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Synthetic approaches of medicinally important Schiff bases: An updated Review

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Abstract

The Schiff base defined by an imine or azomethine (-CH= N-) group, is mostly synthesized by the condensation reaction of carbonyl compounds (Aldehyde or Ketone) with compounds consisting of amine moiety. Schiff bases are among the most chiefly used organic compounds, revealing a wide range of applications, such as electroluminescent effects, fluorescence properties, nonlinear optical and chemosensory properties. The typical Schiff bases are crystalline solids that are basic, although at least some of them combine with strong acids to generate insoluble salt. Schiff bases are widely used in the pharmaceutical, electronic, cosmetic and polymer industries. Schiff bases use various alpha-amino acids and aldehydes in acidic or basic conditions. Schiff bases form a new class of drugs that can strengthen the immune system and also be used in the treatment of various ailments. The C=N imine bond's electrophilic carbon and nucleophilic nitrogen offer great binding chances with many nucleophiles and electrophiles, which can be used to suppress specific diseases, enzymes or DNA replication. These Schiff bases are synthesized from various aldehydes or ketones and amines under stirring conditions, catalyst-free, reflux conditions, conventional methods, microwave irradiation and ultrasonic conditions. Thus, Schiff bases and their derivatives can be synthesized using various techniques and may be further used for enormous biological applications with potent effects.

Keywords: Schiff base; Azomethine; Conventional synthesis; Microwave irradiation; Ultrasonic assisted synthesis

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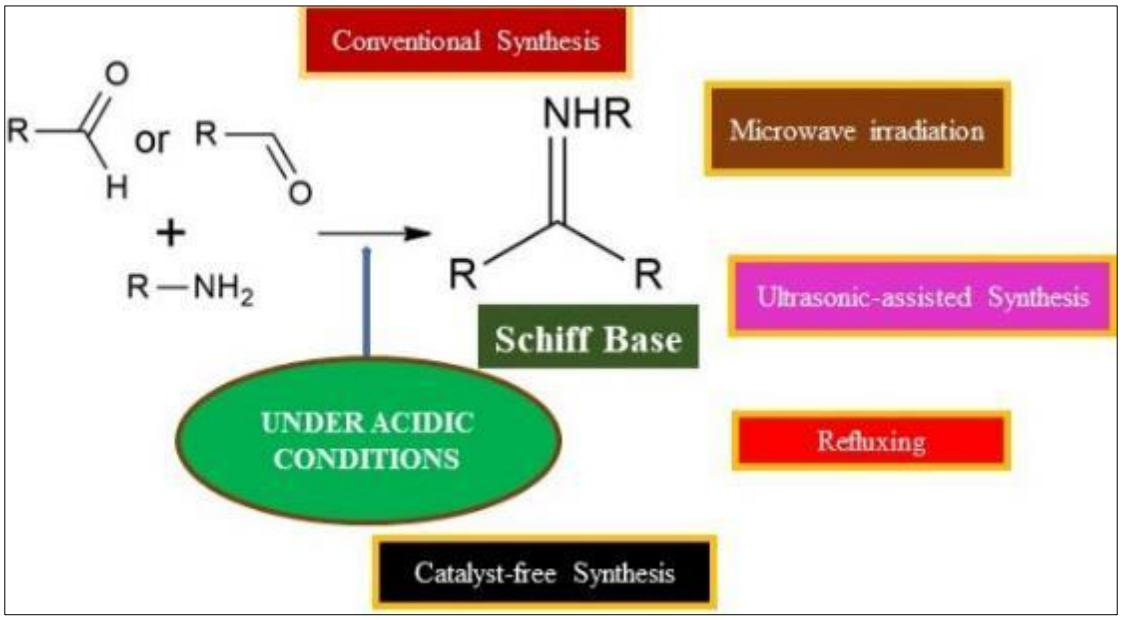
Graphical abstract



1. Introduction

In general, azomethine groups are produced by reacting an amine with aldehydes or ketones to produce Schiff bases, an important class of chemical compounds, which have the general formula R-CH=N-R. While aromatic aldehyde-based Schiff base compounds do not have these issues due to their conjugated structure, aliphatic aldehyde-based Schiff base compounds have because they spontaneously polymerize. The essential component in Schiff base is azo-methine. Usually, acids, bases, or heat act as catalysts in the formation of Schiff bases. Common Schiff bases are crystalline solids that react with strong acids to form insoluble salts. Schiff bases are used as a starting point for the synthesis of amino acids [1,2].

Synthesis of Schiff base analogs was created using a simple one-step process, which involved the condensation of an amine and an aldehyde or ketone [3]. Aldehyde or ketone under reflux conditions with the aid of a catalyst is the most commonly used method. Eg; mineral acids are frequently utilized as catalysts. Numerous Schiff bases are synthesized in mildly acidic conditions because the carbinolamine is suppressed by more acid because a higher acid concentration will protonate the amine and limit its ability to act as a nucleophile [4]. The use of microwave-assisted solvent-free synthesis is regarded as a crucial method for speeding up the process, increasing yield, utilizing less energy, and lowering setup time [5]. Schiff bases and their metal complexes are versatile compounds in coordination chemistry [6].

The Schiff bases and their derivatives can be synthesized using various techniques, which include simple one-step, refluxing technique, condensation, microwave-assisted, ultrasonic-assisted synthesis, etc. [7-13]

Schiff bases are crucial in the biological field because of how closely their structural similarities to naturally existing biological compounds. These compounds show an extensive variety of pharmacological actions, including antibacterial, anti-inflammatory and anticancer properties [14]. Schiff bases may also act as catalysts, polymer stabilizers, intermediates in organic synthesis, pigments and dyes [15] and it also has a wide range of applications such as electroluminescence effects, fluorescence properties, non-linear, optical properties, chemosensory [16], material science, industry, agriculture [17], cosmetic and polymer industries [18].

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 and synthetic approaches, which were used individually and in combination. Here, we summarized the various synthetic approaches of biologically important Schiff bases.

2. Synthetic approaches of Schiff bases and their derivatives

2.1. Synthesis of Schiff base derivatives under stirring and reflux conditions

2-aminopyridine and 2-hydroxy-1-napthaldehyde were dissolved using methanol as solvent. Aldehyde was first dissolved in methanol, followed by the addition of four drops of acetic acid and heated for six minutes on a magnetic hot plate with continuous stirring. After 6 minutes, 2-aminopyridine was added to the reaction mixture, which was then refluxed for 5 hours at 60 ℃ to obtain 1-((pyridine-2-ylimino) methyl) napthalen-2-ol [1] (Scheme 1).

2-[(Z)-(phenylimino)methyl] phenol was synthesized by the reaction between the aromatic salicylaldehyde and aniline with the aid of acetic acid, which was stirred for 1.15-1.30 hours by using the magnetic stirrer at room temperature (Scheme 2).

(1E,2E)-tetraphenyl ethane -1,2-di-imine was prepared by the condensation of the aromatic benzil with aniline, employing ethanol as solvent and the mixture was stirred for 1-2 hours by using the magnetic stirrer (Scheme 3). The aromatic cinnamaldehyde in acetic acid was mixed with P-toluidine and the mixture was stirred for 3.2 hours by using a magnetic stirrer employed (1E,2E)-N-(4-methyl phenyl)4-phenylbut-3-en-1-imine [2] (Scheme 4). The above-discussed schemes are given in Fig. 1.

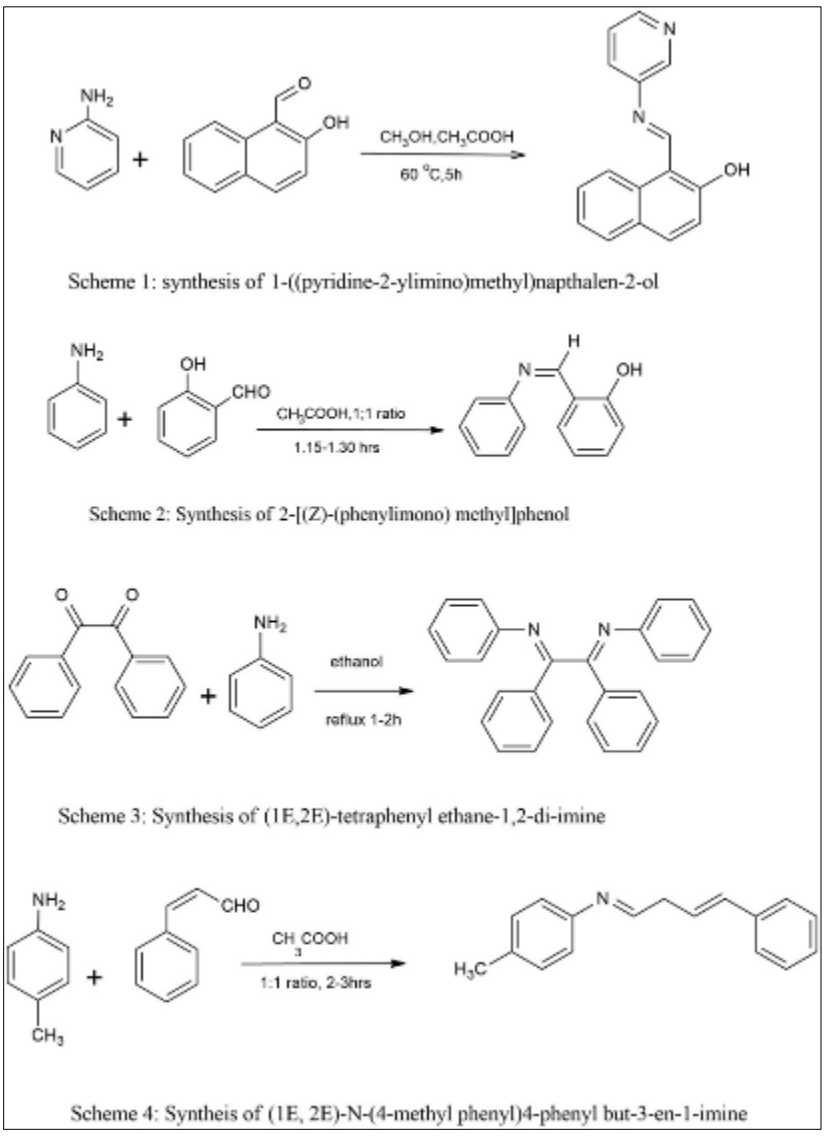


Figure 1 Synthesis of Schiff bases under reflux conditions at an equimolar ratio

2.2. Synthesis of Schiff base containing amino derivatives

The condensation of benzil and p-toluidine under reflux conditions for 1.30 hr in acetic acid yielded (N,N'E,N,N'E)-N,N'-(1,2-diphenylethane-1,2-diylidene)bis(4-methyl aniline) [2] (Scheme 5).

2-amino-benzothiazole Schiff bases were prepared by utilizing 2-aminobenzothiazole as the precursor. Ethanol and 2-aminobenzthiazole were combined with an equal amount of aldehyde. The resulting mixture was left under reflux for 2 hr. Thus, the product was obtained [7] (Scheme 6).

The reaction between 4-amino salicylic acid and corresponding aldehyde employing ethanol as solvent yielded the 4-aminosalicylic Schiff bases (Scheme 7). The 4-amino phenol Schiff bases were reported by Ashraf et al., 2011. He utilized the corresponding aldehyde to obtain 4-aminophenol Schiff bases [7] (Scheme 8). The above-discussed schemes are given in Fig. 2.

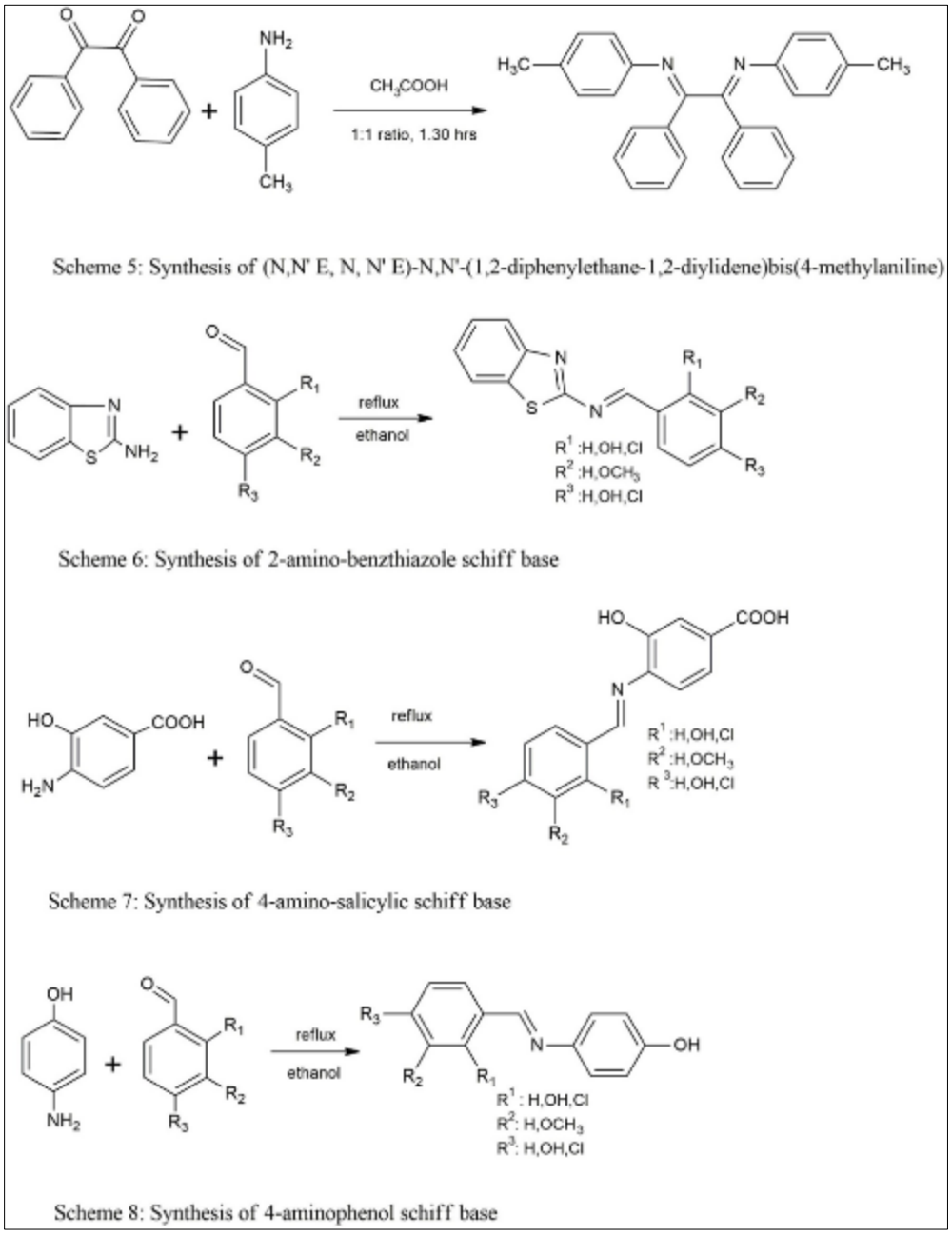


Figure 2 Synthesis of Schiff base containing amino derivatives

2.3. Synthesis of novel Schiff bases using condensation reaction

The condensation of 5-substituted isatins with benzidine 3,3'-dimethoxybenzidine utilizing ethanol as solvent, the N-[(1,3-dihydro)-2H-indole-2-one] 4,4'-diamino-1,1'-biphenyl derivatives and bis N-[(1,3-dihydro)-2H-indole-2-one] 3,3'-dimethoxybenzidine were formed (Scheme 9). The Schiff base, N-[(1,3- dihydro)-2,4 -indol-2 one]pyridine 2,6 – diamine derivative was obtained by the condensation between 5-substituted isatins and 2,6-diamino pyridine in the presence of ethanol [8] (Scheme 10).

3-bromo-2-[6-methylbenzothiazole-2-ylimino] methyl phenol was obtained by the reaction between the mixture of 2-amino-6-methyl benzothiazole and salicylaldehyde or 5-bromo salicylaldehyde in 95%ethanol. It was refluxed for 2 hours to obtain the desired compound [9] (Scheme 11).

Sulfonamide Schiff bases were reported by Durgun et al., 2020. They utilized 3-bromo-2-hydroxy benzaldehyde and 3-amino benzene-1-sulfonamide to obtain 3-{(*E*)-[(3-bromo-2-hydroxyphenyl) methylidene] amino} benzene-1-sulfonamide [10] (Scheme 12). The above-discussed schemes are given in Fig. 3.

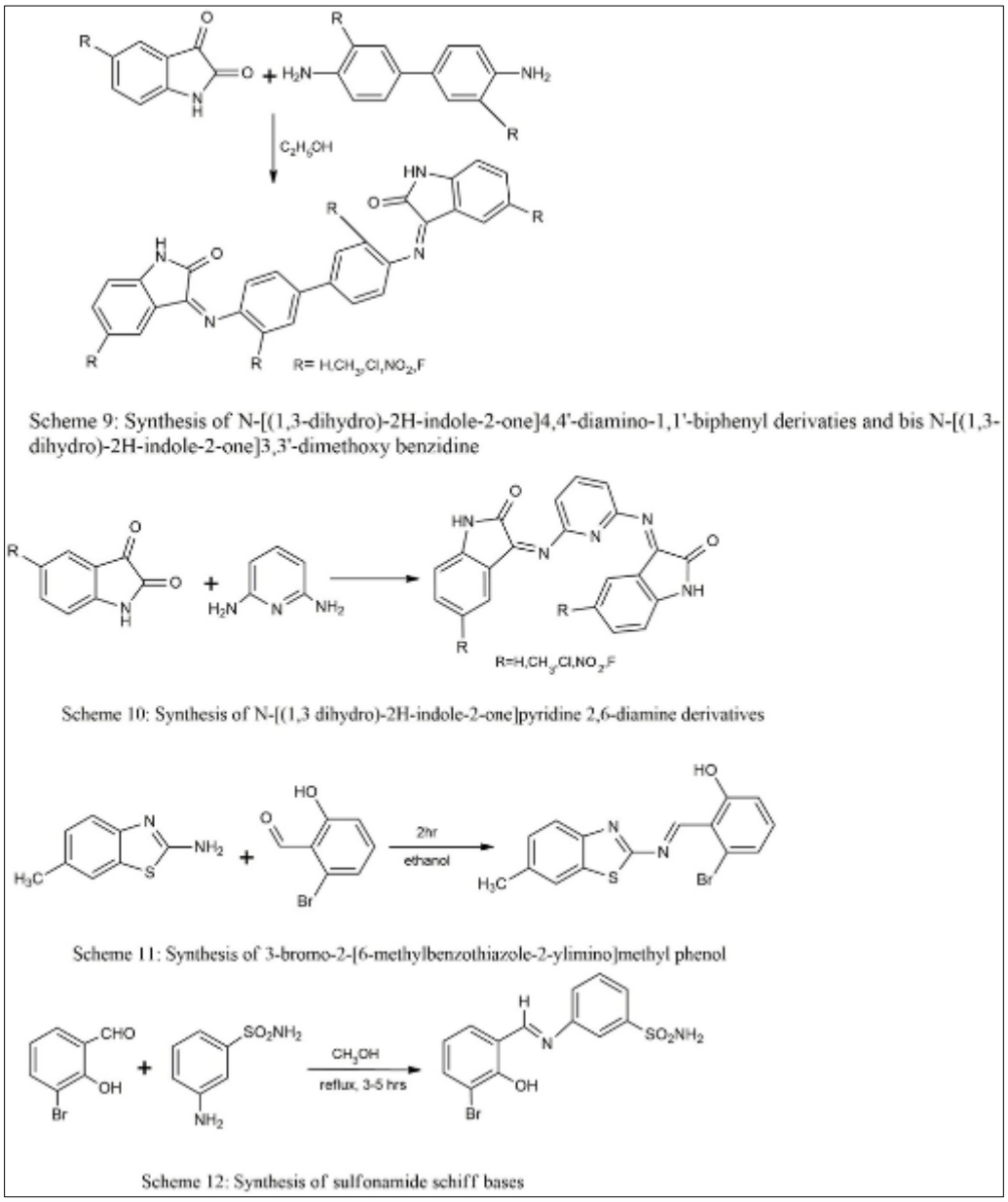


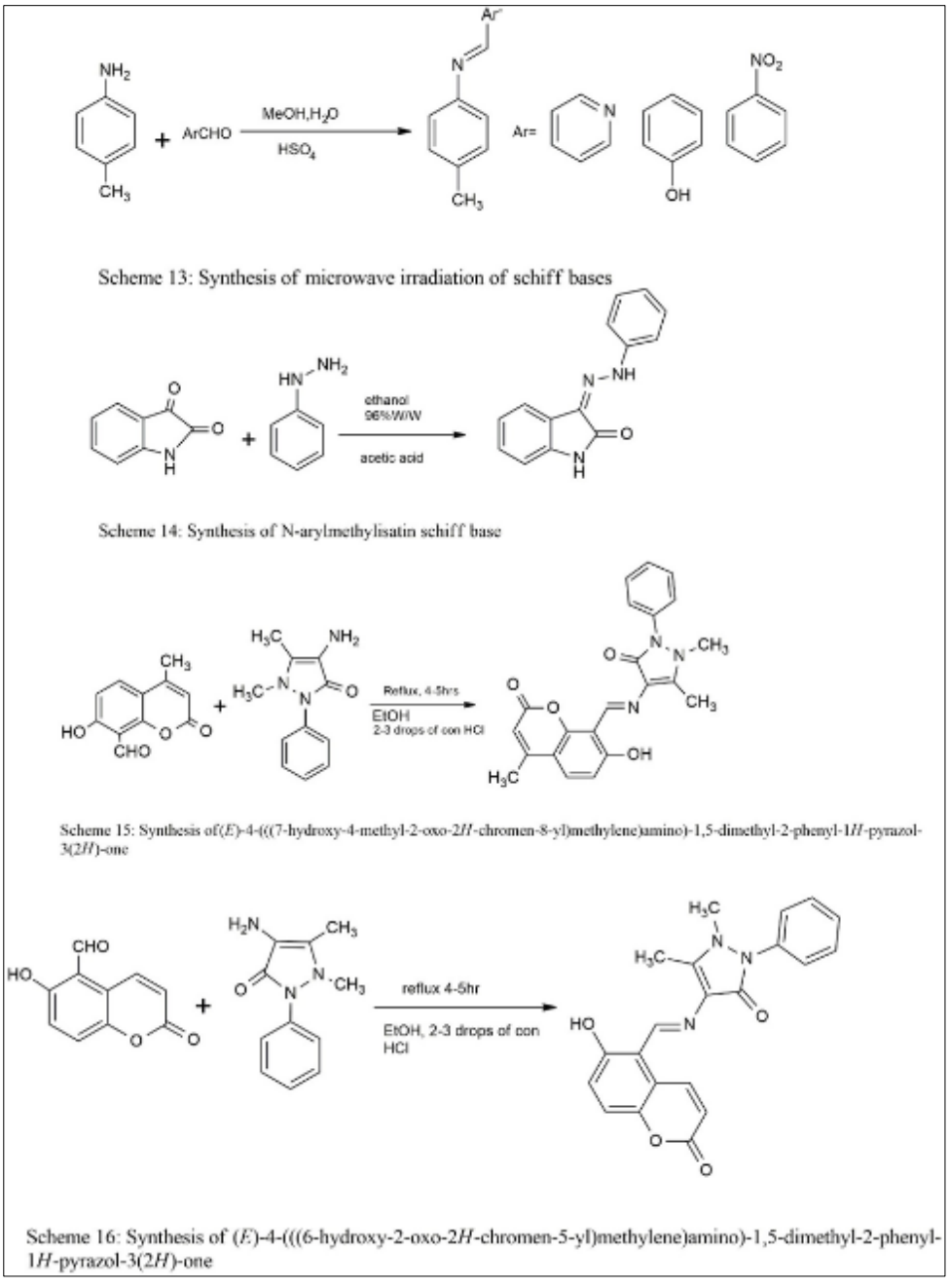
Figure 3 Synthesis of Schiff bases and their derivatives under condensation and reflux conditions

2.4. Microwave assisted synthesis of Schiff bases under acetic conditions

Schiff bases were also synthesized by the condensation of an equimolar mixture of 4-methyl aniline and 4-nitrobenzaldehyde in the presence of methanol and water in a 3:1 ratio through a microwave-assisted synthetic technique [11] (Scheme 13).

N-arylmethylisatin Schiff bases were prepared by utilizing phenylhydrazine under acetic conditions using (96%) w/w ethanol as solvent [12] (Scheme 14).

To the hot ethanolic solution of 4-aminoantipyrine, 8-formyl-7-hydroxy - 4- methylcoumarin was added under reflux conditions yielded (E)-4-(((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one Schiff base (Scheme 15). By utilizing 5-formyl-6-hydroxy coumarin under acidic conditions also yielded the (E)-4-(((6-hydroxy-2-oxo-2H-chromen-5-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one Schiff base derivative [13] (Scheme 16). The above-discussed schemes are given in Fig. 4.



Scheme 13: Synthesis of microwave irradiation of schiff bases

Scheme 14: Synthesis of N-arylmethylisatin schiff base

Scheme 15: Synthesis of(*E*)-4-(((7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one

Scheme 16: Synthesis of (*E*)-4-(((6-hydroxy-2-oxo-2*H*-chromen-5-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one

Figure 4 Synthesis of Schiff bases under reflux and microwave conditions

2.5. Synthesis of 4-amino antipyrine Schiff base derivatives

4-amino antipyrine was added to the solution of different aromatic aldehydes in absolute ethanol and 3- drops of glacial acetic acid were also added and refluxed the mixture for 1-2 hr [14] (Scheme 17A). Teran et al., 2019, synthesized 4-amino antipyrine Schiff bases utilizing 4-amino antipyrine with corresponding aldehydes [15] (Scheme 17B, 17C and 17D). The schemes are given in Fig. 5.

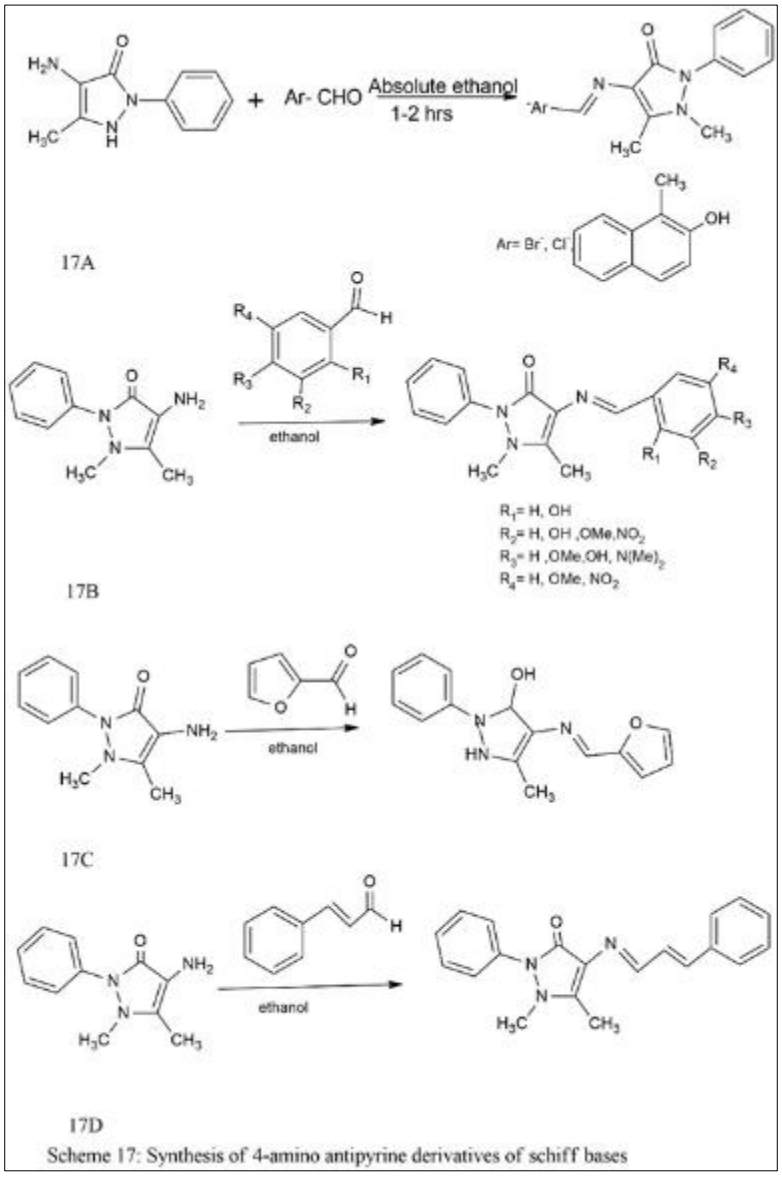


Figure 5 Synthesis of 4-amino antipyrine Schiff base derivatives

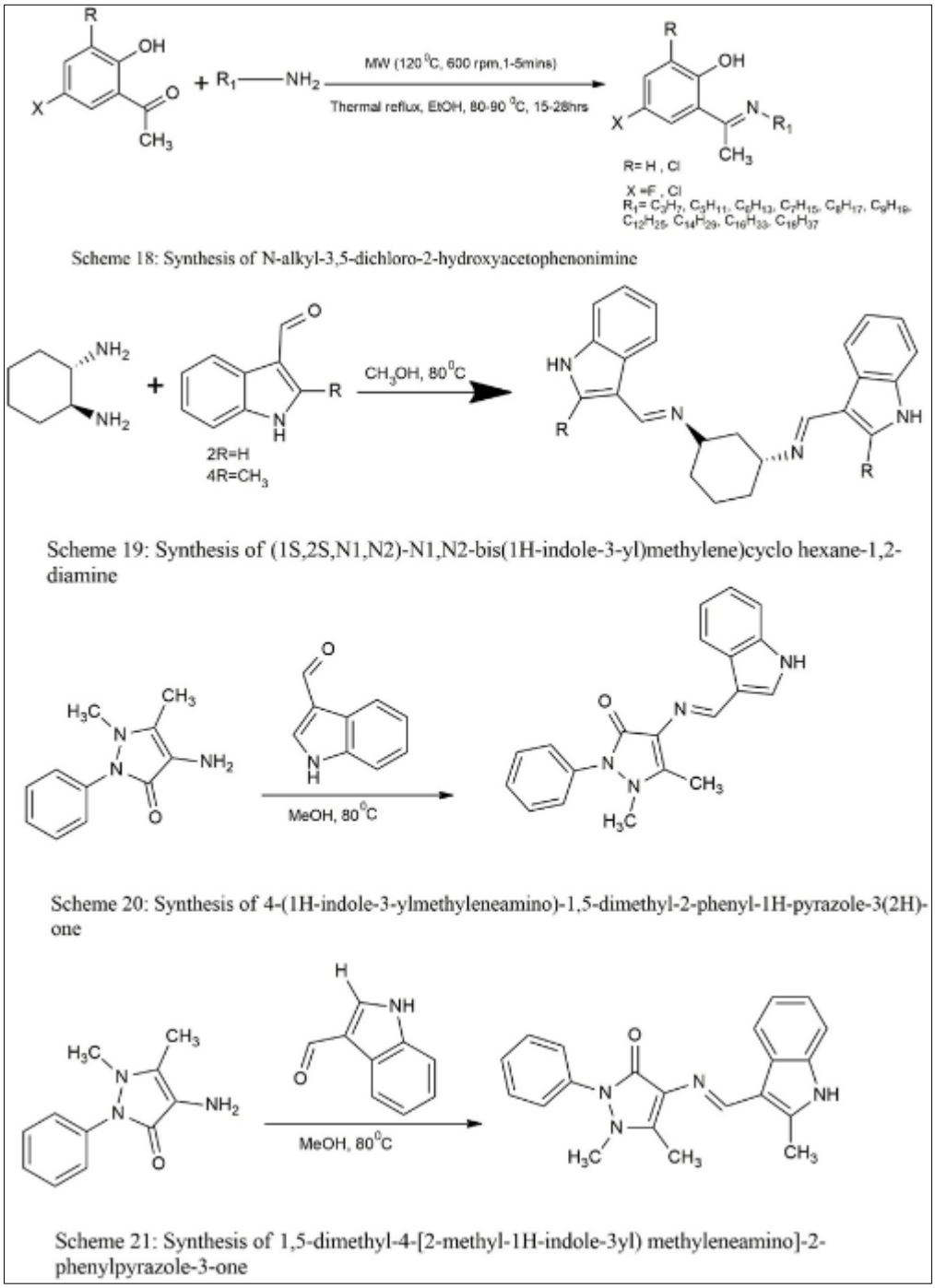
2.6. Synthesis of N-alkyl-3,5-dichloro-2-hydroxyacetophenonimine Schiff base

N-alkyl-3,5-dichloro-2-hydroxyacetophenonimine Schiff base was obtained by treating 5-fluoro-2-hydroxy acetophenone with different alkyl amines under reflux conditions at 80-90 ℃ employing ethanol as solvent [16] (Scheme 18). The scheme is given in Fig. 6.

2.7. Synthesis of Schiff base containing heterocyclic derivatives

Condensation of Trans-cyclohexane-1,2-diamine and indole-3-carbaldehyde in the presence of ethanol at 80 ℃ yielded the compound (1S,2S,N1,N2)-N1,N2-bis(1H-indol-3-yl)methylene)cyclohexane-1,2-diamine, developed by Kizilkaya et al., 2020 (Scheme 19). 4-amino-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one was treated with indole-3-carbaldehyde at 80 ℃ yielded 4-(1H-Indol-3-ylmethyleneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (Scheme 20). They also developed a Schiff base compound, 1,5-dimethyl-4-[2-methyl-1H-indol-3yl)methyleneamino]-2-phenylpyrazol-3-

one by utilizing 4-aminopyridine with methylindole-3-caroboxaldehyde [17] (Scheme 21). The above-discussed schemes are given in Fig. 6.



Scheme 18: Synthesis of N-alkyl-3,5-dichloro-2-hydroxyacetophenonimine

Scheme 19: Synthesis of (1S,2S,N1,N2)-N1,N2-bis(1H-indole-3-yl)methylene)cyclo hexane-1,2-diamine

Scheme 20: Synthesis of 4-(1H-indole-3-ylmethyleneamino)-1,5-dimethyl-2-phenyl-1H-pyrazole-3(2H)-one

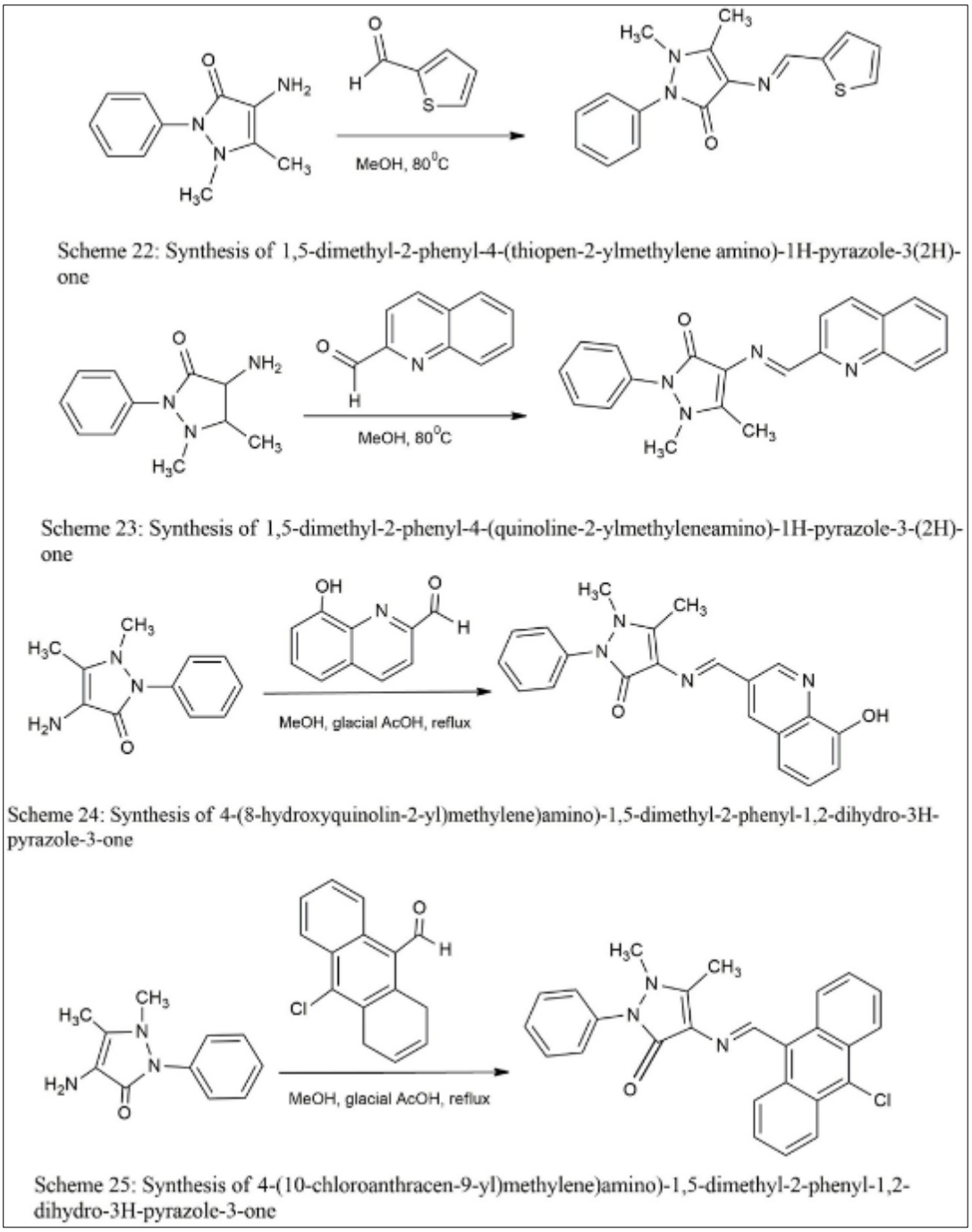
Scheme 21: Synthesis of 1,5-dimethyl-4-[2-methyl-1H-indole-3yl) methyleneamino]-2-phenylpyrazole-3-one

Figure 6 Synthesis of Schiff base containing heterocyclic derivatives

2.8. Synthesis of Pyrazole fused Schiff base derivatives

To yield the product of 1,5-dimethyl-4[2-methyl-1H-indol-3yl)methyleneamino]-2-phenylpyrazol-3-one, 4-aminopyridine was condensed with thiophene-2-carbaldehyde in the presence of methanol at 80 °C (Scheme 22). The reaction between 4-aminopyridine and quinoline-2-carbaldehyde in the presence of methanol obtained the corresponding product of 1,5-dimethyl-2-phenyl-4-(quinoline-2-ylmethyleneamino)-1H-pyrazol-3-(2H)-one [17] (Scheme 23).

4-aminoantipyrine was treated with aromatic aldehydes and it was dissolved in absolute methanol under acetic conditions resulted in the formation of 4-(8-hydroxyquinolin-2-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one and 4-(10-chloroanthracen-9-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one [18] (Scheme 24 and 25). The above-discussed schemes are given in Fig. 7.



Scheme 22: Synthesis of 1,5-dimethyl-2-phenyl-4-(thiopen-2-ylmethylene amino)-1H-pyrazole-3(2H)-one

Scheme 23: Synthesis of 1,5-dimethyl-2-phenyl-4-(quinoline-2-ylmethyleneamino)-1H-pyrazole-3-(2H)-one

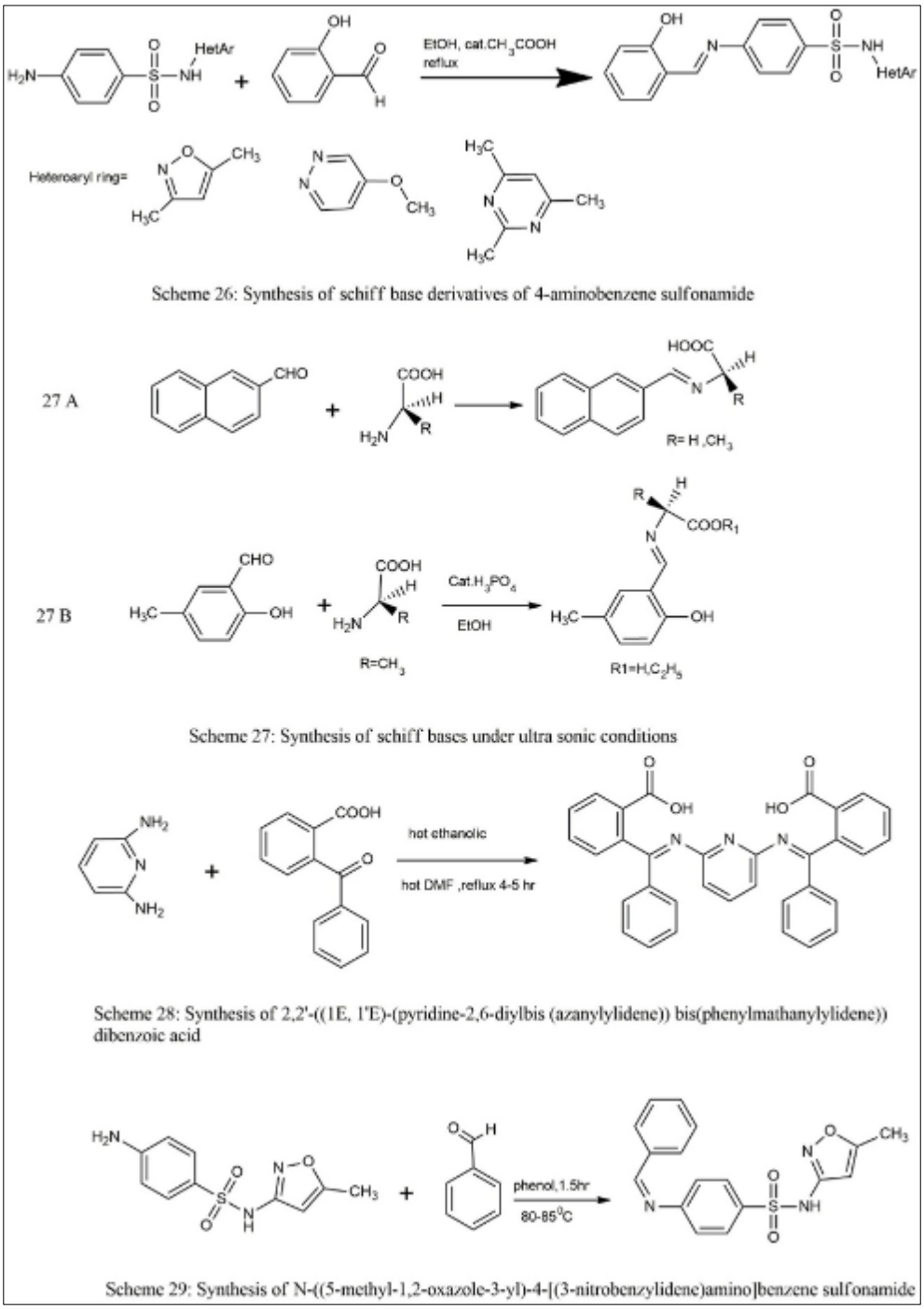
Scheme 24: Synthesis of 4-(8-hydroxyquinolin-2-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazole-3-one

Scheme 25: Synthesis of 4-(10-chloroanthracen-9-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazole-3-one

Figure 7 Synthesis of Pyrazole fused Schiff base derivatives

2.9. Synthesis of Schiff base containing Sulfonamide derivatives and novel compounds under ultrasonic conditions

The Schiff base derivatives of sulfa drugs were synthesized by condensation of sulfamethoxypyridazine, sulfamethazine and sulfamethoxazole with the substituted aromatic aldehydes. Ethanol with a few drops of acetic acid was used as the solvent mixture for this condensation reaction. An overall yield of 35-92 % was obtained by an equimolar quantity of substituted aromatic aldehyde and sulfonamides [19] (Scheme 26).



Scheme 26: Synthesis of schiff base derivatives of 4-aminobenzene sulfonamide

27 A

R= H ,CH_3

27 B

Scheme 27: Synthesis of schiff bases under ultra sonic conditions

Scheme 28: Synthesis of 2,2'-((1E, 1'E)-(pyridine-2,6-diylbis (azanylylidene)) bis(phenylmathanylylidene)) dibenzoic acid

Scheme 29: Synthesis of N-((5-methyl-1,2-oxazole-3-yl)-4-[(3-nitrobenzylidene)amino]benzene sulfonamide

Figure 8 Synthesis of Sulphonamide Schiff bases and Schiff bases under ultrasonic conditions

Sendil et al. 2016, synthesized Schiff bases under ultrasonic conditions by using alpha-amino acids with 2-naphthaldehyde and 5,5'-methylene bis(2-hydroxy benzaldehyde). The corresponding Schiff bases were obtained in the presence of K_2CO_3 [20] (Scheme 27A and 27B).

Synthesis of Schiff base namely 2,2'-((1E,1'E)-(pyridine-2,6-diylbis(azanylylidene))bis (phenylmathanylylidene))dibenzoic acid was synthesized by condensation of o-benzoyl benzoic acid with 2,6-dihydro pyridine. [21] (Scheme 28).

On the treatment of 4-amino-N-(5-methyl-1,2-oxazole-3-yl)benzene-1-sulfonamide with benzaldehyde in the presence of phenol at 80-85 ℃ yielded N-(5-methyl-1,2-oxazole-3-yl)-4-[(3-nitrobenzylidene)amino]benzene sulfonamide [22] (Scheme 29). The above-discussed schemes are given in Fig. 8.

2.10. Synthesis of Cholesteryl-4-(4-((E)-(4'-cyanobiphenyl-4-ylimino)methyl)phenoxy)butanoate Schiff base and Schiff base containing imino benzoic acid derivatives

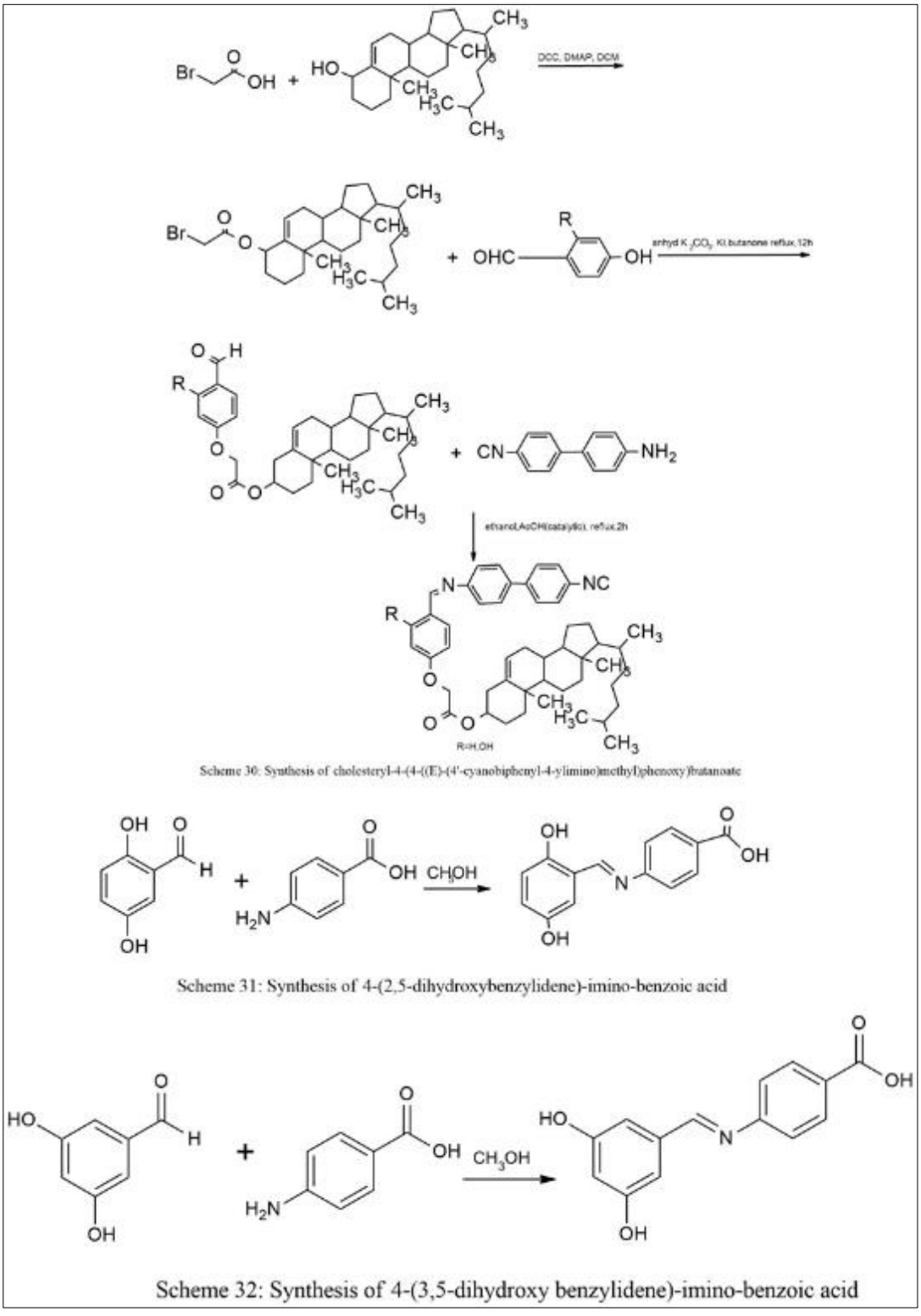


Figure 9 Synthesis of Cholesteryl-4-(4-((E)-(4'-cyanobiphenyl-4-ylimino)methyl)phenoxy)butanoate Schiff base and Schiff base containing imino benzoic acid derivatives

Cholesteryl-4-(4-((E)-(4'-cyanobiphenyl-4-ylimino)methyl)phenoxy)butanoate Schiff base was synthesized from refluxing the equimolar amount of cholesterol aldehyde derivatives and 4'-aminobiphenyl-4-carbonilide [23] (Scheme 30).

2,5-dihydroxybenzaldehyde was treated with 4-aminobenzoic acid in the presence of methanol afforded 4-(2,5-dihydroxybenzylidene)-imino-benzoic acid. The further solvent was removed from the mixture and treated with aqueous sodium bicarbonate solution yielded 4-(2,5-dihydroxybenzylidene)-imino-sodium benzoate [24] (Scheme 31).

3,5-dihydroxy benzaldehyde was treated with 4-aminobenzoic acid in methanol resulted in the formation of 4-(3,5-dihydroxybenzylidene)-imino-benzoic acid and it was refluxed for 24h. After refluxing, it was treated with sodium hydroxide solution in deionized water which offered the product of 4-(3,5-dihydroxybenzylidene)-imino-sodium benzoate [24] (Scheme 32). The above-discussed schemes are given in Fig. 9.

2.11. Synthesis of Schiff bases containing thiazole, pyrazole and indole derivatives

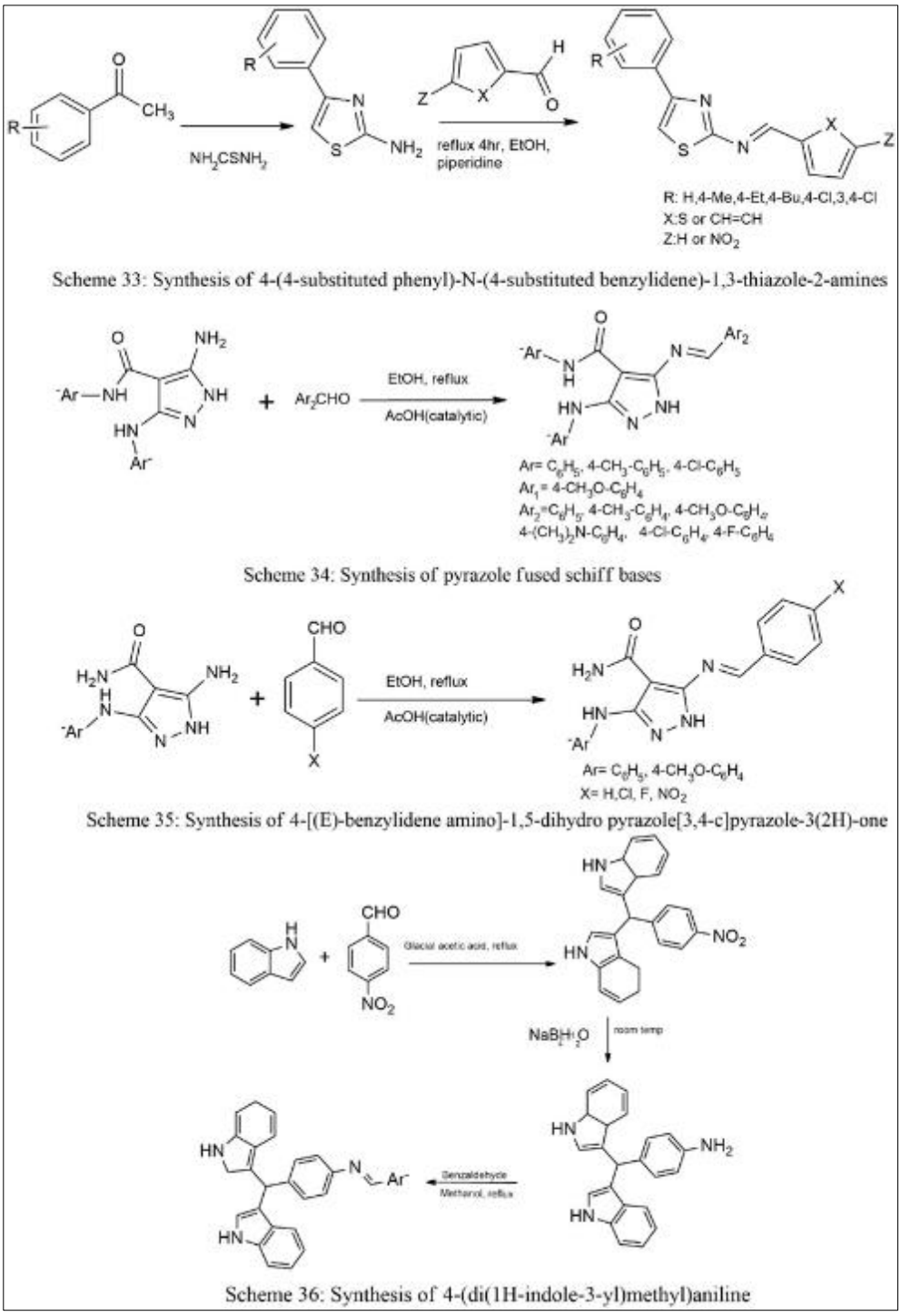


Figure 10 Synthesis of different Schiff base containing thiazole, pyrazole and indole derivatives

4-(4-substituted phenyl)-N-(4-substituted benzylidene)-1,3-thiazole-2-amines were afforded by the reaction between 4-substituted-phenyl-1,3-thiazole-2-amine and different aldehydes at an equimolar ratio by utilizing piperidine as a catalyst [25] (Scheme 33).

5-amino-N-aryl-1H-pyrazole-4-carboxamides condensed with aromatic aldehydes (benzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-(dimethylamino) benzaldehyde, 4-chlorobenzaldehyde and 4-fluorobenzaldehyde in ethanol) under reflux condition obtained the corresponding pyrazole fused Schiff base derivatives [26] (Scheme 34).

Hassan et al., 2018 developed Schiff base derivative namely 4-[(E) -benzylideneamino]-1,5-dihydropyrazolo[3,4-c]pyrazole-3(2H)-one by condensing the 5-aminopyrazole and aromatic aldehyde in absolute ethanol under reflux temperature [27] (Scheme 35).

4-(di(1H-indole-3-yl)methyl)aniline was synthesized through acid-catalyzed electrophilic substitution of indole and para nitro benzaldehyde under an acetic medium. An activating agent such as acetic acid increases the electro positivity of the electrophilic center on p-nitro benzaldehyde, the addition of indole which acts as a nucleophile to produce 4-(di(1H-indole-3-yl)methyl)aniline [28] (Scheme 36). The above-discussed schemes are given in Fig. 10.

3. Conclusion

This study summarizes various environmentally eco-friendly methods for the synthesis of Schiff bases. These are a popular group of organic compounds because they can be synthesized by using a simple reaction with inexpensive catalysts. Various synthetic processes were used for synthesizing Schiff bases, which are summarized in this review. Some of the important techniques such as conventional, microwave irradiation, ultrasound sonication, catalyst-free and solvent-free synthetic approaches were included in this review. The compounds were formed with high yield under acetic and acidic conditions. The main purpose of this survey is to develop a lack of interest in the synthesis of the Schiff base. Schiff bases attracted increasing attention from scientists for the synthesis of new derivatives for applications in medicinal and industrial fields. Beyond synthetic chemistry, we can use green chemistry concepts to enrich the synthetic accessibility and pharmacological aspects of this scaffold. In the field of pharmaceutical chemistry, the discovery of various Schiff base derivatives is constantly developing with numerous applications in coordination chemistry. Thus, the Schiff bases and their derivatives can be used as potent moieties for various medicinal applications and for the development of novel scaffolds.

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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