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Overview of Biological Activities and Synthesis of Schiff Base

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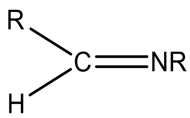
Abstract
The compounds with the azomethine group (-HC=N-) are known as schiff bases.when a primary amine condenses with an aldehyde or ketone.In most cases, heat or acid/base catalysis are used to form Schiff bases. The typical Schiff bases are basic crystalline solids, while some of them can take the form of insoluble salts that are strongly acidic. Schiff bases are employed as ligands to prepare metal complexes with a variety of distinct structures or as intermediates in the synthesis of amino acids. The inhibition of specific diseases, enzymes, or DNA replication is facilitated by the strong binding affinity of the C=N imine bond, where the electrophilic carbon and nucleophilic nitrogen effectively interact with a variety of nucleophiles and electrophiles.These Schiff bases are made from different aldehydes and amines in the following ways: stirring, catalyst-free, reflux, microwave irradiation, and ultrasonic. Both the chemical and pharmaceutical sectors use these molecules for a variety of purposes. These substances have a number of biological properties, such as antibacterial, anti-inflammatory, antiviral, and antioxidant properties. In addition to having therapeutic qualities, Schiff base molecules are crucial ligands in coordination chemistry. As a result, Schiff bases and their derivatives have the potential for use in a broad spectrum of important biological applications.

Keywords: Schiff base; Azomethine; Imine; Pharmacological activities; Coordination chemistry

Introduction:
The process by which aromatic aldehydes and primary amines interact to generate imine derivatives was discovered by Hugo Schiff in 1864 . Schiff bases are an important class of chemical compounds that are generally created when azomethine groups with the general formula R-CH=N-R react as an amine with aldehydes or ketones.[1]. An azomethine functional group or an imine functional group are other names for a schiff base group[2]. These substances are also referred to as azomethines, imines, or anils[3]. Schiff bases usually arise when heat, acids, or bases are catalyzed. Common Schiff bases are crystalline solids that react with strong acids to form insoluble salts, while only having a mild basicity. In coordination chemistry, the Schiff bases are essential because they can be utilized as the building blocks for the synthesis of different amino acids[1]. One class of compounds that is frequently used is schiff bases. Among other things, they are used as polymer stabilisers, catalysts, organic synthesis intermediates, and pigments and dyes[4]. The reversible process of forming a Schiff base from an aldehyde (or ketone) usually occurs when heating or under the action of an acid or base. Typically, the removal of water, the separation of the product, or both, drives the reaction to its conclusion. Many Schiff bases can be hydrolyzed by an aqueous base or acid back into their amines, ketones, or aldehydes[2]. Schiff bases are

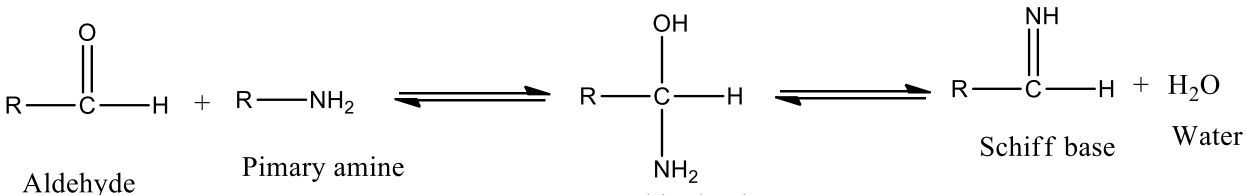
synthesized from various aldehydes and amines using methods such as stirring, catalyst-free conditions, reflux, microwave irradiation, and ultrasonic conditions. These compounds have a broad range of applications in both the pharmaceutical and chemical industries. They exhibit various biological activities, including antimicrobial, anti-inflammatory, antiviral, and antioxidant effects. In addition to their medicinal properties, Schiff bases are significant as ligands in coordination chemistry. Consequently, Schiff bases and their derivatives hold potential for further exploration in numerous biological applications with potent effects[1].



R=Alkyl or Aryl

Fig. : General structure of a Schiff base

The formation of a Schiff base from an aldehyde or ketone is a reversible process that typically occurs under acidic or basic catalysis, or with heating. This reaction is generally driven to completion by either isolating the product or removing water. Additionally, many Schiff bases can be hydrolyzed back to their original aldehydes or ketones and amines using aqueous acid or base[2,5]. The classical method for synthesizing imines involves mixing equimolar quantities of an aldehyde or ketone with a primary amine, as shown in Figure 1 [6, 7]. This reversible reaction produces an imine and a water molecule as byproducts[6].



Scheme 1:Schiff base

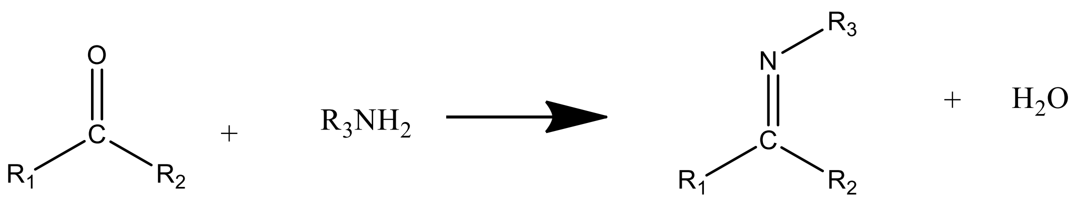


Fig 1:Schiff base(imine)

The formation of imines is typically driven to completion by separating the product or removing water, or both. Many Schiff bases can be hydrolyzed back to their corresponding aldehydes or ketones and amines using aqueous acid or base. The mechanism of Schiff base formation involves a variation of nucleophilic addition to the carbonyl group, with the amine acting as the nucleophile. Initially, the amine reacts with the aldehyde or ketone to form an unstable addition compound known as carbinolamine. This carbinolamine then loses water through either acid- or base-catalyzed pathways. Being an alcohol, the carbinolamine undergoes acid-catalyzed dehydration[8]

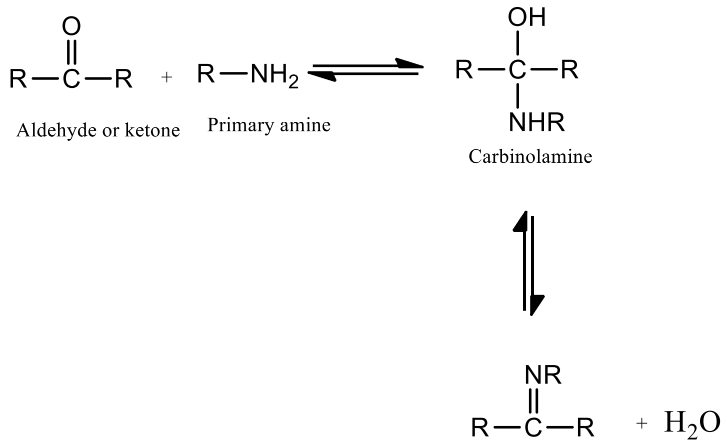


Fig:2 Mechanism of Schiff base formation

1.1Conventional Method:

Schiff bases are synthesized by condensing 0.004 mol of an aldehyde with 0.004 mol of various aromatic amines (2a-e) in 10 ml of water. The mixture is stirred at ambient temperature, and the reaction progress is monitored using TLC. Upon completion, the product is isolated as a yellow-colored amorphous solid, which is then filtered, dried, and recrystallized from methanol[8].

1.2 Novel methods for synthesizing Schiff Base:

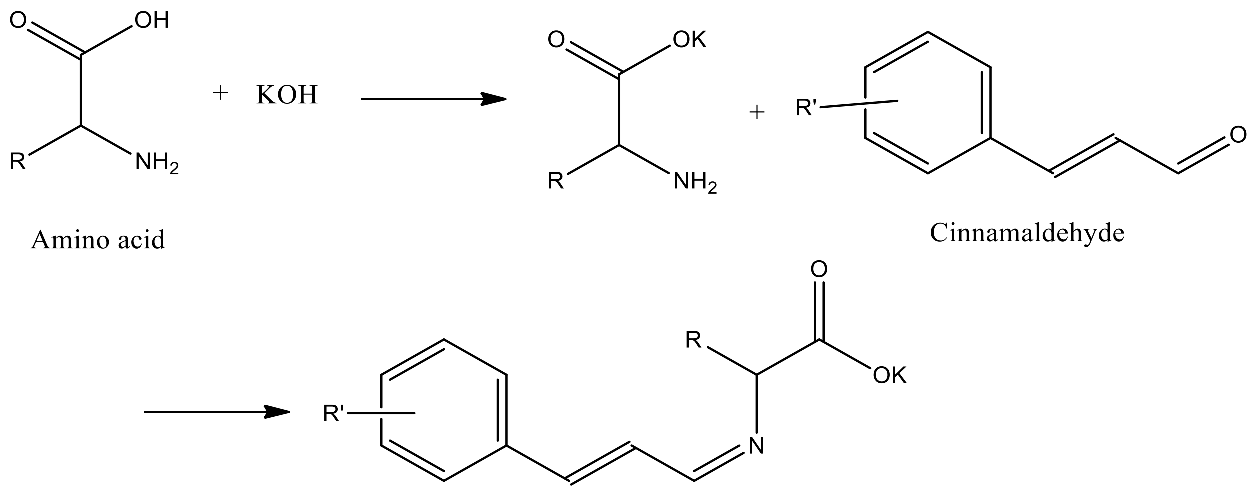
Interestingly, imine compounds have diverse applications in both medicine and industry. Consequently, chemists have dedicated considerable effort to developing excellent methods for synthesizing novel materials containing the imine group[9].

1.3 Microwave method of synthesizing Schiff base:

Recently, the microwave heating technique has emerged as an effective method for stimulating a wide range of chemical reactions. It has been shown that reactions between aniline derivatives and various aromatic aldehydes can be performed quickly, with high purity, and without solvents, using microwave irradiation. The products were purified by recrystallization in suitable solvents, yielding excellent results with high purity [22-26]. Different types of Schiff base compounds were synthesized using the microwave technique in just one or two minutes, compared to the two hours required without a microwave, all at room temperature[9].

1.4 Synthesis of Schiff bases derived from cinnamaldehyde:

Amino acids (0.0067 mol) and potassium hydroxide (0.0067 mol) were dissolved in 40 mL of anhydrous methanol by stirring at 50°C. At room temperature, a 1.25-fold excess of cinnamaldehyde (0.0084 mol) dissolved in 30 mL of anhydrous methanol was added dropwise to the amino acid potassium salt solution. After stirring the mixture at room temperature for 2 hours, it was concentrated to 10-15 mL using rotary evaporation. The resulting precipitate was washed three times with diethyl ether and then oven-dried at 35°C for 5 hours to yield the desired Schiff base compounds. This method, with variations in cinnamaldehyde derivatives and amino acids, produced numerous Schiff base compounds [10].

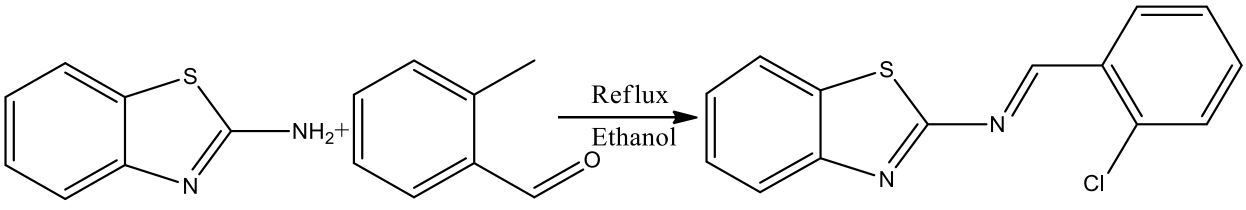


Cinnamaldehyde schiff base of Amino acid

Scheme 2: Synthesis of a Schiff base using cinnamaldehyde.

1.5 Synthesis of Schiff bases from 2-amino-benzothiazole.

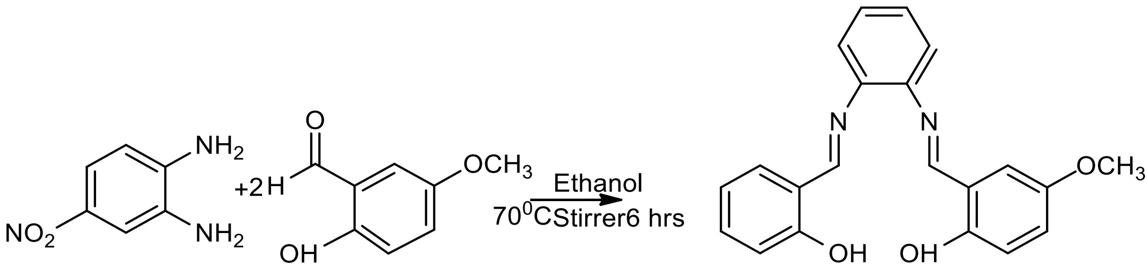
In 25 mL of ethanol, 2 g of 2-amino-benzothiazole was mixed with an equivalent amount of the corresponding aldehyde. The solid product was then isolated by filtration, purified through recrystallization from ethanol, washed with ethanol, and dried after refluxing for 2 hours [10].



2 Aminobenzothizole 2 Chlorobenzaldehyde

R1:H,OH,Cl
R2:H,OCH3
R3:H,OH,Cl

1.6 A Schiff base ligand was synthesized by reacting 4-nitro-o-phenylenediamine with 5-methoxysalicylaldehyde in absolute ethanol. The reaction mixture was continuously stirred and heated at 70°C for 6 hours[11].



Scheme 3: Synthesis of a Schiff base using cinnamaldehyde.

2 Industrial uses:

2.1 Dyes

Chromium azomethine complexes, cobalt Schiff base complexes[12], and unsymmetrical 1:2 chromium complexes provide fast colors to leathers, food packages, and wools. Azo group-containing metal complexes[12] are used for dyeing cellulose polyester textiles, while some metal complexes are used for mass dyeing polyfibers. A cobalt complex of a Schiff base (formed from salicylaldehyde and diamine) shows excellent light resistance and storage stability, and it does not degrade even in the presence of acidic gases (CO2). Additionally, a novel tetradentate Schiff base acts as a chromogenic reagent for determining nickel in certain natural food samples[12].

2.2 Polymer

Photochemical degradation of natural rubber in solution with ethylenediamine produces amine-terminated liquid natural rubber (ATNR). Reacting ATNR with glyoxal forms a poly Schiff base, which improves aging resistance. Additionally, organocobalt complexes with tridentate Schiff bases serve as initiators for the emulsion polymerization and copolymerization of dienyl and vinyl monomers[12].

3.Biological Activities of Schiff base

3.1 Antineoplastic activity:

Benzothiazole-Schiff base exhibited anticancer activity against MCF-7 breast cancer cells and was found to have lower toxicity to normal cells[13].fig 3

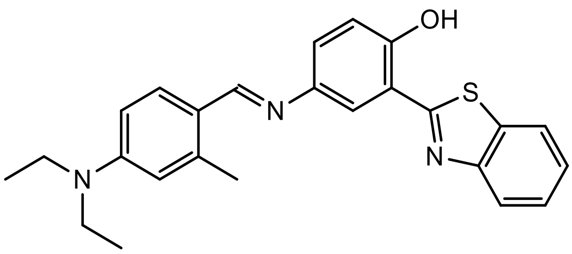


Fig:3 Schiff base-Benzothiozole

1,3,5-Triazine-isatin Schiff base exhibited anticancer activity against lung cancer cells (HOP-92) as well as leukemia cell lines (CCRF-CEM and SR)[13].fig 4

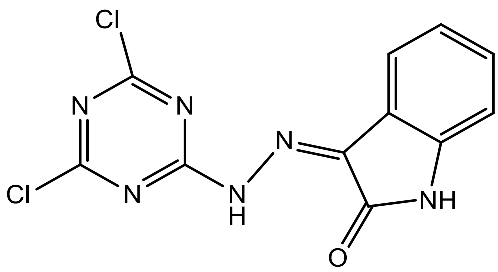
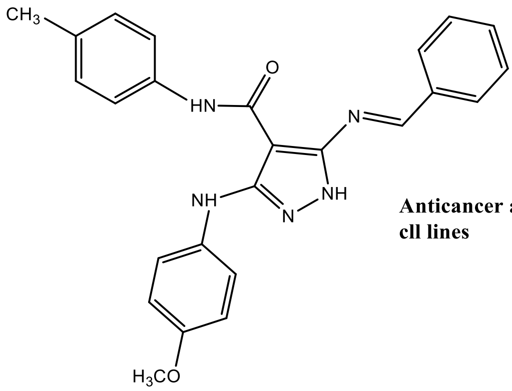
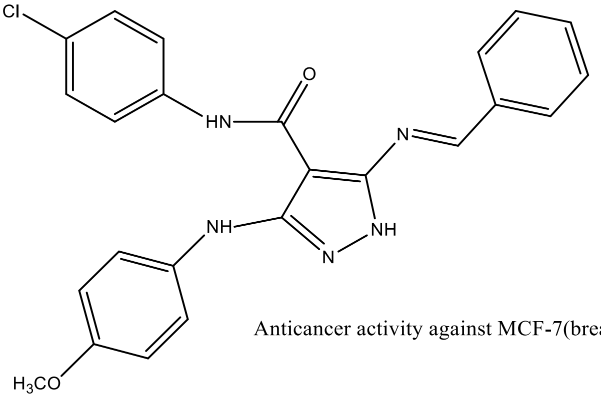


Fig:4 1,3,5-Triazine-isatin Schiff base

Two Schiff bases featuring a pyrazole moiety, demonstrated excellent anticancer activities against liver cancer cells (HepG2) and breast cancer cells (MCF-7), respectively[13] fig 5.



Anticancer activity against HepG2(liver) cll lines

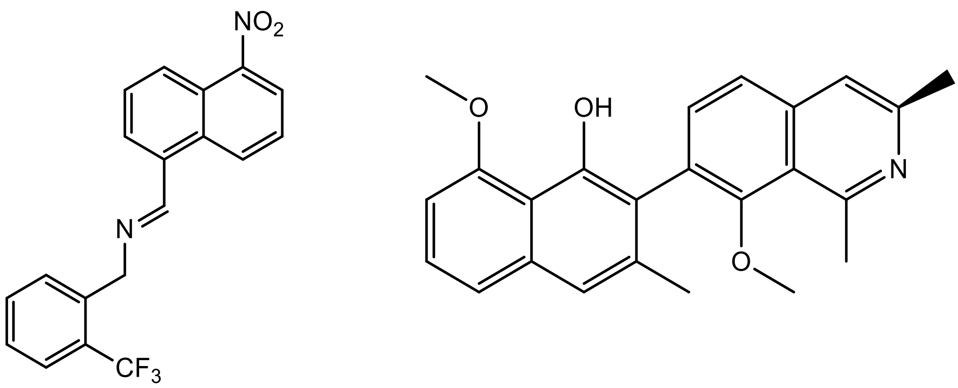


Anticancer activity against MCF-7(breast)cell lines

Fig:5 Schiff bases-pyrazole

3.2 Antimalarial activity:

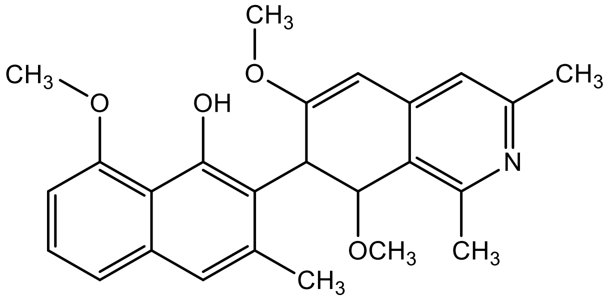
Ancistrocladidine (a; Fig. 6) is a secondary metabolite from Ancistrocladaceae and Dioncophyllaceae plants, characterized by an imine group in its molecular structure. Compound a has demonstrated activity against P. falciparum K1 and 3D7[15].Among the synthesized 5-nitroisoquinoline derivatives, Schiff base (b; Fig.6) was found to be the most effective antimalarial agent [14,15].



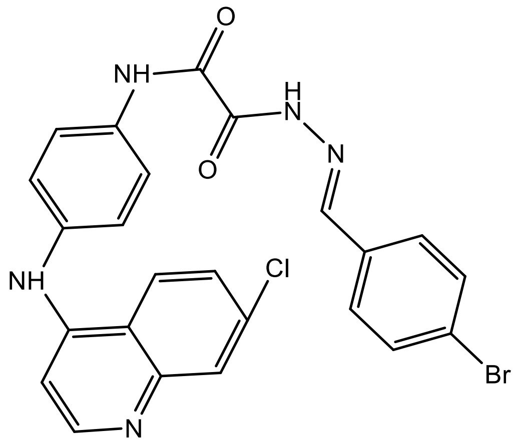
a b

Fig:6 - Chemical structures of synthetic antimalarial Schiff bases

The presence of a quinoline ring endows the compound with strong activity against Plasmodium species, especially P. falciparum. (E)-2-(2-(4-bromobenzylidene)hydrazinyl)-N-(4-((7-chloroquinolin-4-yl)amino)phenyl)-2-oxoacetamide (a) and 2-{(2E)-2-[(4-bromophenyl)methylidene]hydrazinyl}-N-{4-[(7-chloroquinolin-4-yl)amino]phenyl}-2-oxoacetamide (b) were evaluated against the 3D-7 strain of P. falciparum [14,15]. Their antimalarial activity is depicted in Fig.7



a

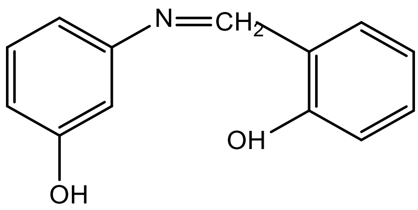


b

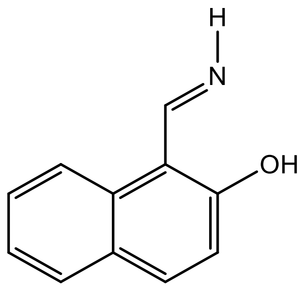
Fig:7 Compounds with antimalarial activity

3.3 Antifungal activity

Schiff bases, such as 3-hydroxysalicyldimine and 2-hydroxy-1-naphthaldimine, include imine derivatives of quinazolinones that possess antifungal properties against Candida albicans, Trichophyton rubrum, T. mentagrophytes, Aspergillus niger, and Microsporum gypseum.[16].



3-hydroxysalicyldimine



2-hydroxy-1-naphthaldimine

Fig:8

3.4 Analgesic activities

Isatin Schiff base have a very good analgesic activity[17].Fig 9

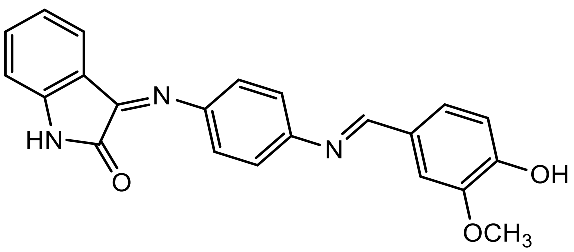
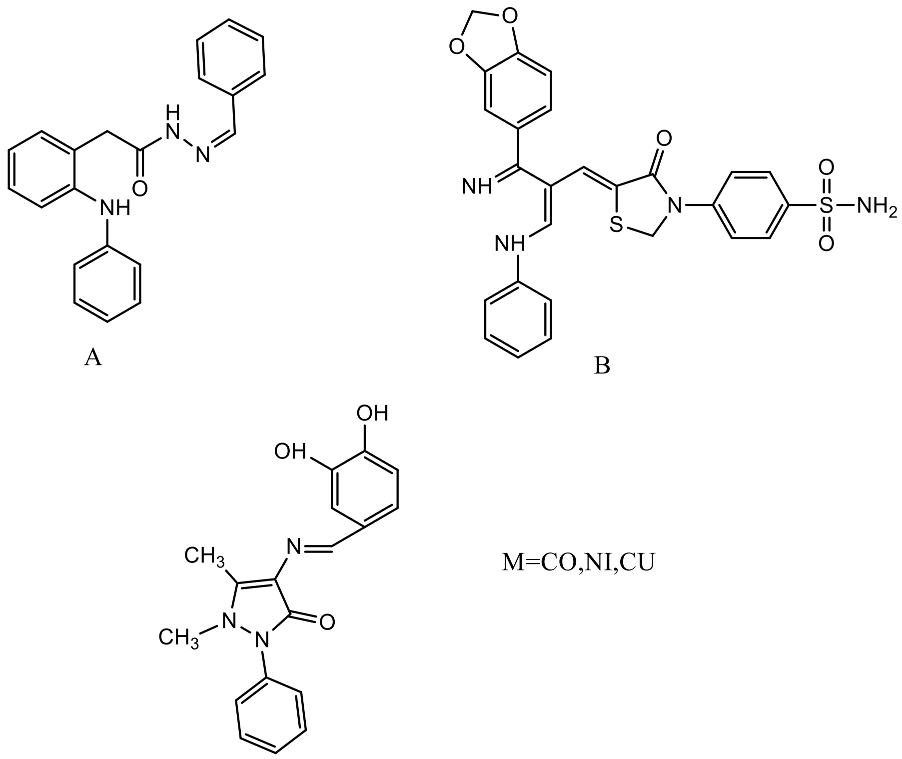


Fig 9: Isatin Schiff base

3.5 Anti-inflammatory activity

The compounds were synthesized by condensing a pyrazole derivative with an aromatic aldehyde, resulting in notable anti-inflammatory activity against COX-1 and COX-2. Specifically, 2-(2-anilinophenyl)-N'-[(Z)-phenylmethylidene]acetohydrazide (A) shows strong activity against COX-2, while 4-((Z)-5-((Z)-2-(benzo[d][1,3]dioxol-5-yl(imino)methyl)-3-(phenylamino)allylidene)-4-oxo-2-

thioxothiazolidin-3-yl)benzenesulfonamide (B) exhibits high selectivity for COX-1/COX-2 inhibition. Additionally, 2-benzyl-4-{(E)-[(3,4-dihydroxyphenyl)methylidene]amino}-1,5-dimethyl-1,2-dihydro-3H-pyrazol-3-one (C) is active against LPS-stimulated COX-2 mRNA levels [16]. The structures of these anti-inflammatory compounds are provided.



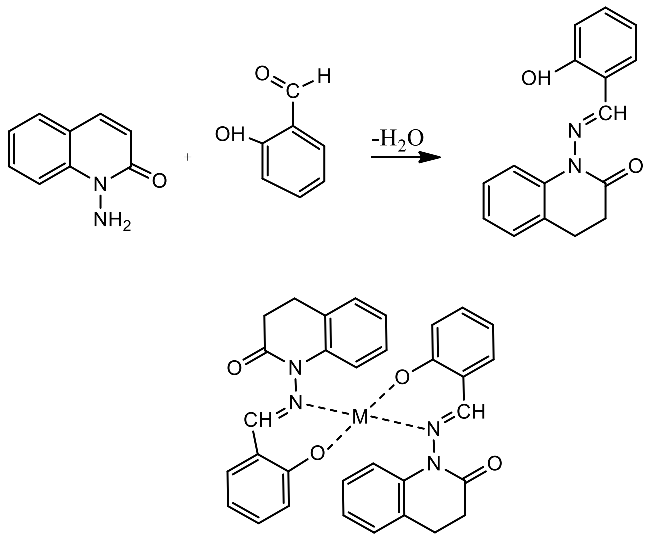
A B C

M=CO,NI,CU

Fig:10 Compounds with anti-inflammatory activity

3.6 Antioxidant activity

A newly synthesized Schiff base, N-(4-phenylthiazol-2-yl)-2-(thiophene-2-ylmethylene)hydrazinecarboxamide, along with its M(II) complexes (where M = Ni, Cu, Zn, or Co), has been reported to exhibit significant antioxidant activities[18].



M=CO,Ni,Cu

Fig:11 compounds with antioxidant activiy

4.Limitations

This review paper aims to comprehensively overview the synthesis, characterization, and biological activities of these compounds. Future reviews could expand on this work by exploring Schiff base conjugates with various structural features, thereby providing a broader understanding of their potential applications.

5.Conclusion

This review highlights the diverse biological activities of Schiff bases and their derivatives, a crucial class of compounds in synthetic chemistry. These compounds exhibit anti-inflammatory, antimalarial, anticancer, antioxidant, and other biological effects. They are effective against various microorganisms and demonstrate enhanced efficacy against multiple cancer cell lines by inhibiting protein kinases, inducing apoptosis, and acting as tubulin-targeting and polymerizing agents. With superior activities against various diseases, these compounds show improved IC50 values and inhibition rates. To further advance the chemistry and biological activities of these scaffolds, reactions can be performed under green chemistry principles. The ongoing development of novel Schiff base derivatives and their metal complexes continues to offer new therapeutic applications, sustaining interest in the field of medicinal chemistry.

Acknowledgments
None

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