Review on Synthesis of Schiff base

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By

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I would like to acknowledge my other labmates for their moral support and motivation, which drives me to give my best.

My special thanks to ***all faculty members*** *ofDepartment of Chemistry, UkaTarsadia University for being another role model for me.*

I never forget to thanks my friends, ***Dhvanil Patel*** *their support and help. I thank the Almighty for giving me the strength and patience to work through all these years so that today I can stand proud with my head held high.*

Finally, I would like to acknowledge the people who mean world to me, ***my parents****. I don't imagine a life without their love and blessings. Thank you mom, dad for showing faith in me and giving me liberty to choose what I desired. I consider myself the luckiest in the world to have such a supportive family, standing behind me with their love and support.*

Patel Heris.s

UKA TARSADIA UNIVERSITY
DEPARTMENT OF CHEMISTRY
MALIBA CAMPUS

CERTIFICATE

This is to certify that the project entitled ***"Review on Synthesis of Schiff Base "*** *was carried out by Mr .Heris S. Patel (EnrollmenSt no: 201904100810030) at* ***Department of Chemistry*** *for the partial fulfillment of M.Sc. (Organic Chemistry) degree to be awarded by UKA TARSADIA UNIVERSITY. This work has been carried out under our supervision and is to satisfaction.*

Date:

Place:

Signature and name of Guide: **Signature and name of Co-Guide:**

Signature and name of Director: **Signature of Examiner**

Index

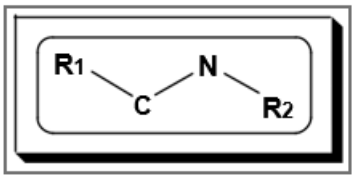
1. Introduction to Schiff bases :

Nowadays, the research field dealing with Schiff base coordination chemistry has expanded enormously. The importance of Schiff base complexes for bioinorganic chemistry, biomedical applications, supramolecular chemistry, catalysis and material science, separation and encapsulation processes, and formation of compounds with unusual properties and structures has been well recognized and reviewed. They also serve as a back bone for the synthesis of various heterocyclic compounds. Schiff bases have been utilized as synthons in the preparation of a number of industrial and biologically active compounds like formazans, 4-thiazolidinines, benzoxazines, and so forth, via ring closure, cycloaddition, and replacement reactions.

Schiff base are organic compounds possessing azomethine group which resulted from condensation of amine with aldehyde or ketone. Schiff base derived from aromatic amine and aromatic aldehydes have a wide variety of application such as biological activity, catalytic activity and also used as ligands to obtain metal complexes because of their excellent abilities of this type of Schiff base are widely used as anticorrosion for different metals in different media.

The synthesis and characterization of transition metal complexes of schiff bases containing nitrogen and oxygen donors atoms has increased manifold in the recent past [1,2]. The Schiff base ligands are considered to be good chelating agents [3], Schiff bases are a special class of ligands with a variety of donor atoms exhibiting interesting coordination modes towards transition metals [4], and azomethine linkage is responsible for the biological activities [5]. The Schiff bases derived from various amines have been widely investigated [6] and find applications in biomimetic catalytic reactions, materials chemistry and industry [7]. Schiffbase complexes have also gained attention as stereo chemical models in transition metal coordination chemistry due to their structural variety [8].

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 [9]. A 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 [10].



The chemistry of carbon-nitrogen double bond plays a vital role in the progresses of chemistry science [11]. 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 [12]. Such type of ligands represents vast utilized classes of new series of compounds in coordination chemistry [13]. Schiff bases are organic compounds with great utility in various fields [14] such as medicine, agriculture, cosmetic products etc. Recently, Schiff base complexes have drawn attention in biochemistry and biomedicine because of their unique properties [15-16].

Several Schiff bases have been reported for their significant biological activities like antitumor, antiviral, anti-inflammatory agents, insecticidal, antibacterial, antituberculosis, antimicrobial, anticonvulsant activity etc. Schiff bases also exhibit antimalarial, antiproliferative, and antipyretic activities [17-18]. The Schiff bases are also used as versatile components in nucleophilic addition with organometallic reagents [19] and cycloaddition reactions [20]. 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 [21]. 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 [22], as amino protective groups in organic synthesis [23-26]. They are also used as liquid crystals [27], in analytical [28], medical [29] and polymer chemistry [30].

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 [31-36]. Schiff bases have been studied for their important properties in catalysis [37]. 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 [38].

The research area on all sides of the imines is broadly studied due to their potential significance in different interdisciplinary fields i.e. catalysis, magneto chemistry and bioinorganic chemistry [39-44].

2.Review of Literature :

2.1 Biological Significance of Schiff bases :

A considerable number of Schiff-base has potential biological interest, not only have they played a seminal role in the development of modern chemistry, but also they can also be found at key points in the development of inorganic biochemistry, catalysis, optical materials and other field [45]. Anti bacterial activities of substituted Schiff bases like nitro & phenyl derivatives possess more active but activity was lesser than the standard drug. Nitro and halo derivatives of Schiff bases are reported to have antimicrobial and antitumor activities. Schiff bases of gossypol show high antiviral activity [46]. Several Schiff bases possess anti-inflammatory, allergic inhibitors reducing activity radical scavenging, analgesic and anti-oxidative action.

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 [47]. 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 [48]. 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 [49].

Schiff bases are characterized by an imine group –N=CH- , which helps to clarify the mechanism of transamination and racemization reaction in biological system [50]. They are also used in the treatment for 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 antimalarials. It could be also used for the immobilization of enzymes [51].

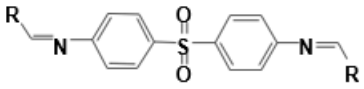
Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base. Schiff bases have been utilized as synthons in the preparation of a number of industrial and biologically active compounds via ring closure, cycloaddition, and replacement reactions

2.2 Antibacterial & Antifungal properties :

Schiff bases shown effective activity against the infectious bacteria, Schiff bases synthesized from 2-hydroxy-1-naphthaldehyde and α-amino acids (L-tyrosine, L-arginine, and L-lysine) and their manganese complexes have been reported to show excellent activity against the Gram positive and Gram negative strains of bacteria[52]Schiff bases derived from salicylaldehyde show potent antibacterial activities, like N-(salicylidene)-2-hydroxyaniline reported as antituberculosis, while Schiff bases of 5-chlorosalicylaldehyde show enhanced antibacterial activity against Escherichia coli (E. coli), Staphylococcus aureus (S. aureus), and Micrococcus luteus (M. luteus)[53]

The development of new antibacterial drugs having more effective mechanisms of action is most essential for medical need [54]. 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 [55]. Isatin derived Schiff bases shown anti-HIV and antibacterial activity

Wadher et al. [56,57] 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.



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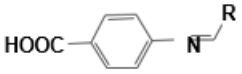
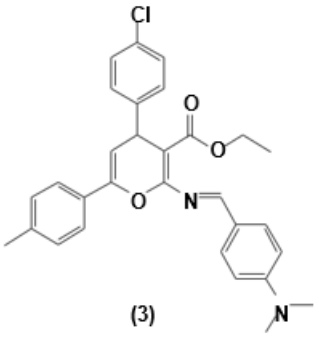


(2)

Debnath et al. observed that Schiff bases of pyran (3) and cyanopyran (4) possess more potential anti-bacterial activity. Kundariya et al. [58] presented a series of novel antimicrobial Schiff bases of 1H-pyrazole [3, 4-b] pyridine-3-amine (5).



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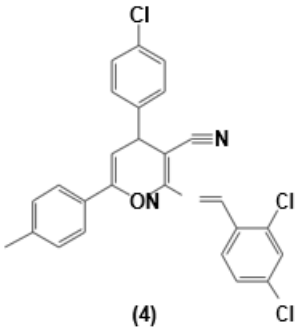

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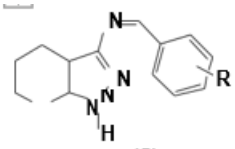
Schiff bases derived from the condensation of 5-chloro-salicylaldehyde and primary amine has recently been reported [59]. The 5-chloro-salicylaldehyde-Shiff base derivatives (6)were most active against bacterial species.



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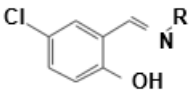
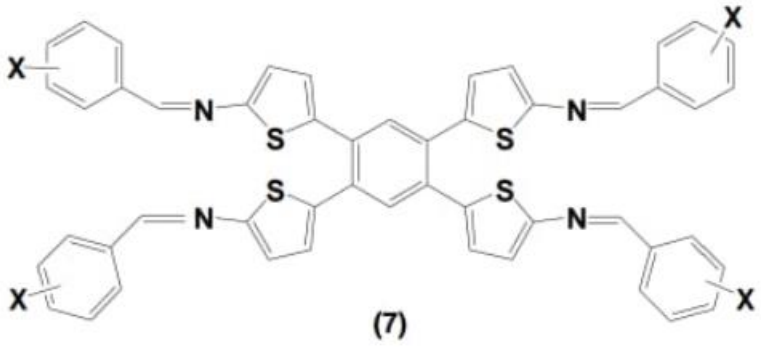


(6)

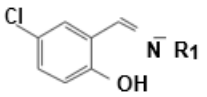
Yousif et al. [60] reported some tetra Schiff bases of 1,2,4,5-tetra-(5-amino-1,3,4-thiadiazole-2-yl) benzene (7) to exhibit potent antimicrobial activity. These compounds exhibit the most potent anti-microbial activity against S. aureus.



(7)

Literature survey [61] reveals that Schiff base of 5-chlorosalicyldehyde (8) 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 increase activity of the compounds (9). This observation also indicated that smaller the alicyclic ring higher is the activity of the compounds.



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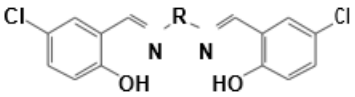
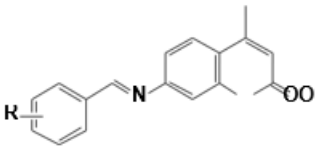


(9)

Ronad et al. [62] reported a series of 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-one derivatives of Schiff bases (10) as good anti-bacterial and anti-fungal agent as compared to the standard antibiotics ciprofloxacin and griseofulvin. N-(3-(5-bromo-2hydroxybenzylideneamino)propyl)-2-hydroxybenzamide (11) was reported as a potential antibiotic by Cheng et al. [63].



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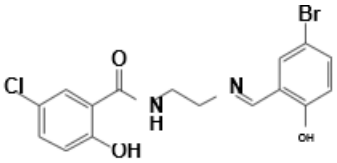
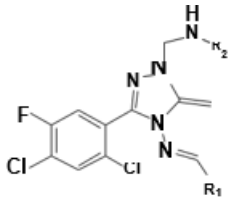


(11)

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.

Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety (12) inhibit the growth of fungi of clinical interest, such as Aspergillus fumigatus, Aspergillus flavus, trichophyton mentagrophytes, and penicillium marneffei. piperonyl-derived schiff bases (13) were active against some fungi. They inhibited the growth of Trichophyton rubrum and Epidermophyton floccosum [64].



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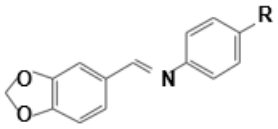
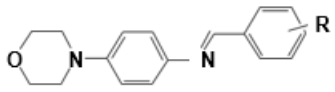


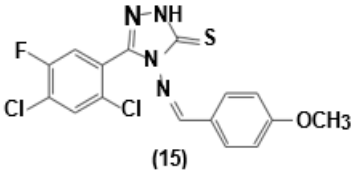
(13)

Sulfanilamide is one of a group of chemotherapeutic agents commonly referred to 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.. 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. Panneerselvam et al. [65] described the in vitro antibacterial activity of morpholine-derived Schiff bases (14) against S. aureus and Micrococcus luteus.



(14)

Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety (15, 16) are completely inhibited the growth of S. aureus, E. coli, Pseudomonas aeruginosa and klebsiella pneumoniae [66]



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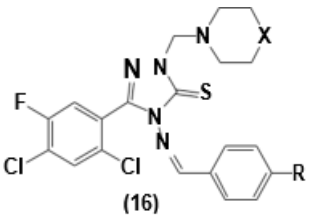


(16)

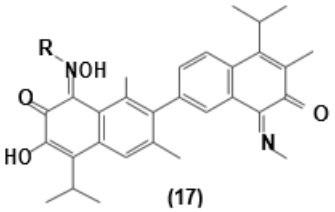
N-(salicylidene)-2-hydroxyaniline and from 3-fluorosalicylaldehyde Schiff bases were reported as antifungal agent. The transition metal complexes of Schiff bases derived from N,Nethylene (bis 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazine-1-yl)-quinoline-3-carboxylic acid reported to show higher antifungal activity than their parent Schiff bases [67]. Chitosan Schiff bases have been reported to stop the growth of many fungal strains including Colletotric humlagenarium and Botrytis cinerea [68]. Isatin Schiff base derivatives also show anti-fungal activity against Cryptococcus neoformans (C. neoformans), Epidermophyton floccosum (E.floccosum) and Candida albicans (C. albicans) [69].

2.3 Anticancer properties :

Schiff bases and these metal complexes were reported as anticancer activities; Cu complexes with vaniline Schiff bases [70] and 5-dimethyl-2-phenyl-4-[(pyridin-2-ylmethylene)-amino]-1,2-dihydro-pyrazol-3-one Schiff bases [71] shown good anti-cancerous activities

Schiff bases shown high antitumor activity. Imines derivatives of N-hydroxy-N'-aminoguanidine block ribonucleotide reductase in tumor cells, so that they are used in the treatment of leukemia [72]. Ozaslan et al. reported that Schiff bases of PDH [N-(1-phenyl-2-hydroxy-2-phenyl ethylidine)-2,4-dinitrophenylhydrazine], PHP [N-(1-phenyl-2-hydroxy-2-phenyl ethylidine)-2′-hydroxy phenyl imine] and HHP [N-(2-hydroxy benzylidine)-2-hydroxy phenyl imine] reduce 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 show protective effect on hematopoietic system [73].

Some bis-Schiff base analogs of chiral gossypol (17) were reported by Zhang et al. [74] as anti-cancer agents. These analogs were evaluated against HELA, U87 and M85 cell. It was found that activity depends on presence of phenolic group and bulk and hydrophilicity of substituents. Chetan et al. [75] synthesized Schiff base compounds with piperazine (18) 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.



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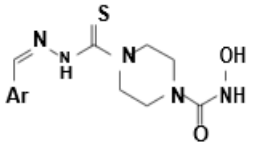
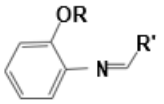


(18)

Shaker et al. [76] reported a series of anionic surfactants containing Schiff base group (19) as biocidal agents against bacteria and fungi. They also found that compound exhibit high activity in vitro system on the tumor cell lines against HEPG2 (liver), HCF7(breast) and HCT116(colon) human tumor cells.

A series of sulfapyridine-polyhydroxyalkylidine (20) 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. [77].



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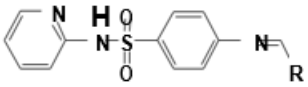
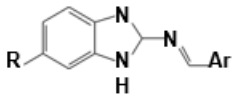


(20)

Anti-proliferative property of Schiff bases (21) on HeLa and MCF-7 cell lines were reported by Hranjec et al. [78]. Nerkar et al. [79] 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 (22) derivatives.



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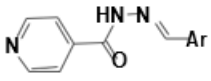

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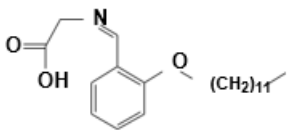
Shaker *et al*.[80] reported antitumor activity against HEPG2, HCF7 and HCT116 human tumor cells. The compound **(23, 24)** showed high activity in vitro system on the tumor cell and the highest cytotoxic effect.



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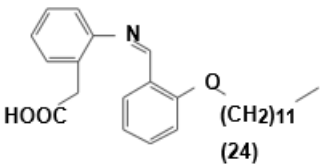
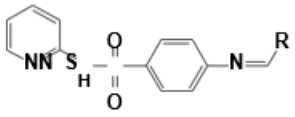


(24)

Mohsen et al. [81] described cytotoxic effect of sulfapyridine-polyhydroxyalkylidine (or arylidene) Schiff's bases) (25), against breast carcinoma cell lines MCF7 and cervix carcinoma cell line HELA. Hranjec et al. [82] reported benzimidazole Schiff bases (26, 27) as anti-proliferative agents.



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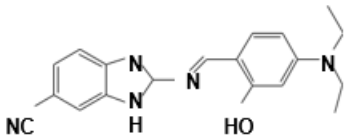

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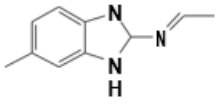
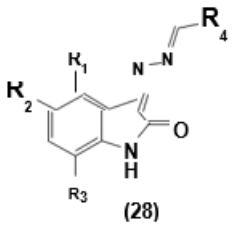


(27)

2.4 Anti-glycation Activity :

Khan et al. [83] synthesized bis-Schiff bases and evaluated the in vitro anti-glycation potential and compounds (28) showed excellent antiglycation activity. The para- and ortho-nitro analogs were found as most active agents. They were also reported as the dihydroxy analog was found as the third most active anti-glycating agent.



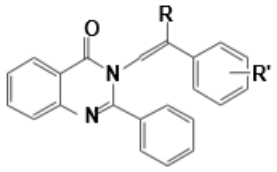
(28)

2.5 Antiviral properties :

Schiff bases can play a vital role due to their reported antiviral nature. Schiff bases derived from isatin and bisisatin are reported to show activities against different strains of viruses [84]. Schiff bases derived from prodrug abacavir (Ziagen) were reported as anti-HIV therapy [85]. Furthermore, Schiff bases of 2-phenylquinazoline-4(3)H-one was reported to show antiviral activity against some strains of viruses like feline corona virus, influenza viruses, and herpes simplex virus [86].

Salicylaldehyde Schiff bases derived from 1-amino-3-hydroxyguanidine tosylate act as new antiviral agents [87]. Isatin Schiff base ligands are marked by antiviral activity, and this fact is very useful in the treatment of HIV [88]. In addition, it was also found that these compounds have anticonvulsant activity and may be included in the anti-epileptic drugs [89]. Gossypol derivatives also present high antiviral

activity. Increasingly, gossypol, often used in medical therapy is replaced by its derivatives, because of their much lower toxicity. Kumar et al. [90] reported anti-viral activity of 2-hydroxy substitution on a series of 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-one (29). Some bis-Schiff bases of isatin, benzylisatin, and 5-fluoroisatin (30) were reported by Jarrahpour et al. [91] as antiviral agents.



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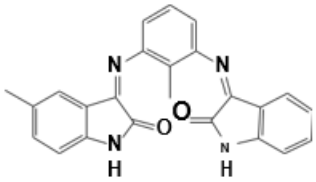
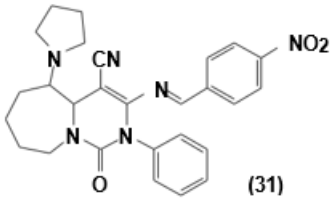


(30)

2.6 Anti-inflammatory activity :

Schiff bases derived from 2-(2,6-dichloroanilino) and 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one [92] have been reported as anti-inflammatory activities [93]. Moreover, transition metal complexes of Schiff bases containing aldose group have also been reported for anti-inflammatory activities [94].

Nehad et al. [95] described anti-inflammatory activity of pyrimidol [1, 6-a] azepines and reported that electron withdrawing nitro group (31) giving highest anti-inflammatory activity and lowest when electron donating methoxy group (32).



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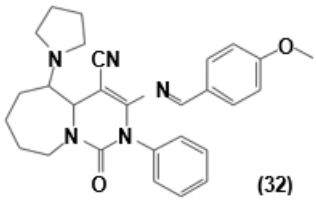
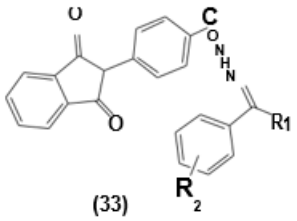


(32)

Schiff bases obtained from phthalimide (33) act as anticonvulsant and neurotoxicity activities which were reported by Bhat et al. [96] observed that nitro substitution at ortho position of the distal aryl ring emerged as most promising anticonvulsant agent with low neurotoxicity. Some Schiff bases of 2-amino-5-aryl-1, 3, 4-thiadiazole derivatives (34) with different aromatic aldehyde were reported as analgesic, anti-inflammatory, anti-bacterial (Staphylococcus aureus and E. coli) and antitubercular activity (Mycobacterium tuberculosis) by Pandey et al. [97]



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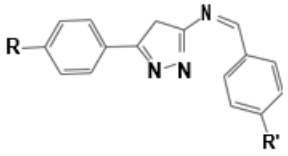
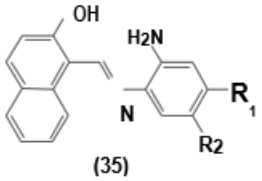


(34)

Sondhi et al. [98] reported that N-(acridin-9-yl)-4-(benzo[d] imidazole/oxazol-2-yl) benzamides (35, 36) act as anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibitions activity.



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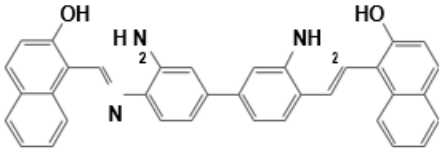
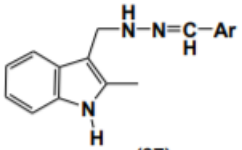


(36)

Rapolu et al. [99] reported a series of Schiff bases 2-methyl -1-H indole-3-carbohydrazide and N-benzylidine-2-methyl-1-Hindole-3-carbohydrazide (37) 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 (38) Schiff base compound against E. coli was reported by Muthumani et al. [100].



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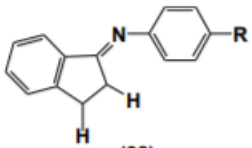
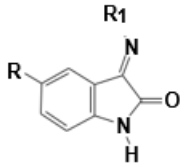


(38)

Analgesic and ulcerogenic activities of novel Schiff base (39) were reported by Ramchandran et al. [101]. Zhou et al.[102] 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. [103] reported anti-inflammatory activity of pyrimidol [1, 6-a] azepines series (40) and found that electron withdrawing nitro group on the phenyl ring showed highest activity and lowest when there was an electron donating methoxy group.



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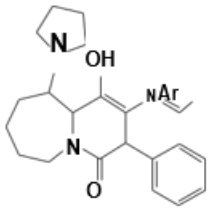
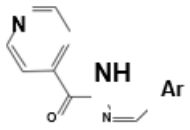


(40)

2.7 Anti-depressant Activity :

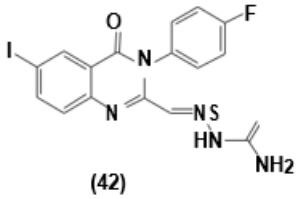
Thomas et al. [104] reported pharmacological evaluation of N'-[(1Z)-(substituted aromatic) methylidene] pyridine-4-carbohydrazides as anti-depressants agent. Compounds N' - [(1Z) - (2, 5 – dimethoxyphenyl) methylidene]pyridine – 4 - carbohydrazides (41) with 2,5-dimethoxy substitution on the aryl ring and para-nitro substitution on the aryl ring exhibited the highest anti-depressants activity.



(41)

2.8 Anticonvulsant Activity :

Aly et al. [105] reported some novel 3-aryl-4(3H)-quinazolinones-2-carboxaldehydes (42) and their corresponding Schiff's bases showed anticonvulsant, analgesic and cytotoxic potential activity due to thiosemicarbazone side chain. Literature survey [106] 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 (43) with no neurotoxicity in this series.



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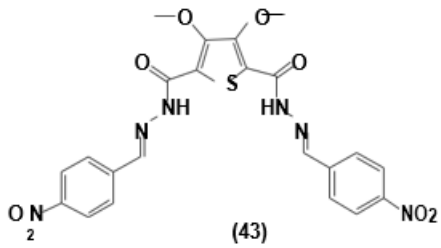
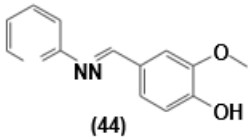


(43)

A series of new Schiff bases of 2-aminopyridine synthesized from 2-aminopyridine (44) with different aldehydes/ ketones and cyclic ketones and their anticonvulsant activity by MES, subcutaneous scPTZ

and scSTY models in mice has been reported [107]. It was reported that Schiff bases showed better anticonvulsant potency against MES and scPTZ induced seizures while found moderately active against scSTY induced seizures. A series of N4-(naphtha[1,2-d]thiazol-2-yl)semicarbazides (45) were designed and synthesized by following one of the main trends of current investigations i.e. search for novel antiepileptic drugs with neuroprotective properties [108].



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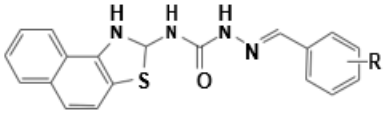
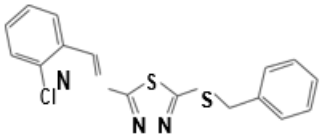


(45)

Neurotoxicity of the compounds was screened through rota rod and ethanol potentiation tests by Bahar et al. [109] Chlorobenzyl substituted compounds showed potent activity same as like as the standard drug phenytoin, while the normal benzyl derivatives (46) have also showed good activity. Schiff bases of phthalimides (47) 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 [110].



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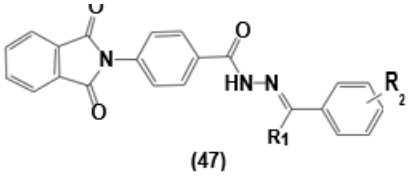
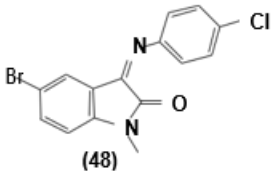


(47)

Verma et al. [111] reported anticonvulsant activity of N-methyl-5-bromo-3- (p-chlorophenylimino) isatin (48) in MES and ScMET models with LD50 > 600 mg/kg.Introduction of chloro group and methoxy group on isatin (49) had shown potential anticonvulsant results [112].



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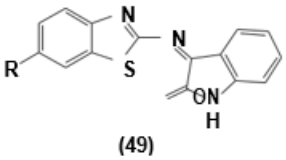
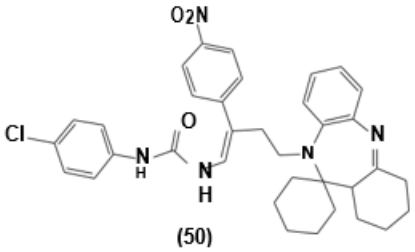


(49)

Schiff bases were synthesized from 1,5-benzodiazepines with p-chloroaniline and p-chloro phenyl semicarbazide Schiff base (50) which showed good anticonvulsant activity and had an advantage of non-sedative nature [113]. Correlation between molecular modeling and the anticnvulsant activity of the compounds (51) was reported by Bayoumi et al. [114]



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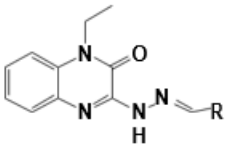
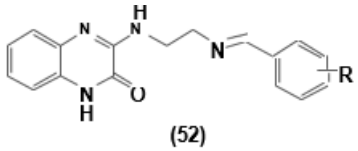


(51)

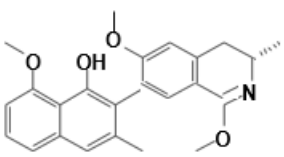
Some novel Schiff bases of 3-{[2-({(E)-[substituted) phenyl] methylidene} amino) ethyl] amino} quinoxalin-2(1H)-one (52) were evaluated for anticonvulsant activity by scPTZ model and observed that compounds having 2-nitro and 3- nitro groups showed significant activity as compared with standard drug [115].



(52)

2.9 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 (53), 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, isolatedfrom African plant Cryptolepis sanguinolenta, also used in the treatment of malaria, is the product of multi-stage reaction, in which Schiff base is involved [116].



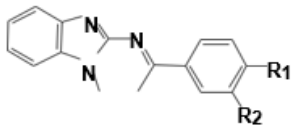
(53)

The literature survey reveals that Schiff bases act as antimalarial agents. Rathelot et al. [117] described the synthesis of Schiff base-functionalised 5-nitroisoquinolines in vitro activity against an ACC Niger chloroquine resistant P. falciparum strain. Schiff base of 5-nitroisoquinolinederivatives was the most effective antimalarial agent.

3.Anti-oxidant Activity :

Production of reactive oxygen species (ROS) increases with the passage of time, in the human body and leads to many physiological disorders including cardiovascular diseases. Schiff bases and their metal complexes play an important role in the production of reactive oxygen species i.e. antioxidant properties [118]. Recently, Schiff bases of natural phenylpropene derived methoxylated cinnamaldehydes [119], and tin metal complexes have been reported for antioxidant activities [120]. Schiff bases of 2-oxoquinoline-3-carbaldehyde reported as excellent anti-oxidizing agents as compare to ascorbic acid used as standard [121].

Neochoritis et al. [122] reported the synthesis and antioxidant property of benzimidazole Schiff bases (51) as inhibitors of lipoxygenase (LOX) and lipid peroxidation (LPO). In vitro antioxidant property of Schiff's bases of benzocoumarin and in vivo antidyslipidemic activity was reported by Sashidhara et al. [123]



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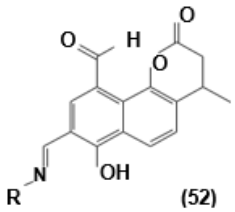


(52)

Schiff base bond enables composites with autofluorescence, attributing to the n− π* transition of the 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 providesextraordinary 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 [124,125].

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 [126].

Application in modern technologies :

Photo- and thermochromic properties of Schiff bases as well as their biological activity make them applicable in modern technology. Among others, they are used in optical computers, to measure and control the intensity of the radiation, in imaging systems, as well as in the molecular memory storage, as organic materials in reversible optical memories and photodetectors in biological systems [127,128]. 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 [130]. Among others, worthy of interest in the properties associated with Schiff rules include: properties of liquid crystal [131], chelating ability, thermal stability, optical nonlinearity [132] and the ability to create the structure of a 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

The optical nonlinearity of these compounds allows us to use them as electronic materials, in optical switches) and photonic components [134]. 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 [135]. 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 [136].

An imine linkage between the aldehyde derived from vitamin A and the protein opsin in the retina of the eye plays an important role in the chemistry of vision. Schiff base polymers with a system of conjugated –C=C- and –C=N- bonds in their main chain has of considerable interest due to their thermal stability used as solid stationary phase for gas chromatography [137]. Schiff base polymers are produced by the poly

condensation of diamines with various dicarbonyl compounds [138]. Morshedi et al. synthesized Schiff base ligand with using of cinnamaldehyde. They have studied the coordination chemistry of their copper (I) complexes [139]. Macrocyclic Schiff bases of Dithiocarbazic acid have many fundamental biological functions, such as photosynthesis and transport of oxygen in mammalian and other respiratory system [140]. Azo groups containing metal complexes [141] give fast colours to leathers, food packages, wools etc. Schiff bases possess excellent light resistance and storage ability and do not degrade even in acidic gases (CO2).

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 the 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, the appropriate amines and cyanamides, β-lactams) [142] etc.

Schiff bases are precursors of reaction 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 cryptats, coronates and podates etc. These compounds lead to reaction between an amino acid and ninhydrin, formation of Ruhemann's purple, which allows to detect and assist in the identification of fingerprints.

Anti-biotic 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 [143], anti-inflammatory agents [144], insecticidal [145], antibacterial [146], antituberculosis [147], antimicrobial [148], anticonvulsant activity

The Schiff bases are also used as versatile components in nucleophilic addition with organometallic reagents [150] and in cycloaddition reactions [151].

One of the most prevalent types of catalytic mechanisms in biochemical process involves condensation a lysine residue, with a carbonyl group of substrate to form an imine or bis-imines.

Compounds containing a benzimidazole moiety attached to a heterocyclic system are important chemical classes as a result of their significant biological activities against several viruses such as HIV, herpes (HSV-1), influenza, and Epstein-Barr [152-154]. Moreover, benzimidazole derivatives have been studied as antiproliferative and anticancer [155,156]. 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 [157-162]. Novel tetra dentate Schiff base acts as a chromogenic reagent for determination of Ni in some natural food samples [163].

Schiff bases are used as an effective corrosion inhibitor, which is based on their ability to spontaneously form a monolayer on the surface to be protected. Due to the C=N bond the Schiff bases act as effective corrosion inhibitor in many cases The inhibitor molecule should have centers capable of forming bonds with the metal surface by electron transfer [165,166).

4.Methods of Synthesis:

The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating. The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base.

Schiff bases that contain aryl substituent are substantially more stable and more readily synthesized, while those which contain alkyl substituent are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable, while those of aromatic aldehydes having effective conjugation are more stabl

Schiff bases can be synthesized from an aliphatic or aromatic amine and a carbonyl compound by nucleophilic addition forming a

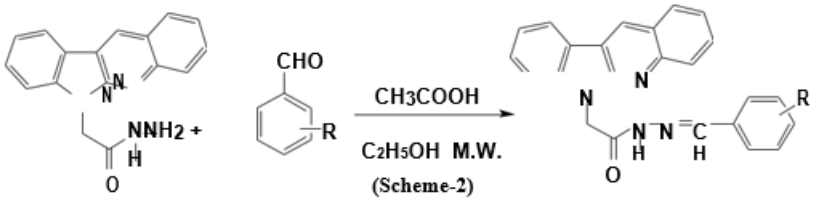
hemiaminal, followed by a dehydration to generate an imine. In 1968 Ryōji Noyori developed a copper-Schiff base complex for the metal-carbenoid cyclopropanation of styrene, this work he was later awarded a share of the 2001 Nobel Prize in Chemistry.

The imine formation is one of the most important reactions in organic and medicinal chemistry [167]. For instance, imines are used as versatile components in the asymmetric synthesis of α-aminonitriles [168], preparation of secondary amines by hydrogenation [169], and in cycloaddition reactions [170].

Synthesis of Schiff bases involves use of anhydrous sodium sulphate, molecular sieves or titanium (IV) chloride [171]. 1990s 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 [172] 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 [173], TiCl4 [174] or MgSO4 etc.

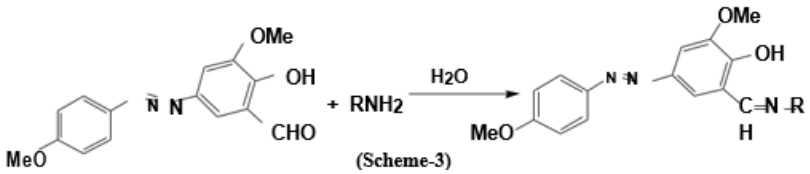
Microwave promoted synthesis of pharmacologically active Schiff bases of indolo [2, 3-b] quinoxaline was described by Nandini R. Pai et al. [175]. Microwave assisted synthesis not only reduced the reaction time drastically but also gave excellent yields of Schiff bases of indolo [2, 3-b] quinoxaline derivatives (Scheme-2).



(Scheme-2)

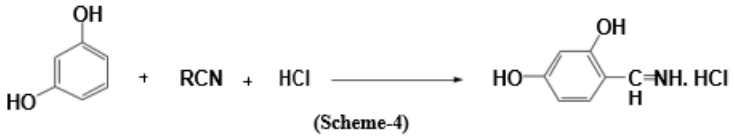
Schiff bases were readily and conveniently accessible in high yields by mixing of the reagents either as aqueous slurry, or by grinding at room

temperature. This method, unlike a classical method, needs neither harsh conditions nor organic solvents
(Scheme-3) by Zarei, M. et al. [176].



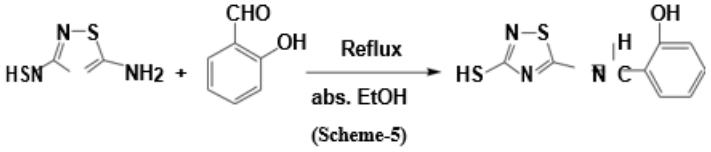
(Scheme-3)

Hoesch and Houben [177,178] found that phenols or their ethers react with alkyl/ aryl cyanides catalyzed by HCl or ZnCl2 to gives ketimines **(Scheme-4)**.



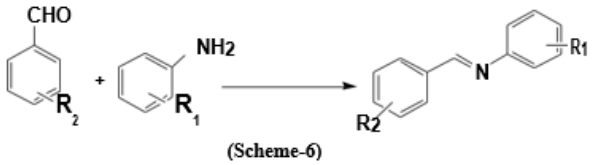
(Scheme-4)

Basim M. AL-Shimary et al. reported [179] Schiff bases (HL) derived from 5-amino-3- mercapto-1,2,4-thiadiazole **(Scheme-5)**.



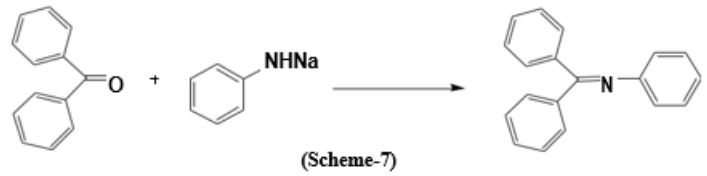
(Scheme-5)

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-6) reported by Suresh Patil et al. [180]



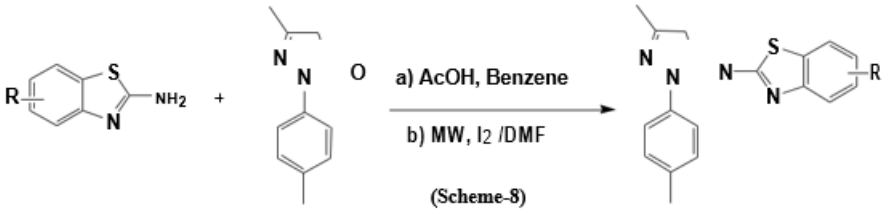
(Scheme-6)

An alkali metal or calcium salt of primary amines react with aromatic ketones to give imines (Scheme-7) reported by Britton et al. [181].



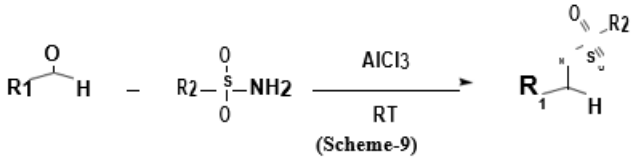
(Scheme-7)

Mistry and Desai [182] reported synthesis of Schiff bases by reaction between 2-aminothiazole with N-substituted pyrazolo-5-one under microwave-irradiation**(Scheme-8)**.



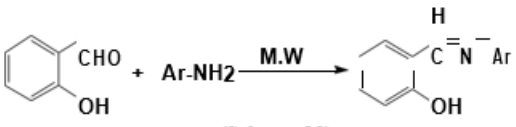
(Scheme-8)

N-Sulfonyl aldimines are powerful synthetic intermediates in organic synthesis and industrial application. They are prepared [183] expeditiously under solvent-free conditions (Scheme-9) by reaction between different aromatic aldehydes and sulfonamides in the presence of AlCl3.



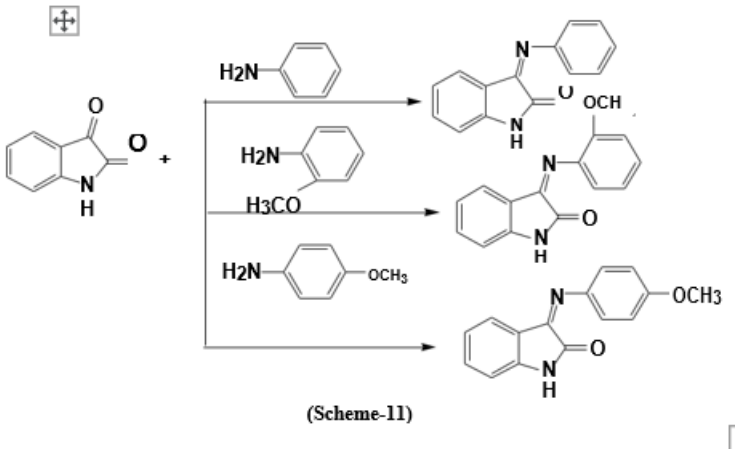
(Scheme-9)

Hai Jian Yang, et al. [185] developed a microwave-assisted preparation of Schiff-base via efficient condensation of salicylaldehyde and aryl amines without solvent is described in high yield as well as environment friendly reaction in organic synthesis **(Scheme-10).**



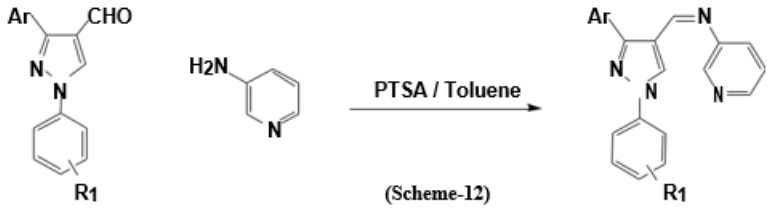
(Scheme-10)

Synthetic approach of obtaining Schiff bases via condensation reactions between various amines and isatin using a 1:1 molar ratio has been described by Kriza, A. et al. [184] **(Scheme-11)**.

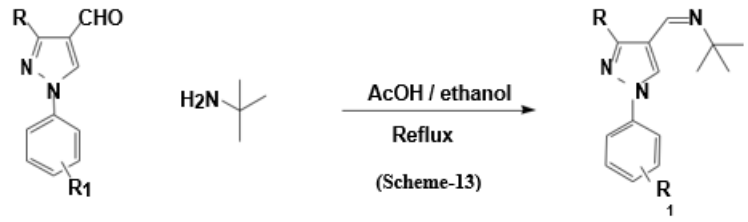


(Scheme-11)

Azomethine compounds were synthesized by Argade and Gill [186] by condensation reactions of 4-formyl pyrazoles with hetero-aromatic amine as well as aliphatic amines **(Scheme-12,13)**.

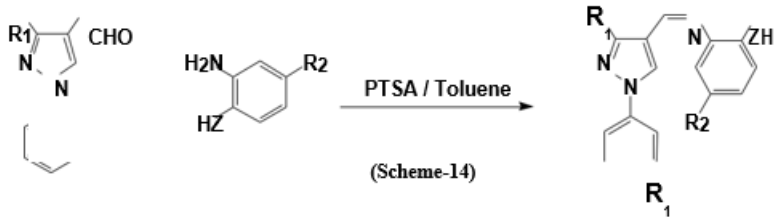


(Scheme-12)



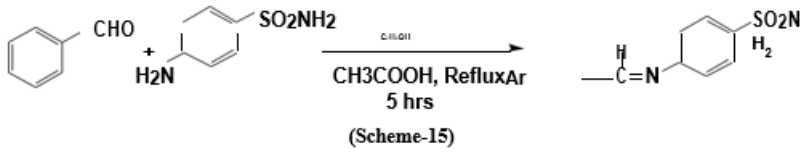
(Scheme-13)

Oxidative cyclization of thiophenolic and phenolic Schiff bases of pyrazole using PTSA in toluene as catalyst starting from 4- formyl pyrazole (Scheme-14) has been reported by Praveen et al. [187]



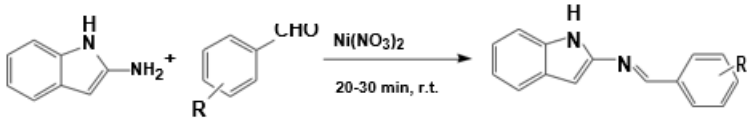
(Scheme-14)

Santosh Kumar, et al.[188] synthesized better antimicrobial compounds using different substituted aromatic aldehydes for the synthesis of Schiff's Bases. Sulfonamide helps to formation of Schiff bases in presences of alcohol and acidic reagent **(Scheme-15)**.



(Scheme-15)

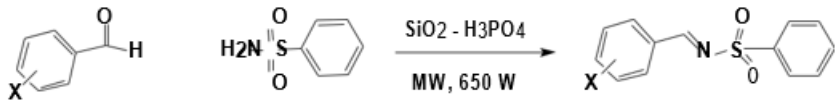
A simple and efficient method has been developed for the synthesis of some novel Schiff bases via the reaction of aromatic aldehydes with 2-aminobenzimidazole by using catalytic amount of M(NO3)2 in an organic solvent at room temperature. Some advantages of this protocol are good yields, use of available catalysts, simple workup procedure, and short reaction times (Scheme-16) which was reported by Akbar Mobinikhaledi, et al. [189].



(Scheme-16)

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 [190].

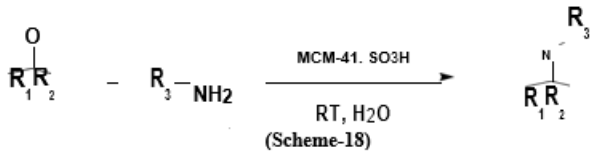
N-[(E)-phenylmethylidene]-benzenesulfonamide derivatives were synthesised using solid SiO2-H3PO4 catalyst under solvent free conditions under microwave irradiation **(Scheme-17)** as reported by Sekar et al. [191].



(Scheme-17)

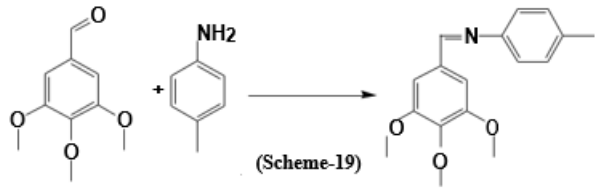
Nano-ordered MCM-41 anchored sulfonic acid (MCM-41-SO3H) was used as an efficient heterogeneous catalyst for the synthesis of Schiff

bases by the reaction of different aryl/alkyl aldehydes or ketones with primary amines at room temperature**(Scheme-18)**.

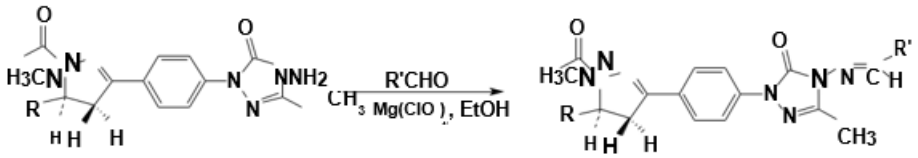


(Scheme-18)

Zhaoq Yang,*etal.*[193]reported the synthesis of(*E*)-4-methyl-N-(3,4,5-trimethoxybenzylidene) benzenamine in different ways, as a result, microwave irradiation is the simple way to synthesis this Schiff base **(Scheme-19)**.

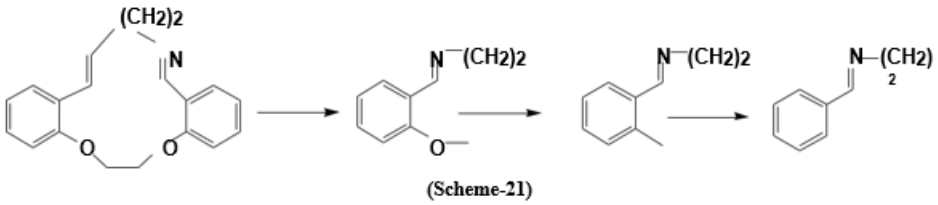

(Scheme-19)

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-20)** to yield the azetidinones with excellent yields [194].



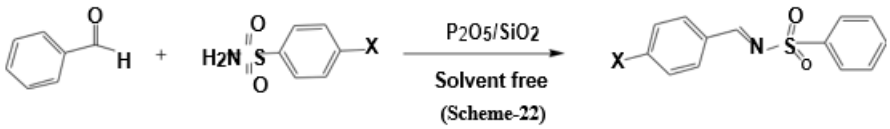
(Scheme-20)

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. Khalil1 et al. [195] **(Scheme-21)**.

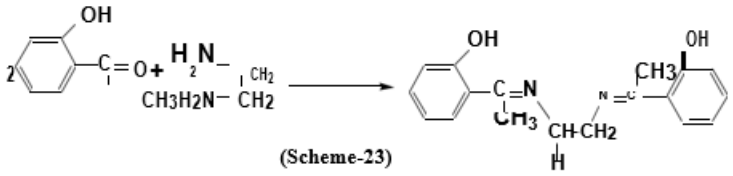

(Scheme-21)

Alireza et al. [196] 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 OC **(Scheme-22)**.

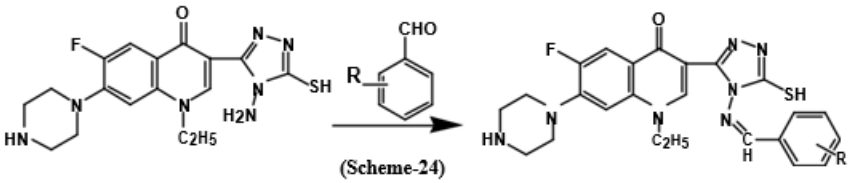


A new Schiff base 2-[2-(E)-(2-hydroxyphenyl)ethylidene]aminoethyl) ethan-imidoyl]phen was synthesized via the reaction of 2-hydroxyacetophenone with ethylene-diamine by Hamil, A. M. et al. [197] **(Scheme-23)**.

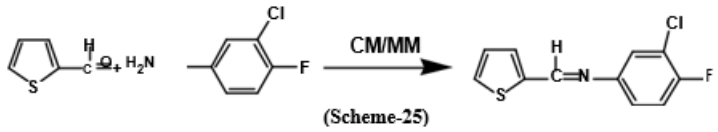


The Schiff base was prepared by Chavan V. L. et al. [198] via the refluxation-precipitation method in 1:2 proportions of o-phenylene diamine and 2-Hydroxy- 1-Naphthaldehyde.

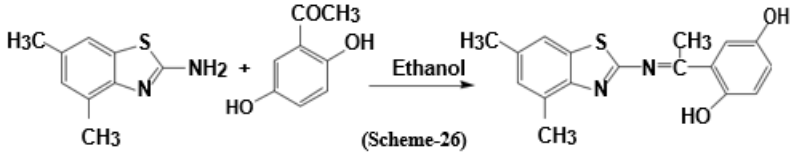
3-Substituted-4-amino-5-mercapto-1, 2, 4-triazole was obtained in an excellent yield in a single step by the condensation of a well known drug norfloxacin having free carboxyl group with thiocarbohydrazide [199] **(Scheme-24**).



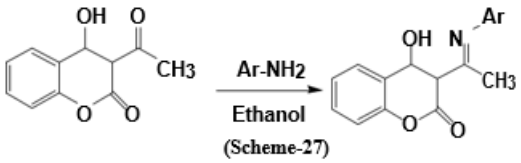
The coordination complexes of Co(II), Ni(II) and Cu(II) derived from 2-thiophenecarboxylidene-3-chloro-4-fluoroaniline (TCC) and 2 - thiophene carboxylidene-4-fluoroaniline (TCF) have been synthesized by conventional as well as microwave methods [200] **(Scheme-25)**.



Praffullkumar A. Kulkarni, et al. [201] synthesized lanthanides (III) complexes of Schiff bases. Schiff bases were obtained by condensation of 2-amino-4,6-dimethyl benzothiazole with 2,5-dihydroxy acetophenone, pyridine 2-aldehyde etc **(Scheme-26)**.



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-hydroxychromen-2-one by Girgaonkar M.V. et al. [202] **(Scheme-27)** .



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