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SYNTHESIS AND BIOLOGICAL EVALUATION OF TRANSITION METAL COMPLEXES OF PYRAZOLE SCHIFF BASE LIGAND

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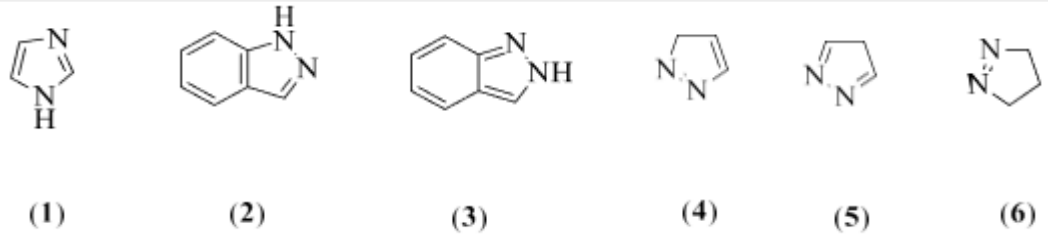
Abstract
Pyrazole is the main component of bioactive agents, which act as antimicrobial, anti- inflammatory, analgesic, anticonvulsant, antibacterial, anxiolytic and antiviral agent. Pyrazole derivatives are also being used as therapeutic drugs which act on central nervous system (CNS). Azomethine derivatives of pyrazole also have biological potential and used as ligand to prepare metal complexes. Keeping the mentioned importance in view, in this research, we use amino pyrazole schiff base as ligand to prepare their metal complexes. The formation of products was monitored by using TLC, and the characterization of target compound has been done by melting point and FT-IR analysis. Antibacterial activity of these derivatives has also been studied.

INTRODUCTION

1.1. Pyrazole

Pyrazole is heterocyclic aromatic compound containing two adjacent nitrogen atoms in their ring with two double bonds and its structure is similar to imidazole **(1)**, indazole **(2)**, and isoindazole **(3)** and some pyrazole derivatives also show non-aromaticity like pyrazolenine **(4)** isopyrazole **(5)** and 4,5-dihydro-1H-pyrazole **(6)** (Khan et al., 2016).

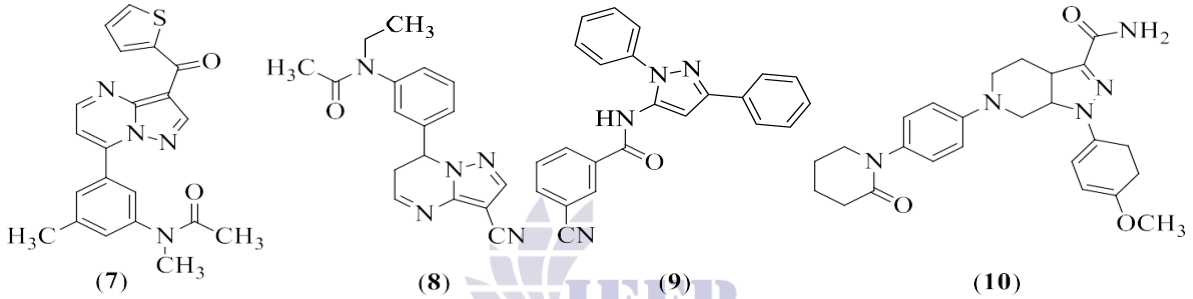


(1) (2) (3) (4) (5) (6)

Figure 1.1: Some chemical structures of pyrazole derivatives

1.2. Drugs containing pyrazole ring

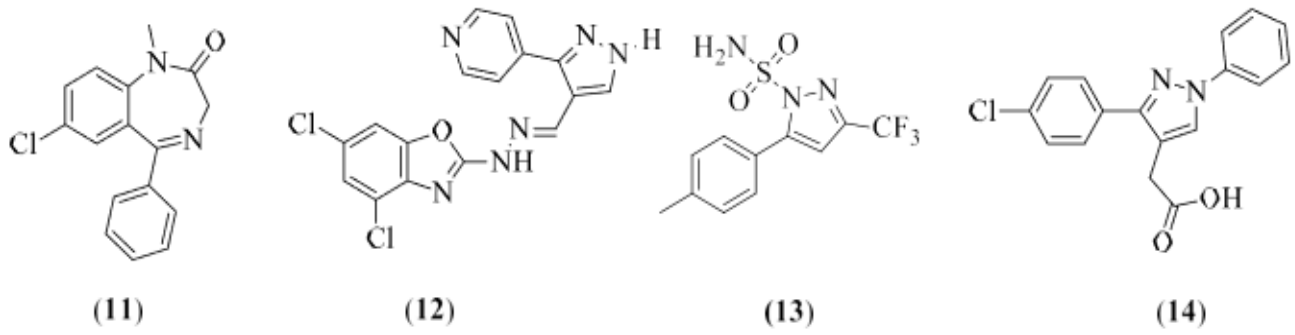
Pyrazole is heterocyclic compound which are used as medicinal drugs. For example, Indiplon **(7)** and Zaleplon **(8)** are drugs which contains pyrazole ring and act as anti-anxiety agent (Xu et al., 2012). CDPPB **(9)** is used for the ministration of dementia and act as neuroleptic agent having pyrazole ring in their structure (Uslaner et al., 2009). Apixaban **(10)** is also a drug having a pyrazole ring and act as anticoagulant agent (Tripodi et al., 2015).



(7) (8) (9) (10)

Figure 1.2: Drugs containing pyrazole ring

Diazepam **(11)** is important tranquilizer with a broad spectrum (Berghot et al., 2003). Similarly, pyrazole and pyrazoline derivatives act as analgesic and anti-erythrogenic agents (Bonesi et al., 2010). For example, Pentazocine **(12)** is a standard drug which contain pyrazole ring and act as analgesic agent (Vijesh et al., 2013). Celecoxib **(13)** is a selective non-steroidal, anti-erythrogenic medicine which is used for the treatment of inflammation of osteoaritis and acute pain in adults. Lonazolac **(14)** is also pyrazole containing non-steroidal anti-inflammatory drug. (Alka et al.,2011).



(11) (12) (13) (14)

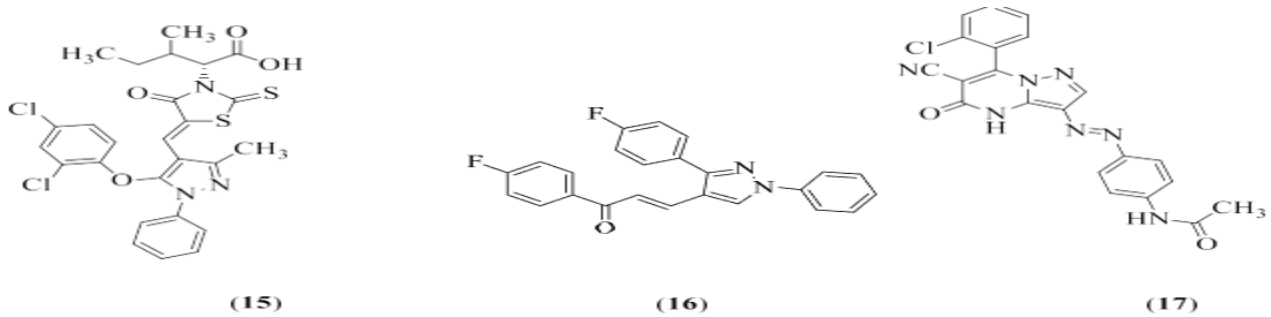
Figure 1.3: Derivatives of pyrazole (11), (12), (13) and (14) acts as pain-relieving and anti- inflammatory agents.

1.3. Pyrazole derivatives

Pyrazolo [3,4-d] pyrimidine (1,3-diazine) derivatives was act as antiviral, antimicrobial, meticidal, insecticidal, herbicidal and antileukemia agents (Abunada et al., 2008). Pyrazole derivatives are also being used as therapeutic drugs which act on the nervous system (CNS).

1.3.1. Antimicrobial activity

The fungal and bacterial infections are important threat and caused to death in immune deficiency persons (Vijesh et al., 2013). Many derivatives of multidrug are discovered which have ability against the microorganisms such as bacteria and fungi (Keche et al., 2012). For example, the compound **(15)** show the highest antimicrobial activity with better result against MRSA and QRSA strains (Song et al., 2013). The synthesized compounds **(16)** having prazole ring in their molecule and most biologically active against Streptococcus aureus. (Shelke et al., 2012). Similarly, the newly prepared compound pyrazolopyrimidine **(17)** act as antibacterial agent with greater MIC against S. aureus (Ghaneya et al., 2011). The compounds having NO_2 group at ortho positions in pyrazole ring are more active against E. coli bacteria (Alka et al.,2011).

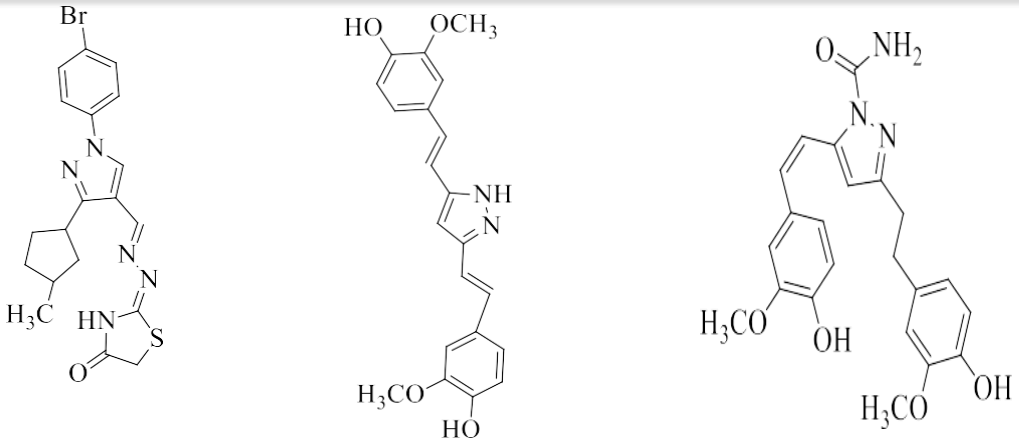


(15) **(16)** **(17)**

Figure 1.4: Antimicrobial activities of pyrazole derivatives

1.3.2. Antimalarial activity

Malaria is a common disease which caused by Plasmodium genera. Female Anopheles mosquito spreads the malaria from one person to another. Mostly its target the underdeveloped countries like Pakistan and Africa due to high population density and poor infrastructure (Green et al., 2016). Many antimalarial drugs are prepared which having pyrazole ring and act as main nuclei against malarial disease. For examples, the compound **(18)** has five times greater potency than chloroquine drug against malaria disease (Bekhit et al., 2015). Similarly, the prepared compound **(19)** is most active agent with higher antimalarial potency against chloroquine (Mowbray et al., 2009). The compound **(20)** is biologically active and act as schizonticidal and parasiticidal agent. Antimalarial activity of all these compounds is confirmed by Plasmodium falciparum (Alka et al., 2011).

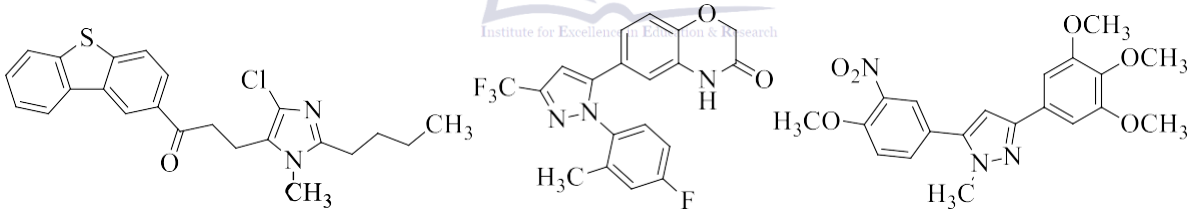


(18) (19) (20)

Figure 1.5: Pyrazole derivatives containing antimalarial activity

1.3.3. Antihypertensive activity

Hypertension is characterized as a mulish medical condition in which blood in the arteries flow with more force than normal. Now-a-days, hypertension has become a major disease throughout the world. There are many antihypertensive agents which contain pyrazole ring in their molecules (Lo et al., 2010). The newly prepared derivatives of pyrazole show antihypertensive activity **(21)** which behave as more potent ACE inhibitor (Alka et al., 2011). The compound **(22)** containing fluorinated pyrazole which show the significant properties of antihypertensive activity and compound **(23)** act as ACE inhibitors (Cui et al., 2013).



(21) (22) (23)

Figure 1.6: Pyrazole derivatives act as antihypertensive agents

1.3.4. Anticancer activity

Cancer is uncontrolled and serious life threating disease in which abnormal cells are produced. Many scientists are trying to discover the best drugs for the treatment of cancer (Alka et al., 2011). Pyrazolopyrazinone derivatives mostly act as anticancer agents (Newhouse et al., 2011). For example, the prepared compounds **(24)**, **(25)** and **(26)** having pyrazole ring and showthe anticancer activities against the apoptosis resistant cell lines HL-60 and K-562 (Jabali et al., 2011).

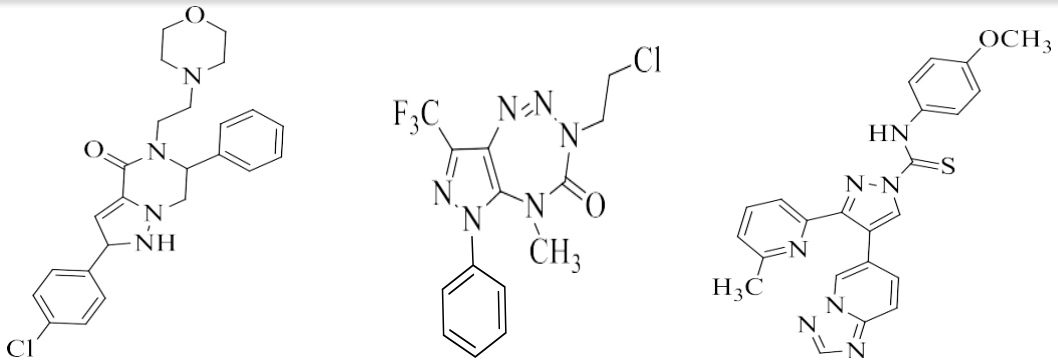
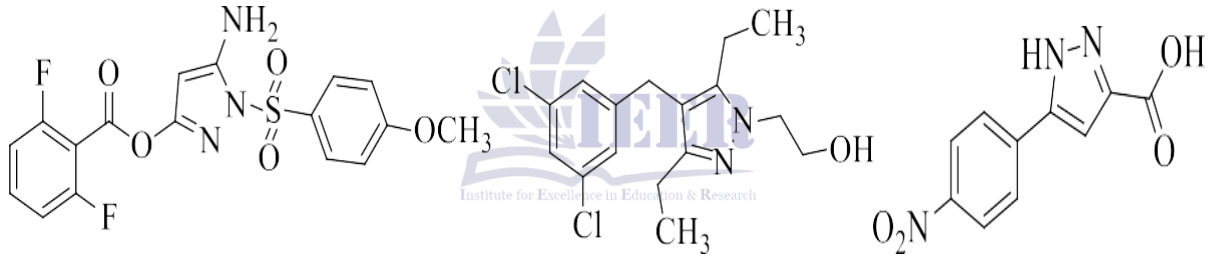


Figure 1.7: Anticancer activity of pyrazole derivatives

1.3.5. Antiviral activity

The infection caused by viruses is termed as viral infection. HCV virus damages the liver and cause the hepatitis C disease. Different pyrazole derivatives act as anti-viral agent (Xing et al., 2006). The newly prepared pyrazole containing compound (**27**) act as allosteric inhibitors in viruses (Koca et al., 2013). The derivative of pyrazole (**28**) act as antiviral agent and prevent the eight diverse viral strains with an IC50 of non-molar concentrations (Ashraf et al., 2018). Similarly, the pyrazole derivatives (**29**) show the antiviral activity against HIV (Wu et al., 2002).



(**27**) (**28**) (**29**)

Figure 1.8: Antiviral activity of pyrazole derivatives

1.3.6. Antifungal activity

Antifungal means kill fungi or stop the growth of fungi. Aspergilli is the main cause in safe traded off parasitic tainted patients (Vadiyala et al., 2017). Different five membered heterocyclic compounds such as pyrazole are very useful in medicinal field, mainly pyrazole have great value in the zone of antifungal agent (Foroumadi et al., 2009). Similarly, compound (**30**) show antifungal activity (Samir et al., 2008) and (**31**) show antifungal activity against Fusarium Oxysporum (Ashraf et al., 2018) and the compound (**32**) exhibit in vitro antifungal activity against B. fabae and F. Oxysporum (Bondock et al., 2011).

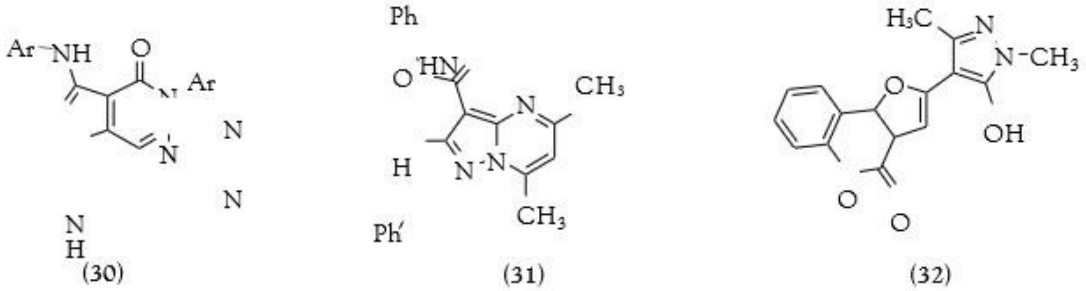


Figure 1.9: Antifungal activity of pyrazole derivatives

1.3.7. Anti-aggravation activity

Aggravation is a multifactorial cycle that demonstrates the response of the living organism to different stimuli. Aggravation is characterized with numerous problems, for example, torment, redness of skin, growing, persistent aggravation may prompt joint inflammation, asthma, and psoriasis (Elena et al., 1999). Diverse pyrazole derivatives show anti-aggravation activity. For example, Celecoxib **(33)** is a particular non-steroidal mitigating drug which is utilized for the treatment of acute pain and aggravation of osteoaritis (Alka et al.,2011), **(34)** show anti-aggravation activity against carrageenan-incited rodent paw edema test (Aziz et al., 2009) and the compound **(35)** additionally show anti-aggravation activity (Ashish et al., 2014).

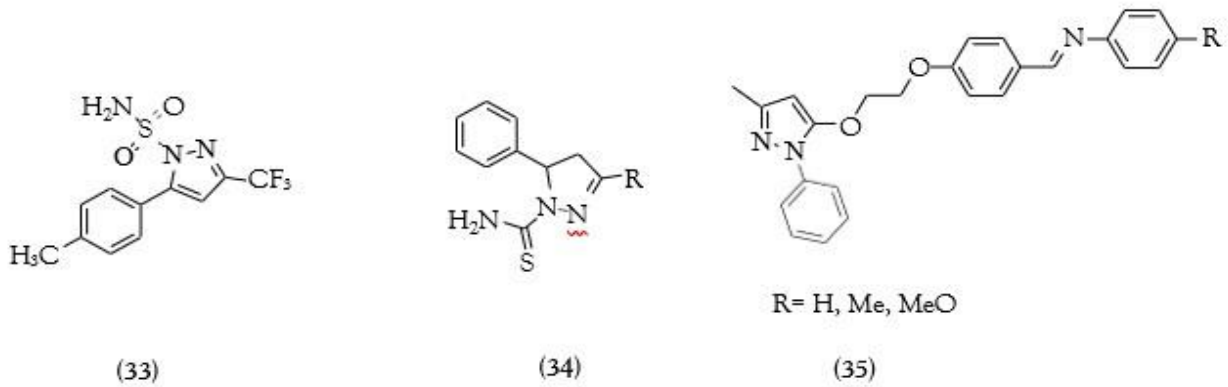


Figure 1.10: Anti-inflammatory activity of pyrazole derivatives

1.3.8. Antioxidant activity

Antioxidants are the compounds which interact and kill the free radical and prevent them from the cause of damage. Body additionally makes some free radical which is known as endogenous free radical which is influenced by age, diet and strength of a person. Free radicals are very reactive and they could damage our body because they affect the healthy cell of a molecule. Free radical can be dangerous for the body because they damage the major component of the cell such as proteins, DNA and cell membrane (Rafat et al., 2014). Pyrazole is an important antioxidant because of the pyrazole ring which has important pharmacological and therapeutic properties. Such as pyrazole derivative **(36)**, **(37)** which are analogue of coumarin derivatives (Aziz et

al.,2009) and **(38)** also show antioxidant activity (Javarappa et al., 2012).

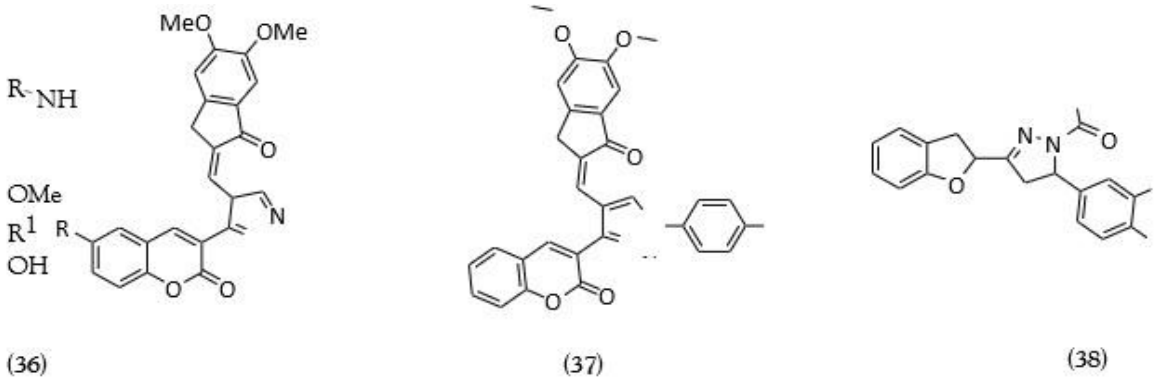


Figure 1.11: Anti-oxidant activity of pyrazole derivatives

1.3.9. Anti-Alzheimer's activity

Alzheimer disease is the cause of neurodegenerative disease which is 70% cause of dementia (Anh et al.,2019). Which is named as short-term loss of memory (Jabali et al., 2011)?
It normally happens gradually however as the infection increases then it became severe. Its normal signs are issue with language, disposition swings, bewilderment and behavioral issues (Chris et al., 2014). Subsequently, new series of pyrazole derivative **(39)** which act as anti-alzheimer and the compound **(40)** also indicate property of alzheimer action (Valeria et al., 2013).

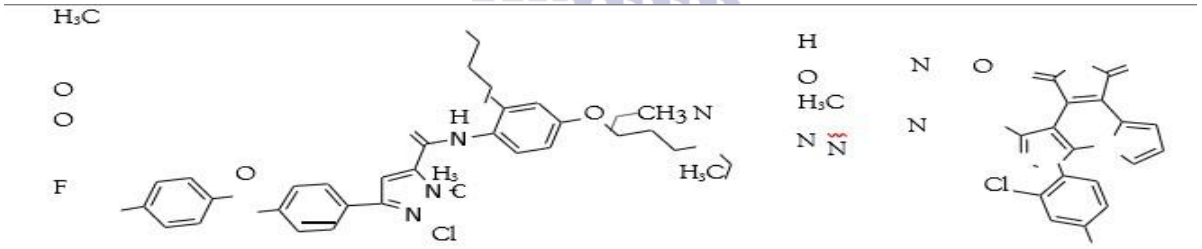


Figure 1.12: Anti-Alzheimer's activity of pyrazole derivatives

1.3.10. Anti-glaucoma activity

Glaucoma is a problem of eyes which effect the optic nerve. This illness may harm the eyes vision for all time if not treated it properly (Francesco et al., 2012). The main reason of glaucoma is visual hypertension for example the increased pressure within eyes. Glaucoma is predominantly treated by drug or either by medical procedure. There are different derivatives of pyrazole which are used as anti-glaucoma agent (Rahmi et al., 2010). The pyrazole ring containing compound **(41)** and **(42)** show antiglaucoma activity. This showed that both of these compounds exhibit their inhibitory effects (Giselle et al.,2005). The pyrazole based compounds **(43)** and **(44)** also exhibit good anti-glaucoma activity (Rahmi et al., 2009).

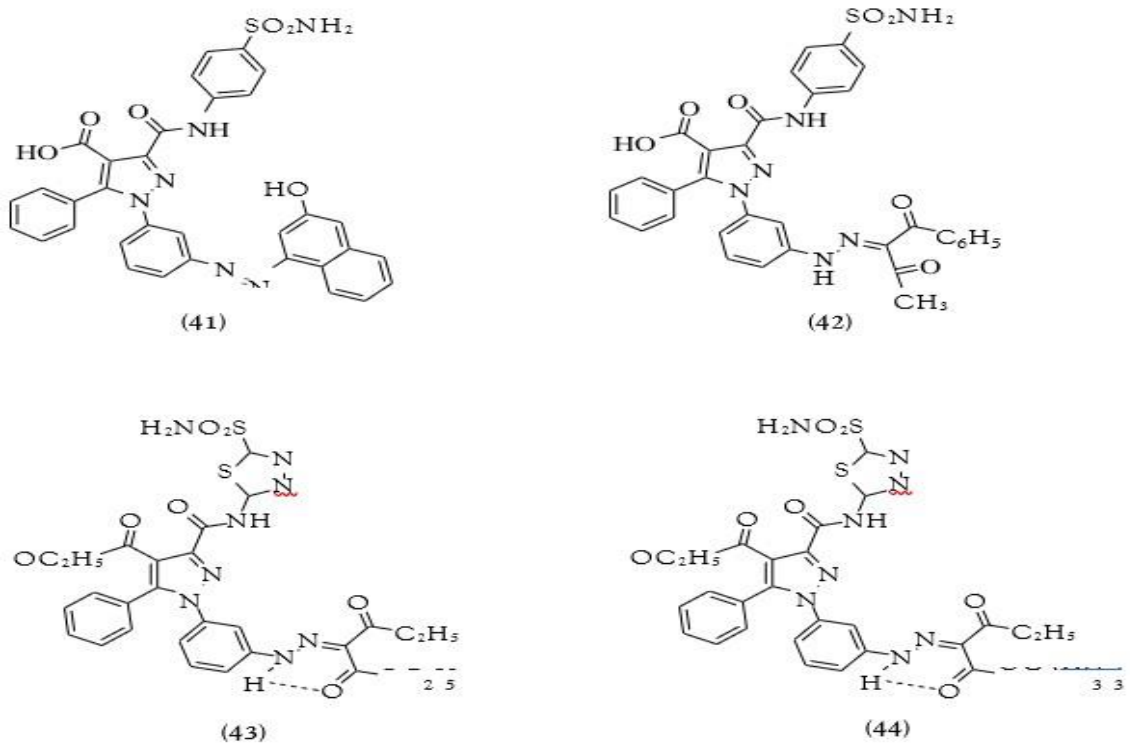
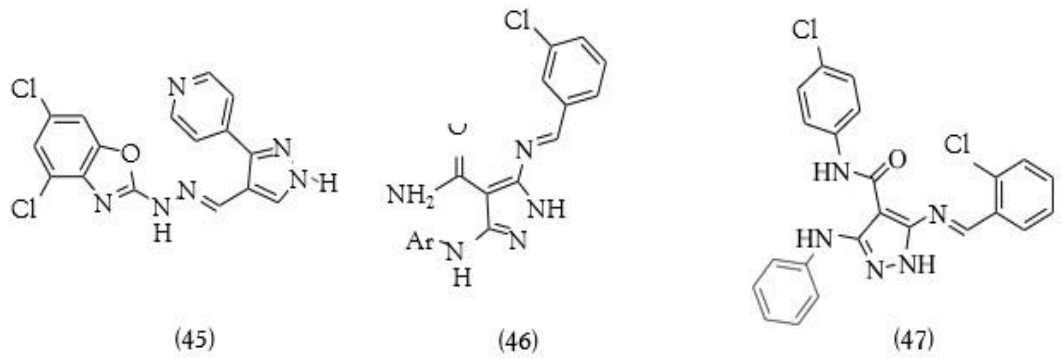


Figure 1.13: Anti-glaucoma activity of pyrazole derivatives

1.4. Schiff base derivatives

Hugo schiff in 1864 reported azomethine derivatives which are commonly being known as schiff bases (Schiff et al., 1864). Azomethine derivatives can be synthesized by the reaction of essential amine with the aldehyde or ketones. Azomethine group is the major part of these compounds whose general formula is RCH=N-R1, here R and R1 should be different substituents. Schiff base derivatives are usually biologically active compounds (Dhar et al., 1982; Przybylski et al., 2009).

For example; schiff base Pentazocine **(45)** is a standard drug containing of pyrazole ring act as analgesic agent and basic component of anthesia for surgery (Vijesh et al., 2013) and the compound **(46)** was studied against for multi-drug-resistant bacteria (Ashraf et al., 2018). Amino pyrazole schiff base derivatives, for example, **(47)** show antitumor activity (Hassan et al., 2016).

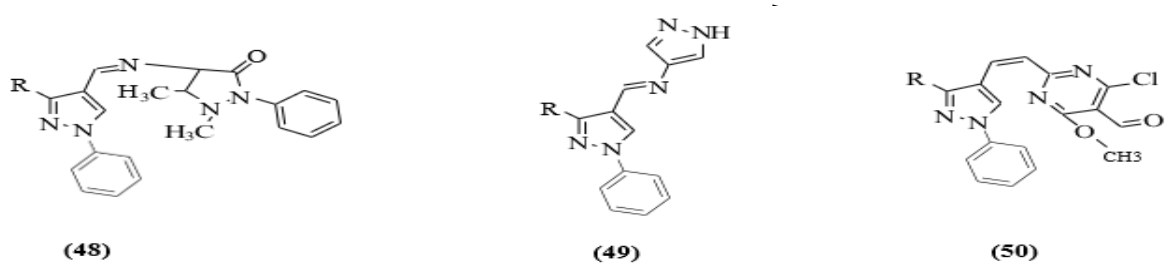


(45) (46) (47)

Figure 14: Pyrazole Schiff base derivatives

1.4.1. Antimicrobial activity

Schiff bases such as **(48)**, **(49)**, and **(50)** show antimicrobial activity (Jabali et al., 2011).

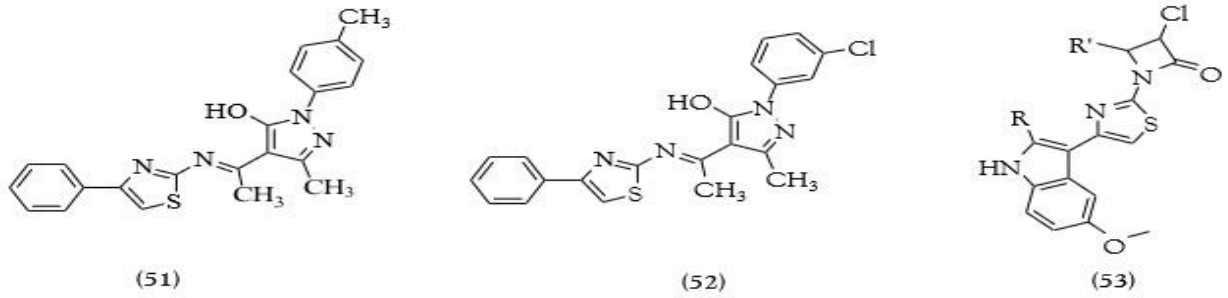


(48) **(49)** **(50)**

Figure 15: Pyrazole Schiff base derivatives showing antimicrobial activity

1.4.2. Anti-bacterial activity

Schiff bases **(51)** and **(52)** synthesized from heterocyclic compound show antibacterial activity (Thakar et al., 2011), similarly compound **(53)** was studied for their antibacterial activity against various strains of bacterium and parasite (Alka et al.,2011).

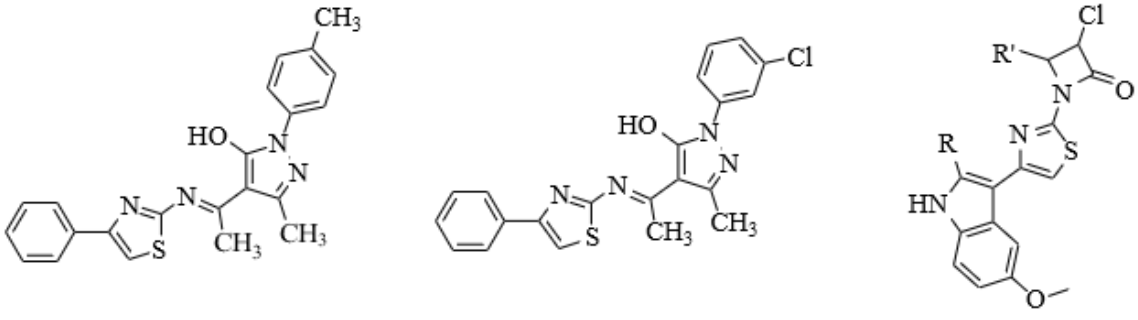


(51) (52) (53)

Figure 1.16: Antibacterial activity of pyrazole Schiff base derivatives

1.4.3. Antifungal activity

Different schiff bases obtained from different heterocyclic pyrazoles and triazoles show antifungal activity such as schiff base **(54)** is used as an antifungal agent (Sumangala et al., 2012), schiff base **(55)** also show antifungal activity (Kouatli et al., 2010) and schiff base **(56)** show antifungal activity against different fungi (Kiran et al., 2012).



(51) **(52)** **(53)**

Figure 1.16: Antibacterial activity of pyrazole schiff base derivatives

1.5. Pyrazole schiff base as a ligand

Pyrazole schiff bases are significant class of ligand in coordination chemistry and have significant application in the field of science such as antifungal, antimalarial, antineoplastic and antiviral agent (Monica et al.,2001). Schiff bases are also used as chelating agents in coordination chemistry when they have stabilizing groups such as -OH close to -HC=N- group. The ligand schiff base are also important in analytical chemistry for determination of metal (Praveen et al., 2007). For example, compound **(57)** is used as a ligand to from palladium complexes and exhibit

1.6. Metal complexes of pyrazole schiff base and their biological importance

Pyrazole schiff bases from metal complex upon coordination with different metals. Schiff base derivative of pyrazole has been employed for complex formation. Schiff base derivatives are commonly used as anti-pyretic, anti-microbial, anti-fungal, anti-inflammatory, anti-malarial, anti-fungal, antiproliferative and antibacterial agents. A coordination complex having metal atom in center is called a metal complex (Nevin et al 2011). Metal complexes of pyrazole along with its derivatives usually used as herbicides, fungicides and in drugs. For example, new schiff base **(60)** from complexes that show antibacterial activity against Staphylococcus bacteria (kiran et al., 2012) and pyrazole-based ligand **(61)** also from complexes (Susmita et al., 2016). Similarly, compound **(62)** these are used as powerful antifungal, antibacterial and antiviral agents (Giselle et al., 2005).

1.6.1. Antitumor and Anticancer activity

The compound **(63)** shows cytotoxic activity which is more than of Cisplatin which is an anticancer drug (Abu et al., 2006) and the compound **(64)** show antitumor and anticancer activity (Ribeiro et al., 2008).

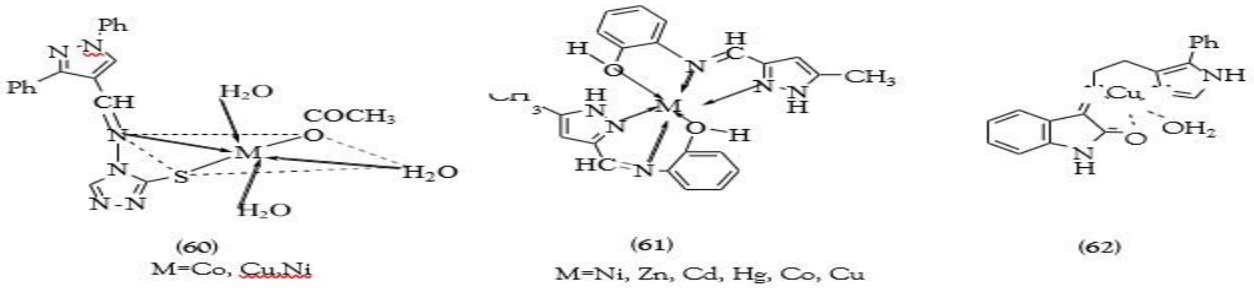


Figure 1.20: Metal complexes of Pyrazole Schiff base

1.6.2. Anti-bacterial activity

To study the biological significance of schiff base, the pyrazole schiff bases and their metal complex **(65)** have been examined for their antibacterial action (Kiran et al., 2012).The metal complex **(66)** possess insulin-mimitic activity and they can be used for storage and detoxification purpose (Aziz et al., 2009) and the metal complex **(67)** has tried for their antibacterial action against Escherichia coli and made to interact with DNA to judge on their binding capacity by absorption (Anupama et al., 2012).

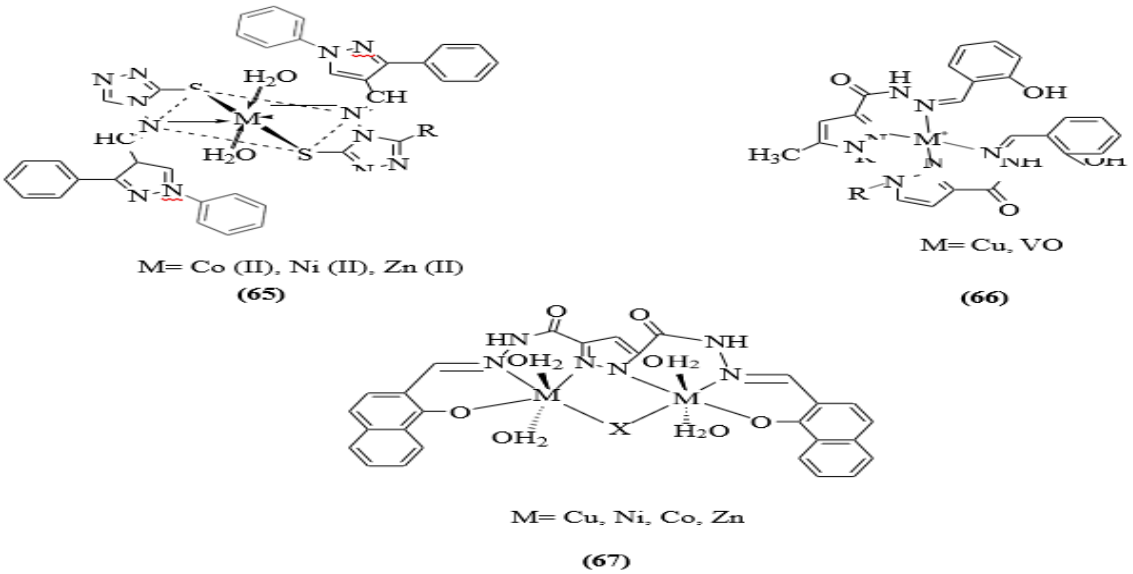


Figure 1.22: Metal complexes (65) show antibacterial, (66) show insulin-mimitic and (67) also have antibacterial activity

1.7. Furan derivatives

The presence of furan ring is much important in natural products which exhibit the biologically activity (Hou et al., 1998; Lipshutz, 1986). Many pharmaceutical products are obtained from substituted aryl furan-2-carbaldehyde (Dunlop et al., 1953). Furfural (2- furaldehyde) is heteroaromtic compound having aldehyde functional group. Commercially, 2- furaldehyde is synthesized from dehydration of pentosans (polysaccharides) in the presence of acid catalysis by using continuous reactor. In the commercial production of 2-furfuraldehyde, large amount of agricultural wastes is used for this purpose which

including almond husks, oat hulls, corncobs etc. (Dias et al., 2010).

2-furfuraldehyde is mostly used for cleansing of diesel fuels as well as lubricating fuels and many solvents such as 2-furancarbinol, 2-methyloxolane, adipic ketone (cyclopentanone) and THF (Yan et al., 2014), 4-valerolactone (GV L) (Bui et al., 2013). Furfural (2-furfuraldehyde) is also used for the preparation of 2-carboxyfuran, 2-Furanmethanol (Zeynizadeh et al., 2005) or 2-furylcyanide (Furan-2-carbonitrile) intermediates (Ghaneya et al., 2011). Furan resins are prepared from furfuryl alcohol, the most important furan derivatives such as 2-carboxyfuran, 2-methyl furan, 4-oxopentanoic acid and furfuryl amine (Zeitsch, 2000).

The furan derivatives are used as medicines like Dantrolene **(68)** Clodanolene **(69)** and Azimilide **(70)** due to high biological activity. Dentrolene (Dentamacrine) and Clodanolene are standard drugs which containing furan ring and used for the treatment of muscle (muscle relaxant) (Mashkovskii et al., 2000). Azimilide is drug which having furan ring and show the activity against heart diseases (Bui et al., 2013).

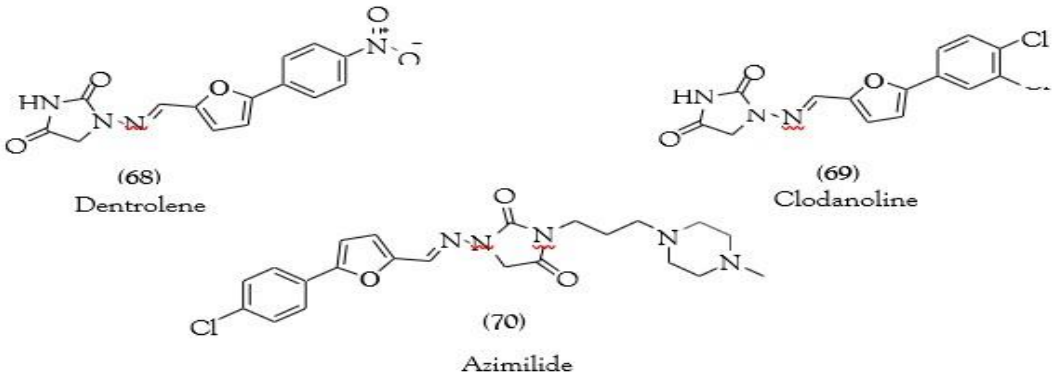


Figure 1.23: Drugs containing furan moiety

The furan derivatives such as 2,5-disubstituted furan are synthesized via cross coupling of palladium based catalyzed reactions of metalated furans. The preparation of 5-aryl-furan-2-carbaldehyde carried out using cross coupling reactions in which palladium used as catalyst with zero oxidation state (Balachari et al., 2000).

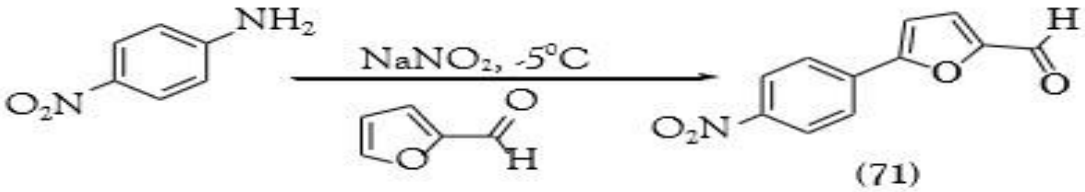
The papulacandin derivatives are prepared by substituted Furfuran derivatives and Papulacandins D are act as antifungal agent. The Papulacandin families are biological active and act as anti-microbial agents. They help in the treatment of are P. carinii pneumonia and control the AIDs (Schmatz et al., 1990).

Mentioning the importance of furan, pyrazole and metal complexes, we have planned to introduce furan derivatives on to 1-phenyl-3-methyl-5-aminopyrazole in order to from schiff bases along with their metal complexes. The aims and objectives of the studies are

- To prepare suitable substituted aryl furfural.
- To prepare schiff base derivatives and their metal complexes using substituted pyrazole and furfural derivatives.
- To characterize all the target compounds through different techniques like M.P, TLC and FTIR.
- To evaluate the target compounds for their antibacterial activity.

3.1. Methods

3.1.1. Synthesis of 5-(4-nitrophenyl)-2-furaldehyde (71)



4-Nitroaniline (0.2g, 5 mmol) was dissolved in the mixture of H2O and concentrated HCl, stirred the mixture 15 minutes followed by heating until the formation of a clear solution. The reaction mixture was cooled in ice bath up to -5 °C. After cooling the reaction mixture, a chilled solution of NaNO2 (0.25g, 5.1 mmol) in H2O (5 mL) was added portion wise into the reaction mixture with constant stirring and kept the temperature below 0°C. The reaction mixture after the addition of sodium nitrite was left for one hour at 0 °C for completion of diazotization. Then to the solution of 2-furaldehyde (0.2g, 2.5mmol) in five ml water and five ml acetone diazonium solution was poured drop wise followed by cupric chloride in water. The temperature of the solution was raised up to 30 °C and the reaction mixture was stirred for 4-6 hours and left for 24 hours. The product obtained on filter paper was dried and recrystallized from suitable solvent (Aslam et al., 2013).

Yield: 55%

M.P: 190-192 ^{0}C (Literature, 196 ^{0}C) (Aslam et al., 2013)

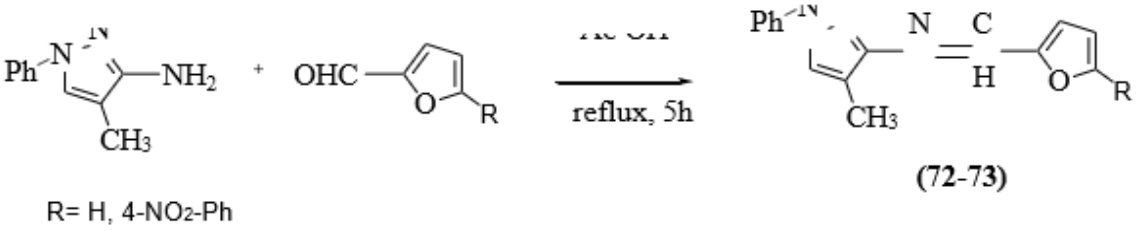
Solubility: Ethyl acetate, methyl alcohol, ethyl alcohol

TLC: n-hexane and Ethyl acetate solution (1:1)

FT-IR: 2750 cm^{-1} (C-H of formyl), 1666.65 cm^{-1} (C=O), 1513.75 and 1326.30 cm^{-1}(NO2),

3.2. Synthesis of Pyrazole Schiff base ligands (72-73)

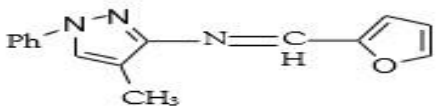
3.2.1. General Procedure



R= H, 4-NO2-Ph

Pyrazole schiff base were by the synthesized through reaction of 1-phenyl-3-methyl-5- amino pyrazole (0.2g, 0.00086 mol) with furfural derivatives (100 mg, 1mmol) in AcOH using 6ml. The reaction mixture was refluxed for five hours. Then this reaction mixture was cooled for ten minutes at room temperature and 6ml of distilled water was added into that reaction mixture to form precipitates. These precipitates were washed with distilled H2O and ETOH and it was recrystallized using ethyl alcohol.

3.2.2. Synthesis of N-(furan-2-yl-methylene)-4-methyl-1-phenyl-1H-pyrazo-3- amine (L1) (72)



(72) |

Yield: 67%

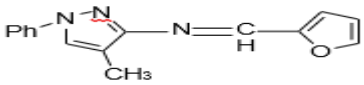
M.P: 180 ^{0}C

Solubility: Ethyl acetate, methyl alcohol, chloroform and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)

FT-IR: 1597 cm^{-1} (C=N), 3117.59 cm^{-1} (aromatic stretching), 2923.70 cm^{-1} (C-H stretching), 1503.9 cm^{-1}shows (C=C), and 1259 cm^{-1} (C-O) and 1335 cm^{-1} (C-N).

3.2.3. Synthesis of 4-methyl-N-(5-(4-nitrophenyl) furan-2-yl-methylene)-1- phenyl-1H-pyrazole-3-amine (L2) (73)



(72)

Yield: 77%

M.P: 190 ^{0}C

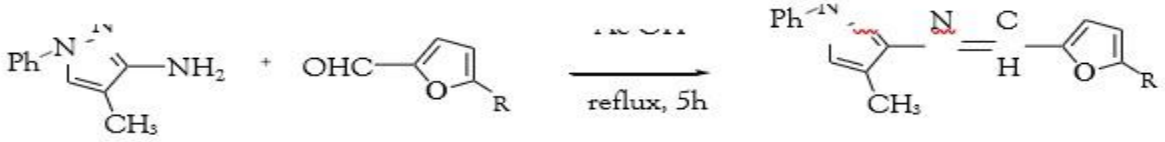
Solubility: Ethyl acetate, methyl alcohol, chloroform and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)

FT-IR: 1601 cm^{-1}(C=N), 3377.38 cm^{-1} (aromatic stretching), 2915.56 cm^{-1} (C-H stretching), 1537.84 cm^{-1} (C=C), 1508.67 cm^{-1} & 1333.84 cm^{-1} (NO2), 1203 cm^{-1} (C-O) and 1333 cm^{-1} (C-N).

3.3. Synthesis of metal complexes of Pyrazole (74-80)

3.3.1. General Procedure



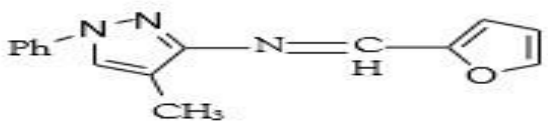
R= H, 4-NO$_2$-Ph

(72-73)

Pyrazole schiff base were by the synthesized through reaction of 1-phenyl-3-methyl-5-amino pyrazole (0.2g, 0.00086 mol) with furfural derivatives (100 mg, 1mmol) in AcOH using 6ml. The reaction mixture was refluxed for five hours. Then this reaction mixture was cooled for ten minutes at room temperature and 6ml of distilled water was

added into that reaction mixture to form precipitates. These precipitates were washed with distilled H2O and ETOH and it was recrystallized using ethyl alcohol.

3.3.2. Synthesis of N-(furan-2-yl-methylene)-4-methyl-1-phenyl-1H-pyrazo-3- amine (L1) (72)



(72)

Yield: 77%

M.P: 190 ^{0}C

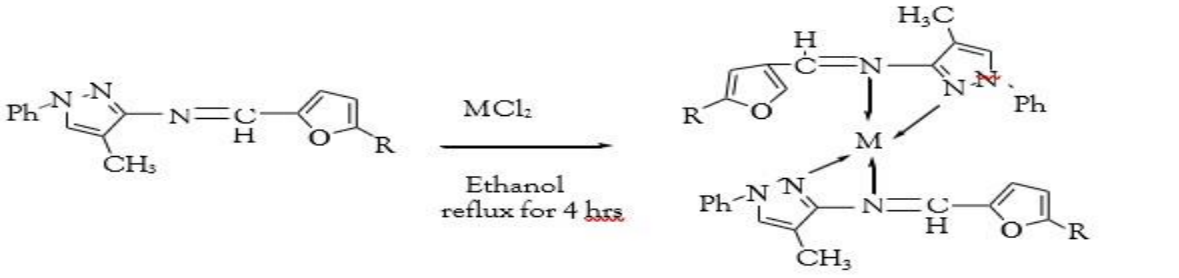
Solubility: Ethyl acetate, methyl alcohol, chloroform and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)

FT-IR: 1601 cm^{-1}(C=N), 3377.38 cm^{-1} (aromatic stretching), 2915.56 cm^{-1} (C-H stretching), 1537.84 cm^{-1} (C=C), 1508.67 cm^{-1} & 1333.84 cm^{-1} (NO2), 1203 cm^{-1} (C-O) and 1333 cm^{-1} (C-N).

3.4. Synthesis of metal complexes of Pyrazole (74-80)

General Procedure



R= H, 4-NO2-Ph

M = Ni^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Fe^{2+}, Co^{2+}

(74-80)

Metal complexes were synthesized by using pyrazole schiff base as ligands. The ligand (0.2g, 0.00086 mol) was dissolved in 5ml of ethanol in a beaker and metal chloride (0.1g, 0.00043) dissolved in 7ml of ethanol in a round bottom flask. The ligand solution was poured into the metal solution and reflux the reaction 4 hours. Precipitates obtained were filtered off and washed several times with distilled H2O and EtOH. It was finally recrystallized by using ethanol.

3.4.1. Synthesis of Cu^{2+} complex using L1 (74)

Yield: 60%

M.P: 305 ^{0}C

Solubility: Ethyl acetate, methyl alcohol and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)

FT-IR: 1541.66 cm^{-1}(C=N), 2360.66 cm^{-1} (aromatic stretching), 1507.68 cm^{-1} (C=C), 1319.69 cm^{-1} (C-N) and 490.67 cm^{-1} (M-N).

3.4.2. Synthesis of Cu^{2+} complex using L2 (75)

Yield: 67%

M.P: 300 ^{0}C

Solubility: Ethyl acetate, methyl alcohol and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)

FT-IR: 1596 cm^{-1}(C=N), 2360.66 cm^{-1} (aromatic stretching), 3032.45 cm^{-1} (OH stretching), 1457.06 cm^{-1} (C=C), and 488.96 cm^{-1} (M-N).

3.4.3. Synthesis of Ni^{2+} complex using ligand L2 (76)
Yield: 60%

M.P: 275 ^{0}C

Solubility: Ethyl acetate, methyl alcohol and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)

FT-IR: 1599 cm^{-1}(C=N), 3336.11 cm^{-1} (OH), 2361 cm^{-1} (aromatic stretching), 1456.30 cm^{-1} (C=C) and 491 cm^{-1} (M-N).

3.4.4. Synthesis of Cd^{2+} complex using ligand L2 (77)
Yield: 69%

M.P:300 ^{0}C

Solubility: Ethyl acetate, methyl alcohol and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)
FT-IR: 1599.17 cm^{-1}(C=N), 2368.19 cm^{-1} (aromatic stretching), 1457.14 cm^{-1} (C=C), 491.42 cm^{-1} (M-N) and 544.22 cm^{-1} (M-O).

3.4.5. Synthesis of Zn^{2+} complex using ligand L2 (78)
Yield: 70%

M.P: 270 ^{0}C

Solubility: Ethyl acetate, methyl alcohol and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)

FT-IR: 1598.48 cm^{-1}(C=N), 2360.31 cm^{-1} (aromatic stretching), 1456.97 cm^{-1} (C=C), 1275.86cm^{-1} (C-N) and 492 cm^{-1} (M-N).

3.4.6. Synthesis of Fe^{2+} complex using L2 (79)
Yield: 60%

M.P: ≥250 ^{0}C

Solubility: Ethyl acetate, methyl alcohol and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)

FT-IR: 1598 cm^{-1}(C=N), 3115.71 cm^{-1} (OH), 2361.39 cm^{-1} (aromatic stretching), 1474.60 cm^{-1} (C=C), 1275 cm^{-1} (C-N) 500 cm^{-1} (M-N).

3.4.7. Synthesis of Co^{2+} complex using ligand L2 (80)
Yield: 73%

M.P: 290 ^{0}C

Solubility: Ethyl acetate, methyl alcohol and ethyl alcohol

TLC: n-hexane and Ethyl acetate Solution (3:1)

FT-IR: 1599 cm^{-1}(C=N), 3245.75 cm^{-1} (OH), 2363.55 cm^{-1} (aromatic stretching), 1454.62 cm^{-1} and 495 cm^{-1} (M-N).

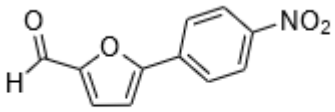
RESULTS AND DISCUSSION

Arylation of furfural to prepare its new derivative is important due to medicinal uses of furan derivatives. For examples, Nitrafudan, Clodanolene and Azimilide have aryl furan moiety in their structures (Obushak et al., 2009). 4-Nitrofurfural furan derivative was synthesized through copper catalyzed Meerwein arylation in

which arenediazonium salt is intermediate. Similarly, pyrazole are one of naturally dynamic compounds utilized in drugs (Elena et al., 1999). These are antiviral, antibacterial, antifungal and antitumor (Shah et al.,2011 & Satish et al.,2008). So, keeping in mind the importance of both compounds some new derivative of pyrazole schiff bases were synthesized by the reaction of pyrazole with furfural derivatives and by utilizing these heteroaryl schiff base different type of metal complexes were synthesized. The formation of derivatives was monitored through thin layer chromatography. The melting point of given compounds was also checked. The structural composition of synthesized compounds was done through FT-IR.

4.1. Synthesis of substituted aryl furfural derivative

4.1.1. Synthesis of 5-(4-Nitrophenly) furan-2-carbaldehyde (71)



(71)

Scheme 4.1: Synthesis of 5-(4-Nitrophenly) furan-2-carbaldehyde (71)

5-(4-Nitrophenly) furan-2-carbaldehyde was synthesized through the Meerwein arylation by using 4-Nitro anilines and furfurals. The completion of reaction and purity of its product was checked by TLC and melting point. The value of melting point of newly arylated product was also correlated with the value of literature. The FT-IR spectra of arylated furfural showed the peak for carbonyl group at 1666.68cm^{-1} and nitro (Nitro group) showed sharp two peaks at 1513.32 and 1326.79cm^{-1}. The FT-IR of the compound (71) is given next.

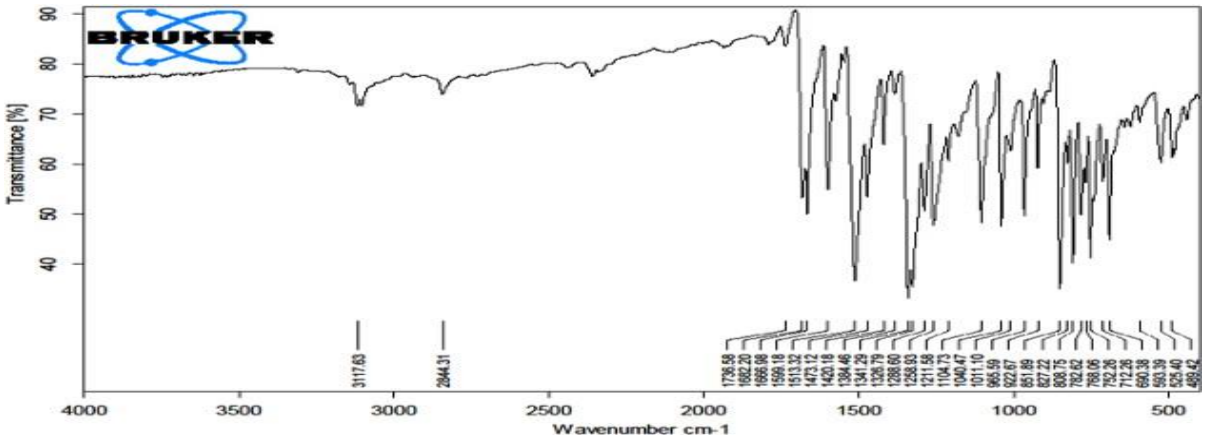
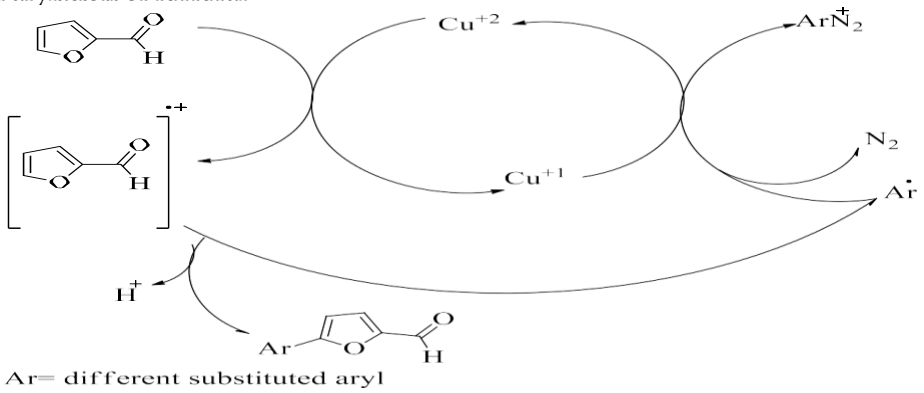


Figure 4.1: FT-IR spectrum of 5-(4-nitrophenyl) furan-2-carbaldehyde

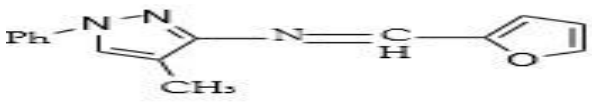
Mechanism of arylation of furfural



Scheme 4.2: Mechanism of arylation of furfural

4.2. Synthesis of pyrazole schiff base ligands (72-73)

4.2.1. Synthesis of N-(furan-2-yl-methylene)-4-methyl-1-phenyl-1H-pyrazo-3- amine L1 (72)



(72)

Scheme 4.4: Synthesis of N-(furan-2-yl-methylene)-4-methyl-1-phenyl-1H-pyrazo-3-amine L1 (72)

Pyrazole schiff base was prepared by the reaction of 1-phenyl-3-methyl-5-amino pyrazole with furfural in acetic acid 6ml. The reaction mixture was refluxed for four hours. The purity of the compound was confirmed through thin layer chromatography and further characterization was done through FT-IR. The melting point of compound **(72)** was 180^{0}C. No signal was observed for carbonyl (C=O) and amino group in the FT-IR spectra of the product which indicate that it is converted into desired product. In spectra peak at 1597cm^{-1} is the peak of (C=N) which show synthesis of schiff base, peak at 3117.59 cm^{-1} shows (aromatic stretching), peak at 2923.70 cm^{-1} shows (C-H stretching), and peak at 1503.9 cm^{-1} shows (C=C), and 1259 cm^{-1} show (C-O) and 1335 cm^{-1} how (C-N) group (Alpana et al., 2009). The FT-IR of **(72)** is given below.

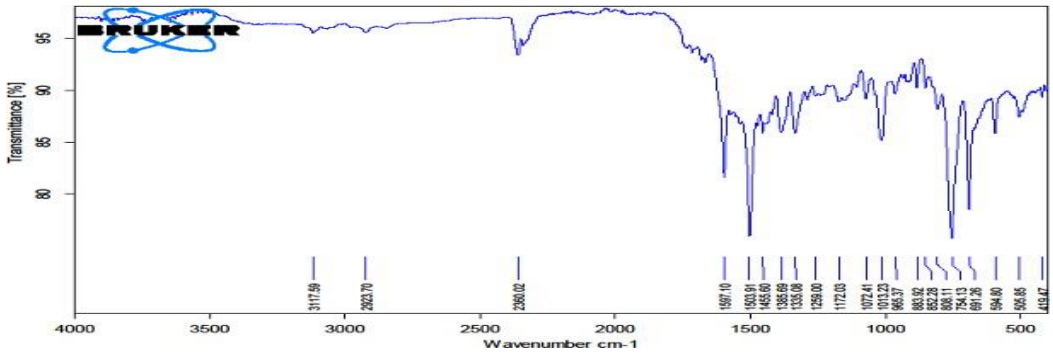
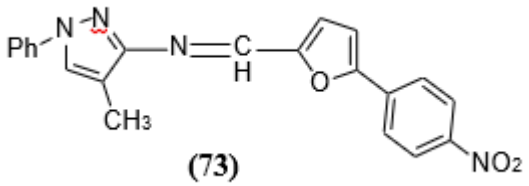


Figure 4.2: FT-IR spectrum of N-(furan-2-yl-methylene)-4-methyl-1-phenyl-1H-pyrazo-3-amine L1 (72)

Synthesis of 4-methyl-N-(5-(4-nitrophenyl) furan-2-yl-methylene)-1- phenyl-1H-pyrazole-3-amine L2 (73)



(73)

Scheme 4.5: Synthesis of 4-methyl-N-(5-(4-nitrophenyl) furan-2-yl-methylene)-1-phenyl-1H-pyrazole-3-amine L2 (73)

Pyrazole schiff base has prepared by the reaction of 1-phenyl-3-methyl-5-amino pyrazole with 5-(4-nitrophenyl)-2-furaldehyde in acetic acid 6ml. The reaction mixture was refluxed for five hours. Thin layer chromatography has confirmed purity of compound and furthermore characterization was done through the FT-IR. The melting point of compound **(73)** was 190^0C and the percentage yield of the reaction was 67%. In FT-IR spectra the peak at 1601 cm^{-1} is of (C=N) which indicate the formation of schiff base. No signal was observed for carbonyl (C=O) and amino group in the FT-IR of spectra of the compound which indicate that it is converted into desired product. Along with other peaks at 3377.38 cm^{-1} show (aromatic stretching), peak at 2915.56 cm^{-1} show (C-H stretching), and show 1537.84 cm^{-1} show (C=C), (NO2) shows two peaks at 1333.84 cm^{-1} &1508.67 cm^{-1}, peak at 1203 cm^{-1} show (C-O) and 1333 cm^{-1} indicate the presence of (C-N) group (Arun et al., 2008) . The FT-IR spectrum of compound **(73)** is given below.

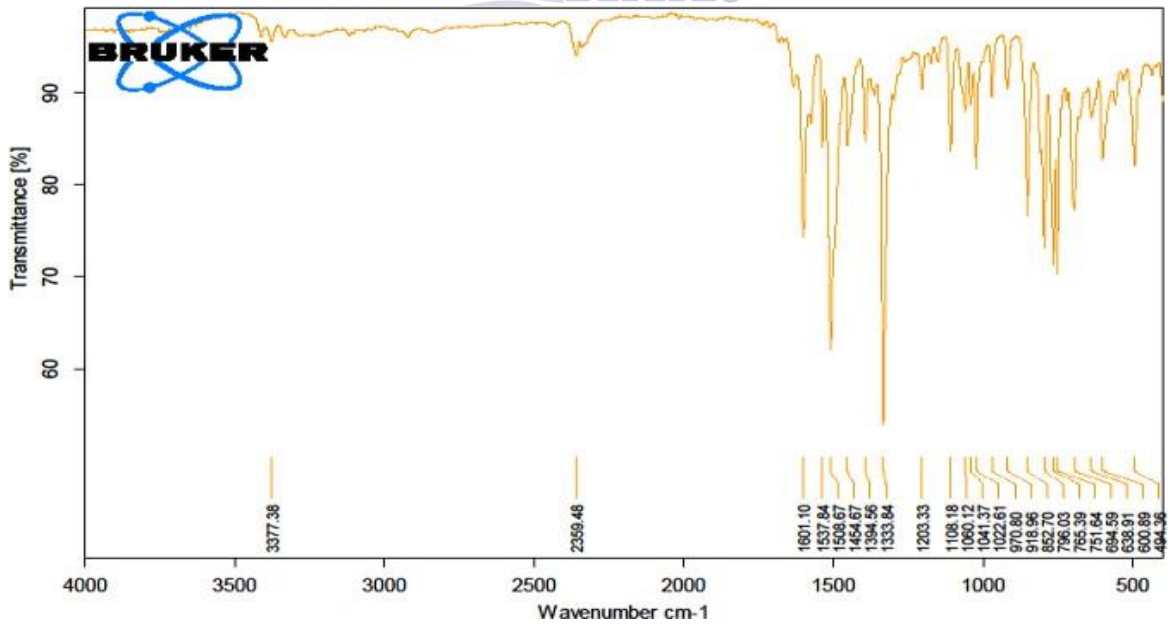


Figure 4.3: FT-IR spectrum of 4-methyl-N-(5-(4-nitrophenyl) furan-2-yl-methylene)-1-phenyl-1H-pyrazole-3-amine L2 (73)

4.3. Synthesis of metal complexes pyrazole schiff base (74-80)

4.3.1. General procedure

Metal complexes were synthesized by using pyrazole Schiff base as ligands. The ligand (0.2g, 0.86 mmol) was dissolved in 5ml of ethanol in a beaker and metal chloride (0.43mmol) dissolved in 7ml of ethanol in a round bottom flask. The ligand solution was poured into the metal solution and reflux the reaction 4 hours. Precipitates formed were filtered off and washed several times with distilled H2O and EtOH. It was finally recrystallized by using ethanol.

Scheme 4.7: Synthesis of Cu^{2+} complex of L1 (74)

Metal [Cu(II)] complex of ligand L1 is synthesized with the reaction of ligand with metal salt of copper (CuCl2.2H2O) in 2:1 using EtOH as solvent. The melting point of the compound (74) was 305 0C. The percentage yield of compound was 60%. The purity of the compound was checked with TLC. In the FT-IR spectra showed the peak at 1541.66 cm-1 which is assigned to (C=N). The peak of (C=N) in case of ligand is observed at 1597 cm-1. The shifting towards lower frequency indicate that the ligand is involved in coordination with metal, peak at 1507.68 cm-1 show (C=C) , peak at 1319.69 cm-1 show (C-N) bond, 2360.66 cm-1 show (aromatic stretching) and peak at 490.67 cm-1 show (M-N) group which show metal coordination bond (Shehab et al., 2004). The FT-IR spectrum of (74) is given below.

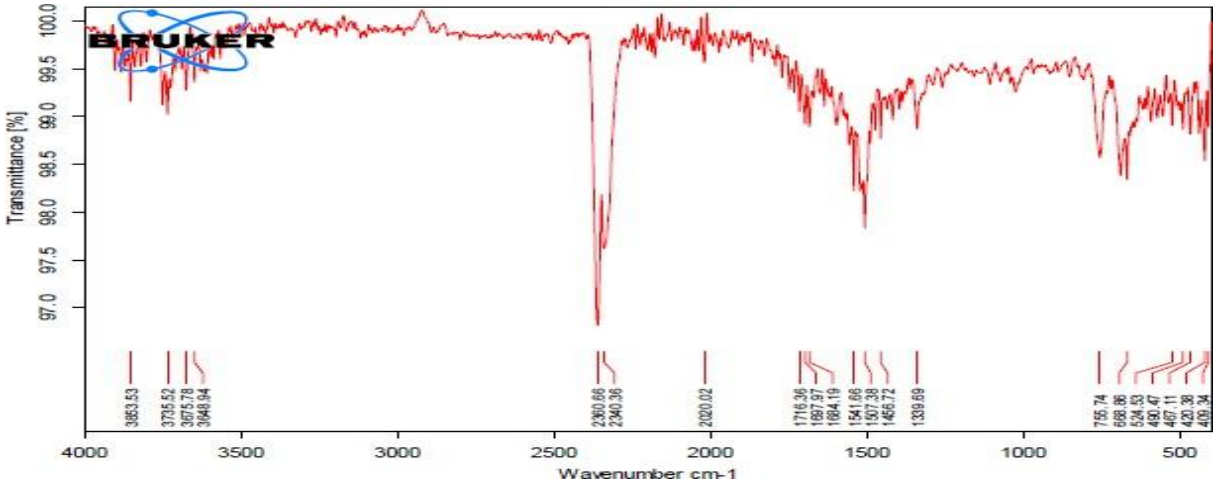
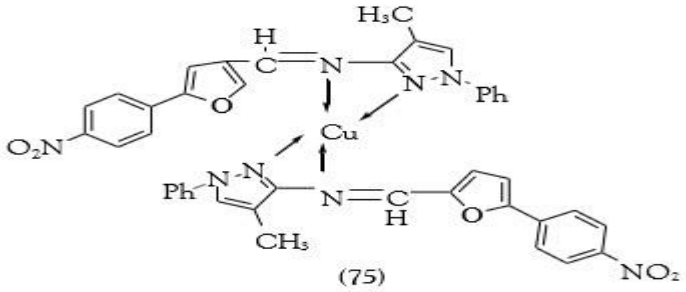


Figure 4.4: FT-IR spectrum of Cu^{2+} metal complex of L1 (74)

4.3.2. Synthesis of Cu^{2+} complex of ligand L2 (75)



(75)

Scheme 4.8: Synthesis of Cu^{2+} complex of L2 (75)

Metal [Cu(II)] complex of ligand L2 is prepared with the reaction of ligand with metal salt of copper (CuCl2.2H2O) in 2:1 using EtOH. The melting point of compound (75) was 3000C. The percentage yield of compound was 67%. The purity of the compound was checked by TLC. In the FT-IR spectra showed the peak at 1596 cm-1 which is assigned to (C=N). The peak of (C=N) in case of ligand is observed at 1601 cm-1. The shifting towards lower frequency indicate that the ligand is involved in coordination with metal, peak at 2360.66 cm-1 show (aromatic stretching), peak at 1457.06 cm-1 show (C=C), and peaks at 488.96 cm-1 shows the existence of (M-N) bond (Kiran et al., 2012). The FT-IR spectrum of (75) given below.

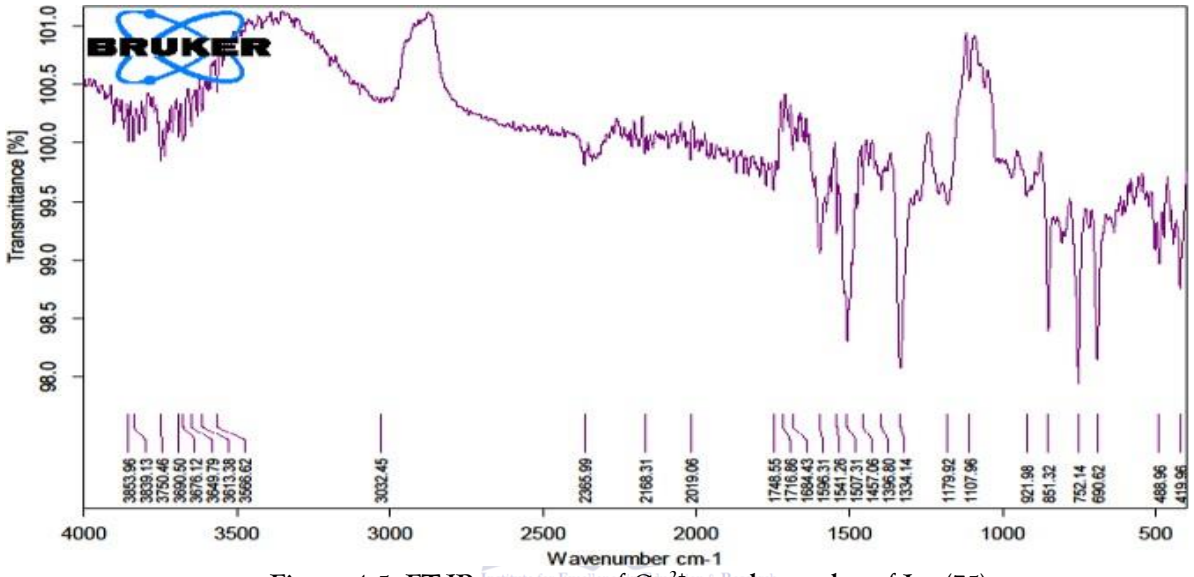
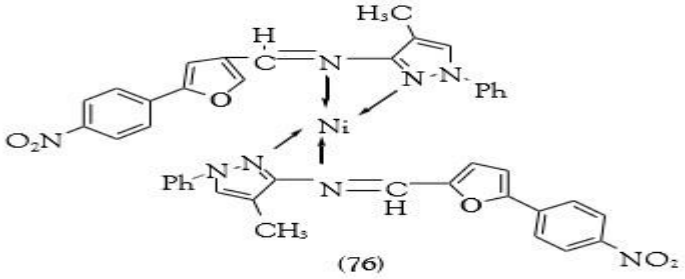


Figure 4.5: FT-IR spectrum of Cu^{2+} metal complex of L2 (75)

4.3.3. Synthesis of Ni^{2+} complex of L2 (76)



(76)

Scheme 4.9: Synthesis of Ni^{2+} complex of L2 (76)

Metal [Ni(II)] complex of ligand L2 is prepared by the reaction of ligand with metal salt of nickel (NiCl2.6H2O) in 2:1 using EtOH. The melting point of compound **(76)** was 275^{0}C. The percentage yield of compound was 60%. The purity of the compound was checked with TLC. In the FT-IR spectra showed the peak at 1599 cm^{-1} which is assigned to (C=N). The peak of (C=N) in case of ligand is observed at 1601 cm^{-1}. The shifting towards lower frequency indicate that the ligand is involved in coordination with metal, and further peak at 3336.11 cm^{-1} show the presence of (OH) group, 2361 cm^{-1} (aromatic stretching), peak at 1456.30 cm^{-1}show (C=C), and 491 cm^{-1}

indicate (M-N) metal coordination bond (Abd et al., 2011). The FT-IR spectrum of (76) is given below.

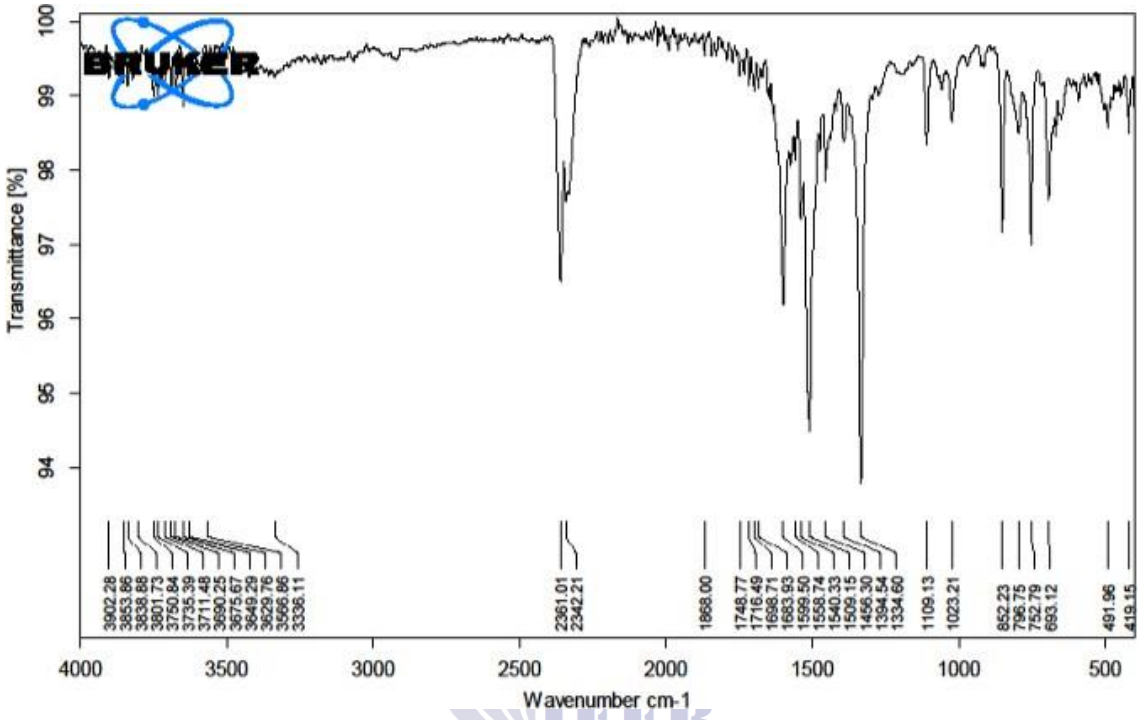
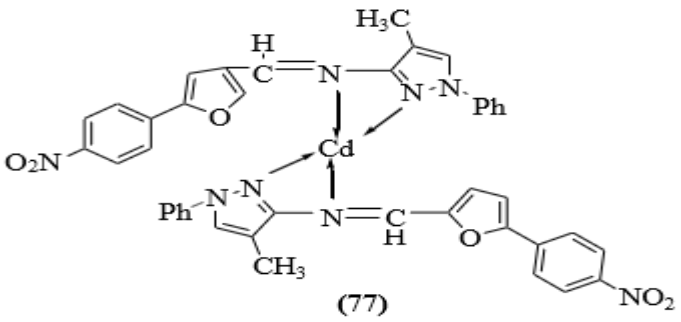


Figure 4.5: FT-IR spectrum of Ni^{2+} metal complex of L2 (76)

4.3.4. Synthesis of Cd^{2+} complex of L2 (77)



(77)

Scheme 4.10: Synthesis of Cd^{2+} complex of L2 (77)

Metal [Cd(II)] complex of ligand L2 is synthesized with the reaction of ligand with metal salt of cadmium (CdCl2.H2O) in 2:1 using EtOH. The melting point of compound (77) was 300^0C. The percentage yield of compound was 69%. The purity of the compound was checked by TLC. In the FT-IR spectra showed the peak at 1599.17 cm^{-1} which is given to (C=N). The peak of (C=N) in case of ligand is observed at 1601 $cm^{-1.}$ The shifting towards lower frequency indicate

that the ligand is involved in coordination with metal, peak at 2361 cm^{-1} show (aromatic stretching) and further peak at 1457.14 cm^{-1} show (C=C), peak at 491.42 cm^{-1} show (M-N) group and peak at 544.22 cm^{-1} show (M-O) group (Saugata et al., 2011). The FT-IR spectrum of (77) is given below.

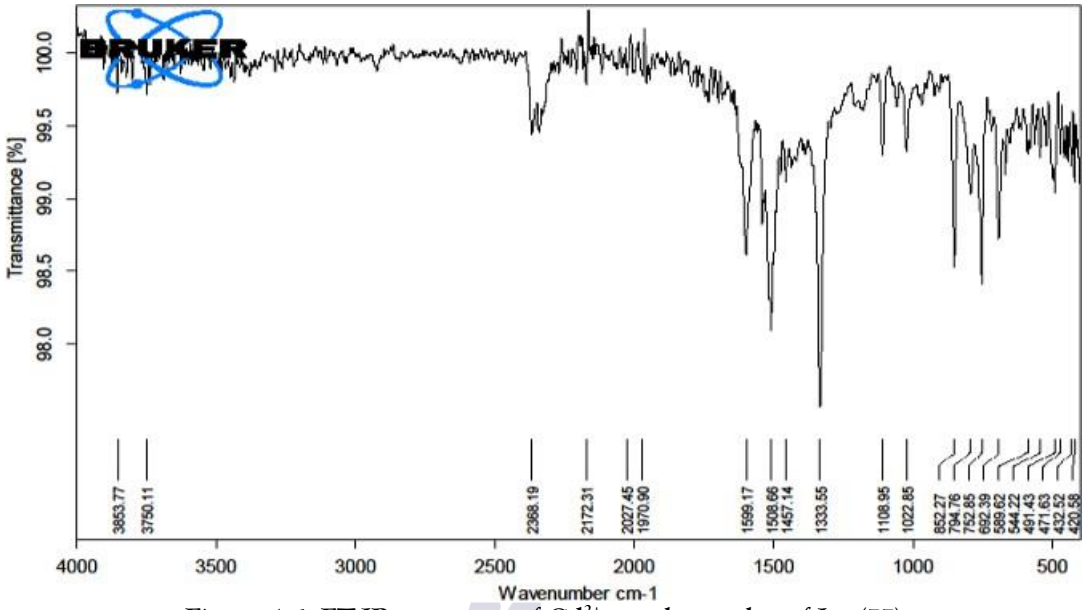
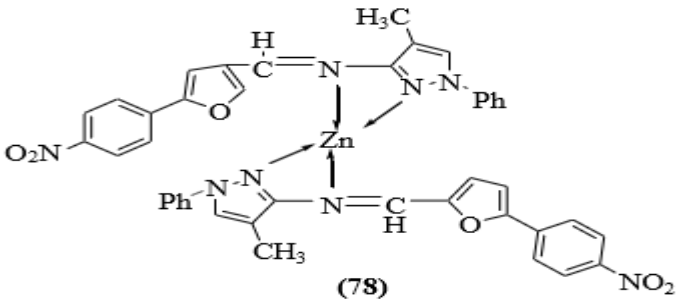


Figure 4.6: FT-IR spectrum of Cd^{2+} metal complex of L2 (77)

4.3.5. Synthesis of Zn^{2+} complex of L2 (78)



(78)

Scheme 4.11: Synthesis of Zn^{2+} complex of L2 (78)

Metal [Zn(II)] complex of ligand L2 is formed by the reaction of ligand with metal salt of Zinc ($ZnCl_2$) in 2:1 using EtOH. The melting point of compound (78) was 275^{0}C. The percentage yield of compound was 70%. The purity of the compound was checked with TLC. In the FT-IR spectra showed the peak at 1598.48 cm^{-1} which is given to (C=N). The peak of (C=N) in case of ligand is observed at 1601 $cm^{-1.}$ The shifting towards lower frequency indicate that the ligand is involved in coordination with metal, peak at 2360.31 cm^{-1} show (aromatic stretching), peak at 1456.97 cm^{-1} show (C=C), peak at 1275.86 cm^{-1} show (C-N) and 492 cm^{-1} show the presence of (M-N) group (Kiran et al., 2012). The FT-IR spectrum of (78) is given below.

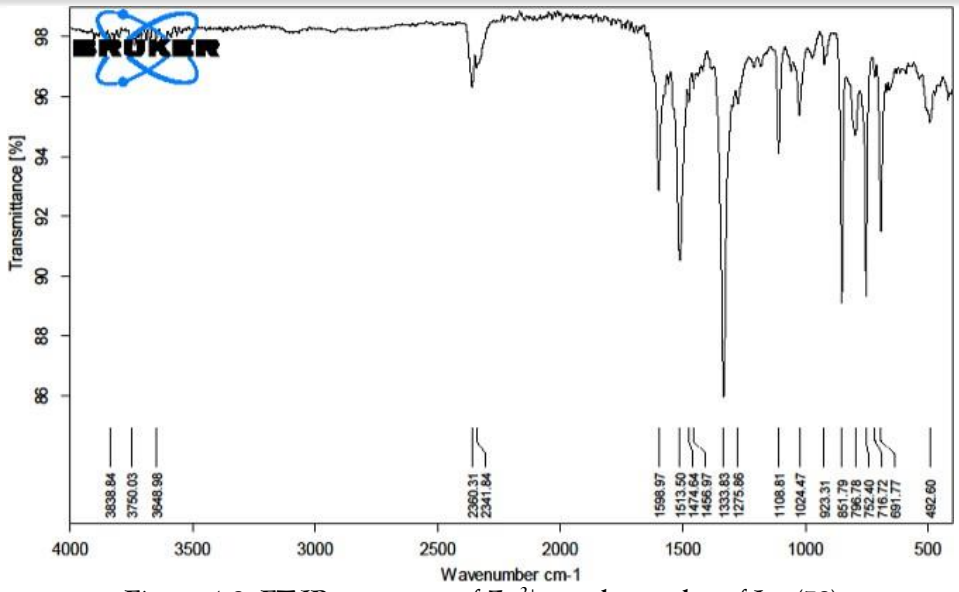
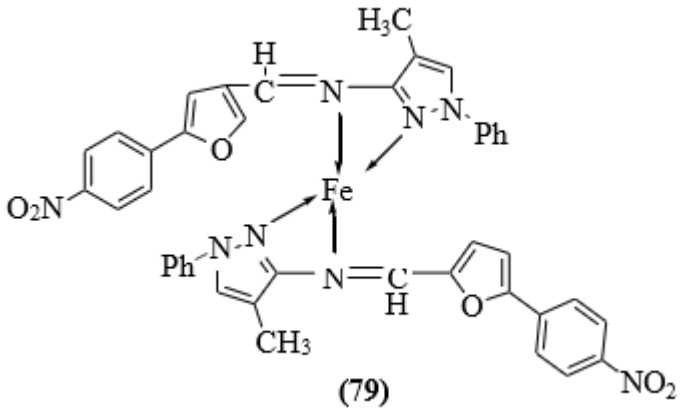


Figure 4.8: FT-IR spectrum of Zn^{2+} metal complex of L2 (78)

4.3.6. Synthesis of Fe^{2+} complex of L2 (79)



(79)

Scheme 4.12: Synthesis of Fe^{2+} complex of L2 (79)

Metal [Fe(II)] complex of ligand L2 is prepared by the reaction of ligand with metal salt of iron (FeCl2) in 2:1 using EtOH as solvent. The melting point of compound **(79)** was ≥250 ^{0}C. The percentage yield of compound was 60%. The purity of the compound was checked with TLC. In the FT-IR spectra showed the peak at 1598 cm^{-1} which is given to (C=N). The peak of (C=N) in case of ligand is observed at 1601 cm^{-1}. The shifting towards lower frequency indicate that the ligand is involved in coordination with metal, peak at 3115.71 cm^{-1} show (OH) group, 2361.39 cm^{-1} show (aromatic stretching) peak at 1474.60 cm^{-1} show (C=C), peak at 1275 cm^{-1} show (C-N) bond and further peak at 500 cm^{-1}indicate (M-N) group (Saugata et al., 2011). The FT-IR spectrum of **(79)** is given below.

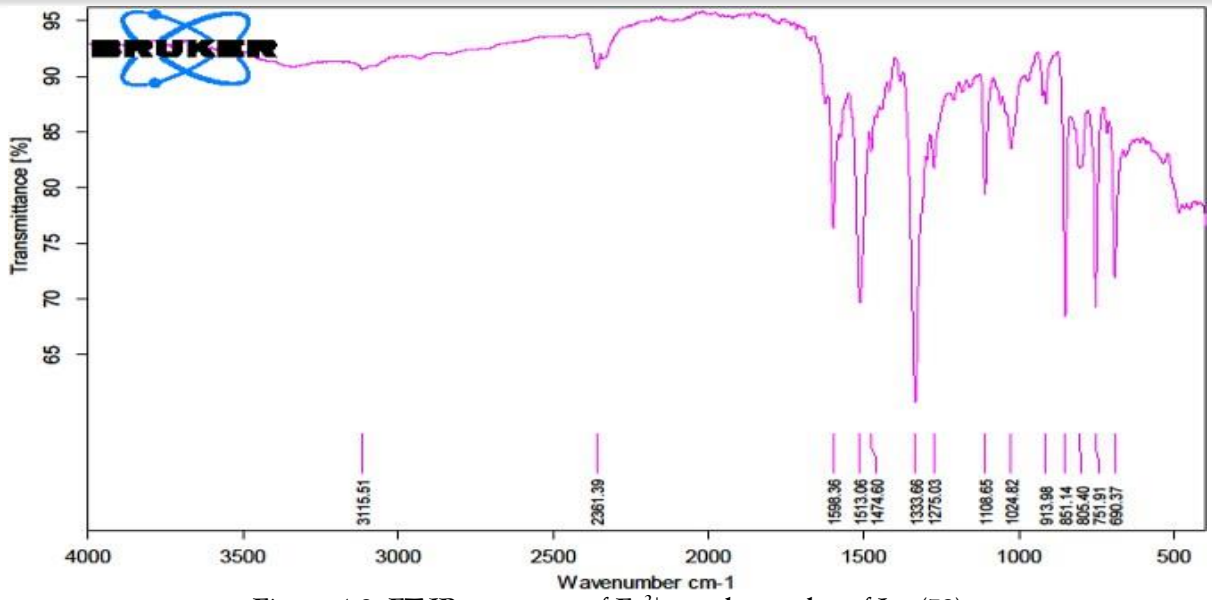
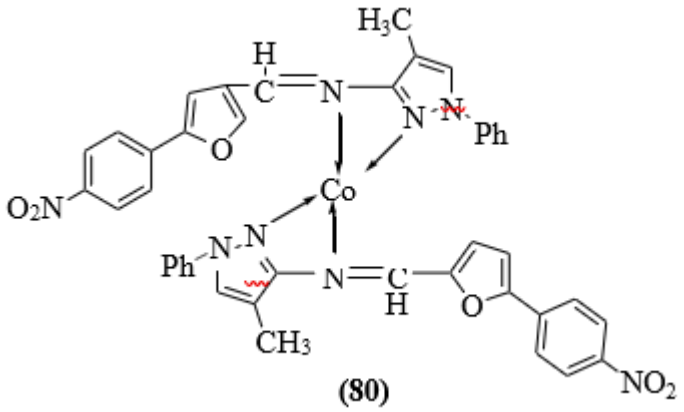


Figure 4.9: FT-IR spectrum of Fe^{2+} metal complex of L2 (79)

4.3.7. Synthesis of Co^{2+} complex of L2 (80)



(80)

Scheme 4.13: Synthesis of Co^{2+} complex of L2 (80)

Metal [Co(II)] complex of ligand L2 is prepared with the reaction of ligand with metal salt of cobalt (CoCl2) in EtOH. The melting point of compound **(80)** was 290^{0}C. The percentage yield was compound is 73%. The purity of the compound was examined by TLC. In the FT-IR spectra showed the peak at 1599 cm^{-1} which is given to (C=N). The peak of (C=N) in case of ligand is observed at 1601 $cm^{-1.}$ The shifting towards lower frequency indicate that the ligand is involved in coordination with metal, 3245.75 cm^{-1} show (OH) group, peak at 1454.62 cm^{-1} show (C=C), 2363.55 cm^{-1} show (aromatic stretching) and 495 cm^{-1} show (M-N) bond (Kiran et al., 2012). The FT-IR spectrum of **(80)** is given below.

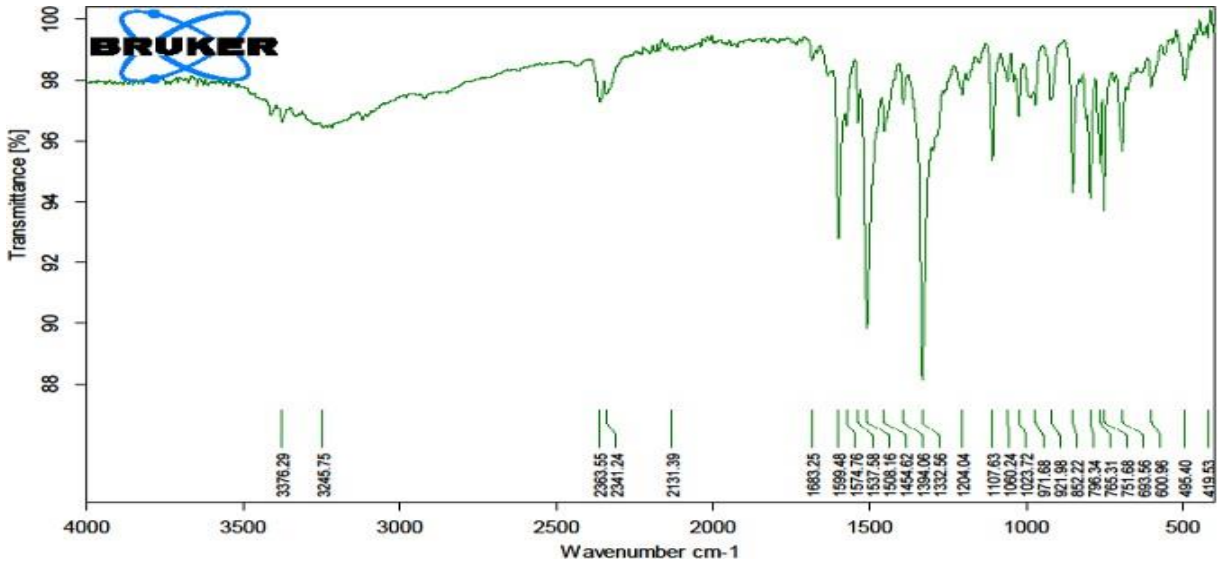


Figure 4.11: FT-IR spectrum of Co^{2+} metal complex of L2 (80)

Physical properties of arylated furfural derivatives are given in table 4.1.

Table 4.1: Physical properties of arylated furfural derivative, pyrazole schiff bases and their metal complexes (71-80)

Compound	Molecular formula	Mol. Mass (g/mol)	Colour and physical state	Solubility	Yield (%)	M.P (^{0}C)
71	C11H7NO4	217	Yellow (powder)	EtOH, MeOH, EtOAc	55	190-192
72	C15H13N3O	251	Black (powder)	EtOH, MeOH, EtOAc	67	180
73	C21H16N4O3	372	Pale yellow (powder)	EtOH, MeOH, EtOAc	77	190
74	2+ C30H26CuN6O2	566	Light brown (powder)	EtOH, MeOH, EtOAc	60	305
75	2+ C42H32CuN8O6	808	Dark red (powder)	EtOH, MeOH, EtOAc	67	300
76	$C42H32NiN8O6^{2+}$	803	Yellow (powder)	EtOH, MeOH, EtOAc	60	275

77	$C_{42}H_{32}CdN_8O_6^{2+}$	857	Light green (powder)	EtOH, MeOH, EtOAc	69	300
78	$C_{42}H_{32}NO_6Zn^{2+}$	808	Dark yellow (powder)	EtOH, MeOH, EtOAc	70	270
79	$C_{42}H_{32}FeN_8O_6^{2+}$	801	Brown (powder)	EtOH, MeOH, EtOAc	60	≥250
80	$C_{42}H_{32}CoN_8O_6^{2+}$	804	Dark yellow (powder)	EtOH, MeOH, EtOAc	73	290

Table 4.2: FT-IR spectral values for arylated furfural derivatives, pyrazole schiff bases and their metal complexes (71-80)

Compound number	FT-IR
71	2750 cm^{-1} (C-H of formyl), 1666.65 cm^{-1} (C=O), 1513.75 and 1326.30 cm^{-1}(NO_2).
72	1597 cm^{-1} (C=N), 3117.59 cm^{-1} (aromatic stretching), 2357.87 cm^{-1} (aromatic ring), 2923.70 cm^{-1} (C-H stretching), 1503.91 & 1455.60 cm^{-1} show (C=C), and 1259 cm^{-1} (C-O) and 1335 cm^{-1} (C-N).
73	1601 cm^{-1}(C=N), 3377.38 cm^{-1} (aromatic stretching), 2915.56 cm^{-1} (C-H stretching) 2357.87 cm^{-1}(Aromatic ring), 1537.84 cm^{-1} (C=C), 1508.67 cm^{-1} & 1333.84 cm^{-1} (NO_2), 1203 cm^{-1} (C-O) and 1333 cm^{-1} (C-N).
74	1541.66 cm^{-1}(C=N) and 490.67 cm^{-1} (M-N).
75	1596 cm^{-1}(C=N), and 488.96 cm^{-1} (M-N).
76	1599 cm^{-1}(C=N), 3336.11 cm^{-1} (OH) and 491 cm^{-1} (M-N).
77	1599.17 cm^{-1}(C=N), 491.42 cm^{-1} (M-N) and 544.22 cm^{-1} (M-O).
78	1598.48 cm^{-1}(C=N) and 492 cm^{-1} (M-N).
79	1598 cm^{-1}(C=N), 3115.71 cm^{-1} (OH) and 500 cm^{-1} (M-N).
80	1599 cm^{-1}(C=N), 3245.75 cm^{-1} (OH) and 495 cm^{-1} (M-N).

Anti-bacterial activity

The prepared derivatives of furan based pyrazole Schiff base derivatives along with their metal complexes were dissolved in suitable solvent and subjected to anti-bacterial activity by disk diffusion method. These derivatives were tested against bacterial strain by using gentamycin as positive control. The zone of inhibition of all the synthesized compounds were measured in millimeter (mm) against E. coli (anti-bacterial) strains. All these derivatives showed zone of inhibition 8.5-11.5 mm as compare to reference gentamycin 21mm (for antibacterial). The results of some selected pyrazole schiff base derivatives and their metal complexes showed the moderate anti-bacterial activity because these derivatives showed lower values of zone of inhibition against two strains as compare to reference gentamycin as shown in figures and table.

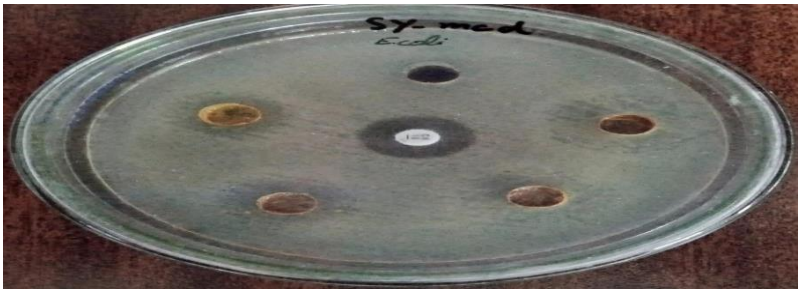


Figure : Zone of inhibitions of compounds against E.coli (Front)

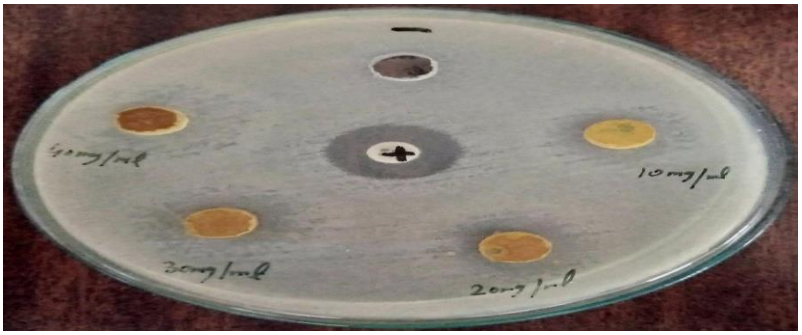


Figure : Zone of inhibitions of compounds against E. coli (Back)

Table: Antimicrobial activity of synthesized compounds

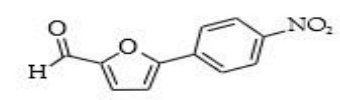
Compound number	Concentration 40mg/ml	Zone of inhibition (mm) Bacteria S. nigrum
Gentamycin	+ev	17mm
73	10mg/ml	12mm
77	20mg/ml	14.5mm

78	30mg/ml	16mm
75	40mg/ml	18.5mm

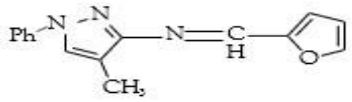
SUMMARY

Different arylated furfurals compounds were prepared by Meerwein arylation. Pyrazole schiff bases were prepared from furfural derivatives. By using pyrazole schiff different kind of metal complexes were prepared. The purity of synthesized products has been determined by TLC and characterization of prepared compounds (products) was done via melting point and FT-IR. The spectra of prepared derivatives show sharp peaks for the presence of different substituents. Some selected derivatives were assessed for antimicrobial activities, among the following series compound **(75)** showed the most highly antimicrobial activity.

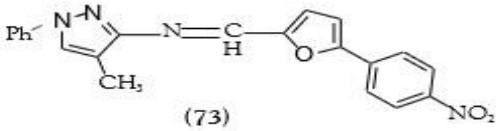
Following arylated furfural derivative, pyrazole schiff bases and their metal complexes were prepared **(71-80)**, which are given below.



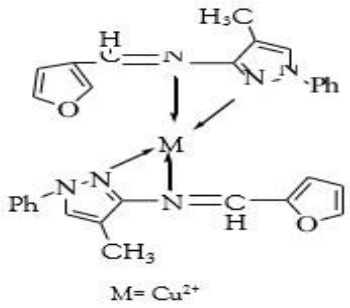
(71)



(72)

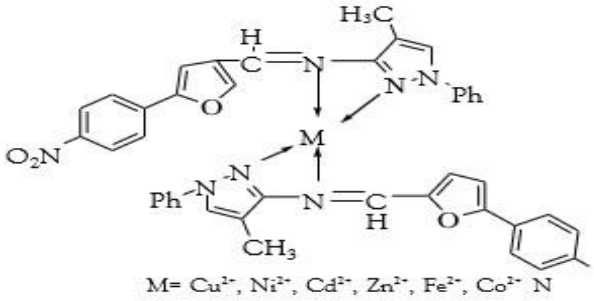


(73)



M= Cu^{2+}

(74)



M= Cu^{2+}, Ni^{2+}, Cd^{2+}, Zn^{2+}, Fe^{2+}, Co^{2+} N

(75-80)

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