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Biological applications of Schiff bases: An overview

Senthil Kumar Raju *, Archana Settu, Archana Thiyagarajan, Divya Rama, Praveen Sekar and Shridharshini Kumar

Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Namakkal, Tamilnadu, India- 637205.

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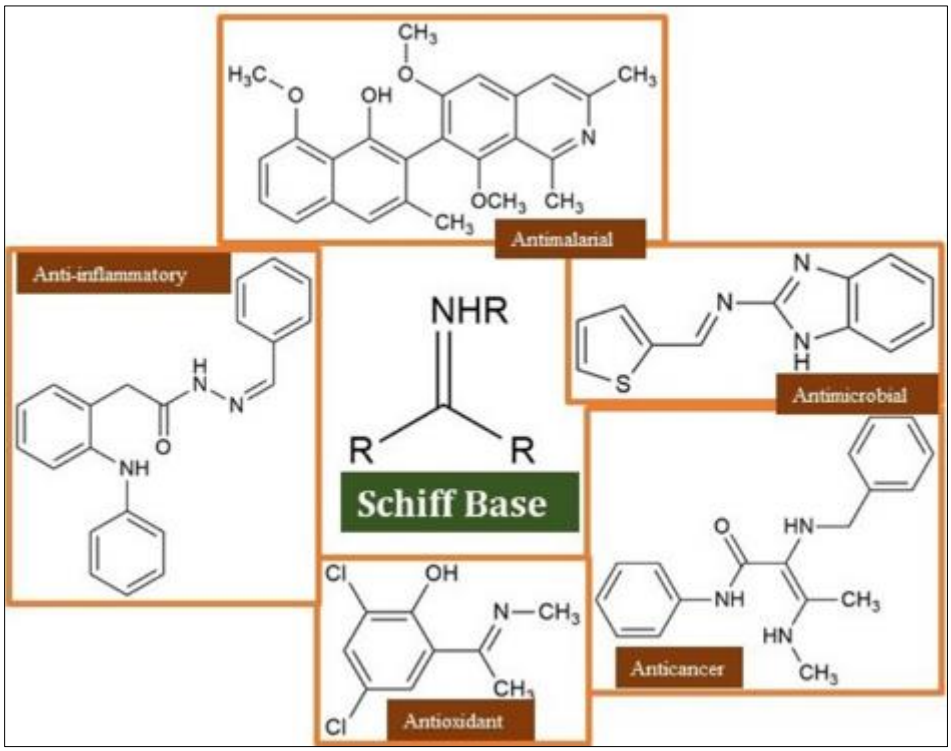
Abstract

Schiff bases are the compounds containing the azomethine group (-HC=N-). They are formed by the condensation of ketones or aldehydes with a primary amine. Formation of Schiff base generally takes place under acid/base catalysis or with heat. The common Schiff bases are crystalline solids, which are basic but at least some form insoluble salts with strong acids. Schiff bases are used as intermediates for the synthesis of amino acids or as ligands for the preparation of metal complexes having a series of different structures. The electrophilic carbon and nucleophilic nitrogen in the C=N imine bond provide excellent binding opportunities with different nucleophiles and electrophiles thereby inhibiting targeted diseases, enzymes or DNA replication. These Schiff bases are synthesized from various aldehydes and amines under stirring conditions, catalyst-free, reflux conditions, microwave irradiation and ultrasonic conditions. These compounds serve a wide range of applications in pharmaceutical industries as well as chemical industries. There are a series of biological activities exhibited by these compounds which include antimicrobial, anti-inflammatory, antiviral and antioxidant activities. Apart from exhibiting medicinal properties, Schiff base compounds play an important role as ligands in coordination chemistry. Thus, Schiff bases and their derivatives may be further used for enormous biological applications with potent effects.

Keywords: Schiff base; Azomethine; Imine; Pharmacological activities; Coordination chemistry

* Corresponding author: Senthil Kumar Raju; Email:thrisen@gmail.com
Department of Pharmaceutical Chemistry, Swamy Vivekanandha College of Pharmacy, Tiruchengode, Tamil Nadu, India-637 205.

Graphical abstract



1. Introduction

Hugo Schiff in 1864 discovered how aromatic aldehydes and primary amines combine to form imine derivatives [1]. In general, azomethine groups with the general formula R-CH=N-R are generated by reacting as an amine with aldehydes or ketones to create Schiff bases, a significant class of chemical compounds. Aliphatic aldehyde-based Schiff base compounds are unstable because they spontaneously polymerize, however aromatic aldehyde-based Schiff base compounds do not experience these problems because of their conjugated structure. Schiff bases typically form under the catalysis of acids, bases or heat. Common Schiff bases are crystalline solids, which are only weakly basic, yet at least some of them combine with strong acids to generate insoluble salts. The Schiff bases can be used as the starting materials in the synthesis of various amino acids and play a crucial role in coordination chemistry i.e., metal complexes. Schiff bases have a variety of flexible and unique forms, which can be prepared more easily by utilizing aldehydes than ketones. Because these compounds have such a flexible and varied structure, a vast variety of Schiff base compounds and their behaviour have been explored [2,3].

Numerous investigations have demonstrated the significant chemical and biological significance of a lone pair of electrons in a sp2 hybridized orbital of the nitrogen atom of the azomethine group. These substances are also known as azomethines, imines and anils. Through ring closure, cycloaddition and replacement reactions, a variety of commercial and physiologically useful chemical moieties can be prepared and developed using Schiff bases as substrates [4,5].

As many proteins contain a heterocyclic ring as a skeleton, these compounds play a crucial role in the distinctive and flexible applications of therapeutic scaffolds and design. One of the most prominent heterocycles is benzothiazole, which has a thiazole ring fused to a benzene ring that contains a variety of molecular designs, optical, liquid and electronic properties. Schiff base derivatives obtained from sulfa drugs has great attention due to their biological properties [6,7].

The imine group which contains electrophilic carbon and nucleophilic nitrogen provides excellent binding opportunities with different nucleophiles and electrophiles, thereby inhibiting targeted diseases, enzymes or DNA replication. Hydrazone derivatives and antipyrine-derived Schiff bases are an interesting class of compounds, especially in antimicrobial drug research [8,9,10].

Due to their structural resemblance of naturally occurring biological molecules, Schiff bases are extremely important in the biological area. These compounds show an extensive variety of pharmacological actions, including antibacterial, anti-inflammatory, anticancer properties [11], analgesic, antidiabetic and antipyretic activities [12]. Schiff bases may

also act as catalysts, polymer stabilizers, intermediates in organic synthesis, pigments and dyes [13], and it also has a wide range of applications such as electroluminescence effects, fluorescence properties, non-linear, optical properties, chemosensory [14], material science, industry, agriculture [15], cosmetic and polymer industries [16].

In this review, only the literature indexed in Science Direct, Springer, Google Scholar, Research square, PubMed, Embase, ResearchGate, ACS and Royal Society of chemistry databases were taken between the time period of 2011-2021. The keywords of this survey include Schiff bases, aromatic Schiff bases, azomethines, imines, antimicrobial, anticancer, antioxidant, anti-inflammatory, antimalarial and Alzheimer's disease, which were used individually and in combination. Here, we summarized the various biological applications of Schiff bases and their derivatives.

2. General mechanism

The aldehyde or ketone Schiff base production is a reversible reaction that typically occurs under acid (or) base catalysis or during heating. In most cases, the product is separated from the formation, the water is removed, or both are done. Aqueous acid or base has the ability to hydrolyze several Schiff bases back to their respective aldehydes, ketones and amines.

With the exception of the fact that it is not a concerted reaction, this reaction is comparable to the E2 elimination of alkyl halides. It goes through an anionic intermediate in two phases. In reality, the Schiff base creation is a series of two different types of reactions, namely addition and elimination. Yet because amines are basic chemicals, the acid concentration cannot be allowed to be excessive. Many Schiff bases are best synthesized at mildly acidic pH because if the amine is protonated and turns non-nucleophile, equilibrium is pulled to the left and carbinolamine production is prevented [3]. The general mechanism is given in Fig. 1.

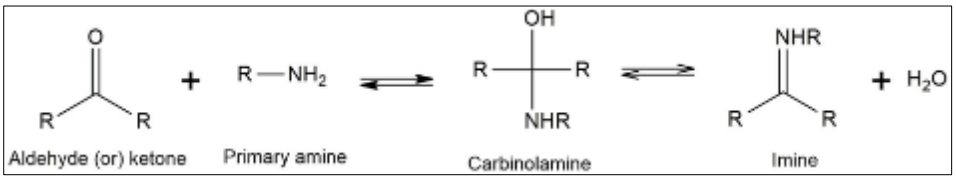


Figure 1 General mechanism for synthesis of Schiff base

3. Biological Applications of Schiff Bases

3.1. Antimicrobial activity

Antimicrobials are considered one of the most successful forms of therapy in medicine though the efficiency of the antimicrobials is compromised due to antibiotic-resistant pathogens [17]. Amino acid Schiff bases were formed by condensation of isatin and amino acids which include simple amino acids such as glycine, valine, phenylalanine, cysteine, leucine and alanine which showed strong antibacterial activity. Cellulose-based Schiff bases are synthesized through the reaction between p-aminophenol and aldehyde groups that exhibited antibacterial activity against *Escherichia coli*, *Enterococcus faecalis*, and *Staphylococcus aureus* [18].

Table 1 Schiff bases possessing antimicrobial activity with their effective microorganisms

Compound No	Compound Name	Effective Microorganisms	Reference
1	(E)-4-((benzo[d]thiazol-2-ylimino)methyl)-2-methoxyphenol	*S. aureus, Bacilus subtilis, E. coli*	[4]
2	(E)-3-((4-chloro-2-hydroxybenzylidene)amino)-5-hydroxybenzoicacid	*A. niger*	[4]
3	(E)-4-((4-chlorobenzylidene)amino)phenol	*A. niger, Chalara Corda*	[4]
4	2-[6-methylbenzothiazole-2-ylimino] methyl phenol	*A. niger, C. albicans*	[6]
5	3-bromo-2-[6-methylbenzothiazole-2-ylimino] methyl phenol	*Pseudomonas aeruginosa, E. coli, Trichomonas*	[6]

		thidurance, Serratia marcens, Acinetobacter baumannii	
6	(E)-4-methyl-N-(4-nitrobenzylidene)aniline	*S. aureus, E. coli, P. aeruginosa, K. pneumoniae*	[8]
7	(E)-N-(2,4-dichlorobenzylidene)-4-methyl aniline	*S. aureus*	[8]
8	(E)-2-(((3-chloro-4-fluorophenyl)imino)methyl)phenol	*S. aureus*	[8]
9	(Z)-2-(5-methyl-2-oxoindolin-3-ylidene)hydrazinecarboxamide	*P. aeruginosa*	[9]
10	(E)-4-(((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one	*P. aeruginosa and A. niger*	[10]
11	(E)-4-(((6-hydroxy-2-oxo-2H-chromen-4-yl)methylene)amino)-1,5-dimethyl-2- phenyl-1H-pyrazol-3(2H)-one	*Aspergillus flavus and A. niger*	[10]
12	4-{[(4-bromophenyl)methylidene]amino}-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one	*K. pneumoniae, Citrobacter freundii*	[11]
13	2-(benzo[d]thiazol-2-yl)-5-((4-(diethylamino)-2-hydroxy benzylidene)amino)phenol	*C. albicans*	[12]
14	4-(2-hydroxy-5-nitrobenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazole-3(2H)-one	*Leishmania promastigotes*	[13]
15	4-fluoro-2-[1-(pentylimino)ethyl]phenol	*Rhizoctonia solani, Sclerotium rolfsii*	[14]
16	4-(8-hydroxyquinoline-2-yl)methylene)amino)-1,5 dimethyl-2-phenyl-1,2-dihydro-3H-pyrazole-3-one	*A. niger*	[16]
17	4-(10-chloroanthracen-9-yl)methylene)amino)-1,5 dimethyl-2-phenyl-1,2-dihydro-3H-pyrazole-3-one	*M. luteus and S. aureus*	[16]
18	2,2'-((1E,1'E)-(pyridine-2,6-diylbis(azanylylidene))bis(phenylmethanylylidene))diBenzoic acid	*S. aureus, B. subtilis, E. coli, and Neisseria gonrrhoeae*	[19]
19	2-fluoro-6-{(*E*)-[(naphthalen-1-yl)imino]methyl}phenol	*C. albicans*	[20]
20	2-{(*E*)-[(2-hydroxyphenyl)imino]methyl} phenol	*P. aeruginosa*	[20]
21	(1*E*)-*N*-benzyl-3-imino-3-(4-methylphenyl)prop-1-ene-1,1,2-triamine	*B. subtilis and P. aeruginosa*	[21]
22	2-amino-1H-benzo[d]imidazole	*Bacillus coagulans, Salmonella typhi, Pseudomonas*	[22]
23	2,2'-(5,5-dimethyl cyclohexane-1,3'diylidene)bis(azan-1-yl-1-ylidene) diphenol	*S. aureus*	[23]
24	N,N'-(5,5-dimethyl cyclohexane-1,3-diylidene)dianiline	*S. aureus*	[23]
25	4-[(E)-2,5 dimethoxy benzylidene) amino]-1,5-dimethyl-2-phenyl-1,2 dihydro-3H-pyrazole-3-one	*Mycobacterium tuberculi*	[24]
26	4-((E)-((5-((E)-((4,5-dimethyl-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-yl)imino)methyl)thiophen-2-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one	*A. niger*	[24]

Various compounds were formed by the condensation of 4-amino salicylic acid with 2-amino thiophenol to produce intermediates and further on treated with ethanol to produce the corresponding product which effectively acts against Bacillus species and fungal strain *Candida albicans*. Some of the compounds were found to be highly active against gram-positive bacteria *Mycobacterium luteus* and *S. aureus* as well as against gram-negative bacteria *Klebsiella pneumoniae* and fungi *Aspergillus niger*. Some of them were formed by reacting with 4-amino antipyrine with 2,5-dimethoxy benzaldehyde which exhibits significant binding affinity with 4KW5 (anti-tubercular drug target) and 1REV (anti-viral drug target) and some of the remaining Schiff base compounds are given below [12,16,18]. The various compounds possessing antimicrobial activity along with their effective microorganisms are given in Table 1 and their structures are given in Fig. 2 and 3.

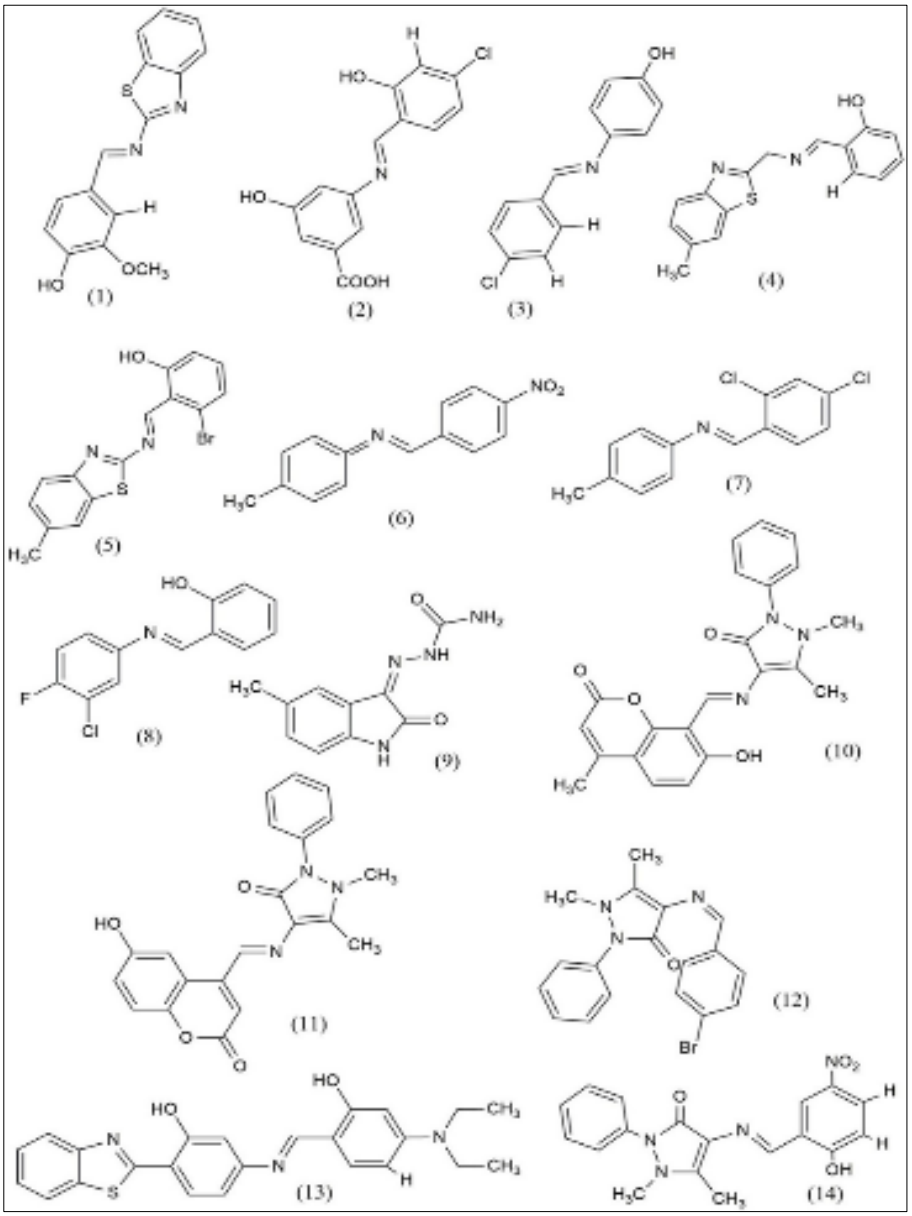


Figure 2 Compounds possessing antimicrobial activity

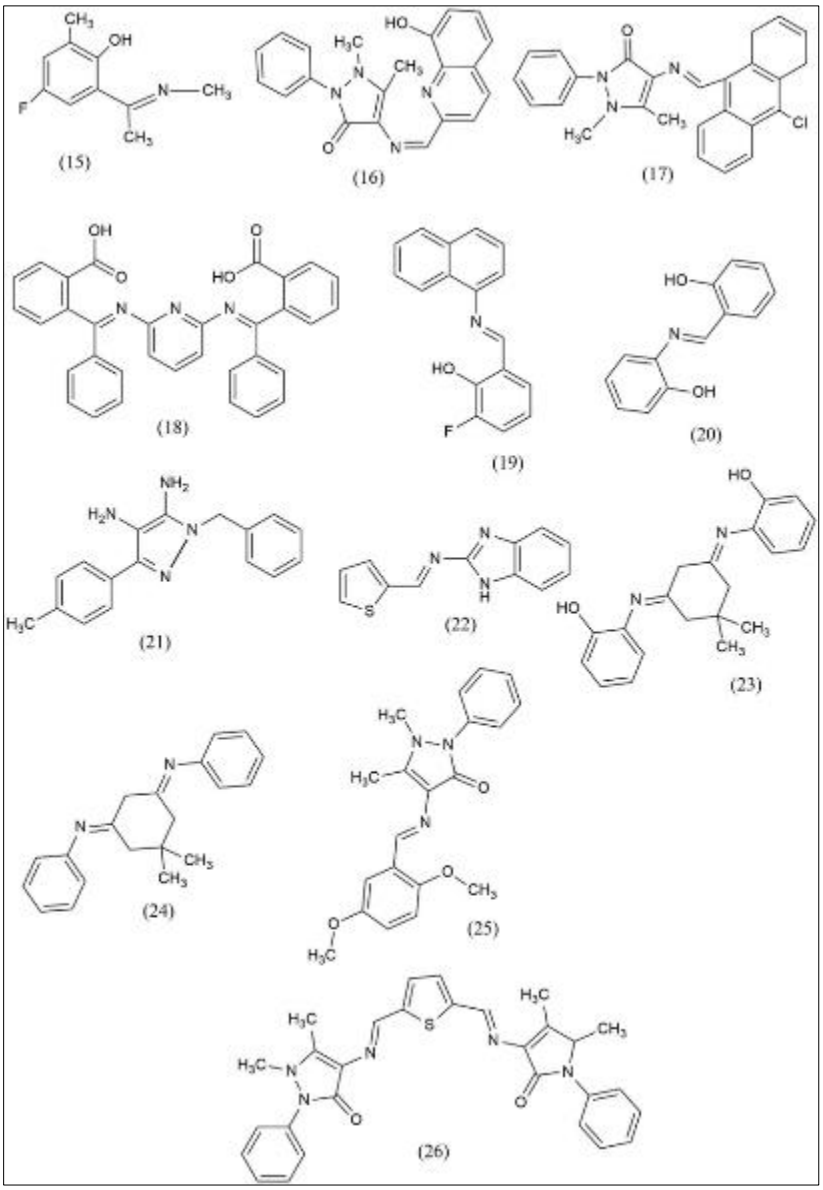


Figure 3 Compounds possessing antimicrobial activity

3.2. Anticancer Activity

Cancer is the body's uncontrolled proliferation of abnormal cells. Old cells do not die when cancer develops in the body. Instead, they grow uncontrollably to give rise to new, abnormal cells. Rapid DNA replication is caused by these abnormal cells and normal cell's production of proteins is inhibited. The most prevalent malignancies that affect people worldwide include lung cancer, breast cancer, cervical cancer and prostate cancer. However, systemic toxicity caused by the harmful effects of the non-specific distribution of anti-cancer medications has significantly hindered its success [25,26].

Schiff bases substituted with nitro, halogen and dimethoxy groups have exhibited significant anticancer activities even at micromolar concentrations. Various compounds showed activity against breast and lung cancer cell lines MCF-7 and H-460. Some of the compounds were formed by the condensation of 2,5-dihydroxybenzaldehyde and 4-aminobenzoic acid showed antiproliferative activity in two breast cancer cell lines (MCF-7 and SkBr-3) and the remaining compounds were listed below [2,27,28]. Table 2 shows the effective anticancer Schiff bases and the structures are given in Fig. 4.

Table 2 Schiff bases possessing anticancer activity with their effective cell lines

Compound No	Compound Name	Effective Cancer Cell Lines	Reference
27	1-((pyridine-2-ylimino) methyl) napthalen-2-ol	MCF-7, SkBr-3	[2]
28	2-[6-methylbenzothiazole-2-ylimino] methyl phenol	MCF-7	[6]
29	3-bromo-2-[6-methylbenzothiazole-2-ylimino] methyl phenol	MCF-7	[6]
30	2-(benzo[d]thiazole-2-yl)-4-((4-(diethylamino)-2-hydroxy benzylidene)amino)phenol	MCF-7	[12]
31	(2E,2'E)-2,2'((1E, 6E)-4-(1-(1,3-dibenzyl-4,5-dihydro-1H-pyrazole-4-yl)ethylidene)-1,7-diphenylhepta-1,6-diene-3,5-diylidene)bis(hydrazinecarboxamide)	-	[20]
32	5-(dimethylamino)-2-{(*E*)-[(6-methyl-1*H*-benzimidazol-2-yl)imino]methyl}phenol	HeLa and MCF-7	[22]
33	(E)-5-((2-chlorobenzylidene)amino)-N-(4-chlorophenyl)-3-((4-methoxyphenyl)amino)-1H-pyrazole-4-carboxamide	HCT-116	[22]
34	4-[(*E*)-benzylideneamino]phenol	PC-3 and HT-29	[22]
35	(2*E*)-2-(benzylamino)-3-(methylamino)-*N*-phenylbut-2-enamide	-	[27]
36	(E) -4-(2,5-dihydroxybenzylidene)-imino-benzoic acid	MCF-7 and SkBr-3	[28]
37	4-{(*E*)-[(3,5-dihydroxyphenyl)methylidene]amino}benzoic acid	Human topoisomerases I and II	[28]

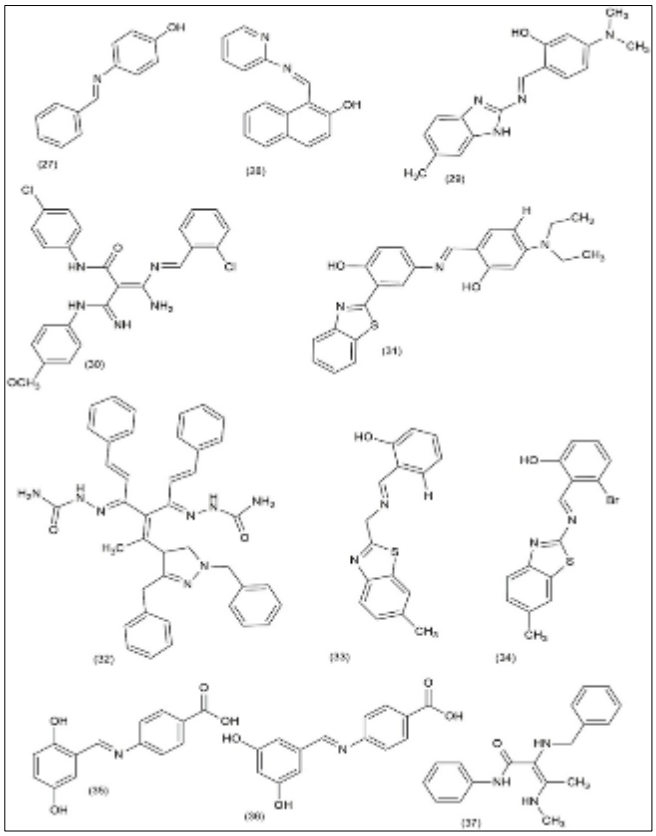


Figure 4 Compounds possessing anticancer activity

3.3. Antioxidant Activity

Table 3 Schiff bases possessing antioxidant activity

Compound No	Compound Name	Reference
38	(E) -3-chloro-4-fluoro-N-(4-fluorobenzylidene)aniline	[8]
39	(E) -3-chloro-N-(2,6-dichlorobenzylidene)-4-fluoroaniline	[8]
40	(E)-3-chloro-4-fluoro-N-(4-methoxy benzylidene)aniline	[8]
41	4-(4-hydroxy-3-methoxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazole-3-(2H)-one	[13]
42	2,4-dichloro-2-[1-(propylimino)ethyl]phenol	[14]
43	4-(1H-Indol-3-ylmethyleneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one	[15]
44	1,5-dimethyl-4-[2-methyl-1H-indol-3yl)methyleneamino]-2-phenylpyrazol-3-one	[15]
45	1,5-dimethyl-2-phenyl-4-(thiophen-2-ylmethyleneamino)-1H-pyrazol-3(2H)-one	[15]
46	(1E,2E)-N-methyl-3-phenylprop-2-en-1-imine	[20]
47	Cholesteryl-4-(4-((E)-(4'-cyanobiphenyl-4-ylimino)methyl)phenoxy)butanoate.	[27]

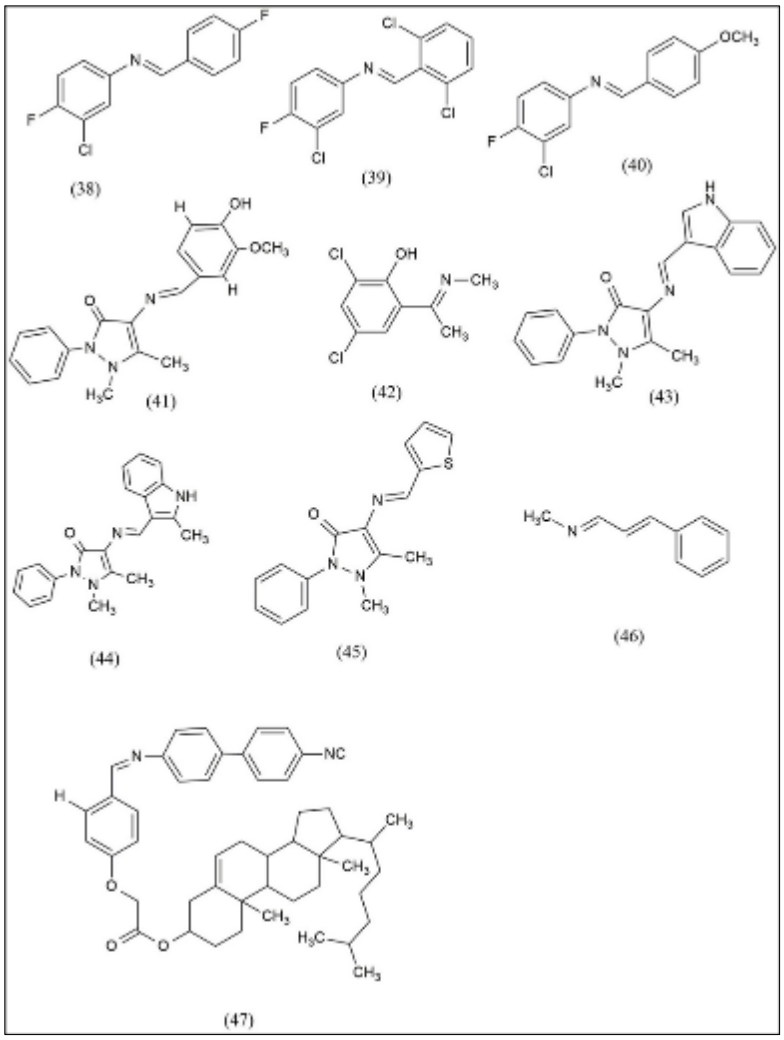


Figure 5 Compounds possessing antioxidant activity

Antioxidants are chemicals that stop the oxidation of other molecules from harming cells. The chemical process of oxidation involves the transfer of electrons from one molecule to an oxidizing substance. Free radicals are known to be produced during oxidation reactions. The outermost shells of these free radicals, which are extremely reactive entities, contain one or more unpaired electrons. The chain reaction begins when they begin to form. When an antioxidant reacts with these free radicals, the chain reaction is stopped by eliminating the intermediate free radicals and other oxidation reactions are prevented by antioxidants oxidizing themselves. Numerous human diseases, including cellular necrosis, CVS disease, cancer, neurological disorder, Parkinson's dementia, Alzheimer's disease, inflammatory disease, etc., are greatly influenced by oxidative stress. Compounds containing hydroxyl groups at the para position of the aromatic ring confer a better radical scavenging activity compared to those with hydroxyl groups in other positions. Various compounds containing pyrazole moiety exhibit strong antioxidant activity and the remaining compounds were given below [13, 15, 29]. Schiff bases possessing antioxidant activity are given in Table 3 and their structures are given in Fig. 5.

3.4. Anti-inflammatory Activity

NSAIDs are FDA-approved for use as antipyretic, anti-inflammatory and analgesic medicines. Because of these effects, NSAIDs can be used to treat a variety of disorders, including muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines and as opioid-sparing drugs in some cases of severe trauma. The given compounds were formed by the condensation of pyrazole derivative with aromatic aldehyde which shows good anti-inflammatory activity against COX-1 and COX-2. 2-(2-anilinophenyl)-*N*'-[(*Z*)-phenylmethylidene] acetohydrazide (48) which has a strong activity against COX-2 and 4-((Z)-5-((Z)-2-(benzo[d][1,3]dioxol-5-yl(imino)methyl)-3-(phenylamino)allylidene4-oxo-2-thioxothiazolidin-3-yl)benzenesulfonamide (49) exhibits high selectivity for COX-1/COX-2 inhibition. 2-benzyl-4-{(E)-[(3,4-dihydroxyphenyl)methylidene]amino}-1,5-dimethyl-1,2-dihydro-3H-pyrazol-3-one (50) which has activity against LPS-stimulated COX-2 mRNA levels [21,30]. The structures of the compounds possessing anti-inflammatory activity are given in Fig. 6.

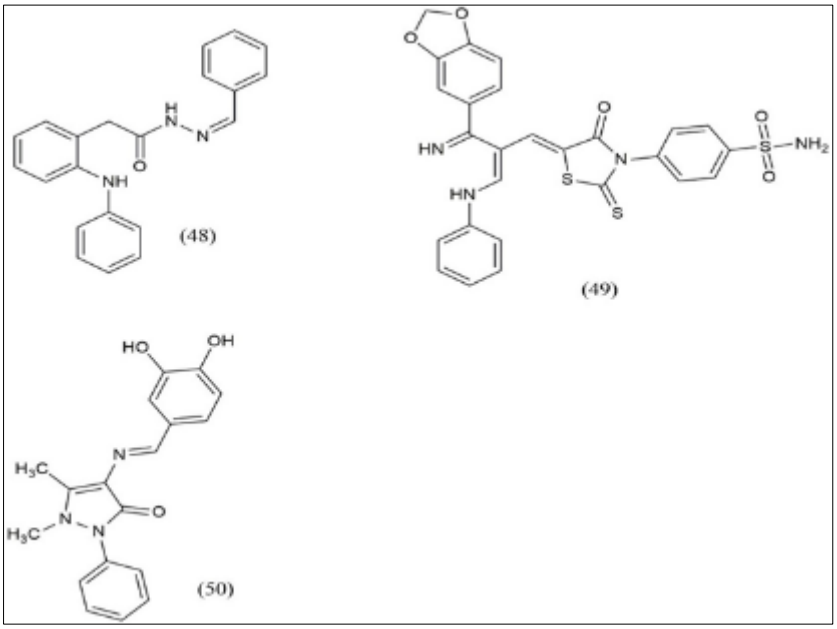


Figure 6 Compounds possessing anti-inflammatory activity

3.5. Neurodegenerative Disorder (Alzheimer's Disease)

Alzheimer's disease (AD) is a neurodegenerative disorder that results in dementia. Extracellular amyloid-b peptide production is one of its major causes. Some of the Schiff base compounds are given below which have strong inhibitory action against Alzheimer's disease. These compounds are formed by the condensation of aromatic aldehyde and amine to give Schiff base compounds. *N*'-[(1*E*)-1-(5-bromo-2-hydroxyphenyl)ethylidene]-3,4,5-trihydroxybenzohydrazide (51) inhibits human acetylcholinesterase enzyme which was used to treat against Alzheimer disease and N'-(2,6-dimethoxybenzylidene)-2-hydroxybenzohydrazide (52) which inhibits acetylcholinesterase and butyrylcholinesterase [21,31]. The compounds possessing anticholinesterase activity are given in Fig. 7.

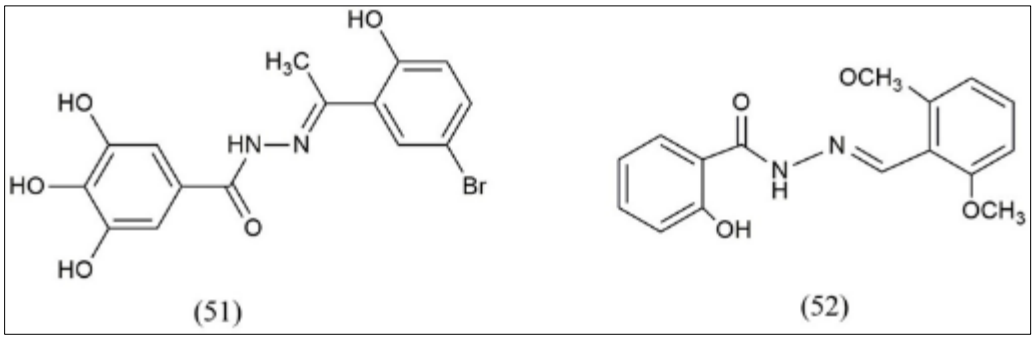


Figure 7 Compounds possessing anticholinesterase activity

3.6. Antimalarial Activity

Malaria is an infectious disease caused by the plasmodium species most commonly *Plasmodium falciparum*. Due to the presence of a quinoline ring in the compound exhibit good activity against plasmodium species especially *P. falciparum*. (E)-2-(2-(4-bromobenzylidene)hydrazinyl)-N-(4-((7-chloroquinolin-4-yl)amino)phenyl)-2-oxoacetamide (53) and 2-{(2E)-2-[(4-bromophenyl)methylidene]hydrazinyl}-N-{4-[(7-chloroquinolin-4-yl)amino]phenyl}-2-oxoacetamide (54) were used against a particular strain of 3D-7 *P. falciparum* [20,21,32]. The compounds possessing antimalarial activity are given in Fig. 8.

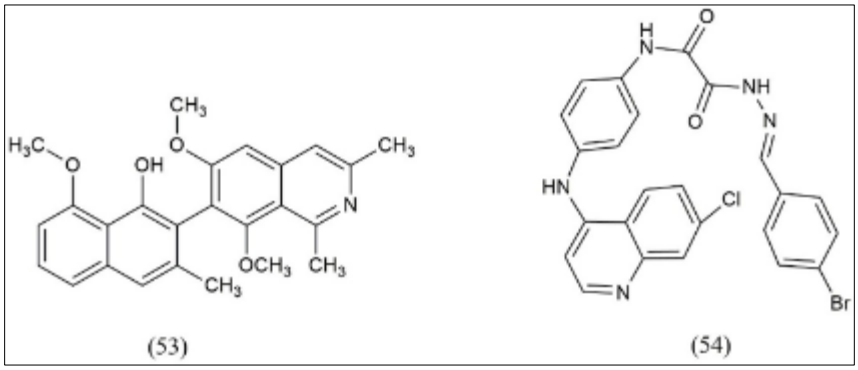


Figure 8 Compounds possessing antimalarial activity

3.7. Inhibition of hCA (Carbonic Anhydrase)

The suppression of hCAs by catecholamines, thiourea derivatives, bromophenols, anions, uracil derivatives and sulfonamides have been studied to inhibit the hCA. 4-((3-chloro-2-hydroxy benzyl)amino)benzene sulfonamide (55) are the inhibitors of cytosolic carbonic anhydrase isozymes hCA-I and hCA-II and cholinesterase enzyme. These inhibitors of hCA-I and II isoenzymes are used for treating several diseases like epilepsy, CHF, mountain sickness, duodenal, gastric ulcer and glaucoma [7]. The structure of this compound is given in Fig. 9.

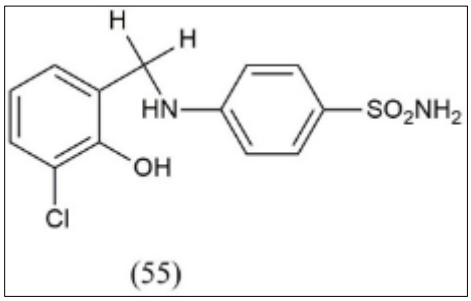
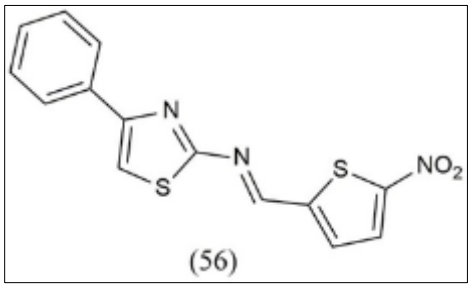


Figure 9 Carbonic anhydrase inhibitors

3.8. Anti-schistosomal Activity

The parasitic trematode Schistosomes are the source of the chronic infectious disease schistosomiasis, which is recognized by the World Health Organization as one of the neglected tropical diseases. Around the world, the disease is thought to affect 230 million individuals per year. (E)-1-(5-nitrothiophene-2-yl)-N-(4-phenyl-1,3 thiazole-2-yl)methanimine (56) acts against *Schistosoma mansoni* adult worms[29]. The structure of this compound is given in Fig. 10.



(56)

Figure 10 Compounds possessing antischistosomal activity

4. Conclusion

The numerous biological actions of Schiff bases and their derivatives are summarized in this review. Being an important class of compounds in synthetic chemistry, the Schiff base and its derivatives had antimicrobial, anti-inflammatory, antimalarial, anticancer, antioxidant and other biological effects. In the case of antimicrobials, it was found to be effective against various microorganisms and in the case of anticancer, it was found to be possessing better efficacy against various cancer cell lines, which particularly inhibited protein kinases, induced apoptosis and acts as tubulin targeting and polymerizing agents. These scaffolds exhibited better activities against various diseases with better IC_{50} values and inhibition rates. To enlarge and enrich the chemistry and biological activities of this scaffold, beyond synthetic chemistry, it can be performed under the reactions of green chemistry principles. The development of novel Schiff base derivatives and their metal complexes are continuously increasing with additional therapeutic applications remains interesting in the field of medicinal chemistry.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors hereby disclose no conflicts of interest regarding the publication of this paper.

Author's contribution

All the authors have contributed equally.

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