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Review Article

A Review on Chemistry, Synthesis and Biological Applications of Chalcone-based Schiff Bases

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Abstract

Heterocyclic compounds are an important class of compounds in the field of pharmaceutical and synthetic organic chemistry. The Schiff bases contain azomethine linkages which are obtained by the condensation of aldehyde/ketone with amines. Among the various types of Schiff bases, the chalcone-based Schiff bases play a vital role in the treatment of various ailments and various applications, which can be synthesized by using different types of chalcones as the starting materials. These types of compounds were synthesized by using various techniques like conventional means of synthesis, microwave-assisted reaction, heterocyclic catalyst-mediated synthesis and also by means of trituration. The chalcone or bis-chalcone-based Schiff bases and their derivatives contain -C=N linkage which exhibits various activities including antimicrobial, anticancer, antioxidant, antidiabetic and immunosuppressant activities. Beyond these activities, these types of Schiff bases are also used in various chemical industries and fluorescent sensors, which also play a major role in the field of synthetic organic chemistry and coordination chemistry as intermediates. This review discusses the numerous synthetic strategies along with their applications in the field of medicine. Thus, this review will be helpful in developing more effective drug-like scaffolds for use in future drug design.

Keywords: Schiff bases, Chalcone-based Schiff bases, Antimicrobial, Anticancer, Antioxidant, Biological Applications

Introduction

The metabolism of living cells depends heavily on heterocyclic compounds, which are organic molecules with at least one carbon atom and at least one extra heteroatom, such as N, O or S. It could be aromatic or not aromatic. Most of them are five or six-membered and some of the rings contain higher than that of three, four, seven or larger rings. Due to the wide spectrum of pharmacological and therapeutic implications of fused heterocyclic compounds, which typically have five or six members, there is a great deal of interest in medicinal chemistry. These heterocyclic rings are found to be widely distributed in nature, which include antibiotics, vitamin B complex, chlorophyll, proteins, amino acids, enzymes, genetic materials and dyestuffs[1,2]. Among the various heterocyclic compounds and derivatives, the Schiff bases, discovered by Hugo Schiff in 1864, received great attention from organic chemists, which was prepared by condensation of an aldehyde/Ketone and amines. These Schiff bases contain the azomethine (C=N) functional groups, which are also known as imines i.e., nitrogen atom attached to the organic or hydrogen group, anils i.e., nitrogen attached to the phenyl group and hydrazones[3,4]. The biological activity of these compounds is due to the lone pair of electrons present in the nitrogen atom of azomethine which is in an sp^2 hybridized state. These compounds were found to possess various pharmacological activities such as anticancer, antimicrobial, anti-inflammatory, anticonvulsant, antimalarial, antischistosomal and antitubercular activities. The Schiff base derivatives like 2,4-dinitrophenylhydrazone derivatives-based Schiff bases exhibited potential DNA-damaging action and acts as mutagenic agents with better optical properties[5,6].

Like the above-described derivatives, the chalcone-based Schiff bases also play a major role in the field of medicinal and pharmaceutical chemistry. The chalcones are also of great importance due to their various therapeutic applications and diverse applications. The Schiff bases based on chalcone derivatives such as pyrazole and 2-pyrazoline derivatives[7], thiosemicarbazone derivatives and other derivatives exhibited various pharmacological activities like antimicrobial[8], anticancer[9], antidiabetic[10] and antioxidant activities[11]. These Schiff base linkages (azo or imine) enhance the sensing properties of the thermotropic liquid crystals, provides thermal stability and also the liquid crystalline properties of the compounds containing chalcone linkages are enhanced[12].

As of now, various semicarbazone, thiosemicarbazone and thiosemicarbazide-based chalcone Schiff bases were reported. These chalcone-based Schiff bases play a major role in the field of coordination chemistry. The metal complexes derived from the chalcone-based Schiff bases majorly exhibited antimicrobial action. The semicarbazone and thiosemicarbazone 3-phenylquinazoline-2,4(1H,3H)-dione active Schiff bases and their metal complexes exhibited better antibacterial activity[11,13]. Like the above derivatives, the heterocyclic Schiff base ligand and corresponding metal

complexes based on isoniazid and chalcone were developed, which were found to be possessing better thermal stability[14]. The ferrocene chalcone-based Schiff bases and their metal (II) complexes also exhibited potent antimicrobial and anticancer activity[15].

Thus, the chalcone-based Schiff bases and their corresponding coordination metal complexes have been found to exhibit better pharmacological applications and these compounds were effectively synthesized by employing oil bath-assisted synthesis[11], the refluxing method[13], trituration[15], microwave-assisted synthesis[16], heterocyclic acid-mediated catalysis[17] and there are various types of Schiff bases, which are involved in the formation of coordination complexes. Generally, bi, tri, tetra and polydentate ligands are involved in the formation of highly stable coordination complexes with transition metals. The chalcone-based Schiff bases were used as corrosion inhibitors, biosensors and were also useful for various analytical purposes and in industries as intermediates. The Schiff bases derived from chalcone and chalcone derivatives exhibited enhanced bioactivity which is due to the high lipophilic character of the Schiff bases. The higher lipophilic nature also enhances the bioavailability of the compounds in the lipid membranes[4,17,18]. Thus, the chalcone-based Schiff bases have essential diversity in synthetic chemistry as intermediates in the synthesis of coordination metal complexes and in the synthesis of various organic derivatives.

In this review, the literature indexed in Google Scholar, Scopus, PubMed, Embase, Web of Science, ResearchGate, ACS and RSC databse were collected by using the keywords chalcone-based Schiff bases, Schiff bases, Chalcone derivatives and imine-linked chalcones, antimicrobial, anticancer and biological activities, individually and in combination. Hence, in this review, various synthetic approaches and their biological applications were reviewed and discussed.

Chalcone-based Schiff base derivatives as antimicrobial agents

The novel chalcone-based Schiff bases namely, N-(2,4-dinitrophenyl)-N'-(1,3-diphenyl-allylidene)-hydrazine **(1)** and N-[3-(4-chlorophenyl)-1-phenyl-allylidene]-N'-(2,4-dinitrophenyl)-hydrazine **(2)** were designed and synthesized from the chalcones 1,3-diphenylprop-2-en-1-one and 1-phenyl-3-(4-chlorophenyl)-prop-2-en-1-one respectively. The chalcones were boiled with 2,4-dinitrophenylhydrazine in presence of 50 % glacial acetic acid. These compounds were evaluated and found to be effective against *Staphylococcus aureus* and *Pseudomonas aeruginosa*[4].

1-(4-Fluorophenyl)-3-(-2-chlorophenyl) prop-2-en-1-thiosemicarbazone **(3)** Schiff base ligand was synthesized by Meena SK and Kumar Y., 2022. The compound **(3)** was synthesized by the reaction between chalcone, 1-(4-Fluorophenyl)-3-(-2-chlorophenyl) prop-2-enone and the amino group-containing compound, thiosemicarbazone. These compounds were found to be active against various microorganisms, viz., *S. aureus*, *Bacillus cereus*, *Escherichia coli*, *Aspergillus niger* and *Fusarium species*[8].

Ibrahim TS et al., 2021 synthesized novel 1,2,4-oxadiazole-chalcone/oxime hybrids Schiff base, (2E)-3-(4-methoxyphenyl)-1-{4-[(3-aryl-1,2,4-oxadiazol-5-yl)methoxy]phenyl}prop-2-en-1-one oxime **(4-6)** from the reaction between 1,2,4-oxadiazole derivatives and hydroxylamine hydrochloride in pyridine solution and stirred for 3 hr at 70 °C. The compound **(4)** was found be effective against *B. subtilis*, *Enterococcus hirae*, *S. aureus*, *Klebsiella pneumonia* and *E. coli*. The DNA Gyrase supercoiling inhibitory activity of the compounds **(5, 6)** exhibited good inhibitory activity against *E. coli gyrase* with an IC_{50} value of 13.4 µM and 16.9 µM, respectively[9].

Dehydrozingerone Semicarbazone Schiff base ligand **(7)** was prepared by refluxing the hydrochloride salt of dehydrozingerone and semicarbazone in an acidic condition using methanol as solvent. It was found to be active against *S. pyogenes* (13.67 ± 0.52 mm) and the molecular docking studies also revealed that the compound exhibited a better binding potential (-8.0 and kcal/mol) against *S. aureus* Gyrase[11].

The antibacterial potency of the hydrazinecarbothiamide **(8)** and hydrazine-carboxamide **(9)** Schiff bases were evaluated by Patange AN et al., 2021. The compounds were synthesized by refluxing the chalcone ((2E)-2-[-(4-substituited Phenyl)-2-oxoehylidene]-3- 2,3dihydroquinazoline-4(1H)-one) with thiosemicarbazide and semicarbazide hydrochloride for 3 hr under the aid of sodium acetate, the corresponding Schiff bases **(8)** and **(9)** were obtained, respectively. The designed compounds were found to be active against *E. coli* and *S. aureus*, determined by the plate diffusion assay method[13].

Ferrocenyl chalcone-based Schiff bases namely, 1-ferrocenyl-3-(2-furyl) propanone diamino (thio) urea **(10, 11)** were synthesized by the reaction between 1-ferrocenyl-3-(2-furyl)-propenone and amino(thio)urea in the presence of p-toluenesulfonic acid as a catalyst and found to be active against various gram-negative bacterial strains (*E. coli, S. aureus*) and fungal species (*Candida albicans* and *A. flavus*)[15]. 2',4'-dihydroxy-4-fluoro chalcone oxime Schiff base **(12)** was synthesized by using a microwave-assisted synthetic approach. In this method, the 2',4'-dihydroxy-4-fluoro chalcone and hydroxylamine hydrochloride were dissolved in ethanol and irradiated using microwaves with an aid of glacial acetic acid under 200 W for 150 sec. The obtained compound was found to be highly effective against both gram-positive (*S. aureus*) and gram-negative (*E. coli*) bacterial species, as determined by the agar disc diffusion method[16].

The antimicrobial activity of Schiff base namely, oximes of steroidal chalcone **(13-15)** was evaluated against *B. subtilis*, *S. epidermidis*, *Proteus vulgaris*, *P. aeruginosa*, *A. niger* and *Penicillium chrysogenum*. The compound **(13)** was found to be active against B. subtilis and S. epidermidis. **(14)** was found to be active against *P. vulgaris* and *P. chrysogenum*. The compound **(15)** was found to be more potent against *P. aeruginosa* and *A. niger*. These compounds were synthesized by the reaction between pregnenolone benzylidene derivatives with hydroxylamine hydrochloride under stirring conditions at room temperature[19]. The novel chalcone-based Schiff bases **(16, 17)** from 4-[3-(4-substituted phenyl)-2-propeme-1-one]-aniline was synthesized and evaluated against *E. coli* and *S. aureus* using the agar diffusion method. Both of the compounds were active against the tested microorganisms[20].

5-Bromo isatin derived chalcone-based Schiff bases **(18, 19)** were synthesized by Patange AN et al., 2015. The synthesized chalcones were refluxed with thiosemicarbazide and semicarbazide hydrochloride with the aid of sodium acetate to obtain the corresponding Schiff bases. The antimicrobial activities of the obtained compounds were determined by the plate diffusion method and were found to be active against different gram-positive and gram-negative microorganisms[21]. Chalcone-based Schiff base of N-(3-aminopropyl) imidazole **(20)** was synthesized by the one-pot condensation of N-(3-aminopropyl) imidazole, 2-hydroxychalcone and piperidine under reflux conditions. The synthesized compound was found to be active against *P. aeruginosa* and *C. albicans*, determined by the disc diffusion method[22].

On the reaction between the chalcone obtained from the 4-chloro acetophenone with nitrobenzaldehyde and the amino group-containing compounds, the corresponding Schiff bases **(21, 22)** were obtained. Semicarbazide and isonicotinyl chloride were used as the amines. The resulted compounds were tested against various microbial substances. The compound, chalcone semicarbazide derivative **(21)** was active against *P. notatum* and chalcone isonicotyl hydrazide **(22)** was found to be potent against *S. aureus*[23]. The structures of these compounds are given in figures 1-3.

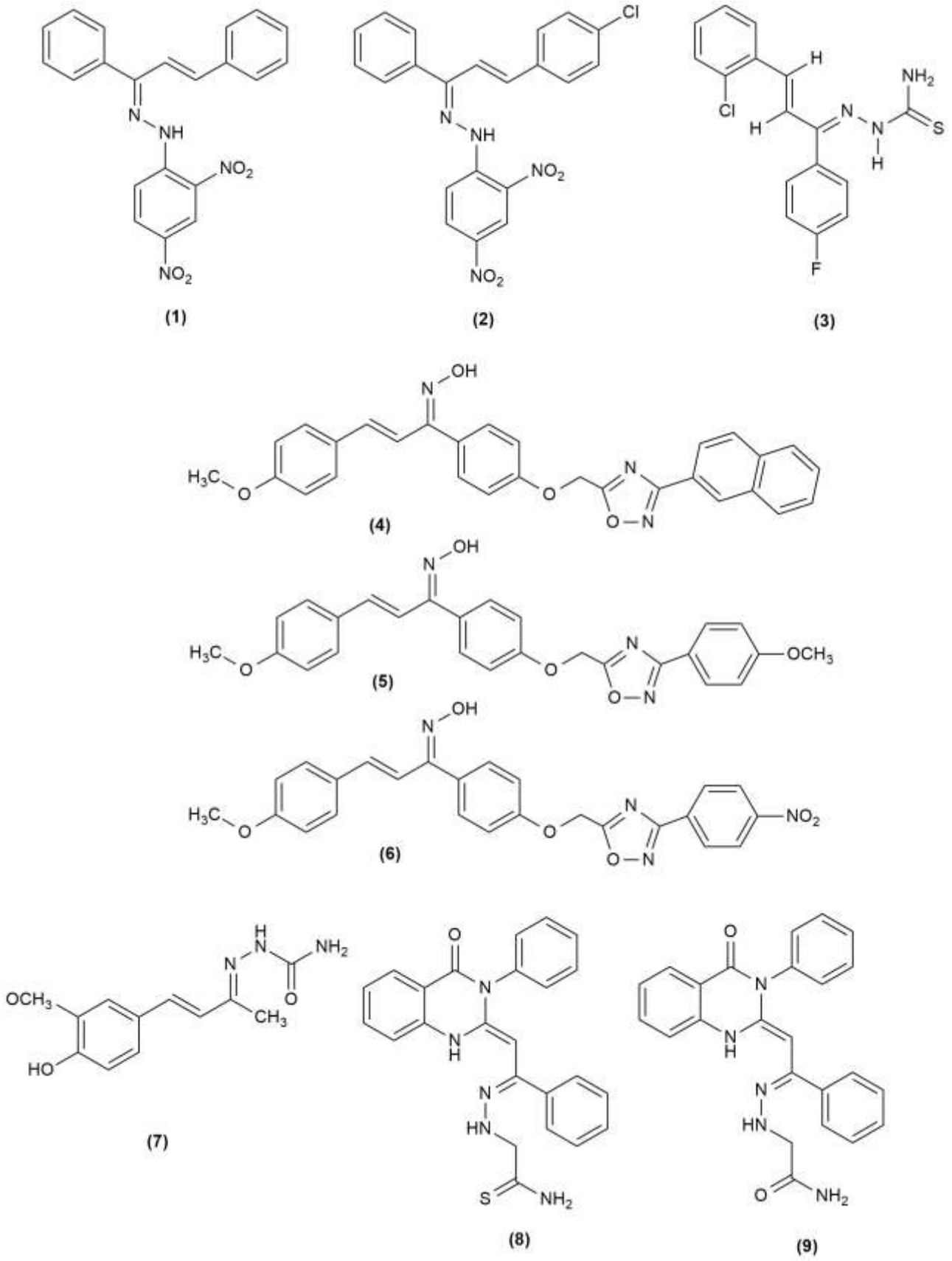


Figure 1: Compounds possessing antimicrobial activity.

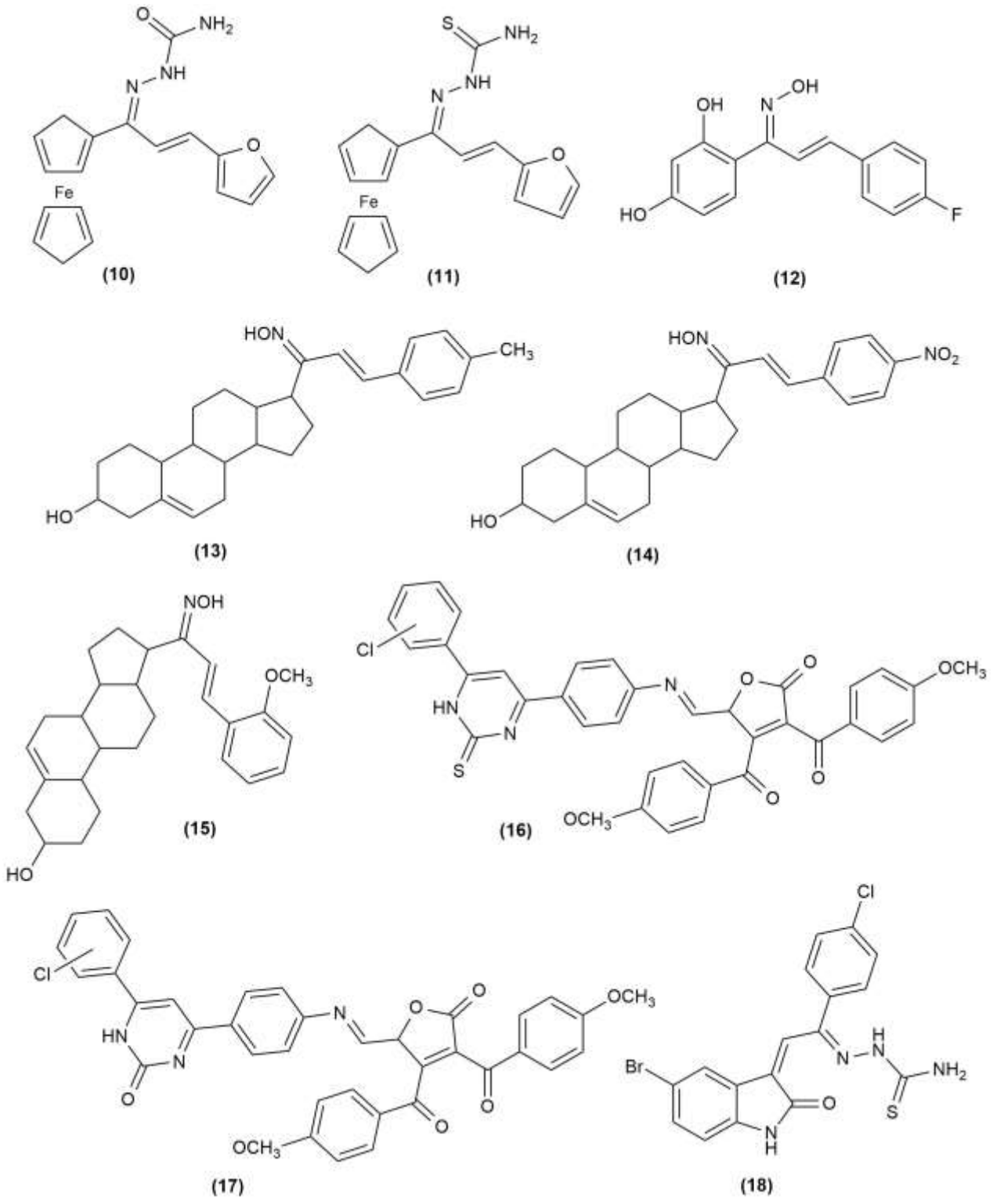


Figure 2: Compound possessing antimicrobial activity.

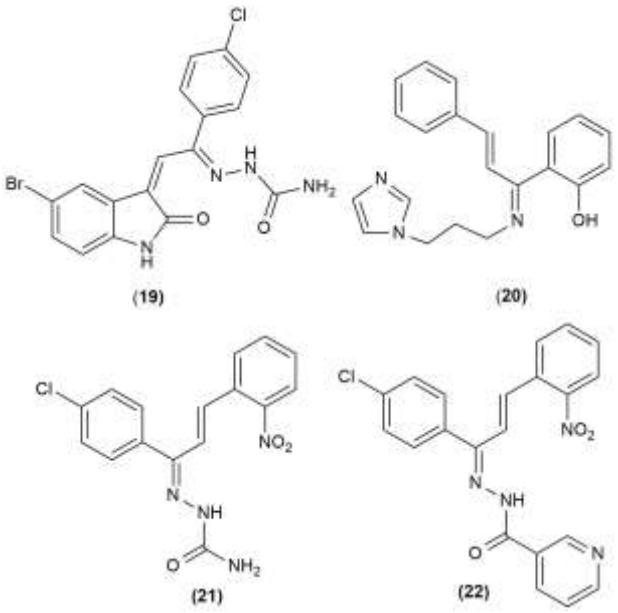


Figure 3: Compound possessing antimicrobial activity.

Chalcone-based Schiff base derivatives as anticancer agents

The Schiff bases namely, 1-ferrocenyl-3-(2-furyl) propanone diamino urea **(23)** and 1-ferrocenyl-3-(2-furyl) propanone diamino thiourea **(24)** were synthesized based on the reaction between ferrocenyl chalcone and urea derivatives with the aid of p-toluenesulfonic acid as the catalyst. The anticancer efficacy of the synthesized compounds was tested against P-388 (B-cell lymphoma) and A-549 (lung) cancer cell lines. The obtained Schiff bases exhibited cytotoxicity against both of the cancer cell lines and proved their anticancer potential[15].

Ligustrazine containing chalcone-based Schiff bases **(25, 26)** was synthesized using hydroxylamine hydrochloride as amine and evaluated their potential against A-375 (human melanoma), MCF-7 (breast), HT-29 (colorectal) and H-460 (lung) cancer cell lines. Both of the compounds were found to be active against tested cancer cell lines and exhibited better cytotoxic potential. The molecular docking study also revealed that these two compounds were active against epidermal growth factor receptor (EGFR) tyrosine kinase and tubulin targets[24]. The structures of these compounds are given in figure 4.

Chalcone-based Schiff base derivatives as antioxidant agents

Muleta F et al., 2022 designed and synthesized the dehydrozingerone semicarbazide Schiff base **(27)** to evaluate its antioxidant potential. The free radical scavenging potential of the synthesized compound was evaluated using the diphenylpicrylhydrazyl (DPPH) assay. The compound exhibited better antioxidant potential with the range of 36 ± 0.45 to 41.46 ± 0.47 percent of inhibition at 12.5 to 100 µg/ml concentration[11].

The steroidal chalcones-based Schiff bases **(28)** were synthesized and reported by Lone IH et al., 2013. The compound was synthesized by the reaction between pregnenolone benzylidene derivatives with hydroxylamine hydrochloride under stirring conditions at room temperature. The antioxidant efficacy was evaluated by using DPPH radical scavenging method and was found to be more highly active than the standard [19]. The structures of these compounds are given in figure 4.

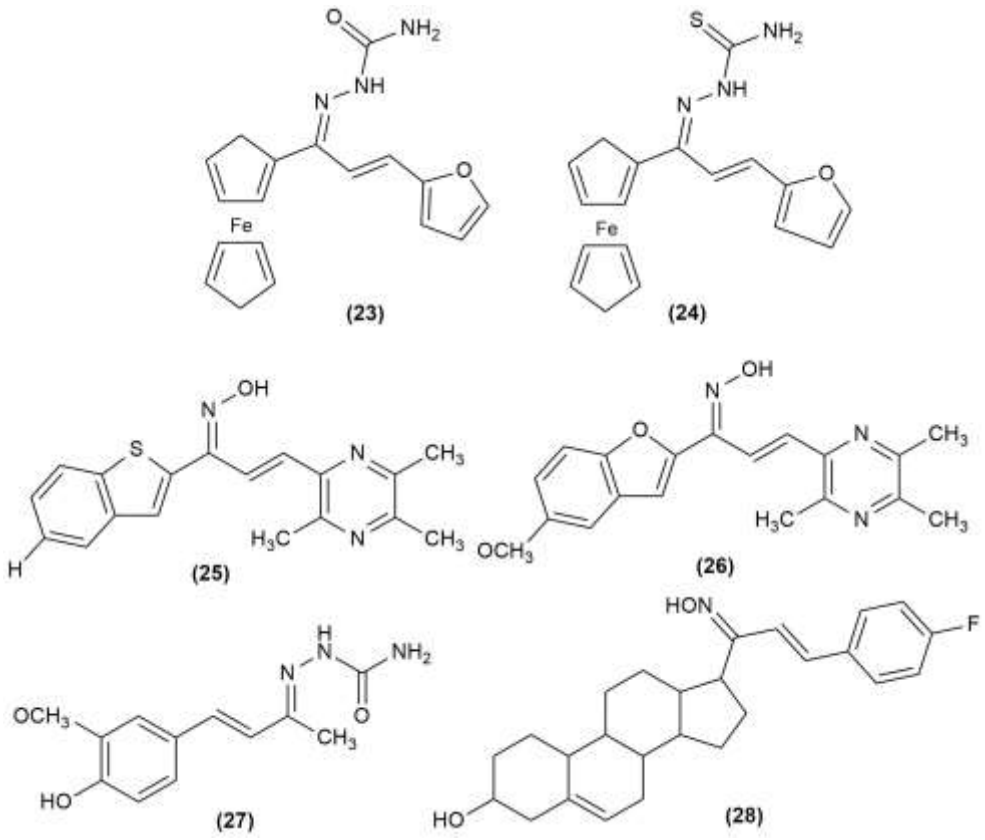


Figure 4: Compounds possessing anticancer **(23-26)** and antioxidant activity **(27, 28).**

Chalcone-based Schiff base derivatives as antidiabetic agents

A series of hydroxy and methoxy-substituted chalcone-based Schiff bases **(29, 30)** were synthesized by the condensation of chalcone and hydroxylamine hydrochloride in pyridine under reflux conditions. The antidiabetic activity of the synthesized ligands was determined by the *α-Glucosidase* inhibition assay against acarbose. Both of the compounds showed significant activity[10] and the structures of these compounds are given in figure 5.

Chalcone-based Schiff base derivatives as immunosuppressive agents

A series of deoxybenzoin chalcone-based Schiff bases **(31, 32)** were synthesized by Luo Y et al., 2012. The immunosuppressive potential of these compounds was evaluated on anti-CD3/anti-CD28 co-stimulated lymph node cells. The western blot analysis was performed to determine the status of the caspase 3 protein by using anti-cleaved caspase 3 antibodies. Thus, these compounds exhibited lesser cytotoxicity with significant immunosuppressive activity in a dose-dependent manner[25]. The structures of these compounds are given in figure 5.

Chalcone-based Schiff base derivatives as Tyrosinase and Melanin inhibitors

A series of hydroxy-substituted chalcone-based Schiff bases **(33, 34)** were synthesized by Radhakrishnan SK et al., 2016. The tyrosinase and melanogenesis inhibitory activity of the synthesized Schiff bases were evaluated in murine B16F10 melanoma cells. These compounds exhibited higher inhibitory activities with IC_{50} values of 4.77 and 7.89 µM, respectively. Molecular docking results also revealed that these compounds actively inhibited melanin production and tyrosinase activity, determined by the interaction with mushroom tyrosinase residues[26]. The structures of these compounds are given in figure 5.

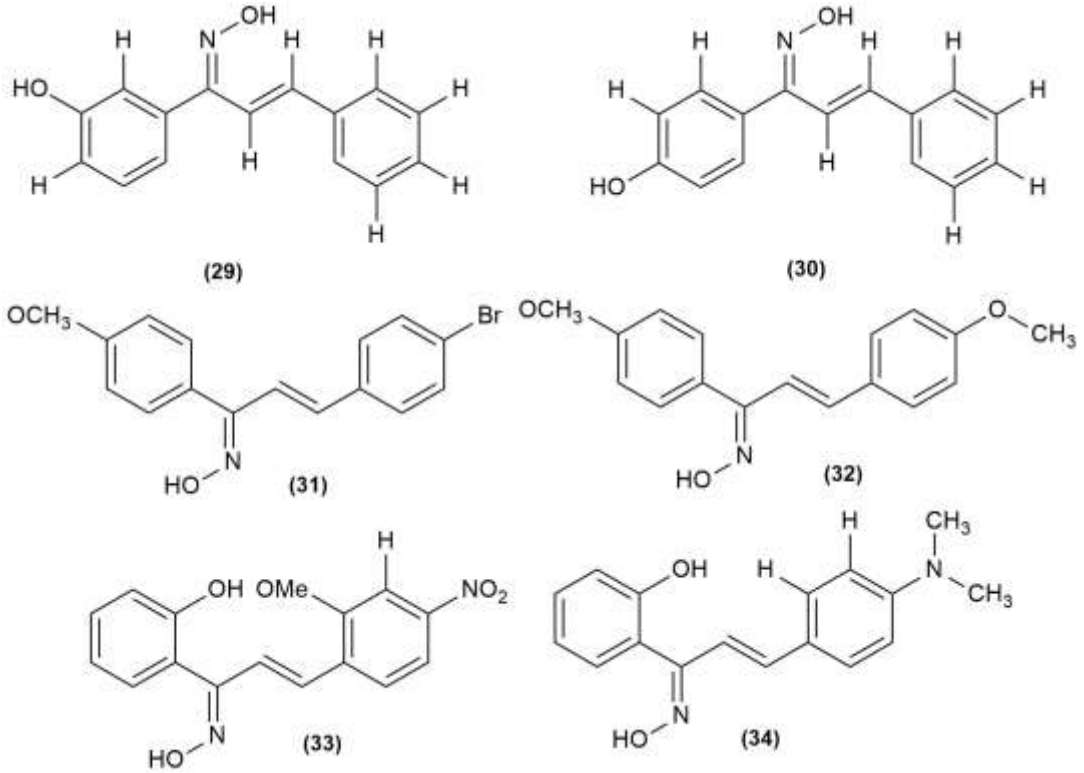


Figure 5: Compounds possessing antidiabetic **(29, 30)**, immunosuppressant **(31, 32)**, tyrosine and melanin inhibition **(33, 34)** activities.

Chalcone-based Schiff base derivatives for iron determination

A novel Schiff base namely, (2E)- 3-(2,5-dimethoxyphenyl)-1-{(4- hydroxybenzylidene)amino]phenyl}prop-2-en-1-one **(35)** was synthesized by the reaction between 4-hydroxy benzaldehyde and chalcone of 4-aminoacetophenone with 2,5-diamino-methoxy benzaldehyde. The synthesized compound was analyzed and found to be having the iron-determining capability in partially aqueous media, which was determined by a simple spectrofluorimetric method[27]. The structure of this compound is given in figure 6.

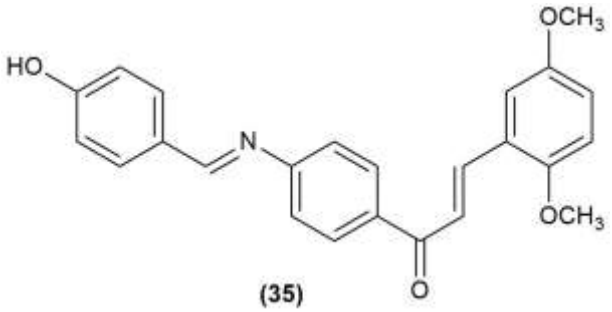


Figure 6: Compound used for iron determination.

Other chalcone-based Schiff base derivatives

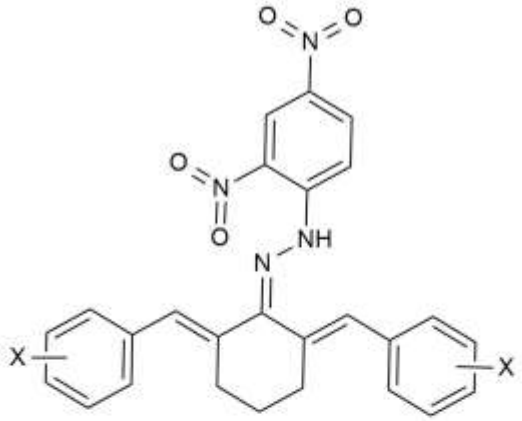
N-(2,6-dibenzylidenecyclohexylidene)-N′-(2,4-dinitrophenyl)hydrazine **(36a-c)** Schiff base was synthesized by the condensation of 2,4-dinitrophenylhydrazine and 2,6-dibenzylidenecyclohexanone with an aid of 10 % hydrochloric acid under reflux conditions for 2 h. The energies of HOMO and LUMO of these compounds were found to be -6.23109 eV and -3.21595 eV **(36a)**, -5.77287 eV and -2.95528 eV **(36b)**, -5.28554 eV and -2.76835 eV **(36c)**, respectively[5].

N'-(1-(4-chlorophenyl)ethylidene)-2-((1-(p-nitrophenyl)- 3-oxo-m-phenylpropyl)thio) acetohydrazide **(37)** and 2-((1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)thio)-N'-(1-(4-nitrophenyl) ethylidene)acetohydrazide **(38)** Schiff bases were synthesized by the multi-step reaction. Initially, the chalcones were prepared by the condensation of acetophenone and 4-nitrobenzaldehyde in ethanol. To the resulted chalcone, 2-mercaptoacetic acid, sulphuric acid and hydrazine hydrate was added to the resulting mixture. To the obtained product, 2-((1-(p-nitrophenyl)-3-oxo-m-phenylpropyl)thio acetohydrazide, 4-nitroacetophenoene and 4-chloroacetophenone was added separately to yield the corresponding Schiff bases, respectively[6]. Jain P et al., 2022 designed and developed a series of chalcone-based Schiff bases **(39)** by the reaction of 4-n-alkoxy benzaldehyde and the chalcones of p-amino benzaldehyde in ethanol under reflux conditions with the help of glacial acetic acid as catalyst[12]. On the reaction of 1-(3-chloro-6-hydroxy-2-methylphenyl)-3-(4-chlorophenyl)prop-2-en-1-one and isoniazid, the novel Schiff base, 3-(3-chloro-6-hydroxy-2-methylphenyl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone **(40)** was obtained[14].

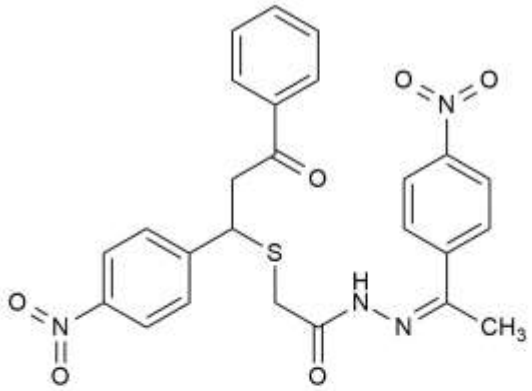
Bis chalcones-based Schiff bases **(41a-e, 42, 43a-d and 44a-c)** were designed and synthesized by Ajani OO et al., 2021. These derivatives were synthesized from the precursor chalcone namely, 1,5-diphenylpenta-1,4-dien-3-one by means of heterocyclic acid catalysis. The derivatives **(41a-e)** were synthesized by refluxing the prepared chalcone with aromatic amines like aniline, 4-chloroaniline, o-phenylenedimine, m-phenylenedimaine and p-phenylenediamine. The chalcone with alpha-naphthylamine resulted in the formation of N-(1,5-diphenylpenta-1,4-dien-3-ylidene)naphthalen-1-amine **(42)**. The Schiff bases of cyclohexyl and aliphatic amine derivatives **(43a-d)** were prepared with the reaction of cyclohexylamine, n-pentylamine, hexadecylamine and oleylamine. Hydrazone related Schiff bases **(44a-c)** were synthesized with the aid of hydrazine hydrate, semicarbazone and 2,4-dinitrophenylhydrazine[17].

(2E)-1-(4-{(E)-[(3,4,5-trimethoxyphenyl)methylidene]amino} phenyl)-3- phenylprop-2-en-1-one **(45)** was obtained by the condensation of (2E)-1-(4-aminophenyl)-3-phenylprop-2-en-1-one and 3,4,5-trimethoxybenzaldehyde in ethanol with an aid of glacial acetic acid[18]. Schiff base derivatives of 2',4'-dihydroxy chalcones **(46a-c)** were synthesized from the para-substituted chalcones with hydroxylamine hydrochloride in ethanol with an aid of sodium acetate[28]. The novel Schiff base ligand **(47)** was synthesized by refluxing the chalcone namely (3-chloro-6-hydroxy-2-methylphenyl)-3-(furan-2-yl) prop-2-en-1-one with isoniazid in ethanol for 6-8 h[29]. Chalcone-linked isatin derivatives-based Schiff bases **(48)** were synthesized by the microwave irradiation of isatin and corresponding amino compounds obtained from the reaction of benzylidene with thiourea with an aid of glacial acetic acid under 200 W for 25 sec[30].

The novel Schiff base **(49a, b)** was obtained from the mixture of hydrazide and aromatic aldehyde with an aid of dry benzene and glacial acetic acid under reflux conditions for 3 h. Initially, the chalcones were prepared by the reaction between acetophenone and benzaldehyde, into which hydroxylamine hydrochloride, sodium hydroxide solution, ethyl α-chloro acetate and ester were mixed and refluxed to obtain the hydrazide compound as an intermediate for the synthesis of Schiff base[31]. 4-[(1E, 2E)-3-(4-hydroxy-3-methoxyphenyl)-N-1,3-thiazol-2-ylprop-2-enimidoyl]benzene-1,3- diol **(50)** was synthesized by Vyas SP., 2018. This compound was synthesized by the reaction of (2Z)-1-(2,4-dimethylphenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one with aminothiazole in ethanol with the catalytic amount of glacial acetic acid under reflux conditions for 5-6 h[32]. The structures of these compounds are given in figures 7 and 8.



(36a-c); a= p-Cl, b= p-OCH_3, c= p-$N(CH_3)_2$



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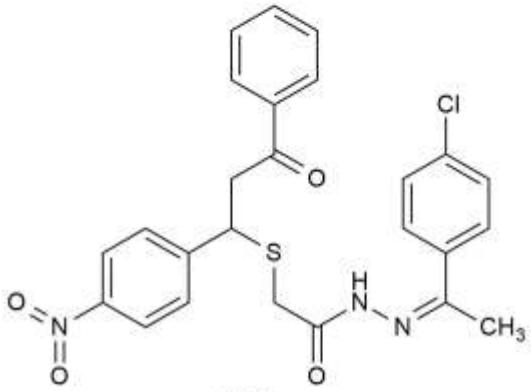

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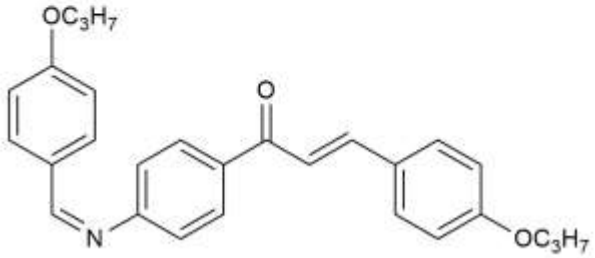

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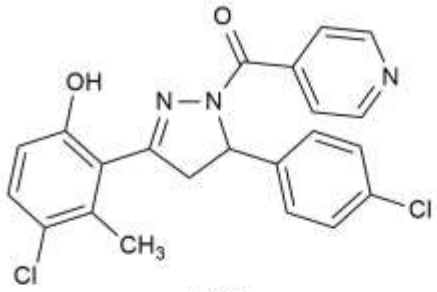

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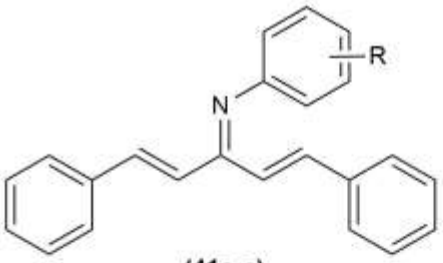
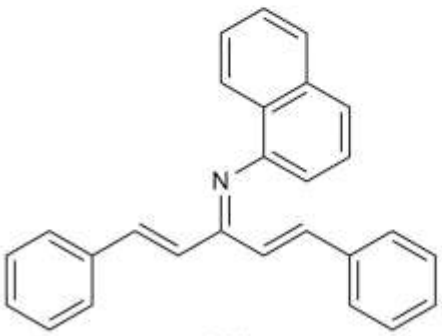


(41a-e)

R = H, 4-Cl, 2-NH_2, 3-NH_2, 4-NH_2



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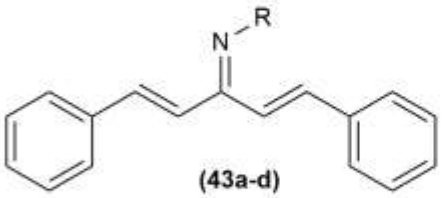
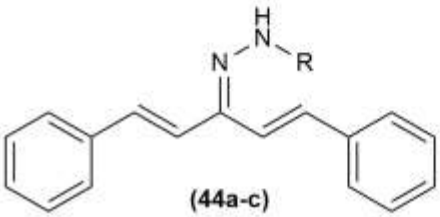


(43a-d)

R = cyclohexyl, n-pentyl, hexadecyl, $C_{18}H_{35}$



(44a-c)

R = H, NH_2C=O, 2,4-dinitrophenyl

Figure 7: Miscellaneous compounds.

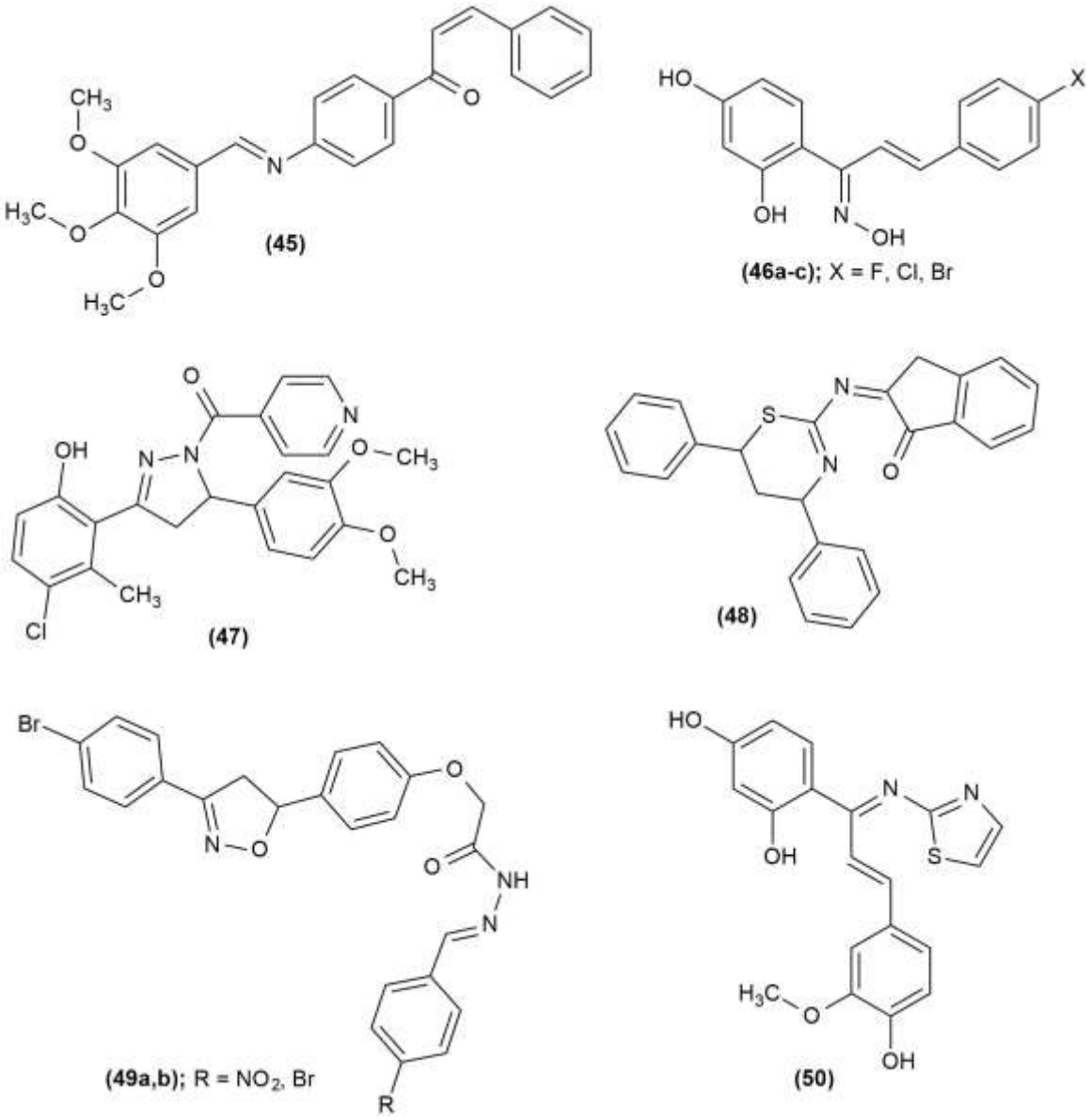


Figure 8: Miscellaneous compounds.

Conclusion

This review summarizes the various synthetic strategies and biological applications of the chalcone-based Schiff bases. These derivatives were synthesized by using various techniques like one-pot condensation, single and multi-step refluxing, microwave-assisted synthesis, heterocyclic catalyst-mediated synthesis, trituration and stirring at room temperature. The microwave-assisted technique was found to be more effective than other conventional synthesis. Being an important class of compounds in synthetic organic chemistry, these medicinally important chalcone-based Schiff bases and their derivatives have been used for various ailments including antimicrobial, anticancer, antioxidant, antidiabetic, immunosuppressants, tyrosinase inhibitors and thermal stabilizers. Particularly, chalcone-based Schiff bases exhibited significant and potent antimicrobial activity. These kinds of Chalcone-based Schiff bases can be further developed into the corresponding metal complexes, Mannich bases and other derivatives like Schiff bases containing pyrazole, isoxazole, pyrimidine and pyrazoline derivatives. Additionally, they are also used in a variety of applications as flexible instruments, such as fluorescent turn-on/turn-off sensors for the quantification of various analytes. Thus, they are interesting compounds in medicinal chemistry because of how simple they are to prepare and how well they can form complexes with all metals practically.

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