Schiff Bases as Important Class of Pharmacological Agents

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Abstract: Therapeutics are compounds, which do not always exhibit healing powers. They sometimes prevent or control roles. Many compounds, well known or less are treated as the therapeutic agents. Among them, there is a specific group of molecules named commonly as Schiff bases, chemically imines. Schiff bases are aldehyde- or ketone-like compounds in which the carbonyl group is replaced by an imine -HN=CH- or azomethine -NHN=CH- group, they are an important class of compounds for new drug development. Schiff base modifications so far proved to be very effective with increased efficacy and reduced toxicity. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activity. The aim of this work was to present some interesting and promising examples of Schiff bases which exhibit biological activity.

Key words: Biological activities, Schiff bases, therapeutic agents.

1. Introduction

Schiff bases are condensation products of primary amines with carbonyl compounds [1], and they were discovered by a German chemist in 1864 [2]. Schiff bases form an important class of the most widely used organic compounds and has a broad wide variety of applications in many fields such as biology, medicine, inorganic and analytical chemistry [3-5]. Schiff bases derived from various heterocyclic compounds, display broad range of biological activities such as antibacterial [6-8], antifungal [9], antimycobacterial [4, 7], antianthrax [10], antiviral [11, 12], anticancer [13], antiprotease [4, 14], antiparasitic [15, 16], anticonvulsant [17], analgesic [18], antiinflammatory [18, 19], antiplatelet [20], antioxidant, antiproliferative [21], antipyretic properties [22, 23], cardioprotective, antidepressant, antihypertensive, herbicidal, antiglycation and cytotoxic activity [5].

The synthesis, characterization and structure activity relationship of Schiff bases are of current interest [4]. The reason of the attention of this specific group of compounds is a presence of a nitrogen atom in the imine (-N=CH-) or azomethine (-NHN=CH-) group (Fig. 1) [5]. Ashraf et al. showed that the presence of alone pair of electrons in an sp^3 hybridized orbital of nitrogen atom of the azomethine group has significant influence on chemical and biological properties [1].

Many methods of Schiff bases synthesis have been developed [24, 25], however the simplest one concerns the condensation in organic medium [5, 26, 27]. Practically, the formation of an imine involves two steps (Fig. 2). At first, the amine nitrogen from primary amine acts as a nucleophile, attacking the electrophilic carbonyl carbon of aldehydes or ketones forming a carbinolamine. In the next step, the nitrogen from the carbinolamine is deprotonated, and the electrons from the N-H bond push the oxygen off of the carbon, leaving a compound with a C=N double bond (an N-substituted imine) and a water molecule displaced. The N-substituted imine is also known as a Schiff base [19].

Both the addition and the elimination phase of the
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[Diagram of Schiff base structure]

Fig. 1 General structure of Schiff bases [5].

Fig. 2 Formation of Schiff base [27].

reaction are accelerated by acid catalysis. Careful control of pH is essential, since sufficient acid must be present to give a reasonable equilibrium concentration of the protonated form of the aldehyde or ketone. Too acidic a reaction medium, however, converts the amine to its protonated form, a form that is not nucleophilic, and retards reaction [27]. Schiff bases rapidly decay or undergo polymerization, if there is at least one aryl group attached to the nitrogen atom or a carbon atom in the -CH=N- double bond [4, 5].

Schiff bases are crystalline or oily substances that are insoluble in water and soluble in organic solvents. They are weak bases, forming salts with acids in an anhydrous medium, in aqueous acid solutions they undergo hydrolysis to yield an amine and aldehyde. The majority of Schiff bases are stable in alkaline solutions. Schiff bases undergo hydrogenation to give secondary amines (RR′CH-NHR″) and add on many compounds containing mobile hydrogen, such as β-dicarbonyl compounds, ketones and imines [28, 29].

Imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds. The imine group presenting in such compounds has been shown to be critical to their biological activities [30-32]. So far, modifications of the Schiff bases have proven highly effective with improved potency and lesser toxicity [5]. Therefore in this work, we present some interesting and promising examples of Schiff bases which exhibit multi- or only one biological activities.

2. Biological activities of Schiff bases

2.1 Antimicrobial Activity

2.1.1 Antibacterial Activity

Growth of mortality is caused by infectious diseases directly related to the bacteria that have multiple resistance to antibiotics [4, 8]. Bacterial infections remain major causes of morbidity and mortality around the world [33]. The lack of effective treatments is the main cause of this problem. The development of new antibacterial agents with innovatory and more effective mechanisms of action is definitely an urgent medical need [4, 34].

Schiff bases are active against a wide range of organisms for example: Escherichia coli, Staphylococcus aureus, Bacillus polymxa [1], Klebsiella pneumoniae, Proteus vulgaris and Pseudomonas aeruginosa [4, 19].

Schiff bases, containing 2,4-dichloro-5-fluorophenyl moieties, take part in effective inhibition of bacterial growth [8, 35]. Imines from this class (compounds 1-2 in Fig. 3) completely inhibited the growth of S. aureus, E. coli, P. aeruginosa and K. pneumonia. On the other hand, the compounds obtained from furyglyoxal and p-toluidine showed antibacterial activity against: E. coli, Pseudomonas fluorescence, S. aureus, Bacillus
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Schiff bases as important class of pharmacological agents have gained considerable interest in recent years due to their versatile structures and diverse biological activities. These compounds are known for their potential use in the treatment of various diseases, including antimicrobial agents.

**Fig. 3** Chemical structures of Schiff bases containing 2,4-dichloro-5-fluorophenyl moieties [4].

**Fig. 4** Synthetic route for the preparation of thienopyrimidine derivatives [36].

E. coli, Proteus shigelloides, Vibrio cholera, Enterococcus faecalis [4].

Hossain et al. synthesized 4-[4'-substituted benzylidene] hydrozono-5, 6-dimethylthieno-[2,3-d]pyrimidine derivatives (Fig. 4) by an initial treatment of 2-amino-4, 5-dimethylthiophene-3-carbonitrile with formic acid affording 5,6-dimethylthieno[2,3-d]pyrimidine-4(3H)-one, which is chlorinated with thionyl chloride and then reacted with hydrazine hydrate. Finally, hydrazine derivatives reacted with different aromatic aldehydes. All the compounds showed antibacterial activities against B. subtilis, B. cereus, S. aureus, Shigella dysenteriae, Salmonella typhi and Pseudomonas spp. [19, 36].

Other Schiff bases derivatives, which exhibited antibacterial activity are: benzimidazole, thiazole,
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pyridine, glucosamine, pyrazolone, hydrazide, thiazolidiones, indole, thiosemicarbazone, p-fluorobenzaldehyde [8].

2.1.2 Antimycobacterial Activity

Tuberculosis kills approximately 2 million people each year. The global epidemic is growing and becoming more dangerous [37]. In addition to this, the increase in Mycobacterium tuberculosis strains resistant to front-line antimycobacterial drugs such as rifampin and isoniazid acid hydrazide (INH) has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of tuberculosis [34].

Schiff bases have been pointed to as promising antitubercular agents. For example, N-(salicylidene)-2-hydroxyaniline (Fig. 5 compound 1) [8], isoniazid-derived Schiff base (Fig. 5 compound 2) [8, 38], hydrazones derivatives and the final products with indole, p-aminosalicylic acid hydrazide derivatives, pyrazolone derivatives, 1-methyl-1H-2-imidazo pyridine carboxylic acid hydrazide-hydrazones triazole derivatives. The last one are known to have excellent antitubercular activity against M. tuberculosis H37Rv [4, 7].

Solak et al. reported of new Schiff bases (compounds 1-2 in Fig. 6) and their screening against M. tuberculosis:

INH has very high in vivo inhibitory activity towards M. tuberculosis H37Rv [39]. Meyer and Mally prepared new hydrazones by reacting isoniazid with benzaldehyde, o-chlorobenzaldehyde and vanilin. Sah et al. prepared INH hydrazide-hydrazones by reacting INH with various aldehydes and ketones. These compounds were reported to have activity in mice which infected with various strains of M. tuberculosis, and also indicated lower toxicity than INH [34, 39]. They also showed less toxicity in these mice than INH. Buu-Hoi et al. synthesized of some hydrazide-hydrazones that were reported to have lower toxicity than hydrazides because of the blockage of -NH₂ group [39].

2.1.3 Antianthrax Activity

Anthrax is a zoonotic infection caused by Bacillus anthracis [40]. The bacterial agent is B. anthracis whose main characteristic is to form spores that can survive outdoors for several decades. Anthrax in

Fig. 5 Chemical structure of Schiff bases.

1: N-(Salicylidene)-2-hydroxyaniline [8]
2: N²-Cyclohexylidenyl isonicotinic acid hydrazide [38]

Fig. 6 Structure of Schiff bases [5].
susceptible animals generally has a fatal evolution characterised by sudden deadly bleeding from natural openings [41]. Humans become infected by contact with infected animals or contaminated animal products. Then, the disease can develop in three forms depending on the route of penetration of the bacterium: cutaneous (non-fatal), pulmonary and gastrointestinal [40, 41]. Inhalation anthrax is extremely rare, with ~30 cases reported in this century, most often associated with industrial exposure to spores. The disease has been almost uniformly fatal because of the difficulty in establishing the diagnosis and the rapid progression of the disease [42].

Heightened the awareness of the possibility that anthrax could be used as a biological weapon [42]. There are known cases of a fatal form characterised by a subacute evolution in drug users as a result of injection of drugs contaminated with anthrax spores. Due to its high capacity to maintain its viability and pathogenicity and for low cost production, B. anthracis is considered as one of the pathogen agents of greatest interest for use as a bacteriological weapon in bioterroristic attack [41, 43].

Anthrax toxin consists of three proteins: protective antigen (PA), edema factor (EF) and lethal factor (LF). The inhibition of LF proteolytic activity is a promising method for treating exposure to B. anthracis. In light of above facts, Hanna et al. generated series of hydrazones (Fig. 7) and analyzed them for their potential anthrax lethal factor inhibition [10]. Studies showed that this compounds has potential antianthrax activity [44].

2.1.4 Antifungal Activity

Fungal species are widely distributed in soil, plant debris and other organic substrates, and make up approximately 7 per cent (611 000 species) of all eukaryotic species on earth [45], although only about 600 species are human pathogens [46]. Recently, there was a considerable increase in the incidence of systemic fungal infections, which are potentially life-threatening [32]. This is caused by an increase in antimicrobial resistance and the restricted number of antifungal drugs, which retain many side effects [47]. Exploration and development of more effective antifungal agents is necessity, and the individual Schiff bases are considered to be promising antifungal medicines [48].

Some of them, such as imine derivatives of quinazolinones possess antifungal properties against Candida albicans, Trichophyton rubrum, T. mentagrophytes, Aspergillus niger and Microsporum gypseum [8].

Schiff bases of chitosan (Fig. 8 structure 1A) presented good antifungal activity against Botrytis cinerea and Colletotrichum lagenarium [9]. The insertion of alkyl and/or aryl groups increased the hydrophobic property of chitosan-derivatives. These characteristics enhanced the interaction with the cell membrane of microorganisms and improved the antimicrobial activity of the chitosan-derivatives. Tamer et al. synthesized a novel Schiff bases of via coupling with 4-chloro benzaldehyde and benzophenone, respectively (Fig. 8 structures 1B and 2). The prepared compounds showed higher activity against Gram-negative bacteria than Gram-positive. Moreover, their activities against fungal strain (C. albicans) were exhibited. The results of cell viability evaluation in vitro proved that these materials...
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Fig. 8 Chemical structures of chitosan Schiff bases.

A: \( R = \text{H or OH} \) [12]
B: \( R = \text{Cl} \) [51]

Fig. 9 Structures of 2,4-dichloro-5-fluorophenyl Schiff bases [9].

have inconsiderable cellular toxicity against fibroblast cell line [49].

Imine derivatives having a 2,4-dichloro-5-fluorophenyl moiety (Fig. 9) inhibited the growth of fungal clinical isolates, such as *Aspergillus fumigatus*, *A. flavus*, *Penicillium marneffei*, *T. mentagrophytes*. Salimon *et al.* prepared new series of 5-[1-(anthracen-9(10H)-ylideneamino)-2-(1H-imidazo 1-5-y1)ethyl]-1,3,4-thiadiazol-2-amine (Fig. 10) by condensation reaction of N-anthracen-9(10H)-ylidenehistidine with thiosemicarbazide in phosphorus oxychloride. Compounds showed good *in vitro* tests fungicidal activity against *Gibberela*, *Cercospora arachidicola*, *Physolospora piricola* and *Fusarium oxysporum* [19].

2.1.5 Antiviral Activity

2.1.5.1 AntiHIV Activity

AIDS stands for Acquired Immune Deficiency Syndrome. AIDS is a serious condition that weakens the body's immune system, leaving it unable to fight off illness. AIDS is the last stage in a progression of diseases resulting from a viral infection known as the Human Immunodeficiency Virus (HIV or AIDS virus). The diseases include a number of unusual and severe infections, cancers and debilitating illnesses, resulting in severe weight loss or wasting away, and diseases affecting the brain and central nervous system.
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Fig. 10  Structure of thiadiazol derivatives Schiff base [19].

Fig. 11  Chemical structure of abacavir-derived Schiff bases.

There is no cure for HIV infection or AIDS nor is there a vaccine to prevent HIV infection. However, new medications not only can slow the progression of the infection, but can also markedly suppress the virus, thereby restoring the body’s immune function. An estimated 35 million people are infected with HIV/AIDS worldwide [50].

Current treatment regimens HIV infection and AIDS are based on the use of two or more drugs that belong to group of inhibitors termed as highly active antiretroviral therapy (HAART). Some thiourea compounds were reported to be non-nucleoside inhibitors (NNIs) of the reverse transcriptase (RT) enzyme of the HIV. Such hydrazones have been reported to be the potent inhibitors of ribonucleotide reductase activity.

Abacavir is a nucleoside analogue capable of inhibiting the activity of reverse transcriptase. A set of imine derivatives of abacavir (Fig. 11) were highly effective against the human immunodeficiency virus-type 1 (HIV-1) [4, 47, 51].

In the last 10 years, many different classes of compounds have been reported to inhibit the HIV-1 IN (integrate). They belong to different classes, namely DNA binders, peptides, oligonucleotides, nucleotides, and polyhydroxylated aromatics.

A number of these compounds are natural products such as aurintricarboxylic acid (ATA), caffeic acid phenethyl ester (CAPE), tyrphostin, and quercetin, which inhibited the IN enzyme at micromolar concentrations.

Di Santo et al. noted that the majority of natural products endowed with anti-IN activity were characterized by one or two 3,4-dihydroxycinnamoyl moieties sometimes incorporated in a ring structure such as in quercetin, and designed a series of cinnamoyl derivatives as geometrically and conformationally constrained structures characterized by a syn disposition of the carbonyl group with respect to the vinylic double bond [11].
Moreover, imino isatin Schiff bases find use in the treatment of HIV [1]. A class of arylene bis(methylketone) compounds was designed to specifically inactivate basic-type HIV-1 NLSs by forming Schiff base adducts with contiguous lysines in the signal. Nuclear translocation (a kind of DNA mutation) of HIV-1 is blocked by arylent bis(methylketone) which form the following from: virus lysine Schiff base (Fig. 12) [12]:

A large part of imines exhibits antiviral activity (adenovirus type Ad5 and Ad8), and their activity is related to the coordination properties that prevent the decoding of genes responsible for the synthesis of amino acids of the virus. Adamantane derivative and 6-hydroxysalicylic aldehyde – oxphaman (Fig. 13) is one of the few antiviral drugs which affect the inhibition of vasoconstriction induced anaphylactic shock (adenovirus type Ad5 and Ad8). Their activity is related to the coordination properties that prevent decoding of genes responsible for the synthesis of amino acids of the virus [52].

2.1.5.2 AntiHSV Activity

Herpes simplex virus (HSV) causes herpes labialis, herpes keratitis, genetic herpes and life-threatening herpes encephalitis. HSV infections are more severe in immunocompromised patients, which are characterized by chronic and extensive lesions of the mucous membranes. Most therapies directed against HSV infections are nucleotides, nucleosides or pyrophosphate analogues, such as acyclovir (ACV), valacyclovir, penciclovir and famciclovir. Although these drugs are effective in the treatment of many acute infections, the intensive use of these drugs can led to the emergence of resistant viral strains [53].

Many studies have reported on the antiviral activity of Schiff bases derived from pyrrole. Interestingly, it was established that this kind of compounds can inhibit HSV replication [53, 54].

Hilmy et al. synthesized a series of novel Schiff bases of 2-amino-3-cyano-1,5-disubstitutedpyrrole. The

![Fig. 12 Scheme block of HIV [12].](image_url1)

![Fig. 13 Chemical structure of oxphaman [52].](image_url2)
compounds in Fig. 14, demonstrated potent antiviral activity against Herpes simplex virus-1 (HSV-1) more than ACV [54].

$N$-arylaminoacetlyhydrazones and $O$-acetylated derivatives of sugar $N$-arylaminoacetyl hydrazones were synthesized and evaluated for their antiviral activity against HSV-1. The compounds (Fig. 15) revealed the highest antiviral activity against HSV-1 [34, 55].

2.2 Anticancer Activity

Cancer is one of the leading diseases responsible for the mortality worldwide. Cancer is a general term to define a disease that is characterized by the uncontrolled proliferation of cells resulting from the disruption or dysfunction of regulatory signaling pathways that are normally under tight control [56].

Therefore various research initiatives are going on worldwide for the treatment of malignancy with the objective to discover some effective antineoplastic agents. Anticancer activities of Schiff bases have also been studied to some extent. Schiff bases derived from benzoin, salicylaldehyde, amino phenol with 2,4-dinitrophenyl hydrazine and acetone semicarbazone have shown pronounced anticancer properties [57].

Imine derivatives of $N$-hydroxy-$N'$-aminoguanidine block ribonucleotide reductase in tumor cells, so that they are used in the treatment of leukemia.

Schiff bases of $[N-(1$-phenyl-2-hydroxy-2-phenyl ethylidine)-2',4'-dinitrophenyl hydrazine] – PDH (Fig. 16 compound 1), $[N-(1$-phenyl-2-hydroxy-2-phenyl ethylidine)-2'-hydroxy phenyl imine]– PHP (Fig. 16 compound 2) and $[N-(2$-hydroxy benzylidine)-2'-hydroxy phenyl imine] – HHP (Fig. 16 compound 3) reduce the average tumor weight (reduction in tumor growth increases with increasing dose) 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 [8, 57-59].
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Fig. 16 Chemical structures of Schiff bases [59].

Fig. 17 Structure of benzothiazole derivatives Schiff base [19].

2-(4-Aminophenyl)benzothiazoles represent a potent and highly selective class of antitumour agent. Hutchinson et al. synthesized fluorinated analogues of 2-(4-aminophenyl) benzothiazoles (Fig. 17), among which 2-(4-aminomethylphenyl)-5-fluorobenzothiazole (5F 203) exhibited selective and potent anticancer activity against a variety of tumour cell lines [19]. The specificity of the benzothiazole series against a range of cell types suggests a novel mode of action, and a pro-drug of 5F 203 is currently in clinical trials [60].

2.3 Antiparasitic Activity

2.3.1 Antimalarial Activity

Malaria is a severe morbidity of humans and other animals. It is caused by protozoa of the genus *Plasmodium* [47]. Every year, approximately 500 million people are afflicted by the disease, of whom around 1-3 million die, 90% of who in sub-Saharan Africa are primarily children [4, 34, 61]. Human malaria is mainly caused by four species of *Plasmodium* (*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malarie*). The female mosquito of the *Anopheles* genus is the vector of *Plasmodium* [4]. It is initiated by a bite from an infected female *Anopheles mosquito*, which introduces the *Plasmodium* through saliva into the circulatory system. In the blood, the protists travel to the liver to mature and reproduce. Typical symptoms of malaria include fever and headache, which, in severe cases, can progress to coma and eventually death [48]. Rapid development of resistance by *P. falciparum* and *P. vivax* to the available conventional antimalarial drugs necessitates search for new antimalarial drugs and a careful re-examination of the existing drugs. In view of above, there is a very urgent and continuous need to develop new antimalarial drugs [14]. The imino-group of Schiff bases has been shown to be valuable function to confer the antimalarial activity [48].

For instance, chloroquine (CQ), amodiaquine (AQ), mefloquine (MQ) (compounds 1-3 in Fig. 18) inhibit the formation of β-haematin (malaria pigment) which is lethal to the parasite [14]. In general, CQ and AQ are called 4-aminoquinolones which are the most important and widely used class of antimalarial drugs.

Chloroquine (CQ) is a cost effective antimalarial drug with a relatively good safety profile which acts by interfering with heme metabolism. However, CQ is no
longer used alone due to the emergence and spread of *P. falciparum* CQ-resistant strains and, more recently, of *P. vivax*. Artemisinin-based combination therapy was the first line treatment in *P. falciparum* malaria. The limited availability of artemisinin was the first line treatment in *P. falciparum* malaria. However, the drug has an effect on the asexual forms of the parasite in the blood (blood schizontocidal effect) [64].

The value of quinoline-based antimalarials has been seriously eroded in recent years, mainly as a result of the development and spread of parasite resistance [65, 66].

Sharma et al. designed and synthesized new series of 4-aminoquinoline Schiff base hybrid coupled with oxalamide functionality as linker. The molecules were evaluated for their antiplasmodial activity against chloroquine-resistant (CQ-R) K1 and chloroquine-sensitive (CQ-S) 3D7 of *P. falciparum* strains. Some of the novel compounds (Fig. 19) were found to be more potent than chloroquine in vitro against CQ-R strain. Furthermore several molecules also showed promising β-hematin inhibitory activity [67].

As well ancistrocladidine (2-{(3s)-6,8-dimethoxy-1, 3-dimethyl-3,4-di-hydroisoquinolin-7-yl}-8-methoxy-3-methylnapthalen-1-ol) (Fig. 20), a secondary metabolite produced by plants from the families Ancistrocladaceae and Dioncophyllaceae, features an imine group in its structure [4, 47]. Ancistrocladidine has been shown to be active against *P. falciparum* K1 [46].

Fig. 18 Structures of chloroquine, amodiaquine, mefloquine and chloroquine analogue AQ13 [14].
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A: \(L=1,4\text{-Dimino butane}; R=4\text{-Ethylphenyl}\)

B: \(L=1,4\text{-Dimino butane}; R=4\text{-Bromophenyl}\)

C: \(L=1,3\text{-Diamino propane}; R=\text{Phenyl}\)

D: \(L=1,3\text{-Diamino propane}; R=4\text{-Isopropylphenyl}\)

Fig. 19 4-Aminoquinoline Schiff base hybrid.

A: \(L=1,4\text{-Dimino butane}; R=4\text{-Ethylphenyl}\)

B: \(L=1,4\text{-Dimino butane}; R=4\text{-Bromophenyl}\)

C: \(L=1,3\text{-Diamino propane}; R=\text{Phenyl}\)

D: \(L=1,3\text{-Diamino propane}; R=4\text{-Isopropylphenyl}\)

Fig. 20 Chemical structure ancistrocladidine Schiff base [4, 8, 48].

and 3D7 [4]. The minimum inhibitory concentrations (MIC values) of ancistrocladidine is necessary to completely abolish \(P. falciparum\) K1 [47] and 3D7 [4].

Some novel aldimine and hydrazone isoquinoline derivatives, prepared by reacting 1-formyl-5-nitroisoquinoline with amines, showed activity against a chloroquine-resistant \(P. falciparum\) strain (ACC Niger). In particular the corresponding Schiff base of formyl-5-nitroisoquinoline (E)-\(N\)-(5-nitroisoquinolin-1-yl)-methylene)-1-(2-(trifluoromethyl)-phenyl) methanamine (Fig. 21) reacts the most effective against \(P. falciparum\) [4, 48].

Cabantchik et al. have reported on the antimalarial activity of deferoxamine (DFO). DFO, is a medication that binds iron and has been extensively used for the treatment of iron overdose. Studies in vitro showed that chelating agents inhibit parasite growth and proliferation by deprivation of the essential nutrient, iron. But that has not used in the clinical treatment of malaria. This is at least partially related to the disadvantages involved in the administration of DFO [68].

The antimalarial activity of DFO prompted several of the researchers to study the antimalarial activities of three aroylhydrazone iron chelators (Fig. 22), namely, 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazine, pyridoxal isonicotinoyl hydrazone and salicylaldehyde isonicotinoyl hydrazone.

These studies showed promising results. Chelators of this class showed greater antimalarial activity than desferrioxamine [68] against chloroquine-resistant and sensitive parasites [34].

Cryptolepine, valid indolchinoline alkaloid, isolated from African plant \(Cryptolepis sanguinolenta\) and used in the treatment of malaria, is the product of multi-stage reaction, in which Schiff base is involved (Fig. 23) [8, 69].

2.4 Antihelminthic Activities

Schistosomiasis or bilharzia is a parasitic disease caused by digenetic trematodes that belong to the family \(Schistosomatoidae\) [71]. Currently, schistosomiasis affects roughly 240 million people in tropical countries, and in certain African communities the process of overcoming schistosomiasis is an important rite of passage. Schistosomiasis causes debilitating nutritional, hematologic and cognitive deficits, with substantial morbidity and mortality in populations [71, 72]. Five
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Fig. 21  Structure of formyl-5-nitroisoquinoline Schiff bases [4, 48].

1: 2-Hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone
2: Pyridoxal isonicotinoyl hydrazone (PIH)
3: Salicylaldehyde isonicotinoyl hydrazone (SIH)

Fig. 22  Structure of the aroylhydrazone chelator [34].

Fig. 23  General method for the synthesis of various 2-substituted cryptolepines [70].

species of Schistosomes are involved in human infection: Schistosoma mansoni, S. intercalatum, S. haematobium, S. japonicum and S. mekongi. S. mansoni and S. intercalatum, S. japonicum and S. mekongi cause intestinal and Asian intestinal schistosomiasis, respectively. S. haematobium resides in the venous plexus, which causes urinary schistosomiasis [73].

9-Acridanone hydrazones (Fig. 24 compound 1) developed by Hoffmann-La Rochewere found to be effective against S. mansoni in mice, killing almost all the skin schistosomuies (24 hr after infection) [15].
Moreover, analogous systems were used by Metwally et al. on mice. The 9-acridanone hydrazone derivative (10-[2-(diethylamino)ethyl]-acridine-9-one (thiazolidine) hydrazone) (Fig. 24 compound 2) expressed the activity relative to S. mansoni, and threefold application of the preparation at a dose of 20 mg/kg after 12 weeks after infection mice led to complete disappearance of all forms of the parasite in the body animals [16].

2.5 Anticonvulsant Activity

Epilepsy is the most common serious neurological disorder worldwide [74], and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain [10], which is affecting about 50 million people [74].

Since majority of antiepileptic drugs are to be consumed life long, the administration of other drugs predisposes to the risk of drug interaction. It is necessary to investigate for antiepileptic agents that are safe, efficacious and free from toxicity [75]. Therefore, it was envisaged that Schiff bases would also exhibit significant anticonvulsant activity.

Schiff base of 3-(4-chloro-phenylimino)-5-methyl-1,3-dihydro-indol-2-one (Fig. 25) was evaluated by Sridhar et al. Studies showed its lesser neurotoxicity compared to phenytoin [75].

Paneersalvam et al. introduced compound structure 3-(3-phenyl-allylideneamino)-6,8-dibromo-2-phenylquinazolin-4(3H)-one Schiff base (Fig. 26). This compound was found to possess high anticonvulsant activity [76].

Ghadage et al. reported novel Schiff base of 3-[(2-aminoethyl) amino] quinoxalin-2(1H)-one (Fig. 27) and evaluated for in vivo anticonvulsant activity by using pentylentetrazole-induced seizure model. Compound, 3-[(2 aminoethyl) amino] quinoxalin-2(1H)-one was synthesized by the reaction between 1,4-dihydroquinoxaline-2,3-dione and ethylene diamine [19, 77]. Some of the synthesized compounds

![Fig. 24 Structure of 9-acridanone hydrazone derivative [15, 16].](image1)

![Fig. 25 Chemical structure of 3-(4-chloro-phenylimino)-5-methyl-1,3-dihydro-indol-2-one [75].](image2)
possessed good anticonvulsant activity compared with the standard drug (pentylentetrazole and diazepam) [77].

2.6 Analgesic, Antiinflammatory and Antiplatelet Activity

An analgesic or painkiller is any member of the group of drugs used to achieve analgesia, relief from pain. Analgesics include paracetamol, the nonsteroidal antiinflammatory drugs (NSAIDs) such as the salicylates, and opioid drugs such as morphine and oxycodone [78].

NSAIDs have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthritis, soft tissue and oral cavity lesions, respiratory tract infections and fever. The cyclooxygenase (COX) enzyme inhibited by NSAIDs was discovered to have at least 2 different isoforms: COX1 and COX2. The two isoforms of COX are poorly distinguishable by most of the classical NSAIDs and these agents actually inhibit COX1 extensively, besides COX2, leading to gastrointestinal injury, suppression of thromboxane A2 (TXA2) formation and platelet aggregation. The combination of these interactions is probably the reason for gastrointestinal bleeding as the most serious complication of these drugs. Some evidences suggest that the hydrazone moiety present in some compounds possess a pharmacophoric character for the inhibition of COX [39, 79].

The gastrointestinal tract (GIT) damage from NSAID is generally attributed to two factors. Local irritation by the direct contact of carboxylic acid (-COOH) moiety of NSAID with GIT mucosal cells (topical effect) and decreased tissue prostaglandin production in tissues which undermines the physiological role of cytoprotective prostaglandins in maintaining GIT health and homoeostasis.

Synthetic approaches based upon chemical modification of NSAIDs have been taken with the aim of improving safety profile NSAIDs. Several studies have described the derivatization of the carboxylate function of representative NSAID with less acidic azoles, viz. 1,3,4-oxadiazole, triazole, which resulted in an increased antiinflammatory activity with reduced ulcerogenicity. Furthermore, it has been reported in the literature that certain compounds bearing 1,3,4-oxadiazole nucleus possess significant anti-inflammatory activity.

Bhandari et al. replaced the carboxylic acid group of diclofenac acid with less acidic heterocycle, in order to accentuate potency and reduce GIT toxicities associated with the parent diclofenac due to its free -COOH group. The compounds (Fig. 28) designed so were found to possess much significant analgesic-antiinflammatory profile with significant
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reduction in potential for ulcerogenic toxicities [79, 80].

Geronikaki et al. reported the synthesis of series of thiazolyl and benzothiazolyl Schiff bases (compounds 1 and 2 in Fig. 29, respectively) having analgesic and antiinflammatory activities against asthma, rheumatoid arthritis and psoriasis [81, 82].

A new series of antinociceptive compounds that belong to the N-acylarylhydrazone class were synthesized from natural safrole. \([4′-N,N\text{-Dimethylaminobenzylidene}-3\text{-}(3′,4′\text{-methylene dioxynaphthyl}) propionylhydrazine]\) (Fig. 30) was more potent than dipyrene and indomethacine, which are used as standard antiinflammatory/antinociceptive drugs [34].

Salgin-Goksen et al. synthesized of hydrazones containing 5-methyl-2-benzoxazoline. The analgesic effects of 2\-\[2\-\(5\text{-methyl-2-benzoxazoline-3-yl}\) acetyl\]-4-chloro-4-methyl benzylidene hydrazine (Fig. 31) were found to be higher than those of morphine and aspirin.

Schiff bases also hold a place in the area of antiplatelet drug. Platelet aggregation is one of the most important factors in the development of thrombotic disorders which plays a central role in thrombosis (clot formation). Barreiro et al. in a series of studies managed to develop some new hydrazones (Fig. 32) which effectively inhibited platelet aggregation with selective inhibitory activity toward

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**Fig. 28** Structure of Schiff base derived from 2\-\[(2,6\text{-dichloroanilino})\text{phenyl}\] acetic acid (diclofenac acid) [80].

**Fig. 29** Thiazolyl and benzothiazolyl Schiff bases [82].

**Fig. 30** Structure of \([4′-N,N\text{-dimethylaminobenzylidene}-3\text{-}(3′,4′\text{-methylene dioxynaphthyl}) propionylhydrazine]\) [34].
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1. Schiff Bases

2. Structures of some analgetic hydrazones [83].

3. Some structures of the general hydrazone derivatives with antiplatelet activity.

platelet aggregation induced by arachidonic acid. They found active group of hydrazones with arylsulfonate acylhydrazone [20], phenothiazine-1-acylhydrazone [84] and N-substituted-phenyl-1,2,3-triazole-4-acylhydrazone [85] structures.

3. Conclusions

Schiff bases have been widely explored for industrial applications. However, the biological activity of this class of compounds deserves further investigation. Although the research on this subject is incipient, a number of reports disclosing the effects of the imines on the pathogens of clinical interest have recently been increasing. Schiff base compounds have been shown to be promising molecules for the design of more efficient antibacterial, antimycobacterial, antianthrax, antifungal, antiviral, anticancer, antiprotozoal, anthelmintic, anticonvulsant, antiinflammatory, analgesic and antiplatelet therapeutics. Advances in this field will require analyses of the structure-activity relationships of the Schiff bases as well as the mechanism of action of these compounds.

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