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Comprehensive Review on Schiff Base Heterocyclic Moiety Conjugates: Synthesis, Reactions and Diverse Applications

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Abstract
Schiff bases exhibit a broad spectrum of uses in the industrial, pharmacological, and biological fields. With a particular focus on Schiff base heterocyclic moiety conjugates, this review paper provides an extensive overview of the synthesis, reactions, applications, and biological activities of Schiff bases. It explores different approaches to synthesizing Schiff base; including water-based media, conventional methods, metal-catalyzed processes, acidic and phase transfer catalysis, ultrasonic and microwave conditions, and grinding chemistry techniques. Furthermore, the industrial applications of Schiff bases, particularly as corrosion inhibitors, are highlighted. The paper also delves into the biological activities of Schiff bases, such as their antimicrobial, anticancer, anti-inflammatory, analgesic, anthelmintic, and antioxidant properties, showcasing their potential in medicinal and industrial applications. The review aims to provide a comprehensive understanding of the versatile roles Schiff bases play and their significant contributions to advancing various scientific and practical domains, emphasizing their wide ranging benefits and applications.

Keywords: Schiff base, Heterocyclic moiety conjugate, Synthesis technique, Biological activity, Industrial applications, Review

Introduction

Compounds having imine or an azomethine (-HC=N-) functional group are known as Schiff bases. Hugo Schiff discovered them as condensation products of primary amines with carbonyl compounds. According to IUPAC guidelines, Schiff bases are classified as chemical sub-stances (imines) with an azomethine group on the nitrogen atom R2C = NR'(R'≠ H) (Figure 1). They are often seen as being equivalent to azomethines [1]. Schiff bases are among the most notable organic compounds. They are used as polymer stabilizers, catalysts, pigments, dyes, and intermediates in chemical synthesis [2]. Schiff bases, particularly those coupled to a heterocyclic moiety, demonstrated a variety of pharmacological and biological actions, including antibacterial, cytotoxic, anti-fungal, antimalarial, anticonvulsant, antioxidant, and anti-inflammatory properties [3-6].

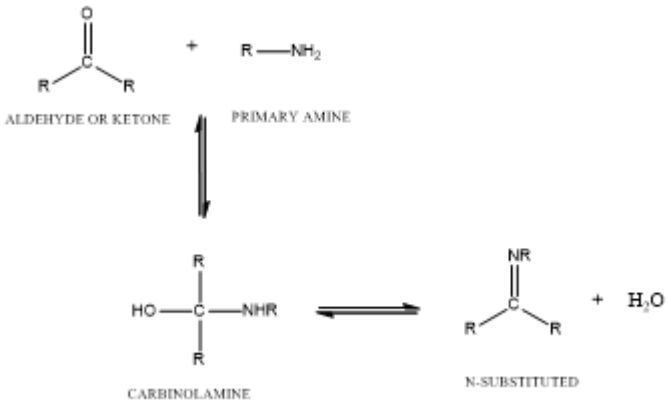
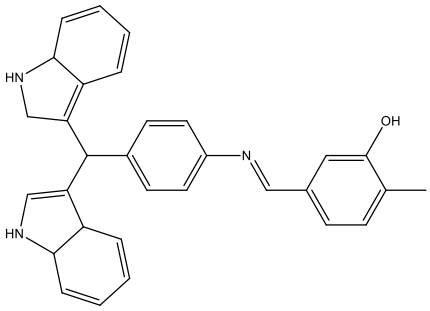


Figure 1 General reaction of Schiff base

(E)-2-(4-(di(1H-Indol-3-yl) methyl) phenyl) amino) methyl) phenol (1) is an example of heterocyclic Schiff bases and showed antibacterial activities [7]. (E)-2-((anthracene-1-amino)methyl) quinoline-8-ol (2) showed antioxidant and antibacterial activities [8]. Also, (E,Z)-N'-(3-Hydroxybenzylidene)-2-((2-oxo-2H-chromen-4-yl) oxy) acetohydrazide (3) exhibited potent inhibition of urease enzyme [9](Figure 2).



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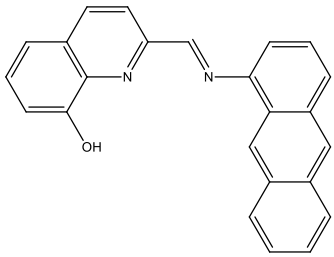

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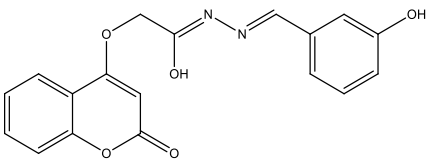

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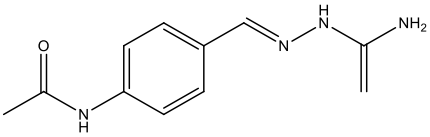

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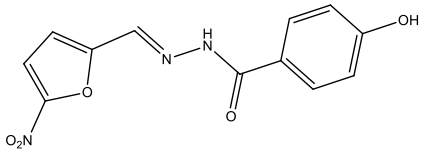

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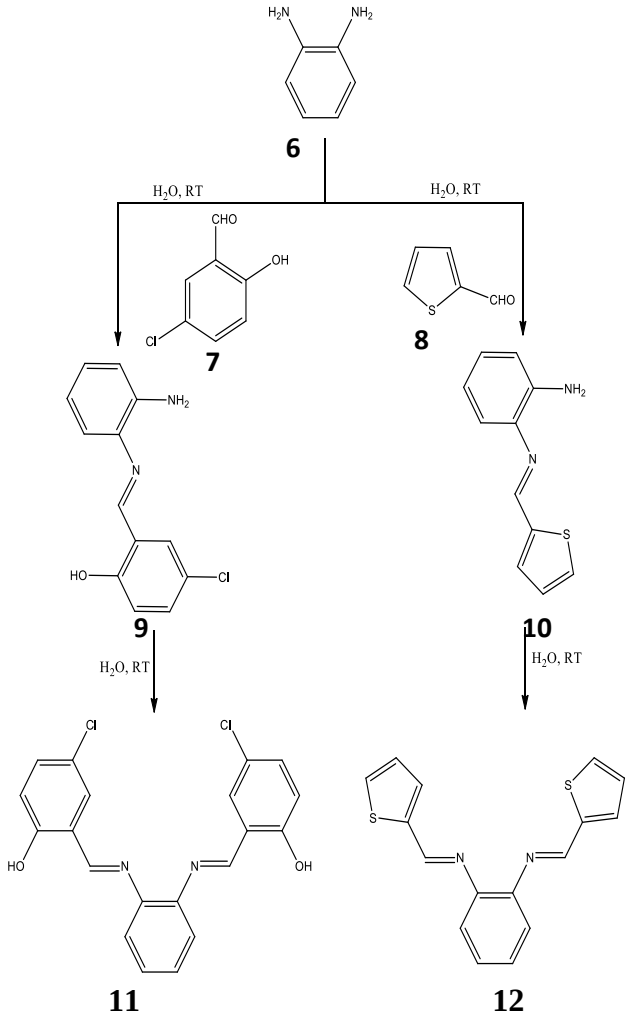
Figure 2 Bioactivities and drugs of heterocyclic Schiff bases

1. Reaction of Schiff base

Schiff bases have been employed in several sectors. Consequently, there are several approaches and procedures in use today for building Schiff bases. Some of them include:

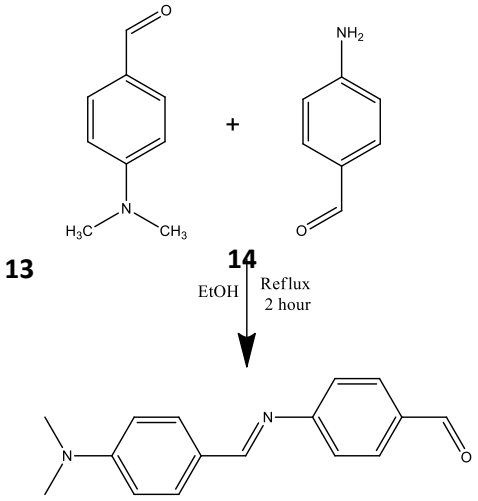
1.1. Water based medium

By mixing 1,2-diaminobenzene (6) with 5-chloro-2-hydroxy benzaldehyde (7) and thiophene-2-carbaldehyde (8), respectively, in water as a solvent, mono-Schiff bases 9 and 10 were created. Then, using water as a solvent, the mono-Schiff bases 9 and 10 were reacted with 5-chloro-2-hydroxy benzaldehyde (7) and thiophene-2-carbaldehyde (8) in presence of water as a solvent, produce the corresponding Bis-Schiff bases 11 and 12 [10].



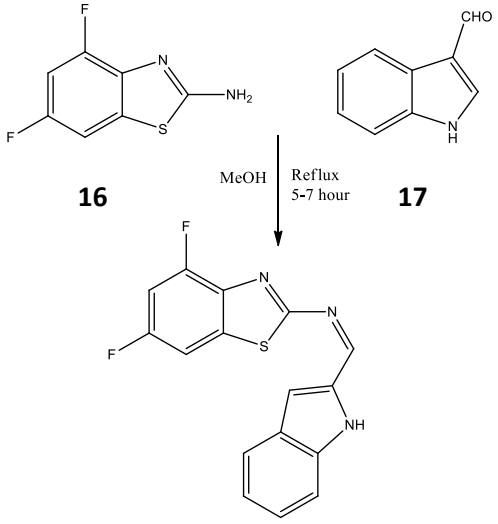
1.2. The conventional method

By reacting 4-(dimethyl amino)benzaldehyde (13) with 4-aminobenzaldehyde (14) in ethanol as a solvent and then refluxing the reaction mixture for two hours, a Schiff base containing Moiety (15) was created [11].



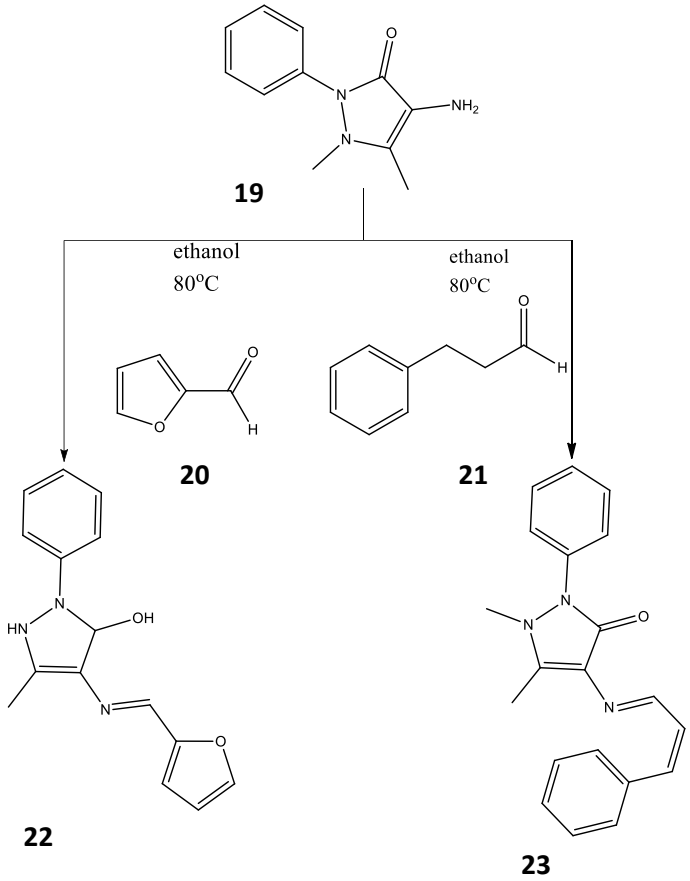
13 14 15

Benzothiazole Schiff base 18 was prepared via the reaction of 4, 6-difluoro-2-amino benzothiazole 16 with 1H-indol-3- carbaldehyde (17) in methanol, and the reaction mixture was refluxed for 5-7 hours [12].

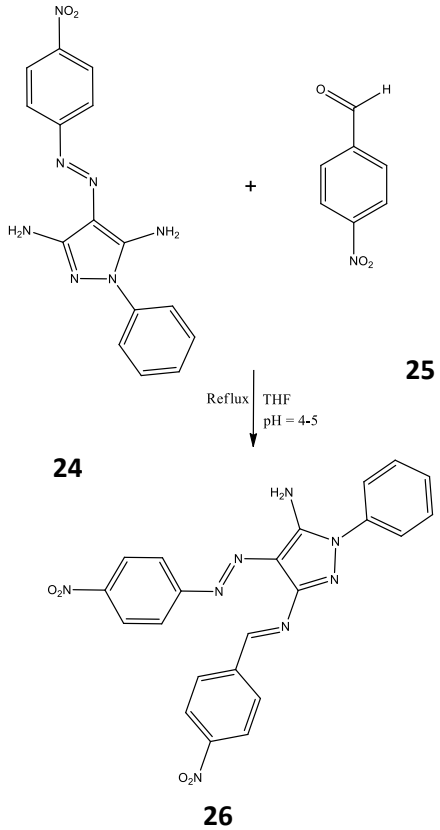


16 17 18

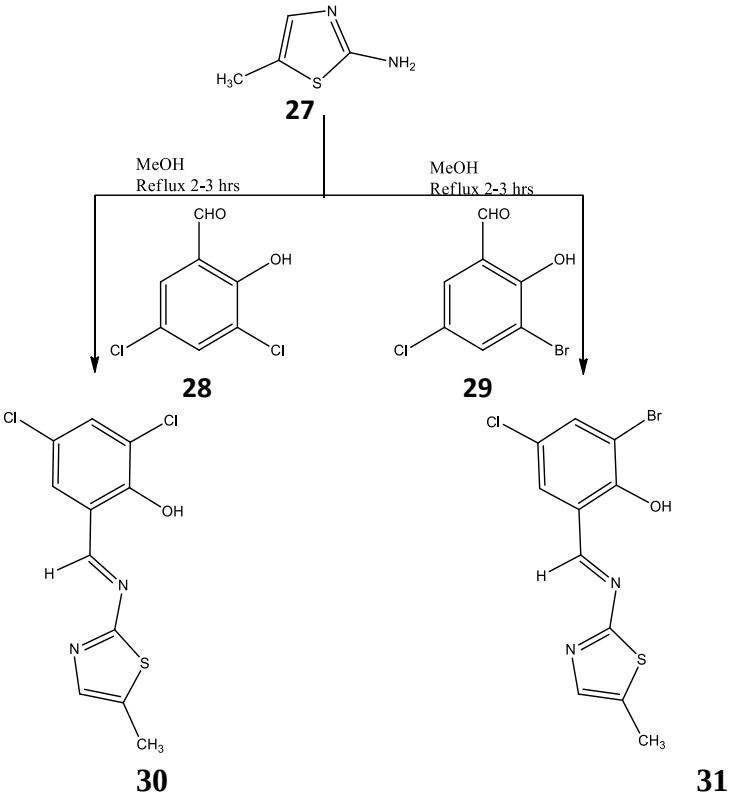
4-amino antipyrine (19) was used to react with Corresponding aldehyde (20) and (21) respectively, in methanol as a solvent at 80^{o}C to create the heterocyclic Schiff bases 22 and 23 [13].



(E)4-nitrobenzylidene)-4-((E)-(4-methoxyphenyl) diazenyl)-1-phenyl-pyrazole-5-amine 24 was combined with 4-nitro benzaldehyde 25 and respectively, to create the pyrazole Schiff base derivative 26. This reaction took place in refluxed THF [14].



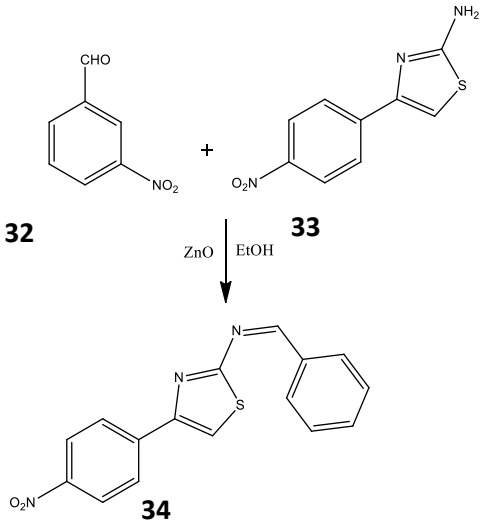
In the presence of methanol as a solvent,5-methyl-1,3-thiazole-2-amine (27) was reacted with 3,5-dichloro-2-hydroxybenzaldehyde (28) and 3-bromo-5-chloro-2-hydroxybenzaldehyde (29) to produce thiazole based Schiff bases 30 and 31 respectively [15].



1.3. Metal Catalysed

1.3.1. Zinc oxide catalyzed

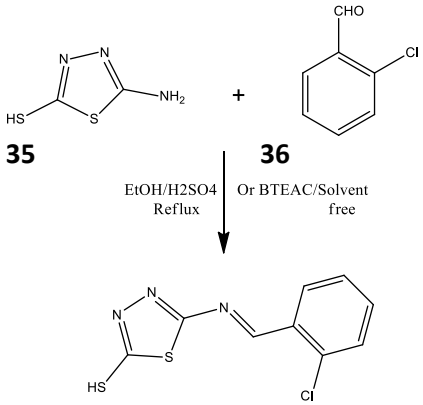
In the presence of ZnO as a catalyst 3-nitro benzaldehyde (32) and 4-(4-nitro phenyl)-1,3-thiazol-2-amine (33) were combined to form Schiff bases 34 in ethanol at room temperature [16].



1.4. Acidic and phase transfer catalyst (PTC)

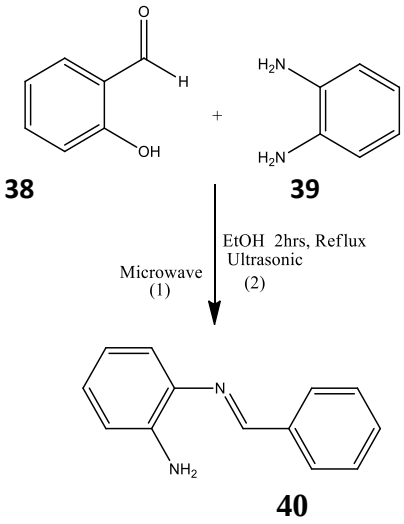
1,3,4-thiadiazole Schiff bases (37) were synthesised by reacting 2-amino-5-mercapto-1,3,4-thiadiazole (35) and 2-chlorobenzaldehyde (36) in ethanol with H2SO4 (acidic conditions). In addition, the reaction

was carried out in a solvent-free environment with benzyl tri-ethylammosynthesizednium chloride (BTEAC) functioning as a catalyst [17].



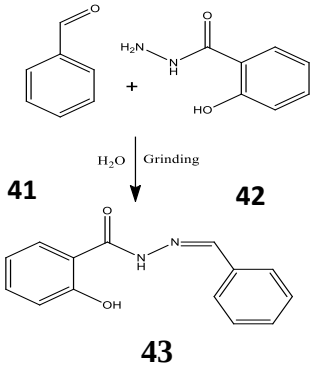
1.5. Ultrasonic and microwave conditions

The Schiff base 40 was synthesised by reacting 4 hydroxy benzaldehyde 38 with 1,2-diamine benzene 39 in the presence of ultrasonic or microwave radiation [18].



1.6. Grinding chemistry technique

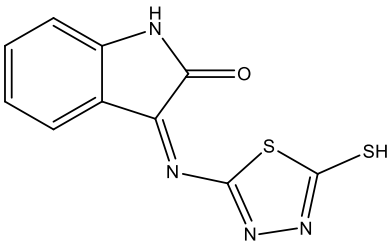
This method included the use of grindstone technology to produce bioactive compounds. Benzaldehyde 41 and 2-hydroxy benzohydrazide 42 were mixed to produce Schiff base 2-hydroxy-N'-[(Z)-phenylmethyllidene] benzohydrazide 43 which was then dissolved in water [18].



2. Industrial application

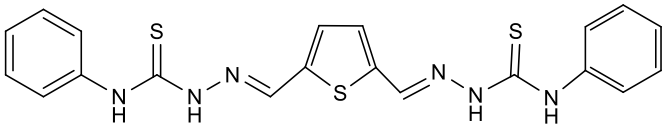
2.1. Corrosion inhibitors

The corrosion inhibition abilities of the Indole Schiff bases moiety 44 against mild steel corrosion were examined. The Schiff base exhibited remarkable corrosion inhibition properties [19].



44

Three Schiff bases based on thiophene 45 and 46 were tested for corrosion inhibition abilities. The Schiff bases have been demonstrated significant inhibitory activity against the corrosion of mild steel [20].



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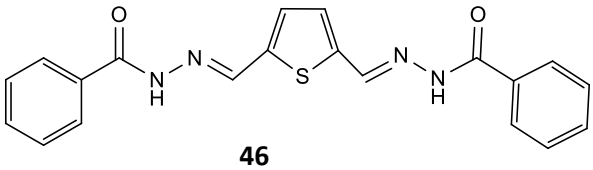
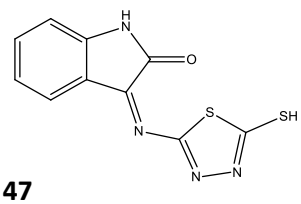


46

The corrosion inhibitory assets of two Schiff bases bearing indole moiety, 47 and 48 were investigated. Two Schiff bases 47 and 48 exhibited their ability to protect mild steel against corrosion [21].



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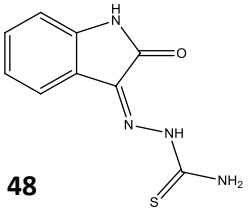

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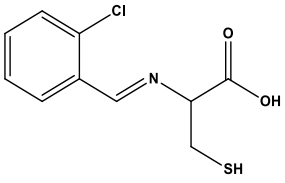
3. Biological activities of Schiff base

3.1. Antimicrobial activities

Schiff bases 49 and 50 shown efficacy against *Escherichia coli*, *Salmonella typhi*, and *Bacillus subtilis*. They also have high antifungal properties against various fungi including *Candida glabrata*, *Aspergillus flavus*, *Candida albicans*, and *Fusarium solani* [22].



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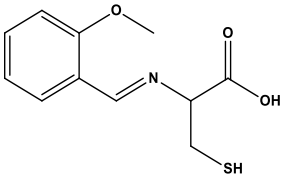
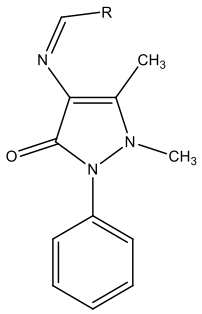


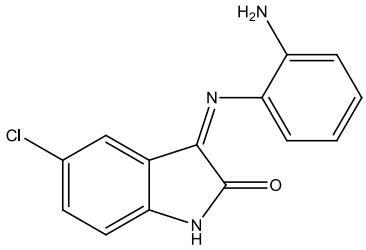
50

The antibacterial activity of pyrazole-Schiff bases 51 was investigated in vitro against four gram positive bacteria (*Micrococcus luteus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus cereus*) and three gram negative bacteria (*Klebsiella aerogenes*, *Escherichia coli*, and *Proteus mirabilis*)[23].



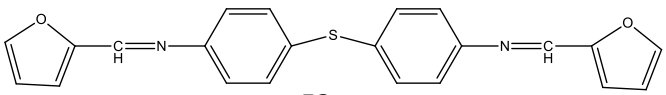
51

Isatin-Schiff base 52 exhibited potent antibacterial activity against *Staphylococcus aureus* (MIC= 16 µg/mL) [24]



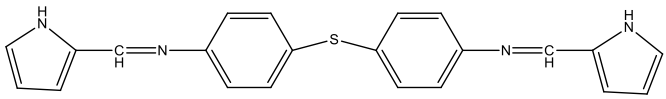
52

Sulphide linked to Schiff base showed 53 exhibited antifungal activity against *Microsporum canis* with MIC= 15.33 µg/Ml [25]



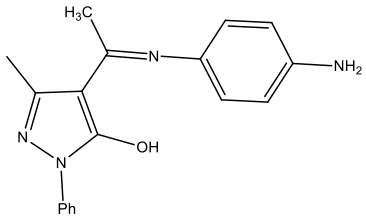
53

Sulfide-linked to Schiff base 54 potent antibacterial activity against *Microsporum canis* [25].



54

Pyrazolone-based Schiff base 55 showed anti-bacterial activities MIC = 3 µg/ml against *Bacillus subtilis* and *Phytophthora Infestanse bacteria [26].*



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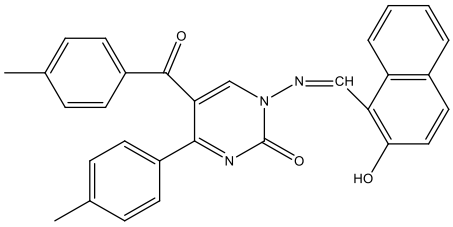
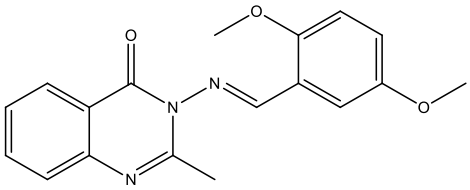
4.2 Anticancer activities

Pyrimidine-Schiff base 56 revealed anticanceractivity towards the human epithelial lung carcinoma cell line (A549) for 72 h [27].



56

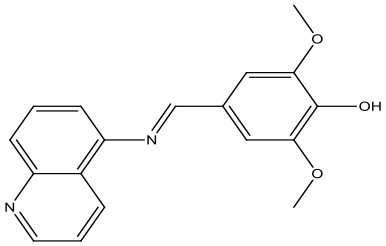
Quinazolinone Schiff base 57 showed anticancer activities against the human breast cancer MCF-7 cell line [28].



57

3.2. Anti-inflammatory activities

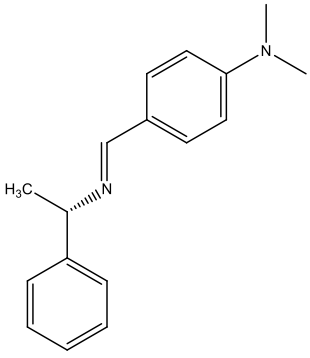
Aminoquinoline Schiff Bases moiety 58 exhibited anti-inflammatory activity [29].



58

3.3. Analgesic activities

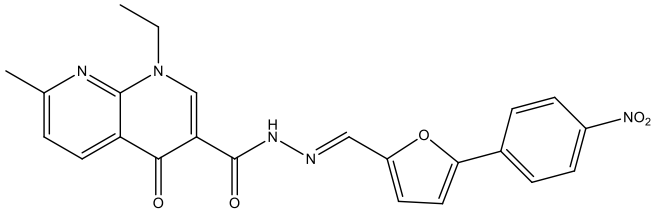
Enantiomeric Schiff base 59 exhibited good analgesic activity [30].



59

3.4. Anthelintic activities

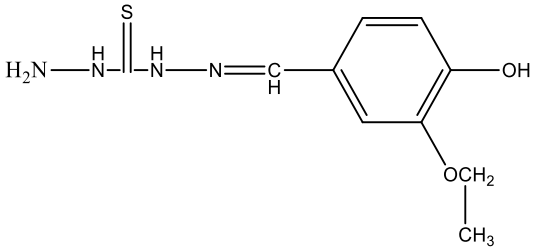
Nalidixic acid Schiff base 60 Showed excellent anthelemintic activities [31].



60

3.5. Antioxidant activities

Thiocarbohydrazone Schiff bases moiety **61** and **62** showed excellent anthelmintic activities [32].



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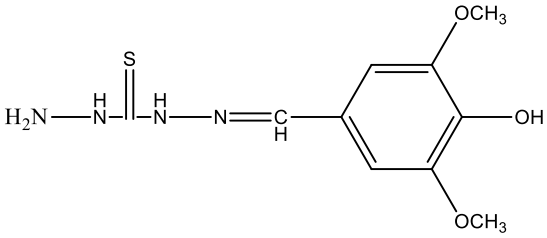

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4. Limitations

This review paper is limited to discussing Schiff base heterocyclic moiety conjugates, excluding other types of conjugates. By concentrating on this specific subset, the paper aims to provide a detailed and comprehensive overview of the synthesis, characterization and biological activities of these compounds. Future reviews could expand on this work by exploring Schiff base conjugates with other structural features to provide a broader understanding of their potential applications.

5. Conclusions

Schiff bases are distinguished by the presence of the imine or azomethine (–C=N–) group. This study concentrated on various methods of synthesis, reactions, uses, and biological effects of Schiff bases. Based on this analysis, it can be inferred that Schiff bases, particularly Schiff bases-heterocyclic moiety combinations, exhibit a diverse array of pharmacological properties. As a result, Schiff bases have garnered growing interest from researchers for the development of new derivatives for application in the medical and industrial sectors.

Acknowledgments

None.

Conflict of interest

The authors declare no conflict of interest.

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