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Overview on Synthesis, Reactions, Applications, and Biological Activities of Schiff Bases

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Abstract

Schiff bases exhibited various pharmacological and biological activities such as antibacterial, cytotoxic effects, antifungal, and antimalarial. Schiff bases were used for designing organic compounds, metal complexes, or nanoparticles. Also, Schiff bases were applied in various fields as corrosion inhibitors, catalysts, and optical properties. Therefore, this review article focused on some synthesis, reactions, applications, and biological activities of Schiff bases especially Schiff bases-heterocyclic moiety conjugates in the ten last years.

***Keywords*:** Schiff bases; Synthesis; Reactions; Biological activities; Applications

Introduction

Hugo Schiff (1864-1915) (Figure 1) is a German scientist. He discovered some bases and named them Schiff bases [1]. Schiff bases are synthesized by the reaction of a primary amine with carbonyl (aldehydes or ketones) under specific conditions. The general structure is $R_1R_2C{=}NR$ ($R \neq H$) therefore the main function is imine or azomethine (–C=N–) group (Figure 2) [2].

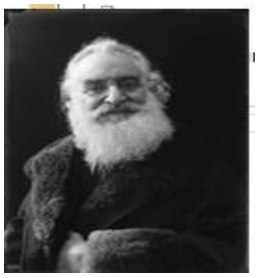

Figure 1. A portrait of Hugo Schiff

Schiff bases especially those linked with heterocyclic moiety exhibited various pharmacological and biological activities such as antibacterial, cytotoxic effects, antifungal, antimalarial, anticonvulsant, antioxidant, and anti-inflammatory [3-10].

(*E*)-2-((4-Hydroxybenzylidene)amino)-9-((2-hydroxyethoxy)methyl)-1,9-dihydro-6*H*-purin-6-one (**A**) is an example of heterocyclic Schiff bases and showed antibacterial activities [11]. (*E*)-2-((Pyren-1-ylimino)methyl)pyridin-3-ol (**B**) showed antioxidant and antibacterial activities [12]. Also, 4-((*E*)-[(4-chloro-2-hydroxyphenyl)methylidene]amino)-*N*-(6-methoxypyridazin-3-yl)benzene-1-sulfonamide (**C**) exhibited potent inhibition of urease enzyme [13].

In addition, there are some market drugs bearing heterocyclic Schiff base e.g. *Dantrolene*®, *Nitrofurantoin*®, and *Nifurtimox*® [14-16] (Figure 3).

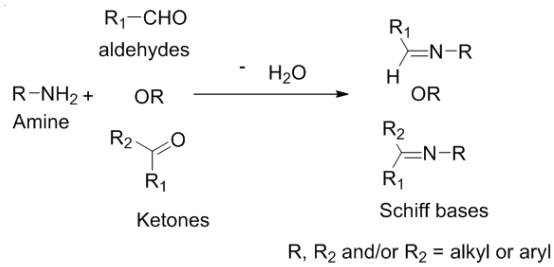

Figure 2. General formation of Schiff bases

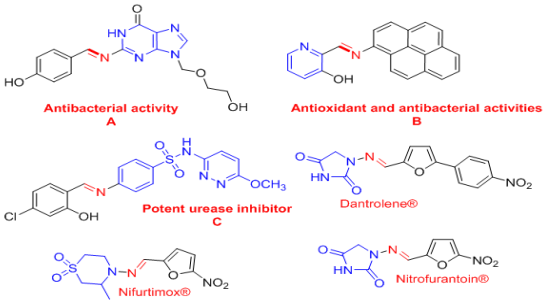

Figure 3. Bioactivities and drugs of heterocyclic Schiff bases

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From the above important biological activities facts of Schiff bases and in continuation of our work [17-36], the goal of this review is to shed an overview on some synthesis, reactions, applications, and biological activities of Schiff bases especially Schiff bases-heterocyclic moiety conjugates (Figure 4).

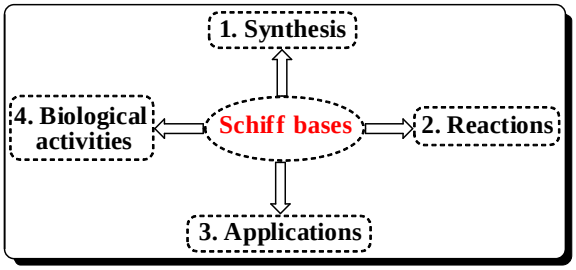


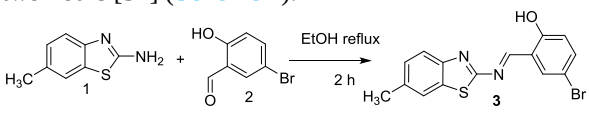
Figure 4. The goal of the review

1. Synthesis of Schiff bases

Schiff bases were applied in different fields. Therefore, there are various methods and new techniques for the preparation of Schiff bases, some of them have been reported as following:

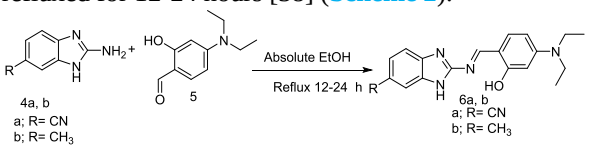
1.1. The conventional or traditional heating method.

Schiff base bearing benzothiazole **3** was prepared by the reaction of 2-amino-6-methylbenzothiazole **(1)** with 5-bromo-2-hydroxybenzaldehyde (**2)** in ethanol as a solvent and the reaction mixture was refluxed for two hours [37] (Scheme 1).



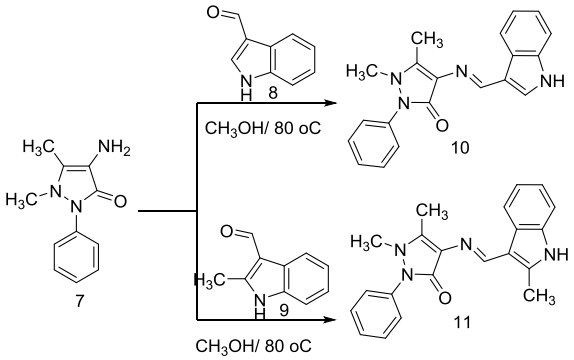
Scheme 1

Benzimidazole Schiff bases **6a, b** were prepared *via* the reaction of 2-aminobenzimidazole derivatives **4a, b** with 4-(diethylamino)-2-hydroxybenzaldehyde **(5)** in absolute ethanol, and the reaction mixture was refluxed for 12-24 hours [38] (Scheme 2).



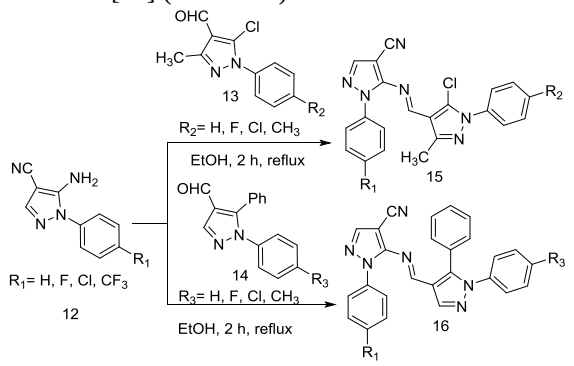
Scheme 2

Heterocyclic Schiff bases **10** and **11** were prepared by the reaction of 4-amino-antipyrine (**7)** with 1*H*-indole-3-carbaldehyde **(8)** and 2-methyl-1*H*-indole-3-carbaldehyde (**9)**, respectively, in methanol as a solvent at 80 ° C [39] (Scheme 3).



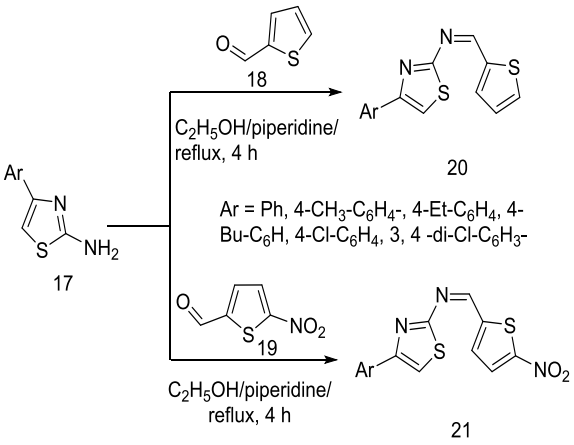
Scheme 3

Double-pyrazole Schiff base derivatives **15** and **16** were prepared by the reaction of 5-amino-1-aryl-pyrazole **12** with 1-aryl-5-chloro-1*H*-pyrazole-4-carbaldehyde **13** and 1-aryl-1*H*-pyrazole-4-carbaldehyde **14**, respectively, in refluxed ethanol for two hours [40] (Scheme 4).



Scheme 4

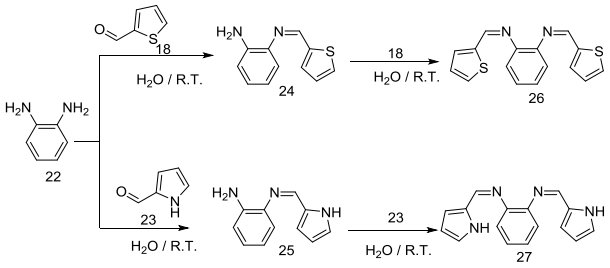
4-Aryl-2-aminothiazoles **17** were reacted with thiophene-2-carboxaldehyde **(18)** and 5-nitrothiophene-2-carboxaldehyde **(19)** in refluxing ethanol and in the presence of piperidine as a catalyst to yield thiazole-thiophene Schiff bases **20** and **21**, respectively [41] (Scheme 5).



Scheme 5

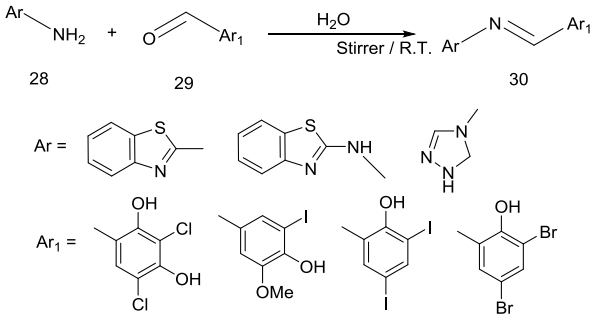
1.2. Aqueous medium

Mono-Schiff bases **24** and **25** were prepared by the stirring of 1,2-diaminobenzene (**22**) with thiophene-2-carbaldehyde **(18)** and 1*H*-pyrrole-2-carbaldehyde **(23)**, respectively, in H_2O as a solvent. Then, mono-Schiff bases **24** and **25** were reacted with thiophene-2-carbaldehyde **(18)** and 1*H*-pyrrole-2-carbaldehyde (**23)** using the water as a solvent to form the *Bis*-Schiff bases **26** and **27**, respectively [42] (Scheme 6).



Scheme 6

Schiff bases containing heterocyclic moiety **30** were prepared by the condensation of aromatic amines **28** with various aromatic aldehydes **29** using water as a solvent at room temperature [43] (Scheme 7).

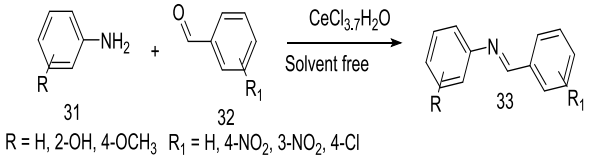


Scheme 7

1.3. Metal catalyzed

1.3.1. Cerium (III) chloride catalyzed

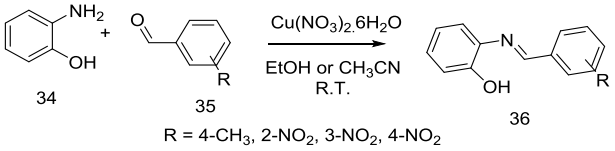
Schiff bases **33** were prepared *via* the reaction of aromatic amines **31** with aldehydes **32** in the presence of $CeCl_3.7H_2O$ as a catalyst under solvent-free conditions [44] (Scheme 8).



Scheme 8

1.3.2. Copper nitrate catalyzed

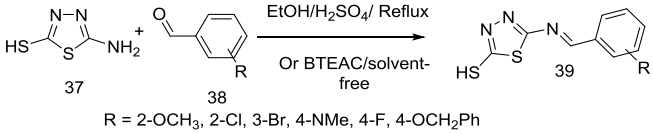
Schiff bases **36** were synthesized by the reaction of 2-aminophenol (**34**) with aromatic aldehydes **35** in the presence of $Cu(NO_3)_2.6H_2O$ as a catalyst in ethanol or acetonitrile at room temperature [45] (Scheme 9).



Scheme 9

1.4. Acidic and phase transfer catalyst (PTC) conditions

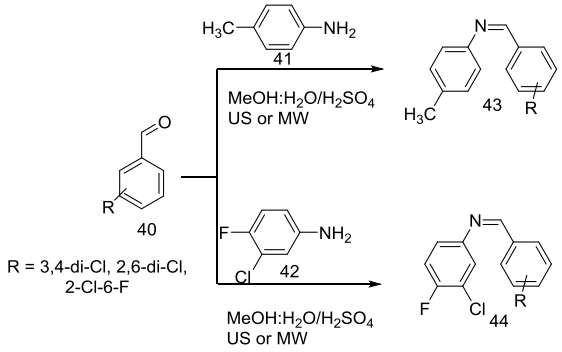
1,3,4-Thiadiazole Schiff bases **39** were synthesized by the reaction of 2-amino-5-mercapto-1,3,4-thiadiazole **(37)** with aromatic aldehydes **38** in ethanol in the presence of H_2SO_4 (acidic conditions). Also, the reaction was carried out in the presence of benzyl triethylammonium chloride (BTEAC) as a catalyst under solvent-free [46] (Scheme 10).



Scheme 10

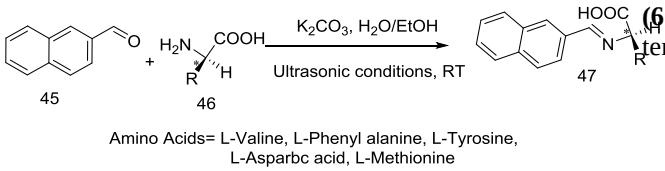
1.5. Ultrasonic and microwave conditions

Schiff bases **43** and **44** were synthesized *via* the reaction of disubstituted benzaldehyde **40** with 4-methyl aniline **(41)**, and 3-chloro-4-fluoro aniline **(42)**, respectively, using microwave irradiation or ultrasound sonication methods [47] (Scheme 11).



Scheme 11

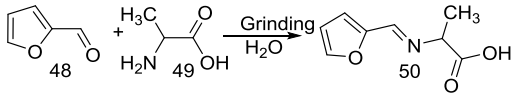
Chiral-Schiff bases **47** were prepared from the reaction of 2-naphthaldehyde **(45)** with chiral α-amino acids **(46)** in the presence of K_2CO_3 using water/ethanol as a solvent under ultrasonic conditions [48] (Scheme 12).



Scheme 12

1.6. Grinding chemistry technique

In this method, grindstone technology was used for the synthesis of bioactive compounds. Schiff base (*E*)-2-(furan-2-ylmethyleneamino)propanoic acid **(50)** was synthesized by the reaction of furan-2-carbaldehyde **(48)** with DL-alanine **(49)** in the water as a green solvent [49] (Scheme 13).

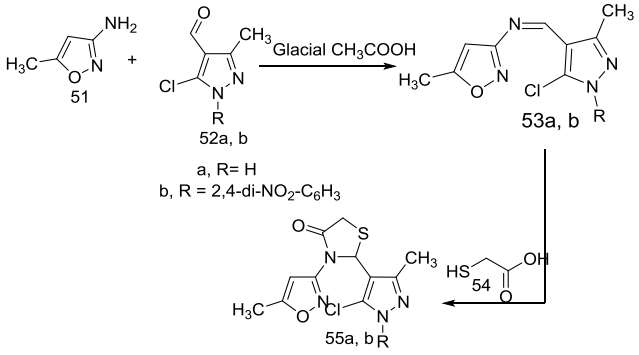


Scheme 13

2. Reactions of Schiff bases

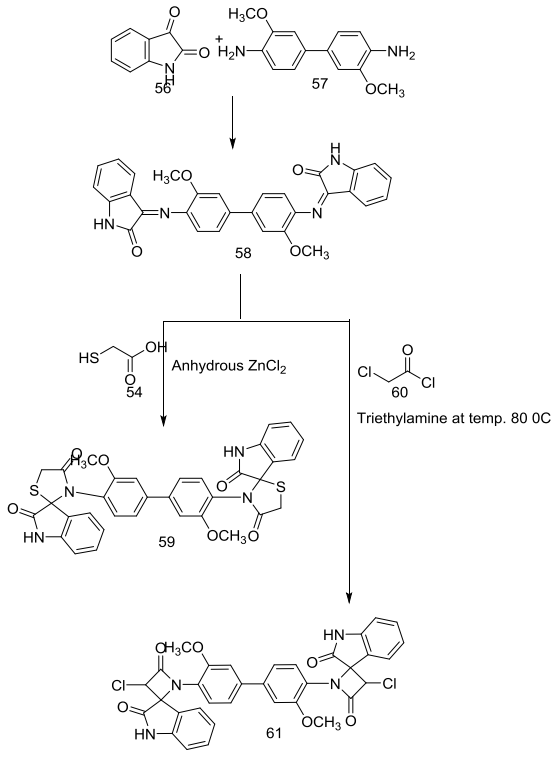
2.1. Preparation of organic compounds

Schiff bases are used as intermediates for the preparation of organic compounds [50]. Isoxazol-pyrazole Schiff bases **53a, b** were prepared by the condensation of 3-amino-5-methylisoxazole (**51**) with pyrazole carbaldehydes **52a, b** in the presence of glacial CH_3COOH. When isoxazol-pyrazole Schiff bases **53a, b** were reacted with thioglycolic acid **(54)**, the corresponding thiazolidine-4-one derivatives **55a, b** were produced [51] (Scheme 14).



Scheme 14

Bis-Schiff base, (3'*Z*)-3,3'-(3,3'-dimethoxybiphenyl-4,4'-diyl)*bis*(azan-1-yl-1-ylidene)diindolin-2-one **(58)**, was prepared by the condensation of isatin (**56**) with 3,3'-dimethoxybenzidine **(57)**. Next, when *bis*-Schiff base **58** was allowed to react with thioglycolic acid **(54)** in the presence of anhydrous $ZnCl_2$, *bis*-spirothiazolidin-4-one derivative **59** was produced. Also, *bis*-spiroazetidinone derivative **61** was prepared by the condensation of **58** with chloroacetyl chloride **(60)** and in the presence of triethylamine at temperature 80 ^{0}C [52] (Scheme 15).



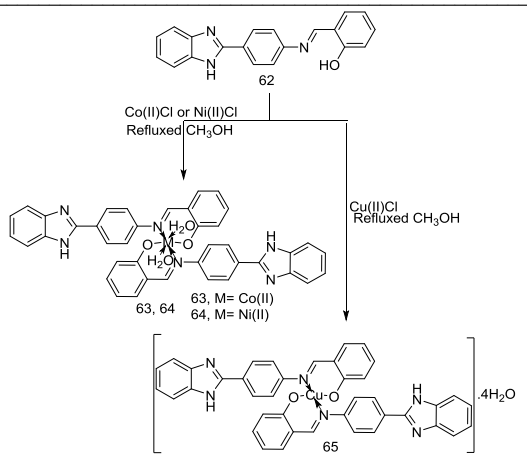
Scheme 15

2.2. Preparation of metal complexes

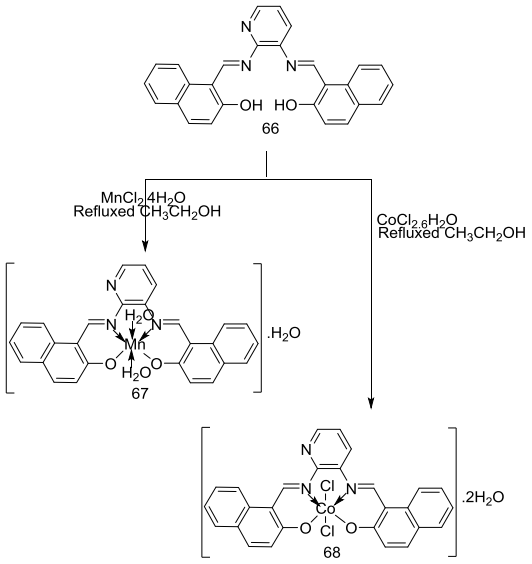
Schiff bases act as chelating ligands where easy forming coordinate bonds with metal ions *via* azomethine (–C=N–) group. Therefore, Schiff bases were used in the preparation of metal complexes [53, 54]. Recently, there is a growing interest in the preparation of Schiff bases metal complexes due to their various pharmacological and biological activities [55-60].

The three Schiff base metal complexes **63-65** were prepared from Schiff base, 2-((4-(1*H*-benzo[*d*]imidazol-2-yl)phenylimino)methyl)phenol **(62)**, with chloride salts of Cu (II), Co (II), and Ni (II) in refluxed methanol with molar ratio (2L:1M). The Co (II) complex **63** and Ni (II) complex **64** have an octahedral geometry, while the Cu (II) complex **65** has a square planar geometry [61] (Scheme 16).

The two Schiff base metal complexes **67** and **68** were prepared by the reaction of Schiff base ligand **66** with metal salts ($MnCl_2.4H_2O$ and $CoCl_2.6H_2O$) in refluxed ethanol. The Mn (II) complex **67** and Co (II) complex **68** have an octahedral geometry [62] (Scheme 17).

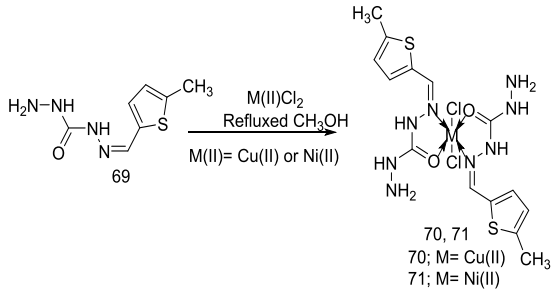


Scheme 16



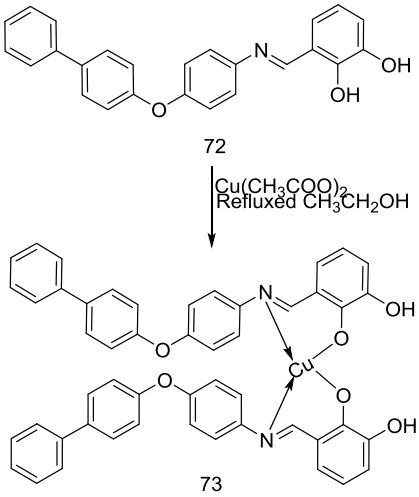
Scheme 17

The two metal (Cu (II) **70**, and Ni (II) **71**) complexes were prepared by the reaction of Schiff base ligand **69** with chloride salts of Cu (II), and Ni (II) in refluxed methanol. The general formula of the metal complexes **70, 71** is $[M(L)_2Cl_2]$ (where M = Cu(II), and Ni(II)) and the geometrical structure is orthorhombic [63] (Scheme 18).



Scheme 18

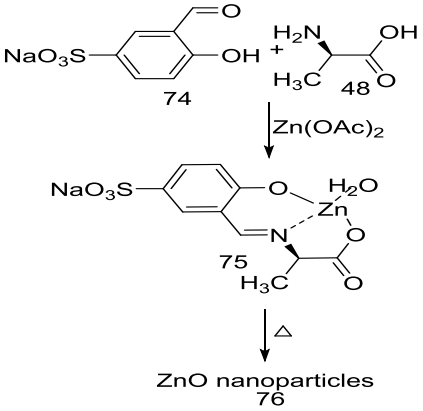
Reaction of the ligand Schiff base (*E*)-3-((4-(biphenyl-4-yloxy)phenylimino)methyl)benzene-1,2-diol **(72)** with anhydrous copper (II) acetate in ethanol afforded copper (II) complex **73** in 73 % yield. The complex formula is $(Cu(L)_2)$. The geometrical structure is a square planar with a little tetrahedral distortion around Cu ion [64] (Scheme 19).



Scheme 19

2.3. Preparation of nanoparticles

The Zn (II) Schiff-base complex **75** was obtained from the reaction of alanine **(48)**, sodium salicylaldehyde-5-sulfonate (**74**), and $Zn(OAc)_2$. Zinc oxide nanoparticles (ZnO NPs) **76** were produced by heating the Zn (II) Schiff-base complex **75** through a solid-state decomposition process [65] (Scheme 20).



Scheme 20

3. Industrial application

Schiff bases are applied in various fields [66-75]. Some of these applications are illustrated as the following:-

3.1. Corrosion inhibitors

The two ferrocene Schiff bases **77** and **78** were evaluated for their corrosion inhibition activities against corrosion of mild steel. The two Schiff bases were characterized by excellent corrosion inhibition activities [76] (**Figure 5**).

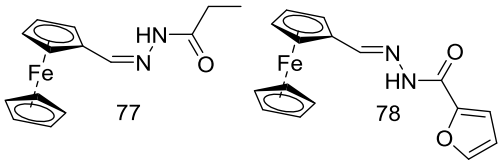


Figure 5. Ferrocene Schiff bases **77** and **78**

Three Schiff bases based on pyrrole **79-81** were evaluated for their corrosion inhibition activities. The Schiff bases had exhibited a good inhibitory action against corrosion of mild steel [77] (**Figure 6**).

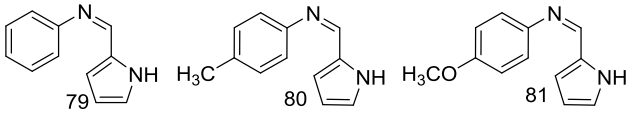


Figure 6. Schiff bases based on pyrrole **79-81**

Two Schiff bases based on thiophene moiety **82** and **83** were described and studied their activities as corrosion inhibitors. Two Schiff bases **82** and **83** exhibited inhibition capability towards the corrosion of stainless steel [78] (**Figure 7**).

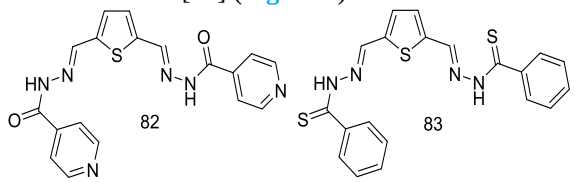
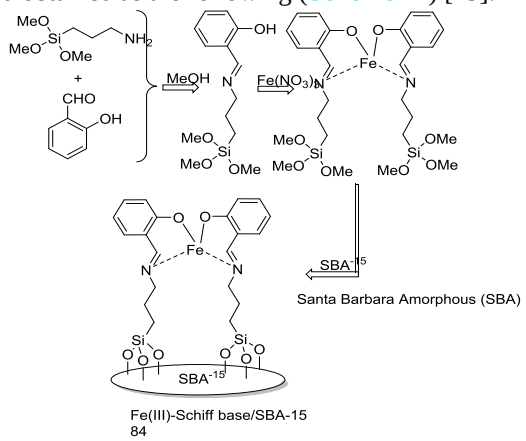


Figure 7. Schiff bases based on thiophene moiety **82** and **83**

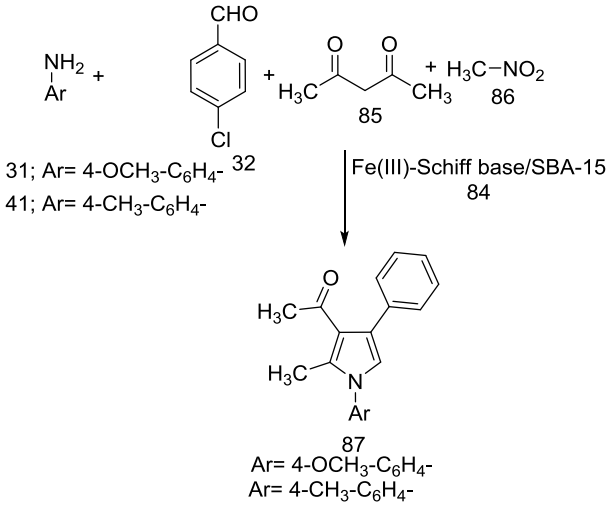
3.2. Catalysts

Fe(III)-Schiff base/SBA-15 **84** is a metal complex and obtained as the following (**Scheme 21**) [79].



Scheme 21

Fe(III)-Schiff base/SBA-15 is a heterogeneous nanocatalyst used for the synthesis of pyrrole derivatives **87** through a four-component reaction of aromatic amines **31** or **41**, 4-chlorobenzaldehyde **(32)**, acetylacetone **(85)**, and nitromethane **(86)** [80] (**Scheme 22**).



Scheme 22

3.3. Solvent extraction of metal ions

Schiff bases are used as selective and efficient chelates ligands of some metal ions. Therefore; this concept will pave the way for solvent extraction application to remove metal ions for heavy metal pollution control [81].

4. Biological activities of Schiff bases

4.1. Antimicrobial activities

Triazole-Schiff bases **88** possessed significant antibacterial activities against *Escherichia coli*, *Salmonella typhi*, and *Bacillus subtilis*. Also, they possessed significant antifungal activities against *Candida albicans*, *Aspergillus flavus*, *Fusarium solani*, and *Candida glabrata* [82] (**Figure 8**).

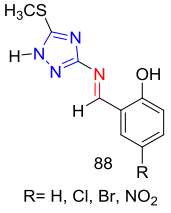


Figure 8. Triazole-Schiff bases **88**

The two series of Schiff bases, pyrazole-Schiff bases **89** and antipyrine-Schiff bases **90**, were evaluated for their *in vitro* antibacterial activities against four G^+ bacterial {*Micrococcus luteus*, *Staphylococcus aureus*, *Staphylococcus*

epidermidids, and *Bacillus cereus*} and against three G⁻ bacterial {*Klebsiella aerogenes*, *Escherichia coli*, and *Proteus mirabilis*}. The results revealed that the two series having antibacterial activities and the pyrazole-Schiff base series **89** are more active than antipyrine-Schiff bases **90** [83] (**Figure 9**).

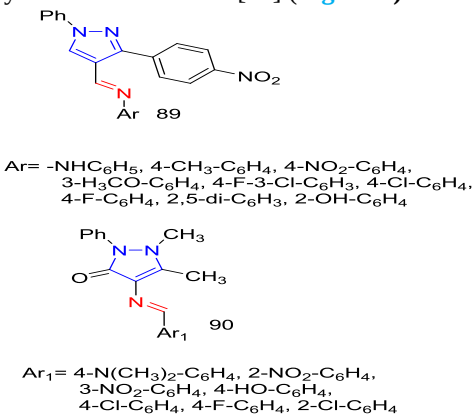


Figure 9. Pyrazole-Schiff bases **89** and antipyrine-Schiff bases **90**

Isatin-Schiff base **91** exhibited potent antibacterial activity against *pseudomonas aeruginosa* (MIC= 6.25 mg/mL) [84] (**Figure 10**).

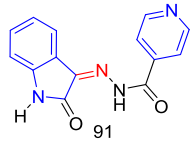


Figure 10. Isatin-Schiff base **91**

Acetylenic indole-Schiff base **92** showed antibacterial activity against *Staphylococcus aureus* with MIC= 7.81 µM. Also, indole-Schiff base **93** exhibited antifungal activity against *Candida krusei* with MIC= 15.62 µM [85] (**Figure 11**).

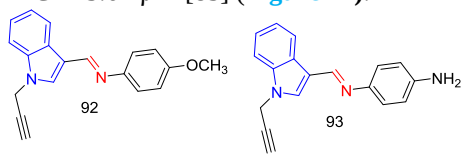


Figure 11. Acetylenic indole-Schiff bases **92** and **93**

Piperazine-sulphonamide-linked to Schiff base **94** showed potent antibacterial activity against *Bacillus subtilis* with MIC= 26.1 µg/mL [86] (**Figure 12**).

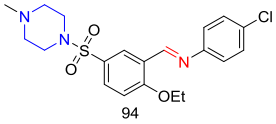


Figure 12. Piperazine-sulphonamide linked to Schiff base **94**

Pyrazole-Schiff base **95** showed antibacterial activities (MIC= 7.81 mg/ml) against *Staphylococcus aureus* and *Staphylococcus epidermis* bacteria [87] (**Figure 13**).

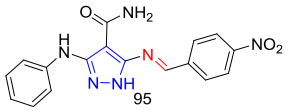


Figure 13. Pyrazole-Schiff base **95**

4.2. Anticancer activities

Benzothiazole-Schiff base **96** showed anticancer activity against breast (MCF-7) cancer cells and also, exhibited less toxicity to normal cells [88] (**Figure 14**).

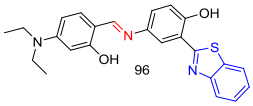


Figure 14. Benzothiazole-Schiff base **96**

1,3,5-Triazine-isatin Schiff base **97** showed anticancer activities against lung (HOP-92), leukemia (CCRF-CEM), and leukemia (SR) cancer cell lines [89] (**Figure 15**).

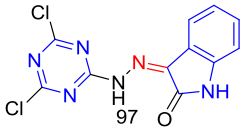


Figure 15. 1,3,5-Triazine-isatin Schiff base **97**

Two Schiff bases based on pyrazole moiety **98** and **99** displayed an excellent anticancer activities against liver (HepG2) and breast (MCF-7) cell lines, respectively [90] (**Figure 16**).

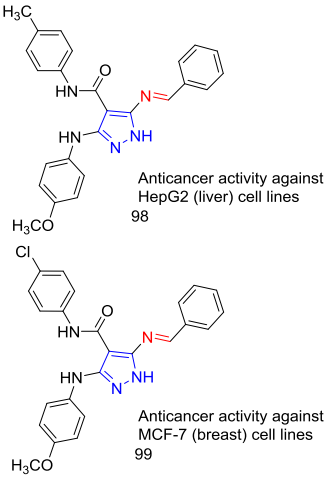


Figure 16. Pyrazole-Schiff bases **98** and **99**

4.3. Anti-inflammatory activities

Schiff base based on quinazolin-4-one linked with 1, 3, 4-oxadiazole moiety **100** showed anti-inflammatory activity [91] (**Figure 17**).

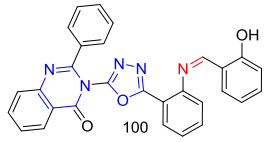


Figure 17. Schiff base based on quinazolin-4-one with 1,3,4-oxadiazole **100**

4.4. Analgesic activities

Isatin-Schiff base **101** exhibited good analgesic activity [92] **(Figure 18)**.

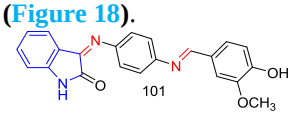


Figure 18. Isatin-Schiff base **101**

4.5. Anthelmintic activities

Antipyrine-coumarin linked to Schiff bases **102** and **103** showed excellent anthelmintic activities [93] **(Figure 19)**.

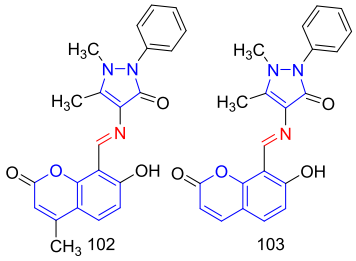
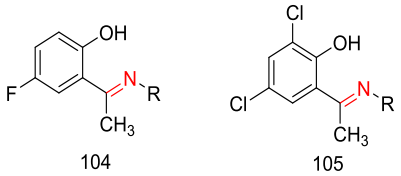


Figure 19. Antipyrine-coumarin linked to Schiff bases **102** and **103**

4.6. Antioxidant activities

Two series of halogenated Schiff bases **104** and **105** showed very low to moderate antioxidant activities [94] (**Figure 20**).



R= C_3H_7, C_5H_{11}, C_6H_{13}, C_7H_{15} R= C_3H_7, C_5H_{11}, C_6H_{13}, C_7H_{15}

Figure 20. Halogenated Schiff bases **104** and **105**

Conclusion

Schiff bases were characterized by the presence of the imine or azomethine (–C=N–) group. This survey focused on some synthesis, reactions, applications, and biological activities of Schiff bases. From this review, it can be concluded that Schiff bases especially Schiff bases-heterocyclic moiety conjugates display a wide range of pharmacological activities. For that, Schiff bases attracted increasing attention to the scientists for the synthesis of new derivatives for applications in medicinal and industrial fields.

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Conflict of interest

The authors declare that they have no competing interests.

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