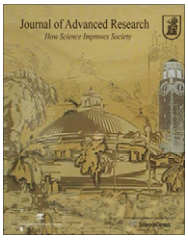
Journal of Advanced Research (2011) 2, 1–8

Cairo University

Journal of Advanced Research



REVIEW

Schiff bases: A short review of their antimicrobial activities

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Available online 9 June 2010

KEYWORDS

Schiff bases;
Antimalarial;
Antifungal;
Antibacterial;
Antiviral;
In vitro activity

Abstract Schiff bases are aldehyde- or ketone-like compounds in which the carbonyl group is replaced by an imine or azomethine group. They are widely used for industrial purposes and also exhibit a broad range of biological activities. This short review compiles examples of the most promising antimalarial, antibacterial, antifungal, and antiviral Schiff bases. An overview of synthetic methodologies used for the preparation of Schiff bases is also described.

Introduction

Schiff bases, named after Hugo Schiff [1], are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as imine or azomethine) (Fig. 1) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C═O) has been replaced by an imine or azomethine group.

Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilisers [2]. Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties [2,3]. Imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds (see Fig. 2 for some examples). The imine group present in such compounds has been shown to be critical to their biological activities [4–6].

In this review we present the general approaches to the synthesis of Schiff bases. We also highlight the most significant examples of compounds belonging to this class, which exhibit antimalarial, antibacterial, antifungal, and/or antiviral activities to have been reported in the literature. The relationship between Schiff bases and other pharmacological activities, such as antiproliferative activities, are not included in this review.

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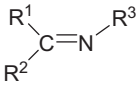
2090-1232

Peer review under responsibility of Cairo University.
doi:10.1016/j.jare.2010.05.004

Production and hosting by Elsevier



R^1, R^2, and/or R^3 = alkyl or aryl

Fig. 1 General structure of a Schiff base.

Synthesis of Schiff bases

The first preparation of imines was reported in the 19th century by Schiff (1864). Since then a variety of methods for the synthesis of imines have been described [7]. The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation [8]. Molecular sieves are then used to completely remove water formed in the system [9]. In the 1990s an *in situ* method for water elimination was developed, using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate [10,11]. In 2004, Chakraborti et al. [12] demonstrated that the efficiency of these methods is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. They proposed as an alternative the use of substances that function as Brönsted-Lowry or Lewis acids to activate the carbonyl group of aldehydes, catalyze the nucleophilic attack by amines, and dehydrate the system, eliminating water as the final step [12]. Examples of Brönsted-Lowry or lewis acids used for the synthesis of Schiff bases include $ZnCl_2$, $TiCl_4$, $MgSO_4$-PPTS, $Ti(OR)_4$, alumina, H_2SO_4, $NaHCO_3$, $MgSO_4$, $Mg(ClO_4)_2$, H_3CCOOH, $Er(OTf)_3$, P_2O_5/Al_2O_3, HCl [12–24].

In the past 12 years a number of innovations and new techniques have been reported, including solvent-free/clay/microwave irradiation, solid-state synthesis, K-10/microwave, water suspension medium, [bmim]BF_4/molecular sieves, infrared irradiation/no solvent, $NaHSO_4{\cdot}SiO_2$/microwave/solvent-free, solvent-free/CaO/microwave, and silica/ultrasound irradiation [25–33]. Among these innovations, microwave irradiation has been extensively used due to its operational simplicity, enhanced reaction rates, and great selectivity [32]. The use of microwave irradiation commenced with the independent studies of Rousell and Majetich groups [34,35]. Microwave irradiation is less environmentally problematic than other methods because it abolishes the excessive use of aromatic solvents and the Dean-Stark apparatus for azeotropic removal of water. Another feature of this technique is that the reactions achieve high efficiency in a shorter period of time.

Biological activities of schiff bases

Antimalarial activity

Malaria is a neglected disease that still causes serious public health problems. Every year, approximately 500 million people are afflicted by the disease, of whom around 1–3 million die, 90% of who in sub-Sahara Africa are primarily children [36]. Malaria is currently found in more than 100 countries throughout Africa, Latin America, Asia, and Oceania. Human malaria is mainly caused by four species of *Plasmodium* (*P. falciparum*, *P. vivax*, *P. ovale,* and *P. malariae*). The female mosquito of the *Anopheles* genus is the vector of *Plasmodium* [37]. The search for new drugs, vaccines, and insecticides to prevent or treat this disease is clearly a priority.

Schiff bases have been shown to be interesting moieties for the design of antimalarial agents. Ancistrocladidine (**1**; Fig. 2) is a secondary metabolite produced by plants from the families Ancistrocladaceae and Dioncophyllaceae that present an imine group in its molecular scaffold. Compound **1** has been shown to be active against *P. falciparum* K1 and 3D7. The minimum inhibitory concentrations (MIC values) of ancistrocladidine necessary to completely abolish *P. falciparum* K1 and 3D7 growth were 0.3 and 1.9 μg/mL, respectively. Interestingly, compound **1** was 90- and 10-fold more selective to *P. falciparum* K1 and 3D7,respectively than to rat skeletal myoblast L-6 cells [4]. Rathelot et al. [38] described the synthesis of Schiff base-functionalised 5-nitroisoquinolines and investigated the *in vitro* activity of these compounds against an ACC Niger chloroquine resistant *P. falciparum* strain. Schiff base **5** (Fig. 3) was the most effective antimalarial agent among the synthesised 5-nitroisoquinoline derivatives. The concentration of compound **5** necessary to inhibit *P. falciparum* growth by 50% (IC_{50}) was 0.7 μg/mL. Under the same experimental conditions the IC_{50} value for chloroquine was 0.1 μg/mL [38].

Antibacterial activity

The increase in the mortality rate associated with infectious diseases is directly related to bacteria that exhibit multiple resistance to antibiotics. The lack of effective treatments is the main cause of this problem [39,40]. The development of new antibacterial agents with novel and more efficient mechanisms of action is definitely an urgent medical need [41].

Schiff bases have been pointed to as promising antibacterial agents. For example, *N*-(salicylidene)-2-hydroxyaniline (**4**; Fig. 2) is effective against *Mycobacterium tuberculosis* H37Rv, exhibiting an MIC value of 8 μg/mL [5]. The selectivity of compound **4** was checked by performing experiments with J774 macrophages. No cytotoxic effect on J774 macrophages was observed for compound **4**, even when it was tested at concentrations as high as 1000 μg/mL. More than 80% of macrophage cells were viable at such experimental conditions, demonstrating the high selectivity of compound **4**.

The synthesis and antimicrobial activity of a series of Schiff bases derived from the condensation of 5-chloro-salicylaldehyde and primary amines has recently been reported [42]. The 5-chloro-salicylaldehyde-Shiff base derivatives **6–15** (Fig. 3) were most active against at least one of the evaluated bacterial species. *Pseudomonas fluorescence* was the strain most sensitive to compounds **6–11** and **13–15**, with MIC values ranging from 2.5 to 5.2 μg/mL. The MIC value for the reference drug kanamycin against the same bacterial strain was 3.9 μg/mL. The Schiff bases **6**, **7**, **9–11**, **14,** and **15** presented MIC values in the range of 1.6–5.7 μg/mL against *Escherichia coli*, while the MIC value for kanamycin was 3.9 μg/mL. *Bacillus subtilis* was sensitive to the Schiff base **14** only (MIC = 1.8 μg/mL). The MIC values for compounds **6** and **7** against *Staphylococcus aureus* were, respectively, 3.1 and 1.6 μg/mL [42].

Isatin-derived Schiff bases have also been reported to possess antibacterial activity [43]. Twenty-eight bacteria of clinical interest were used in the studies performed by Pandeya and colleagues. The authors disclosed the isatin-derived Schiff base **16** (Fig. 3) as the most potent compound amongst those syn-