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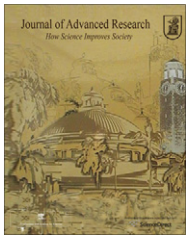

REVIEW

Schiff bases: A short review of their antimicrobial activities

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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as imine or azomethine) (Fig. 1) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C═O) has been replaced by an imine or azomethine group.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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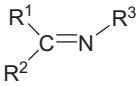

R^1, R^2, and/or R^3 = alkyl or aryl

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-

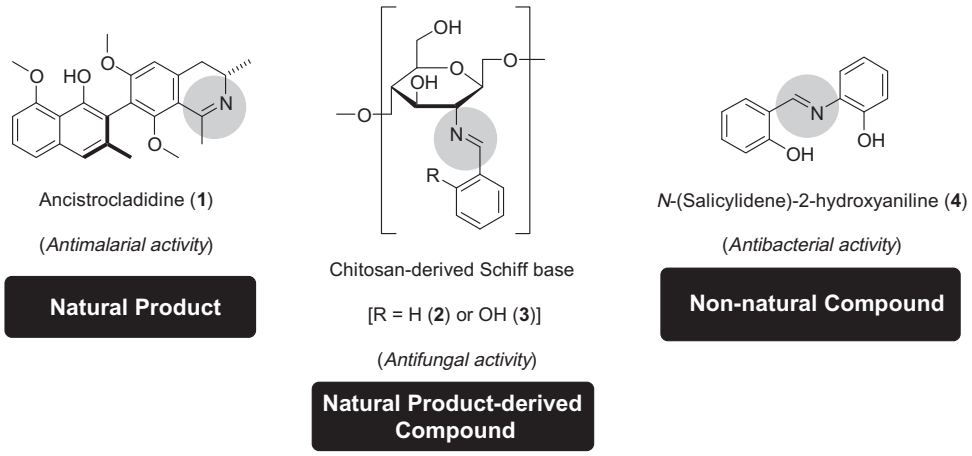

Fig. 2 Examples of bioactive Schiff bases. The imine or azomethine group present in each molecular structure is shaded.

thesised against all the pathogenic bacteria studied. The MIC values for compound **16** against *E. coli* NCTC 10418, *Vibrio cholerae* non-01, *Enterococcus faecalis*, *Proteus shigelloides* were 2.4, 0.3, 1.2, and 4.9 μg/mL, respectively, while the MIC values for sulfamethoxazole (reference drug) against the same bacterial strains were in the range of 312–5000 μg/mL. Thus compound **16** was notably 1040-, 1040-, 4160-, and 1020-fold more potent than sulphamethoxazole. Other isatin-derived Schiff bases have been described in the literature, but with no expressive antibacterial activities [44,45].

The isoniazid-derived Schiff base **17** (Fig. 3) was active against *M. tuberculosis* H37Rv, exhibiting an MIC value of 0.03 mg/L [46]. In this respect, compound **17** was slightly more potent than isoniazid, its immediate synthetic precursor. Additionally, the isoniazid-derived Schiff base **17** was not toxic against the cell line VERO (epithelial cells from healthy monkey kidney). The IC_{50} for compound **17** against VERO cells was as high as 1 g/mL, indicating that this isoniazid-derived Schiff base is selective for bacterial cells. The therapeutic safety and effectiveness for compound **17** is higher than 40,000, making this Schiff base an excellent lead for the development of antitubercular agents [46].

In 2005, Panneerselvam et al. [21] described the synthesis and *in vitro* antibacterial activity of eleven morpholine-derived Schiff bases. Fig. 3 shows the chemical structure of three of them (compounds **18**–**20**). The authors found that *S. aureus* and *Micrococcus luteus* were the bacteria most sensitive to the morpholine-derived Schiff base **18** (MIC = 20 and 32 μg/mL, respectively). *Streptococcus epidermidis* was more sensitive to the morpholine-derived Schiff base **19** (MIC = 17 μg/mL) and *Bacillus cereus* and *E. coli* were more sensitive to compound **20** (MIC = 21 and 16 μg/mL, respectively).

Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety are also effective in the inhibition of bacterial growth. Schiff bases from this class (compounds **21**–**24** in Fig. 3) completely inhibited the growth of *S. aureus*, *E. coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* [47]. MIC values for these compounds varied from 6.3 to 12.5 μg/mL, which are comparable to those obtained for the reference drug ciprofloxacin [47].

Madurahydroxylactone Schiff bases are imines derived from natural products. Madurahydroxylactones are secondary metabolites produced by the plant *Actinomadura rubra* [48]. The imines **25**–**30** (Fig. 4) are examples of Schiff bases belonging to this class. With the exception of compounds **25** and **30**, all madurahydroxylactone-derived compounds were effective in the *in vitro* inhibition of *B. subtilis*, *Micrococcus flavus*, *Sarcina lutea,* and *S. aureus* growth, with MIC values varying from 0.2 to 3.1 μg/mL [49]. These same compounds (**26**–**29**) presented very low activity against *Mycobacterium phlei* or *Proteus vulgaris* (MIC values higher than > 50.0 μg/mL) [49].

Other molecules of natural or non-natural origin that are platforms for the synthesis of Schiff bases for antibacterial activities include amino acids, coumarins, sulfonamides, or resacetophenones, aminothiazolyl bromocoumarins, crown ethers, *O*-phthaldehyde, or 2-aminophenol and 1,2,4-triazoles [24,50–56]. The antibacterial property of compounds representative of these classes was examined. However, they did not exhibit any notable activity.

Antifungal activity

Fungal infections are not usually limited to the superficial tissues; indeed, a significant increase in life threatening systemic fungal infections has been reported [57]. The fundamental reason for this is the increasing number of patients at risk, including those with advanced age, major surgery, immunosuppressive therapy, acquired immunodeficiency syndrome (AIDS), cancer treatment, and solid-organ and hematopoietic stem cell transplantation [58]. The search and development of more effective antifungal agents are mandatory [59,60] and some Schiff bases are known to be promising antifungal agents.

Alternaria brassicae and *Alternaria brassicicola* are phytopathogenic fungi that severely affect the production of most cruciferous crops (broccoli, cauliflower, mustard, turnip, cabbage, rape, and radish). *N*-(Salicylidene)-2-hydroxyaniline **4** (Fig. 2) at the concentration of 500 ppm inhibited the growth of these fungi by 67–68% [61]. Compounds **2** and **3** (Fig. 2) are examples of chitosan-derived Schiff bases with antifungal activity. They inhibited the growth of *Botrytis cinerea* and *Colletotrichum lagenarium* by 26–33% and 35–38% when used at 1000 ppm, respectively [6]. Overall, studies evaluating the effect of Schiff bases on phytopathogenic fungal growth have been modest and deserve more investigation.

Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety, such as compounds **21** (Fig. 3) and **31**–**34** (Fig. 5) have been demonstrated to inhibit the growth of fungi of clinical interest, such as

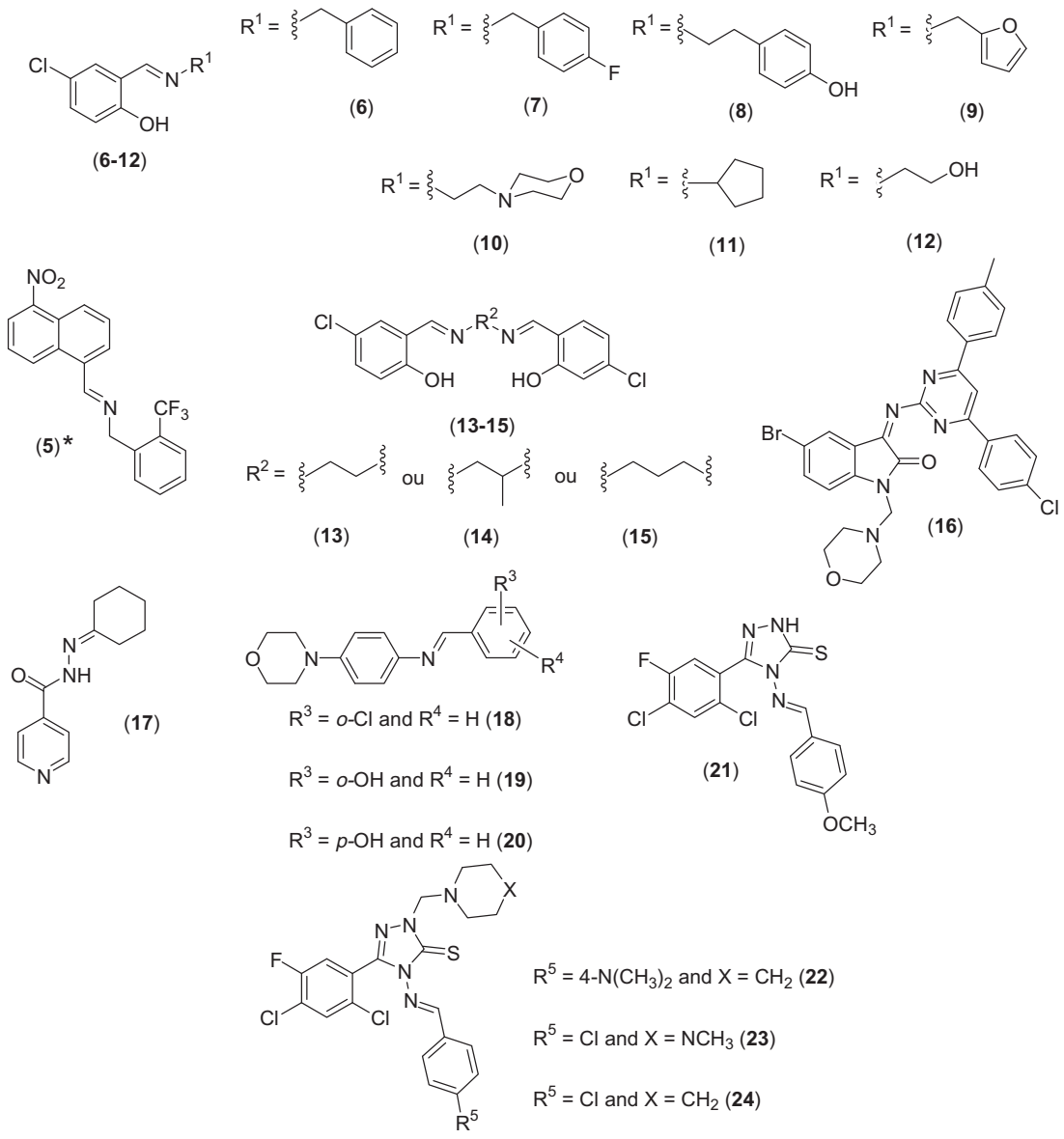

Fig. 3 Chemical structure of some synthetic antibacterial Schiff bases. *Compound **5** is an antimalarial agent.

Aspergillus fumigatus, *Aspergillus flavus*, *Trichophyton mentagrophytes,* and *Penicillium marneffei*. The MIC values for these compounds were in the range of 6.3–12.5 μg/mL, indicating that they are as potent as the reference fluconazole [47].

Piperonyl-derived Schiff bases (**35**–**40**, Fig. 5) were active against some fungi at micromolar concentrations. They inhibited the growth of *Trichophyton rubrum* (MIC = 820–980 μM) and *Epidermophyton floccosum* (MIC = 200–930 μM) [62]. The isatin-derived Schiff bases **16** (Fig. 3) and **41**–**51** (Fig. 5) were considerably active against *Microsporum audouinii* (MIC values ranging from 2.4 to 9.7 μg/mL) and *Microsporum gypseum* (MIC values ranging from 1.2 to 9.7 μg/mL) [43]. Compounds **16** and **41**–**51** also inhibited the growth of *Candida albicans*, *Aspergillus niger*, *Cryptococcus neoformans*, *T. mentagrophytes*, *E. floccosum*, and *Histoplasma capsulatum* at MIC values higher than 10 μg/mL and lower than 79 μg/mL [43]. In another study, Panneerselvam et al. [21] showed that the growth of both *C. albicans* and *A. niger* was compromised by treatment with compound **20** (Fig. 3) at 20 μg/mL or compound **52** (Fig. 5) at 30 μg/mL.

As for antibacterial activity, natural product-derived Schiff bases are also promising for the design of new antifungal agents. Domb and colleagues have described an interesting approach to synthesize a nystatin-dextran-derived Schiff base (**53**, Fig. 5). This approach dramatically improved nystatin solubility in water [63]. Compound **53** completely inhibited the growth of *C. albicans* and *C. neoformans* at 20 μg/mL, while a concentration of 10 μg/mL was required for free nystatin to have a similar effect. Although the nystatin-dextran-derived Schiff base **53** was less active than nystatin itself, the former was shown to be much less toxic to normal cells [63].

Antiviral activity

The use of vaccines may lead to the eradication of viral pathogens, such as smallpox, polio, and rubella. However, virus-re-

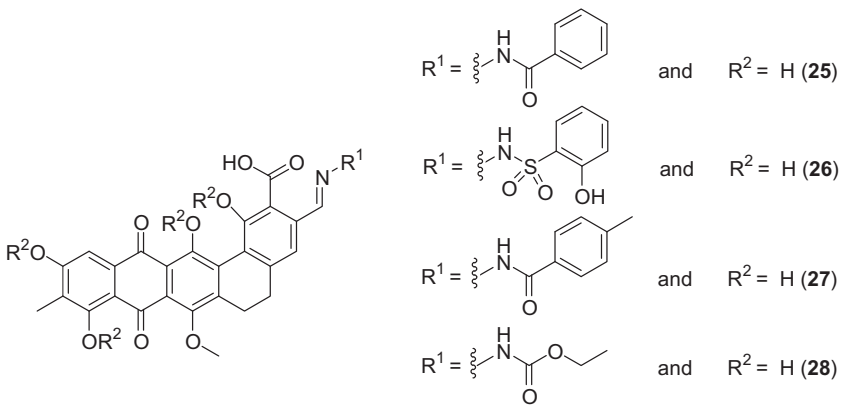

Fig. 4 Examples of antibacterial Schiff bases derived from plant natural products.

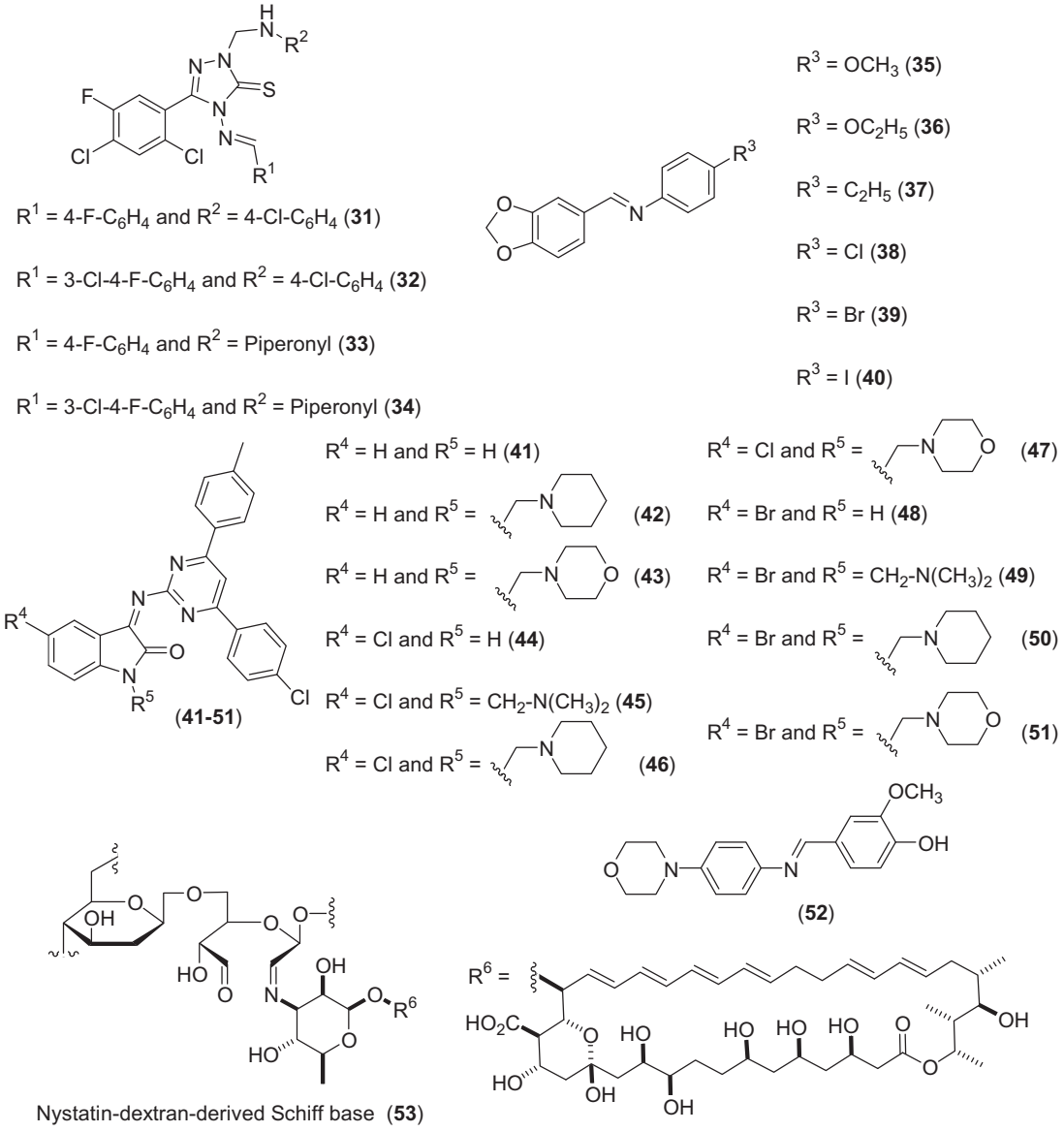

Fig. 5 Chemical structure of some antifungal Schiff bases derived from natural or non-natural compounds.

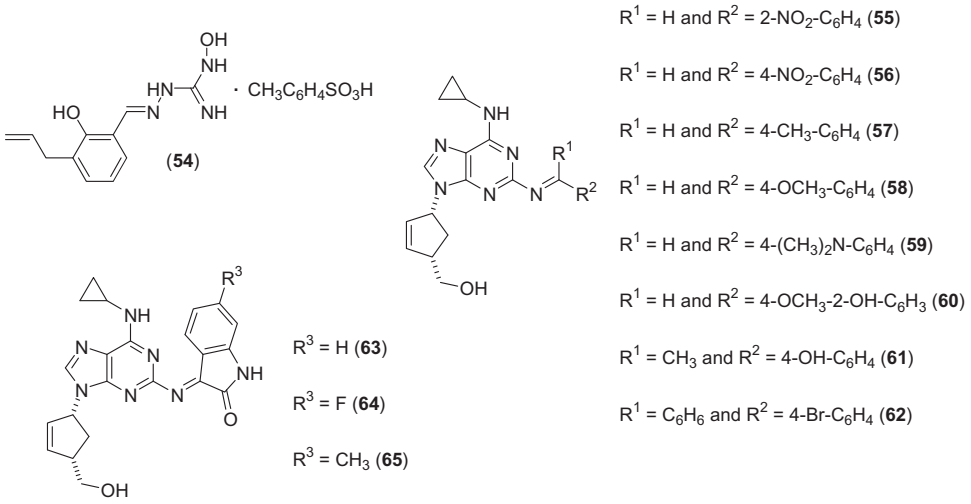

Fig. 6 Examples of antiviral synthetic Schiff bases.

lated and hepatitis C human immunodeficiency diseases have been the drawback of vaccine approaches [64]. Viral diseases are life-threatening for immunocompromised patients and a prompt treatment is required to overcome this problem. Although there are many therapeutic options for viral infections, currently available antiviral agents are not yet fully effective, probably due to the high rate of virus mutation. They may also present any of a number of side effects.

Salicylaldehyde Schiff bases of 1-amino-3-hydroxyguanidine tosylate are a good platform for the design of new antiviral agents [65,66]. In fact, from a set of different 1-amino-3-hydroxyguanidine tosylate-derived Schiff bases, compound **54** (Fig. 6) was shown to be very effective against mouse hepatitis virus (MHV), inhibiting its growth by 50% when employed at concentrations as low as 3.2 μM [66].

Recently, Sriram and colleagues [66] reported the synthesis and antiviral activity of the abacavir-derived Schiff bases **55**–**65** (Fig. 6). These compounds are a new series of abacavir prodrugs. Abacavir is a nucleoside analogue capable of inhibiting the activity of reverse transcriptase. It is used to treat human immunodeficiency virus (HIV) and AIDS, and is available under the trade name Ziagen® (GlaxoSmithKline). Compounds **55**–**65** were significantly effective against the human immunodeficiency virus-type 1 (HIV-1). The effective concentration (EC_{50}) of these abacavir-derived Schiff bases necessary to achieve 50% protection of human leukemic cells (CEM) against the cytopathic effect of HIV-1 was lower than 6 μM [66]. Notably, compound **57** was the most potent Schiff base, being effective at 50 nM. This compound is only toxic to CEM cells at concentrations higher than 100 μM, indicating its potential as a lead compound for the design of new anti-HIV-1 [66].

Concluding remarks

Schiff bases have been widely explored for industrial applications. However, the biological activity of this class of compounds deserves further investigation. This becomes clear when plant pathogens are considered. Although the research on this subject is incipient, a number of reports disclosing the effects of the Schiff bases on the pathogens of clinical interest have recently been increasing. Schiff base compounds have been shown to be promising leads for the design of more efficient antimicrobial agents. 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.

Acknowledgements

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References

[1] Schiff H. Mittheilungen aus dem universitätslaboratorium in Pisa: Eine neue reihe organischer basen. Justus Liebigs Ann Chem 1864;131(1):118–9.
[2] Dhar DN, Taploo CL. Schiff bases and their applications. J Sci Ind Res 1982;41(8):501–6.
[3] Przybylski P, Huczynski A, Pyta K, Brzezinski B, Bartl F. Biological properties of schiff bases and azo derivatives of phenols. Curr Org Chem 2009;13(2):124–48.
[4] Bringmann G, Dreyer M, Faber JH, Dalsgaard PW, Staerk D, Jaroszewski JW, et al. Ancistrotanzanine C and related 5,1′- and 7,3′-coupled naphthylisoquinoline alkaloids from *Ancistrocladus tanzaniensis*. J Nat Prod 2004;67(5):743–8.
[5] de Souza AO, Galetti FCS, Silva CL, Bicalho B, Parma MM, Fonseca SF, et al. Antimycobacterial and cytotoxicity activity of synthetic and natural compounds. Quim Nova 2007;30(7):1563–6.
[6] Guo Z, Xing R, Liu S, Zhong Z, Ji X, Wang L, et al. Antifungal properties of Schiff bases of chitosan, *N* -substituted chitosan and quaternized chitosan. Carbohydr Res 2007;342(10):1329–32.
[7] Zheng Y, Ma K, Li H, Li J, He J, Sun X, et al. One pot synthesis of imines from aromatic nitro compounds with a novel Ni/SiO_2 magnetic catalyst. Catal Lett 2009;128(3-4):465–74.
[8] Moffett RB. In: Rabjohn N, editor. Organic syntheses, vol. 4. New York (USA): John Wiley & Sons, Inc.; 1963. p. 605–8.
[9] Taguchi K, Westheimer FH. Catalysis by molecular sieves in the preparation of ketimines and enamines. J Org Chem 1971;36(11):1570–2.
[10] Love BE, Ren J. Synthesis of sterically hindered imines. J Org Chem 1993;58(20):5556–7.

[11] Look GC, Murphy MM, Campbell DA, Gallop MA. Trimethylorthoformate: a mild and effective dehydrating reagent for solution and solid phase imine formation. Tetrahedron Lett 1995;36(17):2937–40.
[12] Chakraborti AK, Bhagat S, Rudrawar S. Magnesium perchlorate as an efficient catalyst for the synthesis of imines and phenylhydrazones. Tetrahedron Lett 2004;45(41):7641–4.
[13] Billman JH, Tai KM. Reduction of Schiff bases. II. Benzhydrylamines and structurally related compounds. J Org Chem 1958;23(4):535–9.
[14] White WA, Weingarten H. A versatile new enamine synthesis. J Org Chem 1967;32(1):213–4.
[15] Branchaud BP. Studies on the preparation and reactions of tritylsulfenimines. J Org Chem 1983;48(20):3531–8.
[16] Armstrong III JD, Wolfe CN, Keller JL, Lynch J, Bhupathy M, Volante RP, et al. A novel synthesis of disubstituted ureas using titanium(IV) isopropoxide and sodium borohydride. Tetrahedron Lett 1997;38(9):1531–2.
[17] Liu G, Cogan DA, Owens TD, Tang TP, Ellman JA. Synthesis of enantiomerically pure *N-tert*-butanesulfinyl imines (*tert*-butanesulfinimines) by the direct condensation of *tert*-butanesulfinamide with aldehydes and ketones. J Org Chem 1999;64(4):1278–84.
[18] Roman G, Andrei M. New Schiff bases from *ortho*-hydroxyaryl aldehydes. Bull Chem Technol Macedonia 2001;20(2):131–6.
[19] Samec JSM, Backvall JE. Ruthenium-catalyzed transfer hydrogenation of imines by propan-2-ol in benzene. Chem Eur J 2002;8(13):2955–61.
[20] Baricordi N, Benetti S, Biondini G, de Risi C, Pollini GP. A new 'one-pot' synthesis of 2-substituted 3-nitropyrrolidines through a multicomponent domino reaction. Tetrahedron Lett 2004;45(7):1373–5.
[21] Panneerselvam P, Nair RR, Vijayalakshmi G, Subramanian EH, Sridhar SK. Synthesis of Schiff bases of 4-(4-aminophenyl)-morpholine as potential antimicrobial agents. Eur J Med Chem 2005;40(2):225–9.
[22] Dalpozzo R, de Nino A, Nardi M, Russo B, Procopio A. Erbium(III) triflate: a valuable catalyst for the synthesis of aldimines, ketimines and enaminones. Synthesis 2006;7:1127–32.
[23] Naeimi H, Salimi F, Rabiei K. Mild and convenient one pot synthesis of Schiff bases in the presence of P_2O_5/Al_2O_3 as new catalyst under solvent-free conditions. J Mol Catal A Chem 2006;260(1–2):100–4.
[24] Kulkarni A, Patil SA, Badami PS. Synthesis, characterization, DNA cleavage and *in vitro* antimicrobial studies of La(III), Th(IV) and VO(IV) complexes with Schiff bases of coumarin derivatives. Eur J Med Chem 2009;44(7):2904–12.
[25] Varma RS, Dahiya R, Kumar S. Clay catalyzed synthesis of imines and enamines under solvent-free conditions using microwave irradiation. Tetrahedron Lett 1997;38(12): 2039–42.
[26] Schmeyers J, Toda F, Boy J, Kaupp G. Quantitative solid–solid synthesis of azomethines. J Chem Soc Perkin Trans 2 1998:989–93.
[27] Vass A, Dudás J, Varma RS. Solvent-free synthesis of *N*-sulfonylimines using microwave irradiation. Tetrahedron Lett 1999;40(27):4951–4.
[28] Tanaka K, Shiraishi R. Clean and efficient condensation reactions of aldehydes and amines in a water suspension medium. Green Chem 2000;2(6):272–3.
[29] Andrade CKZ, Takada SCS, Alves LM, Rodrigues JP, Suarez PAZ, Brandão RF, et al. Molecular sieves in ionic liquids as an efficient and recyclable medium for the synthesis of imines. Synlett 2004;12:2135–8.
[30] Vázquez MÁ, Landa M, Reyes L, Miranda R, Tamariz J, Delgado F. Infrared irradiation: effective promoter in the formation of *N*-benzylideneanilines in the absence of solvent. Synth Commun 2004;34(15):2705–18.
[31] Gopalakrishnan M, Sureshkumar P, Kanagarajan V, Thanusu J, Govindaraju R. Silica gel supported sodium hydrogen sulfate as an efficient and reusable heterogeneous catalyst for the synthesis of imines in solvent-free conditions under microwave irradiation. J Chem Res 2005;5:299–303.
[32] Gopalakrishnan M, Sureshkumar P, Kanagarajan V, Thanusu J. New environmentally-friendly solvent-free synthesis of imines using calcium oxide under microwave irradiation. Res Chem Intermed 2007;33(6):541–8.
[33] Guzen KP, Guarezemini AS, Órfão ATG, Cella R, Pereira CMP, Stefani HA. Eco-friendly synthesis of imines by ultrasound irradiation. Tetrahedron Lett 2007;48(10):1845–8.
[34] Gedye R, Smith F, Westaway K, Ali H, Baldisera L, Laberge L, et al. The use of microwave ovens for rapid organic synthesis. Tetrahedron Lett 1986;27(3):279–82.
[35] Giguere RJ, Bray TL, Duncan SM, Majetich G. Application of commercial microwave ovens to organic synthesis. Tetrahedron Lett 1986;27(41):4945–8.
[36] Bohach GA, Fast DJ, Nelson RD, Schlievert PM. Malaria. In: Rodes J, Benhamou JP, Blei A, Reichen J, Rizzetto M, editors. The textbook of hepatology: from basic science to clinical practice. Oxford (UK): Wiley Blackwell; 2007. p. 1029–34.
[37] Kayser O, Kiderlen AF, Croft SL. Natural products as potential antiparasitic drugs. Parasitol Res 2003;90(Suppl 2):S55–62.
[38] Rathelot P, Vanelle P, Gasquet M, Delmas F, Crozet MP, Timon-David P, et al. Synthesis of novel functionalized 5-nitroisoquinolines and evaluation of *in vitro* antimalarial activity. Eur J Med Chem 1995;30(6):503–8.
[39] Baquero F. Gram-positive resistance: challenge for the development of new antibiotics. J Antimicrob Chemother 1997;39(Suppl.A):1–6.
[40] Alekshun MN, Levy SB. Molecular mechanisms of antibacterial multidrug resistance. Cell 2007;128(6):1037–50.
[41] Rice LB. Unmet medical needs in antibacterial therapy. Biochem Pharmacol 2006;71(7):991–5.
[42] Shi L, Ge HM, Tan SH, Li HQ, Song YC, Zhu HL, et al. Synthesis and antimicrobial activities of Schiff bases derived from 5-chloro-salicylaldehyde. Eur J Med Chem 2007;42(4):558–64.
[43] Pandeya SN, Sriram D, Nath G, de Clercq E. Synthesis and antimicrobial activity of Schiff and Mannich bases of isatin and its derivatives with pyrimidine. IL Farmaco 1999;54(9):624–8.
[44] Pandeya SN, Sriram D, Nath G, de Clercq E. Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and *N*-[4-(4′-chlorophenyl)thiazol-2-yl] thiosemicarbazide. Eur J Pharm Sci 1999;9(1):25–31.
[45] Jarrahpour A, Khalili D, de Clercq E, Salmi C, Brunel JM. Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives. Molecules 2007;12(8):1720–30.
[46] Hearn MJ, Cynamon MH. Design and synthesis of antituberculars: preparation and evaluation against *Mycobacterium tuberculosis* of an isoniazid Schiff base. J Antimicrob Chemother 2004;53(2):185–91.
[47] Karthikeyan MS, Prasad DJ, Poojary B, Bhat KS, Holla BS, Kumari NS. Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety. Bioorg Med Chem 2006;14(22):7482–9.
[48] Paulus EF, Dornberger K, Werner W, Fenske D. Madurahydroxylactone. Acta Crystallogr 1994;50(12):2064–7.
[49] Heinisch L, Roemer E, Jutten P, Haas W, Werner W, Mollmann U. Semisynthetic derivatives of madurahydroxylactone and their antibacterial activities. J Antibiot (Tokyo) 1999;52(11):1029–41.
[50] Chohan ZH, Arif M, Sarfraz M. Metal-based antibacterial and antifungal amino acid derived Schiff bases: their synthesis, characterization and *in vitro* biological activity. Appl Organomet Chem 2007;21(4):294–302.

[51] Baluja S, Solanki A, Kachhadia N. Evaluation of biological activities of some Schiff bases and metal complexes. J Iran Chem Soc 2006;3(4):312–7.
[52] Venugopala KN, Jayashree BS. Microwave-induced synthesis of Schiff bases of aminothiazolyl bromocoumarins as antibacterials. Indian J Pharm Sci 2008;70(1):88–91.
[53] Yildiz M, Kiraz A, Dülger B. Synthesis and antimicrobial activity of new crown ethers of Schiff base type. J Serb Chem Soc 2007;72(3):215–24.
[54] Abdallah SM, Mohamed GG, Zayed MA, El-Ela MSA. Spectroscopic study of molecular structures of novel Schiff base derived from *O*-phthaldehyde and 2-aminophenol and its coordination compounds together with their biological activity. Spectrochim Acta Part A: Mol Biomol Spectrosc 2009;73(5):833–40.
[55] T'ang A, Lien EJ, Lai MMC. Optimization of the Schiff bases of *N*-hydroxy-*N*′-aminoguanidine as anticancer and antiviral agents. J Med Chem 1985;28(8):1103–6.
[56] Bayrak H, Demirbas A, Karaoglu SA, Demirbas N. Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities. Eur J Med Chem 2009;44(3):1057–66.
[57] Sundriyal S, Sharma RK, Jain R. Current advances in antifungal targets and drug development. Curr Med Chem 2006;13(11):1321–35.
[58] Nucci M, Marr KA. Emerging fungal diseases. Clin Infect Dis 2005;41(4):521–6.
[59] Martins CVB, da Silva DL, Neres ATM, Magalhães TFF, Watanabe GA, Modolo LV, et al. Curcumin as a promising antifungal of clinical interest. J Antimicrob Chemother 2009;63(2):337–9.
[60] Martins CVB, de Resende MA, da Silva DL, Magalhães TFF, Modolo LV, Pilli RA, et al. *In vitro* studies of anticandidal activity of goniothalamin enantiomers. J Appl Microbiol 2009;107(4):1279–86.
[61] Rehman W, Baloch MK, Muhammad B, Badshah A, Khan KM. Characteristic spectral studies and *in vitro* antifungal activity of some Schiff bases and their organotin (IV) complexes. Chin Sci Bull 2004;49(2):119–22.
[62] Echevarria A, Nascimento MG, Gerônimo V, Miller J, Giesbrecht A. NMR spectroscopy, hammett correlations and biological activity of some Schiff bases derived from piperonal. J Braz Chem Soc 1999;10(1):60–4.
[63] Domb AJ, Linden G, Polacheck I, Benita S. Nystatin-dextran conjugates: synthesis and characterization. J Polym Sci Part A: Polym Chem 1996;34(7):1229–36.
[64] de Clercq E. Strategies in the design of antiviral drugs. Nat Rev Drug Discov 2002;1:13–25.
[65] Wang PH, Keck JG, Lien EJ, Lai MMC. Design, synthesis, testing and quantitative structure–activity relationship analysis of substituted salicylaldehyde Schiff bases of 1-amino-3-hydroxyguanidine tosylate as new antiviral agents against coronavirus. J Med Chem 1990;33(2):608–14.
[66] Sriram D, Yogeeswari P, Myneedu NS, Saraswat V. Abacavir prodrugs: microwave-assisted synthesis and their evaluation of anti-HIV activities. Bioorg Med Chem Lett 2006;16(8):2127–9.