Review Article
Schiff Bases: A Versatile Pharmacophore

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Schiff bases are condensation products of primary amines with carbonyl compounds gaining importance day by day in present scenario. Schiff bases are the compounds carrying imine or azomethine (–C=N–) functional group and are found to be a versatile pharmacophore for design and development of various bioactive lead compounds. Schiff bases exhibit useful biological activities such anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, anthelmintic, antiglycation, and antidepressant activities. Schiff bases are also used as catalysts, pigments and dyes, intermediates in organic synthesis, polymer stabilizers, and corrosion inhibitors. The present review summarizes information on the diverse biological activities and also highlights the recently synthesized numerous Schiff bases as potential bioactive core.

1. Introduction

Schiff bases are the compounds carrying imine or azomethine (–C=N–) functional group. These are the condensation products of primary amines with carbonyl compounds and were first reported by Hugo Schiff [1–3]. Schiff bases form an important class of the most widely used organic compounds and have a wide variety of applications in many fields including analytical, biological, and inorganic chemistry. Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory [4–7], analgesic [5–8], antimicrobial [9, 10], anticonvulsant [11], antitubercular [12], anticancer [13, 14], antioxidant [15], anthelmintic [16], and so forth. The nitrogen atom of azomethine may be involved in the formation of a hydrogen bond with the active centers of cell constituents and interferes in normal cell processes [17, 18]. Apart from biological activities, Schiff bases are also used as catalysts, intermediates in organic synthesis, dyes, pigments, polymer stabilizers [3], and corrosion inhibitors [19]. Studies enlightened that metal complexes show greater biological activity than free organic compounds [20]. Augmentation of biological activity was reported by implementation of transition metals into Schiff bases [21]. Schiff bases played an influencing role in development of coordination chemistry and were involved as key point in the development of inorganic biochemistry and optical materials [22]. Schiff bases have been utilized as synths in the preparation of a number of industrial and biologically active compounds like formazans, 4-thiazolidinines, benzoxazines, and so forth, via ring closure, cycloaddition, and replacement reactions [23]. Schiff base derivatives in various processes promoted the researchers for designing of novel heterocyclic/aryl Schiff bases for development of new environmental-friendly technology [24].

2. Biological Activities

2.1. Antimicrobial Activity.

As a series of some novel 5-substituted Schiff and Mannich bases of isatin derivatives, that is, 7-(4-((3-(4-(substituted benzylideneamino)phenyl-imino)-5-fluoro-2-oxindolin-1-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, I(a-I), (Figure 1) were synthesized and characterized for in vitro antibacterial activity. Antimicrobial activity of synthesized compounds was assessed by minimum inhibitory concentration (MIC) in comparison with standard antimicrobial drugs, that is, ciprofloxacin and ketoconazole. Compound Ic was reported to be more active than both of the standard drugs against tested microorganisms which proves the significance of substituted electron-donating groups in improving the antimicrobial activity [25].
A novel series of Schiff bases, that is, 6-bromo-2-[2-(6-dichlorophenyl)amino]benzyl-3-(substituted benzylideneamino)-quinoxalin-4(3H)-one, 2(a–k), (Figure 2) has been synthesized and tested for antimicrobial activity [26].

Evaluation was carried out for the in vitro antimicrobial activity by cup plate method. For this, S. aureus, P. aeruginosa, B. subtilis, and C. albicans were employed. Penicillin G and amphotericin B were taken as standard drugs. Results revealed that all compounds have moderate to poor antifungal activity and good antibacterial activity [26].

A novel series of pyrazole-based Schiff bases, 3(a–j), (Figure 3) 4-[(3-substituted-1H-pyrazol-3-yl)methyleneamino]-5-substituted-4H-1,2,4-triazole-3-thiols, was synthesized and screened for antibacterial activity against the microbial strains of S. aureus, P. aeruginosa, B. subtilis, and E. coli. From the results, compound 3f was found to be equally as active as standard drug ceftriaxone against P. aeruginosa, B. subtilis, and E. coli and most active against S. aureus [27].

Synthesis of new open (4–6) (Figures 4–6) and macrocyclic (7) (Figure 7) Schiff bases has been done and evaluated for the antimicrobial activity. Open Schiff bases were synthesized by the condensation of salicylaldehyde and α-vanillin with 4,4′-diaminodiphenylmethane, 4,4′-diamino diphenyl sulphide, and diethyl ester of terephthalic acid, respectively.

Macrocyclic Schiff bases were reported as the condensation product of 1,6-bis(2-formylphenyl)hexane with thiocarbonyldrazide. In order to test the biological activity of the synthesized compounds, four microorganisms (K. pneumoniae, E. coli, S. aureus, and S. typhimurium) were employed. All the synthesized compounds were found to be moderate to strongly active [28].

A few novel solid complexes, 8, (Figure 8) of La(III), Ce(III), Pr(III), Nd(III), Sm(III), and Gd(III) with Schiff base, that is, 9, (Figure 9) 4-hydroxy-3-(1-[2-(hydroxybenzylidene)-amino-phenylmimo]-ethyl)-6-methyl-pyran-2-ones, were synthesized and screened for the antibacterial activity against S. aureus, E. coli, and Bacillus species and antifungal activity against A. niger, Trichoderma, and F. oxysporum. Results revealed that the complexes were biologically active and have exhibited enhanced antimicrobial activity than the free ligand (Schiff base) [29].

Some novel Schiff bases, macrocyclic tetradentate nitrogen donor (N₄) 6,7,14,15-tetrahydroxy-1,4,9,12-tetraazacyclohexadecane-5,8,13,16-tetron lignad-based metal complexes, 11, (Figure 11) from 10, (Figure 10) were synthesized and screened for the in vitro antifungal activity and toxicity studies. Minimum inhibitory concentration (MIC) along with ergosterol composition assay against C. albicans (ATCC 10261), C. glabrata (ATCC 90030), and C. tropicalis (ATCC 750) was performed. The antimicrobial results indicated that all the synthesized compounds were found to be active against all fungal strains. It was observed that Ni(II) complex and...
Co(II) complex drastically reduced ergosterol content of cell membrane followed by the Cu(II) complex and the ligand itself [30].

2.2. Antidyslipidemic Activity. A series of novel keto-enamine Schiff bases, 12(a–h), (Figure 12) derived from 8-hydroxyquinoline was synthesized and subjected for *in vitro* antioxidant, *in vivo* antidyslipidemic, and postheparin lipolytic activity.
Piperazine citrate was used as a reference standard while DMSO as a control for comparison. Results revealed that all the synthesized compounds were moderately active except compound 14c which was found to be the most potent anthelmintic agent due to presence of chloro group. Chloro group may improve the conductance of worm muscle membrane that causes reduction in hyperpolarization and excitability which leads to flaccid paralysis that results in expulsion of worm by peristaltic movement [33].

A series of twelve new N-substituted-2-hydroxycetophenonimine derivatives, 15(a–l) (Figure 15) was synthesized by conventional as well as microwave method. Synthesized compounds were evaluated for their antinemic activity by calculating LC50 values of different synthesized imines against J2s of M. incognita. Carbofuran was employed as a standard.

Although all the compounds possessed activity against M. incognita, N-hexyl-2-hydroxycetophenonimine (15j), N-ethyl-2-hydroxypropionophenonimine (15k), and N-propyl-2-hydroxypropionophenonimine (15l) were found to possess significant activity with LC50 values of 99.60, 74.46, 109.53, and mgL−1, respectively, as compared to other imines. The above observations enlightened that bioactivity increased with increase in chain length up to 6 carbon atoms whereas further increase in chain length decreased the activity [34].

2.4. Antitubercular Activity. A novel series of forty-four, 17(I–xxxxiv), (Figure 17) Schiff bases of isonicotinic acid hydrazide (INH) was synthesized by structural modification of 16 (Figure 16) in which hydrazine unit was chemically blocked at N2 position by deactivating acetylation by N-arylaminocetyl transferase (NATs) enzyme. The deactivation phenomenon seems to be associated with rise of resistance. Synthesized Schiff bases were blocked toward the enzymatic deactivation process. The results revealed that compound 17(xv) was found to be the most potent antitubercular agent with MIC 0.05 μg/mL and logP 4.04 [35].

A series of Schiff bases of indoline-2,3-dione derivatives and nalidixic acid carbohydrazides, 18(a–n) (Figure 18) was synthesized and screened for antitubercular activity against four Mycobacterium strains (M. xenopi, M. cheloneo, M. intracellulare, and M. smegmatis) using isonicotinic acid hydrazide as a standard drug. Agar dilution method was opted for screening the activity. From the results, compound 18f was found to be the most potent antitubercular agent with MIC 0.625 μg/mL which is 20 times higher than the MIC of standard drug (12.5 μg/mL) [36].

Synthesis of six D-mannitol-derived Schiff bases, 19(a–f) (Figure 19) 1,6-dideoxy-1,6-bis-[[E(aryl)methylidene]amino]-D-mannitol was carried out and synthesized compounds were evaluated for their in vitro antitubercular activity against M. tuberculosis H37R×v by employing microplate Alamar Blue assay (MABA). Compounds 19e, 19d, and 19f have shown significant inhibitory activity when compared with standard drug ethambutol (first-line drug) due to presence of nitro group while chlorine-containing compounds (19a, 19b, and 19c) have shown resistance. MIC values for 19e, 19d, and 19f were found to be 12.5, 25.0, and 25 μg/mL, respectively [37].
$M = \text{Cu(II), Co(II), and Ni(II)}$

**Figure 11**

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**Figure 14**
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### Figure 16

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### Figure 17

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2.5. Antidepressant Activity. Schiff bases of isonicotinoyl hydrazone, $N^\prime-[[1Z]$-(substituted aromatic)methylidene]pyridine-4-carbohydrazides, 20(a–k) (Figure 20) were synthesized by green route of microwave synthesis and sonication. Synthesized compounds were evaluated for in vivo antidepressant and nootropic activities. The results revealed that the test compounds substituted with nitro, halogen, and dimethoxy groups exhibited significant antidepressant and nootropic activities. $N^\prime-[(1Z)$-(2,5 dimethoxyphenyl)methylidene]pyridine-4-carbohydrazide was found to exhibit the highest antidepressant activity [38].

2.6. Anticonvulsant Activity. A series of Schiff bases of phthalimide, 4-(1,3-dioxo-1,3-dihydro-2H-isouindol-2-yl)-$N^\prime$-(substituted phenyl)methylene/ethylidene benzohydrazide, 21(a–i) (Figure 21) was synthesized and evaluated for anticonvulsant and neurotoxic activities [39].

From the results, it was concluded that all the compounds were found to be active and less toxic than phenytoin which was employed as a standard drug. Compound 21l substituted with nitro group at ortho position of distal aryl ring was reported as the most potent anticonvulsant agent [39].

Synthesis of a series of 3,3’-[[6-[2,3-dichlorophenyl]-1,2,4-triazine-3,5-diyl]dinitrolo]bis-(substituted-1,3-dihydro-2H-indol-2-one), 22 (Figure 22) of lamotrigine with isatin and substituted isatin was carried out and screened for the anticonvulsant activity. MES (maximal electroshock seizure) test method was opted to carry out the anticonvulsant activity by incorporation of lamotrigine and phenobarbitone sodium as standard drugs. Results revealed that the synthesized compounds possessed better anticonvulsant activity than the standard lamotrigine [40].

Some novel 3-aryl-(4H)-quinazolinones-2-carboxaldehydes and their corresponding Schiff bases, 23 (Figure 23) and thiosemicarbazone derivatives, have been synthesized. Compounds showed anticonvulsant, analgesic, and cytotoxic potential due to thiosemicarbazone side chain at position ending with a free amino group and fluorine atom [41].

2.7. Anti-Inflammatory, Analgesic, and Nonulcerogenic Activities. A novel series of Schiff bases containing synadine that is, 3-[1-(4-isobutylphenyl)ethyl]-4-(3-substituted-4-sydnonylidene) amino 5-mercapto-1,2,4-triazoles, 24(a–c), (Figure 24) was synthesized and screened for their anti-inflammatory and analgesic activities. Results revealed that compound 24c, 3-[1-(4-isobutylphenyl)ethyl]-4-[3-(p-anisyl)-4-sydnonylidene) amino 5-mercapto-1,2,4-triazole, exhibited good anti-inflammatory and analgesic activities as compared to 24a and 24b which indicated that presence of electron-releasing group in synadine has resulted in better anti-inflammatory and analgesic activities [42].

Synthesis of novel Schiff base analogues of 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one, 25(a–m), (Figure 25) was carried out. Synthesized compounds were screened for
the anti-inflammatory and antioxidant activities. Compound 25f was found to be the most potent anti-inflammatory agent and antioxidant. The anti-inflammatory activity of 25f was evaluated in terms of its potential of nitric oxide (NO) production inhibition in LPS-pretreated RAW 264.7 cells using the Griess method.

Lipopolysaccharide (LPS), an endotoxin which is derived from the cell wall of Gram-negative bacteria, can induce multiple signaling pathways to stimulate the production of inflammatory modulators involving NO, PGE$_2$, TNF-$\alpha$, and interleukins. The results indicated that 50$\mu$g/mL of 25f inhibited the LPS-stimulated COX-2 mRNA levels [43].

A series of S-substituted phenacyl 1,3,4-oxadiazoles and Schiff bases 26(a–k) (Figure 26) derived from 2-[(2,6-dichloroanilino) phenyl] acetic acid (diclofenac acid) was synthesized and screened for the analgesic, anti-inflammatory, and nonulcerogenic activities. Acetic-acid-induced writhing test and carrageenan-induced rat paw edema method were employed for analgesic and anti-inflammatory activities, respectively. From the studies it was concluded that synthesized compounds were devoid of gastrointestinal toxicities. Among all the synthesized compounds, N-(4-bromo-benzylidene)-[2-(2,6-dichloroaniline)benzyl carbazide] 26k was found to be the most potent anti-inflammatory agent. The analgesic effect of 26k (68.66%) was found to be better than that of diclofenac sodium (64.65%) [44].

2.8. Antitumor Activity. A novel series of fluoroquinolone C-3 heterocycles (IV), that is, triazole Schiff 27(a–k) (Figure 27) and mannich bases derivatives of ofloxacin was synthesized and evaluated for in vitro antitumor activity against a murine leukemia cell line (L1210), a human leukocytoma cell line (HL60), and a Chinese hamster ovary cell line (CHO) using the MTT assay. From the observed results it was concluded that a free phenol group containing compounds 27c, 27g, and 27h exhibited more potent activity than the other test compounds [45].

A series of thirteen quinolin-2(1H)-one-derived Schiff bases 28(a–m) (Figure 28) and their Cu(II) 29(a–m) (Figure 28) complexes was synthesized. Selected compounds were screened for their in vitro anticancer and antifungal activities. Human hepatic carcinoma cell line, Hep-G$_2$ was employed for screening of the anticancer potential. Cisplatin was used as a standard drug for the comparison. Screened compounds were found to be active antifungal agents and compound (7E)-7-(3-ethoxy-2-hydroxybenzylideneamino)-4-methylquinolin-2(1H)-one was reported as a potent cytotoxic agent which enlightened the good potential of Cu(II) complexes of Schiff base ligands as therapeutic agents [46].

A series of three Schiff bases 4-{{[3-(4-substituted phenyl)-1H-pyrazol-4-yl] methylene}amino}-5-{{[substituted phenoxymethyl]-1,2,4-triazole-3-thiol, 30(a–c) (Figure 29) was evaluated for their in vivo antitumor activity against Ehrlich-ascites-carcinoma-(EAC-) bearing Swiss albino mice. Schiff bases were used in two different doses, that is, 50 mg/kg and 100 mg/kg of the body weight of mice. Mean survival time (MST) and percentage increase in lifespan (% ILS), that is, total number of days an animal survived from the day of tumor inoculation were calculated. Body weights...
of all animals were measured on days 0, 3, 5, 7, 10, 12, and 14 [47].

The results revealed that cisplatin (3.5 mg/kg, i.p. single dose) significantly enhanced MST of EAC-infected mice. Among the three Schiff bases 4-([3-(4-fluorophenyl)-1H-pyrazol-4-yl]methylene)amino)-5-[(2 methylphenoxy)methyl]-1,2,4-triazole-3-thiol, 30c, at the dose of 100 mg/kg body weight was found to enhance the mean survival time of tumor-bearing mice. MST and deviated hematological parameters of infected mice were found to be normal after treatment with 30c [47].

2.9. Antioxidant Activity. A series of substituted-N\textsuperscript{1}-(1E)-substituted phenylmethylenedibenzyldrazide analogs, 31(a–n) (Figure 30) was synthesized and evaluated for their in vitro antioxidant, anti-inflammatory, and antimicrobial activities. The antioxidant activity of all the synthesized compounds was evaluated by the phosphomolybdenum method. Compounds 31c, 31d, and 31f were reported to show good antioxidant activity due to presence of 4-nitro, 4-methyl, and 3-nitro groups, respectively, whereas 31a having 4-hydroxy group did not possess such activity. From the results, it can be concluded that substitutions like nitro and alkyl lead to enhancement in antioxidant activity through one-electron transfer mechanism [48].

A new Schiff base ligand N-(2-hydroxylacetophenone)-3-oxapentane-1,5-diamine (HL), 32, and its Ni complex, [Ni\textsubscript{2}(L)\textsubscript{2}(NO\textsubscript{3})\textsubscript{2}], 33, were synthesized and evaluated for antioxidant and DNA-binding properties. The complex showed inhibitory activity and the suppression ratio of OH radical increases with increase in the concentration of the complex. Mannitol and vitamin C were employed as the standard antioxidants for comparison. According to the results the 50% inhibitory concentration (IC\textsubscript{50}) value of 33 was found to be 8.1 ± 0.078 μM whereas IC\textsubscript{50} for mannitol was 9.6 μM and 32 was devoid of antioxidant activity. Both 32 and 33 bind to DNA in intercalation mode but the binding strength of 33 was found to be better than 32 [49].

2.10. Antiviral Activity. A series of 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-one, 34(a–l) (Figure 31) was synthesized and evaluated for their cytotoxicity and antiviral activity. Compounds having 2-hydroxy substitution showed better antiviral activity [50].

A series of thiazolines and azetidinones was synthesized by reaction of Schiff bases, 35(a–i) (intermediate reaction) with thioglycolic acid and chloral acetyl chloride, respectively. Schiff bases were evaluated for antibacterial and antiviral (against HIV-I) potential. All the compounds were found to be good HIV-I inhibitors except 35f and 35g [51].

2.11. Antihypertensive Activity. Schiff bases of 2-phenyl-3-(amino substituted arylidene)quinazoline-4-(3H)-ones, 36(a–b). (Figure 33) were synthesized and evaluated for...
antihyperlipidemic activity. Hyperlipidemia was induced in rats by atherogenic diet. After 45 days, levels of serum total cholesterol (TC) and LDL cholesterol were recorded to be 231.6 ± 1.435 mg/dL and 164.53 ± 1.26 mg/dL which were comparatively higher than normal rat serum TC (71.36 ± 1.195 mg/dL) and LDL-C (100.66 ± 0.88 mg/dL) levels whereas serum HDL-C level was found to be lower (19.012 ± 0.66 mg/dL) as compared to the normal level (50.66 ± 0.88 mg/dL).

Results revealed that 36a reduced TC and LDL-C levels to 172.41 ± 4.1 mg/dL and 91.10 ± 0.97 mg/dL and raised serum HDL-C level to 60.07 ± 0.67 mg/dL whereas 36b reduced serum TC and LDL-C levels to 93.63 ± 1.292 and 81.35 ± 0.81 mg/dL and raised serum HDL-C level to 59.40 ± 0.45 mg/dL at the dose of 200 mg/kg, p.o., once daily [52].

### 2.12. Antidiabetic and Antiglycation Activities

A series of oxovanadium complexes with mixed ligands, a bidentate NN ligand, 37, and a tetradeinate ONO-donor Schiff base ligand, 38 (Figure 34) was synthesized and evaluated for protein tyrosine phosphate (PTP) inhibition. PTP1B has been identified as key enzyme related to insulin resistance. Thus the inhibition of PTP1B has emerged out as an important approach to enhance insulin sensitivity. The kinetic analysis results revealed that oxovanadium complexes displayed potent reversible competitive inhibition PTP1B with IC\textsubscript{50} values in low nanomolar range [53].

A series of twenty-seven bis-Schiff base of isatin, 39(i–xxvii) (Figure 35) was synthesized and evaluated for their in vitro antiglycation activity. Compounds 39(xx) and 39(xxi) substituted with nitro groups at para and ortho positions,
respectively, were found to be the most potent antiglycation agents with IC$_{50}$ (257.61 ± 5.63 μM) and 243.95 ± 4.59 μM better than IC$_{50}$ (294.46 ± 1.50 μM) of rutin which was employed as standard. The 3,4-dihydroxy analog 39(vii) was found as the third most potent antiglycation agent with IC$_{50}$ (291.14 ± 2.53 μM) [54].

3. Conclusion

Schiff bases are one of the most important chemical classes of compounds having a common integral feature of a variety of medicinal agents. This review reflects the contribution of Schiff bases to the design and development of novel lead having potential biological activities with fewer side effects. This bioactive core has maintained the interest of researchers in gaining the most suggestive and conclusive access in the field of various Schiff bases of medicinal importance from last decades. The present paper is an attempt to review all the biological activities reported for Schiff bases in the current literature with an update of recent research findings.

References


