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RECENT PHARMACOLOGICAL ADVANCEMENTS IN SCHIFF BASES: A REVIEW

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Abstract: Schiff bases are the biologically privileged scaffolds in organic chemistry, commonly synthesized from the condensation reaction of carbonyl functional group with amines. Naturally occurring and synthetically prepared Schiff bases are active molecules with many pharmacological activities like antibacterial, anti-cancer, anti-fungal, anti-malarial, antioxidant and many more. This review article summarizes pharmacological developments in the recent few years and gives a brief overview of their therapeutic potential.

Keywords: aldehydes, antibacterial, antifungal, ketones, antiinflammatory, anti-cancer, antioxidant, Schiff bases

"Schiff bases" were named after the German chemist Hugo Schiff and are produced by reacting the aldehyde or ketone with primary amines (1), they can be used as reactive intermediates for the synthesis of many natural products (2). Schiff bases are reported to show a wide range of pharmacological activities and are used as antimicrobial agents with the activities including antibacterial, anti-fungal, anti-malarial and anti-viral agents as well as the anti-inflammatory, antioxidant and anti-cancerous agents (3, 4). Pharmacological activities attributed by Schiff bases are mainly due to characteristic C=N functionality (Figure 1). Synthetically, condensation of amine with carbonyl compound occurs under reflux conditions with complete removal of water molecule formed in the system by using molecular sieves; removal of water can also be done by using well known dehydrating solvents *in situ* i.e., trimethylorthoformate or tetramethylorthosilicate (1).

Other methods has also been reported for synthesis of Schiff bases, that involve the use of Lewis or Bronsted-Lowry acids, some common are $ZnCl_2$, $TiCl_4$, $MgSO_4$-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 and HCl, as catalyst (1, 3–6). New cost effective and efficient methods including, microwave accelerated, solvent free synthesis, and solid state synthesis are also being used and reported for the synthesis of Schiff bases and their metal complexes (1, 7, 8)

This brief review summarizes the pharmacological importance of different synthetic Schiff bases derived from some natural products or from commercially available precursors and also suggest the future perspectives of potential research areas.

PHARMACOLOGICAL SIGNIFICANCE OF SCHIFF BASES

Biologically active molecules, Schiff bases, are known to show a variety of pharmacological activities. The literature available and used in this review has been summarized in Table 1.

Antimicrobial activities

Anti-plasmodium activity

Malaria, a disease caused by genus *Plasmodium*, claims approximately one million death tolls annually and is a serious threat to developing countries. World Health Organization report-

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ed over 500 million affected people, 90% are children in sub-Sahara, Africa. A female mosquito *Anopheles* is responsible for the cause of malaria, widely spread in more than 100 countries (9).

Plasmodium falciparum (*P. falciparum*) is getting resistant against the available drugs in the market; therefore, there is a constant need for the introduction of new therapeutic agents to act against the disease. Schiff bases are the potential molecules, which can be affective against the problem of drug resistance. In addition to the synthetic derivatives, ancistrocladidine having iminium group moiety, is a natural product produced by plants belonging to family Dioncophyllaceae and Ancistrocladiceae and is known as anti-malarial agent with activity against *P. falciparum* strains 3D7 and K1 (1). Moreover, metal complexes like ruthenium complexes of Schiff bases derived from aryl and ferrocyl group show activity against the *P. falciparum* strains (3). Schiff bases obtained by the condensation of 2,6-diarylsubstituted piperidin-4-ones with 7-chloro-4-hydrazinoquinoline have also been tested for anti-malarial activities and reported to show strong anti-malarial activity against the *P. falciparum* strains (10). Therefore, in the quest of new effective drug molecules against malaria, Schiff bases can be a potential avenue of research.

Table1. Literature of activities of Schiff bases.

No.	Activity	References
1	Anti-plasmodium	1, 3, 10
2	Antibacterial	1, 11–23
3	Anti-fungal	1, 17, 24–32
4	Anti-viral	1, 33–37
5	Anticancer	38–41
6	Antioxidant	42–46
7	Anti-inflammatory	47–51

Antibacterial activity

Drug resistance against available antibiotic drugs is also a fast growing issue that the modern world has to face in the coming years. This can

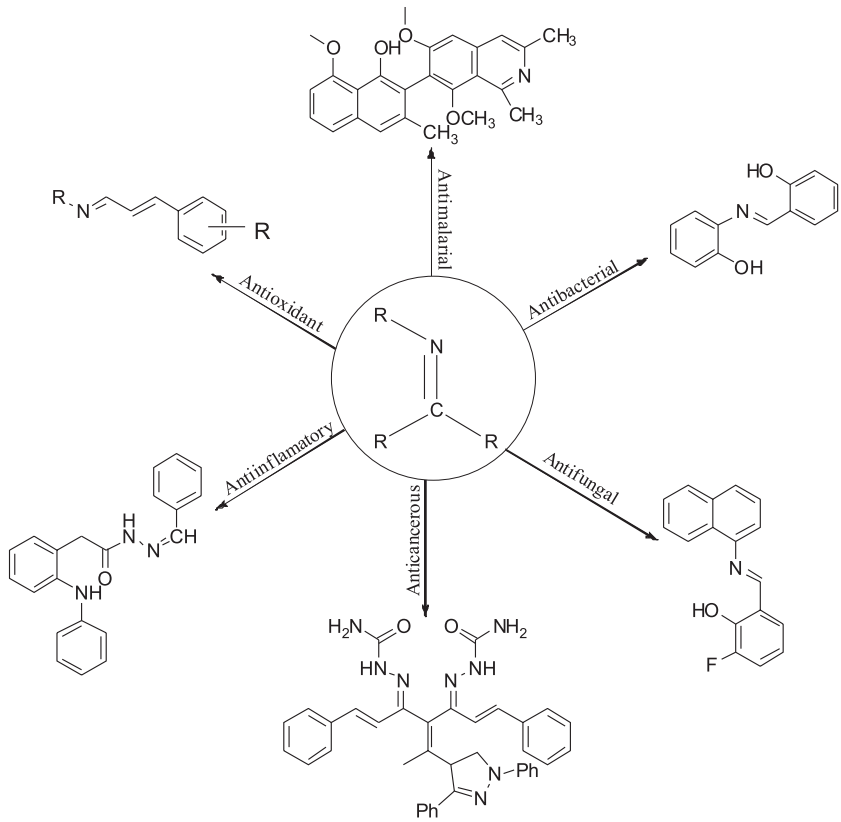

Figure 1. Pharmacologically active Schiff bases (1, 14, 29, 38, 43, 49)

potentially result in a dramatic increase in death rate and infectious diseases especially after accidental and surgical cases (11). Therefore, in order to cope with these problems, there is an immediate and constant need of new synthetic moieties with better and acceptable therapeutic index (12). Schiff bases have been considered the agents, which have more effective activity against the infectious bacteria, Schiff bases synthesized from 2-hydroxy-1-naphthaldehyde and α-amino acids (L-tyrosine, L-arginine, and L-lysine) and their manganese complexes have been reported to show excellent activity against the Gram positive and Gram negative strains of bacteria (13). Additionally, Schiff bases derived from salicylaldehyde show potent antibacterial activities, for example, *N*-(salicylidene)-2-hydroxyaniline has been reported to show a prominent activity against *Mycobacterium tuberculosis* (1), while Schiff bases of 5-chlorosalicylaldehyde show enhanced antibacterial activity against *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), and *Micrococcus luteus* (*M. luteus*) strains of bacteria (14). However, Schiff bases derivatives have also been reported to act as bacteriostatic agents e.g., Schiff bases of 2,4-dichloro-5-fluorophenyl are useful to stop the bacterial growth (1, 15). Moreover, Schiff bases bearing nitroimidazole moiety show good antibacterial activities against various bacterial strains (16). In addition, Schiff bases, derivatives of isatin, has been reported to show antimicrobial activity comparable with that of the standard drug sulfamethoxazole (17). Schiff bases synthesized from other substrates, including, morpholines, coumarins, *o*-phthaldehyde, aminothiazolylbromocoumarins, sulfonamides, acetophenones, crown ethers, amino acids and 2-aminophenol and 1,2,4-triazoles, were reported to show very low antibacterial activities (1, 4, 18–23).

Anti-fungal activity

Fungal infections are not limited to tropical areas but can also lead to increased risk of systemic infections, which may be life threatening (24). Factors for an increase in systemic fungal infections are geriatric patients, surgeries, AIDS, treatment of various tumors, transplantation of hard organs, hematopoietic stem cells and immunosuppressive treatment (25–27). Therefore, it is important to develop and formulate more effective and safe antifungal drugs, which can be effectively used in various medical conditions (28). Schiff bases have been reported to show good anti-fungal activity, e.g., Schiff bases of *N*-(salicylidene)-2-hydroxyaniline and from 3-fluorosalicylaldehyde are reported to show antifungal activities (1). However, transition metal complexes of Schiff bases derived from *N,N*-ethylene (bis 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazine-1-yl)-quinoline-3-carboxylic acid reported to show higher antifungal activity than their precursor Schiff bases (29). Oxovanadium (IV) complexes of Schiff bases show more activity as compared to their ligand (30). In addition, chitosan Schiff bases have been reported to stop the growth of many fungal strains including *Colletotric humlagenarium* and *Botrytis cinerea* (1, 31). Moreover, isatin based Schiff bases has been reported to show remarkable antifungal activity against various fungal strains like *Microsporum gypseum* and *Microsporum audouinii*, furthermore, isatin Schiff base derivatives also show anti-fungal activity against *Cryptococcus neoformans (C. neoformans)*, *Epidermophyton floccosum (E. floccosum)* and *Candida albicans (C. albicans)* (1, 17, 32).

Antiviral activity

Presently, a large number of viral diseases are treated either adopting vaccination or by using antiviral drugs. Drug resistance reported in viral diseases is a serious issue for humanity; therefore, new therapeutic molecules are constantly required (33). Some common viral diseases like, influenza, rubella, small pox, chicken pox and polio can be controlled by vaccines administration, while viral diseases like *hepatitis* 'C' is still under the process of vaccine discovery (1, 34). Therefore, Schiff bases can play a vital role due to their reported antiviral nature. Schiff bases derived from isatin and bis-isatin are reported to show activities against diffent strains of viruses (1, 34, 35). Moreover, Schiff bases derived from prodrug abacavir (Ziagen) are reported to show good antiviral activity and trials revealed that they are potent lead molecules for further clinical use as anti-HIV therapy (1, 36). Furthermore, Schiff bases of 2-phenylquinazoline-4(3)H-one are reported to show antiviral activity against some strains of viruses like feline corona virus, influenza viruses, and herpes simplex virus type 1 and 2 (37). The antiviral potential of these Schiff bases is evident from reported literature and therefore more targeted research can help to discover and develop new potential lead compounds to use them as drug candidates.

Anticancer activity

Cancer is a disease which leads to death. More than 200 cancer types have been reported in the human body. Schiff bases obtained from cumarin and pyrazole aldehyde has been tested against cancerous cell lines and showed mild anti-cancerous

activities (38). Moreover, in another study, mono and bis-Schiff bases have been reported effective against five cancer cell lines (39). Furthermore, Schiff bases can effectively form complexes with transition metals and these metal complexes are reported to show good anticancer activities; Cu-complexes with vaniline Schiff bases (40) and 5-dimethyl-2-phenyl-4-[(pyridin-2-ylmethylene)-amino]-1,2-dihydro-pyrazol-3-one Schiff bases (41) has been reported for their anti-cancerous activities. Extensive literature is available on the effectiveness of Schiff bases against cancer cell lines, therefore, a more systematic and extensive research, both *in vitro* and *in vivo*, is suggested to extend their therapeutic use to alleviate the disease.

Antioxidant activity

Aging is an evident phenomenon that a human has to face. Production of reactive oxygen species (ROS) increases with the passage of time, in the human body and leads to many physiological disorders including cardiovascular diseases. Schiff bases and their metal complexes play an important role in the production of ROS (42) and therefore, can show antioxidant properties. Recently, Schiff bases of natural phenylpropene derived methoxylated cinnamaldehydes (43), and tin metal complexes have been reported for antioxidant activities (44). In a recent study on thymol and carvacrol Schiff base derivatives in 5 µg/mL concentration showed 60–90% inhibition for antioxidant activity (45). Moreover, Schiff bases of 2-oxoquinoline-3-carbaldehyde have been reported as excellent anti-oxidizing agents and their activity was comparable with the ascorbic acid used as standard (46). Literature reveals their effectiveness in the antioxidant behavior; therefore, more targeted research can possibly lead to their use in the therapy of various ailments.

Anti-inflammatory activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are being used for the treatment of pain and perform their function by inhibiting the production of prostaglandins (PG), which are involved in many physiological activities (47, 48). Occasionally, these NSAIDs are not targeted for the particular enzyme involved in the biosynthesis of prostaglandins; therefore, for more targeted attack on the particular isozyme new effective molecules are required. Therefore, Schiff bases derived from 2-(2,6-dichloroanilino) (49) and 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one have been reported for excellent anti-inflammatory activities (50). Moreover, transition metal complexes of Schiff bases containing aldose group have also been reported for anti-inflammatory activities (51). Further investigations are suggested for their preferential therapeutic use in sickness and accidental case of inflammation.

CONCLUSION

Schiff bases and their derivatives are a class of compounds with literature evident pharmacological importance and applications. Therapeutic spectrum is also wide and less explored for Schiff bases, therefore, a scientific approach is required to establish the structure activity relationships of these biologically and medicinally viable molecules. Concisely, Schiff bases are among the molecules which have therapeutic potential for the treatment of various human diseases.

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