CHAPTER - 2
2.0 Ethyl ammonium nitrate (EAN):

Recently, use of ionic liquids (ILs) is an increasing interest in the field of organic synthesis because of its mild reaction condition, negligible vapour pressure, solvating ability and easy recyclability [1]. Ionic liquids are used as green reaction media due to their unique chemical and physical properties such as non-volatility, non-inflammability, thermal stability, and controlled miscibility. They are playing a significant role in reactions as a solvent/catalyst. Several reactions have been recently reported, using ionic liquids as reaction media and rate enhancers [2].

Ionic liquids have been defined as salts which are liquid at or below room temperature or more broadly as salts which melt at, below, or around 100 °C. Over the past ten years, there has been an exponential growth in publications and patents relating to ionic liquids. Majority of reports investigate their use as alternative solvents for volatile organic compounds owing to their non-volatile properties. They also enhance yield of products and reaction rates. Ionic liquids do not boil at elevated temperatures, but they do have upper thermal stability limits because of their nature.

The first report of a room temperature molten salt was made by Walden in 1914, i.e. ethyl ammonium nitrate (mp 12-14 °C) formed by the reaction of ethylamine with concentrated nitric acid [3]. Ethyl ammonium nitrate (EAN) is colorless to slightly yellow colored ionic liquid having no characteristic odour. It is a protic room-temperature ionic liquid and classified into an amphoteric solvent [4].

Ethylammonium nitrate is liquid electrolyte at room temperature, involves dissociable protons and called as protic ionic liquid [5-7]. It can be used as medium electrolytes for fuel cells [8] and polymer membrane separators [9]. The properties and applications of EAN were recently reviewed in the literature [10]. Ethylammonium nitrate is miscible with water to form mixtures at any composition, and both of the component ions, favorably form hydrogen bonds with water [11].
EAN has many potential applications in protein chemistry [12] because; it has hydrophobic and ionic character and the ability of hydrogen bonding. It may be used as an additive, a detergent, a precipitating agent or to deliver ligands into protein crystals. EAN has been used to enhance the recovery of denatured-reduced hen egg white lysozyme. EAN has the ability to prevent aggregation of the denatured protein [13].

Ethyl ammonium nitrate ionic liquid (EAN) was used in various reactions such as Biginelli reaction, Condensation reaction, Nitration of phenol, Synthesis of β-amino ketone etc. Nitration of phenol using ferric nitrate and Clayfen in the ionic liquid ethyl ammonium nitrate has been reported under ultrasound irradiation [14]. Jaeger and Tucker et al. reported Diels-Alder reaction using ethyl ammonium nitrate ionic liquid [15]. Ionic liquid ethyl ammonium nitrate was prepared as per literature method. Ethyl ammonium nitrate is liquid at room temperature and is miscible with water, thus the separation and isolation of the product becomes easier. Its autoprotolysis constant is high, the large electroactivity area and conductivity allow it to use as a potential solvent. Araos, M. U. et al. [16] reported the stability of a variety of lyotropic liquid crystals formed by number of polyoxyethylene nonionic surfactants in room temperature ionic liquid ethyl ammonium nitrate. Stephane Duvivier et al. [17] had done the thermodynamics study of adsorption of dodecyltrimethyl ammonium bromide onto laponite in fused ethylammonium nitrate and its aqueous solutions.

Kanzaki, R. et al. [18] composed ethylammonium nitrate of C₂H₅NH⁺ and NO₃⁻ ions, which behave as an acid and a base respectively and reported that H₃O⁺ is a stronger acid than HNO₃ in an ethyl ammonium nitrate solution unlike water.

Zech’s, O. et al. [19] reported high temperature stable microemulsions composed of the room-temperature ionic liquid ethylammonium nitrate (EAN) as polar phase. Byrne, N. et al. [20] reported on the solubility of hen Lysozyme (HEWL) in aqueous ethylammonium nitrate as a function of water content. The structure of micelles formed by nonionic polyoxyethylene alkyl ether nonionic surfactants, in the room temperature ionic liquid, ethyl ammonium nitrate by small angle neutron scattering as a function of alkyl and ethoxy chain length, concentration and temperature were reported by Araos et al.[21]

Ethyl ammonium nitrate and ethyl ammonium formate [22] are used as mobile phase solvents for liquid chromatography. Methylammonium formate replaces methanol in reversed-phase liquid chromatography lower viscosity. Poole et al [23-24] studied tetraalkylammonium nitrate and thiocyanate ionic liquids in gas and liquid
chromatography at range from room temperature to high temperature around 150-180 °C because of significant vapor pressure. The viscosity of these ionic liquid is conveniently controlled by working at elevated temperatures or through dilution with a co-solvent. Alkylammonium salts are used as electroosmotic flow modifiers in some capillary electrophoresis [25-27].

Andrew P. Abbott et al. reported moisture-stable, Lewis-acidic ionic liquids made from metal chlorides and quaternary ammonium salts that are commercially available. These offer required physical properties e.g. melting point, viscosity and conductivity, and to tune the Lewis acidity by choosing a different metal or indeed combinations of metals [28].

Pralhad A. Ganeshpure, reported [29] use of triethylammonium sulfate, triethylammonium dihydrogen phosphate and triethylammonium tetrafluoroborate ionic liquid as a catalyst and medium for the esterification of carboxylic acids with primary alcohols. Esterification of aliphatic carboxylic acids in the presence of triethylammonium sulfate gave the corresponding esters in excellent yield.

Hu, Y. et al.[30] reported condensation of Meldrum's acid with aldehydes in ionic liquid i.e. ethyl ammonium nitrate which reused as green solvent as well as catalyst.

Madje et al. reported Biginelli reaction [31] using ethyl ammonium nitrate as an solvent as well as catalyst with high yield of product.

Triethyl ammonium acetate (TEAA) [Et3NH][CH3COO] ionic liquid has been reported for the effective synthesis of 1,5-benzodiazepine. This process benefits the use of TEAA in organic reaction medium as well as the catalyst [32].

Shafeek A. R. Mulla et al. [33] developed an efficient synthesis of bis(indolyl)methane in excellent yields using ethyl ammonium nitrate (EAN) as reusable ionic liquid at room temperature. This method involves an electrophilic
substitution reaction of indoles with several aldehydes. Ethyl ammonium nitrate acts as reaction media as well as catalyst.

Diels-Alder reaction occurs in high yield in Lewis acidic quaternary ammonium zinc- or tin-containing recyclable ionic liquids reported by Abbott et al. [34].

Pravin G. Ingole et al. [35] synthesized a series of 2,4,6-triarylpyridines and their hydroxy substituted analogues using cheap ionic liquid, Ethyl ammonium nitrate (EAN) using reaction of acetophenone and aryl aldehydes and ammonium acetate. This method has several advantages like reducing the use of volatile organic solvents, simplicity of the process with good yields.

Ionic liquids act as catalysts in biomedicine mainly for the synthesis of pharmacologically active compounds. Dake and co-workers developed a novel high-yield route for the synthesis of α-aminophosphonate derivatives [36]. The synthesis is done via one-pot room-temperature reaction of three components: aromatic aldehydes, amines and diethylphosphite. The reaction method is superior due to short reaction time, high yields, recyclability, reusability of catalyst etc.

Our group also reported synthesis of β-amino ketone using ethyl ammonium nitrate (EAN) as reusable ionic liquid at room temperature. This method has several advantages like reducing the use of volatile organic solvents, simplicity of the process, high yield and mild reaction conditions [37].
Synthesis of 2-phenyl-4H-chromen-4-ones from 1-(2-hydroxyphenyl)-3-phenyl-1,3-propane diones under microwave irradiations using [EtNH\textsubscript{3}]NO\textsubscript{3} ionic liquid has been reported [38].

Sarda et al. described an efficient and mild protocol for the synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile [39] using EAN Chalcones on condensation with malononitrile and ammonium acetate in the presence of ionic liquid ethylammonium nitrate affords the corresponding 2-amino-4,6-diphenylpyridine-3-carbonitrile in excellent yield. The ionic liquid is recycled and reused several times. The method offers several advantages such as high yields, shorter reaction time, simple work up procedure and cleaner reaction profiles.

Sarda et al. [40] developed synthesis of tetrahydroquinolin using ionic liquid ethylammonium nitrate as a catalysts.

2.1 Schiff bases:

Nowadays, heterocyclic compounds both synthetic and natural, bearing nitrogen-containing simple (pyrrole, pyrimidine, indole, quinoline and purine rings) and fused heterocyclic skeletons such as (4-anilinoquinazolines, pyrazolopyrimidines, triazolopyrimidines, pyrrolopyrimidines, pyrazolopyridazines and imidazopyrazines), have been discovered with excellent anticancer activity and many of them are presently in clinical trials [41].

Schiff bases form an important class of the most widely used organic compounds and has a wide variety of applications in many fields, e.g., biological, inorganic and analytical chemistry. Some of them are the basic units in certain dyes and also used as liquid crystals. In organic synthesis, Schiff base reactions are useful tools in making carbon-nitrogen bonds. Schiff bases appear to be important intermediates in a number of enzymatic reactions. The research field dealing with Schiff base chemistry has expanded enormously. The chemistry of Schiff bases and their fused heterocyclic
derivatives have received considerable attention owing to their synthetic and effective biological importance.

Schiff bases are the condensation products of primary amines and carbonyl compounds. They were discovered by a German chemist, Nobel Prize winner, Hugo Schiff in 1864. Structurally, Schiff base (also known as imine or azomethine) is an analogue of a ketone or aldehyde in which the carbonyl group has been replaced by an imine or azomethine group. Organic compounds containing the azomethine (–HC=N–) group in their structure is called imines [42]. Schiff base compound with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group [43].

The chemistry of carbon-nitrogen double bond plays a vital role in the progress of chemical science [44]. Schiff base ligands are essential in the field of coordination chemistry, especially in the development of complexes of Schiff bases because these compounds are potentially capable of forming stable complexes with metal ions [45]. Such type of ligands represents vast utilized classes of new series of compounds in coordination chemistry [46]. Schiff bases are organic compounds with great utility in various fields [47] such as medicine, agriculture, cosmetic products etc. Recently, Schiff base complexes have drawn attention in biochemistry and biomedicine because of their unique properties [48-49].

Several Schiff bases have been reported for their significant biological activities like antiviral, anti-inflammatory, insecticidal, antibacterial, antituberculosis, antitumor, antimicrobial, anticonvulsant activity etc. Schiff bases also exhibit antimalarial, antiproliferative, and antipyretic activities [50-51]. The Schiff bases are also used as versatile components in nucleophilic addition with organometallic reagents [52] and cycloaddition reactions [53]. Schiff bases are used as ligands in the preparation of a number of industrial and biologically active compounds via ring closure, cycloaddition, and replacement reactions [54]. The utility of Schiff bases lies in their usefulness as synthons in the synthesis of bioactive molecules such as 4-thiazolidinones, 2-azetidinones, benzoxazines, formazans, etc.
Schiff bases are widely used as organic intermediates for the production of pharmaceutical or rubber additives [55], as amino protective groups in organic synthesis [56-59]. They are also used as liquid crystals [60], in analytical [61], medical [62] and polymer chemistry [63].

A large number of different Schiff base ligands have been used as cation carriers in potentiometric sensors as they have shown excellent selectivity, sensitivity, and stability for specific metal ions [64-69]. Schiff bases have been studied for their important properties in catalysis [70]. An interesting application of Schiff bases is their use as an effective corrosion inhibitor, which is based on their ability to form a monolayer on the surface to be protected. Many commercial inhibitors include aldehydes or amines, but presumably due to the C=N bond the Schiff bases function more efficiently in many cases [71].

The research area on all sides of the imines is broadly studied due to their potential significance in different interdisciplinary fields i.e. catalysis, magnetochemistry and bioinorganic chemistry [72-77].

2.2 Review of Literature:

2.2.1 Biological Significance of Schiff bases:

Schiff bases, derived mostly from variety of heterocyclic rings, were reported to possess a broad spectrum of pharmacological activities with a wide variety of biological properties [78]. Development of new chemotherapeutic Schiff bases is now attracting the attention of medicinal chemist. They are known to exhibit a variety of potent activities. The pharmacologically useful activities include antibacterial, anticonvulsant, antiinflammatory, anticancer, anti-hypertensive, anti-fungal, antipyretic, antimicrobial, anti-HIV, cytotoxic activity, hypnotic and herbicidal activities [79]. Metal complexes of Schiff bases have been reported and these are used as chelating agent in coordination chemistry of transition metals as radiopharmaceuticals for cancer targeting and agrochemicals [80].

Schiff bases are characterized by an imine group –N=CH– which helps to clarify the mechanism of transamination and racemization reaction in biological system [81]. They are also used for treatment of diabetes and AIDS. As biological models, they help in understanding the structure of biomolecules and biological processes occurring in living organisms. They participate; they are involved in the treatment of cancer drug
resistance, and often tested as antimalariais. It could be also used for the immobilization of enzymes [82].

**Antibacterial & Antifungal properties**

The development of new antibacterial drugs having more effective mechanisms of action is most essential for medical need [83]. Schiff bases are identified as promising antibacterial agents. Schiff bases containing 2,4-dichloro-5-fluorophenyl moieties also take part in effective inhibition of bacterial growth [84]. Isatin derived Schiff bases shown anti-HIV and antibacterial activity.

Wadher et al. [85,86] reported a series of Schiff bases of 4, 4'-diaminodiphenylsulphone (1) and substituted 2-azetidinone (2), compounds shown to be more potent anti-microbial agent.

![Chemical Structures](image1)

Debnath et al. [87] observed that Schiff bases of pyran (3) and cyanopyran (4) possess more potential anti-bacterial activity. Kundariya et al. [17] presented a series of novel antimicrobial Schiff bases of 1H-pyrazole [3, 4-b] pyridine-3-amine (5).

![Chemical Structures](image2)

Yousif et al. [88] reported some tetra Schiff bases of 1,2,4,5-tetra-(5-amino-1,3,4-thiadiazole-2-yl) benzene (6) to exhibit potent antimicrobial activity. These compounds exhibit most potent anti-microbial activity against *S. aureus*.

![Chemical Structures](image3)

Literature survey [89] reveals that Schiff base of 5-chlorosalicyldehyde (7) act as anti-bacterial and anti-fungal agents. It is also observed that compounds with
aromatic rings were more active than compounds with aliphatic chains. It is also implied that heteroatoms such as oxygen and nitrogen increases activity of these compounds (8). This observation also indicated that smaller the alicyclic ring higher is the activity of the compound.

Ronad et al. [90] reported a series of 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-one derivatives of Schiff bases (9) as good anti-bacterial and anti-fungal activity as compared to the standard antibiotics ciprofloxacin and griseofulvin. N-(3-(5-bromo-2hydroxybenzylideneamino)-propyl)-2-hydroxybenzamide (10) was reported as a potential antibiotic by Cheng et al. [91].

Recently, there was a considerable increase in the incidence of systemic fungal infections, which are potentially life threatening. The Schiff bases are considered to be promising antifungal medicines. Some of imine derivatives of quinazolinones possess antifungal properties against Candida albicans, Trichophyton rubrum, T. mentagrophytes, Aspergillus niger and Microsporum gypseum. Schiff bases of furan or furylglycoxal exhibit antifungal activity.

Sulfanilamide is one of a group of chemotherapeutic agents commonly referred as Sulfa drugs discovered in the 1930's. Sulfa drugs were the first synthetic compounds found to be effective against such grave bacterial infections as meningitis, pneumonia and blood poisoning, and saved thousands of lives in World War II (1939-1945). Today, safer and more powerful antibiotics such as penicillin and tetracycline are available, but some Sulfa drugs are still being used in the treatment of meningitis and urinary tract infections.

**Anticancer properties**

Some Schiff bases showed high antitumor activity. Imine derivatives of N-hydroxy-N-aminoguanidine block ribonucleotide reductase in tumor cells, so that they are used in the treatment of leukemia [92]. Ozaslan et al. reported that Schiff bases of PDH [N-(1-phenyl-2-hydroxy-2-phenylethylidine)-2,4-dinitrophenylhydrazine], PHP
Shaker et al. [96] reported a series of anionic surfactants containing Schiff base group (13) as biocidal agents against bacteria and fungi. They also found that compound exhibit high activity in-vitro system on tumor cell lines against HEPG2 (liver), HCF7(breast) and HCT116(colon) human tumor cells.

A series of sulfapyridine-polyhydroxyalkylidine (14) has considerable cytotoxic effect against breast carcinoma cell lines MCF7 and cervix carcinoma cell line HELA in comparison with 5-flurouracil and doxorubicin as reported by Mohsen et al. [97].

Some bis-Schiff base analogs of chiral gossypol (11) were reported by Zhang et al. [94] as anti-cancer agents. These analogs were evaluated against HELA, U87 and M85 cell. The activity is depending on the presence of phenolic group and hydrophilicity of substituents. Chetan et al. [95] synthesized Schiff base compounds with piperazine (12) in linker region and hydroxamate as Zinc Binding Group (ZBG). They were screened against three cancer cell-lines against HL60, human promyelocytic leukemia cell-line.

Shaker et al. [96] reported a series of anionic surfactants containing Schiff base group (13) as biocidal agents against bacteria and fungi. They also found that compound exhibit high activity in-vitro system on tumor cell lines against HEPG2 (liver), HCF7(breast) and HCT116(colon) human tumor cells.

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Anti-proliferative property of Schiff bases (15) on HeLa and MCF-7 cell lines were reported by Hranjec et al. [98]. Nerkar et al. [99] reported in vitro anticancer evaluation against five human cancer cell-lines for anticancer cytotoxicity assay of 2-phenyl-3-(substituted-benzilidine-amino) quinazolinones (quinazolinone Schiff’s bases) and pyridine-4-carbohydrazide Schiff’s bases (16) derivatives.

[N-(1-phenyl-2-hydroxy-2-phenylethylidene)-2'-hydroxy phenyl imine] and HHP [N-(2-hydroxy benzylidine)-2-hydroxy phenyl imine] reduces the average tumor weight and decrease the growth of cancer cells in mice EAC cells. In addition, they have ability to rebuild depleted haematological parameters, such as hemoglobin, red blood cells (RBC) and white blood cells (WBC) towards the right content. They also showed protective effect on hematopoietic system [93].
Anti-glycation Activity

Khan et al. [100] synthesized bis-Schiff bases and evaluated in-vitro anti-glycation potential and compounds (17) showed excellent antiglycation activity. The para and ortho-nitro analogs were found as most active agents. Their dihydroxy analog was found as the third most active anti-glycating agent.

Antiviral properties

Salicylaldehyde Schiff bases derived from 1-amino-3-hydroxyguanidine tosylate act as new antiviral agents [101]. Isatin Schiff base ligands are marked by antiviral activity, and this fact is very useful in the treatment of HIV [102]. In addition, it was also found that these compounds have anticonvulsant activity and may be included in the anti-epileptic drugs [103]. Gossypol derivatives also possess high antiviral activity. Increasingly, gossypol, often used in medical therapy is replaced by its derivatives, because of their much lower toxicity. Kumar et al. [104] reported antiviral activity of 2-hydroxy substitution on a series of 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-one (18). Some bis-Schiff bases of isatin, benzylisatin, and 5-fluoroisatin (19) were reported by Jarrahpour et al. [105] as antiviral agents.

Anti-inflammatory activity

Schiff bases obtained from phthalimide (20) act as anticonvulsant and neurotoxicity activities which were reported by Bhat et al. [106]. They observed that nitro substitution at ortho position of the aryl ring emerged as most promising anticonvulsant agent with low neurotoxicity.
Some Schiff bases of 2-amino-5-aryl-1,3,4-thiadiazole derivatives (21) with different aromatic aldehydes were reported as analgesic, anti-inflammatory, antibacterial (*Staphylococcus aureus* and *E.coli*) and antitubercular activity (*Mycobacterium tuberculosis*) by Pandey *et al.* [107]

Sondhi *et al.* [108] reported that *N*(acridin-9-yl)-4-(benzo[*d*] imidazole/oxazol-2-yl) benzamides (22, 23) act as anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibitions activity.

Rapolu *et al.* [109] reported a series of Schiff bases 2-methyl-1-*H*-indole-3-carbohydrazide and *N*-benzylidene-2-methyl-1-*H*-indole-3-carbohydrazide (24) as anti-inflammatory agents. They conclude that one or two hydroxyl groups and one methoxy group on the phenyl ring showed excellent anti-inflammatory and analgesic activity. Anti-inflammatory activity of indazolone (25) Schiff base compound against *E. coli* were reported by Muthumani *et al.* [110].

Analgesic and ulcerogenic activities of novel Schiff base (26) were reported by Ramchandran *et al.* [111]. Zhou *et al.* [112] discovered anti-inflammatory properties of novel Schiff’s bases which can be able to treat chronic pain from inflammation. The effect of side chains of amino acid residues of these Schiff’s bases on the analgesic activity was explained with 3D QSAR. Nehad *et al.* [113] reported anti-inflammatory activity of pyrimidol [1, 6-α] azepines series (27) and found that electron withdrawing nitro group on the phenyl ring showed highest activity and lowered when there was an electron donating methoxy group.
Anti-depressant Activity

Thomas et al. [114] reported pharmacological evaluation of $N^\prime$-[(1Z)- (substituted aromatic) methylidene] pyridine-4-carbohydrazides as anti-depressants agent. Compounds $N^\prime$-[(1Z)-(2,5-dimethoxyphenyl)methylidene]pyridine-4-carbohydrazides (28) with 2,5-dimethoxy substitution on the aryl ring and para-nitro substitution on the aryl ring exhibited the highest anti-depressants activity.

\[
\begin{align*}
\text{(28)}
\end{align*}
\]

Anticonvulsant Activity

Aly et al. [115] reported some novel 3-aryl-4(3H)-quinazolinones-2-carboxaldehydes (29) and their corresponding Schiff's bases showed anticonvulsant, analgesic and cytotoxic activity due to thiosemicarbazone side chain. Literature survey [116] reveals that the anticonvulsant activity of the compounds was established by MES test, scPTZ test and 6 Hz screens and emerged as an active compound (30) with no neurotoxicity in this series.

\[
\begin{align*}
\text{(29)}
\end{align*}
\]

A series of new Schiff bases of 2-aminopyridine synthesized from 2-aminopyridine (31) with different aldehydes or ketones and cyclic ketones and their anticonvulsant activity by MES, subcutaneous scPTZ and scSTY models in mice has been reported [117]. Schiff bases showed better anticonvulsant potency against MES and scPTZ induced seizures while found moderately active against scSTY induced seizures. A series of $N^\prime$-(naphtha[1,2-d]thiazol-2-yl)semicarbazides (32) were designed.
and synthesized by following one of the main trends of current investigations i.e. search for novel antiepileptic drugs with neuroprotective properties [118].

![Chemical Structure 31](image1.png) ![Chemical Structure 32](image2.png)

Neurotoxicity of the compound was screened through rota rod and ethanol potentiation tests by Bahar et al. [119]. Chlorobenzyl substituted compounds showed potent activity same as like as the standard drug phenytoin, while the normal benzyl derivatives (33) have also showed good activity.

All the Schiff bases of phthalimides (34) were found to be active in MES test at a dose of 300 mg/kg, indicative of their ability to prevent seizure spread. It is also reported that compound having nitro substitution at ortho position of the distalaryl ring emerged as most promising anticonvulsant agent with low neurotoxicity profile [120].

![Chemical Structure 33](image3.png) ![Chemical Structure 34](image4.png)

Verma et al. [121] reported anticonvulsant activity of N-methyl-5-bromo-3-(p-chlorophenylimino) isatin (35) in MES and ScMET models with LD50 > 600 mg/kg. Introduction of chloro group and methoxy group on isatin (36) had shown potential anticonvulsant results [122].

![Chemical Structure 35](image5.png) ![Chemical Structure 36](image6.png)

Schiff bases were synthesized from 1,5-benzodiazepines with p-chloroaniline and p-chloro phenyl semicarbazide Schiff base (37) which showed good anticonvulsant activity and non-sedative nature [123]. Correlation between molecular modeling and anticonvulsant activity of the compounds (38) was reported by Bayoumi et al. [124]

![Chemical Structure 37](image7.png) ![Chemical Structure 38](image8.png)
Some novel Schiff bases of 3-[(2-((E)-[substituted] phenyl methylidene) amino) ethyl] amino] quinoxalin-2(1H)-one (39) were evaluated for anticonvulsant activity by scPTZ model and observed that compounds having 2-nitro and 3-nitro groups showed significant activity as compared with standard drug [125].

\[ \text{Antimalarial properties} \]

Human malaria is largely caused by four species of the genus *Plasmodium* (*P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*). Schiff bases are interesting compounds, which could be part of antimalarial drugs. For example, the compound with such effect is Ancistrocladidine (40), which is a secondary metabolite produced by plants of the family Ancistrocladaceae and Dioncophyllaceae, and presenting an imine group in a molecular chain. Cryptolepine, valid indolchinoline alkaloid, isolated from African plant Cryptolepis sanguinolenta, also used in the treatment of malaria, is the product of multi-stage reaction, in which Schiff base is involved [126].

\[ \text{Anti-oxidant Activity} \]

Neochoritis *et al.* [127] reported the synthesis and antioxidant property of benzimidazole Schiff bases (41) as inhibitors of lipoxygenase (LOX) and lipid peroxidation (LPO). *In vitro* antioxidant property of Schiff’s bases of benzocoumarin (42) and *in vivo* antidyslipidemic activity was reported by Sashidhara *et al.* [128]

Schiff base bond enables composites with autofluorescence, attributing to the \( n-\pi^* \) transition of C=N bonds. The autofluorescent property would be beneficial in monitoring the safety and efficacy of drug carriers *in-vivo* while avoiding the use of external fluorochromes for biological tracing. The Schiff base structure provides
extraordinary reversibility with changing pH values and the stability of these bonds decreases as the pH decreases. This feature is highly preferable for specific pH-triggered drug release. These systems carry encapsulated drugs to predetermined sites and release them in a controlled manner. Controlled drug release could minimize unwanted side effects, protect drugs from enzymatic degradation, and allow stimulus-responsive release or targeted release [129, 130].

Aldehyde groups can easily react with primary amino groups under mild conditions to form a Schiff base bond. This provides a versatile, simple and convenient method for enzyme immobilization. Immobilization of enzymes through a Schiff base bond has been demonstrated to induce higher resistance to temperature, denaturants, organic solvents and employed as bioreactor [131].

**Application in modern technologies**

Photo and thermochromic properties of Schiff bases as well as their biological activity makes them applicable in modern technology. Among others, they are used in optical computers, to measure and control the intensity of radiation, in imaging systems, as well as in molecular memory storage, as organic materials in reversible optical memories and photodetectors in biological systems [132,133]. Due to photochromic properties, Schiff compounds could behave as photostabilizers, dyes for solar collectors, solar filters. They are also exerted in optical sound recording technology [134]. Among others, worthy interest in the properties associated with Schiff rules include; properties of liquid crystal [135], chelating ability, thermal stability, optical nonlinearity [136] and the ability to create the structure of new type of molecular conductors using electrical properties to proton transfer. Because of its thermal stability Schiff bases can be used as stationery phase in gas chromatography [137]. The optical nonlinearity of these compounds allowed us to use them as electronic materials, in optical switches) and photonic components [138]. Schiff bases as an electrical conductor possess a wide range of uses, as catalysts in photoelectrochemical processes, electrode materials and micro-electronic equipment, organic batteries or electrochromic display device [139]. Due to presence of the imine group, electron cloud of the aromatic ring and electronegative nitrogen, oxygen and sulfur atoms in the Schiff bases molecules, these compounds effectively prevent corrosion of mild steel, copper, aluminium and zinc in acidic medium [140].
Application in synthesis and chemical analysis

Schiff bases are a group of organic intermediates, which are very often used in the synthesis and chemical analysis. They are exerted in the production of pharmaceutical and agrochemical industry. In reaction with hydrogen cyanide; Schiff bases may form amino acid precursors (Strecker synthesis). Moreover, chiral Schiff bases are used as initial substrates for the asymmetric synthesis of amino acids, and as catalysts in asymmetric synthesis. Furthermore, the imines obtained by the condensation reaction of arylamines and carbonyl compounds have determined a group of intermediates used in the preparation of important compounds (arenediazonium nitrates, N-arylarene carboxamides and cyanamides, β-lactams) [141] etc.

Schiff bases are precursors of polycyclic derivatives of quinoline and isoquinoline receiving by oxidative ring closure under the influence of ultraviolet light. They are also used for the preparation of acyclic and macrocyclic compounds, such as cryptondes, coronates and podates etc. These compounds lead to reaction between an amino acid and ninhydrin, formation of Ruhemarren's purple, which allows detecting and assisting in the identification of fingerprints.

Antibiotic properties are used in metal transport across membrane or to attach the antibiotics to specific site from which it can interface the growth of bacteria. One of the most prevalent types of catalytic mechanisms in biochemical process involves condensation of lysine residue, with a carbonyl substrate to form Schiff base.

Several Schiff bases have been reported for their significant biological activities like antitumor [142], anti-inflammatory agents [143], insecticidal [144], antibacterial [145], antituberculosis [146], antimicrobial [147], anticonvulsant activity [148]. The Schiff bases are also used as versatile components in nucleophilic addition with organometallic reagents [149] and in cycloaddition reactions [150].

One of the most prevalent types of catalytic mechanisms in biochemical process involves condensation of lysine residue with carbonyl group of substrate to form an imine or bis-imines. Schiff bases derived from aromatic amines and aromatic aldehydes are also a very important class of organic compounds because of their applications in many fields [151-156].
2.2.2 *Methods of Synthesis:*

Schiff bases can be synthesized from an aliphatic or aromatic amine and a carbonyl compound by nucleophilic addition forming a hemiaminal, followed by dehydration to generate an imine. In 1968 Ryoji Noyori developed a copper-Schiff base complex for the metal-carbenoid cyclopropanation of styrene, this work he was later awarded a share of the 2001 Nobel Prize in Chemistry.

The imine formation is one of the most important reactions in organic and medicinal chemistry [157]. For instance, imines are used as versatile components in the asymmetric synthesis of α-aminonitriles [158], preparation of secondary amines by hydrogenation [159], and in cycloaddition reactions [160].

Synthesis of Schiff bases involves use of anhydrous sodium sulphate, molecular sieves or titanium (IV) chloride [161] *in-situ* method for water elimination was developed, using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate involving interaction of an enzyme with an amino or a carbonyl group of the substrate.

The most common method for preparing imines is the reaction of aldehydes and ketones with amines. This reaction was first discovered by Schiff [162] and compounds are often referred to as Schiff’s bases (Scheme-1). The reaction is acid catalyzed and is generally carried out by refluxing the carbonyl compound and amine with an azeotroping agent, molecular sieves [163], TiCl₄ [164] or MgSO₄ etc.

\[
R_2CO + H_2NR_1 \rightleftharpoons \begin{array}{c} \text{OH} \\ \text{R}_2 \end{array}, \quad \text{R}_2N\text{R}_1 + H_2O
\]

(Scheme-1)

Hoesch and Houben [165,166] found that phenols or their ethers react with alkyl/ aryl cyanides catalyzed by HCl or ZnCl₂ to gives ketimines (Scheme-2).

\[
\begin{array}{c} \text{OH} \\ \text{R}_2 \end{array}, \quad \text{RCN} + \text{HCl} \rightarrow \begin{array}{c} \text{OH} \\ \text{R}_2 \end{array}, \quad \text{C} = \text{NH}\cdot\text{HCl}
\]

(Scheme-2)

The reaction of primary aromatic amines with aryl aldehydes is found to be catalyzed by lemon juice as natural acid under solvent-free conditions to give the corresponding Schiff bases (Scheme-3) reported by Suresh Patil *et al.* [167]
An alkali metal or calcium salt of primary amines react with aromatic ketones to give imines (Scheme-4) reported by Britton et al. [168].

Mistry and Desai [169] reported synthesis of Schiff bases by reaction between 2-aminothiazole with N-substituted pyrazolo-5-one under microwave-irradiation (Scheme-5).

Basim M. AL-Shimary et al. reported [170] Schiff bases (HL) derived from 5-amino-3- mercapto-1,2,4-thiadiazole (Scheme-6).

A synthetic approach for obtaining Schiff bases via condensation reactions between various amines and isatin using a 1:1 molar ratio (Scheme-7) has been described by Kriza, A. et al. [171].
Hai Jian Yang, et al. [172] developed a microwave-assisted preparation of Schiff-base via efficient condensation of salicylaldehyde and aryl amines without solvent in high yield as well as environment friendly reaction in organic synthesis (Scheme-8).

Azomethine compounds were synthesized by Argade and Gill [173] by condensation reactions of 4-formyl pyrazoles with hetero-aromatic amine as well as aliphatic amines (Scheme-9, 10).

Oxidative cyclization of thiophenolic and phenolic Schiff bases of pyrazole using PTSA in toluene as catalyst starting from 4-formyl pyrazole (Scheme-11) has been reported by Praveen et al. [174]

N-Sulfonyl aldimines are powerful synthetic intermediates in organic synthesis and industrial application. They are prepared [175] expeditiously under solvent-free conditions (Scheme-12) by reaction between different aromatic aldehydes and sulfonamides in the presence of AlCl₃.
Santosh Kumar, *et al.* [176] synthesized better antimicrobial compounds using different substituted aromatic aldehydes for the synthesis of sulfonamide Schiff’s bases in presences of alcohol and acidic reagent (Scheme-13).

\[
\text{CHO} + \text{HZN}_2 \text{SO}_2 \text{NH}_2 \xrightarrow{\text{C}_2\text{H}_6\text{OH}, \text{Reflux} \ 5 \text{hrs}} \text{Ar}-\text{C}=\text{N}\text{SO}_2\text{NH}_2
\]

(Scheme-13)

A simple and efficient method has been developed for the synthesis of some novel Schiff bases via the reaction of aromatic aldehydes with 2-aminobenzimidazole by using catalytic amount of $\text{M(NO}_3)_2 \cdot \text{xH}_2\text{O}$ in an organic solvent at room temperature. Some advantages of this protocol are good yields, use of available catalysts, simple workup procedure, and short reaction time (Scheme-14) which was reported by Akbar Mobinikhaledi, *et al.* [177].

\[
\text{NH}_2^+ \xrightarrow{\text{Ni(NO}_3)_2 \ 20-30 \text{min, r.t.}} \text{N} = \text{N} \text{Ar}
\]

(Scheme-14)

Magnesium perchlorate has been found to be an efficient catalyst for the synthesis of imines and phenylhydrazones by the reaction of carbonyl compounds with amines and phenylhydrazine [178].

$\text{N-[(E)-phenylmethylidene]-benzenesulfonamide derivatives}$ were synthesized using solid $\text{SiO}_2-\text{H}_3\text{PO}_4$ catalyst under solvent free conditions under microwave irradiation (Scheme-15) as reported by Sekar *et al.* [179].

\[
\text{H} + \text{H}_2\text{N}^+ \xrightarrow{\text{SiO}_2-\text{H}_3\text{PO}_4 \ \text{MW, 650 W}} \text{H}_2\text{N}^+ \text{SO}_2\text{Ph}
\]

(Scheme-15)

Nano-ordered MCM-41 anchored sulfonic acid (MCM-41-SO$_3$H) was used as an efficient heterogeneous catalyst for the synthesis of Schiff bases by the reaction of different aryl/alkyl aldehydes or ketones with primary amines at room temperature [180] (Scheme-16).

\[
\text{R}_1^+\text{R}_2 + \text{R}_3\text{NH}_2 \xrightarrow{\text{MCM-41. SO}_3\text{H} \ \RT, \text{H}_2\text{O}} \text{N}^+\text{R}_3
\]

(Scheme-16)

Zhaoqi Yang, *et al.* [181] reported the synthesis of $(E)$-4-methyl-$\text{N-(3,4,5}$-trimethoxybenzylidene) benzenamine in different ways, as a result, microwave irradiation is the simple way to synthesize this Schiff base (Scheme-17).
The synthesis of Schiff bases of 1-amino-2-aryl-3-oxo-1,2,4-triazoles was reported under Mg(ClO₄)₂ as catalyst followed by the reaction with chloroacetyl chloride in solvent-free conditions (Scheme-18) to yield the azetidinones with excellent yields [182].

The synthesis of macro-cyclic Schiff base ligand resulted from the condensation of bisaldehyde and ethylenediamine was prepared and its complexes were synthesized by Mostafa M. H. Khalil et al. [183] (Scheme-19).

Alireza et al. [184] described silica-supported P₂O₅ catalytic system for the synthesis of N-sulfonyl imines via condensation of sulfonamides with several aldehydes under solvent-free conditions at 110 °C (Scheme-20).

A new Schiff base 2-[2-(E)-(2-hydroxyphenyl)ethylidene]aminoethyl) ethanimidoyl)phen was synthesized via the reaction of 2-hydroxyacetophenone with ethylene-diamine by Hamil, A. M. et al. [185] (Scheme-21).

The Schiff base was prepared by Chavan V. L. et al. [186] via the refluxation-precipitation method in 1:2 proportions of o-phenylene diamine and 2-Hydroxy-1-Naphthaldehyde (Scheme-22).
Schiff bases were readily and conveniently accessible in high yields by mixing the reagents either as aqueous slurry, or by grinding at room temperature. This method, unlike a classical method, needs neither harsh conditions nor organic solvents developed (Scheme-23) by Zarei, M. et al. [187].

3-Substituted-4-amino-5-mercapto-1,2,4-triazole was obtained in an excellent yield in a single step by the condensation of a well known drug norfloxacin having free carboxyl group with thiocarbohydrazide [188] (Scheme-24).

The coordination complexes of Co(II), Ni(II) and Cu(II) derived from 2-thiophene carboxylidene-3-chloro-4-fluoroaniline (TCC) and 2-thiophene carboxylidene-4-fluoroaniline (TCF) have been synthesized by conventional as well as microwave methods [189] (Scheme-25).

Microwave promoted synthesis of pharmacologically active Schiff bases of indolo [2, 3-b] quinoxaline was described by Nandini R. Pai et al. [190]. Microwave assisted synthesis not only reduced the reaction time drastically but also gave excellent yield of Schiff bases of indolo [2, 3-b] quinoxaline derivatives (Scheme-26).
Praffullkumar A. Kulkarni, et al. [191] synthesized lanthanides (III) complexes of Schiff bases. Schiff bases were obtained by the condensation of 2-amino-4,6-dimethyl benzothiazole with 2,5-dihydroxy acetophenone, pyridine 2-aldehyde etc (Scheme-27).

Bidentate Schiff base ligands, 4-hydroxy-3-(1-(arylimino)ethyl)chromen-2-ones were synthesized by condensation of primary aromatic amines with 3-acetyl-4-hydroxycromen-2-one by Girgaonkar M.V. et al. [192] (Scheme-28).
2.3 **Present Work:**

Schiff bases have a great contribution in the development of pharmaceutical chemistry. This fact is supported by a large number of publications in this field. Nowadays, the research field dealing with Schiff base coordination chemistry has expanded enormously. The chemistry of Schiff bases and their fused heterocyclic derivatives have received considerable attention owing to their synthetic and effective biological importance. Schiff bases are an important class of organic compounds, which occupy a central place in biogenesis. They display many biological activities such as antiviral, anti-inflammatory, antimicrobial, antimitotic, antitumor, analgesic, antipyretic etc. They also act as potential anti-ulcer, antifungal, anti-cancer and antimalarial agents.

In addition, these compounds are of high interest due to their use as starting materials in the synthesis of various heterocyclic compounds like, 4-thiazolidinones, 2-azetidinones, α-aminophosphonates etc. The synthetic and medicinal importance of Schiff bases and their derivatives promoted us to synthesize Schiff base and their derivatives.

Removing organic solvents in chemical synthesis is an important drive towards benign chemical technologies. The chemistry of chalcones is still a blossoming field, has generated intensive scientific interest due to their biological and industrial applications. In present investigation, Schiff bases were synthesized by the condensation of substituted aromatic aldehydes with amino moiety drugs in presence of ethyl ammonium nitrate ionic liquid and the mixture was stirred for appropriate time periods at 100 °C (Scheme-I).

The synthesized Schiff bases were further confirmed by TLC, melting point and spectral data analysis IR, \(^1^H\) NMR and Mass spectra etc.

\[
\begin{align*}
\text{R}_1\text{-NH}_2 & + \text{C} = \text{O} \quad \text{[EtNH]NO}_3 \\
\text{[Scheme-I]} \\
\text{Amino moiety compound} & \quad \text{aromatic aldehydes} \\
\text{Schiff base} \\
\end{align*}
\]

The reaction proceeds cleanly and no undesirable side products were observed. Different halogenated aromatic aldehyde and amino moiety drugs were used for the synthesis of new Schiff bases. The structures of synthesized Schiff base were assigned on the basis of M.P. and spectral data (IR, \(^1^H\) NMR & MS).
2.4 Experimental:

A) Preparation of ethyl ammonium nitrate:

The ionic liquid was synthesis by reported methods as follows [39]. In a cooled aqueous solution of ethylamine (70%, 100 ml), nitric acid (30%, 330 ml) was added drop-wise with vigorous stirring, maintaining the temperature below 10 °C. As soon as the pH of the mixture attained the value of 7.3, the addition was stopped and the mixture was stirred further for 0.5 hr. Water was removed first by rotary evaporator, the traces of water was removed at 100 °C, affording the colorless or faint yellow IL ethyl ammonium nitrate.

B) Synthesis of Schiff base

Equimolar quantities of substituted aromatic aldehyde (1 mmol) and amino moiety drugs (1 mmol) were dissolved in ethyl ammonium nitrate ionic liquid (2 ml) and the mixture was stirred at 100 °C temperatures for appropriate time. The progress of the reaction was monitored by TLC. After completion of reaction, the content of the flask was poured over crushed ice. The solid obtained was filtered, washed with cold water, dried and recrystallized from ethanol (Table-2.1). The purity of synthesized Schiff base was checked by TLC. The spots were visualized after exposed in iodine chamber or ultra violet light.

The aqueous layer was distilled at 80 °C under vacuum to remove water, leaving behind the ionic liquid (about 90%), which was recycled for several times. The crude was purified by column chromatography using hexane-ethyl acetate (8:2) as eluent and characterized by comparison of IR, \(^1\)H NMR and melting point.
Scheme-I: Synthesis of Schiff Base

\[
\begin{align*}
R_1-\text{NH}_2 + \text{R}_2\text{H} & \xrightarrow{[\text{EtNH}_3]\text{NO}_3} \text{R}_1\text{R}_2\text{N} \\
100 °C & \\
2-3 \text{ hr} & \\
\end{align*}
\]

Amino moiety compound + aromatic aldehydes \rightarrow Schiff base

[Scheme-I]

<table>
<thead>
<tr>
<th>Aromatic aldehydes ( R_2 )</th>
<th>Amino moiety compound ( R_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>D</td>
<td>4</td>
</tr>
</tbody>
</table>

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2.5 Result and Discussion:

In Scheme-I ethyl ammonium nitrate ionic liquid \([\text{EtNH}_3\text{NO}_3]\) was used for conversion of aromatic aldehyde and amino moiety drugs to corresponding Schiff Base. The reaction proceeds cleanly without formation of any side product except water. The protocol of process offers advantages in terms of simple procedure and work up, mild reaction conditions and excellent yields. The ionic liquid used for reaction was recovered and reused with identical results (Table-2.2).

Ionic liquid ethyl ammonium nitrate was prepared as per literature method. The ethyl ammonium nitrate was found to be a more suitable solvent and catalyst for these reactions. In presence of EAN the reactions proceed in a shorter time, under milder condition with excellent yield of products. Ethyl ammonium nitrate is liquid at room temperature and is miscible with water, thus the separation and isolation of the product becomes easier. Its autoprotolysis constant is high, the large electroactivity area and conductivity allow it to use as a potential solvent.

In a typical reaction, a mixture of aromatic aldehyde and amino moiety drugs in EAN was stirred at 100 °C temperatures for appropriate time. After completion of reaction as monitored by TLC, the usual work-up affords pure Schiff base in excellent yield (Table-2.1). The reaction proceeds cleanly at 100 °C temperatures. However, at room temperature the reaction required more time (12-15 hr) with very poor yield and at higher temperature the yield of the product decreases. Ionic liquid is water-soluble, thus goes to the aqueous layer, which was distilled at 80 °C under vacuum to remove water, living behind the ionic liquid. The recovered EAN was recycled and reused several times to carry out the same experiment (Table-2.2).

No undesirable byproduct formation takes place. Most of the reactions were completed within 2-3 hours affording the product in 80-90% yield. However at room temperature the reaction time increases with a decrease in the yield of product. The reported methods by using different catalyst required much longer reaction time and harsh reaction conditions (Table-2.3).

EAN was found to be a more suitable solvent and catalyst for these reactions. In presence of EAN the reactions proceed in a shorter time, under milder condition and with excellent yield of products. This method has been implemented for the synthesis of Schiff base due to easy work up and isolation and eco-friendly reaction condition.
### Table 2.1: Synthesis of Schiff Base

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino moiety drugs</th>
<th>Schiff Base</th>
<th>Time (hr)</th>
<th>M. P. (°C)*</th>
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</thead>
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## Synthesis of Schiff Base

### Chapter-2

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<th>Time (hr)</th>
<th>M. P. (°C)*</th>
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### Table-2.2: Recycling of the ionic liquids

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<tr>
<th>Entry</th>
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<th>Recycle-3</th>
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<td>S-2</td>
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### Table-2.3: Effect of solvent and catalyst at different temperature.

<table>
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<tr>
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<th>Solvent</th>
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<th>Reaction Time</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>CH₃COOH</td>
<td>C₂H₅OH</td>
<td>RT</td>
<td>20 hr.</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>CH₃COOH</td>
<td>C₂H₅OH</td>
<td>reflux</td>
<td>7 hr.</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>FeCl₃</td>
<td>C₂H₅OH</td>
<td>reflux</td>
<td>9 hr.</td>
<td>70</td>
</tr>
<tr>
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<td>EAN</td>
<td>-</td>
<td>RT</td>
<td>10 hr.</td>
<td>30</td>
</tr>
<tr>
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<td>-</td>
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<td>5 hr</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>EAN</td>
<td>-</td>
<td>100 °C</td>
<td>3 hr</td>
<td>75</td>
</tr>
</tbody>
</table>
2.6 Spectral analysis:

Infrared Spectra:

The infrared spectra of Schiff bases were obtained over a spectral range of 4000-400 cm\(^{-1}\). In the infrared spectra of the Schiff base are found the absence of absorption bands associated with the –CHO aldehydic group and –NH\(_2\) amino groups indicating the absence of –CHO, 1740-1720 and –NH\(_2\), 3500-3100 cm\(^{-1}\) stretching respectively, which confirmed the formation of product. These results are in agreement with those observed by several research groups. The IR spectra of synthesized compounds showed the presence of C=N stretching new bands at 1626-1600 cm\(^{-1}\). The band at 3395 cm\(^{-1}\) is stretch absorption spectrum of O-H bond of phenol. The others at 1599 cm\(^{-1}\) and 1580 cm\(^{-1}\) are stretch absorption spectrum of C=C bonds of aromatic skeleton.

\(^1\)H NMR spectra:

The \(^1\)H NMR spectra of Schiff base showed the characteristics sharp singlet peak near 8.1 to 8.9 ppm which was assigned for –CH=N- proton in all compound. The chemical shift of proton of phenolic hydroxyl group is 4.5~8.0 in many literature examples. But, the proton shifts of phenolic hydroxyl group of Schiff base (III) and (IV) are 13.10 and 13.11 respectively. The obvious downshift was caused by forming of hydrogen bond. Multiplet at 7.1 to 8.1 is due to aromatic protons. The appearance of broad singlet at 6.93 is due to OH (exchangeable with D\(_2\)O) further confirmed the formation of the product, which are in good agreement with earlier observations.

**Compound [S-5]:**

| IR \(v_{\text{max}}\) cm\(^{-1}\) | 740, 839, 1003, 1514, 1635, 2805, 3056, 3334 |
| \(^1\)H NMR (DMSO) | \(\delta\) 2.8 (t, 2H, -CH\(_2\)) |
| 200 MHz | \(\delta\) 3.5-3.75 (t, 2H, -CH\(_2\)-N), |
| | \(\delta\) 8.26 (s, 1H, -N=CH), |
| | \(\delta\) 6.70-7.26 (m, 8H, Ar-H), |
| | \(\delta\) 9.1 & 13.4 (s, broad, Ar-OH), |
| GC MS; ES\(^+\) | 242 (M\(^+\), 100%) |
| m/z | (% Relative intensities) |
**Compound [S-8]:**

<table>
<thead>
<tr>
<th><strong>IR ν max cm⁻¹</strong></th>
<th>732, 1153, 1256, 1299, 1428, 1509, 1595, 1665, 2963, 3268, 3434</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>¹H NMR (DMSO)</strong></td>
<td>δ 1.2-1.3 (t, 3H, -CH₃)</td>
</tr>
<tr>
<td><strong>200 MHz</strong></td>
<td>δ 2.8 (q, 2H, -CH₂)</td>
</tr>
<tr>
<td></td>
<td>δ 3.8 (s, 1H, -OCH₃ ),</td>
</tr>
<tr>
<td></td>
<td>δ 6.90-7.62 (m, 5H, Ar-H),</td>
</tr>
<tr>
<td></td>
<td>δ 8.52 (s, 1H, -N=CH ),</td>
</tr>
<tr>
<td></td>
<td>δ 9.7 (d, 1H, Ar-H),</td>
</tr>
<tr>
<td></td>
<td>δ 10.05 (broad, 1H, Ar-OH),</td>
</tr>
<tr>
<td><strong>GC MS ; ES⁺</strong></td>
<td>m/z 301 (M⁺, 100%)</td>
</tr>
<tr>
<td><strong>Mol. Wt.</strong></td>
<td>300.38</td>
</tr>
</tbody>
</table>

(% Relative intensities)
1H NMR (DMSO)
2.8 (t, -CH2)
3.5-3.75 (t, -Cl2-N)
8.26 (N=CH)
6.70-7.26 (m, Ar-H)
9.1 & 13.4 (brod, Ar-CH)
1H NMR (DMSO)
1.2-1.3 (t, -CH3)
2.8 (q, -CH2)
3.8 (s, -OCH3)
6.90-7.62 (m, Ar-H)
8.52 (-N=CH)
9.7 (d, Ar-H)
10.05 (broad, Ar-OH)
2.7 References:


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