Chapter 1
Introduction

The basic idea behind the thesis is to study the aspects of novel ligands having general structure,

![Chemical structure of a molecule with a pyrazole moiety and other functional groups.]

So, after examining the structure, it seems proper to review the aryl azo pyrazole moiety, complexing agents and salicylic acid and lanthanide series elements.

1.1 Brief note on aryl azo pyrazole derivatives.

Condensation of oxybutyrate and hydrazide derivatives yielded aryl azo pyrazole.

Pyrazoles and their derivatives have long been used as precursors for the synthesis of biologically active molecules. Because of their wide spectrum of activity shown by the pyrazole moiety, numerous pyrazole substituted with different groups at various positions have been prepared. In recent years several new methods for the preparation of pyrazole derivatives and reaction have been reported.

Wide spectrum of biological activity of these derivatives lead us to undertake the studies on various aspects of pyrazole derivatives.

Pyrazole refers both to the class of simple aromatic ring compounds of the heterocyclic series characterized by a five membered ring structure composed of three
carbon atoms and two nitrogen atoms in adjacent positions (I). Being so composed and having pharmacological effects on humans, they are not known to occur in nature.

![Pyrazole Structure](image)

Pyrazole exhibits characteristic reactions of pyrrole and pyridine because of containing pyrrole type and pyridine type nitrogen atoms at the position-1 and position-2. Pyridine type nitrogen is susceptible to electrophilic attack but it is less nucleophilic than the pyridine nitrogen atom. The hydrogen atom attached to the nitrogen atom in pyrazole is more acidic than the pyrrolic N-H in pyrrole and can be easily removed by nucleophiles.

Pyrazole exists in two tautomeric forms:

![Pyrazole Tautomers](image)

Heterocyclic compounds are predominant among the types of compounds used as pharmaceutical, agrochemical and veterinary products. One of the most useful classes in this category is pyrazole. The pyrazole ring consists of a doubly unsaturated five-membered ring containing two adjacent nitrogen atoms. In 1883, Knorr [1,2] first synthesized a compound by the reaction of ethyl acetoacetate with phenyl hydrazine, which yields 1-phenyl-3-methyl-5-pyrazoline. The name pyrazole was given to such compounds because the nucleus was derived from pyrrole by replacement of carbon by nitrogen [3]. Much research has been carried out with the aim to find the therapeutic values of pyrazole moiety since their discovery [4, 5]. Various pyrazole and its derivatives have been used in many drugs [6-9].
Different methods of preparation of pyrazoles are available in literature. Palmey synthesized two structurally isomeric pyrazoles by the reaction of the substituted hydrazines with 1, 3-dicarbonyl compounds [10]. Also, Esribano et al synthesized some pyrazoles [11] by the reaction of ethyl acetoacetate with aryl hydrazine hydrate. Jacobs also reported the synthesis by the reaction of acetylene with diazomethane [12] where as Singh and Ojha synthesized pyrazoles by the reaction of ethyl acetoacetate with aryl hydrazines [13]. Some workers reported synthesis by reaction of acetonitrile derivatives with (DMF-DMA) [14] whereas others synthesized by the cyclocondensation of monosubstituted hydrazines with enamines afforded pyrazoles [15].

Various methods for the preparation of pyrazoles have been cited in literature.

(1) L. Knorr [16] synthesized two structurally isomeric pyrazoles by the condensation of substituted hydrazines with 1,3-dicarbonyl compounds.

(II)

(III)

R. C. Boruah [18] et al suggested one pot synthesis of pyrazoles from formylenamides.

By the reaction of 1,3-dinitroalkanes with hydrazines [19].

H. V. Pechamann [20] has synthesized pyrazoles by the reaction of acetylene and diazomethane.
Pyrazole derivatives have been reported to be associated with diverse biological activities. Drug molecules having pyrazole nucleus with good pharmacological activities are listed below.

Zaleplon  
(Sedative, Hypnotic)

Tepoxalin  
(Antiinflammatory)

Celecixib  
(Antiinflammatory)

Novalgin  
(Antipyretic, Analgesic)

Pyrafluprole  
(Insectiside)

Oxyphenbutazone  
(Antiarthritic)
Aryl azo pyrazole:

The synthesis and chemistry of nitrogen heterocyclic azo compounds have been extensively studied. Many derivatives of this type were proved to be excellent dyes. In spite of the enormous number of reports on the utility of these compounds in the dye industry, to the best of our knowledge, this subject has never been surveyed. It was thus decided to give details of all recently synthesized aryl azo pyrazoles according to dyeing methods in this review.

Pyrazoline-5-one dyes 1 were prepared in 67-94 percent yield by cyclocondensing E-3-oxo-3-furylpropionate with PhNHNH₂ and coupling the resulting 3-furyl-1-phenyl-2-pyrazolin-5-one with diazotized p-RC₆H₄NH₂. Acetate, polyester, and polyamide fibers were dyed in yellow to brown shades by these dyes [21].

\[
R = \text{Cl, NO}_2, \text{COOH, SO}_2\text{H}
\]

\[
\text{1}
\]
Pyrazolone monoazo dyes 2 are used for dyeing polyester fibers. The dyes are prepared by diazotization of 4-(2-phenoxylethoxycarbonyl) aniline and, coupled with 1-phenyl-3-allyloxy-carbonyl-5-pyrazolone, it has fast yellow shade on polyester fiber [22].

\[
\begin{align*}
XO_2C & \quad - \quad \begin{array}{c}
\text{N} = \text{N} \\
\text{N} \\
\text{HO} \\
\text{N} \\
\text{Ph}
\end{array} & \quad \begin{array}{c}
\text{CO}_2R
\end{array}
\end{align*}
\]

\[X = \text{phenoxy ethyl, benzyl}; R = \text{Alkenyl}\]

Pyrazolone azo dyes 3 are prepared in 93 percent yield by condensing 3-methyl-1-phenylpyrazole-4,5-dione with (5-nitro-2-pyridyl) hydrazine in HOAc at room temperature [23].

\[
\begin{align*}
\text{R}^1 \quad \text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{R}^2
\end{align*}
\]

\[\text{R} = (\text{un})\text{substituted carboxylic or heterocyclic aromatic groups}\]
\[\text{R}^1 \text{ and } \text{R}^2 = (\text{un}) \text{substituted alkyl, or heterocyclic aromatic group}\]

The azo disperse dyes 4 with methylsulfonyl groups are used for dyeing polyester, polyamide and acrylic fibers in light fast yellow shades. It is prepared by diazotizing and coupling 3-aminophenyl -β-chlorovinyl sulfone with 3-methyl-1phenyl-5-pyrazolone and the resultant material was heated and filtrated [24].

\[
\begin{align*}
\text{Me} & \quad \text{N} = \text{N} \quad \begin{array}{c}
\text{N} \\
\text{OH}
\end{array} \quad \begin{array}{c}
\text{SO}_2\text{Me}
\end{array} \quad \begin{array}{c}
\text{Ph}
\end{array}
\end{align*}
\]
Pyrazolone monoazo dyes 5 have good dyeing power and fastness in dyeing of hydrophobic fibers, especially poly (ethylene-terephthalate) fibers in yellow shades. An example of derivatives of these dyes was prepared by diazotizing p-carbotetrahydrofurfuryloxyaniline and coupling with 1-phenyl-3-carbo-(n-hexyloxy) pyrazolone. They showed maximum absorption at 425nm [25].

\[ \text{R} = \text{alkyl, alkenyl; } R^1=R^2= \text{H, Cl, Br; } R^3 = \text{C}_{5-8} \text{ alkyl, aralkyl} \]

Pyrazolone monoazo reactive dyes 6 are useful for dyeing or printing of hydroxyl and carbonamide group containing fabrics. These dyes are prepared from a neutral solution of the sodium salt of 4-(β-sulfatoethylsulfonyl) aniline was diazotized and the diazonium salt cyclo-condensed and coupled with diacetylsuccinate, the dyes produced with \( \lambda_{\text{max}} 418\text{nm} \) dyed cellulose-containing fabrics in fast yellow shades [26].

\[ \text{D = Benzene ring residue or } \text{C}_6\text{H}_4\text{NHCOC}_6\text{H}_4; } \\
\text{R = CO}_2\text{H, } R^1, R^3 = \text{H, Me, MeO, } R^2, R^4 = \text{H, Me, X, } \\
\text{Y = thiosulfoethyl, vinyl} \]
Pyrazole-reactive azo dyes 7 are useful for dyeing cotton in yellow shades and were prepared by condensation of 2,4-diaminobenzenesulfonic acid and cyanuric chloride and then coupled with 1-(4,8-disulfo-2-naphthyl)-3-methyl-5-pyrazolone. The coupling product was then condensed with m-EtNH$_2$H$_4$SO$_2$CH$_2$CH$_2$OSO$_3$H and salted out to give the corresponding dyes [27].

\[
\begin{align*}
R &= 4,8\text{-disulfo-2-naphtyl}; R^1 = \text{Et}; R^2 = R^3 = H; R^4 = \text{Me} \\
R^5 &= \text{OH}; R^6 = \text{Cl}; R^7 = SO_2CH_2CH_2OSO_2H; Z = m-C_6H_4.
\end{align*}
\]

Pyrazole monoazo reactive dyes 8 are used for dyeing and printing fiber materials showing good colour fastness, levelling, water solubility and build-up properties on cotton and have the free acid form. The colour of these dyes show yellow shades on cotton fibers, which are prepared by condensation of cyanuric chloride with 1-(4-aminophenyl)-3-methyl-5-pyrazolone. The condensate was coupled with diazotized 1,2,5-H$_2$NC$_{10}$H$_5$(SO$_3$H)$_2$ and the coupling product was condensed with p-EtNH$_2$H$_4$SO$_2$CH$_2$CH$_2$OSO$_3$H and then with m-H$_2$NC$_6$H$_4$SO$_2$CH$_2$CH$_2$OSO$_3$H [28].
Naphthylazo pyrazolone reactive yellow dyes 9 are useful for dyeing or printing of hydroxyl or carbonamide group-containing fabrics, were prepared, where 4-(β-sulfatoethylsulfonyl) aniline was diazotized and cyclized with acetylsuccinic acid diester at pH = 4 and the pyrazolone intermediate was coupled with diazotized (6-β-sulfatoethylsulfonyl)-1-sulfo-2-naphthylamine with λmax 433nm, which dyed cellulosic fiber in a fast yellow shade [29].

Benzotriazole group-containing reactive azo dyes 10 are useful for dyeing or printing of wool, synthetic polyamides or cellulose fabrics, were prepared where 2-amino-4-[2-amino-4-(β-hydroxyethylsulfonyl) phenylamino] benzenesulfonic acid was diazotized and coupled with 3-methyl-1-(β-hydroxyethyl-sulfonylphenyl)-5-pyrazolone and the intermediate was sulfonated with oleum, forming the
corresponding dye with $\lambda_{\text{max}}$ 385nm, which dyed cellulosic fabrics in a fast yellow tone [30].

\[ \text{N} \text{N} \text{SO}_{3}\text{H} \]
\[ \text{N} = \text{Me} \text{SO}_{2}\text{CH}_{2}\text{CH}_{2}\text{OSO}_{3}\text{H} \]

$R = \text{H, OH, halogen; } Y = \text{CH}_{2}\text{CH}_{2}X; X = \text{Alkali cleavable substituent; } R = \text{Water-soluble. azo chromophore}$

10

The pyrazolo-monoazo dyes having general structure 11 and 12 are suitable for dyeing or printing materials having OH group and/or an amide group [31].

\[ QN=N \]
\[ \text{N} = \text{Cl} \text{F} \text{CCl}_{2}\text{F} \text{SO}_{3}\text{H} \]
\[ \text{N} = \text{Me} \text{SO}_{3}\text{H} \]
\[ \text{N} = \text{COOH} \]

$Q = \text{(un)Substituted Ph or naphthyl; } R' = \text{Me, CO}_{2}$
$R^2 = \text{OH, NH}_{2}; R^3 =\text{H, Me, SO}_{3}\text{H}; R^6, R^7 = \text{H}; R^8, R^9 = \text{H, Ph}; Y = \text{CH, CH}_{2}$

12
Pyrazolone monoazo dyes 13 have a high colour yield and are useful for dyeing hydroxyl group-containing fibers (e.g. cotton, wool). These dyes were prepared by diazotization of 4-(2-sulfatoethylsulfonyl)-3-(2-sulfatoethylsulfonylmethyl) aniline and coupling with 1-(4-sulfophenyl)-3-carboxy-5-pyrazolone [33].

![Pyrazolone Dye Structure](image)

Derivatives of triazine azo dyes 14 are useful for printing or dyeing natural and synthetic textiles, particularly polyamide [34].

![Triazine Dye Structure](image)

Water-soluble pyrazolone dyes 15 were prepared by coupling diazotized 3-aminophenylmethylsulfone with 3-carboxy-1-(4-sulfophenyl)-5-pyrazolone and hydrolysis in alkali medium. The dyes obtained are soluble in water and dyed polyamide fibers and wool in yellow to red shades with good fastness light, rubbing, washing and sweat [35].
Azoic dyes are insoluble azo dyes which are prepared in situ. Some azoic dyes derived from 7-hydroxy-3-phenylquinoline was evaluated as azoic coupler, together with several compounds derived from it. In an example 7-hydroxy-3-(4-nitrophenyl) quinoline reduced and benzyolated to give 3-(4-benzamidophenyl)-7-hydroxyquinoline by reaction with PhCH₂CN to give 5-(7-hydroxy-3-quinolinyl)-3-phenyl-2-benzisoxazole and by azo coupling to give reddish-brown dyes on cotton [36].

The cationic pyrazole monoazo dyes are useful for dyeing or printing of acrylonitrile, acid-modified polyamide, and acid-modified polyester fibers. The cationic dyes were prepared by diazotization of 5-amino-3-methyl-1-phenylpyrazole and coupled with N,N-dipropylaniline and then alkylated with Me₂SO₄ [37].
Pyrazolone group-containing monoazo pigments 18 are manufactured by mixing 3-methyl-5-pyrazolone with the corresponding diazotized aniline derivatives at 10-30°C in water containing an acetate buffer solution [38].

P. J. Shah reported synthesis of new aryl azo pyrazolones substituted with thiazolyhydrazone 19 and studied their antimicrobial activity [39].
Recently Mohammed Amir and co-workers prepared new series of aryl azo pyrazoles 20 from reaction of 2,4-dichlorobenzoic acid hydrazide with ethyl-2-aryl hydrazono-3-oxo- butyrates. Produced compounds showed moderate to good antibacterial and antifungal activity [40].

Where, $R = H, Br, OCH_3, CH_3$
1.1.1 Hydrazide derivatives:

Hydrazine is the pivotal derivative of hydrazide. Hydrazones have been demonstrated to possess, among other, antimicrobial, anticonvulsant, analgesic, antiinflammatory, antiplatelet, antitubercular and antitumoral activities. For example, isonicotinoyl hydrazones are antitubercular; 4-hydroxybenzoic acid [(5-nitro-2-furyl)methylene]-hydrazide (nifuroxazide) is an intestinal antiseptic; 4-fluorobenzoic acid[(5-nitro-2-furyl)methylene]-hydrazide [41] and 2,3,4-pentanetrione-3-[4-[[5-nitro-2-furyl)methylene] hydrazino]carbonyl]phenyl]-hydrazone [42], have antibacterial activity against both Staphylococcus aureus and Mycobacterium tuberculosis at a concentration of 3.13 μg/mL. N1-(4-Methoxybenzamido) benzoyl]-N2-[5-nitro-2-furyl] hydrazine, demonstrated antibacterial activity [43]. In addition, some of the new hydrazide-hydrazones have recently synthesized were active against the same strain of M. Tuberculosis between the concentrations of 0.78-6.25 μg/mL [44].
Isonicotinic acid hydrazide (isoniazid, INZ) has very high in vivo inhibitory activity towards M. tuberculosis. Sah and Peoples synthesized INZ hydrazide-hydrazones 21 by reacting INZ with various aldehydes and ketones. These compounds were reported to have inhibitory activity in mice infected with various strains of M. tuberculosis [45]. They also showed less toxicity in these mice than INZ [46, 47]. Buu-Hoi et al synthesized some hydrazide-hydrazones that were reported to have lower toxicity than hydrazides because of the blockage of –NH₂ group. These findings further support the growing importance of the synthesis of hydrazide-hydrazones compound [48].

It has been known that the hydrazides (like INZ) form α-ketoglutaric acid and form hydrazones with vitamin B₆ and pyruvic acid. It is clinically important that when tuberculosis patients are treated with INZ, reaction of INZ with vitamin B₆ leads to the formation of a hydrazone and development of vitamin B₆ deficiency (Scheme 1.1) in patients who are treated with INZ. Such patients should be administered vitamin B₆.
The most important antiinflammatory derivative 2-(2-formylfuryl) pyridylhydrazone 22 presented a 79% inhibition of pleurisy at a dose of 80.1 μmol/kg. The authors also described the results concerning the mechanism of the action of these series of N-heterocyclic derivatives in platelet aggregation that suggests a Ca\(^{2+}\) scavenger mechanism. Compound 22 was able to complex Ca\(^{2+}\) in invitro experiments at 100 μM concentration, indicating that these series of compounds can act as Ca\(^{2+}\) scavenger depending on the nature of the aryl moiety present at the imine subunit [49].

The antiplatelet activity of novel tricyclic acylhydrazone derivatives 23 was evaluated by their ability to inhibit platelet aggregation in rabbit’s platelet-rich plasma induced by platelet-activating factor (PAF) at 50 nM. Benzyldiene- / 4’-bromobenzyldene 3-hydroxy-8-methyl-6-phenylpyrazolo [3,4-b] thieno-[2,3-d]
pyridine-2-carbohydrazide were evaluated at 10 μM, presenting, respectively, 10.4 and 13.6% of inhibition of the PAF-induced platelet aggregation [50].

![Chemical structure](image1)

1-Substituted phenyl-N’-[(substitutedphenyl)methylene]-1H-pyrazole-4-carbohydrazides 24 were synthesized and their leishmanicidal and cytotoxic effects were compared to the prototype drugs (ketoconazole, benznidazole, allopurinol and pentamidine) in vitro. The 1H-pyrazole-4-carbohydrazide derivatives with X = Br, Y = NO₂ and X = NO₂, Y = Cl demonstrated the highest activity and they were more effective on promastigotes forms of L. amazonensis than on L. chagasi and L. braziliensis species [51].

![Chemical structure](image2)
Ethyl 2-arylhydrazono-3-oxobutyrate 25 were synthesized in order to determine their antimicrobial properties [52].

\[
\text{H} - \text{N} - \text{N=N=CH} - \text{C} - \text{O-CH}_2\text{-CH}_3
\]

\[
X = \text{O, S}
\]

25

Nifuroxazide and six analogs 26 were synthesized by varying the substituent at the p-position of the benzene ring and the heteroatom of the heterocyclic ring. These compounds were evaluated for their antimicrobial activity against S. aureus and found to be active at concentration 0.16-63.00 μg/mL [53].

\[
\text{R} - \text{N=N=CH} - \text{C} - \text{NO}_2
\]

26

4-Substituted benzoic acid [(5-nitro-thiophene-2-yl)methylene]hydrazides 27 were synthesized as potential bacteriostatic activity and some of them indeed showed bactericidal activity [54].

\[
\text{R}_1 \quad \text{R}_2
\]
Isonicotinoylhydrazones have been further reacted with pyridinecarboxaldehydes to give the corresponding pyridylmethyleneamino derivatives 28. The new synthesized hydrazones and their pyridylmethyleneamino derivatives were tested for their activity against mycobacteria, Gram-positive and Gram-negative bacteria. The cytotoxicity was also tested. Several compounds showed a good activity against M. tuberculosis H37Rv and some isonicotinoylhydrazones showed a moderate activity against a clinically isolated M. tuberculosis (6.25-50 μg/mL) which was INZ resistant [55].

![Diagram of 28]

The reaction of 2-acetylimidazo [4,5-b] pyridine with INZ yielded the corresponding hydrazidehydrazones 29. This compound exhibited activity against M. tuberculosis, isolated from patients and resistant against INZ, ethambutol, rifampicine at 3.13 μg/mL [56].

![Diagram of 29]

Novel fluoroquinolones 30 containing a hydrazone structure were synthesized and evaluated in vivo against M. tuberculosis in Swiss albino mice by Shindikar et al. Results of the study indicated the potent antitubercular activity of the test compounds [57].
N’-Arylidene-N-[2-oxo-2-(4-aryl-piperazin-1-yl)ethyl]hydrazide derivatives containing INZ hydrazide-hydrazones were synthesized and evaluated antimycobacterial activity against M. tuberculosis and M. tuberculosis clinical isolates [58].

A series of hydrazones were synthesized from INZ, pyrazineamide, p-aminosalicylic acid (PAS), ethambutol and ciprofloxacin. 2-Hydroxy-4-{{isonicotinoylhydrazono}methyl}amino]-benzoic acid 32 showed the highest inhibition (96%) of M. tuberculosis [59].
1.1.2 Oxybutyrate derivatives.

Oxybutyrate derivatives were synthesized by reaction of primary amine with ethyl aceto acetate in presence of sodium nitrite in hydrochloric acid. One of recent example is shown below, in which Mohammad Amir and co-workers [40] reported various oxybutyrate derivatives starting from various substituted aromatic amines.

\[
\text{R} = \text{Cl, 4-Cl, 3-Cl-4-F, 4-Br, 2-CH}_3, \text{3,4-di Cl, 4-F, 4-Carboxy, 2-carboxy}
\]

A. P. Rajput and co-workers [60] synthesize and evaluate microbial activity of seven membered ring compounds from 1,2-do amino benzene
1.2 Salicylic acid and its derivatives as complexing agents.

Salicylic acid and its bi-substituted derivatives are well known complexing agents. Salicylic acid forms water soluble complexes [61-64]. In aqueous solution the salicylate ion generally functions as a divalent bidentate ligand [65] and forms uncharged chelates with divalent cations. In fact this reagent finds many applications in analytical chemistry of inorganic species [66].

Complexes of several transition metals with salicylic acid and mono-substituted salicylic acid have been investigated. The UO$_2^{+2}$ complexes of salicylic acid and various bi-substituted salicylic acid have been reported [67].

Complexes of various 4-substituted salicylic acid have been investigated. Water insoluble metal complexes of 4-aminosalicylic acid (PAS) have been reported and investigated for tuberculostatic effect [68-79]. The UO$_2^{+2}$ complex of 4-iodosalicylic acid have been reported. Both 4-chloro and 4-bromosalicylic acid are reported. However, transition metal complexes of only 4-bromosalicylic acid have been investigated [80].

Aromatic carboxylic acid and phenolic compounds can mimic the Al(III)-binding ability of the rather complicated high molecular mass, fulvic acid and humic acid present in soil. These functional groups may be of importance in the binding of Al(III) in microorganisms (catecholate-based siderophores) or in plants (e.g. tea).

Because of the high basicity of the donor groups, salicylates ($\Sigma pK \sim 17$) and especially catecholates ($\Sigma pK \sim 22$) chelate Al(III) through the two negatively charged O donors with high stabilities. The binding strength however is reduced considerably by proton competition in neutral aqueous solution [81]. A cooperative $^{27}$Al and $^{13}$C-NMR study of the Al(III)-phyhalic acid (PA), -salicylic acid (SA) and -tiron (TR) systems revealed that the binding constants at pH $\sim 3$ obeyed the sequence TR$>$SA$>$PA, indicating that the stabilities of the complexes depend on the chelate ring size in the order of 5$>$6$>$7-membered ring [82].
Salicylic acid and its derivatives form mono and bis-chelates, the latter loses two protons above pH~6, resulting in the mixed hydroxo complexes \([\text{AlL}_2(\text{OH})]^2-\) and \([\text{AlL}_2(\text{OH})_2]^3-\) [83-87]. In spite of some indications [88, 89], it does not readily form an octahedral tris complex since the binding strength of a third salicylate chelate is not competitive enough to suppress metal ion and complex hydrolysis or even the precipitation of \(\text{Al(OH)}_3\) at pH > 7. An\(^{27}\text{Al}-\text{NMR}\) study of the hydrolysis of Al(III) in the presence of salicylate demonstrated that formation of the \([\text{Al}_{13}(\text{OH})_{32}]^{7+}\) hydroxo tridecamer is hindered at a ligand to metal ratio higher than 0.5, but colloids are produced above pH ~ 4.5. The 1:1 complex is detected at ~3ppm (downfield from the signal due to \([\text{Al(H}_2\text{O})_6]^{3+}\)) [90,91]. The signal corresponding to the complex \([\text{AlL}_2]^-\) is assumed to be too broad to be detected. The rate of exchange of water molecules on the Al(III) ion is increased by over three orders of magnitude when salicylate or sulphosalicylate ligands are present in the inner coordination sphere (\(^{17}\text{O}-\text{NMR}\) study). There is apparently a correlation between the exchange rate and the ligand basicity. The potentiometric speciation study by Di Marco et al. [92] with two structurally similar ligands, 2-hydroxyphenylethanone and 2- hydroxybenzeneacetic acid, revealed very similar Al(III)-binding ability with that of salicylate.

In contrast with salicylates, catechol derivatives have much higher affinity for Al(III) in the basic pH range, where the precipitation of Al(OH)\(_3\) is prevented by formation of the octahedral tris complex AlL\(_3\) [93-96]. The stability of this complex is so high that it can efficiently hinder formation of the very stable tetrahedral hydroxo complex \([\text{Al(OH)}_4]^-\), even at pH~12. Oligomeric hydroxo-bridged species are also assumed to be present in low concentration in the pH range 5-7. A multinuclear (\(^{27}\text{Al}, \text{^{13}C}\) and \(^{1}H\))NMR study of catechol complexation confirmed the pH-metric speciation model [97]. The different resonances observed in the \(^{27}\text{Al}-\text{NMR}\) spectra were assigned to the following species: the tris chelate at 31.3 ppm (with respect to \([\text{Al(H}_2\text{O})_6]^{3+}\), the hydroxo complex \([\text{AlL}_2(\text{OH})]^2-\) at between 31.5 and 32 ppm, the bis chelate complex \([\text{AlL}_2]^-\) at 26 ppm and \([\text{AlL}]^+\) at 11 ppm (a very broad signal). The bandwidth of the tris chelate signal is relatively low (\(v_{1/2} \sim 340 \text{ Hz}\)), revealing the threefold symmetry of this species (species with symmetry lower than octahedral or tetrahedral usually give rise to broad signals; the \(D_3\) symmetry of the catechol tris chelate is not cubic symmetry, but relatively narrow signals are generally observed for
this species). At pH >9.5, new peaks are detected in the range 50-60 ppm; they are assigned to tetrahedral mixed hydroxo complexes. With tiron (4,5-dihydroxy-1,3-benzenedisulfonic acid), the meridional and facial isomers of the chelate \([\text{AlL}_3]^{3-}\) (tiron is a unsymmetrical bidentate ligand) were identified in the \(^1\text{H}\)- and \(^{13}\text{C}\)-NMR spectra [98,99]. In the facial isomer, the ligands are magnetically equivalent; in the meridional isomer, the three ligands are distinct. The meridional to facial ratio was found to be 3:1, as expected from statistical consideration.

Catecholamines that attain significant concentrations in various body fluids, e.g. in the cerebrospinal fluid, can be important Al(III) binder in humans. As a hard metal ion, Al(III) prefers chelation at the negatively charged catecholate locus rather than at the side-chain amino group of catecholamines, and catechol-like binding therefore predominates in a wide pH range. Even for L-DOPA (3,4-dihydroxyphenylalanine), with its chelating glycinate locus, only catecholate coordination occurs. At physiological pH, the main species is an (O’,O’)-coordinated tris complex, with ammonium groups remaining protonated.

1.3 **Brief note on Lanthanide series elements.**

The lanthanide or lanthanoid chemical elements comprises the fifteen metallic chemical elements with atomic numbers 57 through 71, from lanthanum through lutetium [100-102]. These fifteen lanthanide elements, along with the chemically similar elements scandium and yttrium, are often collectively known as the rare earth elements.

The informal chemical symbol Ln is used in general discussions of lanthanide chemistry to refer to any lanthanide. All but one of the lanthanides are f-block elements, corresponding to the filling of the 4f electron shell; lutetium, a d-block element, is also generally considered to be a lanthanide due to its chemical similarities with the other fourteen. All lanthanide elements form trivalent cations, Ln\(^{3+}\), whose chemistry is largely determined by the ionic radius, which decreases steadily from lanthanum to lutetium.
In presentations of the periodic table, the lanthanides and the actinides are customarily shown as two additional rows below the main body of the table,\(^\text{[2]}\) with placeholders or else a selected single element of each series (either lanthanum or lutetium, and either actinium or lawrencium, respectively) shown in a single cell of the main table, between barium and hafnium, and radium and rutherfordium, respectively. This convention is entirely a matter of aesthetics and formatting practicality; a rarely used wide-formatted periodic table inserts the lanthanide and actinide series in their proper places, as parts of the table's sixth and seventh rows (periods).

**Ln(III) compounds**

The trivalent lanthanides mostly form ionic salts. The trivalent ions are hard acceptors and form more stable complexes with oxygen-donor ligands than with nitrogen-donor ligands. The larger ions are 9-coordinate in aqueous solution, \([\text{Ln(H}_2\text{O)}_9]^{3+}\) but the smaller ions are 8-coordinate, \([\text{Ln(H}_2\text{O)}_8]^{3+}\). There is some evidence that the later lanthanides have more water molecules in the second coordination sphere \(^\text{[103]}\) Complexation with monodentate ligands is generally weak because it is difficult to displace water molecules from the first coordination sphere. Stronger complexes are formed with chelating ligands because of the chelate effect, such as the tetra-anion derived from 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

Lanthanide metals are particularly useful in technologies that take advantage of their reactivity to specific wavelengths of light. Certain life science applications take advantage of the unique fluorescence properties of lanthanide ion complexes (Ln(III) chelates or cryptates). These are well-suited for this application due to their large Stokes shifts and extremely long emission lifetimes (from microseconds to milliseconds) compared to more traditional fluorophores (e.g., fluorescein, allophycocyanin, phycoerythrin, and rhodamine). The biological fluids or serum commonly used in these research applications contain many compounds and proteins which are naturally fluorescent. Therefore the use of conventional, steady-state fluorescence measurement presents serious limitations in assay sensitivity. Long-lived fluorophores, such as lanthanides, combined with time-resolved detection (a delay
between excitation and emission detection) minimizes prompt fluorescence interference.

Due to their sparse distribution in the earth's crust and low aqueous solubility, the lanthanides have a low availability in the biosphere, and are not known to naturally form part of any biological molecules. Compared to most other nondietary elements, non-radioactive lanthanides are classified as having low toxicity [104].

Lanthanum is a chemical element with the symbol La and atomic number 57. Lanthanum is a silvery white metallic element that belongs to group 3 of the periodic table and is the first element of the lanthanide series. It is found in some rare-earth minerals, usually in combination with cerium and other rare earth elements. Lanthanum is a malleable, ductile, and soft metal that oxidizes rapidly when exposed to air. It is produced from the minerals monazite and bastnasite using a complex multistage extraction process. Lanthanum compounds have numerous applications as catalysts, additives in glass, carbon lighting for studio lighting and projection, ignition elements in lighters and torches, electron cathodes, scintillators, and others. Lanthanum carbonate (La$_2$(CO$_3$)$_3$) was approved as a medication against renal failure.

Lanthanum is a soft, malleable, silvery white metal which has hexagonal crystal structure at room temperature. At 310 °C, lanthanum changes to a face-centered cubic structure, and at 865 °C into a body-centered cubic structure. Lanthanum is easily oxidized (a centimeter-sized sample will completely oxidize within a year) and is therefore used in elemental form only for research purposes. For example, single Lanthanum atoms have been isolated by implanting them into fullerene molecules. If carbon nanotubes are filled with those lanthanum-encapsulated fullerenes and annealed, metallic nanochains of lanthanum are produced inside carbon nanotubes.

Lanthanum exhibits two oxidation states, +3 and +2, the former being much more stable. For example, LaH$_3$ is more stable than LaH$_2$. Lanthanum burns readily at 150 °C to form lanthanum (III) oxide:

$$4 \text{La} + 3 \text{O}_2 \rightarrow 2 \text{La}_2\text{O}_3$$
However, when exposed to moist air at room temperature, lanthanum oxide forms a hydrated oxide with a large volume increase [105].

**Praseodymium** is a chemical element that has the symbol Pr and atomic number 59. Praseodymium is a soft, silvery, malleable and ductile metal in the lanthanide group. It is too reactive to be found in native form, and when artificially prepared, it slowly develops a green oxide coating.

The element was named for the color of its primary oxide. In 1841, Swedish chemist Carl Gustav Mosander extracted a rare earth oxide residue he called "didymium" from a residue he called "lantana," in turn separated from cerium salts. In 1885, the Austrian chemist Baron Carl Auer von Welsbach separated didymium into two salts of different colors, which he named praseodymium and neodymium. The name praseodymium comes from the Greek prasinos, meaning green, and didymos means twin.

Like most rare earth elements, praseodymium most readily forms trivalent Pr(III) ions. These are yellow-green in water solution, and various shades of yellow-green when incorporated into glasses. Many of praseodymium's industrial uses involve its use to filter yellow light from light sources.

Praseodymium is a soft, silvery, malleable and ductile metal in the lanthanide group. It is somewhat more resistant to corrosion in air than europium, lanthanum, cerium, or neodymium, but it does develop a green oxide coating that spalls off when exposed to air, exposing more metal to oxidation a centimeter-sized sample of Pr completely oxidizes within a year. For this reason, praseodymium is usually stored under a light mineral oil or sealed in glass.

Praseodymium metal tarnishes slowly in air and burns readily at 150°C to form praseodymium (III, IV) oxide:

\[
12 \text{ Pr} + 11 \text{ O}_2 \rightarrow 2 \text{ Pr}_6\text{O}_{11}
\]

**Neodymium** is a chemical element with the symbol Nd and atomic number 60. It is a soft silvery metal that tarnishes in air. Neodymium was discovered in 1885 by the Austrian chemist Carl Auer von Welsbach. It is present in significant quantities
in the ore minerals monazite and bastnasite. Neodymium is not found naturally in metallic form or unmixed with other lanthanides, and it is usually refined for general use. Although neodymium is classed as a "rare earth", it is a fairly common element, no rarer than cobalt, nickel, and copper ore, and is widely distributed in the Earth's crust [106]. Most of the world's neodymium is mined in China.

Neodymium, a rare earth metal, was present in the classical mischmetal at a concentration of about 18%. Metallic neodymium has a bright, silvery metallic luster, but as one of the more reactive lanthanide rare-earth metals, it quickly oxidizes in ordinary air. The oxide layer that forms then peels off, and this exposes the metal to further oxidation. Thus a centimeter-sized sample of neodymium completely oxidizes within a year.

Neodymium commonly exists in two allotropic forms, with a transformation from a double hexagonal to a body-centered cubic structure taking place at about 863 °C.

Neodymium metal tarnishes slowly in air and it burns readily at about 150 °C to form neodymium(III) oxide:

$$4 \text{Nd} + 3 \text{O}_2 \rightarrow 2 \text{Nd}_2\text{O}_3$$

**Samarium** is a chemical element with symbol Sm and atomic number 62. It is a moderately hard silvery metal that readily oxidizes in air. Being a typical member of the lanthanide series, samarium usually assumes the oxidation state +3. Compounds of samarium (II) are also known, most notably the monoxide SmO, monochalcogenides SmS, SmSe and SmTe, as well as samarium (II) iodide. The last compound is a common reducing agent in chemical synthesis. Samarium has no significant biological role and is only slightly toxic.

Samarium is a rare earth metal having the hardness and density similar to those of zinc. With the boiling point of 1794 °C, samarium is the third most volatile lanthanide after ytterbium and europium; this property facilitates separation of samarium from the mineral ore. At ambient conditions, samarium normally assumes a trigonal structure (α form). Upon heating to 731 °C, its crystal symmetry changes into hexagonal close-packed (hcp), however the transition temperature depends on the
metal purity. Further heating to 922 °C transforms the metal into a body-centered cubic (bcc) phase. Heating to 300 °C combined with compression to 40 kbar results in a double-hexagonal close-packed structure (dhcp). Applying higher pressure of the order of hundreds or thousands of kilobars induces a series of phase transformations, in particular with a tetragonal phase appearing at about 900 kbar. In one study, the dhcp phase could be produced without compression, using a nonequilibrium annealing regime with a rapid temperature change between about 400 and 700 °C, confirming the transient character of this samarium phase. Also, thin films of samarium obtained by vapor deposition may contain the hcp or dhcp phases at ambient conditions.

Samarium is quite electropositive and reacts slowly with cold water and quite quickly with hot water to form samarium hydroxide:

\[ 2 \text{ Sm (s)} + 6 \text{ H}_2\text{O (l)} \rightarrow 2 \text{ Sm(OH)}_3 \text{ (aq)} + 3 \text{ H}_2 \text{ (g)} \]

**Gadolinium** is a chemical element with symbol Gd and atomic number 64. It is a silvery-white, malleable and ductile rare-earth metal. It is found in nature only in combined (salt) form. Gadolinium was first detected spectroscopically in 1880 by de Marignac who separated its oxide and is credited with its discovery. It is named for gadolinite, one of the minerals in which it was found, in turn named for chemist Johan Gadolin. The metal was isolated by Paul Emile Lecoq de Boisbaudran in 1886.

The Gadolinium(III) ion occurring in water-soluble salts is quite toxic to mammals. However, chelated Gadolinium(III) compounds are far less toxic because they carry Gadolinium(III) through the kidneys and out of the body before the free ion can be released into tissue. Because of its paramagnetic properties, solutions of chelated organic gadolinium complexes are used as intravenously administered gadolinium-based MRI contrast agents in medical magnetic resonance imaging. However, in a small minority of patients with renal failure, at least four such agents have been associated with development of the rare nodular inflammatory disease nephrogenic systemic fibrosis. This is thought to be due to the gadolinium ion itself, since Gadolinium(III) carrier molecules associated with the disease differ.
Individual gadolinium atoms have been isolated by encapsulating them into fullerene molecules and visualized with transmission electron microscope. Individual Gd atoms and small Gd clusters have also been incorporated into carbon nanotubes.

Gadolinium combines with most elements to form Gd(III) derivatives. nitrogen, carbon, sulfur, phosphorus, boron, selenium, silicon and arsenic at elevated temperatures, forming binary compounds.

Unlike other rare earth elements, metallic gadolinium is relatively stable in dry air. However, it tarnishes quickly in moist air, forming a loosely adhering gadolinium(III) oxide (Gd$_2$O$_3$), which spalls off, exposing more surface to oxidation.

$$4 \text{Gd} + 3 \text{O}_2 \rightarrow 2 \text{Gd}_2\text{O}_3$$

**Terbium** is a chemical element with the symbol Tb and atomic number 65. It is a silvery-white rare earth metal that is malleable, ductile and soft enough to be cut with a knife. Terbium is never found in nature as a free element, but it is contained in many minerals, including cerite, gadolinite, monazite, xenotime and euxenite.

Terbium is used to dope calcium fluoride, calcium tungstate and strontium molybdate, materials that are used in solid-state devices, and as a crystal stabilizer of fuel cells which operate at elevated temperatures. As a component of Terfenol-D (an alloy that expands and contracts when exposed to magnetic fields more than any other alloy), terbium is of use in actuators, in naval sonar systems and in sensors.

The terbium(III) cation is brilliantly fluorescent, in a bright lemon-yellow color that is the result of a strong green emission line in combination with other lines in the orange and red. The yttrofluorite variety of the mineral fluorite owes its creamy-yellow fluorescence in part to terbium. Terbium easily oxidizes, and is therefore used in its elemental form specifically for research. Single Tb atoms have been isolated by implanting them into fullerene molecules.

The most common valence state of terbium is +3. The +4 state is known in TbO$_2$ and TbF$_4$. Terbium burns readily to form a mixed terbium (III,IV) oxide.

$$8 \text{Tb} + 7 \text{O}_2 \rightarrow 2 \text{Tb}_3\text{O}_7$$
Dysprosium is a chemical element with the symbol Dy and atomic number 66. It is a rare earth element with a metallic silver luster. Dysprosium is never found in nature as a free element, though it is found in various minerals, such as xenotime. Naturally occurring dysprosium is composed of 7 isotopes, the most abundant of which is $^{164}\text{Dy}$.

Dysprosium metal tarnishes slowly in air and burns readily to form dysprosium(III) oxide:

$$4 \text{Dy} + 3 \text{O}_2 \rightarrow 2 \text{Dy}_2\text{O}_3$$

Holmium is a chemical element with the symbol Ho and atomic number 67. Part of the lanthanide series, holmium is a rare earth element. Holmium was discovered by Swedish chemist Per Theodor Cleve. Its oxide was first isolated from rare earth ores in 1878 and the element was named after the city of Stockholm.

Holmium is a relatively soft and malleable element that is fairly corrosion-resistant and stable in dry air at standard temperature and pressure. In moist air and at higher temperatures, however, it quickly oxidizes, forming a yellowish oxide. In pure form, holmium possesses a metallic, bright silvery luster.

Holmium oxide has some fairly dramatic color changes depending on the lighting conditions. In daylight, it is a tannish yellow color. Under trichromatic light, it is a fiery orange red, almost indistinguishable from the appearance of erbium oxide under the same lighting conditions. The change is related to the sharp emission bands of the trivalent ions of these elements, acting as phosphors.

Holmium metal tarnishes slowly in air and burns readily to form holmium (III) oxide:

$$4 \text{Ho} + 3 \text{O}_2 \rightarrow 2 \text{Ho}_2\text{O}_3$$
1.4 Research gaps about aryl azo pyrazole-saliclyc acid condensate:

Looking to systematic literature survey of arylazo pyrazole, it was found that number of pyrazolone azo dyes were synthesis by different researchers. But not major reports were found for pyrazoline derivative employed for metal complexation, except few references [107-115]. Hence, metal complexation study of aryl azo pyrazole-salicylic acid clubbed compound i.e. ligand has not been reported. Hence, aryl azo pyrazole-salicylic acid clubbed compound has been thought to prepare for novel ligands.

1.5 Objectives:

The objective of the thesis work is to synthesis, characterization and studies the chelating properties of aryl azo pyrazole-salicylic acid merged condensate.

1.6 The present work:

According to the objectives, the PhD research work was carried out. The work is bifurcated into following chapters of the proposed thesis.

Various techniques used for characterization are discussed briefly and presented in chapter-2 of the thesis.

4-amino-salicylic acid taken as starting material, which reacts with ethyl acetoacetate followed by NaNO₂ yields ethyl-2-aryl hydrazono-3-oxo- butyrates [199]. Which in turn undergoes reaction with various acid hydrazide (3a-g) to form new series of aryl azo pyrazole-salicylic acid derivatives and they were characterized by preliminary properties. The details about the synthesis of these compounds are being presented in chapter- 3.

The compounds mentioned are designated as ligands and characterized by elemental analysis and spectral features. The non-aqueous conductometric titration of all the compounds was carried out to estimate the number of acid groups. The
compounds were also studied for their thermo gravimetric analysis behavior. All these are included in chapter-3.

The various Transition series metal chelates of all the novel ligands (mentioned in chapter-3) are prepared and characterized primarily. The methods for metal chelates preparation and metal: ligand (M:L) stoichiometry are presented in chapter – 4. The various transition metal Chelates of all the novel ligands are characterized by Infrared and reflectance spectral studies, electrical conductivity and magnetic moment measurements. All these are also presented in chapter-4 of the thesis.

The various lanthanide series metal chelates of all the novel ligands (mentioned in chapter-3) are prepared and characterized primarily. The methods for metal chelates preparation and metal: ligand (M:L) stoichiometry are presented in chapter – 5. The various lanthanide metal Chelates of all the novel ligands are characterized by Infrared and reflectance spectral studies, electrical conductivity and magnetic moment measurements. All these are presented in chapter-5 of the thesis.

The chapter -6 comprises the evaluation of antimicrobial activity of all the ligands and their metal chelates. The plant pathogens have been selected for this study.

*The work is summarized in scheme – 1.1 to 1.3*
Scheme - 1.1
Scheme 1.2

Where, $R =$

$M = \text{Cu}^{2+}, \text{Co}^{2+}, \text{Ni}^{2+}, \text{Zn}^{2+}, \text{Mn}^{2+}$
(APL-1 to APL-5)
Ligand

Metal (III) Chloride

Metal Chelate

Where, $R = \begin{array}{l}
\text{Cl, Br, } \\
\text{NO}_2, \\
\text{OCH}_3
\end{array}$

$M = \text{La}^{3+}, \text{Pr}^{3+}, \text{Nd}^{3+}, \text{Sm}^{3+}, \text{Gd}^{3+}, \text{Tb}^{3+}, \text{Dy}^{3+}, \text{Ho}^{3+}$

**Scheme 1.3**
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