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The chemistry of the benzimidazoles ligand

Research project
Submitted to the department of (chemistry) in partial fulfillment of the requirements for the degree of B.A BSc. in(science)

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I support the student Dlsoz Masud Nuri that she completes all the requirements of her research project under the title of

(The chemistry of the benzimidazoles ligand)

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SUPERVISOR

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*To begin with, I thank **(Allah)** for His blessing, which made me able to complete and perform this study with success, the lord of the universe, blessing, and peace be on **Muhammad** (Allah's peace and prayers be upon him).*

Finally, I want to say thanks to my Supervisor Lec. Nhiyat Hamadamen and all those I forgot them here to mention his/her name, who assisted me even by one useful scientific word directly or indirectly.

Abstract:

Benzimidazole is an aromatic heterocyclic ring system. It contains benzene and imidazole ring fused together at 4 and 5 position. It has other names such as benzimidazole and 1,3-benzodiazole.

Benzimidazole derivatives constitute an important class of heterocyclic compounds for their versatile pharmacological activities such as antibacterial, antifungal, anthelmintic, antiallergic, local analgesic, antihistaminic, hypotensive and spasmolytic activities

Keywords: Benzimidazole, Transition Metals (II).

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1. Introduction

1.1 Benzimidazole

Benzimidazoles and their derivatives are important compounds because of their pharmacological properties. (Selcen .A, 2009)

Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including anti ulcers, anti-hypertensives, antivirals, antifungals, anticancers.(Veenu.B, 2009)

Benzimidazole is an aromatic heterocyclic ring system. It contains benzene and imidazole ring fused together at 4 and 5 position.

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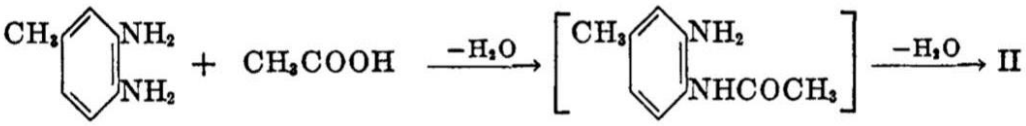
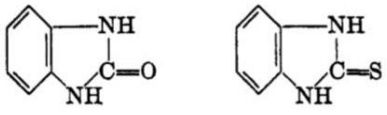
The benzimidazoles contain a phenyl ring fused to an imidazole ring, as indicated in the structure for benzimidazole (I).

I

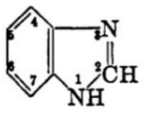
Several years later Ladenburg obtained the same compound by refluxing 3,4-diaminotoluene with acetic acid.

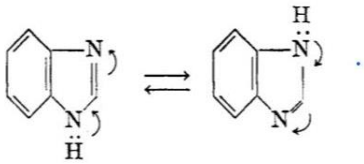




IV V

The numbering system for the benzimidazoles is as follows





The ring system in which a benzene ring is fused to the 4,5-positions of imidazole is designated as benzimidazole. .(John B. wright, 1951)

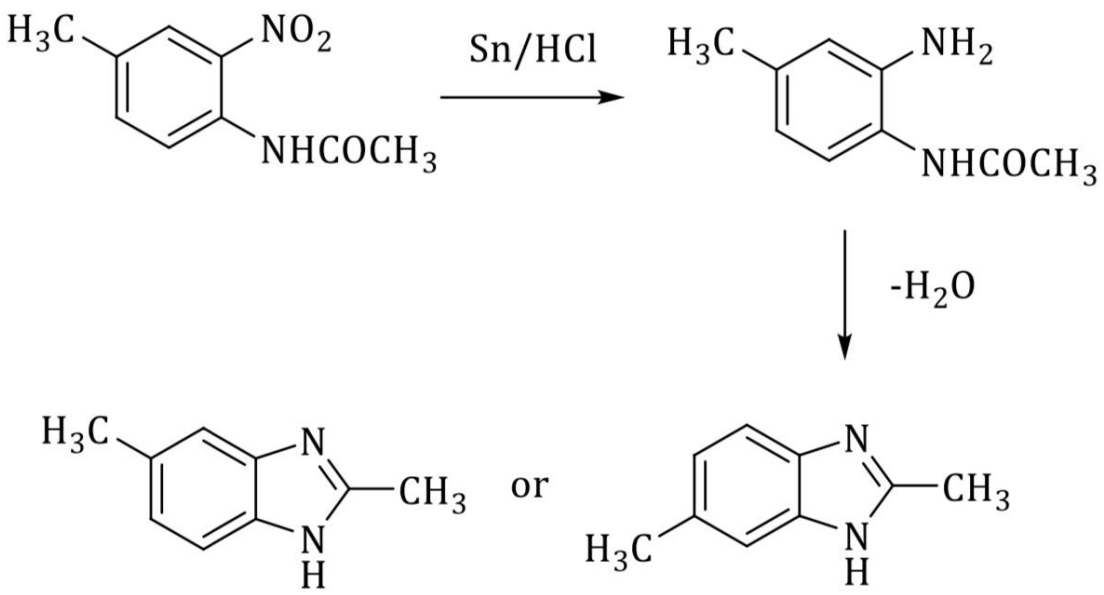
Benzimidazole is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole . (Syeda.F ,2011)

Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic compound consistsof the fusion of benzene and imidazole. Heterocyclic compounds are occupied prominent place among various class of aromatic organic compounds. Benzimidazole are having a variety of therapeutic uses including antitumor, antifungal, antiparasitic, analgesics, antiviral, antihistamine.

1.2 synthesis of benzimidazole

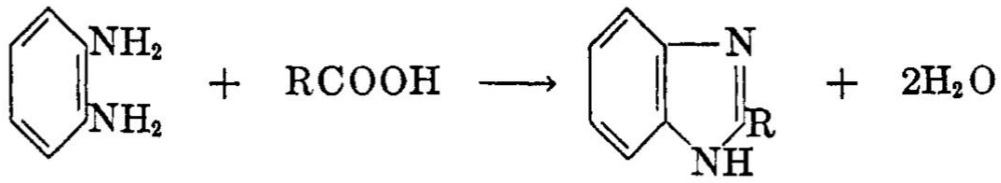
Benzimidazole is synthesized from o-phenylenediamine and different aromatic acids. In this method, the diamine is initially refluxed with aromatic acid. The corresponding acid is converted into benzimidazole.

The first benzimidazole was prepared in 1872 by Hoebrecker, by the reduction of 2-nitro-4-methyl acetanilide gave 2,5- dimethyl benzimidazole or 2,6-dimethyl benzimidazole

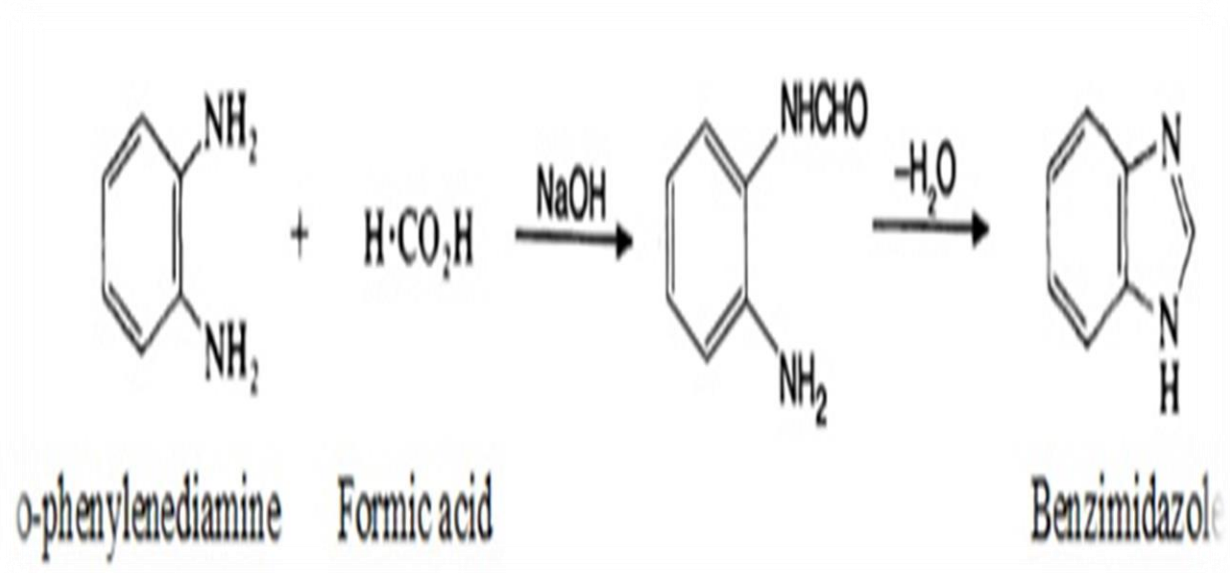


Synthesis of benzimidazole from 2-nitro-4-methyl acetanilide

O -Phenylenediamines react readily with most carboxylic acids to give 2-sub- stituted benzimidazoles. (Aneel.B,2010)

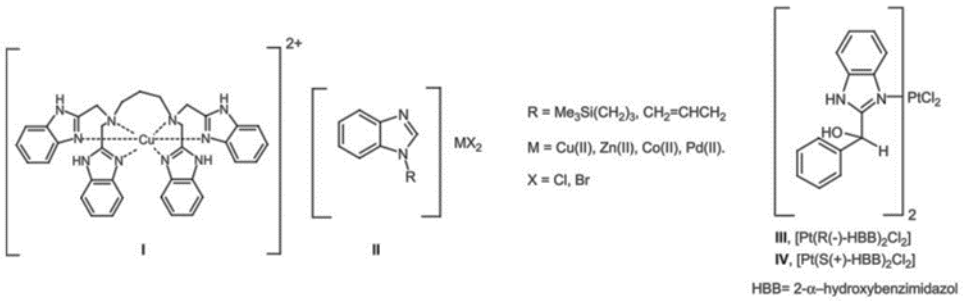


Benzimidazole is produced by condensation of o-phenylenediamine with formic acid, or the equivalent trimethyl orthoformate. (Hitesh., 2004)



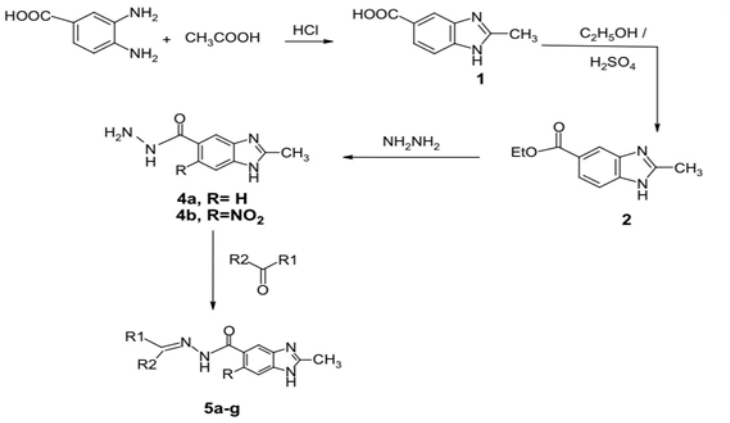
1.3 Metal complexes of benzimidazole

Cu(II) complex of CuL($clo_4)_2$) (L=N,N,N',N'-tetrakis [2benzimidazolyl) methyl]-1,3-diaminopropane (I) can electrostatically bind to the phosphate groups of DNA backbone and partially intercalate into the double helix of DNA . N-Trimethylsilylpropylbenzimidazole (II) metal complexes exhibit cytotoxic activity on four monolayer tumor cell lines:

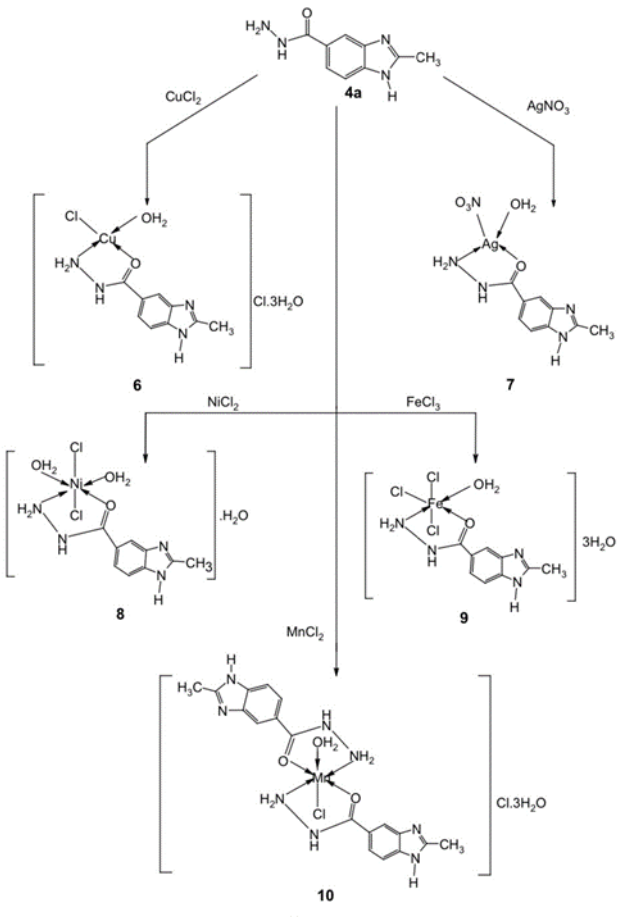


I II

III, $[Pt(R(-)\text{-}HBB)_2Cl_2]$
IV, $[Pt(S(+)\text{-}HBB)_2Cl_2]$
HBB= 2-α--hydroxybenzimidazol



5a, R = H, $R_1 = R_2 = CH_3$
5b, R = NO_2, $R_1 = R_2 = CH_3$
5c, R = NO_2, R_1 = H, R_2 = 2-furyl
5d, R = NO_2, R_1 = H, R_2 = 5-methyl-2-furyl
5e, R = NO_2, R_1 = H, R_2 = 2-pyridyl
5f, R = NO_2, R_1 = H, R_2 = 3-indolyl
5g, R = NO_2, R_1 = H, R_2 = 4-methylphenyl

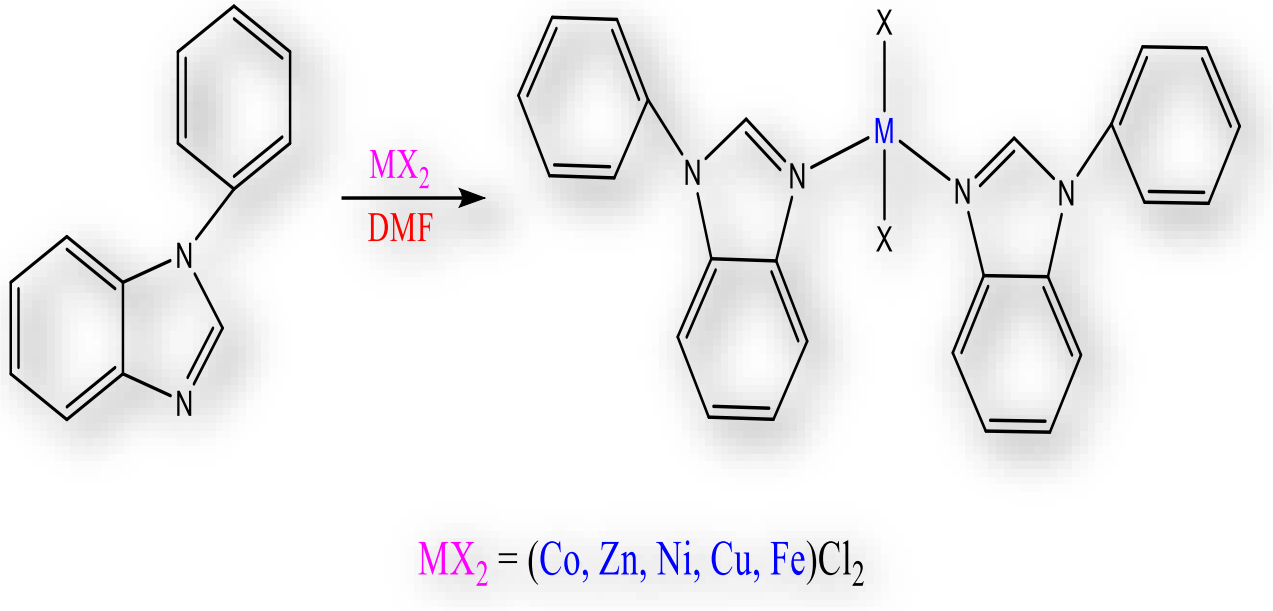


The interaction of N-monosubstituted benzimidazoles with various metal salts [$cocl_2$, $NiCl_2$ and Zn($(OAC)_2$)2)] were yielded stable solid metal benzimidazole complexes.(Mwlla.A,2017) All the metal complexes were identified by 1H NMR, FT-IR spectroscopic techniques, elemental analysis

The preparation and spectral characterisation of 2-[6-(benzimidazolylazo)] as an organic heterocyclic azo dye compound containing benzimidazole.The reaction of benzimidazole diazoniumbromid with 2,4-dibromo phenol in alkaline alcoholic solution yielded -2,4-dibromo phenol (BIADBrP). Spectral analyses have been used to study the structure of the azo dye ligand such as H1NMR, mass spectrum, IR, UV-Vis and element analysis. New six complexes with CO(III), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) ions were prepared and identification by several physiochemical techniques; such as C.H.N element, magnatic susceptibility, atom absorption, molar conductivity, IR and electronic spectra.The used techniques showed the formation of all complexes 1:2 [M:L] complexes and suggested octahedral geometry.(Kerwin.S,2009)

The Co(II), Zn(II), Ni(II), Cu(II), and Fe(II) complexes of 1-phenylbenzimidazole were synthesized and characterized by NMR and elemental analyses. The crystal structures of dichlorobis(1-phenyl-1 H-benzimidazole-kN^3)cobalt(II) and dichlorobis(1-phenyl-1 H-

benzimidazole-kN^3)zinc(II) have been determined by single-crystal X-ray diffraction (Ülkü et al., 2011)



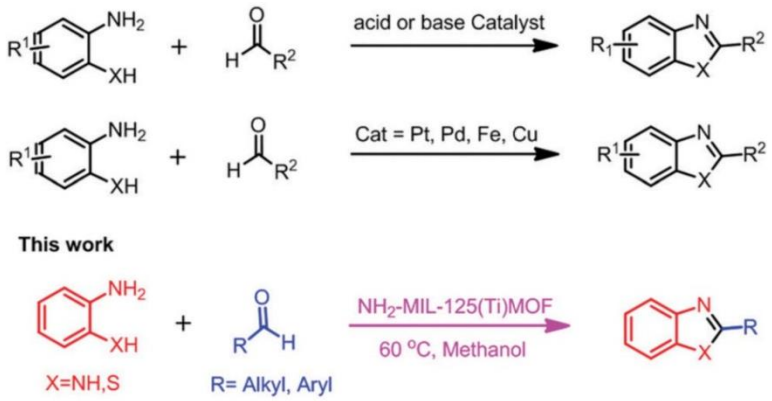
$MX_2 = (Co, Zn, Ni, Cu, Fe)Cl_2$

Synthesis of 1-phenylbenzimidazoles metal complexes

1.4 Application of benzimidazole

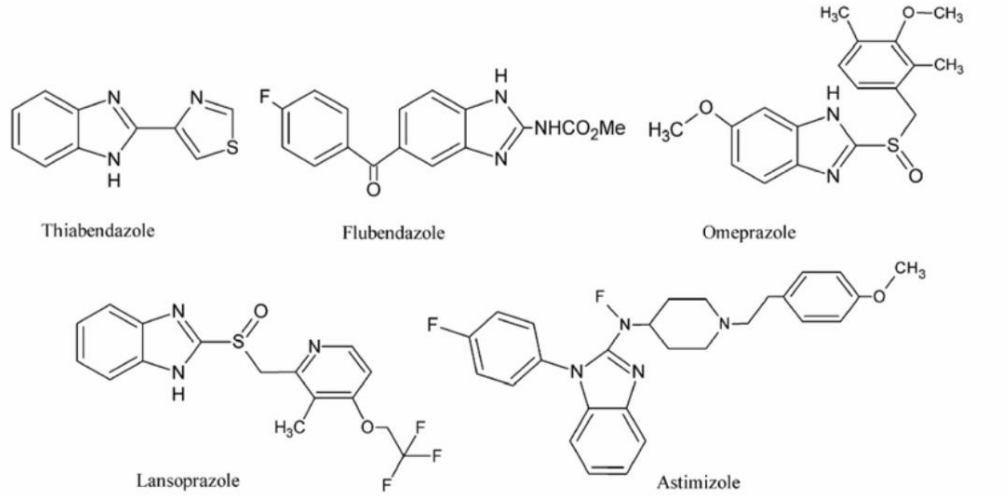
Benzimidazole ring acts as ligand toward transition metal ions in a variety of biologically important molecules. These compounds show a wide range of biological activities like antibacterial, antifungal, antitubercular, antimalarial, anti- inflammatory, analgesic, ant amoebic, antihistamine, ant ulcerative, antioxidant, antiproliferative, antihypertensive, antiallergic, antitumor, angiokinase and anti-HIV-1 properties. Some benzimidazoles have also been evaluated as cholinesterase inhibitors and drugs against parasites. (Dorota. W ,2015)

Nitrogen and sulfur-containing heterocyclic compounds offer a significant range of applications including agrochemicals, pharmaceuticals, natural products and functional materials for industries.1–3 Heterocyclic compounds, particularly five-membered ring systems such as benzimidazole and benzothiazole, have gained great attention towards various biological activities including antifungal, antibacterial, anticancer and antiulcer due to their unique properties.4–6 Because of their wide range of applications.

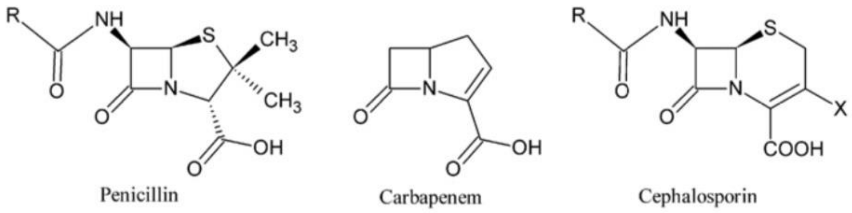


Catalytic strategies for the synthesis of benzimidazoles and benzothiazoles. (Velayudham .S 2019)

K F Ansari and C Lal



Clinically used benzimidazoles.



Antibiotics containing β- lactam ring.

Benzimidazoles reported as ,antiviral , antidiabrtic , antihypertensive ,antitumor , and antioxidants .(Imran .I 2019)

Many different benzimidazoles have found commercial applications in the medical and agricultural fields where the derivatives have such activities as bacteriostats and bactericides, insecticides, fungicides, sedatives anticarcinogens and phycopharmacological agents.

(Leovac.V.M ,1999). Many scientists have worked on benzimidazole derivatives and they found that this compound has the diverse role in the field of medicinal chemistry.

A benzene ring fused with an imidazole ring structure results in the development of a benzimidazole ring. wide application of the substituted benzimidazole derivative have been understood in the antifungal, antiulcer, antiviral and others therapeutic advances. (Drhitesh.p,2019) ligands containing benzimidazole (or imidazole) rings play important roles in coordination chemistry, and they can coordinate with a variety of transition metals to form one-, two- and three-dimentional coordination compounds through using nitrogen atoms of benzimidazole (or imidazole).

Few benzimidazole derivatives are currently in the market as a drug candidate against various disease. Moreover, the benzimidazole derivatives exhibit pharmacological activities such as anti-tuberculosis, anti-malarial, anti-histamine, antimicrobial, antiviral, antidiabetic, anticancer, anti-fungal, anti-inflammatory, analgesic, anti-HIV.(Mahesh.S,2019)

2. Heterocyclic compound

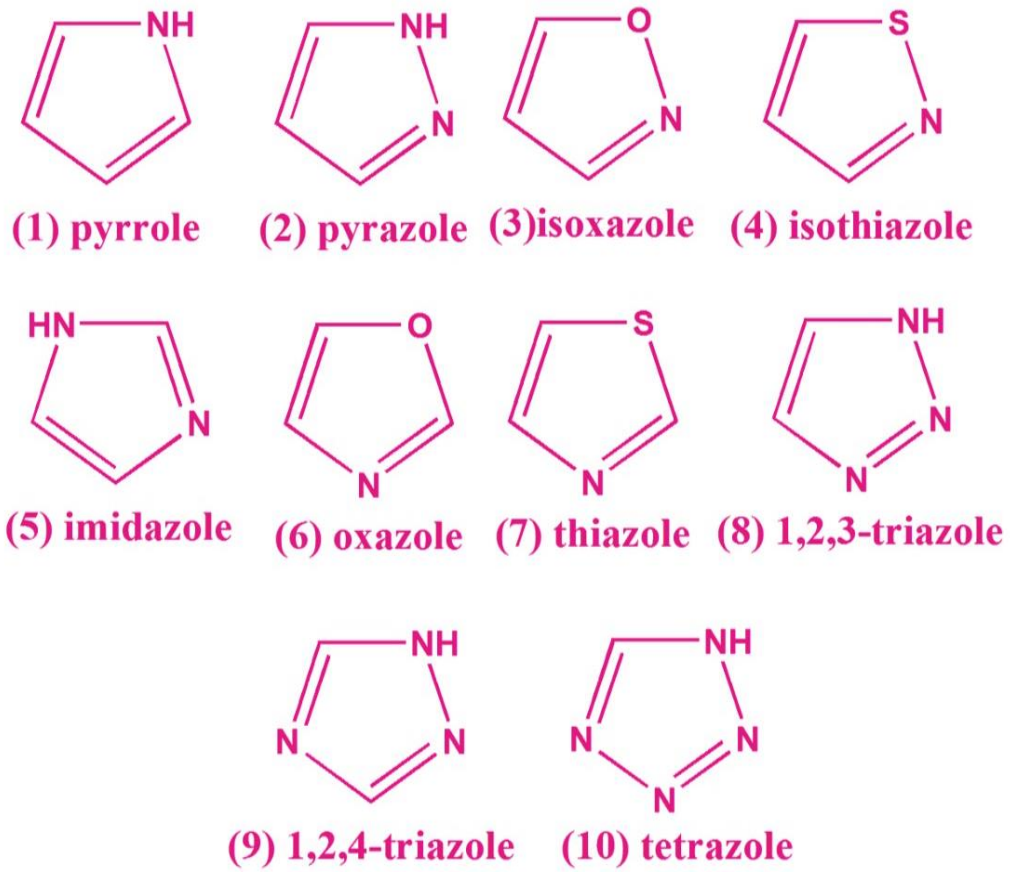
Heterocycles are organic compounds containing at least one atom of carbon, and at least one element other than 1 carbon, such as sulfur, oxygen or nitrogen within a ring structure. Heterocyclic chemistry is the branch of chemistry dealing with synthesis, properties, and applications of heterocycles.

Heterocyclic system occure in a wide variety of natural and synthetic compounds and are essential to life in a various way.

Heterocyclic compounds are essential for life and extensively distributed in nature; they play a significant role in the metabolism of all living cells. Among them, Nitrogen based heterocyclic compounds play important role for mankind. Also, many synthetic nitrogen heterocycles are highly relevant to pharmacology and medicine. Particularly, benzimidazole has an immense importance not only biologically but also industrially among all the nitrogen based heterocyclic compounds. Moreover, benzimidazole has been an intriguing field of study since decade. It is a standout amongst the most encouraging moieties that is available in numerous clinically valuable drug candidate (Divya.G,2019)

Five membered heterocyclic compounds containing one or more heteroatoms, at least one of which must be nitrogen are termed as azoles. The simplest azole, pyrrole (1) contains one nitrogen atom. The ring containing two nitrogen atoms; one oxygen and one nitrogen atom; one sulphur and one

nitrogen atom in 1, 2-position are designated as pyrazole (2), isoxazole (3) and isothiazole (4) respectively. When both the heteroatoms are representing in a 1,3- relationship then they are referred as imidazole (5), oxazole (6) and thiazole (7) respectively. A five membered ring containing three nitrogen atoms is known as triazole such as 1, 2,3-triazole (8) and 1,2,4-triazole (9). While a five membered ring containing four nitrogen atoms is known as tetrazole (10). Azoles are found widely in natural sources and there are several drugs available which contain azole ring in their molecular framework.



Heterocyclic compounds are a very wide and an expanding area of chemistry as well as pharmacology, (Shameela.R,2016)

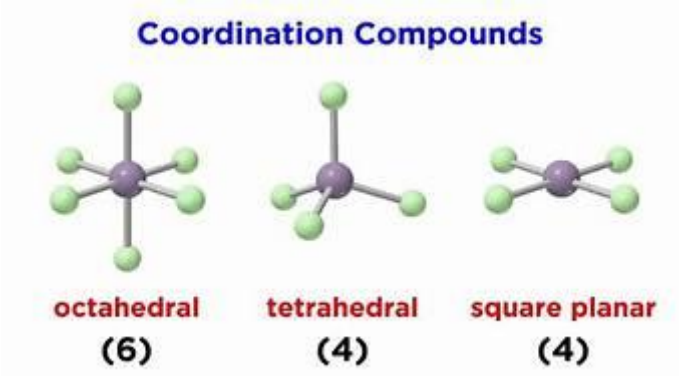
this compounds are very often used in the development of novel drugs with new mechanisms of action. Among heterocyclic compounds, arylaziridines . and benzimidazole derivatives have very important role because of their wide spectrum of biological activities. Benzimidazole and its derivatives are reported to be physiologically and pharmacologically active and some applications are found in the treatment of several diseases including epilepsy, diabetes and infertility. (Pavel .K ,2015)

3. Coordination compound

Coordination chemistry involves the study of compounds, their structures, properties and application. The term coordination used to describe these compounds stems from the nature of chemical bond that leads to the formation of these compounds. This chemical bond called coordinate covalent bond involves donation of electron pair(s) by a molecule or negatively charged ion, a Lewis base (ligand), to a neutral metal or positively charged ion, a Lewis acid (metal). The species providing the electron pair (the electron-pair donor) is thought of as being coordinated to the species receiving that lone pair of electrons (the electron-pair accepter). The coordinating entity, the ligand, can be as small as a monoatomic ion (e.g. F^-) or as large as a polymer. The key characteristic is the presence of one or more lone pairs of electrons on an electronegative donor atom. Donor atoms often met are heteroatoms like N, O, S and P as well as halide ions, but this is by no means the full range. Moreover, the vast majority of existing organic molecules can act as ligands, or else can be converted into molecules capable of acting as ligands (Pradyot, 2002).

3.1.Applications of Coordination Compounds

A primary application of coordination compounds is their use as catalysts that serve to alter the chemical reaction's rate. For example, Certain complex metal catalysts play a key role in polypropylene and polyethylene production. In addition, a very stable class of organometallic coordination compounds has provided the impetus to organometallic chemistry development. Occasionally, "sandwich" configurations describe organometallic coordination compounds, where two molecules of unsaturated cyclic hydrocarbon, missing one or more atoms of hydrogen, bond to either side of a metal atom. This results in an aromatic system, which is highly stable.



coordination compounds have specific colours. Therefore, they find a common place in industries for intense colourations. Phthalocyanine is a class of coordination complexes that the dyes and pigments industry extensively use. They use it to impart specific colouration to fabrics.

Some of the cyanide complexes find their use for electroplating a protective layer on surfaces.

There are complexes that find the application of coordination compounds in photography.

EDTA is another complex compound we use for the determination of hardness of water. Uses of coordination compounds also involve their application as catalysts. These days, they are becoming increasingly popular in the polymer industry as well.

We apply the concept of coordination compounds in the extraction of metals from their ores too frequently these days. Extraction of nickel and cobalt involves uses a major use of these compounds. These metals are extracted by hydro-metallurgical processes requiring a lot of complex ions.

As more and more coordination compounds are getting synthesised, scientists and engineers are now having a wide range of options for improving and optimising the processes that require them. (Kassab . A,2008)

4.Transition elements

Transition metal complexes are cationic, neutral or anionic species in which a transition metal is coordinated by ligands. Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. It's important in catalysis, materials synthesis, photochemistry, and biological systems (Aliyu, 2012). Transition metal complexes have applications in clinical and analytical and industrial in addition to their important roles in a catalysis and organic synthesis (Progathi et al., 2011).

The elements in the periodic table are often divided into four categories:

(1) main group elements,

(2) transition metals,

(3) lanthanides, and

(4) actinides.

The main group elements include the active metals in the two columns on the extreme left of the periodic table and the metals, semimetals, and nonmetals in the six columns on the far right. The transition metals are the metallic elements that serve as a bridge, or transition, between the two sides of the table. The lanthanides and the actinides at the bottom of the table are sometimes known as the inner transition metals because they have atomic numbers that fall between the first and second elements in the last two rows of the transition metals.

Interactive **periodic table** showing names, electrons, and oxidation states. Visualize trends,

5. Refrences

Aliyu, A. W. 2011.Transition metal complexes and their application in drugs and cosmetics – A Review. Journal of Chemical and Pharical. Vol. 3 No. 4; pp 951-958

Alpan, A.S., Zencir, S., Zupkó, I., Coban, G., Réthy, B., Gunes, H.S. and Topcu, Z., 2009. Biological activity of bis-benzimidazole derivatives on DNA topoisomerase I and HeLa, MCF7 and A431 cells. Journal of Enzyme Inhibition and Medicinal Chemistry, 24(3), pp.844-849.

Ansari, K.F. and Lal, C., 2009. Synthesis and biological activity of some heterocyclic compounds containing benzimidazole and beta-lactam moiety. *Journal of Chemical Sciences*, *121*(6), pp.1017-1025.

Asif, M., 2019. Green synthesis of benzimidazole derivatives: an overview on green chemistry and its applications. *Chemical Methodologies*, *3*(6), pp.620-631..

Al-Mulla, A., 2017. A review: biological importance of heterocyclic compounds. *Der Pharma Chemica*, *9*(13), pp.141-147.

Chhonker, Y.S., Veenu, B., Hasim, S.R., Kaushik, N., Kumar, D. and Kumar, P., 2009. Synthesis and pharmacological evaluation of some new 2-phenyl benzimidazoles derivatives and their Schiff's bases. *E-journal of chemistry*, *6*(S1), pp.S342-S346.

Galal, S.A., Hegab, K.H., Kassab, A.S., Rodriguez, M.L., Kerwin, S.M., Abdel-Mo'men, A. and El Diwani, H.I., 2009. New transition metal ion complexes with benzimidazole-5-carboxylic acid hydrazides with antitumor activity. European journal of medicinal chemistry, 44(4), pp.1500-1508.

Hitesh G. R. 2004. practical in organic chemistry, pp 301

Imran, M., 2019. Preparation of benzimidazole based coumarin derivatives as antimicrobial and antioxidant agents. *Oriental Journal of Chemistry*, *35*(4), p.1392.

Kumar, J.R., Jawahar L, J. and Pathak, D.P., 2006. Synthesis of benzimidazole derivatives: as anti-hypertensive agents. E-Journal of chemistry, 3(4), pp.278-285

Metal–organic framework mediated expeditious synthesis of benzimidazole and benzothiazole derivatives through an oxidative cyclization pathway

Mohamed, G.G., Ibrahim, N.A. and Attia, H.A., 2009. Synthesis and anti-fungicidal activity of some transition metal complexes with benzimidazole dithiocarbamate ligand. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *72*(3), pp.610-615.

Pragathi J. K., Padmaja, M., Lakshmi M. and Gyanakumari, C. 2011. Synthesis, Characterization and Antibacterial Studies of Some Transition Metal Complexes of a Schiff Base Derived from 2-(Aminomethyl)-benzimidazole and Thiophene-2-carbaxaldehyde. Journal of chemistry. Vol. 8 No. 4, pp 1662-1669

Pradyot, P., 2002. Handbook of inorganic chemicals

Ranjith, R., 2016. The chemistry and biological significance of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone nucleus. Journal of Chemical and pharmaceutical Research, 8(5), pp.505-526.

Reddy, B.A., 2010. Synthesis, characterization and biological evaluation of 1, 2-disubstituted benzimidazole derivatives using Mannich bases. *E-journal of Chemistry*, *7*(1), pp.222-226.4. Kassab.

Ülkü, Y., Mehmet, A., Hasan, K. and Orhan, B. 2011. Synthesis of 1-substituted benzimidazole metal complexes and structural characterization of dichlorobis(1-phenyl-1 H -benzimidazole- κN_3)cobalt(II)and dichlorobis(1-phenyl-1 H -..., Journal of Coordination Chemistry. Vol. 64, No. 11, pp 1894-1902

Wright, J.B., 1951. The chemistry of the benzimidazoles. *Chemical reviews*, *48*(3), pp.397-541.