Chelation theory.

**Insecticidal Activity:**

Insecticides are agents of chemical or biological origin that control insects. All the beginning of World War II (1940), our insecticide selection was limited to several arsenicals, petroleum oils, nicotine, pyrethrum, rotenone, sulfur, hydrogen cyanide gas, and cryolite. It was World War II that opend the Modern Era of chemical control with the introduction of a new concept of insect control involve the use of inorganic, natural and synthetic organic insecticides. Several inorganic compounds have been used as insecticides: mercury, boron, thallium, arsenic, antimony, selenium, and fluoride. Schiff bases and their VO(II) and Cu(II) metal complexes were evaluated for their insecticidal activity on cockroaches (Periplanata americana) as the test insect. The time was death was noted as the KD value (knock down value) and results of compounds. The Schiff bases and their metal complexes are highly active against insects. The activity increases with increasing concentration.

**Anti-diabetic activity:**

Redox chemistry of early 3d-transition metals may be fascinating from the view point of biology. It was discovered nearly 25 years ago that vanadium as V (IV) and V(V) can mimic some of the effects of insulin(Stimulate glucose uptake and oxidation as well as glycogen synthesis). Vanadium complexes with organic ligands are often less toxic and can have improved aqueous solubility and lipophilicity. The orally active complex bis-(maltolato) oxovanadium(IV) is three times more effective in vivo as an insulin-mimetic agent than $VOSO_4$ . In aerobic aqueous solutions, the complex is rapidly oxidized to the dioxovanadium(v) species. Low molecular weight chromium-binding substance (LMWCr), a naturally occurring oligopeptide (ca. 1500 Da, consisting of CrIII, Asp,Glu,Gly, and Cys in a 4:2:4:2:2 ratio), has been found to

activate the insulin-dependent tyrosine kinase activity of the insulin receptor protein. Its potential for diabetes treatment has yet to be established.

Vanadium ions and their complexes exert various insulinomimetic and antidiabetic effects involving the enhancement of glucose transport and metabolism in isolated adipocytes and hepatocytes, skeletal muscle, stimulation of glycogen synthesis and lipogensis, inhibition of lipolysis. Since inorganic, vanadium ions are less absorbed by the digestive tract (low bioavailability), the complexation of vanadium ions with organic ligands may be a useful method of reducing toxicity and improving bioavailability and tissue uptake of ions. The main advantage of these vanadium compounds relative to insulin is that they may be administred orally. Our results show that VO(II)-complexes demonstrated hypoglycemic or anti-hyperglycemic effects in diabetic rats in both fasting and post-prandial states respectively. The similar or much better activity of the VO(II)-complexes that Glibenclamide, may indicate that the VO(II)-complexes act by simulation of the Islet-cells and thus requires functional pancreatic β-cells for its action.

**Anti-inflammation activity:**

The Anti-inflammatory activity was carried out using carrageenan-induced rat paw oedema model. The results have been compared with standard drug Dicofenac sodium which is categorized as a NSAID (Non-steroid anti-inflammatory drug) this category of drug acts at the periphery and not at CNS. Vanadium complexes are showing moderate to very good anti-inflammatory activity up to 1h, which goes on reducing with the time. The probable mechanisum of action of carageenan induced oedema is bi-phasic, the first phase is attributed to release of histamine –HT, kinnis in the first hour while the second phase is attributed to release of prostaglandin like substance in 2-3h. The activity of VO(II)- complexes are structure dependent and is excellent in inhibiting carageenan induced oedema.

**Anti-Cancer Activity:**

Platinum complexes are now amongst the most widely used drugs for the treatment of cancer. Four injectable Pt(II) compounds have been approved for clinical use and several other cis-dian(m)ine complexes are on clinical trials, including an oral pt(IV) complex. Cisplatin is one of the most widely used. Next generation anticancer drugs of platinum are –carboplatin [Pt(NH3)2(CBDCA-0,0')], glycolato complex(nedaplatin)and oxalipltin, wich contains R,R-1,2-diaminocyclohexane, DACH), have been approved for clinical use in countries like japan and france. Guanine N7 is the most electron-rich site on DNA (most easily oxidized) and the major adducts of platinum drugs with DNA are 1,2-GpG and 1,2-ApG insrastrand crosslinks. These drugs are particularly effective in combination chemotherapy for treatment of advanced lung, colorectal and ovarian cancer.

Ag(I) is being used as an anticancer agent in several human cancers. The Anti-cancer activity of Ag(I) complexes against Ehrlich Ascites tumor a cell (EACs) has been reported. So some new water soluble Ag(I) mixed ligand complexes containing nitrogen and sulfer base derived from L-lysine and thiouracil with 2,2' –bipyridyl; 2-aminopyridine with thiouracil have been synthesized and investigated. The reliable criteria for judging the efficacy of any anticancer drug are prolongation of life span, improving the clinical, hematological, and biochemical profile, as well as reduction in viable tumor cell count in the host. We have observed that mixed ligands complexes of Ag(I) in water or DMSO Exhibit potent cytotoxic activity against EACs. It is known that the anticancer available drug inhibits the hematological and biochemical parameters (hemoglobin (Hb), red blood cells count (RBCs), and white blood cells count (WBCs); blood pictures). The ultimate goal of this project is to develop mixed ligands complexes containg nitrogen bases effective against cancer without side effects on the hematological and biochemical parameters.

The Anticancer activity of Ag(I) complexes showed remarkable efficacy manifested by survival and activity, as well as reduction of tumor size. V,W and X Ag(I) complexes more active comparison to other Y and Z Ag(I) complexes because V, W and X contains sulfer and nitrogen. The hematological parameters including Hb, RBCs and WBCs data are reported. It is clear that the hematological parameters of tumor bearing mice treated with Ag(I) complexes exhibits better doses of (0.01 mg/mice/day) with the standard (5-fu), the market drug( approx 0.4mg/mice/day).

**Antitubercular Activity:**

The Schiff bases and metal chelates have been tested for their possible anti-tubercular activities against. Mycobacterium tuberculosis and M. avium by Tuberculosis Antimicrobial Acquisition and Coordinating Facility. NAID Birmingham. Some of the compounds exhibited activities more than ~90% and hence are under further investigations. The principal of efficacy and novelty of metal mediated chemotherapeutic action can be interpreted in the light of biocoordination chemistry.

**Anti HIV Activity:**

Pt(IV) complexes came into the medicinal stage soon after the toxicity of cisplatin became a moajor clinical issue for cancer treatment. It is believed that octahedral Pt(IV) complexes are kinetically more inert in blood stream but can be activated once enters into the cells by reducing agents to give cytotoxic Pt(II) species; it offers potential advantage over Pt(II) compounds regarding oral availability, reduced drug resistance and toxicity; thousands of Pt(IV) complexes have been synthesized and tested as prodrugs. The purpose after synthesizing Pt(IV)

complexes is tunning of their redox potential, kinetic stability, hydrophilicity/lipophilicity to achieve desired reactivity and activity by selecting axial and equatorial ligands. Thiopyrimidine-Platinum and Palladium compounds may be looked upon, as a new class of futuristic antitumor or antiviral agents. Sadler suggested that active metal complexes will provide many new therapeutic and diagnostic agents over the coming years and will direct medicinal inorganic chemistry into a discipline of central importance in medicine and science[33-37].

**Summary**:

Biomedical inorganic chemistry and medicinal inorganic chemistry are fairly recent offshoot of bioinorganic chemistry, which itself is a science still with much to learn. It is at the interface between medicine and inorganic chemistry and includes metal-based drugs, metal sequestering or mobilizing agents, metal-containing diagnostic aids and the medicinal recruitment of endogenous metal ions. It offers the potential for the design of novel therapeutic and diagnostic agents and hence for the treatment and understanding of diseases which are currently intractable. Inorganic elements play crucial roles in biological and biomedical processes and it is evident that many organic compounds used in medicine do not have a purely organic mode of action; some are activated or biotransformed by metal ions including metalloenzymes, others have a direct or indirect effect on metal ion metabolism.

The unique properties of metal complexes tend to offer advantages in the discovery and development of new drugs. The metal complexes are amenable to combinational synthetic methods and an immense diversity of structural scaffolds can be achieved. Metal centers are capable of organizing surrounding atoms to achieve pharmacophore geometries that are not readily achieved by other means. Additionally, the effects of metals can be highly specific and can be modulated by recruiting cellular processes that recognize specific types of metal-macromolecule interactions. Metals can be useful probes of cellular functions. Understanding these interactions can lead the way towards rational design of metallopharmaceticals and implementations of new co-therapies. Metal-based agents can modify both DNA and RNA with a high degree of regiochemical, sequential and conformational specificity. Simply targeting DNA is no longer a sufficient rational for testing a compounds (Whether organic or inorganic). Cell selectivity in m-RNA expression makes it an attractive target. The metal complex-based selective enzyme inhibition is an under explored area. Metals may be useful in active site recognition and in bifunctional agents as secondary contacts to increase inhibitor affinity[38-43].

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# EVOLUTION OF GREEN CHEMISTRY AND THEIR MULTIDIMENSIONAL IMPACT ON MODERN HUMAN ENVIRONMENT

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**Abstract:**

The developing system of industrialization was an achievement for world monetary advancement. Since the 1940s, social developments have reformed green science and given shifts in modern positions and maintainable cycles with propels in ecological effect and attention to organizations and populace. Green science is otherwise called feasible science. It is utilized to plan of compound items and systems that diminish age of risky synthetic substances. Green science applies askew the existence pattern of a substance item, including its production, use, plan, and eventually removal. Green science is extremely useful in anticipation of contamination at the atomic level, it gives inventive logical arrangements, it decreases the adverse consequences of compound items on human and the climate wellbeing. Green science's 12 standards Prevent squander, Maximize iota economy, Design less risky substance union, Design more secure synthetics and items, Use more secure solvents and response conditions and Increase energy productivity and so forth Green science assume significant part in drug in creating innovatory drug conveyance techniques which are not so much harmful but rather more valuable, powerful with least aftereffects and could help a huge number of patients. The utilization of UV-energy Microwave light in is additionally critical method for accomplishing the objective of green chemistry.This paper clarify philosophy, certain models and use of green science in daily existence, in industry, the research center and inschooling.

**Keywords:** Green Chemistry, Environment, Sustainability, Green analytical chemistry, Multidimensional impacts, Future.

## Introduction:

Green Chemistry is characterized as creation, plan, advancement and utilization of compound items and cycles to decrease or to wipe out the utilization and age of substances dangerous to human wellbeing and climate [1]. An interesting system was started by (EPA) the Environmental Protection Agency of US in 1991 to execute maintainable advancement in compound innovation and science by industry, government and the scholarly community. There Poul T. Anastas utilized the word green science [2-4]. Science has enjoy the advantageous things

as medication, colors, beauty care products, food items, nano particles, fluid precious stone, polymers, paints, biomolecules, agrochemicals. By and by, different complex items can be fabricated without any problem. Regardless, synthetic cycle yields the expected item as well as the undesirable or undesired and destructive substance in enormous amounts as fluid, gases, and strong. This has turned into the enormous danger for the science. So for the manufactured physicists the decrease of the substance contamination has turned into the basic criticalness [5-13]. Maintainability and Green science go in one breath. Maintainable advancement is a course of arriving at the necessities of the current period without arranging the capability of unborn age gathering to finish their own requirements. The ideas of Green science are not new or unused rather it is new methodology towards the supportability. Accidents happen essentially because of the substance/actual properties of the atoms we break down. By the planning of the medication at atomic level, and sort of response conditions and the response we select, we can likewise manage fundamental issues like sustainability, poisonousness, and worldwide effect [14-17]. Because of these rationales, Green Chemistry is a high level synthetic way of thinking. Its ideas move the planning of imaginative cycles and natural substances that limits the use of unsafe substance and their production.Green science's ideas represents two most significant parts:-

1. First, Green science portrays the quandary of productive utilization of beginning materials for union and the related decrease of waste because of their utilization.
2. Second, it concurs with the security, ecological issues and wellbeing which are connected with the assembling, use of synthetic substances and their removals.

Individuals who are rehearsing science in the business, exploration, and instruction to them the changes in the Green science gives a more than adequate number of difficulties. With these difficulties yet, there are practically equivalent opportunity to light upon and utilize progressed science in everyday life, to improve financial aspects of synthetic assembling and to redesign the better picture of science. Green science is ended up being a development part of science which is acquired from the requirements to diminish the damaging impact of synthetics and to limit how much ecological contamination get from unsafe synthetics [17]

**History of Green Chemistry:**

The term green science was first used in 1991 by P.T. Anastas in a phenomenal program dispatched by the US Environmental Protection Agency (EPA) to execute efficient improvement in science and substance advancement by industry, the academic local area and government. In 1995 the yearly US Presidential Green Chemistry Challenge was accounted for. Relative distinctions were after a short time got comfortable European countries. In 1996 the Working Party on Green Chemistry was made, acting inside the arrangement of International Union of Applied and Pure Chemistry. Following one year, the Green Chemistry Institute (GCI) was outlined with segments in 20 countries to work with contact between managerial workplaces and current endeavors with universities and assessment associations to design and execute new

advances. The chief social affair highlighting green science was held in Washington in 1997. Since that time other similar sensible social events have after a short time hung reliably. The principle books and journals in regards to the issue of green science were introduced during the 1990s, including the Journal of Clean Processes and Products (Springer-Verlag) and Green Chemistry, upheld by the Royal Society of Chemistry. Various journals, as Environmental Science and Technology and the Journal of Chemical Education, have given regions to green science.

The developing system of industrialization was an achievement for the world monetary advancement. Notwithstanding the commitment to the expansion in personal satisfaction, the worldwide government strategies stayed a long way from the ecological effect that the development of modern exercises could cause in our planet. The fast expansion in populace brought about expanded food creation with exorbitant industrialization, which prompted expanded contamination and asset exhaustion. Along these lines, regular assets started to be utilized as though there were no results on ecological issue [18].

Albeit the principal worries about the climate happened starting around 1949 at United Nations Scientific Conference on the Conservation and Use of Resources (UNSCCUR) in the USA, ecological issues came into center in 1968 from the Intergovernmental Conference of Experts on the Scientific Bases for Rational Use and Conservation of Biosphere Resources, known as the Biosphere Conference [19]. During the 1960s the distribution of the book "Silent Spring" animated a contemporary ecological development. The chronicled book has brought issues to light about environmental discernment and has given significant government drives set apart by worry about the dangers related with over-abuse of normal assets. Robert Downs, recorded the book as "the book that changed America" and John Kenneth Galbraith referred to it as one of the main books in Western writing [20].

The Stockholm Conference happened in Sweden in 1972, and it was gone to by agents from various nations, including individuals from the United Nations (UN) and nongovernmental associations, where ecological regulation was likewise thought to be in the legitimate field [21]. From this meeting, the world started to be alarmed on the natural harms that the exhaustion of the environment could cause to humankind [22]. The 1980s were set apart by various world meetings on the Environment. After an assessment of the 10 years of the proposed activities at Stockholm Conference, the UN established the World Commission on Environment and Development in 1983 to create a report on world turn of events and climate. This commission was laid out during a period of phenomenal strain on the worldwide climate and a developing acknowledgment that a large part of the advancement was not feasible [23].

The report known as the "Brundtland Report" accommodated natural and social issues and was distributed in 1987, which interestingly characterized the idea of maintainable

improvement as advancement that addresses the issues of the current age without compromising the group of people yet to come. The report likewise underlined the risks of ozone consumption and the consequences for an Earth-wide temperature boost, expressing that researchers' capacity to assess and propose arrangements were lower than the speed of environmental change [24].

In 1985, during a gathering of the Environment Ministers of the nations of the Organization for Economic Co-activity and Development (OECD), a few choices were made on three principles topics: Economic Development and Environment, Pollution Prevention and Control and Environmental Information and National Reviews, these choices continued until the year 1990.

Intercessions in light of these fundamental subjects were vital to issues of compound item risk decrease and contamination avoidance and control [25]. The US Environmental Protection Agency (EPA) sent off the "Alternative Synthetic Routes for Pollution Prevention" program in 1991 that detailed another way of thinking and strategy on controlling the dangers of harmful compound items to forestall issues with these substances, accentuating that the right would be the non-creation of these items in the primary occasion [26].

Starting around 1992, the consideration of different themes as harmless to the ecosystem solvents and more secure substance intensifies has been the extension and rename of this program, which from that point forward formally embraced the name of green science [19]. The 1990s were set apart by an overall agreement on ecological conservation. In Brazil there was a United Nations International Conference on Environment and Development in 1992 called (ECO-92). The support of heads of state brought about the elaboration of an archive named "Agenda 21", which had the responsibility of nations to esteem feasible improvement by moving ecological issues, monetary arrangements and decision-production [27]. Albeit the advances in the climate had been stirred around the world, the natural familiarity with the organizations was exceptionally uncertain. The organizations were submitted to controls laid out by the public authority when they were forced by the media and common society, accepting this natural aspect as a means to an end [28]. To change the business area, a program called "Responsible Care", was created in 1984 in Canada and until the current day it is drilled in 68 economies all over the planet, enhancements in the conduct of ventures corresponding to the climate, the wellbeing and security of laborers [29].

With this program, human exercises started to be acted in quest for progress, supplanting hurtful exercises with exercises that underscored personal satisfaction and a protected climate, for example, interests in framework security; upgrades in energy effectiveness; representative wellbeing records; intentional development of cycle occurrences and decrease of perilous emanations to air, earth and water [29]. Albeit ecological issues significantly affect modern and monetary areas, an overview of the European Chemical Industry Council (CEFIC) in 1994 showed that the populace's perspectives on the synthetic business were not positive. By and

large, the populace was more mindful of the drug and plastics areas due to the advantages related with their requirements [30]. Most interviewees didn't really accept that that the substance enterprises were worried about the advancement of practical activities. Sentiments produced hates about the transportation, well being and misuse of these enterprises, making conclusions better to the oil, gas, power, wood and paper businesses [31].

The US Government in 1995 declared the Presidential Green Chemistry Challenge (PGCC) program. It ponders the mechanical advancements that were comprised in the compound businesses to decrease the creation of waste in a few areas of creation. The works are granted every year in five distinct classifications: Academic; Small Business; Alternative Synthetic Routes; Reactive Alternative Conditions and Safer Chemical Designs [32]. In 1997 the Green Chemistry Institute (GCI) was made as a non-benefit organization to advance through the information, experience and limit, moves of the synthetic organization toward manageability, which cutting-edge in the utilizations of green science [33]. The GCI joined the American Chemical Society (ACS) in 2001 to resolve worldwide issues in the gathering of science and climate. Through research, work has incorporated green science in each viewpoint, for example, ventures, business, schooling, arranging gatherings as well as getting sorted out endeavors with worldwide networks[33].

The earth shattering book Green Chemistry: Theory and Practice, introducing Paul Anastas and John C. Warner as co-creators in 1998, was one more significant advancement for green science. In the book, the 12 Principles of Green Chemistry are obviously illustrated with a way of thinking that has generally supported scholarly researchers and businesses to seek after ecologically right activities [34]. In 2002, following 30 years of the Stockholm Conference, an occasion called Rio + 10 or the World Summit on Sustainable Development occurred in the city of Johannesburg, South Africa, went to by large number of individuals [35]. Administrative and non-legislative associations, huge organizations, sectoral affiliations, appointments and writers went to this gathering to relegate a solitary goal: to examine the arrangements proposed in "Agenda 21", with the goal that the public authority can apply them, yet everybody, as well as executing what had been talked about in ECO-92 [24]. The ACS's Green Chemistry Institute (GCI) and the worldwide drug enterprises laid out a board conversation in 2005 to empower and support green science and green designing in the drug businesses. The board conversation characterized "persistent handling" as the way in to the execution to propel "the green" [36].

The International Union of Pure and Applied Chemistry (IUPAC), along with ACS and GCI, held four gatherings on Green Chemistry somewhere in the range of 1997 and 2011. The gatherings included points, for example, green items and cycles to the climate, creation energy, sustainable wellsprings of synthetic waste as well as taking on green approaches and schooling in green science [37]. Despite the fact that advances in science and biological designing

examination have taken on practical cycles throughout the long term, proceeding to put resources into modern procedures and approaches will be critical during the time spent executing natural enhancements [38].

**Green Chemistry and Sustainable Development:**

"Green science" and "backing capacity" are short clasps, but another perspective that promises to lastingly influence the investigation of science. Green science and viability essentially go inseparable. Viable headway is tending to the necessities of the current age without compromising the limit of individuals in the future to resolve their own issues. We truly needed greener science that successfully utilizes boundless crude parts, kills waste and avoids the use of hurtful as well as unsafe solvents and reagents in the two things and cycles to achieve this good goal. Green science typifies two central parts. In any case, it settle the issue of useful utilization of normal substances and the going to removal of waste. Second, it deals with the prosperity, security and environmental issues related with the creation, use and expulsion or re-usage of manufactured compounds. Green science is perhaps the most vital and staggering resource for use while heading to help capacity. For sure, without green science and green planning, it is absolutely impossible to help capacity.

From the beginning Paul Anastas and John Warner highlighted the new guidelines of Green Chemistry and the better approach for believing that should be followed to achieve the conservative Eco-improvement of the compound business later on. Green Chemistry is by and large presented as a lot of twelve norms proposed by Anastas and Warner [39].The principles include directions for proficient scientists to carry out new synthetic compound, new union and new mechanical cycles.

**Definition of Green Chemistry:** Green Chemistry is utilization of a set principle that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical product.

**Significance of Green Chemistry:** A clever methodology that mixes the utilization of science with monetary development and ecological protection.

- Accomplish protection of restricted assets through cost viability and contamination anticipation.
- To foster technique for economical compound interaction businesses.
- Consequently fundamental aphorism of green science is to plan item and cycles that lessen or dispense with the age, everything being equal.

**Objective of Study:**

- The plan of cycles to augment how much unrefined substance that winds up in the item.
- To concentrate on the green science utilized in day to day existence and familiarity with the social orders.
- Outline writing review on the organic movement of human existence and combination of

New Non-harmful part.

- The utilization of inexhaustible material feed stock and energy sources.
- To concentrate on the utilization of safe, ecologically harmless substances, including solvents, whenever the situation allows.
- The plan of energy effective cycles.
- Staying away from the creation of waste which is seen as the best type of waste administration.
- This reviews the nuclear and energy financial aspects involve conspicuous spots, as well as the utilization of sustainable and harmless unrefined components.
- The fundamental point of this study is to foster novel, effective, advantageous, particular and naturally harmless engineered strategies in natural science, which helps the medication revelation and therapeutic science and agrochemicals.

**Principles of Green Chemistry:**

The accompanying rundown of twelve standards diagrams an early origination of what might make a greener synthetic, interaction or item beneath Fig,1.

**1. Prevention:** It is smarter to forestall squander than to treat or tidy up squander after it is shaped. It returns to the well-known adage "anticipation is superior to fix". It is smarter to forestall squander than tidy it up afterward [40].

**2. Atom Economy:** Synthetic strategies ought to be intended to expand the consolidation of all materials utilized in the process into the end result.

**3. Less Hazardous Chemical Synthesis:** Synthetic procedures ought to be intended to utilize and produce substances that have next to zero harmfulness to human wellbeing and climate [41]. A few poisonous synthetic compounds are substituted by more secure ones for a green innovation.

**4. Designing Safer Chemicals:** This guideline is pointed toward planning items with wanted work while limiting their harmfulness [42].

**5. Safer Solvents:** This standard spotlights on making Safer Solvents and assistants substances (e.g., solvents, detachment specialists, and so forth) for laborers and the climate [43]. Clearly water is the most cheap and ecologically harmless dissolvable.

**6.Design for Energy Efficiency:** This rule centers around making items and materials in an exceptionally effective way and decreasing related contamination and cost [44].

**7. Use of Renewable Feed Stocks:** Raw materials or feedstock ought to be sustainable rather than draining. Biodiesel is an illustration of this where analysts are attempting to observe elective powers that can be utilized for transportation [45].

**8. Reduce Derivatives:** Unnecessary derivatization (impeding gathering, insurance/deprotection) ought to be stayed away from whenever the situation allows, on the grounds that such advances require extra reagents and can produce more waste [46].

**9. Catalysis:** Catalysis and new reactant reagents (compounds, as specific as could be expected) are better than stoichiometric reagents [47].

**10. Design for Degradation:** Chemical items ought to be planned so that toward the finish of their capacity they separate into harmless debasement items and don't persevere in the climate [48].

**11. Pollution Prevention:** Everyone realizes that avoidance is superior to fix from this contamination is superior to contamination control. Contamination counteraction is utilizing materials, cycle or practices that lessen or take out contamination or squanders at the source.

**12. Safer Chemistry for Accident Prevention:** This standard spotlights on security for the laborer and the encompassing local area where an industry lives. It is smarter to utilize materials and synthetic compounds that won't detonate, get on fire going, light in air, and so on while making an item [49].


**Figure 1: Principles of Green Chemistry**

**Green Analytical Chemistry:**

In 1999, Paul Anastas distributed a paper in which he talked about the significance of utilizing the 12 standards of Green Chemistry, proposed by him and John Warner in the earlier year (1998), in the improvement of new strategies and insightful methods, to lessen their natural effects [50]. One of the most dynamic areas of Research and Development in Green Chemistry is the improvement of insightful strategies. New strategies and procedures that can decrease and kill the utilization and age of unsafe substances in all phases of compound investigation are the

principle focuses of the alleged Green Analytical Chemistry [51]. Galuszka, Migaszewski and Namiénski, in 2013, adjusted the 12 standards of Green Chemistry, to more readily fit the Green Analytical Chemistry [52]. In this manner, the 12 standards of Green Analytical Chemistry are depicted in Table 1. The standards recommended by Galuszka, Migaszewski and Namiénski (2013) depend predominantly on the end or minimization of the utilization of synthetic substances, on the minimization of the utilization of power, on the right treatment of the produced logical buildups and on the more noteworthy wellbeing of the administrators [52].

**Table 1: 12 Principles of Green Analytical Chemistry, proposed by Galuszka, Migaszewski and Namiénski (2013)**

| Number | Principle and description |
|---|---|
| 1 | Direct analytical techniques should be applied to avoid the sample treatment step |
| 2 | The size and quantity of samples should be as small as possible |
| 3 | *In situ* analyzes should be carried out |
| 4 | Integration of analytical processes and operations must be performed, as it promotes energy savings and reduces the use of reagents |
| 5 | Automated and miniaturized methods must be selected |
| 6 | Derivatizations should be avoided as they require the use of additional reagents and, therefore, generate waste |
| 7 | Generation of large volumes of analytical waste must be avoided and the correct handling of this waste must be provided |
| 8 | Multi-analyte methods should be preferred over methods that analyze one analyte at a time |
| 9 | The use of electric energy should be minimized |
| 10 | Reagents obtained from renewable sources should be preferred |
| 11 | Hazardous reagents should be discarded |
| 12 | Safety of operators should be increased |

**The Challenges to Chemists:**

Viable progression is by and by recognized by state run organizations, industry and general society as a fundamental goal for achieving social, monetary and regular objections. Inside this, science has an imperative influence to play in staying aware of and dealing with our own fulfillment, the reality of the compound business and the standard territory. This occupation for science isn't generally seen by government or thepublic. Honestly manufactured substances, science and physicists are truly considered by various people to be explanations behind the issues.

The test for researchers and others is to encourage new things, cycles and organizations that achieve the social, monetary and environmental benefits that are presently required. This requires another philosophy which chooses to diminish the materials and energy power of manufactured cycles and things, limit or get rid of the dispersing of disastrous engineered compounds in the environment, expand the usage of boundless resources and widen the strength and reuse capacity of things in a way which increases current reality. A piece of the hardships for logical specialists join the disclosure and headway of new designed pathways using elective feed

stocks or more specific science, recognizing elective reaction conditions and solvents for additional created selectivity and energy minimization and arranging less destructive and intrinsically safer manufactured compounds. In manufactured mixture, the ideal will be a mix of different environmental, prosperity and security and money related targets. Though various researchers, and a few colossal and more unobtrusive associations, are really pursuing 'green science' there are at this point various limits to progress. These recall a general shortfall of care and getting ready for schools, universities and industry and an organization acumen that green science is a cost without benefits. The drive towards clean development in the manufactured business with a growing complement on the reduction of waste at source will require a level of progression and new advancement that the compound business has not found in various years. Mature compound cycles that are routinely established on advancement made in the important portion of the 20th century may by and by don't be palatable in these naturally mindful days. 'Enviro-monetary issues' will transform into the primary purpose for new things and cycles. This should be visible to thinking about the continuously raising and different 'costs of waste'. The costs of waste can truly be enormous.

The term green science was first used in 1991 by Poul T. Anastas in an extraordinary program dispatched by the US Environmental Protection Agency (EPA) to do prudent progression in science and substance advancement by industry, the insightful world and government. In 1995 the yearly US Presidential green science challenge was accounted for. Similar distinctions were after a short time got comfortable European countries. In 1996 the working party on green science was made, acting inside the arrangement of International Union of Pure and Applied Chemistry (IUPAC). Following one year the Green Chemistry Institute (GCI) was outlined with segments in 20 countries to work with contact between administrative associations and current organizations with schools and investigation establishments to plan and do new advances. The essential gathering including green science was held in Washington in 1997. Since that time other sensible social occasions have been in a little while hung reliably. The primary book and journals in regards to the question of green science were introduced in 1990, including the Journal of Clean Processes and Green Chemistry, upheld by the Royal Society of Chemistry. Green science intertwines one more method for managing the blend, dealing with and use of engineered substances in such manner as to diminish threats to prosperity and environment.

This new methodology is otherwise called:

- Ecologically harmless science.
- Clean science.
- Particle economy.
- Harmless by-plan science.

**Impacts of Green Chemistry:**

**1. Pharmaceutical analysis:**

Right now the compound drug enterprises and research centers should examine green science through, and not just, their analysis.The picked technique, reagents, embellishments, work force capability, time to assess the nature of an item are essential for the naturally right reasoning, displayed in Fig. 2 [53].The strategy for decision for the assurance of dynamic drug fixings as well as the examination of pollutions and corruption items is elite execution fluid chromatography (HPLC). A large portion of these strategies use as natural solvents, acetonitrile or potentially methanol. Many likewise choose cradle arrangements. This is undeniable. In any case, the vast majority of them have never at any point endeavored to involve one more natural dissolvable notwithstanding the acetonitrile/methanol blend or don't involve support arrangements in the portable phase.Why? Absence of information, carelessness of outcomes, ease or potentially convenience? [54].

Support arrangements, as well as requiring a specific measure of time to get ready, have a low time span of usability which requires another readiness and accordingly a more drawn out administering time. Its utilization likewise requires a broad cleaning interaction of both the section and the whole chromatographic system.Toxic natural solvents, for example, acetonitrile and methanol, as well as harming day to day to these solvents additionally requires appropriate waste administration for the removal of this impurity. This has an expense that will surely be remembered for the eventual outcome [55]. Indeed, even the frill utilized in the strategies for investigation can ponder green reasoning. Chromatographic pre-sections are regularly not required, yet are utilized by absence of information on the examiner who comprehends that it should be available. Steps, that are excessive but rather, which are completed by absence of information on the expert who gets that in the event that he doesn't do it the technique will be erroneous and will prompt an outcome out of detail. Gadgets that can be reused however that are not on the grounds that the organization generally purchases more thus it is more advantageous to discard and trust that the upgraded one will show up [56]. Frequently qualified staff are appointed to foster trite undertakings, reiteration of errands like a robot, over handling items and cycles as opposed to creating, making, and develop inside their workspace. This is a misuse of mind, one of the eight squanders we have today. It is a complex and qualified labor force employed to perform unremarkable administrations [53].

Is the ideal opportunity for each cycle or examination estimated? It should be. It is essential for green science. The more drawn out a movement takes, the more extended the expert should be subject to it and less exercises he will create and hence there will be less creation and the eventual outcome will be more costly. Time, a thing that begins a whole interaction or administration, has direct outcomes on the last product[53]. Subsequently, quicker and less

expensive techniques with faculty enough qualified for the help, utilizing materials and extras deserving of examination and with naturally right reagents are at present required. In the writing there are numerous physical-substance and microbiological techniques for the assessment of medications and drugs which ponder green logical science things, for example, HPLC strategies involving just ethanol and water in the versatile stage [57], Spectrophotometry in the ultraviolet area (UV) involving fluid arrangement as diluent [58] , Spectrophotometry in the noticeable district (Vis) using aqueous arrangement as diluent [59], Spectrophotometry in the infrared locale (IR) utilizing only potassium bromide as reagent, fine electrophoresis (CE) with relocation time under 5 min. [60] and microbiological techniques with brings about 4 hours.

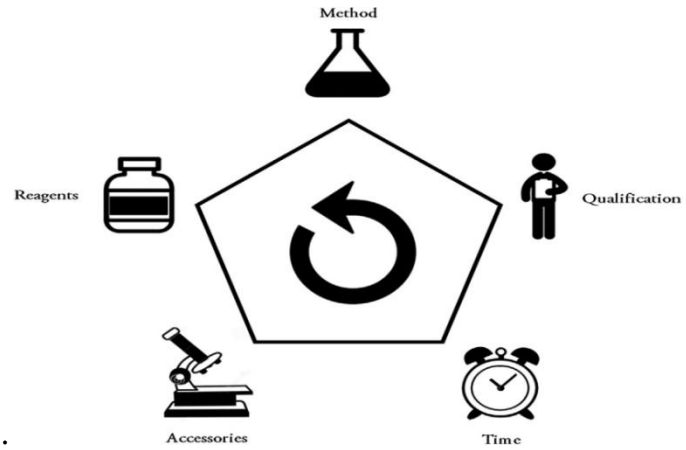


**Figure 2: The pentagon of ecologically correct thinking**

**2. Environment:**

The deposits produced in the compound drug investigates should be pre-treated prior to being gotten back to the climate. In any case, this cycle requires an expense that is more costly relying upon the poisonousness and haphazardness of the dissolvable. Acetonitrile, for instance, is burned and this cycle creates squander that adds to corrosive downpour. In any event, utilizing a cycle to kill the harmfulness of the dissolvable, it adversely influences us in any case (World Health Organization, 1993). Corrosive downpour harms vehicles, structures, landmarks, vegetation, waterways, lakes, etc. The vegetation can consider manors that feed large number of individuals. The waters can be impacted with a lower pH and change the living space already ideal for specific organic entities that lived there. An impact like this won't ever be separated! This is when waste is dealt with, however when are not? At the point when modern squanders are unloaded straightforwardly into the waters biological catastrophes can happen. Fish and vegetation kick the bucket, defiled water changes its qualities and eutrophication happens (World Health Organization,1997). At times this water would be utilized for the water system of ranches, which for this situation would likewise be hindered, as displayed in Fig. 3

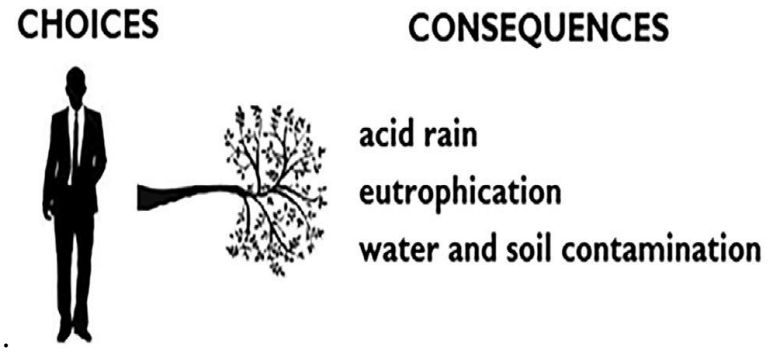


**Figure 3: The consequences of analytical choices on the environment**

**3. Population:**

The populace is affected by current science in various ways and on various fronts. Patients who as often as possible get their prescription from drug stores or wellbeing focuses are impacted by the selection of strategies for investigation and reagents utilized by investigators or substance drug administrators. A costly technique creates a costly item available. A costly technique with embellishments (not generally vital) creates a more costly item available. A costly technique with extras and a few stages (not generally important) creates a much more costly item available.

A tedious technique that deliveries results inside 24 h or more, for example, microbiological results for anti-microbials, will make items costly or on the other hand, whenever delivered without this examination, maybe wasteful which can advance the over-burden of the wellbeing framework and add to microbial resistance[61]. The patient is without a doubt impacted by the scientific choice in the examination of a drug, in the assessment of the nature of an unrefined substance and in the improvement of a modern or research center cycle [62]. Every one of the means of an interaction have an expense that is given to the end result that the patient pays and is additionally impacted by its belongings, positive or negative.

**4. Investigator:**

The physical-compound expert has immediate and everyday contact with the drug dissects. He is the first impacted by the whole scientific chain. Harmful solvents, for example, acetonitrile are retained rapidly by the body and its digestion creates cyanide that weakens breath (World Health Organization, 1997). Another model, which is likewise exquisite by drug dissects, is methanol. As well as being discharged more leisurely than ethanol the results of its digestion produces formaldehyde and for the most part formic corrosive which are liable for extreme inebriation [53].

The expert can likewise experience the ill effects of the execution of tedious and non-reproducible insightful strategies or that require explicit extras or that have a few phases or that rely upon different experts, at any rate, the examiner, notwithstanding all openness to poisonous solvents and reagents, can likewise endure inwardly. A tedious strategy deters the examiner and

creates misuse of insight and time. An important opportunity approaching from a certified proficient who could be fostering another movement. As indicated by William Edwards Deming Fig. 4, the techniques that don't replicate bring an inclination that the expert isn't qualified, and 85% of the time the issue isn't the investigator yet the strategy that should be improved [53]


**Figure 4: William Edwards Deming, one of the quality gurus**

Explicit adornments will bring about costly items. Is it conceivable to change the frill or framework that doesn't utilize it? They won't continuously be conveyed immediately. What will occur assuming that the embellishment creation is ceased? The reality of relying upon an individual to play out a movement is genuinely debilitating. How often did somebody hang tight for one more to have the option to play out specific movement? As of now clearly the capability of this holding up individual was squandered. Pausing and mind are squanders that should be dispensed with for the outcome of an organization. Then, at that point, notwithstanding actual wellbeing, the expert can likewise experience the ill effects of enthusiastic wellbeing. Demoralization, sensation of insufficiency and dread are instances of variables that influence the examiner's enthusiastic. Furthermore, this can likewise influence actual wellbeing. Quality instruments can be utilized in process improvement, association among individuals and lessening of the ice sheet of the quality expense [53].

**5. Organization:**

Substance drug organizations should progressively consider the standards of green science as well as green logical science, since turning off the light until picking the reagent to be utilized in the assessment of a drug, since the communication with the associate until the arrangement of preparing for a group. Green science should be viewed as a practical thought since a superior world until a superior organization, individuals and gaiety. An organization that esteems this sort of disposition, present day and current, will surely succeed. In it there will be no workers except for teammates. In it there will be no boss except for pioneers. In it there will be no the vision just in the eventual outcome however in the entire chain, to be practical, green and clean [63]. Along these lines, naturally, the organization develops. The vision of the organization is likewise benefited, on the grounds that it turns into a model and reference of the biologically right, spotless and practical, other than being cutthroat on the lookout. Organizations like Coca-ColaTM, GoogleTM, AppleTM are instances of this idea [64-66].

**6. Future:**

World pioneers have effectively started this hypothetical interaction through the United Nations Conference on the Human Environment in Stockholm in 1972, Conference of Nairobi in 1982, United Nations Conference on Environment and Development in Rio de Janeiro in 1992, World Summit on Sustainable Development in Johannesburg in 2002, United Nations Conference on Sustainable Development in Rio de Janeiro in 2012 and the Paris Agreement in 2015 [67]. In the scholarly expert setting there is the "Green and Sustainable Chemistry Conference" that unites scholastic and business agents to show work and trade thoughts and learning [68]. These drives show that many work for green science, supportable, clean and environmentally right. One method for accomplishing the unimaginable is to plan the conceivable. So we simply need to do our part. Assuming every one has an impact, it doesn't make any difference in the event that it is little, when we join every one of the parts they will be huge. At long last, we should have uplifting outlooks for the eventual fate of green science since it includes the fate of our reality. Green science isn't confined to a substance examination wherein a less harmful dissolvable is utilized. This isn't green science. Green science is a bunch of activities and mentalities, it is multi-layered [69]. It is pondering the entire cycle and limits reagents, steps, expenses and energy. In this situation, the hero should likewise be thought of. The physical and passionate strength of the associate is the differential of the organizations, since they realize that a man alone won't ever add the abilities of a viable group.

**Industrial Interesting Green Chemistry:**

Many forward-looking associations are tolerating Green Chemistry, not only to get the environment and to make extraordinary publicizing, yet furthermore since it is as often as possible valuable to the primary concern it is also evaluated to cost US adventures between $ 100 and $ 150 billion consistently to concur with natural rules. Furthermore, cleaning up perilous waste districts will cost a large number of dollars. In numerous associations, the cost of overseeing normal rules routinely outperforms their utilization for research. Greater associations monetary arrangement close $ 1 billion consistently for regular consistence. Accepting an association can basically decrease this utilization, these resources can be spent in more valuable areas and result in a chipped away at essential concern. Therefore, Green Chemistry (pollution aversion) isn't only valuable for the environment yet furthermore for industry.

**Green Chemistry in Education:**

Convincing logical specialists to think in an innocuous to the environment way begins with tutoring. Recalling Green Chemistry for science guidance was first best in class in 1994. Barely any Green science perusing material have also been conveyed. Graduates, post graduated class, teachers and researchers will find these books of tremendous use. Both Environmental Protection Agency (EPA) and American Chemical Agency (ACS) have seen the meaning of

conveying Green Chemistry to the review lobby and the exploration office. Together they have dispatched a basic mission to cultivate Green Chemistry informative materials and to help the 'greening' of the science instructive program. Student relationship in Green Chemistry guidelines and practices is fundamental for the consolidation the biologically innocuous advances in academic local area and industry. ACS Student Affiliate Chapters may be seen as "green" areas by taking part in something like three Green Chemistry practices during the academic year. Thoughts for these activities include: Hosting a Green Chemistry speaker

- Arranging an interdisciplinary Green Chemistry studio nearby.
- Working with a nearby organization on a Green Chemistry project.
- Fostering a Green Chemistry action with a neighborhood school.
- Changing over a current research center analysis into a greener one.
- Arranging a Green Chemistry banner meetings nearby.
- Circulating a Green Chemistry Newsletter to the neighborhood local area.
- Planning a green Chemistry site page.

**Global Education and Recognition of Green Chemistry:**

**(A)Education:** Many organizations offer course and degrees on Green Chemistry. Models from across the globe are Denmark's Technical University, and a few in the US, for example at the Universities of Massachusetts-Boston, Michigan, and Oregon. An experts level course in Green Technology, has been presented by the Institute of Chemical Technology, India. In the UK at the University of York University of Leicester, Department of Chemistry and MRes in Green Chemistry at Imperial College London. In Spain various colleges like theCollege at JaumeI or the Universalized de Navarra, offer Green Chemistry ace courses. There are likewise sites zeroing in on green science, for example, the Michigan Green Chemistry Clearinghouse at www.migreenchemistry.org. Aside from its Green Chemistry Master courses the Zurich University of Applied Sciences ZHAW presents a piece and website page "Making science green" for a more extensive public, showing the 12 standards.

**(B)Awards:** Several logical social orders have made grants to energize research in green science.

1. Australia's Green Chemistry Challenge Awards administered by The Royal Australian Chemical Institute (RACI).
2. The Canadian Green Chemistry Medal.
3. In Italy, Green Chemistry exercises base on a between college consortium known as INCA.
4. In Japan, The Green and Sustainable Chemistry Network supervises the GSC grants program.
5. In the United Kingdom, the Green Chemical Technology Awards are given by Crystal Faraday.
6. In the US, the Presidential Green Chemistry Challenge Awards perceive people and organizations.

**(C) Scientific Journals Specialized in GreenChemistry:**

Several scientific global diaries which are well versed in the field of green science.

1. Green Chemistry (RSC)
2. Green Chemistry Letters and Reviews (Open Access) (Taylor and Francis)
3. ChemSusChem (Wiley)
4. ACS Sustainable Chemistry and Engineering (ACS)

**Conclusion:**

Green Chemistry is certifiably not a shiny new part of science. It is a pristine methodology that through application and expansion of the standards of unpracticed science will add to property advancement. They are applied not exclusively in amalgamation, cycle and double-dealing of substance compounds. A few new scientific strategies portrayed that are finished in sync with unpracticed science rules. They are useful in directing substance processes and in examination of their impacts on the setting. By abuse unpracticed science methods, we can limit the misuse of materials, keep up with the particle economy and hinder the work of hazardous synthetic substances. Explores and Pharmaceutical enterprises became propelled to consider the standards of unpracticed science where as concocting the cycles and choosing reagents. Understudy even the slightest bit levels should be acquainted with the Philosophy and apply ofunpracticed science. A great deal of endeavors are being embraced to plan non contaminating beginning materials and to get more secure items without side items. The best test is too fuse the green science in everyday life. Numerous effective endeavors have been made yet a ton must be finished. This can be accomplished via preparing and teaching new age of physicists. Green Chemistry must be presented in the prospectus of the understudies at all degrees of degree, So that every individual is made mindful to pick greener way in their ordinary life.Research propels have empowered supportable cycles over the course of the years with interests in ecologically right logical and strategy methods in accordance with world meetings since 1968.Despite these endeavors, ventures need to envision the financial practicality of applying green science to their cycles, which keeps us from utilizing the utilization of this belief system. Ventures and dispersal on the significance of green science and how they influence straightforwardly from the beginning of drug investigates, representatives and patient wellbeing until to the ecological manageability are critical for the course of future enhancements.

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# ORGANOCATALYSTS

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## Introduction:

Sustainable development *is* that meets the needs of the present without compromising the ability of future generations to meet their own needs. Two key aspects of sustainable development from an energy and chemical perspective point of view involve the development of renewable forms of energy and reduction in pollution. Chemistry during the twentieth century changed the living standard of human beings. Two significant achievements of chemistry are petrochemical and pharmaceutical industries. However, these industries are often blamed for polluting the environment. Consequently, the challenge for the present-day chemical industry is to continue to provide the benefits of chemistry to society in an environmentally friendly manner.

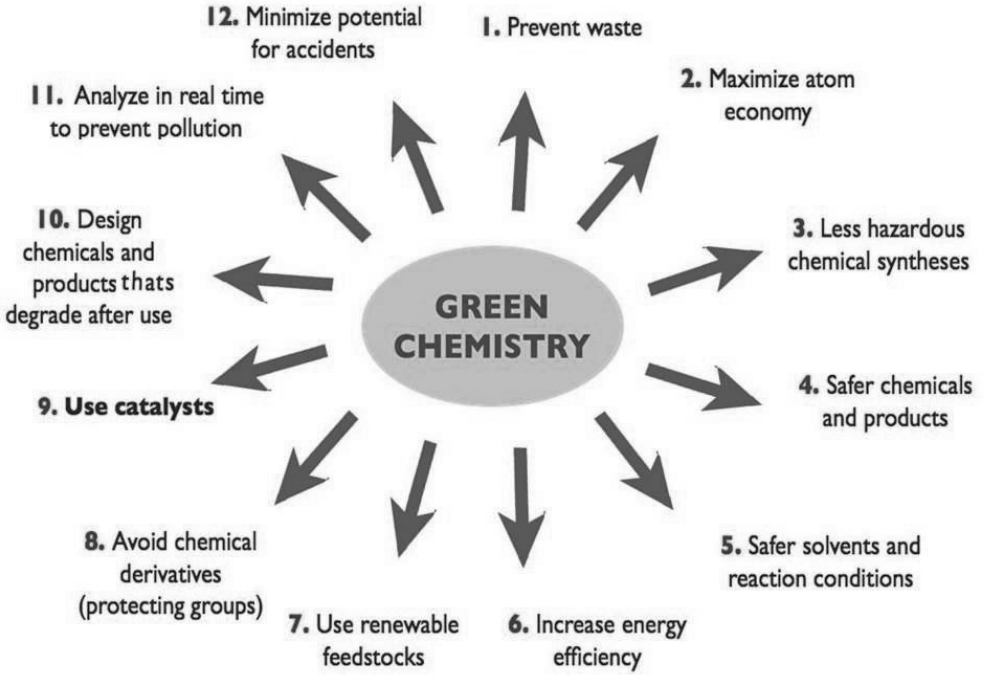



**Figure 1: Principals of Green Chemistry**

Over the past few decades, green chemistry has emerged as a culture and methodology in achieving sustainable development.[1, 2] Anastas and Warner have defined the twelve principles of green chemistry **(Figure 1)** and catalysis has been identified to be at the heart of greening of chemistry.[3] This branch of science is found to reduce the environmental impact of chemical processes.[4] The term catalysis was coined by A. Berzelius who tried to explain the power of certain chemical substances to influence the rates of few chemical transformations and according to Ostwald defined catalyst as the substance that accelerates chemical reaction without affecting the position of the equilibrium. Catalysis has played a crucial role in the triumph of the chemistry industry in the twentieth century. More than 90 % of the chemical manufacturing processes in the world utilize catalysts.[5,6] The catalyst is known to interact with the reactants to generate intermediates that react to give products. A good catalyst must possess both high activity and long term stability. But, the most important quality is its selectivity as well as specificity which reflect its ability to direct conversion of reactants in a specific way. The specificity of a catalyst enables a chemical process to proceed more efficiently with less waste. Catalysts are mainly classified as Homogeneous catalysts and Heterogeneous catalysts. Homogeneous catalysts are well defined chemical compounds which, together with the reactants, remain dispersed in the reaction medium. On the other hand, heterogeneous catalysis takes place between different phases and it has now grown into an important branch of science.

**Organocatalysis:**

The use of small-molecule organic catalysts in organic synthesis has been increased in last few decades. It has become widely valued that small molecule organic catalysts can hold a wide range of practical advantages relative to precious metal catalysts, including air and water stability, low cost, availability from renewable resources, and relative no toxicity. The term ***organocatalyst*** is a concatenation of the words ***organic*** and ***catalyst***. The definition corresponds to low molecular weight organic molecules which in sub-stoichiometric amounts catalyze a chemical reaction. Liebig's synthesis of oxamide is the first organocatalytic reaction reported.[7] Dakin in 1909 demonstrated that in Knoevenagel type condensation between aldehydes and active methylene compounds, the amine catalysts essential could be mediated by amino acids.[8] Langenbeck is remembered for developing enamine type reactions and the application of simple amino acids and small oligopeptides as catalysts.[9-11] Natural products, in particular, strychnine, brucine, and cinchona alkaloids and amino acids (including short oligopeptides), were among the few more organic catalysts tested.[12, 13] An asymmetric transformation with an organic molecule was published in 1912 by Bredig and Fiske.[14] Pracejus applied cinchona alkaloids in the asymmetric conversion of ketenes to (S)-methyl hydratropate.[15-17] In 1970, Hajos and Parrish

reported L-proline catalyzed Robinson annulation in excellent enantioselectivities[17-19] while Eder *et al.* reported organocatalytic aldol reactions in good enantioselectivities.[20] There are also evidences that prove their pivotal role in the synthesis of building blocks for life.[21]

Organocatalysts are often based on nontoxic organic compounds originating from biological materials and are composed of C, H, N, S, and rarely P. They can be Lewis bases, Lewis acids, Brønsted bases or Brønsted acids and could be achiral or chiral. Organocatalysis, being an alternative to the prevalent transition metal catalysis, has become one of the hot research topics in advanced organic chemistry. Structures of few commonly used organocatalysts are shown in **Fig. 2.**

Easy preparation or availability, Easy handling; inert towards moisture and air, Easy scale-up / screening, No metal contamination, useful in complex reactions, etc. are the advantages of organocatalysts, while in many cases it requires high catalyst loading and this is the main disadvantage of it.

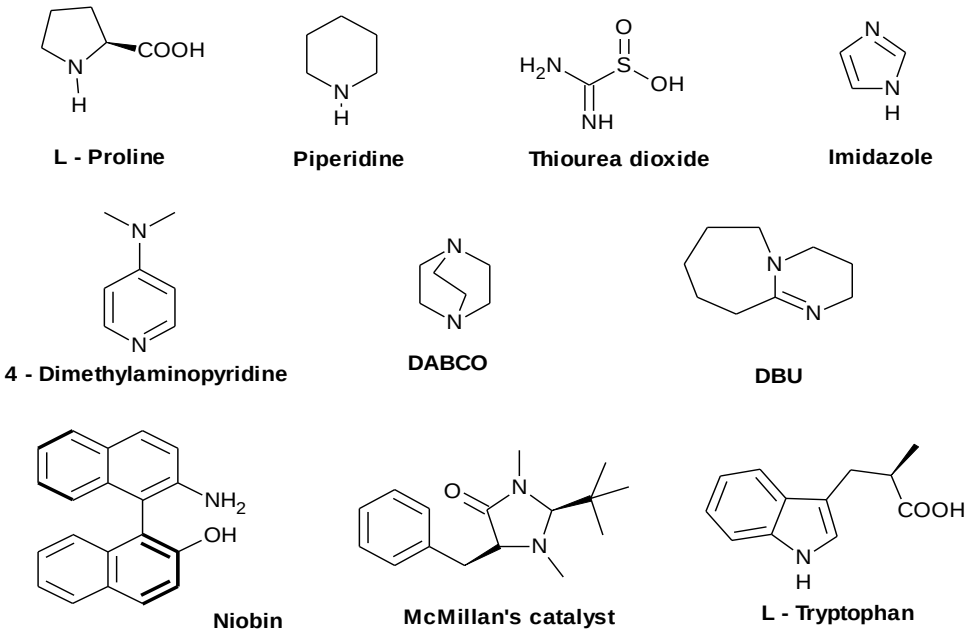



**Figure 2: Structures of few commonly used organocatalysts**

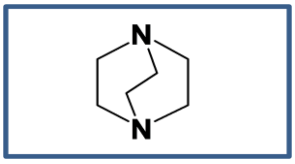
In 2006, Professor Pavel Kocovsky pointed out that words asymmetric and organocatalysis are closely linked in the minds of the many scientists working in this field, chiral compounds are not the only valuable ones which can be prepared employing this methodology.[29] The well known attractive aspects of organocatalysis such as environmentally friendly conditions (no need for anhydrous conditions or of transition metals) without any doubt apply also to transformations affording achiral molecules as products.

The use of achiral organocatalysts, without emphasising much on the phenomenon of organocatalysis, had started too earlier. They were mainly explored as catalysts in simple, two component reactions. Their use in multicomponent reactions started at the dawn of this millennium. However, compared metal borne catalysts they have been explored to very limited extent. Their use in the reported transformations cannot be regarded as "inevitable" because, there exists every possibility that, the same transformation / synthesis could be achieved using other organocatalysts. For instance, for the synthesis of Biginelli reaction products, more than ten organocatalysts have been reported and all of them work equally well.

Some commonly used organocatalysts in variety of organic transformations are listed below.

**Organocatalysts:**

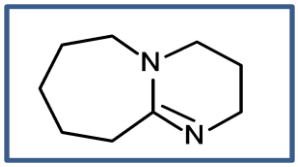
**1) DABCO:**



**1,4-Diazabicyclo[2.2.2]octane (DABCO)**

DABCO is bicyclic compound having two tertiary amine groups. Use of DABCO as a base catalyst has been frequently reflected in copious organic transformations. It is also a good nucleophile. It catalyzes variety of reactions like Baylis-Hillmann reaction, Henry reaction, coupling, cycloadditions, ring opening, etc. It is green, highly reactive, economical and nontoxic catalyst.

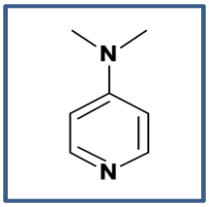
**2) DBU:**



**1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)**

1,8-Diazabicyclo[5.4.0]undec-7-ene (**DBU**) is an organic solvent soluble amidine non-nucleophilic base. It can be effectively used for a variety of base-mediated organic transformations like elimination, isomerization, esterification, amidation, etherification, carboxylation / carbonylation, as well as halogenation reactions. In recent years, DBU has been explored in multicomponent synthesis of heterocyclic frameworks.

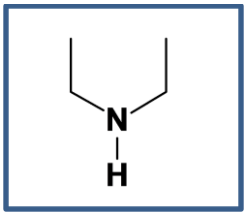
**3) DMAP:**



**N, N- Dimethylaminopyridine (DMAP)**

This is another commercially available but slightly expensive, colourless solid catalyst. It is more basic than pyridine and used commonly for acylation of tertiary or hindered alcohols or phenols, in macro-lactonization reaction, and for direct esterification of carboxylic acids and alcohols in the presence of dicyclohexylcarbodiimide. This catalyst is used in multicomponent reactions very rarely.

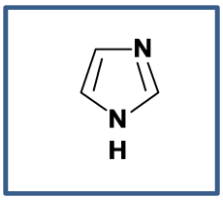
**4) Diethylamine:**



**Diethylamine (DEA)**

Use of diethylamine as an organocatalyst had remained unexplored for several years. This is possibly because; on basicity scale (pKb value) diethylamine is very close to triethylamine as well as piperidine and boiling point of diethylamine being too low, it cannot be used under elevated temperature condition.

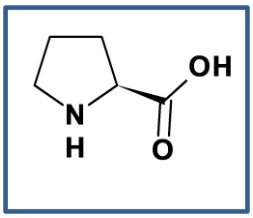
**5) Imidazole:**



**Imidazole**

Presence of aza (–N=) and amine (–NH–) functionalities in imidazole ring makes it a unique reagent widely used in organic synthesis. Presence of pyridine - like nitrogen atom in imidazole ring makes it weakly basic. The mild catalytic nature of imidazole minimizes side product formation and improves the yield of products.

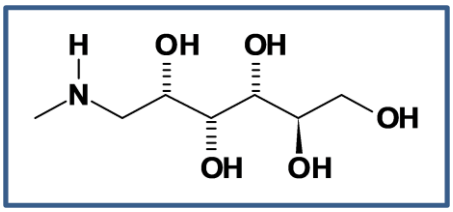
**6) L-Proline:**



**L-Proline**

Proline is also an amino acid, It may remain in it's any one form; Chiral or achiral. Proline is a α-amino acid and it is used in the biosynthesis of proteins. Under biological conditions, it contains in protonated α-amino deprotonated – $COO^-$ group. It has pyrrolidine as a side chain. It is available in racemic as well as both the enantiomeric forms. Availibity of proline in both the enantiomeric forms brings advantages over enzymatic methods. In recent years especially L-proline is used in fine chemical as well as pharmaceutical industries in Diels - Alder reactions, Michael addition, Mannich reaction, etc.

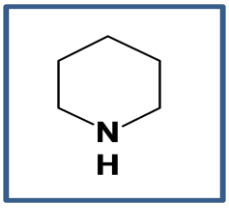
**7) Meglumine:**




**Meglumine**

Introduction of Meglumine as an organocatalyst is quite recent. Meglumine is an amino sugar derived from sorbitol and it does not contain Bronsted or Lewis acid / base centers in it. It contains amino and primary as well as secondary hydroxyl groups in it. These groups are believed to activate nucleophilic as well as electrophilic components of the reactions by hydrogen bonding and donation of lone pair of electrons, respectively. It is endowed with few extraordinary properties like, extremely low price, physiological inertness, biodegradability, low toxicity as well as possibility of reuse has attracted the attention of scientists in a recent past.

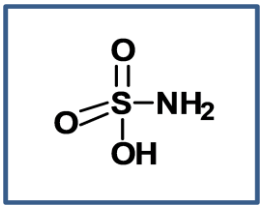
**8) Piperidine:**




**Piperidine**

Piperidine is a secondary amine and is used as an organo-basic catalyst since last several years. In recent years, it is mainly used in many in the synthesis of biologically important compounds employing multicomponent condensation pathway.

**9) Sulfamic acid:**

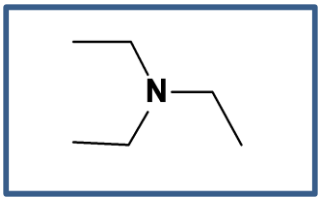



**Sulfamic acid (SA)**

Sulfamic acid is another organo-catalyst available commercially at extremely low cost. Ease of handling, possible reusability and non - toxicity are the noteworthy features of this

catalyst. Specialty of the catalyst is it's zwitter-ionic nature. Thus it has been explored as an acid as well as a base catalyst.

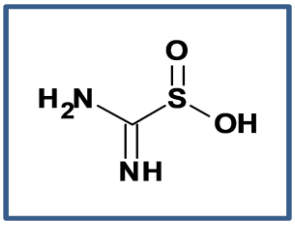
**10) Triethylamine:**




**Triethylamine (TEA)**

Triethylamine is the commercially available, inexpensive and easy to handle catalyst and it has remained as the choice of scientists in many base catalyzed multicomponent reactions. To take an account of it's in synthesis of heterocyclic frame works is a herculean task.

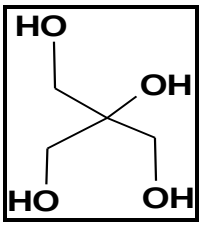
**11) TUD:**




**Thiourea dioxide (TUD)**

Thiourea dioxide is easily prepared by oxidation of thiourea with hydrogen peroxide. It is an easy to handle, non-toxic solid used earlier in oxidation of sulfides and in the synthesis of chromamone from salicylaldehyde.

**12) THAM**




**Tris-hydroxymethylaminomethane, THAM**

It is well known that, Tris-hydroxymethylaminomethane, THAM is a biodegradable, non-corrosive, physiologically inert and thermally stable compound available commercially at extremely low cost. It contains an amino and three primary alcoholic groups and when dissolved in water or water – ethanol medium, it generates basic reaction medium (pH ≈ 7.5 to 8.5). The catalyst has earlier been explored for the synthesis of tetrahydrobenzo[b]pyrans as well as pyran-annulated heterocycles.

**Summary:**

Resurgence of organocatalysis has been observed at the beginning of this century. Considering the principles of "green chemistry" and the economics in synthesis, absence of

metal in organocatalyst brings an indisputable advantage presenting an environmental advantage over metal based catalysts for development of organic synthetic methodologies. The area of organocatalyzed reactions is expanding very rapidly. Thus, there certainly exists scope for the introduction of new organic catalysts as well as to explore their applications in organic synthesis.

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# FOOD ADULTERATION: EFFECTS AND DETECTION

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Food is essential for sustenance of life. We all eat food and gain energy for different metabolic activities. All living organisms need food for growth, work, repair and maintaining life processes. Adulterants are added to pure substance to extend the quantity while reducing the quality. Adulterant acts as a contaminant when combined with other substances. Adulterant are the substance or poor-quality products added to food items for economic and technical benefits. Addition of these adulterants reduces the value of nutrients in food and also contaminates the food, which is not fit for consumption. An adulterant is a substance found within other substance such as food, cosmetic, pharmaceuticals, fuel or other chemicals that compromises the safety or effectiveness of said substance.

Adulteration is an illegal practice of adding raw and other cheaper ingredients to excellent quality products to increase the quantity. Natural adulteration occurs due to the presence of certain chemicals. Food adulteration is an act of adding or mixing of poor quality, harmful, substandard, unnecessary substance to food. This act of spoiling the nature and quality of food items is considered food adulteration.

Food adulteration are of two types: i) Intentional adulteration ii) Incidental adulteration

**Methods of food adulteration: Adulterants added.**

1. Adding certain natural and chemical dyes to attract consumers.
2. Mixing of clay, pebbles, stones, sand and marble chips to the grains, pulses and other crops.
3. Mixing of decomposed fruit and vegetable with good ones.
4. Cheaper and inferior substances are added to good ones for increase the weight of the product.
5. Adding certain chemicals for faster ripening of fruits.

**Advantage of food adulteration:**

It includes a better appearance in the food and may increase the selling price.

**Disadvantage of food adulteration:**

It includes the increased risk of illness and allergic reaction due to the inedible products that are added.

**Detection Tests:**

**Table 1: Food adulteration testing**

| Sr. No. | Food materials | Adulterant | Test for Adulteration | Observations | Inference |
|---|---|---|---|---|---|
| 1. | Tea leaves | 1) Used Tea leaves or colouring matter | 1) Put a little tea powder over moist filter paper | 1) Appearance of coloured spot-on filter paper | Tea powder is adulterated with dye |
| | | 2) Saw dust | 2) Tea leaves + $H_2O$ | 2) Saw dust floats on water | Tea powder is adulterated with saw dust |
| | | | | 3) Neither colour spot nor saw dust | Sample is pure |
| 2. | Powdered sugar | 1)Baking Soda Sodium bicarbonate ($NaHCO_3$) | 1) Powdered sugar + dil. HCl | 1) Effervescence of $CO_2$ | Sugar powder is adulterated |
| | | | 2) Sugar powder + Water | 2) Red litmus paper turns to blue colour | Sugar powder is adulterated |
| | | | | 3) Neither effervescence of $CO_2$ nor red litmus paper turns to blue colour | Sample is pure |
| 3. | Edible oil | Argemone oil, mineral oils and lubricating oil | 1) Sample of edible oil + conc. $HNO_3$ | 1) Red Colour developed | Sample of oil is adulterated with Argemone oil or mineral oil |
| | | | | 2) No red colour developed | Sample is pure |
| 4. | Turmeric powder | 1) Metanil yellow | 1) Turmeric powder + dil. HCl | 1) Pink colouror yellow colour changes to orange | Turmeric powder is adulterated |
| | | 2) Yellow oxide of lead | 2) Turmeric powder + dil. $HNO_3$ . Heat and filter. Filtrate + $K_2CrO_4$ | 2) Yellow ppt. | Turmeric powder is adulterated |
| | | | | 3) Neither pink colour nor yellow ppt. | Sample is pure |
| 5. | Jaggery | Contaminated with Metanil yellow for good colour | Jaggery sample + dil. HCl | 1) Magenta Red colour | Jaggery sample is adulterated |
| | | | | 2) No red colour | Sample is pure |

**Table 2: Food adulteration testing**

| Sr. No. | Food | Adulterants | Test for safety |
|---|---|---|---|
| 1. | Milk | Unhygienic water, Chalk powder<br>Soap powder, Starch, Hydrogen peroxide, Urea | Milk on a slanted surface drop leaves a white trail - its sign of pure milk.<br>Milk turns yellow when heated and leaves a bitter and soapy kind of after taste - synthetic substance. |
| 2. | Coffee powder | Tamarind seed<br>Chicory powder | Sprinkle powder on the surface water contained in a glass. Coffee will remain a float.<br>Whereas the chicory in it will sink to the bottom leaving behind a coloured tail. |
| 3. | Tea | Coloured and processed used tea leaves | Sprinkle powder on a damp blotting paper change in the colour of the blotting paper to something similar to yellow, orange or red proves the presence of artificial colour in it. |
| 4. | Chilli powder | Artificial colours, Brick powder, Salt powder, Talc powder, Saw dust | Teaspoon of chilli powder + plain water.<br>Water changes it's colour - reddish brown |
| 5. | Turmeric | Colourants: Metanil yellow<br>Yellow aniline dye | Add concentrated Hydrochloric acid, appearance of pink, purple or violet hues in the mixture confirms adulteration. |
| 6. | Green chillies | Malachite green (a coloured dye) | Soak a small cotton piece in paraffin and rub it against a small portion of the outer surface of green chilli or any other green vegetable for that matter. If the cotton turns green it means that the vegetable is artificially coloured. |
| 7. | Mustard seed and oil | Argemone seeds | Argemone seeds on being crushed will reveal a whitish structure on the inside. Mustard seeds on the other hand have a yellow inner surface. |
| 8. | Black pepper (Glucotropaeolin) | Black papaya seeds, Green chilli, Red chilli | Papaya seeds floats on the surface of water. |
| 9. | Ghee | Vegetable oil<br>Animal body fats | 0.5 gm of ghee + 1 ml of water. Boil and then Cool. Add a drop of iodine (or iodine tincture solution) to it. If the final output is blue in colour, then it is adulterated with starchy substances. |

| | | | |
|---|---|---|---|
| | | | Ghee melts immediately and turns dark brownish in colour - Pure ghee<br>If takes time to melt and turns into light yellow in colour then it is adulterated |
| 10. | Ice cream | Washing powder | If the ice cream starts to froth on adding a few drops of lemon juice to it, it indicates the presence of washing powder in it. |
| 11. | Sugar | Chalk powder | Chalk powder will remain at the surface of the water. |

**Table 3: Test for detection of original natural drug with their adulterants**

| Sr. No. | Original natural drug | Adulterant | Detection test |
|---|---|---|---|
| 1. | Honey | Water | A cotton wick dipped in pure honey burns when ignited with a match stick. If adulterated presence of water will not allow the honey to burn, if it does will produce a cracking sound. |
| 2. | Coffee | Chicory | Gently sprinkle the coffee powder on surface of water in a glass. The coffee floats over the water but chicory begins to sink down within few seconds and powder particles leave behind them a trail of colour, due to presence of large amount of caramel. |
| 3. | Tea | Colored tea | Rub leaves on white paper, artificial colour comes out on paper. |
| 4. | Turmeric, chilly, curry powder etc. | Colors | Extract the sample with petroleum ether and add 13N $H_2SO_4$ to the extract. Appearance of red colour indicates the presence of added colours. However, if the colour disappears upon adding distilled water the sample is not adulterated. |
| 5. | Coriander powder | Dung powder | Soak in water. Dung will float and can be easily detected by its foul smell. |
| 6. | Cardamom big | Cardamom small | Separate out the seeds by physical examination. The seeds of big cardamom have nearly plain surface without wrinkles or streaks while seeds of small cardamom have pitted or wrinkled ends. |

| | | | |
|---|---|---|---|
| 7. | Red chilli powder | Brick powder grit, sand, dirt, filth etc | Brick powder settles fast, chilli powder settles slowly when put in water. |
| 8. | Cumin seeds (Black jeera) | Grass seeds coloured with charcoal dust | Rub the cumin seeds on palms. If palms turn black adulteration in indicated. |
| 9. | Mustard seeds | Argemone seeds | Argemone seeds have rough surface and mustard seeds on pressing is yellow inside while Argemone seed is white. |
| 10. | Turmeric powder | Lead chromate | Ash the sample. Dissolve it in 1:7 $H_2SO_4$ and filter. Add 1 or 2 drops of 0.1% dipenylcarbazide, A pink colour indicates presence pf Lead Chromate. |
| 11. | Black pepper | Papaya seeds/ Light berries | Float the sample in alcohol or carbon tetrachloride. The mature black pepper berries sink while papaya seeds and light black pepper float. |
| 12. | Asafoetida | Soap stone or earthy matter | Shake a little portion of sample with water and allow to settle. Soap stone or earthy matter will settle down at the bottom. |
| 13. | Saffron | Colored dried tendrils of maize cob | Pure saffron will not break easily like artificial. Pure saffron when allowed to dissolve in water will continue to give its colour so long as it lasts. |
| 14. | Vegetable Oil | Castor oil | Take 1 ml of oil in a clean dry test tube. Add 10 ml of acidified petroleum ether. Shake vigorously for 2 minutes. Add 1 drop of Ammonium Molybdate reagent . The formation of turbidity indicates presence of castor oil in the sample. |

**Table 4: Harmful effects due to food adulteration**

| Sr. No | Food Product | Adulterant | Harmful Effect |
|---|---|---|---|
| 1. | Milk and Curd | Water and starch powder, Soap powder and Urea, Hydrogen Peroxide | Stomach disorder, Vomiting. |
| 2. | Ghee, cheese and butter | Mashed potatoes, Vanaspati,Vegetable oil and starch powder | Gastro-intestinal disturbances and other stomach disorders |
| 3. | Grains | Dust, pebbles, stones, straw, weed seeds, damaged grain etc. | Liver disorders, Toxicity in the body |
| 4. | Pulses | Dyes, lead chromate | Stomach disorders |
| 5. | Coffee powder | Chicory, tamarind seeds powder | Diarrhoea |
| 6. | Tea | Artificial colouring agent | Liver disorders |
| 7. | Sugar | Chalk powder, Baking soda, urea | Stomach disorder and kidney failure |
| 8. | Black Pepper | Dried papaya seeds and black barriers | Allergic reaction including stomach and skin irritations |
| 9. | Mustard seeds | Argemone seeds | Abdominal contractions, sluggishness and increased excretion |
| 10. | Edible oil | Mineral oil, Karanja oil,Castor oil and Artificial colours | Gallbladder cancer, allergies, paralysis, cardiac arrest and increased LDL cholesterol. |
| 11. | Turmeric powder | Saw dust, Industrial dyes,Metanil yellow dye,yellow aniline dye, Chalk dust, As and Pb metal, Pesticide residues | Cancer and Stomach disorders |
| 12. | Chilli and Coriander | Redbrick powder, Rhodamine B dye, Red | Metal toxicity, Stomach related disorders. Lead poisoning, cancer, |

| | | | |
|---|---|---|---|
| | powder | lead, Dung powder, Soluble salts, Water soluble synthetic colours and Other common salts | tumour, variations in blood pressure |
| 13. | Cinnamon sticks | Cassia bark | Liver damage, Low blood sugar, Mouth Sores and increased risk of cancer. |
| 14. | Cumin seeds | Saw dust, charcoal dust, coloured grass seeds | Stomach disorders |
| 15. | Jam juice and candies | Metanil yellow and other artificial dyes. | These dyes are highly carcinogenic |
| 16. | Jaggery | Washing soda, chalk powder | Vomiting and other stomach disorders |
| 17. | Honey | Molasses, dextrose sugar and corn syrups | Stomach disorders |
| 18. | Fruits and vegetables | Chemical dyes, Malachite green, Calcium carbide, Copper sulphate, Oxytocin Saccharin wax | Stomach disorders, vomiting and dyes used are highly carcinogenic |
| 19. | Tomato sauces | Pumpkin pulp, non-edible artificial colours and flavours | Gastritis and inflammation of vital organs |
| 20. | Ice Cream | Pepper oil, ethyl acetate, butyraldehyde, nitrate, washing powder | Dreadful Diseases that affect organs including lungs, kidney and heart. |

The main reasons for adulterating food products are:

1. In India rapidly growing population results increased food demand.
2. Producer makes maximum profit from food itemsby less investment.
3. Producer increases the quantity of food production and sales i.e it follows business strategy.
4. In society people have lack of knowledge of proper food consumption.

The prevention of food adulteration act 1954 (Amended in 1964, 1976, 1986). The act provides the protection from adulteration / contamination of food that may lead to the health risk of consumers. The adulteration food is highly toxic and leads to several health issues, including certain nutrition deficiency diseases, failure of organs system including heart, kidney and liver. Every year the 7$^{th}$ of April is celebrated as the World Health Day globally for awareness about the adulterations of food products and motivates everybody to healthy and balance diet.

**Adulteration in Pharmacy:**

Substituting original crude drug partially or wholly with other similar looking substance which is mixed, is free from or inferior in chemical and therapeutic property. Adulterants are deliberately added to increases bulk. Evaluation methods of adulteration: Evaluation means determination of identity, quality and purity of any drug.

Generally, adulterants and substituent are detected in the original drug morphologically, , microscopically, chemical test, physical evaluation method, microbiological techniques and instrumental methods. Oils are detected by odour, viscosity, colour, clarity, followed by specific gravity, optical rotation, refractive index and finally by gas chromatography analysis.

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# AYURVEDIC PLANTS USED IN BRAIN DISORDERS

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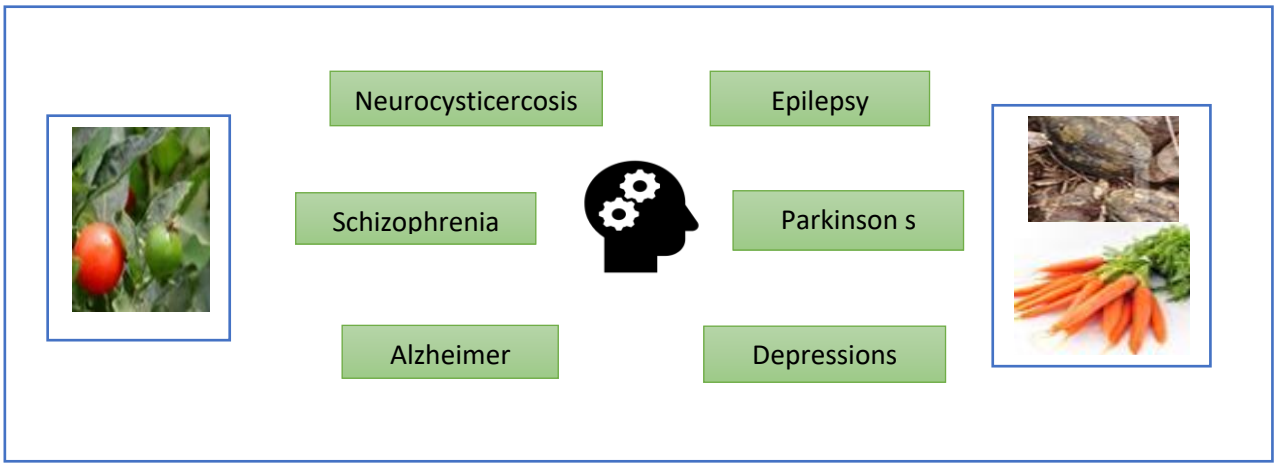
**Abstract:**




**Keywords:** Ayurvedic Plants, Disease, Chemical Constituents, Brain, Ethnomedicinal

## Introduction:

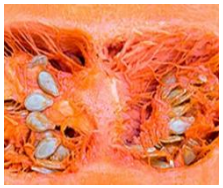
Plants are the most incredible gift of our nature. A number of medicinal plants have been described for a range of mental disorders, including migraine, epilepsy, convulsion, hysteria, paralysis, memory loss, insomnia, anxiety, Parkinson's disease, insanity, and depression, etc. Plantshave many bioactive constituents which are used for improve mental performance in healthy people.

The nervous system can be affected by a wide range of diseases and medical conditions and there are hundreds of medicines available to treat them. Symptoms of Parkinson's disease are often managed with medicines such as co-beneldopa, co-careldopa, or ropinirole.

**Table 1: Plants used in Ayurveda**

| Botanical Name with Family | Local Name | Part Used | Chemical constituents |
|---|---|---|---|
| *Acorus Calamus (Araceae)* | Vachaa  | Leaves and rhizomes | Alpha-asarone, beta-asarone, Glycosides, sterols, mono and Triterpenes, saponins, alkaloids, Phenylpropanoids, Triterpenoid and Sesquiterpenoids. |
| *Areca Nut or Areca catechu (Arecaceae)* | betel nut  | Seeds from the fruit | Alkaloids, Tannins, Flavones, Polyphenols, fatty acids, Steroids, Triterpenes, Polysaccharidesand a small amount of protein and vitamins. |
| *Bacopa Monnieri (Scrophulariaceae)* | Brahmi  | Whole plant | Bacosides, Bacopasides and Bacosaponins, Jujubogenin, Bisdesmosides, Betulic acid, Polyphenols, sulfhydryl, Sterols, and Alkaloids. |

| | | | |
|---|---|---|---|
| *Celastrus Paniculatus (Celastraceae)* | Malkangni or Jyotishmati  | Seed Oil | Alkaloids as Celastrine, Paniculatine, Celapanin, Celapanigin, Celapagin & sesquiterpene alkaloids (Celapanol). Oil of the plant also contains proteins, carbohydrates, fats, Mineral elements, vitamin C and tannins. |
| *Centella asiatica Apiaceae (Umbelliferae)* | Gotu Kala  | Whole Part | Asiaticosides, trisaccharides as a glyconeasiatic acid, madecassoside, and madasiatic acid. Other components isolated are brahmoside and brahminoside |
| *Commiphora wightii, (Burseraceae)* | Gugal, Mukul  | Gum resin | Gallic acid, quercetin, and guggulsterones .diterpenoids |
| *Cinnamomum camphora (Lauraceae)* | Camphor  | Distillation of bark from camphor tree | Safrole, linalool, eugenol and terpeneol,-cineole. |

| | | | |
|---|---|---|---|
| *Convolvulus pluricaulis (Convolvulaceae)* | Shankhpushpi  | Whole plant | Palmitic acids, linoleic acids, myristic acids, flavonoids, steroids-phytosterols, alkaloids like shankhapushpine, Convolvuline, convolidine, convolvine, convolamine, convoline, confoline, convozine Evolvulus Alsinoides contains Pentatriacontane, Triacontane and Beta Sitosterol. |
| *Curcuma longa Zingiberaceae* | Turmeric  | Rhizome | Curcuminoid a linear diarylheptanoid includes curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Turmerone, germacrone, atlantone, and zingiberene are its major constituents. |
| *Cucurbita maxima Duchesne Cucurbitaceae* | Red Pumpkin  | seed | Alkaloids cucurbitacins, cucurbitinae and vernin,peporesin,isoprenoside,beta-sitosterin, glycerides Citrullic acid, Leucine, tyrosine, peponin. Phytolecithin, vitamin A and E, Arginine and mineral micronutrients. |
| *Daucus-carota (Umbelliferae) Apiaceae* | Carrot  | Root | Beta-carotene, an antioxidant found in carrots compounds called luteolin kaempferol, quercetin and various glycosides. |

| | | | |
|---|---|---|---|
| *Glycyrrhiza glabra* *(Leguminosae)* | liquorice Mulethi.  | Root | Glycyrrhizin a triterpene saponin. Iso-flavonoids, chalcones, coumarins, triterpenoids andsterols, lignans. |
| *Hypericum perforatum* *(Hypericaceae)* | St John's-wort  | Leaves And Flower | Naphthodianthrone derivatives hypericin and pseudohypericin, rutin, quercetin, hyperoside, methyl hesperidin, caffeic, chlorogenic, p-coumaric, ferulic, p-hydroxybenzoic and vanillic acids. |
| *Melissa officinalis* *(Lamiaceae)* | lemon balm  | Leaves | Geranial, neral, caryophyllene oxide. Caffeicacidrosmaric acid. Cymaroside, cosmosiin, hamnocitrin, isoquercitrin. Triterpene acid. |
| *Mucuna pruriens* *(Fabaceae)* | Kaunch or velvet seed  | Stem, 78eaves and root | L-dopa, dimethyl tryptamine, alkaloid, mucunain, prurienine, serotonin, beta-sitosterol, Gluthione, lecithin, vernolic and gallic acids |

| | | | |
|---|---|---|---|
| *Morinda citrifolia* | Noni or Indian Mulberry  | Fruit | lignans, oligo- and polysaccharides, flavonoids, iridoids, fatty acids, scopoletin, catechin, beta-sitosterol, damnacanthal, and alkaloids. |
| *Salvia officinalis (Lamiaceae )* | Salvia  | Leaves and flower | Rosmarinic acid and carnosic acid are their main active ingredients. Cirsiliol, linalool and alpha-terpineol, constituents of the volatile oil, exhibit CNS depressant activities |
| *Terminalia chebula (Combretaceae)* | Haritiki  | fruit | Shikimic,gallic,triacontanoic,beta-sitosterol, daucosterol, triethyl ester of chebulic acid and ethyl ester of gallic acid, ellagitannin, terchebulin, punicalagin and teaflavin.Ethyl gallate, luteolin |
| *Withania somnifera Solanaceae)* | Ashwagandha Winter cherry  | root | withanolides, Withaferin A, withanine, withananine, withananinine, pseudo-withanine, somnine, somniferine, somniferinine. |

The progression of Alzheimer's disease may be slowed by medicines such as donepezil or memantine. Epilepsy covers a range of conditions where over-activity of the brain leads to seizures. Seizures can be controlled with anticonvulsant medicines such as carbamazepine, lamotrigine, levetiracetam, or sodium valproate. A benzodiazepine. Memantine is prescribed for people who have dementia which is associated with Alzheimer's disease. Oxcarbazepine prevents fits (seizures).

In this view, the main aim of this study is to document the knowledge of ethnomedicinal uses and create awareness about the uses of the plant in ayurvedic System of Medicine to cure various disorders.

**Conclusion:**

Plants that support mental performance, such as perception and memory, combine them with a healthy, active lifestyle that may help strengthen and nurture our mind for a long life.It has been well-evidenced that natural products are effective, multi-targeted, and really safe as they are the roots of Ayurveda systems.

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# TANDEM KNOEVENAGEL-MICHAEL REACTION FOR THE SYNTHESIS OF 4,4′-(ARYLMETHYLENE)BIS(1H-PYRAZOL-5-OLS) IN AQUEOUS MEDIUM

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**Abstract:**

A Green, an environmentally benign un-catalyzed one-pot synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) has been reported via tandem Knoevenagel-Michael reaction of aldehydes with two equivalents of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one in aqueous medium.

**Key words:** Knoevenagel reaction, Michael addition, aldehydes, 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one, aqueous medium

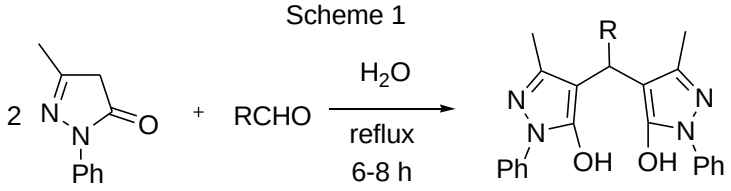
## Introduction:

The sub-structural unit of 2,4-dihydro-3*H*-pyrazol-3-one including 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)pyrazole is most frequently present in various bioactive molecules showing a wide range of pharmacological properties such as anti-inflammatory,[1] antipyretic,[2] anti-bacterial,[3] gastric secretion stimulatory,[4] antidepressant,[5] and antifilarial agents.[6] Some pyrazoles also display agrochemical properties (i.e. herbicidal and soil fungicidal activity)[7] and have applications as pesticides[8] and insecticides.[9] The utility of certain pyrazole derivatives has also been demonstrated in the extraction of different metal ions.[10]

3-Methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one is a versatile building block with highly nucleophilic enolic carbon at 4-position. It has been recently used in several multi-component reactions (MCRs) for the synthesis of wide range of heterocycles.[11] While carrying out three component reaction of aromatic aldehydes, Meldrum acid and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one in aqueous medium, we noticed the formation of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)pyrazole as one of the major product. The literature survey showed that the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)pyrazole can be accomplished by two methods (i) Knoevenagel reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one with aldehydes to form the corresponding arylidene pyrazolones followed by base

promoted Michael reaction with second equivalent of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one,[12] (ii) one-pot tandem Knoevenagel-Michael reaction of aldehydes with two equivalents of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one under various reaction conditions.[13] The first set of conditions requires piperidine as the base catalyst and the desired products are formed in poor 15-30% yield.[14] The second set of method has been demonstrated in refluxing benzene or ethanol under neutral conditions with long duration of time up to 24 hours involving product isolation with ether extraction. The other improved protocol for the tandem Knoevenagel-Michael reaction either in water or ethanol utilizes the electrolytic system using NaBr as electrolyte,[15] sodium dodecyl sulfate (SDS) as the surfactant catalyst (5 mol%),[16] ceric ammonium nitrate (CAN) as Lewis acid[17] and silica-bonded *S*-sulfonic acid (SBSSA) as a recyclable catalyst.[18] In spite of these literature reports, we have observed that the one-pot tandem Knoevenagel-Michael reaction of aldehydes with two equivalents of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one can be effected in aqueous medium without any use of catalyst or additive to form 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)pyrazole in good to excellent yields (Scheme 1).

Scheme 1

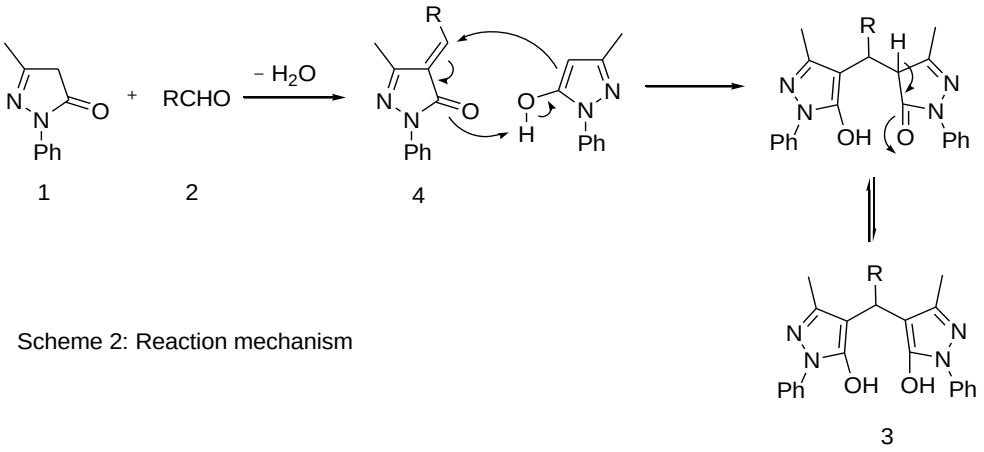



**1** **2** **3a-j**

**Results and Discussion:**

In a typical reaction procedure, a mixture of benzaldehyde (2 mmol) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (4 mmol) was refluxed in water (20 mL) for 7-8 hours. After the completion of the reaction, the resulting solid was filtered and recrystallized from methanol to afford **3a**, m. p. 168-169 $^{o}$C (lit. mp. 166-167$^{o}$C) in 76% yield. The results reported in the Table 1 showed that a variety of aromatic aldehydes with electron releasing and withdrawing substituents reacted efficiently with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one to afford the product **3a-j** in good to excellent yields. The reaction is also extended to the use of aliphatic aldehydes such as isobutyraldehyde. The products were characterized by IR, $^{1}$H NMR and LCMS analysis. For example, the $^{1}$H NMR spectra of **3c** indicated the presence of singlet at δ 4.89 due to aryl methylene proton and two broad peaks around δ 12.4 and δ 13.91 reminiscent of two enolisable -OH groups. The IR spectra of **3c** indicated peaks at 3497 cm$^{-1}$ due to -OH and 1583 cm$^{-1}$ due to C=N functional groups. The LCMS of **3c** corresponds to the expected m/z = 467.35.

The tentative reaction mechanism for the formation of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)pyrazole is shown in Scheme 2. It involves un-catalyzed Knoevenagel condensation of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **1** with aldehydes **2** to form **4** which undergoes Michael addition with second equivalent of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **1** to form the product **3**.




1 2 4 3

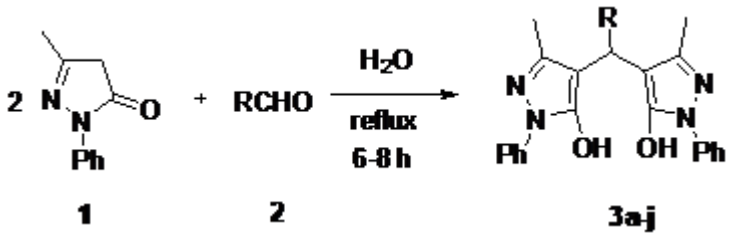
Scheme 2: Reaction mechanism

In conclusion, we have demonstrated an environmentally benign un-catalyzed one-pot tandem Knoevenagel-Michael reaction in aqueous medium for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)pyrazole in good yields. This method also eliminates the use of hazardous organic solvents and toxic catalysts, and thus provides a better and practical alternative to existing procedures.

**Table 1: Synthesis of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)pyrazole in aqueous medium**

| Entry | R | Product **3** | Time (h) | Yield[a] (%) | Mp ($^{o}$C) | Lit. Mp ($^{o}$C) |
|---|---|---|---|---|---|---|
| a | $C_6H_5$- | 3a | 8 | 76 | 172-173 | 171-172[16] |
| b | 4-$MeC_6H_4$- | 3b | 7 | 83 | 198-200 | 203[12a] |
| c | 4-$MeOC_6H_4$- | 3c | 7 | 81 | 173-175 | 176-177[15] |
| d | 3,4-$(MeO)_2C_6H_3$- | 3d | 8 | 79 | 189-190 | 195-197[18] |
| e | 4-$HOC_6H_4$- | 3e | 8 | 73 | 149-150 | 152-153[16] |
| f | 3-$HOC_6H_4$- | 3f | 8 | 76 | 164-166 | 165-168[18] |
| g | 4-$ClC_6H_4$- | 3g | 6 | 82 | 199-201 | 210[12a] |
| h | 4-$BrC_6H_4$- | 3h | 6 | 84 | 183-185 | -- |
| i | 3-$NO_2C_6H_4$- | 3i | 6 | 81 | 146-147 | 149-150[16] |
| j | $(CH_3)_2CH_2$- | 3j | 8 | 72 | 208-209 | 213-214[16] |

[a] Isolated yield after recrystallization.




1 2 3a-j

**Experimental:**

Melting points were determined on electro-thermal melting point apparatus and are uncorrected. IR (KBr) spectra were recorded using Perkin-Elmer FTIR spectrophotometer. Mass spectral data were recorded on liquid chromatography mass spectrometer (Shimadzu 2010EV) using ESI probe. The $^1$H NMR spectra were recorded on Varion spectrometer at 400 MHz using TMS as an internal standard.

**General procedure**

A mixture of appropriate aldehyde (2 mmol) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (4 mmol) was refluxed in water (20 mL) for the time period as shown in Table 1. The progress of the reaction was monitored by TLC. After the completion of reaction, the resulting solid was filtered and recrystallized from methanol to afford 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)pyrazole in good yields.

**Spectral data of the products:**

**4,4′-(Phenylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (3a):**

$^1$H NMR (DMSO, 400 MHz): δ 2.13 (s, 6H, 2$CH_3$), 4.79 (s, 1H, CH), 7.09-7.24 (m, 8H, ArH), 7.28-7.30 (m, 3H, ArH), 7.59 (d, 4H, *J* = 8 Hz, ArH), 12.78 (s, 1H, br., OH).

IR (KBr): 3352, 3066, 2960, 2912, 1597, 1579, 1492, 1415, 1271, 761, 732, 690 cm$^{-1}$.

MS (ESI) m/z $(M+H)^+$ Calculated for $C_{27}H_{24}N_4O_2$: 436.19. Found: 437.3.

**4,4′-[(4-Methylphenyl)methylene]bis(3-methyl-1-phenyl-1*H*pyrazol-5-ol) (3b)**

$^1$H NMR (DMSO, 400 MHz): δ 2.24 (s, 3H, Ar$CH_3$), 2.30 (s, 6H, 2$CH_3$), δ 3.69 (s, 3H, O$CH_3$), 4.92 (s, 1H, CH), 7.06 (d, 2H, *J* = 8 Hz, ArH), 7.06 (d, 2H, *J* = 7.6 Hz, ArH), 7.24 (m, 2H, ArH), 7.43 (t, 4H, *J* = 7.6 Hz, ArH), 7.70 (d, 4H, *J* = 8 Hz, ArH), 12.39 (s, 1H, br., OH), 13.96 (s, 1H, br., OH).

IR (KBr): 3045, 2920, 1600, 1579, 1500, 1406, 1296, 1024, 802, 748 cm$^{-1}$.

MS (ESI) m/z $(M+H)^+$ Calculated for $C_{28}H_{26}N_4O_2$: 450.21. Found: 451.35.

**4,4′-[(4-Methoxyphenyl)methylene]bis(3-methyl-1-phenyl-1*H*pyrazol-5-ol) (3c)**

$^1$H NMR (DMSO, 400 MHz): δ 2.30 (s, 6H, 2$CH_3$), δ 3.69 (s, 3H, $OCH_3$), 4.89 (s, 1H, CH), 6.83 (d, 2H, *J* = 8.4 Hz, ArH), 7.14-7.25 (m, 4H, ArH), 7.43 (t, 4H, *J* = 7.6 Hz, ArH), 7.70 (d, 4H, *J* = 8 Hz, ArH), 12.40 (s, 1H, br., OH), 13.91 (s, 1H, br., OH).

IR (KBr): 3498, 3064, 2924, 1606, 1581, 1506, 1404, 1246, 1166, 1030, 823, 752, 696 cm$^{-1}$.

MS (ESI) m/z $(M+H)^+$ Calculated for $C_{28}H_{26}N_4O_3$: 466.2. Found: 467.35.

**4,4′-[(3,4-Dimethoxyphenyl)methylene]bis(3-methyl-1-phenyl-1*H*pyrazol-5-ol) (3d)**

$^1$H NMR (DMSO, 400 MHz): δ 2.31 (s, 6H, 2$CH_3$), δ 3.65 (s, 3H, $OCH_3$), δ 3.7 (s, 3H, $OCH_3$), 4.87 (s, 1H, CH), 6.8-6.88 (m, 4H, ArH), 7.22-7.26 (m, 2H, ArH), 7.43 (t, 4H, *J* = 7.6 Hz, ArH), 7.70 (d, 4H, *J* = 8 Hz, ArH), 12.41 (s, 1H, br., OH), 14.01 (s, 1H, br., OH).

IR (KBr): 3068, 2928, 1676, 1595, 1581, 1512, 1496, 1274, 1136, 1024, 798, 765 cm$^{-1}$

MS (ESI) m/z $(M+H)^+$ Calculated for $C_{29}H_{28}N_4O_4$: 496.21. Found: 497.35.

**4,4′-[(3-hydroxyphenyl)methylene]bis(3-methyl-1-phenyl-1*H*pyrazol-5-ol) (3f)**

$^1$H NMR ($CDCl_3$, 400 MHz): δ 2.35 (s, 6H, 2$CH_3$), 4.93 (s, 1H, CH), 6.67-6.69 (m, 2H, ArH), 6.82 (t, *J* = 8 Hz, 2H, ArH), 7.12-7.22 (m, 4H, ArH), 7.35 (t, 4H, *J* = 8 Hz, ArH), 7.71 (d, *J* = 8 Hz, 2H, ArH), 12.42 (s, 1H, br., OH).

IR (KBr): 3153, 3072, 2953, 1593, 1577, 1498, 1274, 1047, 877, 756 cm$^{-1}$.

MS (ESI) m/z $(M+H)^+$ Calculated for $C_{27}H_{24}N_4O_3$: 452.18. Found: 453.3.

**4,4′-[(4-Chlorophenyl)methylene]bis(3-methyl-1-phenyl-1*H*pyrazol-5-ol) (3g)**

$^1$H NMR (DMSO, 400 MHz): δ 2.31 (s, 6H, 2$CH_3$), 4.96 (s, 1H, CH), 7.25 (d, 4H, *J* = 8 Hz, ArH), 7.33 (d, 2H, *J* = 8.4 Hz, ArH), 7.43 (t, 4H, *J* = 7.6 Hz, ArH), 7.69 (d, 4H, *J* = 8 Hz, ArH), 12.57 (s, 1H, br., OH), 13.83 (s, 1H, br., OH).

IR (KBr): 3066, 2920, 1600, 1579, 1500, 1487, 1406, 1296, 1197, 1014, 810, 748, 690 cm$^{-1}$.

MS (ESI) m/z $(M+H)^+$ Calculated for $C_{27}H_{23}ClN_4O_3$: 470.15. Found: 471.3.

**4,4′-[(4-bromophenyl)methylene]bis(3-methyl-1-phenyl-1*H*pyrazol-5-ol) (3h)**

$^1$H NMR (DMSO, 400 MHz): δ 2.33 (s, 6H, 2$CH_3$), 4.97 (s, 1H, CH), 7.18-7.24 (m, 4H, ArH), 7.41-7.47 (m, 6H, ArH), 7.69 (d, 4H, *J* = 8 Hz, ArH), 12.37 (s, 1H, br., OH), 13.81 (s, 1H, br., OH).

IR (KBr): 3064, 2958, 1599, 1579, 1500, 1483, 1404, 1296, 1197, 1010, 808, 746, 688 cm$^{-1}$

MS (ESI) m/z $(M+H)^+$ Calculated for $C_{27}H_{23}BrN_4O_2$: 516.1. Found: 517.3.

**4,4′-[(3-Nitrophenyl)methylene]bis(3-methyl-1-phenyl-1*H*pyrazol-5-ol) (3i)**

$^1$H NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 6H, $2CH_3$), 4.95 (s, 1H, CH), 7.2 (t, 2H, *J* = 7.2 Hz, ArH), 7.37 (t, 2H, *J* = 8 Hz, ArH), 7.44 (t, 2H, *J* = 8.8 Hz, ArH), 7.67 (d, 4H, *J* = 8 Hz, ArH), 8.07 (d, 4H, *J* = 6.4 Hz, ArH), 12.38 (s, 1H, br., OH).

IR (KBr): 3078, 2918, 1599, 1523, 1502, 1346, 1269, 1093, 758, 734, 696 $cm^{-1}$.

MS (ESI) m/z $(M+H)^+$ Calculated for $C_{27}H_{23}N_5O_4$: 481.18. Found: 482.3.

**4-[1-(5-hydroxy-3-methyl-1-phenyl-1*H*pyrazol-4-yl)-2-methylpropyl]-3-methyl-1-phenyl-1*H*-pyrazol-5-ol (3j)**

$^1$H NMR ($CDCl_3$, 400 MHz): δ 0.83 (d, 6H, *J* = 8 Hz, $2CH_3$), 2.06 (s, 6H, $2CH_3$), 2.73 (m, 1H, CH), 2.84 (d, 1H, *J* = 10.8 Hz, CH), 7.13 (t, 4H, *J* = 7.6 Hz, ArH), 7.32 (t, 4H, *J* = 8 Hz, ArH), 7.65 (d, 2H, *J* = 8 Hz, CH), 12.87 (s, 1H, br., OH).

IR (KBr): 3064, 2955, 2922, 1597, 1579, 1502, 1413, 1296, 790, 746, 692 $cm^{-1}$

MS (ESI) m/z $(M+H)^+$ Calculated for $C_{24}H_{26}N_4O_2$: 402.21. Found: 403.3.

**Acknowledgement:**

The authors are thankful to the Principal, Yeshwant Mahavidyalaya, Nanded for providing the facilities and University Grants Commission, New Delhi, India (No. MRP 32-245/2006 SR) for the financial support.

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# ZEOLITES AS MOLECULAR SIEVES AND SOLID ACID CATALYSTS

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**Introduction:**

There are catalysts which fall under two major categories: i) liquid acid catalysts and ii) solid acid catalysts. In recent past, owing to hazardous consequences of the liquid acid catalysts, concern has been paid to replace these with eco-friendly and green solid acid catalysts. Some of the examples of solid acid catalysts are sulfated zirconia ($ZrO_2/SO_4^{-2}$), silicoaluminophosphates (SAPO), halide treated alumina etc. Recently, zeolites are emerging as suitable solid acid catalysts for hydrocarbon conversions related to petroleum and petrochemical industries.

Zeolites occur in nature and have been known for almost 250 years as aluminosilicate minerals. There are examples like faujasite, mordenite, offretite, ferrierite, erionite and chabazite. The term ‘zeolite’ is a combination of the Greek words *zeein* and *lithos* meaning ‘boiling stone’.Cronstedt invented this term to characterize the behavoiur of a new mineral (stilbite) which, on heating, seemed to melt and boil at the same time [1,2]. One of the most striking features of the porousstructure of zeolitic materials is that pore openingsare of molecular dimensions situatedin the range that adsorption scientists would labelas ultra-micropores, leading to the widely used designation of molecular sieves. Today, these and other zeolite structures are of great interest in catalysis, yet their naturally occurring forms are of limited value, because (i) they almost always contain undesired impurity phases, (ii) their chemical composition varies from one deposit to another and even from one stratum to another in the same deposit, and (iii) nature did not optimize their properties for catalytic applications. It was only with the advent of synthetic zeolites from ca. 1948 to 1955 (thanks, mostly, to the pioneering work of Barrer and Milton) that this class of porous materials began to play a role in catalysis [3]. A landmark event was the introduction of synthetic faujasites (zeolites X and Y) on an industrial scale in fluid catalytic cracking (FCC) of heavy petroleum distillates in 1962, one of the most important chemical processes worldwide. The new zeolitic catalysts were not only orders of magnitude more active than the previously used amorphous silica–alumina catalysts (which enabled drastic process engineering improvements), but they also brought about a significant increase in the yield of gasoline, the most valuable product from FCC plants [4]. It can be estimated that this yield enhancement alone resulted in an added value in the order of at least several billion US

dollars per year [5]. It has further been estimated that, as a whole, the cost of petroleum refining worldwide would be higher by at least 10 billion US dollars per year, if zeolite catalysts were not available today [6]. In the period after 1962, zeolite catalysts rapidly conquered additional processes in the fields of petroleum refining and basic petrochemistry. The most important of these processes are hydrocracking of heavy petroleum distillates [7], octane number enhancement of light gasoline by isomerization [8], the synthesis of ethylbenzene (the precursor of styrene and polystyrene) from benzene and ethane after the Mobil–Badger process [9], the disproportionation of toluene into benzene and xylenes and the isomerization of xylenes(to produce *para*-xylene, the precursor chemical for terephthalic acid)[10].In the manufacture of fine chemicals, the application of zeolite catalysts is still limited, even though their potential is considered to be very high in this area as well [11,12].

**Properties of Zeolite:**

The interest in zeolitic catalysts arises from their unique properties, namely:

1. Their unique microporous structure which allows them to have the well-known molecular sieving behavior that justifies their use in a wider field than catalysis and that makes their activity related to both the composition and the geometry of the structure;
2. The large number of available structures, ranging from the very narrow pore systems to those having pores large enough to process heavy molecules.
3. The possibility to control, in a variety of ways, not only the geometry of the structure but also its composition in a relatively wide range. This feature assumes a particular importance in the area of catalysis where zeolites have the largest impact - acid catalysis;
4. The capability of zeolites to act as hosts for a variety of guests with catalytically attractive properties, such as transition metal ions, small metal clusters or transition metal complexes.

**Zeolite structure:**

The elementary building units of zeolites are $SiO_4$ and $AlO_4$tetrahedra. Adjacent tetrahedra are linked at their corners via a common oxygen atom, and this result in an inorganic macromolecule with a structurally distinct three-dimensional framework [13]. It is evident from this building principle that the net formulae of the tetrahedra are $SiO_2$ and $AlO_2^-$, i.e. one negative charge resides at each tetrahedron in the framework which has aluminum in its center. The framework of a zeolite contains channels, channel intersections and/or cages with dimensions from ca. 0.2 to 1 nm. Inside these voids are water molecules and small cations which compensate the negative framework charge. The chemical composition of a zeolite can hence be represented by a formula of the type

$$A_{y/m}^{m+}[(SiO_2)_x.(AlO^-_2)_y.zH_2O$$

Where A is a cation with the charge *m*, (*x*+*y*) is the number of tetrahedra per crystallographic unit cell and *x*/*y* is the so-called framework silicon /aluminum ratio$\boldsymbol{n_{Si}/n_{Al}}$(or simply Si/Al). Lowenstein's rule precludes that two contiguous tetrahedra contain aluminum on tetrahedral positions, i.e. Al–O–Al linkages are forbidden, or $\boldsymbol{n_{Si}/n_{Al}} \geq 1$ [14]. Silicon and aluminum in aluminosilicate zeolites are referred to as the T-atoms.

Fig. 1 shows the structures of four selected zeolites along with their respective void systems and pore dimensions. In these commonly used representations, the T-atoms are located at the vertices, and the lines connecting them stand for T–O–T bonds. For example, if 24 tetrahedra are linked together as shown in the top line of Fig. 1, the cubo-octahedron, also referred to as a sodalite unit or β-cage, results. It is an important secondary building unit from which various zeolite structures are derived. If sodalite units are connected via their hexagonal faces as shown in Fig. 1, the structure of the mineral faujasite results. It is identical with the structures of the synthetic zeolites X ($1 \leq \boldsymbol{n_{Si}/n_{Al}} \leq 1.5$) and Y ($\boldsymbol{n_{Si}/n_{Al}} > 1.5$). Zeolite Y is of utmost importance in heterogeneous catalysis, for example it is the active component in catalysts for fluid catalytic cracking [15]. Its pore system is relatively spacious and consists of spherical cages, referred to as supercages, with a diameter of 1.3 nm connected tetrahedrally with four neighboring cages through windows with diameter of 0.74 nm formed by 12 $TO_4$tetrahedra. Zeolite Y is therefore classified to possess a three dimensional, 12-membered-ring pore system [16]. An example of a zeolite with unidimensional, 12-membered-ring pores is zeolite ZSM-12 (Fig.1, line 2) [17]. Its pores are slightly elliptical with dimensions of 0.57 x 0.61 nm. Zeolite ZSM-5 (Fig. 1, line 3) and its all-silica analogue silicalite-1 ($\boldsymbol{n_{Si}/n_{Al}} = \infty$) are built from the pentasil unit. They contain intersecting systems of ten-membered-ring pores, one being straight and one sinusoidal. ZSM-5 is another example of a zeolite which has gained huge importance in heterogeneous catalysis[18]. It is used industrially in the synthesis of ethylbenzene, the isomerization of xylenes and the disproportionation of toluene and it is often looked upon as the prototype of shape selective catalysts. Several zeolites with unidimensional, ten-membered-ring pores exist as well, one example being Theta-1 which is iso-structural to zeolite ZSM-22 (Fig. 1, bottom line).

Among the unique features of zeolites compared to more conventional solid catalysts or catalyst supports are (i) their strictly uniform pore diameters and (ii) pore widths in the order of molecular dimensions. According to IUPAC classification [19],these are

1. Micropores: $2 \text{ nm} \geq d_p$,
2. Mesopores: $2 \text{ nm} < d_p \leq 50 \text{ nm}$ and
3. Macropores: $d_p > 50 \text{ nm}$

With $d_P$being the pore diameter.

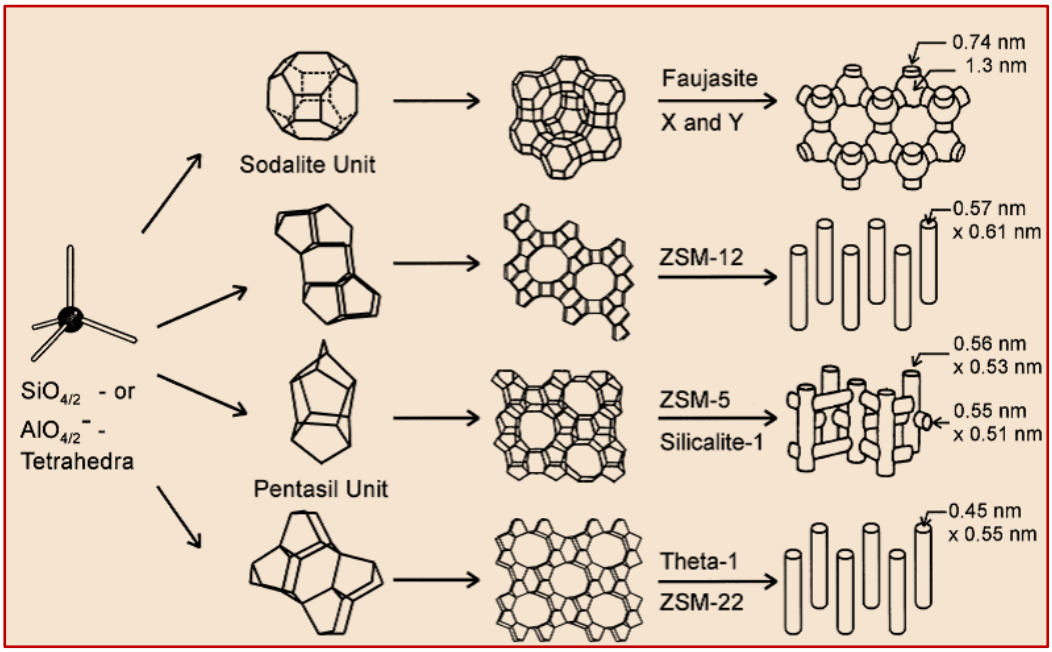



**Figure 1: Structures of four selected zeolites (from top to bottom: faujasite or zeolites X, Y; zeolite ZSM-12; zeolite ZSM-5 or silicalite-1; zeolite Theta-1 or ZSM-22) and their micropore systems and dimensions**

**Synthesis of Zeolite:**

Theprimary building units of a zeolite or a porous material are the individual tetrahedral $TO_4$ unit, where T is Si, Al or other metal like Ti, Fe, and V etc. These tetrahedral ($TO_4$) units can be monomeric, dimeric, trimeric, tetrameric etc. [22]. The primary building units condense and form various polymeric units known as secondary building units (SBU). A SBU is basically a selected grouping of the above mentioned terahedra. There are 18 such building units which are shown in Fig. 2. The different combinations of 18 secondary building units can form all the known zeolite structures.

There are several basic steps in the synthesis of the zeolite and related molecular sieves. The basic materials are generally a silica source, an aluminum source, a generally one organic quaternary ammonium salt either in the form of hydroxide or halide, and few inorganic bases like NaOH, KOH depending upon the choice of the molecular sieve to be prepared. Normally they are synthesized in a stainless steel autoclave under autogenous pressure. However, certain zeolite can also be synthesized in reflux conditions under atmospheric pressure. The basic steps which normally take place during a zeolite /molecular sieve synthesis are as follows.

(i) Hydrolysis of the silica/aluminum/metal source to form an initial gel phase.

(ii) Dissolution/mineralization of the gel phase.

(iii) A series of events that lead to nucleation of zeolite structure. This could be from the gel or solution phase.

(iv) Continued crystallization and crystal growth of the structure from either the gel or from the solution.

(v) Dissolution of any initial but metastable phases.

(vi) Continued crystallization and crystal growth of new, more stable crystalline phases while initial metastable crystals are dissolving.

(vii) Dissolution of further metastable phases.

(viii) Nucleation of the equilibrium phases.

(ix) Crystallization and final growth of the final crystalline condensed phases.

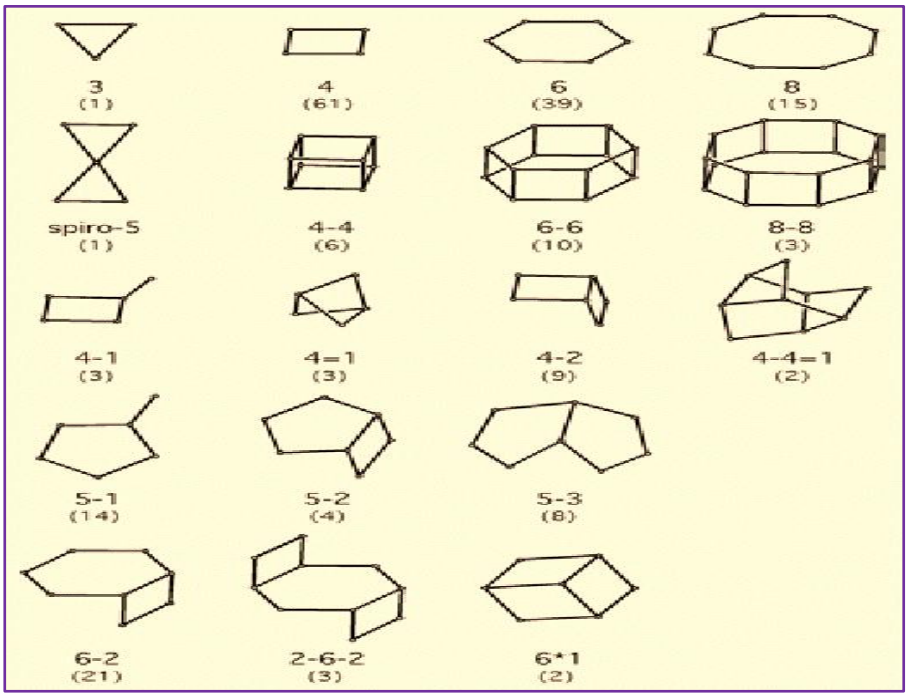



**Figure 2: Secondary building units and their symbols**

**(Number in parenthesis = frequency of occurrence)**

**Factors influencing Zeolite synthesis:**

There are several factors which influence some or all above mentioned processes, as given below

1) Chemical parameters: i) $SiO_2/Al_2O_3$ molar ratio, ii) alkalinity i.e. $OH^-$ concentration, iii) organic template cation, iv) inorganic cation, v) amount of $H_2O$
2) Physical parameters: Temperature and time
3) Historical parameters: Aging, seeding and stirring

**1] Chemical parameters:**

***i) $SiO_2/Al_2O_3$ molar ratio:*** The $SiO_2/Al_2O_3$molar ratio in the gel places a constraint on the framework compositions of the zeolite produced. Ideally the desired $SiO_2/Al_2O_3$molar ratio of a zeolite chosen for a specific application should be obtainable through adjusting that ratio in the synthesis mixture. Generally, an increase in the $SiO_2/Al_2O_3$molar ratio in the framework leads to an increased thermal stability, acid resistance and hydrophobicity and decreased ion exchange capacity.

***ii) $OH^-$ ion concentration:*** The main role of hydroxide ions in the synthesis of zeolite and related molecular sieves is to act as mineralizer (by dissolving polymeric silicate anions into suitable monomeric/oligomeric anions). Hence, the hydroxide ($OH^-$) ion concentration helps in transport of the various silicate/aluminate ions from the solid to liquid phase. The free $OH^-$ ion concentration influences the zeolite synthesis as a structure directing agent through the control of the hydrolysis and the degree of polymerization of silicate and aluminate ions in the solution.

***iii) Template/Organic additive :*** In early 60's, it was found that certain organic quaternary ammonium cations and amines can act as structure directing agent (SDA), void filler and/or gel modifier/mineralizer. These amines/organic cations are trapped inside the pores of the molecular sieve during crystallization. The role of the organic cation in the synthesis can be visualized as follows

a) Structure directing or templating role.
b) Gel modifier, which would result in the formation of structures with higher $SiO_2/Al_2O_3$ molar ratio, than could be obtained in the absence of it.
c) Interact chemically with other components of the gel, altering the character of the gel. This is true particularly of week organic bases, which could alter or buffer the pH of the crystallizing gel.
d) Interact physically with other components of the gel so as to alter the gelling process, solubility of various species, aging characteristics, transport and thermal properties.

Interestingly, a particular organic molecule can lead to different molecular sieve framework and different organic molecules can be used for the synthesis of a particular molecular structure. Table 1 gives some examples of templates and the zeolite structure type.

***iv) Inorganic cation:*** The role of the inorganic cation is somewhat complex in the synthesis of molecular sieves. The role of inorganic cation can be categorized as: structure directing; balancing the framework charge; morphology; crystal purity and yield. The morphology of the zeolite crystals produced can be altered by the presence of various inorganic cations in the synthesis gel. Adjustment of the cation content of the gel can be used to eliminate the intergrowth of the one zeolite with another.

***v) Water:*** In the presence of water it is not only organic cations which remains hydrated, but also the silicate precursors for the particular molecular sieves. As a result water along with organic cation is responsible for the structure direction and not the free silicate or free template alone. Sometimes the higher dilution level slower downs the crystallization process. Water also sometimes determines the structure of the molecular sieve that will be formed under similar conditions. Generally, an increase in the water content in the gel leads to an increase in overall synthesis time (longer induction period) and larger crystallites.

**Table 1: Organic templates and correspondingly formed zeolite structure**

| Organic Type | Zeolite Structure |
|---|---|
| Tetramethyl ammonium $(TMA)^+$ | Gismodine,Sodalite, Faujasite, Zeolite E, Zeolite A, ZSM-4, Offretite, ZSM-47, ZSM-6 |
| Tetraethyl ammonium $(TEA)^+$ | ZSM-8, ZSM-12, ZSM-20, ZSM-5, Beta, Mordenite |
| Tetrapropyl ammonium $(TPA)^+$ | ZSM-5 |
| Tetrabutyl ammonium $(TBA)^+$ | ZSM-11 |
| 1,2-Diaminoethane | ZSM-5, ZSM-21, ZSM-35 |
| 1,3-Diaminopropane | ZSM-35, ZSM-5 |
| 1,4-Diaminobutane | ZSM-35, ZSM-5 |
| 1,5-Diaminopentane | ZSM-5 |
| 1,6-Diaminohexane | ZSM-5, ZSM-22 |
| 1,7-Diaminoheptane | ZSM-11 |

**2] Physical parameters:**

***i) Temperature:*** Temperature influences several factors in the zeolite synthesis. It can alter the zeolite phase obtained as well as change the induction period before the start of the crystallization period. This induction period decreases with increase in temperature. Also, for any mixture as the temperature increases, the rate of the crystallization also increases.

***ii) Time:*** Time has an important role on the formation of a particular structure. At constant mixture composition, the transformation proceeds from amorphous to metastable to more stable phase. Therefore, monitoring the time any particular phase can be identified. The crystallization increases with time. However, after an optimum time, it may decrease or a less metastable phase may transform to the more stable phase.

**3] Historical parameters:**

When the initial reaction mixture or gel is cured at certain temperature, it is called aging. This process helps in distribution of particular type of precursor units required for the desired

zeolites. Seeding means the addition of 2-5 wt.% of pre-synthesized material in the gel aimed to get the same materiel. It is believed that seeding helps in providing desired nuclei at the initial stages of the synthesis. Sometimes agitation or stirring either during aging or crystallization helps in obtaining a desired zeolite structure.

**Some important aluminosilicate type Zeolitic structures**

Out of almost176 listed structural types, a little over a dozen are currently used in industrial application. An overview concerning many of these zeolitic structures has been recently published. Here a brief description of the structure of four aluminosilicate zeolite of interest due to their industrial application or potential is given:

1. FAU (the X and Y synthetic zeolites, isotypes of natural faujasite),
2. MOR (Mordenite),
3. MFI ( ZSM-5),
4. BEA (Beta).

**1. Faujasite**

This structure of faujasiteshown in **Fig. 3** can be described as assembly of any three secondary building units: a hexagonal prism (double hexagon with 12 tetrahedra), a square (4 tetrahedra) or a hexagon (6 tetrahedra).

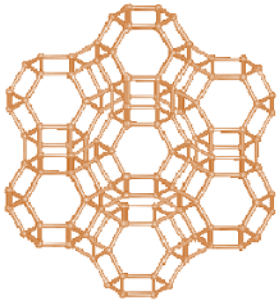


**Figure 3: Faujasite view**

It is more convenient to represent it as an assembly of polyhedra called cuboctahedra (or sodalite cages), connected together via hexagonal prism. This type of arrangement leaves a large free volume which can be described as a 26-face polyhedron (8 square faces, 4 hexagonal faces and 4 twelve membered ring), called a ‘α’ super cage, whose diameter is approximately 1.3nm. It is observed that these large 26 faces polyhedra are connected together by their 12 membered rings forming large opening of diameter 0.74 nm.The two X and Y synthetic zeolite have the faujasite structure. Their only difference is the chemical composition: the ratio n = Si/Al of the X and Y zeolite lies between 1-1.5 and 1.5 to 3 respectively. Y zeolite is mainly used in two important industrial catalytic operations: cracking and hydrocracking.

**2. Mordenite**

The sodic form of mordenite, chemical formula $Na_2O.Al_2O.9\text{-}10SiO_2.xH_2O$, was probably synthesized for the first time towards the end of the 1920's [23]. It can be obtained in a silica enriched form (e.g. $SiO_2/Al_2O_3 = 20$) by adding an organic base in the synthesis medium. Its complex structure can be represented as assembly of chains parallel to the c-axis composed of 5-1 SBUs as shown in Fig. 4 (consisting of a pentagon of tetrahedra to which a sixth tetrahedron is connected).

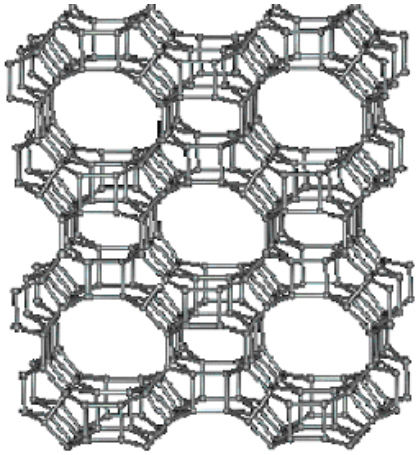


**Figure 4: Mordenite view**

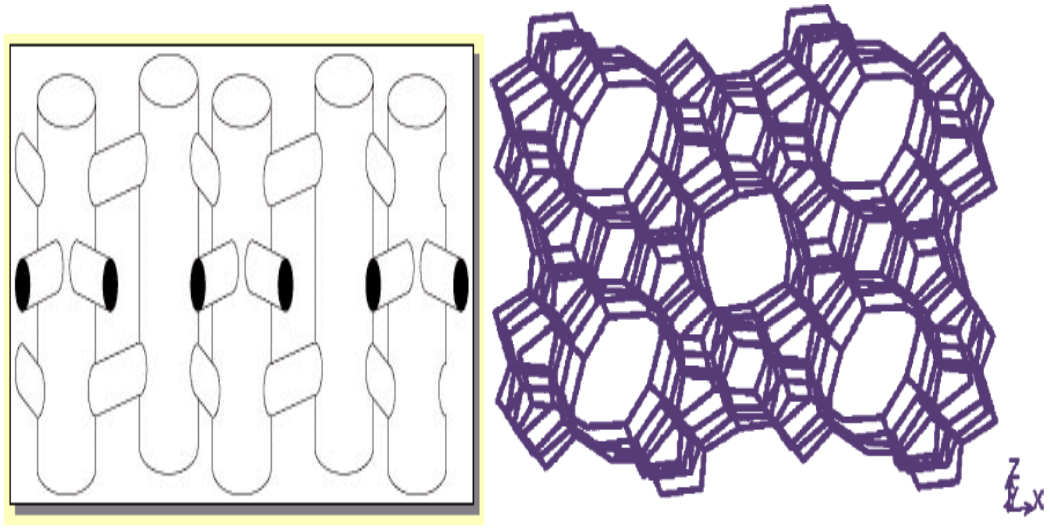
Mordenite is used in the industrial isomerization of light paraffins with 5 and 6 carbon atoms and in the conversion of aromatics.

**3. ZSM-5**

The zeolite ZSM-5, of structure type MFI (Mobil FIVE), was discovered towards the end of the 1960's by Mobil Oil [24]. But the corresponding patent was only published in 1972 [25]. At the time it was synthesized in a medium containing sodium and / tetrapropylammonium ions [26]. Its composition may vary within wide range since, in its formula $Na_2O.Al_2O.2nSiO_2.xH_2O$, n is $\geq$ 6 and can reach extremely high values, well above 1000 [27]; the aluminium still present must then be considered as an impurity. A typical value of 'n' is ~60.

The porous structure of this zeolite shown in Fig.5 (a & b) consists of a three dimensional network of interconnected cylindrical channels, with opening between 0.51 and 0.56 nm. The porosity of this zeolite is therefore much less open than that of Y zeolite (= 0.74nm.).

The accessibility of the ZSM-5 acid can be seen more clearly on the highly diagrammatic representation of Fig. 5(a) which shows that there are two categories of perpendicular, interconnected channels forming a three dimensional porous system. Zeolite ZSM-5 was and still is used in many industrial refining and petrochemical application**.**



**(a)** **(b)**

**Figure 5: ZSM-5 view**

**4. Zeolite βeta (Bea structure)**

Discovered by the Mobil scientists towards the end of 1960's [28], Beta zeolite was the first zeolite with an $SiO_2/Al_2O_3$ ratio greater than 10 ( n = Si/Al > 5). It is synthesized in silica rich medium ($SiO_2/Al_2O_3$ ratio from 10 to approximately 200), containing tetramethyl ammonium and sodium ions. Its composition may vary within a very wide range ($SiO_2/Al_2O_3$ from 5 to approximately 100). Its complex structure, which has no natural equivalent, was only determined in 1988, some 20 years after its discovery [29]. Zeolite Beta is very complex and difficult to understand. Zeolite Beta (Fig. 6) has a disordered growth of two three-dimensional 12-ring zeolite frameworks with high density stacking faults [30]. It consists of an intergrowth of two distinct structures termed Polymorphs A and B. The two hypothetical polymorphs are depicted in Fig. 7. The polymorphs grow as two-dimensional sheets randomly alternate between the two. Both polymorphs have a three dimensional network of 12-ring pores.

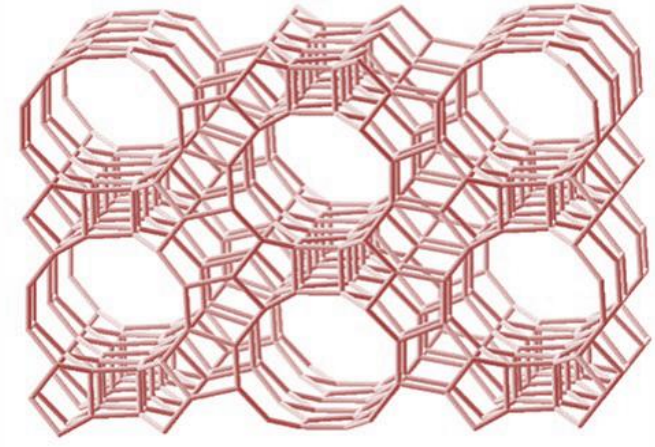
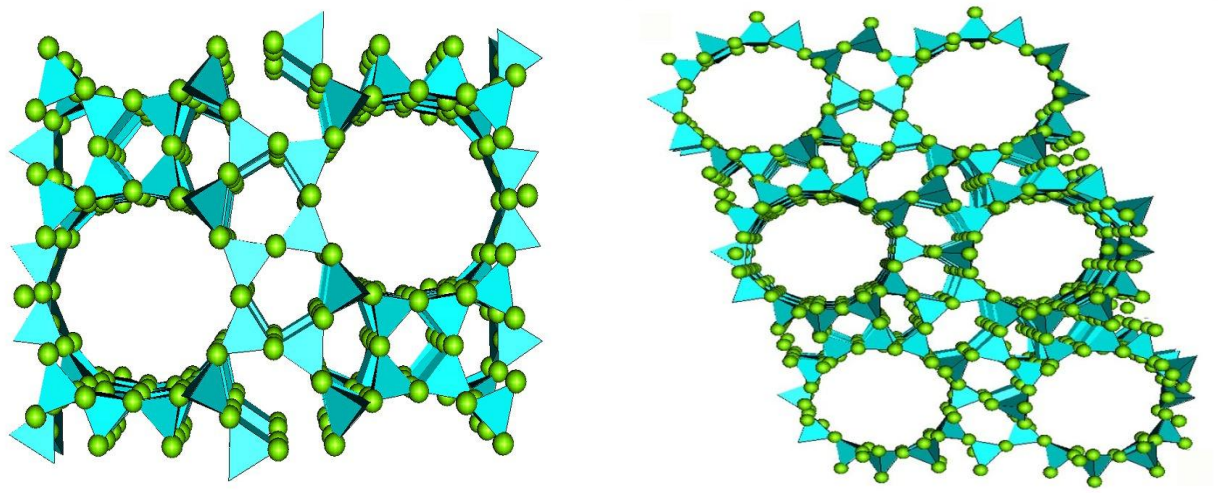


**Figure 6: Zeolite BEA view**

It has three-dimensional tetragonal crystal structure (lattice parameters about 12.6 X 12.6 X 26.2 Å) and three dimensional channel system consisting of straight 12 membered ring channels ( 7.6 X 6.4 Å) which intersect crossed 10-membered ring sinusoidal channels (5.5 X 6.5 Å) at right angles.

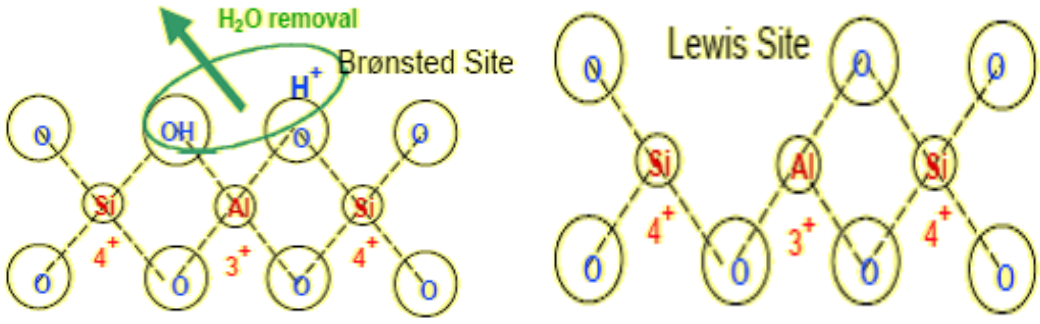


**Polymorph A** **Polymorph B**

**Figure 7: Structure of zeolite beta Poly type A and Poly type B**

**Acidity of Zeolites:**

Activity of the zeolite catalyst is mainly due to the presence of acid sites, which are created by charge imbalance between the silicon and aluminum ions in the framework. Thus each aluminum atoms present in the framework constitutes an active site. Classical Bronsted and Lewis acid modes have been used to classify the active sites in the zeolite. Bronsted acid sites arise when the cation balancing the anionic frame work charge is proton ($H^+$). Where astrigonally coordinated aluminum atom which acts as an electron pair acceptor behaves as Lewis acid site. The Bronsted and Lewis acid sites are depicted below in Fig.8.




**(a)** **(b)**

**Figure 8: Acid sites of zeolite a) Bronsted acid sites b) Lewis acid sites**

Acidity can be introduced into a zeolite by anumber of different ways, and can be achieveddue to the particular charge balance of zeoliticframeworks. The existence of aluminum in a tetrahedrally coordinated silicon structure requiresthe existence of compensating cations that arelocated in the porous system of the structure.These cations are accessible for ion exchange,and, thus, acidity can be achieved by:i) ion exchange with $NH_4^+$, followed by thermal decomposition;ii) hydrolysis of ion-exchanged polyvalentcations;iii) reduction of exchanged metal ions to alower valence state.

In all the examples above, Bronsted acid sitesare formed. These sites can be further involved indehydroxylation reactions, to form Lewis acidsites, under thermal treatments at temperatures usually in excess of 500 °C [21].The acidic catalytic properties of zeolites havebeen extensively used in many commercial processes. The hydroxyl groups with very acidic hydrogens have been recognized as the main source ofthese properties, especially of the efficient carboniogenic activity of zeolites [31,32]. Several parameters have to be taken into account to evaluatethe acidity of a zeolite in relation to a particularapplication. Besides the structure, other parameters such as thetotal number of Bronsted andLewis sites, their strength distributions and theirlocation, have a significant influence on the effective acidity of any particular acid site in relation to a particular reaction.At the same Al content, the strength of theBronsted sites for several zeolites [33], and thecorresponding activities for o-Dichlorobenzeneisomerisation [34], follows the order HZSM-5 > HM >HBeta>HOff, showing the influenceof the structural factors. Another example is thecatalytic ability of faujasitic zeolites and ZSM-5,with similar compositions, which may differ bytwo orders of magnitude on the n-hexane cracking [35]. Similar observations, of purely structuralfactors influencing catalytic activity, have beenmade when comparing Y zeolite with ZSM-20 [36, 37]. Choudhary *et al.* compared the acidity/siteenergy distributions in some catalytically important zeolites, and found the following order, if thezeolites were arranged according to the amount ofstrong acid sites:HY ~ HM >CeNaX>CeNaY> HZSM-8> HZSM-5 > HKL >> HZSM-11[38]. The catalytic activities per strong acid site, aswell as the acidity of the Bronsted sites was shownto depend strongly on both the structure and thetopology of the zeolite, and the chemical composition of its environment inparticular on the Si/Al ratio [39].

There is usually an increase in the number ofstrong Bronsted acid sites when the Si/Al ratio isincreased, despite the reduction of the totalamount of sites [40]. Also, theoreticalapproaches, such as those using an electronegativity model for evaluating the charge on the hydrogen atoms in zeolites [41], or the study of protonaffinity [35],or quantum chemical methods [42,43], confirmed this fact. The aluminiumatoms induce a higher degree of electron

donationthan silicon, resulting in a higher oxygen chargeand proton-oxygen interaction [44, 45]. Many data for acidcatalyzed processes revealed a parallel trend withthe aluminium framework content [46, 47], forlimited Si/Al ranges. Generally, the catalyticactivity goes through a maximum under furtherSi/Al increase [48, 49]. This optimumvalue depends on the framework density of thezeolite.Some dealumination processes, commonlyused, can originate the formation and depositionon the porous structure of cationic aluminium species, which can act as Lewis sites or poison thestrongest acid sites [50, 51]. The presence ofLewis acid sites also has some influence on theBronsted acidity strength. The inductive effectassociated with the Lewis sites on the neighboring protonic sites increases the latter's acidstrength, resulting in an enhancement of some catalytic reactions [52, 53].One way to control the relative amount of protonic sites is the regulation of the extent of ionexchange achieved on the zeolite preparation. Several examples are known on how the activity of Y zeolites changes when the $Na^+$ exchangelevel is altered [54, 55] and similar behavior hasalready been observed in other zeolites, such as ZSM-20 [56].The effect of the nature of the compensatingcation on the acid strength, although quite smallerthan the framework composition, is not negligible. The exchange of protons by $K^+$ ions on Y zeolitebrings a more significant acid strength decreasethan the exchange by $Na^+$ cations [57, 58].

**Shape selectivity of Zeolite in catalysis:**

The fact that the pores of zeolites and moleculesinteracting with the surface of zeolites have dimensions in the same order of magnitude, leads to unique effects in catalysis for which thegeneric term shape-selective catalysis is in use today.Shape-selective catalysis encompasses all effects inwhich the selectivity of the heterogeneously catalyzed reaction depends unambiguously on the porewidth or pore architecture of the microporous catalyst [59]. Numerous such effects are known today. They can be classified into one of the following categories:

**(i) *Reactant shape selectivity*:** There are at leasttwo reactants with differences in their molecular dimensions. If the diffusion of the bulkier reactant molecules inside the pores is hindered, the less bulky molecules will react preferentially (Fig. 9). The limiting caseis a complete size exclusion of one reactant which leaves the catalytic reactor unconverted.

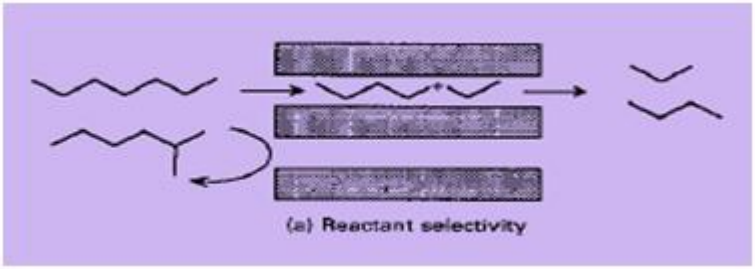



**Figure 9: Reactant shape selectivity of Zeolite**

**(ii) *Product shape selectivity*:** At least two products with differences in their molecular dimensionsmay form in parallel or consecutive reactions. If thediffusion of the bulkier product molecules inside thepores is hindered, the less bulky molecules will beformed preferentially. The limiting case is a complete suppression of the formation of the bulkier molecules (Fig. 10).

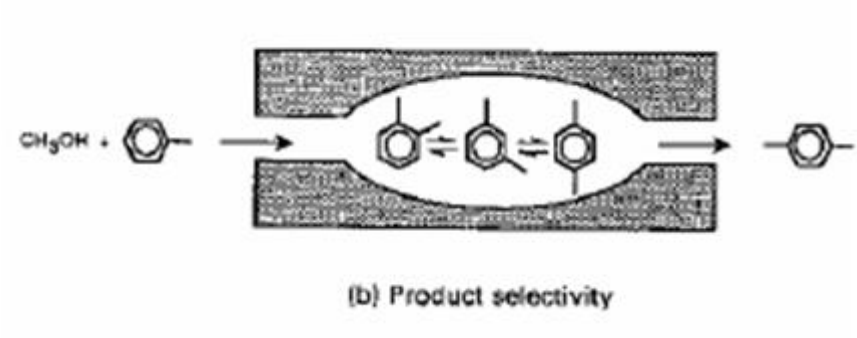



**Figure 10: Product shape selectivity of zeolite**

**(iii) *Restricted transition state shape selectivity*:** Neither the reactant nor the product moleculesexperience a hindered diffusion. However, out of atleast two (parallel or consecutive) reactions, one isgoing via a bulky transition state or intermediatewhich cannot be accommodated inside the zeolitepores. In favorable cases, this reaction is entirelysuppressed (Fig. 11). The chances for achieving restrictedtransition state shape selectivity in a suitably selectedzeolite are usually very good, if the same reactant canundergo a monomolecular and a bimolecularreaction.

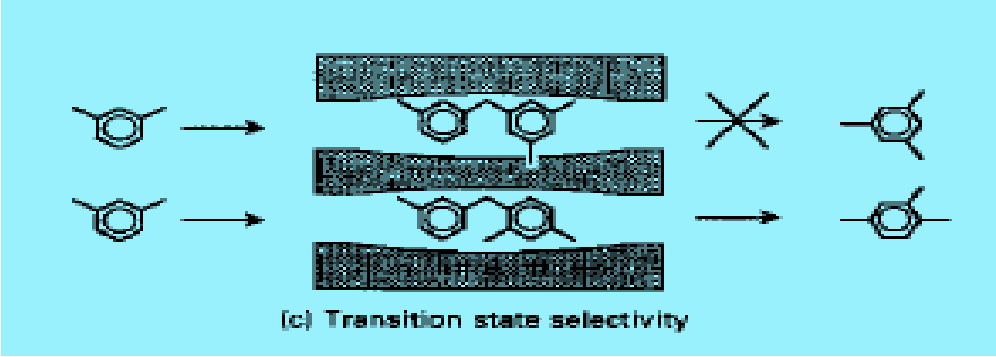



**Figure 11: Transition state shapeselectivity of Zeolite**

Shape selective catalysis in zeolites is alreadyexploited in a number of large-scale processes [60]. Inmost cases, the observed selectivity effects can berationalized satisfactorily in terms of the traditionalclassification outlined above. To account for morerecent research results, however, a number of novelconcepts for shape-selective catalysis in zeoliteswere advanced.

Among these are cage or windoweffects, a directed (e.g. tip-on) adsorption of molecules at the active sites, secondary shape selectivity, inverse shape selectivity and pore mouth catalysis.

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# Advances in Chemical Science Volume I

ISBN: 978-93-91768-59-1

## About Editors

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ISBN 978-93-91768-59-1
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