Schiff Bases: Multipurpose Pharmacophores with Extensive Biological Applications

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Abstract: Schiff bases are substances prepared generally by the condensation reaction of aldehydes or ketones with amines. They may have substituted aliphatic or aromatic side chains, and hence show extensive biological activities. It is reported that these molecules play an important role in the synthesis of various drugs. This paper focus on the biological activities of Schiff bases of various types and hence makes them important precursors in designing drugs for medical treatment. The biological applications of Schiff bases can be extended from antimicrobial, plant growth regulator, antioxidant, enzymatic, anticancer, anti-inflammatory, anti-malarial, antiviral, neuroprotective, analgesic, anti-convulsant to neurotoxic activities. They also serve as a dominant class of ligands with a variety of binding sites for coordination with metals.

Keywords: Schiff bases, anti-microbial, anticancer, antiviral, antioxidant, anti-malarial.

1. INTRODUCTION

Schiff bases are substances having a general formula $R^1R^2C=NR^3$, where R^1-R^3 is an organic side chain. In this sense a Schiff base is similar to azomethine and due to some restriction its formula is modified to RCH=NR'. Schiff bases are derivatives of a carbonyl and an amino compound, and show extensive biological activities. It is reported that these molecules play an important role in various drugs [1]. The biological applications of Schiff bases can be extended from antimicrobial to antitumor [2]. These vast biological properties make it a suitable substance for chemists to exploit its properties and to synthesize new molecules. They serve as a dominant class of ligands. Attachments of metals are preferred due to the back donation phenomena of the azomethine group. Designing a suitable Schiff base ligand with metal ion can give chemists the ability to tailor metal complexes for different applications including, enzymes preparations [3], chemical analysis, medicine and pharmacy. Apart from their biological properties Schiff bases show diversity properties in non-biological applications like heterogeneous and homogeneous catalysts [4], corrosion inhibitors [5] as well. The development of interest in Schiff base metal complexes are increasing among scientists as indicated by the increasing number appearing in publications annually (500 approximately) [6].

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1.1. Biological Applications

Biological applications of Schiff bases are extensively reported in the literature. In fact the first utilization of Schiff bases was the synthesis of β-lactams which is considered the back bone of diverse antibiotic families [7].

1.1.1. Antimicrobial Activities

The comparative biological activities of Schiff bases **L_1-L_4** were studied against various bacteria and fungus by using levofloxacin [8]. Antimicrobial studies of the ligands **L_1** (R)-2-((4-hydroxypent-3-en-2-ylidene)amino)-3-(4-hydroxyphenyl) propanoic acid, **L_2** (2S)-3-hydroxy-2-((4-hydroxypent-3-en-2-ylidene)amino) butanoic acid, **L_3** (S)-6-amino-2-((4-hydroxypent-3-en-2-ylidene) amino) hexanoic Acid, **L_4** 5-guanidino-2-((E)-((E)-4-hydroxypent-3-en-2-ylidene) amino) pentatonic acid was reported against *Candida albicans*, *Escherichia coli, Streptococcus pyogenes*, and *Pseudomonas aeruginosa* strains. It was observed that **L_2** showed maximum activity compared to other ligands.

A.A. Jarrahpour *et al.,* (2013) developed a computational model to evaluate *in vitro* antibacterial and antifungal activities. It was observed that synthesized compounds **L_5–L_8** were ineffective against *Candida albicans* and *Saccharomyces cerevisiae.* These compounds could form stable pharmacophore sites, which could lead to the design of therapeutically active compounds with high chemical stability [9].

Recently M. Rajarajan *et al.,* (2016) synthesized derivatives of 4-((*E*)-2-benzylidenehydrazinyl)benzoni-

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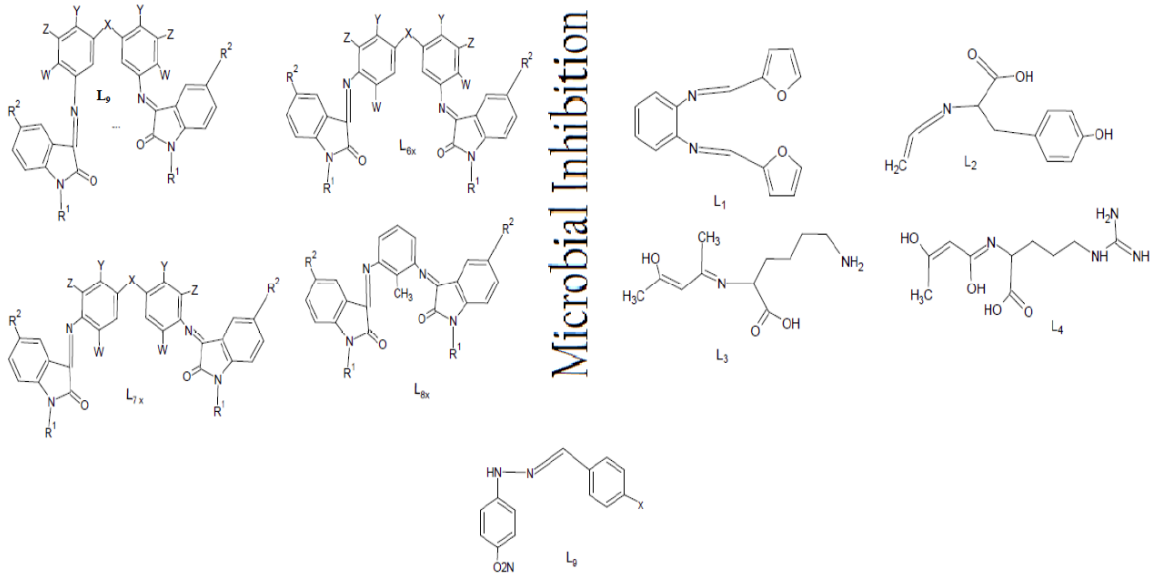


Figure 1: Structures of some Important Antimicrobial Schiff Bases.

Table 1: Groups Attached with Compounds L_5-L_9

Symbol	X	Y	Z	W	R^1	R^2	Symbol	X	Y	Z	W	R^1	R^2	Symbol	X
$L_{5.1}$	CH_2	H	H	H	H	H	$L_{7.5}$	O	H	H	Bu	H	F	$L_{9.5}$	4- Cl
$L_{5.2}$	CH_2	H	H	H	H	F	$L_{7.6}$	CO	H	H	H	H	H	$L_{9.6}$	4-F
$L_{5.3}$	CH_2	H	H	H	Bu	H	$L_{8.1}$	CH_2	H	H	H	H	H	$L_{9.7}$	4-CH_3
$L_{6.1}$	---	H	H	CH_3	H	H	$L_{8.2}$	O	H	H	H	H	H	$L_{9.8}$	4-OCH_3
$L_{7.1}$	CH_2	H	H	H	H	F	$L_{9.1}$	H	-	-	-	-	-	$L_{9.9}$	3-NO_2
$L_{7.2}$	CH_2	Cl	Et	Et	Et	Et	$L_{9.2}$	3-Br	-	-	-	-	-	$L_{9.10}$	4-NO_2
$L_{7.3}$	CH_2	H	H	H	Bu	H	$L_{9.3}$	4-Br	-	-	-	-	-	-	-
$L_{7.4}$	O	H	H	H	H	F	$L_{9.4}$	3-Cl	-	-	-	-	-	-	-

triles **$L_{9.1}$-$L_{9.3}$** which were studied against gram positive *Escherichia coli, Micrococcus, Staphylococcus aureus* and *Bacillus subtilis* and gram negative *Pseudomonas aeruginosa,* using Ciprofloxacin as a standard. The data showed that compound **$L_{9.2}$** showed maximum inhibition against *Pseudomonas aeruginosa*, *Escherichia coli* and *Bacillus subtilis.* Antifungal activities of these compounds were also studied against *Aspergillus niger*, *Trichoderma viride* using Micnazole as standard [10]. Figure **1** shows the structures of some important antimicrobial Schiff bases.

1.1.2. Plant Growth Regulator

Schiff bases generally show inhibition in plant growth hormones mainly on root growth (auxin) when screened with seedlings of rye, wheat and barley [11], whereas thiodiazole Schiff bases can enhance the growth regulator activity of auxin and cytokine [12]. Some synthesized compounds were tested with the seeds of radish and wheat plants and their growth was studied in comparison to water as a control. It was observed that compounds **$L_{10.1}$-$L_{10.6}$** containing 3-(*D*-glucoheptonic-hexitol-1-yl)-1*H*-1,2,4-triazole-5-thione show improvement in the growth of a radish and the stalk of radish but inhibition was observed in case of wheat [13]. Figure **2** shows structures of thiodiazole.

1.1.3. Anti Oxidant Activities

El Hassane *et al.,* (2013) studied antioxidant activities of about 30 (**$L_{11.1}$-$L_{11.25}$ & L_{12}-L_{16}**) different Schiff bases. Structure antioxidant relationship and density functional theory (DFT) within the polarizable continuum model revealed that free radical scavenging by these compounds dominates mainly through proton couple electron transfer rather than sequential proton loss electron transfer, which required a high pH. The data showed that compounds with more phenolic OH i.e. **$L_{11.1}$–$L_{11.10}$, $L_{11.15}$–$L_{11.18}$ & $L_{11.22}$** have significant

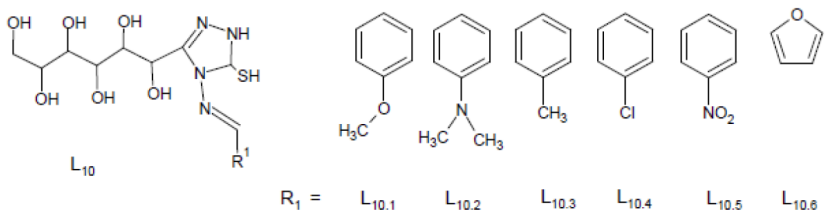


Figure 2: Structures of Thiodiazole.

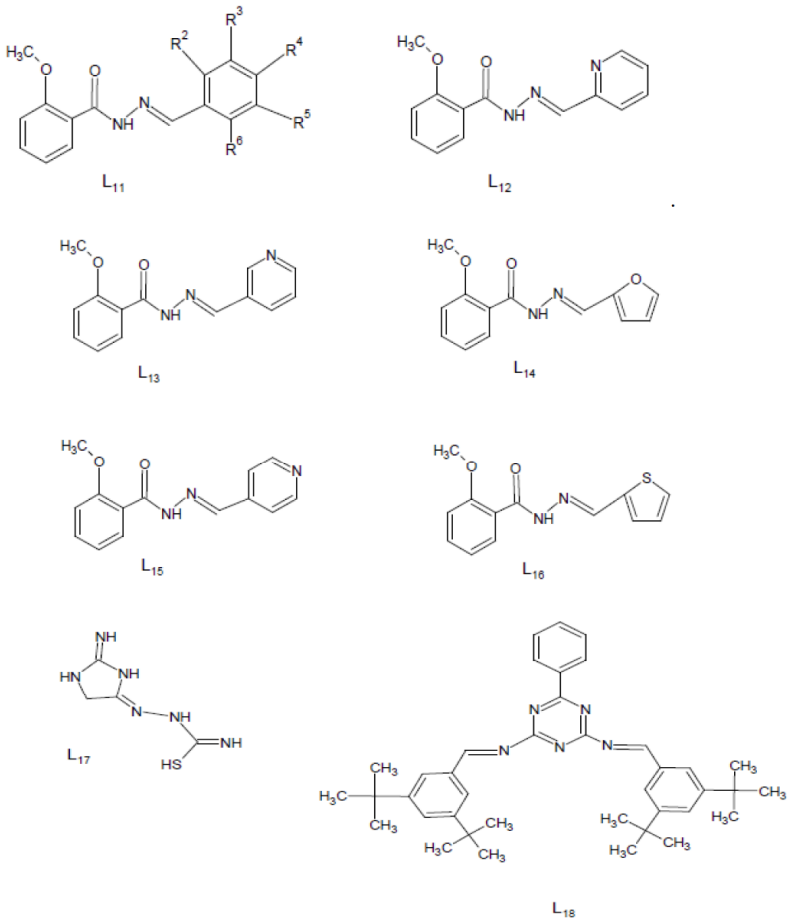


Figure 3: Structures of Antioxidant Schiff Bases.

results in comparison to compounds without OH groups mainly $L_{11.11}$-$L_{11.14}$, $L_{11.19}$-$L_{11.21}$, $L_{11.23}$-$L_{11.25}$, L_{12}-L_{16}. Position of the OH group also matter. Compounds with an OH group at the *ortho* and *para* positions are more effective in comparison to compounds with an OH group at the *meta* position. The DFT studies showed that O-H BDE (Bond Dissociation Energy), spin density distribution and BDE_d can explain the difference in antioxidant activity [14]. Abdual Aziz Ali *et al.,* (2013) studied antioxidant activity of ligand L_{17}. It was observed that the antioxidant ability of Schiff bases are in direct relation to the concentration and also dependent on the substitution on the aromatic ring. Substituents that enhance the conjugated system have enhanced antioxidant activity [9]. Ahmed A. Al-Amiery *et al.,* (2012) studied antioxidant studies of L_{18} which show effective results [15]. Figure **3** shows structures of antioxidant Schiff bases.

1.1.4. Enzymatic Activity

Schiff bases $L_{19.1}$ - $L_{19.2}$ derived from glycine and tryptophan act both as inhibitor and activator for specific enzymes, and were analyzed for *in vitro* enzymatic activity on phosphatidic acid phosphatase (PAP), nitrophenyl acetate (NPA) and acyl carrier protein (ACP) enzymes.

Results showed that $L_{19.1}$ exhibits activity on phosphatidic acid phosphatase (PAP) enzyme and inhibits activity of nitrophenyl acetate (NPA) and acyl

Table 2: Groups Attached with Compound L_{11}

Symbol	R^1	R^2	R^3	R^4	R^5	R^6	Symbol	R^1	R^2	R^3	R^4	R^5	R^6
$L_{11.1}$	H	OH	H	H	H	H	$L_{11.14}$	H	H	OH	H	OH	H
$L_{11.2}$	H	H	OH	H	H	H	$L_{11.15}$	H	OH	H	OCH_3	H	H
$L_{11.3}$	H	H	H	OH	H	H	$L_{11.16}$	H	OH	H	H	H	H
$L_{11.4}$	H	OH	H	H	OH	H	$L_{11.17}$	H	OH	H	H	OCH_3	H
$L_{11.5}$	H	OH	H	OH	H	H	$L_{11.18}$	H	H	Br	OH	H	H
$L_{11.6}$	H	OH	H	H	OH	H	$L_{11.19}$	H	H	Br	Cl	H	H
$L_{11.7}$	H	H	OH	OH	H	H	$L_{11.20}$	H	H	H	F	H	H
$L_{11.8}$	H	H	OH	H	OH	H	$L_{11.21}$	H	H	H	Cl	H	H
$L_{11.9}$	H	OH	H	OH	H	OH	$L_{11.22}$	H	I	OH	OCH_3	H	H
$L_{11.10}$	H	H	OH	OH	OH	H	$L_{11.23}$	H	H	$COOCH_3$	H	H	H
$L_{11.11}$	H	H	OCH_3	H	H	H	$L_{11.24}$	H	H	H	NO_2	H	H
$L_{11.12}$	H	H	H	OCH_3	H	H	$L_{11.25}$	H	H	H	H	H	H
$L_{11.13}$	H	H	OCH_3	OCH_3	H	H							

carrier protein (ACP), whereas **$L_{19.2}$** showed considerable activation of nitrophenyl acetate (NPA) and acyl carrier protein (ACP) at low concentrations [16]. Figure **4** shows structures of enzyme active Schiff bases.

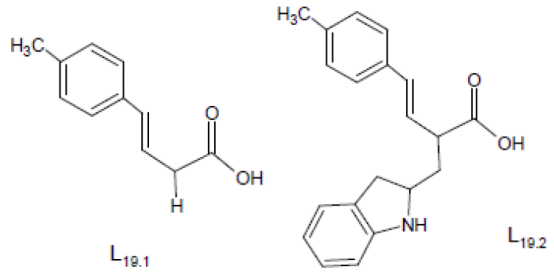


Figure 4: Structures of Enzyme Active Schiff bases.

1.1.5. Anticancer Activities

Cancer is a deadly disease and it has more than two hundred types in the affected human body. Schiff bases are reported to have high antitumor capability. Imine based Schiff bases like N-hydroxy-N′-aminoguanidine **L_{20}** block ribo-nucleotide reductase in tumor cells, hence they are used in the treatment of leukemia [17].

Schiff bases like PDH [N-(1-phenyl-2-hydroxy-2-phenyl ethylidine)- 2′,4′-dinitrophenyl hydrazine] **L_{21}**, PHP [N-(1-phenyl-2-hydroxy-2- phenyl ethylidine)- 2′-hydroxy phenyl imine] **L_{22}** and HHP [N-(2-hydroxy benzylidine)-2′-hydroxy phenyl imine] **L_{23}** can decrease average tumor growth in mice Ehrlich Ascites Carcinoma cells and also rebuild disordered hematological parameters in the right direction. They also have the ability to protect the hematopoietic system [18].

Similarly Schiff bases based on cumarin and pyrazole aldehyde **L_{24}** showed mild anti-cancerous capabilities [19]. Some mono and bis-Schiff bases are effective against five cancer cell lines [20]. In this perspective more systematic and extensive research, both *in vitro* and *in vivo*, is suggested to extend their therapeutic use to overcome the disease.

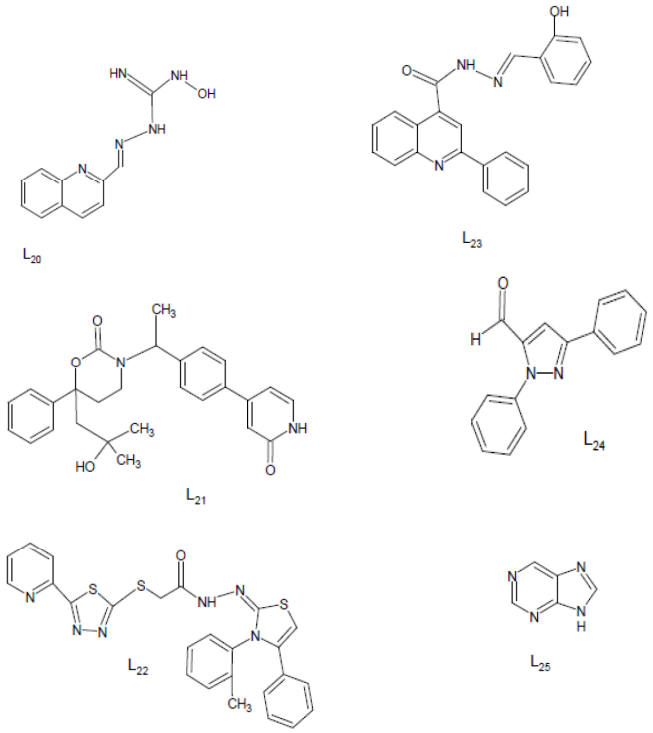


Figure 5: Structures of Anticancer Schiff Bases.

Moreover, Schiff bases like purine bases **L_{25}** with their derivatives have diverse biological actions [21-23] including antitumor activity [24, 25]. Figure **5** shows structures of anticancer Schiff bases.

1.1.6. Anti-Inflammatory Activities

Non-steroidal anti-inflammatory drugs (NSAIDs) are being used as pain killers which function by inhibiting the production of prostaglandins (PG) [26, 27]. Unfortunately these drugs are not targeted for the particular enzyme involved in the biosynthesis of prostaglandins, so new effective molecules which target specific isozymes are required. In this regard, Schiff bases derived from 2- (2,6-dichloroanilino) [27] **L_{26}** and 4-amino-1,5-dimeth-yl-2-phenylpyrazol-3-one **L_{27}** have been found to have excellent anti-inflammatory activity [27].

Mostafa *et al.,* (2012) reported anti-inflammatory activity of some Schiff bases **L_{28}** - **L_{30}** by a paw induced edema method [28] using Indomethacin as a reference as well as comparator.

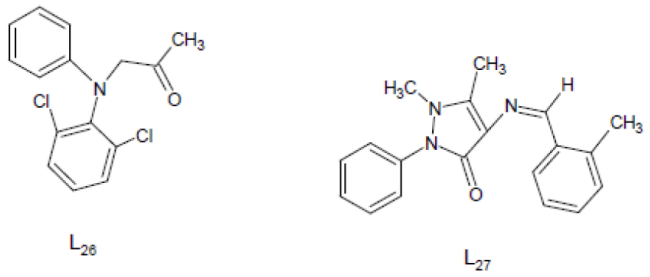
Sachdeva *et al.,* (2013) synthesized derivatives of compounds **$L_{31.1}$ – $L_{31.5}$** and **$L_{32.1}$-$L_{32.9}$** and evaluated them as anti-inflammatory active using a carrageenan-induced acute paw edema method (Turner, 1965) [29] in rats. It was found that addition of Cl and OCH_3 groups into the phenyl ring increase anti-inflammatory activity of compounds whereas in triazole derivatives, substitution at the *para* position is more potent than at the *ortho* and *meta* positions.

Sathe *et al*., (2011) reported that Fluorobenzothiazole Schiff base derivatives **L_{33}** have remarkable anti-inflammatory activity with better therapeutic values and low toxic levels as compared to Ibuprofen as the standard reference anti-inflammatory drug [30].

Hussein *et al*., (2011) synthesized compounds **$L_{34.1}$ – $L_{34.5}$** that exhibited anti-inflammatory activities on the liver enzymes in rats. Among the tested compounds **$L_{34.5}$** showed excellent results [31].

Rana *et al*., (2012) studied the Schiff bases containing amino acid and pyridine for analgesic activities. He reported five good analgesic different compounds **$L_{35.1}$ – $L_{35.5}$** when compared to the reference drugs diclofenac potassium and valdecoxib [32]

Nithinchandra *et al.,* (2012) studied Schiff bases **$L_{36\cdot1}$–$L_{36.3}$** containing sydnone, 3-[1-(4-isobutylphenyl) ethyl]-4-(3-substituted-4-sydnonylidene) amino 5-mercapto-1, 2,4-triazoles, for anti-inflammatory activity. Results showed that compound **$L_{36.3}$**, 3-[1-(4-isobutylphenyl)ethyl]-4-[3-(panisyl)-4-ydnonylidene] amino-5-mercapto-1,2,4-triazole, proved good for anti-inflammatory activity as compared to **$L_{36\cdot1}$** and **$L_{36\cdot2}$** **which** might be due to **the** presence of an electron-releasing group in sydnone [33]. All of the above anti-inflammatory Schiff bases are given in Figures **6**-**16**.

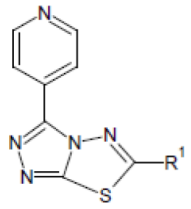


L_{26} L_{27}

Figure 6: Structures of Compounds L_{26} & L_{27}.

Table 3: Groups Attached with L_{28}

Symbol	R^1
$L_{28.1}$	CH_3
$L_{28.2}$	C_6H_5
$L_{26.3}$	3-Pyridyl
$L_{28.4}$	4-Pyridyl



L_{28}

Figure 7: Structure of Compound L_{28}.

Table 4: Groups Attached with L_{29}

Symbol	Ar
$L_{29.1}$	C_6H_5
$L_{29.2}$	4-$NO_2C_6H_4$
$L_{29.3}$	4-ClC_6H_4
$L_{29.4}$	4-BrC_6H_4
$L_{29.5}$	4-$CH_3OC_6H_4$
$L_{29.6}$	4-FC_5H_4

1.1.7. Anti Malarial Activities

Malaria is a global disease and its negligence can cause fatal health issues. In humans malaria is due to

Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, and Plasmodium vivax. Schiff bases enhance the action of antimalarial drugs. For instance, such effect is shown by a Schiff base Ancistrocladidine which is a secondary metabolite produced by the plant family *Ancistrocladaceae* and *Dioncophyllaceae* [34]. Cryptolepine, a valid indolchinoline alkaloid, isolated from the African plant *Cryptolepis sanguinolenta*, also used in the treatment of malaria, is the product of a multi-stage reaction, in which a Schiff base is involved [35].

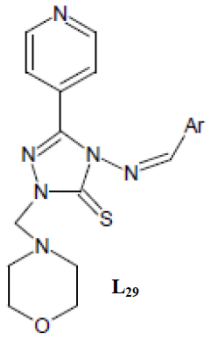


Figure 8: Structure of Compound L_{29}.

Table 5: Groups Attached with L_{30}

Symbol	R^1
$L_{30.1}$	H
$L_{30.2}$	CH_3
$L_{30.3}$	OCH_3

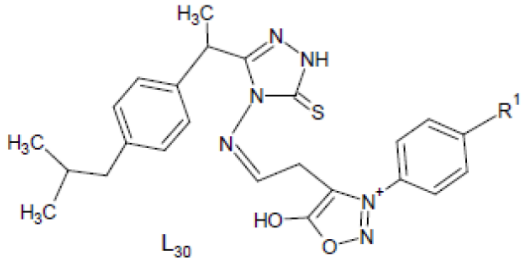


Figure 9: Structure of Compound L_{30}.

Table 6: Groups Attached with L_{31}

Symbol	R
$L_{31.1}$	H
$L_{31.2}$	5-Cl
$L_{31.3}$	5-Br
$L_{31.4}$	5-CH_3
$L_{31.5}$	5-NO_2

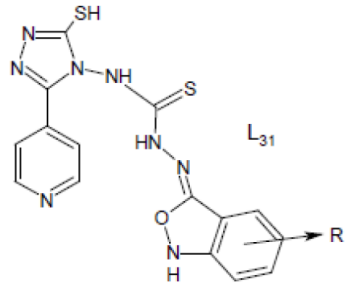


Figure 10: Structure Compound L_{31}.

Table 7: Groups Attached with L_{32}

Symbol	Ar
$L_{32.1}$	C_6H_5
$L_{32.2}$	4-$NO_2C_6H_5$
$L_{32.3}$	3-ClC_6H_4
$L_{32.4}$	4-ClC_6H_4
$L_{32.5}$	4-$OCH_3C_6H_4$
$L_{32.6}$	3,4,5-trimethoxyphenyl
$L_{32.7}$	3-OHC_6H_4
$L_{32.8}$	3-OH, 4-$OCH_3C_6H_4$
$L_{32.9}$	4-FC_6H_4

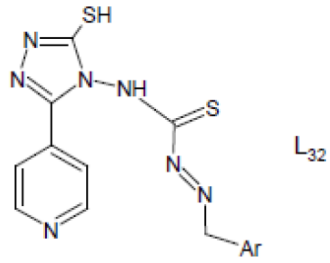


Figure 11: Structure of Compound L_{32}.

Table 8: Groups Attached with L_{33}

Symbol	R^1
$L_{33.1}$	4-[C_6H_4-2-CH_3]
$L_{33.2}$	4-[C_6H_4-3-CH_3]
$L_{33.3}$	4-[C_6H_4-,4-CH_3]

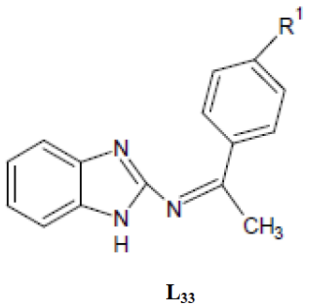


Figure 12: Structure of Compound L_{33}.

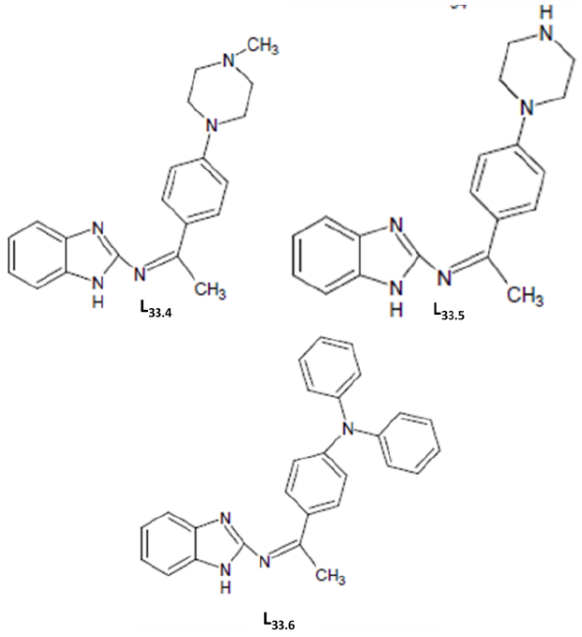


Figure 13: Structures of Compound $L_{33.1}$-$L_{33.3}$.

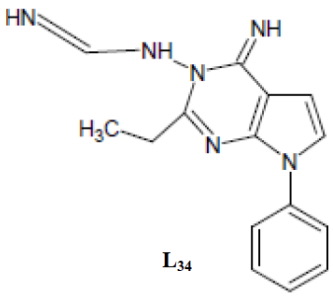


Figure 14: Structure of Compound L_{34}.

Table 9: Groups Attached with L_{35}

Symbol	R^1
$L_{35.1}$	2,6-Cl_2
$L_{35.2}$	3,4-Cl_2
$L_{35.3}$	2-Cl, 6-F
$L_{35.4}$	4-OCH_3
$L_{35.5}$	3,4,5-$(OCH_3)_3$

Table 10: Groups Attached with L_{36}

Symbol	R^1	R^2
$L_{36.1}$	CH_3	CH_2CH_3
$L_{36.2}$	CH_2CH_3	CH_2CH_3
$L_{36.3}$	$CH{=}C_6H_4(4\text{-}CH_3)$	-

Rathelot *et al*., [36] synthesized some Schiff base-functionalised 5-nitroisoquinolines and reported their *in vitro* activity against an ACC Niger chloroquine resistant *Plasmodium falciparum* strain.

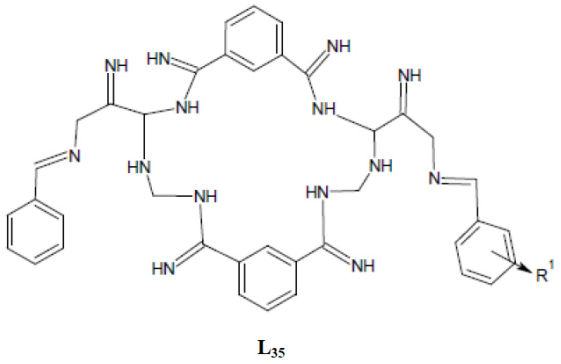


Figure 15: Structure of Compound L_{35}.

1.1.8. Antiviral Activities

The use of vaccines for the treatment of viruses may lead to the eradication of viral pathogens, such as smallpox, polio, and rubella. However, virus-related and hepatitis C human immunodeficiency diseases have been the drawback of vaccine approaches [37]. Schiff bases have been reported to be naturally antiviral active. Schiff bases derived from 1-amino-3-hydroxyguanidine tosylate are good material for the design of new antiviral agents [34]. Isatin Schiff base ligands are found to be antiviral active and successfully used in the treatment of HIV [38] . Gossypol derivatives are also antiviral active and often used in therapeutic treatment. Some Schiff bases are antiviral active against cucumber mosaic virus [3]. A series of Schiff bases **$L_{37.1}$ –$L_{37.12}$** were synthesized and evaluated for their cytotoxicity and antiviral activity. Compounds having a hydroxyl group at the ortho position showed better antiviral activity [39].

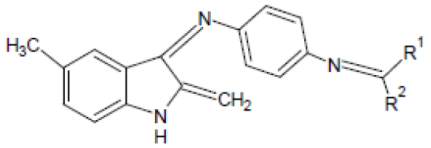
Another series of thiazolines and azetidinones derived from Schiff bases was synthesized and were evaluated for their antibacterial and antiviral (against HIV-I) potential. All the compounds were found to be good HIV-I inhibitors except **$L_{38.1}$** and **$L_{38.9}$** [40]. Schiff bases 1-amino-3-hydroxyguani- dine tosylate are a good source for the design of new antiviral agents [41]. In fact, from a set of different 1-amino-3-hydroxyguanidine tosylate-derived Schiff bases, compound **L_{39}** was very effective against mouse hepatitis virus (MHV).

Isatin and bis-isatin based Schiff bases are active against different strains of viruses [42]. Similarly, Schiff bases derived from prodrug abacavir (Ziagen) are reported to show good antiviral activity against anti-HIV therapy [37]. Schiff bases of 2-phenylquinazoline-

4(3)H-one are reported to show anti-virally active against viruses like feline corona, influenza, and herpes simplex type 1 and 2 [39]. On the basis of the above facts the antiviral potential of Schiff bases targeted research can help to discover new drugs. All of the above anti-viral Schiff bases are given in Figures **17-19**.

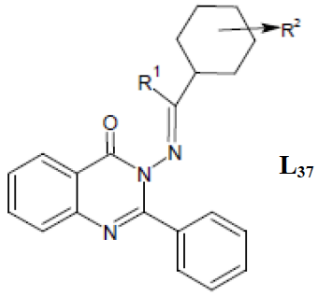
Table 11: Groups Attached with L_{37}

Symbol	R^1	R^2
$L_{37.1}$	H	2-OH
$L_{37.2}$	H	2-NO_2
$L_{37.3}$	H	4-OCH_3
$L_{37.4}$	H	4-$N(CH_3)_2$
$L_{37.5}$	CH_3	4-Cl
$L_{37.6}$	H	H
$L_{37.7}$	H	4-OH
$L_{37.8}$	CH_3	H
$L_{37.9}$	CH_3	4-OH
$L_{37.10}$	H	4-Cl
$L_{37.11}$	H	3-OH, 4-OCH_3
$L_{37.12}$	H	2-OCH_3



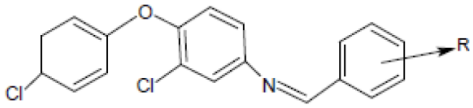
L_{36}

Figure 16: Structure of Compound L_{36}.



L_{37}

Figure 17: Structure of Compound L_{37}.

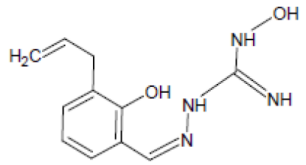


L_{38}

Figure 18: Structure of Compound L_{38}.

Table 12: Groups Attached with L_{38}

Symbol	R
$L_{38.1}$	H
$L_{38.2}$	2-OH
$L_{38.3}$	4-OH
$L_{38.4}$	4-OH ,3-OCH_3
$L_{38.5}$	-CH=CH-C_6H_5
$L_{38.6}$	4-Cl
$L_{38.7}$	4-NO_2
$L_{38.8}$	4-OCH_3
$L_{38.9}$	3,4,5-$(OCH_3)_3$

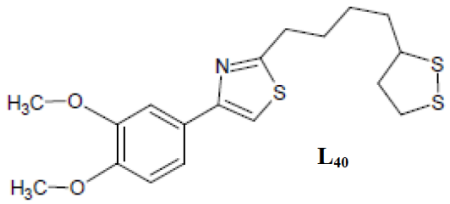


L_{39}

Figure 19: Structure of Compound L_{39}.

1.1.9. Neuroprotective Activity

Koufaki *et al.,* (2007) [43] designed and synthesized new Schiff bases (thiazole) in which compound **L_{40}** was found highly neuroprotective due to replacement of the amide functionality by the aromatic heterocycle. Figure **20** shows the structure of **L_{40}.**



L_{40}

Figure 20: Structure of Compound L_{40}.

1.1.10. Analgesic activities

Pandeya *et al.,* (2012) compared the analgesic effect of Schiff bases **L_{41}, $L_{42.1}$-$L_{42.3}$, $L_{43.1}$-$L_{43.3}$** and **$L_{44.1}$-$L_{44.3}$** with the diclofenac reference drug using the peripheral analgesic assay. Screening the most active compound using acetic acid induced writhing test reviled **$L_{39.3}$**. Against a hotplate test it was found that compounds **$L_{43.1}$, $L_{43.3}$** and **$L_{44.1}$** were active as central analgesics and among all the derivatives tested for the central analgesics compound **$L_{44.1}$** was the most active [44]. The Schiff bases with *p*-chloroanilne and *p*-cholrophenylsemicarbazide were found to be potent analgesics.

Shan P Mohammed *et al.,* (2016) studied the analgesic activity in mice by acetic acid induced writhing test through the *in vivo* method and found **$L_{45.2}$** out of **$L_{45.1}$, $L_{45.3}$** in close agreement with the standard drug of diclofenac sodium.

Sondhi *et al.,* (2006) identified that N-(acridin-9-yl)-4 (benzo[d]imidazol/oxazol-2-yl) benzamides Schiff bases showed analgesic activity. Compounds **L_{46}** and **L_{47}** proved to be good for analgesic activity [45].

Chinnasamy *et al.,* (2010) reported the analgesic activity by the tail-immersion method. 3-(4-(4-Hydroxy-3-methoxylbenzylideneamino) phenylimino) indoline-2-one showed good analgesic activity in comparison with standard pentazocine. It was found that if the compounds have electron-donating groups they have better analgesic activity as compared to compounds with electron-withdrawing groups. **L_{48}** showed better analgesic activity due to the presence of electron donating groups [46].

Bhandari *et al*., (2008) synthesized novel potential analgesic Schiff bases and in the series compounds **L_{49}** showed very good analgesic activity as compared with the reference drug diclofenac sodium. The structures of these Schiff bases are shown in Figures **21-29**.

Table 13: Groups Attached with L_{42}

Symbol	R^1
$L_{42.1}$	H
$L_{42.2}$	NO_2
$L_{42.3}$	Cl

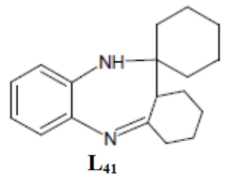


Figure 21: Structure of Compound L_{41}.

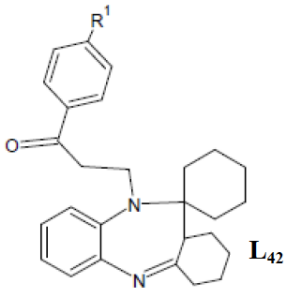


Figure 22: Structure of Compound L_{42}.

Table 14: Groups Attached with L_{43}

Symbol	R^1
$L_{43.1}$	H
$L_{43.2}$	NO_2
$L_{43.3}$	Cl

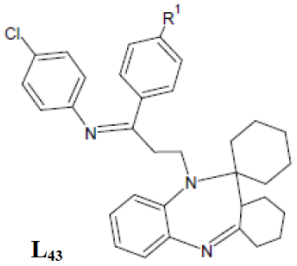


Figure 23: Structure of Compound L_{43}.

Table 15: Groups Attached with L_{44}

Symbol	R^1
$L_{44.1}$	H
$L_{44.2}$	NO_2
$L_{44.3}$	Cl

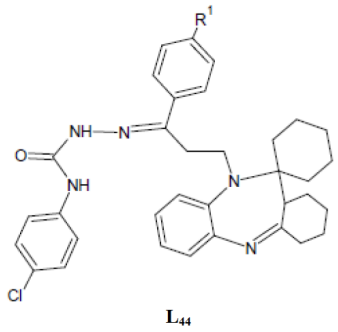


Figure 24: Structure of Compound L_{44}.

Table 16: Groups Attached with L_{45}

Symbol	R^1
$L_{45.1}$	C_6H_5
$L_{45.2}$	$N(CH_3)_2$ C_6H_5
$L_{45.3}$	$CH_3OC_6H_5$

1.1.11. Anticonvulsant and Neurotoxic Activities

Schiff bases of phthalimide, 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-*N*′-(substituted phenyl)methylene/ethylidene benzohydrazide, **$L_{50.1}$ – $L_{50.12}$** were studied for anticonvulsant and neurotoxic activities. It was observed that all the compounds are less effective than

phenytoin a standard drug. Screening of compounds containing lamotrigine with substituted isatin for anticonvulsant activity was performed using a maximal electroshock seizure test with lamotrigine and phenobarbitone sodium as the standard drug. It was observed that compounds **$L_{51.1}$ – $L_{51.2}$** show better results than standard drugs [47].

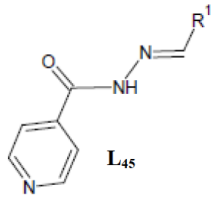


Figure 25: Structure of Compound L_{45}.

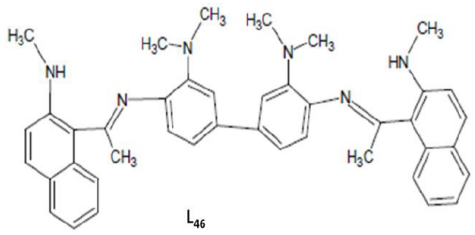


Figure 26: Structure of Compound L_{46}.

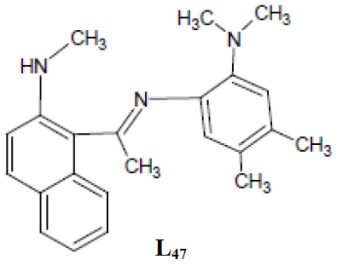


Figure 27: Structure of Compound L_{47}.

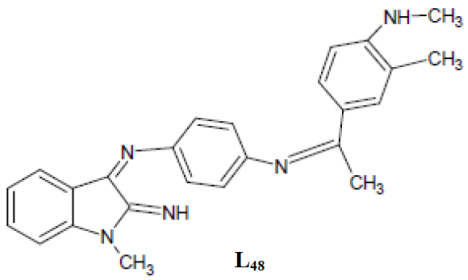


Figure 28: Structure of Compound L_{48}.

Table 17: Groups Attached with L_{49}

Symbol	R^1
$L_{49.1}$	4-[C_6H_4-3-CH_3]
$L_{49.2}$	4-[C_6H_4-3,4-$(CH_3)_2$]
$L_{49.3}$	4-[C_6H_4-4-NH(CH_3)]
$L_{49.4}$	4-[C_6H_4-,4-CH_3]

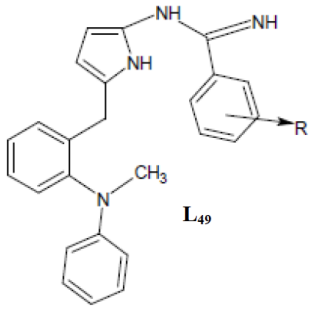


Figure 29: Structure of Compound L_{49}.

Aly *et al.,* (2010) studied 3-aryl-4(3H)-quinazolinones-2-carboxaldehydes compound **L_{52}** It exhibited the anticonvulsant properties due to the thiosemicarbazone side chain at the C-2 position ending with a free amino group and fluorine atom [48].

Bhat *et al.,* (2011) studied Schiff bases with phthalimide pharmacophores for anticonvulsant and neurotoxic properties [49]. Among Schiff bases **$L_{53.1}$ – $L_{53.12}$**, **$L_{53.12}$** having nitro substitution at *ortho* position was found as the most promising anticonvulsant agent with low neurotoxicity.

Table 18: Groups Attached with L_{50}

Symbol	R^1	R
$L_{50.1}$	H	4-OH
$L_{50.2}$	H	3,4$(OCH_3)_2$
$L_{50.3}$	H	3-NO_2
$L_{50.4}$	CH_3	2-OH
$L_{50.5}$	CH_3	4-OH
$L_{50.6}$	CH_3	4-CH_3
$L_{50.7}$	CH_3	4-Cl
$L_{50.8}$	CH_3	4-NO_2
$L_{50.9}$	CH_3	4-OCH_3
$L_{50.10}$	CH_3	2,4-$(Cl)_2$
$L_{50.11}$	CH_3	2-OH, OCH_3
$L_{50.12}$	CH_3	2-NO_2

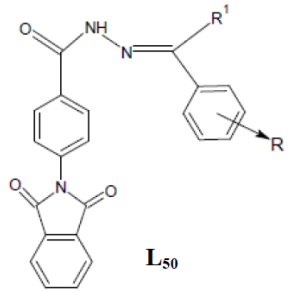
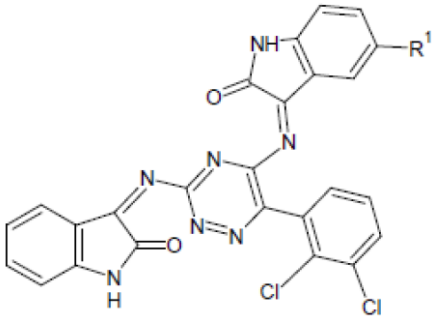
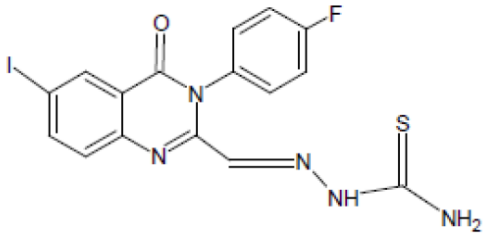


Figure 30: Structure of Compound L_{50}.



L_{51}

Figure 31: Structure of Compound L_{51}.



L_{52}

Figure 32: Structure of Compound L_{52}.

CONCLUSION

The medicinal and biological value of Schiff bases is promising and noticeable. This field requires special attention to explore medicinal aspects of Schiff bases. Schiff bases are a dominant class of ligands, which are synthesized simply by the condensation of a ketone or aldehyde and amines. These substances have a variety of biological applications. This paper extended some important biological application of Schiff bases, which are antimicrobial, plant growth regulator, antioxidant, enzymatic, anticancer, anti-inflammatory, anti-malarial, antiviral, neuroprotective, analgesic, anti-convulsant and neurotoxic.

In this review, the recently reported biological activities of Schiff base have been summarized.

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