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Schiff Bases and their Pharmaceutical Applications: A review

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Abstract

Schiff bases are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. The first imines were prepared in the nineteenth century by a classical method that involves the condensation of a carbonyl compound with an amine under zeotropic distillation. Molecular sieves are used to remove water formed in the system. Later, many ways of synthesising Schiff bases were invented. Schiff bases exhibit various biological activities and are commonly used for industrial purposes. They are the most widely used intermediates in organic synthesis as: catalysts, pigments and dyes, polymer stabilisers, and other essential uses. Due to its broad importance, many different preparation methods for this moiety have been presented in this article.

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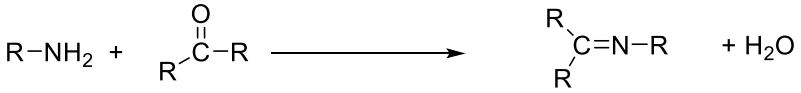
INTRODUCTION

Schiff bases are imines in which the nitrogen atom is attached to an aryl or alkyl group, not a hydrogen atom. They were named after their discoverer, the German scientist Hugo Schiff, who won the Nobel Prize and prepared them for the first time in 1864.

Schiff bases have the general formula $R_1R_2C=N-R_3$ [(1)]

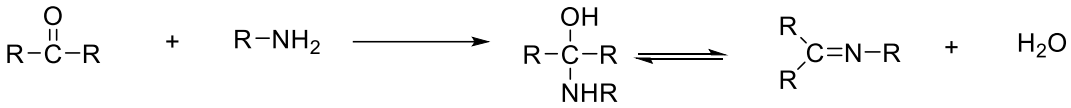
Which is obtained from the bonding of the nitrogen atom in the primary amine with the carbonyl group in various aldehydes or ketones to form an azomethine group (-C=N-), as shown below [(2)]



R= alkyl ,Aromatic group

Schiff bases containing aryl groups are more stable[(3)] due to resonance and formation faster than alkyl groups, as those produced from aliphatic aldehydes are unstable and ready for polymerisation [(4)]. In contrast, aromatic aldehydes that contain effective electron exchange are more stable.

The reaction of Schiff base formation from an amine with aldehyde or ketone is reversible. Usually, it occurs in the presence of an acid, base or heating, as shown below.



R= alkyl group

The product of this reaction is obtained either by separating the product or removing water since many Schiff bases decompose into their original components (aldehydes or ketones, primary amines) by aqueous solutions of metallic acids and are stable in aqueous solutions of bases[5].

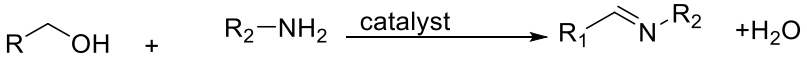
Schiff's bases have several names, including azomethines, relative to the primary azomethine group (C=N). They are also called imines, aniles and benzaniles, depending on the nature of the R_1, R_2, and R_3 groups. They are called imines when R1 is an aryl group, R2 is a hydrogen atom, and R3 is an alkyl or aryl group. As for the aniles, R_1, R_2, are aliphatic or aromatic groups or a hydrogen atom, while R_3 is a substituted or un-substituted phenyl group. Schiff bases derived from aldehydes and amines are called aldimines, while those derived from ketones and amines are called ketimines[6]. They are also known as hydrozones when they result from the condensation of ketones or aldehydes with suitable acid hydrazides in an appropriate solvent [7]

It is worth noting that we mention the benefits of Schiff bases as catalysts[8] in electrochemical reactions, organometallic chemistry, medicine and biotechnology, pharmaceutical industries, environmental chemistry, analytical chemistry and many other uses.

Schiff-bases have attracted the attention of researchers because of their wide range of biological and pharmacological properties; some of them were prepared and showed antibacterial, anticonvulsant, anti-inflammatory, anti-cancer, anti-hypertensive, anti-fungal, antipyretic, anti-microbial, anti-viral, anti-HIV drug, treating of toxic cells, antidepressants, sedatives and hypnotics [9], herbicide activities [10], and have also been used effectively against bacteria and evaluate toxic cells [11]. They have importance in organic synthesis and preparation of polymers, dyes and intermediate catalysts [12] and have also become a basic building block in the formation of essential ligands that form with metal ions (transition elements) and some coordination complexes [13]

There are many ways to prepare Schiff bases, including the following [10, 11]. The reaction of aldehydes or ketones with primary amines is one of the most important and common methods, as the reaction includes the nucleophilic addition of the primary amine to the aldehyde or ketone, followed by the deletion of a water molecule.

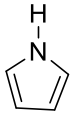
The other method is the oxidation of alcohols, where oxidation of alcohols occurs, forming aldehydes or ketones, depending on the type of alcohol, which is followed by the reaction with the primary amine to form Schiff bases [10, 11].



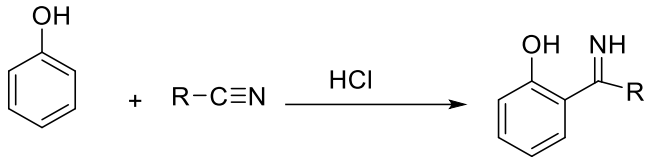
R= Alkyl Group

R1= $NH_2\ CH_2CH_2$ -

R2 =



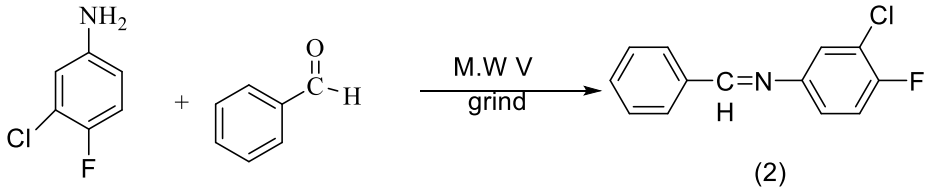
In addition to the reaction of phenol - ether with nitriles, where the alkyl or aryl cyanide reacts with phenol or phenolic ether derivatives to give ketimine in the presence of acid as a catalyst. This reaction is preferred by mixing nitrile with phenol and ether and adding (HCl) [12, 13].



(1)

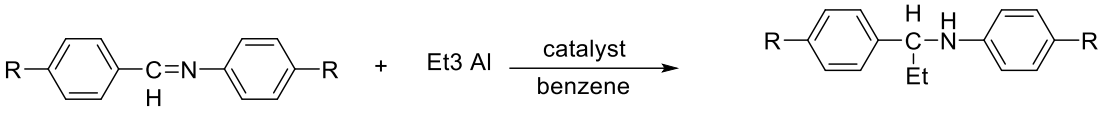
Schiff bases were also obtained from nitriles as a raw material by reducing it with lithium aluminium hydride [(12)] and another method by adding Grignard reagent to the nitriles [(13)]

Several other methods have been used to prepare Schiff bases, including the microwave, in addition to the grinding stone method, which is considered one of the green methods [(14)].



(2)

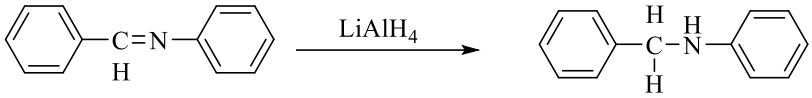
Several reactions are involved in Schiff bases, including the reaction with tri-ethyl aluminium in the presence of lanthide as a catalyst and benzene as a solvent at lab temperature [(15),] as in the equation.



(3)

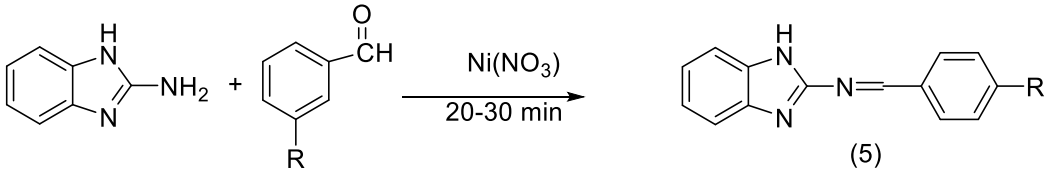
R= CH_3 , Cl

Schiff bases may be reduced to obtain secondary amines using reducing agents such as $LiAlH_4$ Lithium Aluminium Hydride [(16)], as shown below.



(4)

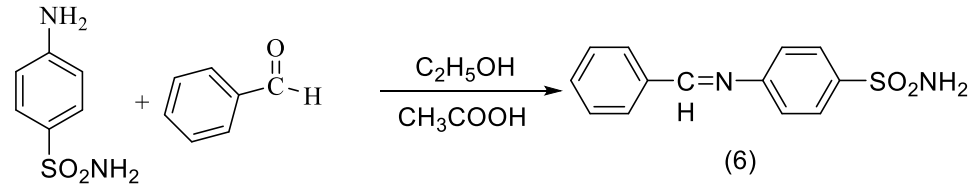
Akbar Mobinikhaledi et al. (2010) were able to develop a simple and effective method for preparing some new Schiff bases in a good yield by reacting aromatic aldehydes with 2-aminobenzimidazoles using a certain amount of $M(NO_2)_2$ as a catalyst in an organic solvent at room temperature[(17)], as shown below:



(5)

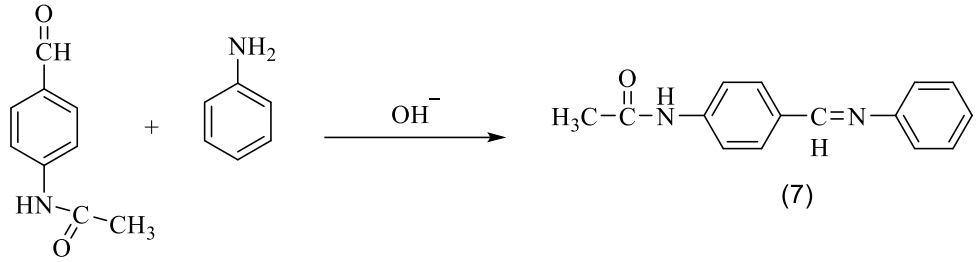
R= Cl, NO_2 ,OCH3

Santosh Kumar et al. (2010) [(18)] prepared antimicrobial compounds by using various substituted aromatic aldehydes with sulphonamides using alcohol and acid, to prepare Schiff bases as shown below:



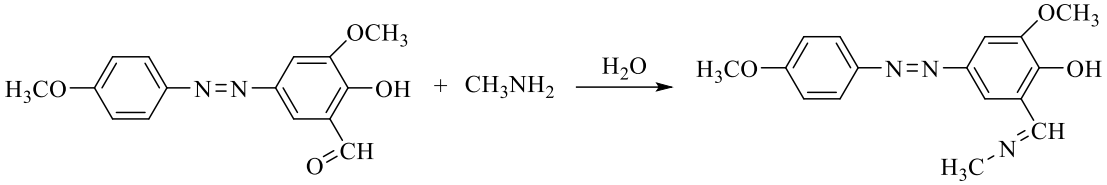
(6)

Tariq.M. (2010) [19] was able to obtain Schiff bases by reacting (4-acetamidobenzaldehyde) with aniline in the basic medium as shown below:



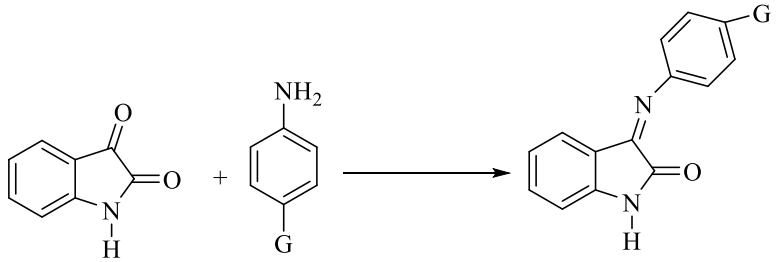
(7)

Zarei.M.et.al (2011) [20] was also able to obtain Schiff bases with a high yield by mixing the reagents in an aqueous slurry by grinding at room temperature and without a solvent, which is one of the green chemistry methods, and is one of the non-traditional or classical methods in preparation, as shown below:



(8)

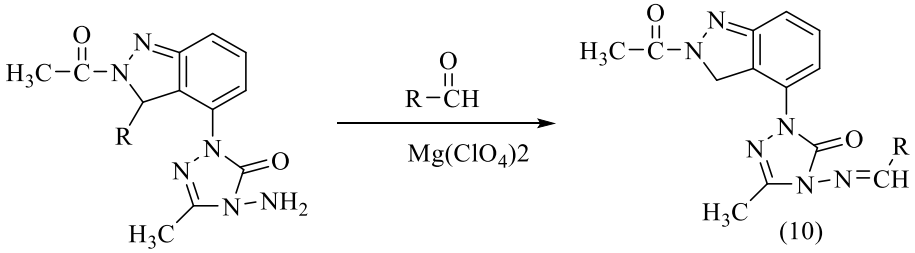
Kriza. A. et al. (2011) [21] were able to prepare Schiff bases by condensation reaction between different amines and indoline-2,3-dione using a molar ratio of 1:1, as shown below:



(9)

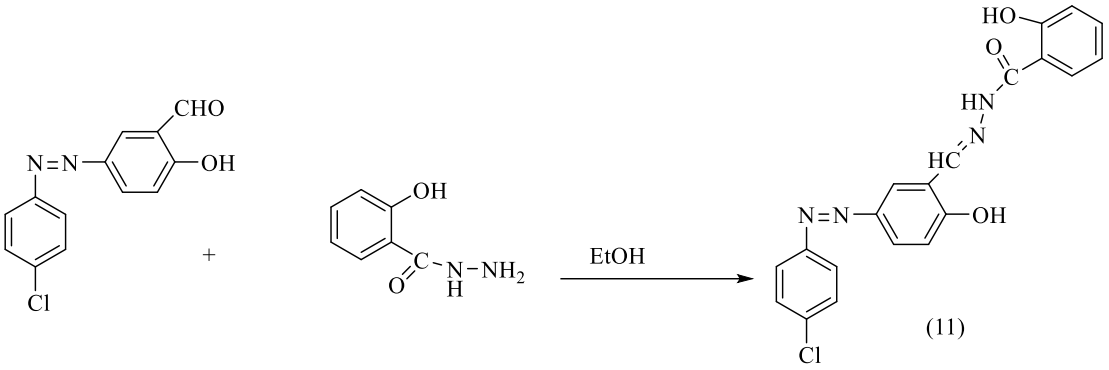
G= H, Cl ,2-OCH_3 -3,4,5 -OCH_3, 4-NO_2

Schiff bases were obtained by Tosneem Taj et al. (2011) [22, 23] by reacting substituted of 1-amino-2-aryl-3-oxo-1, 2, 4-triazoles with aldehyde using Mg $(ClO_4)_2$ as a catalyst with high yield, as shown below:



(10)

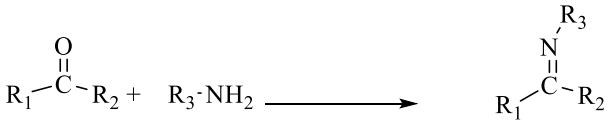
Anitha.C. et al. (2011) [24] also obtained azo-schiff by reacting 5-[(4-chlorophenyl) diazenyl]-2-hydroxy benzaldehyde with 2-Hydroxy benzohydrazide by reflux for 2 hours as shown below:



(11)

This, in turn, was used as a ligand to prepare a number of complexes.

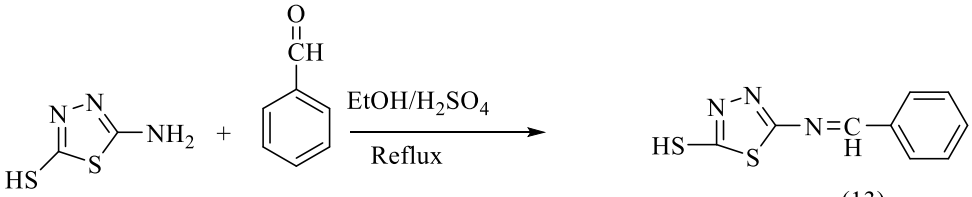
Schiff bases were also prepared in a modern way using nanotechnology by Chavan (2011) [25]. He obtains a number of derivatives of Schiff bases, where sulfonic acid was used as a heterogeneous catalyst and by reacting aliphatic or aromatic primary amines with aldehydes or ketones of different alkyl or aryl at room temperature and in conditions free from organic solvents as shown below:



R_1,R_2,R_3 = Alkyl Group

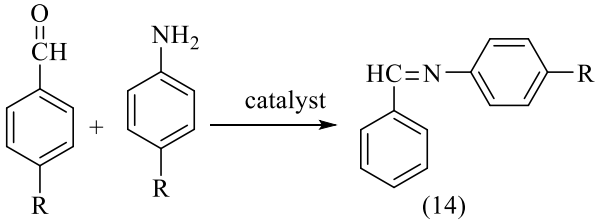
(12)

Schiff bases were obtained by Mobinikhaled et al. (2011) [26] from the reaction of 2-amino-5-mercapto1,3,4-thiadiazole with aromatic aldehydes in the presence of ethanol containing sulfuric acid as a catalyst, as shown below:



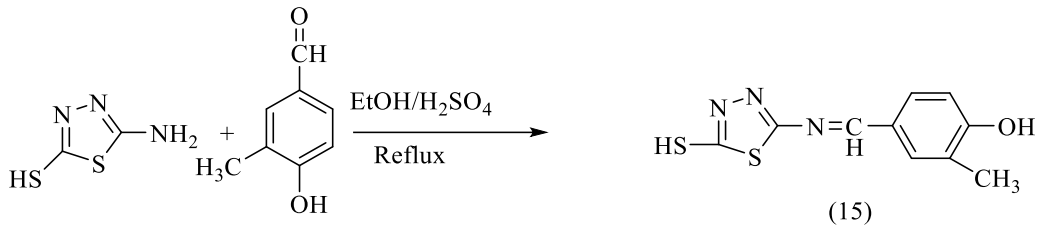
(13)

Suresh. P. et al. (2012) [27] prepared a number of Schiff bases by reacting aromatic primary amines with aromatic aldehydes and using natural lemon juice as a catalyst under free solvents conditions as shown below:



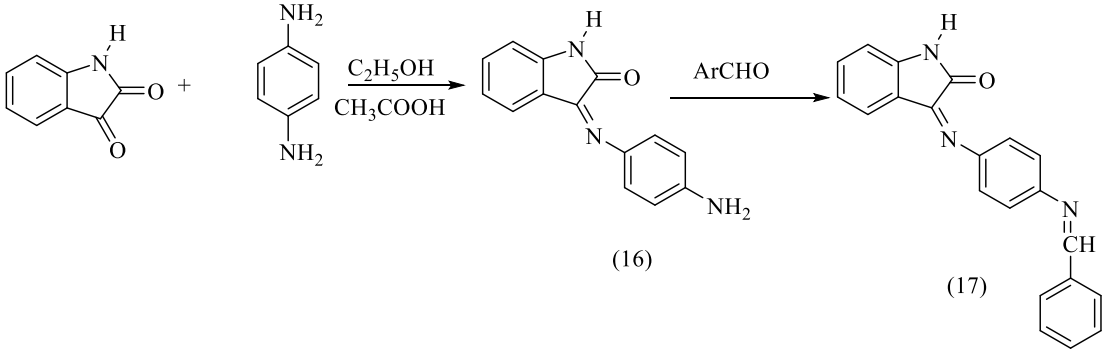
(14)

Ameen and Qasir prepared Schiff bases (2012) [28] by reacting equimolar of 5-amino1, 3, 4-thiadazole-2-thiol, and vanillin using absolute ethanol as a solvent, as shown below:



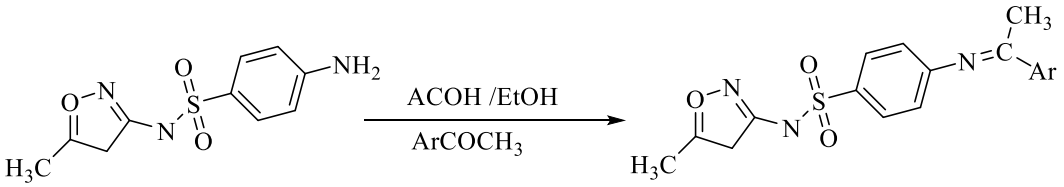
(15)

Aditya.j.et.al (2012) [29] was able to prepare a number of Schiff base compounds with biological activity from indoline-2,3-dione with phenylenediamine, and then the resulting compound was condensed with a number of substituted benzaldehyde in an acidic medium; the prepared compounds were proven effective against bacteria and fungi



(16) (17)

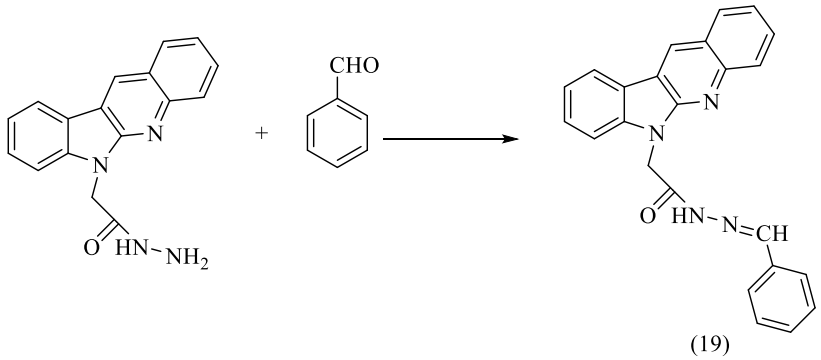
Khammas (2012) [30] was also able to prepare Schiff bases from the reaction of sulfonyl aniline isoxazole with different aromatic ketones in the presence of glacial acetic acid and using absolute ethanol as a solvent with reflux, as shown in the equation.



(18)

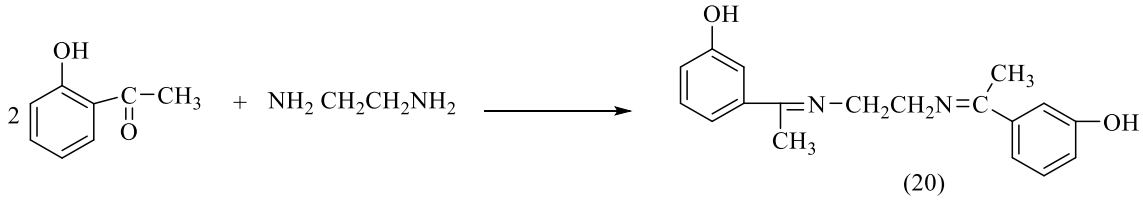
Ar = 4- Cl C_6H_4 , 4-OH C_6H_4

Nandini and Krishnakant (2012) [31] were able to prepare Schiff bases as a derivative of Indoio (2, 3-b) quinoxaline, which is pharmacologically active by microwave technology with a high yield.



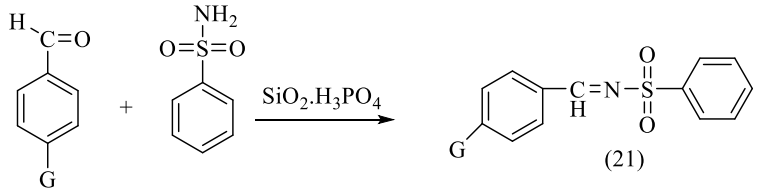
(19)

New Schiff bases 2-(2-(E)-(2-hydroxyphenyl) (ethylidene) aminoethyl)ethanimidoyl)phen were prepared by Hamil.A.Metal (2012)[32] from the reaction of 2-hydroxyacetophenone with ethylene diamine.

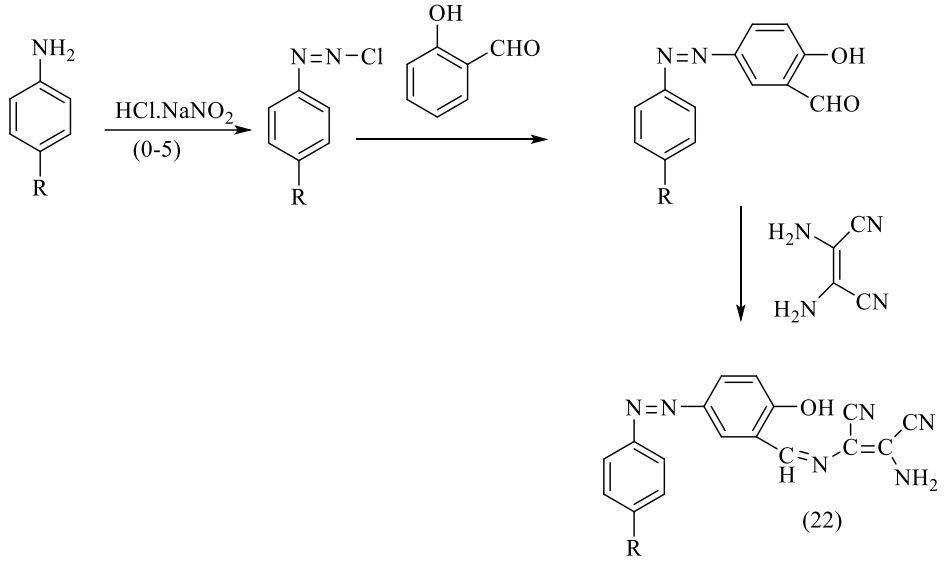


(20)

Sekar. G. et al. (2013) [33] obtained N-((E)-phenyl methylidene)-benzenesulfonamide derivatives using solid SiO_2-H_3PO_4 as a catalyst under solvent-free conditions and using micro irradiation as shown below:

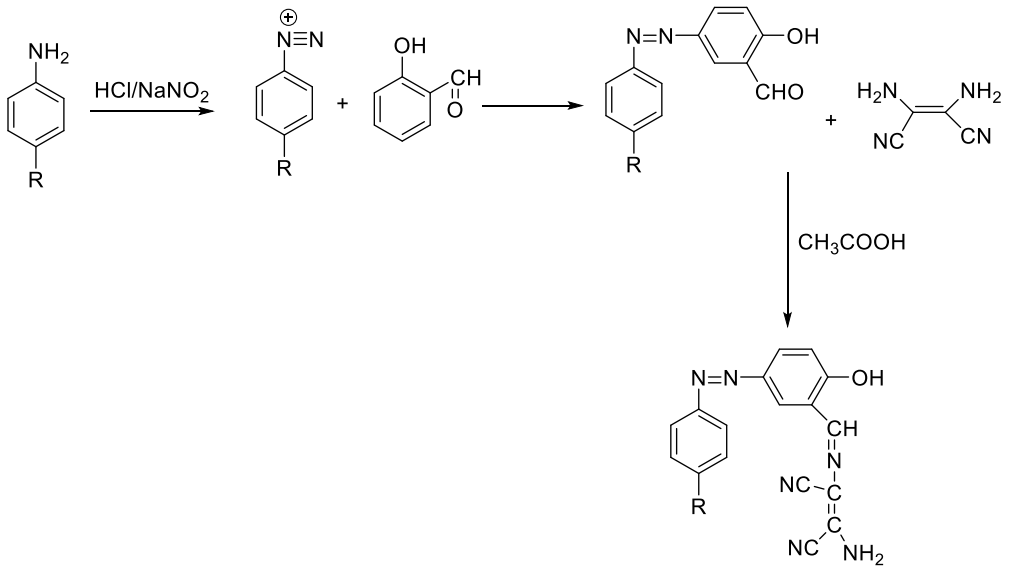


(21)

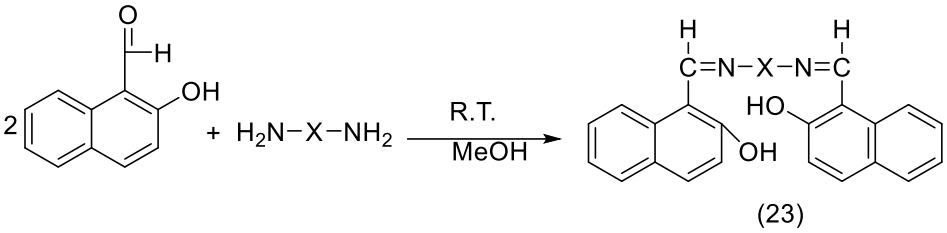


(22)

Asieh, Y. et al. (2013) [34] were able to prepare new Schiff bases through azo compounds to obtain an azo-Schiff, as shown below:



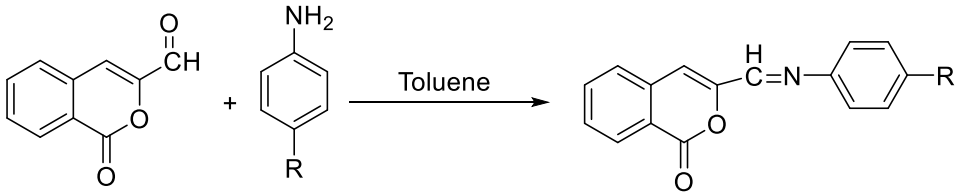
Nasifi, H. et al. (2013) [35] were able to prepare Schiff bases from the condensation of 2-hydroxynaphthaldehyde with various di- amines in molar ratios of 1:2 using stirring and methanol as a solvent, as in the equation



(23)

x= CH_2CH_2 :

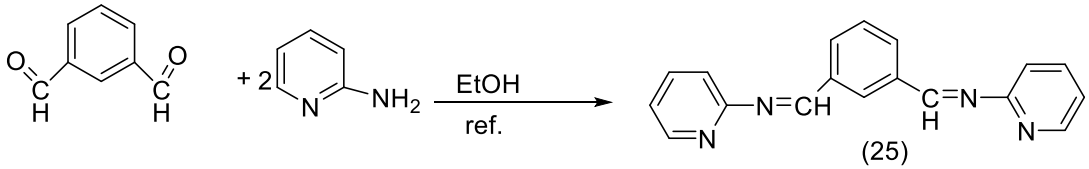
Uday. C.M. et al. (2013) [36] obtained new Schiff bases from reacting equimolar of 4-aniline substitutes with aromatic aldehydes using toluene as a solvent, as shown below:



(24)

R= $-OCH_3$,CH_3 , Cl

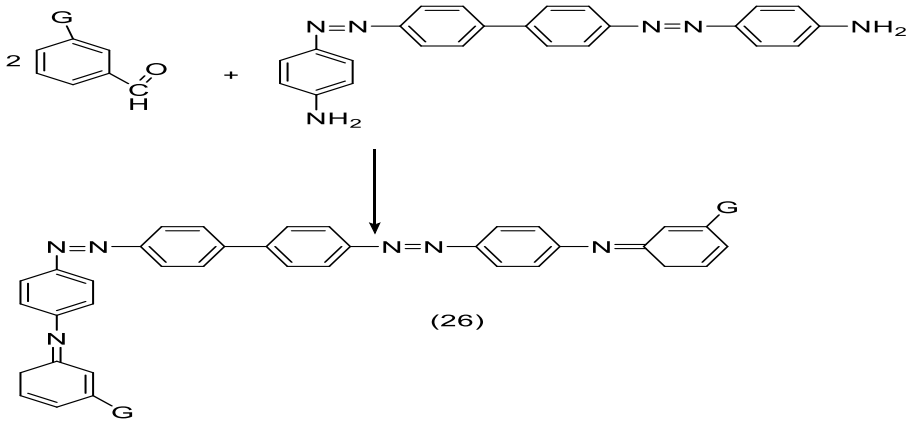
Rajaa Abdel-Amir (2014) [37] was able to prepare Schiff bases from the reaction of m-formalbenzaldehyde with two moles of 2-aminopyridine using ethanol as a solvent and reflux, as shown below:



(25)

This Schiff base is used in the preparation of azetidine-2-en compounds.

AL-jobory.A and AL-janaby. M.M (2014) [38] prepared Schiff bases from the reaction of some substituted aromatic aldehydes with N-phenyl azoaniline to produce 2-(P-phenylazo)-1,4- phenylenamine, as shown below:

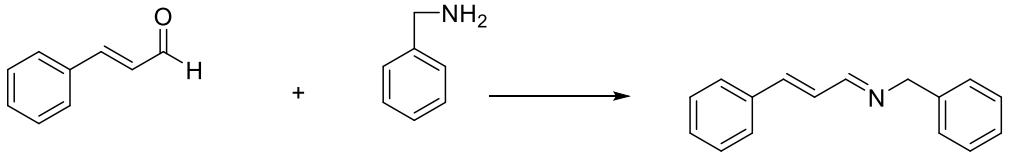


(26)

:

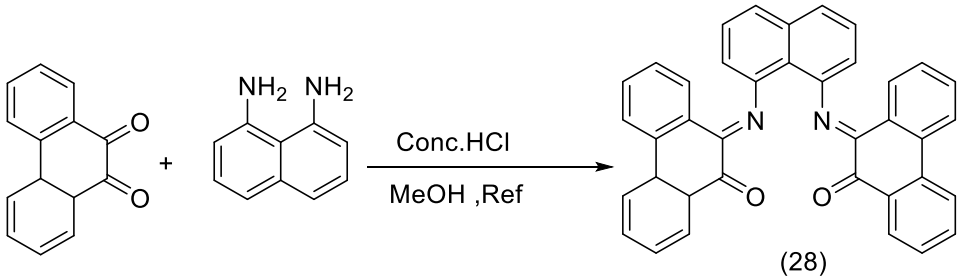
This Schiff base is used in the synthesis of seven-membered ring heterocyclic compounds (oxazapines).

Ubani et al. (2015) [(39)] were also able to use cinnamaldehyde to prepare new Schiff bases containing unsaturated double bonds by reacting the benzylamine with unsaturated alpha-beta carbonyl compounds



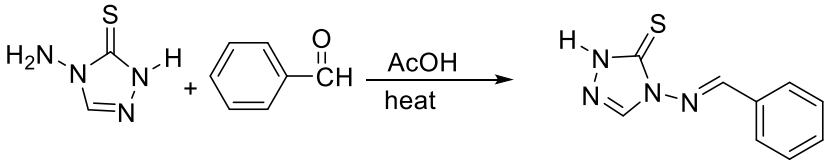
(27)

David et al. (2015) prepared [(40)] Bis-Schiff bases from the reaction of two moles of 9,10-phenanthrone with one mole of 1,8-diamino naphthalene using concentrated hydrochloric acid as a catalyst, as shown below:



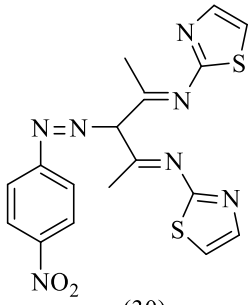
(28)

Tehrani et al. (2015) [(41)] also prepared Schiff bases from 4-amino 2, 4-dihydro-3H-1, 2, 4-triazole-3-thione with aromatic aldehydes as shown below- :



(29)

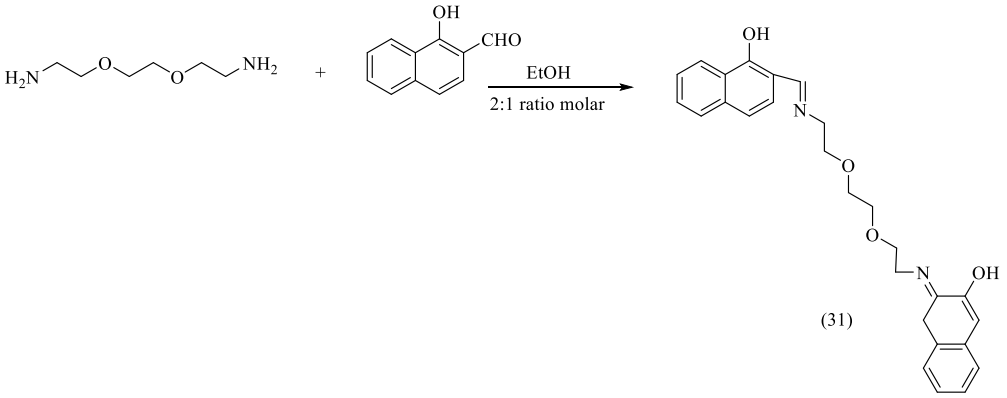
Muhammad. A. et al. (2015) [(42)] were also able to prepare Schiff bases containing an azo group with antibacterial properties, as shown in the compound (30) below:



(30)

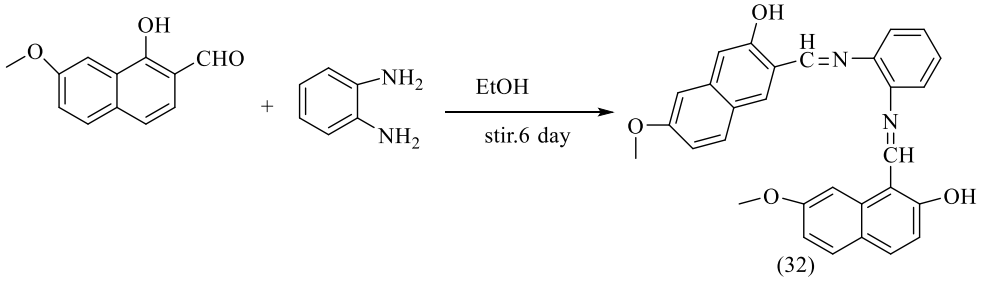
Biologically active Schiff bases have been synthesised by Khalid .j.AL-adilee and Haider .M. The year (2015) [43] was the year of using ligands to prepare many complexes with some transition elements.

Devia,j. et al. (2016) [44] were able to synthesise Schiff bases with antibacterial properties, as shown below:



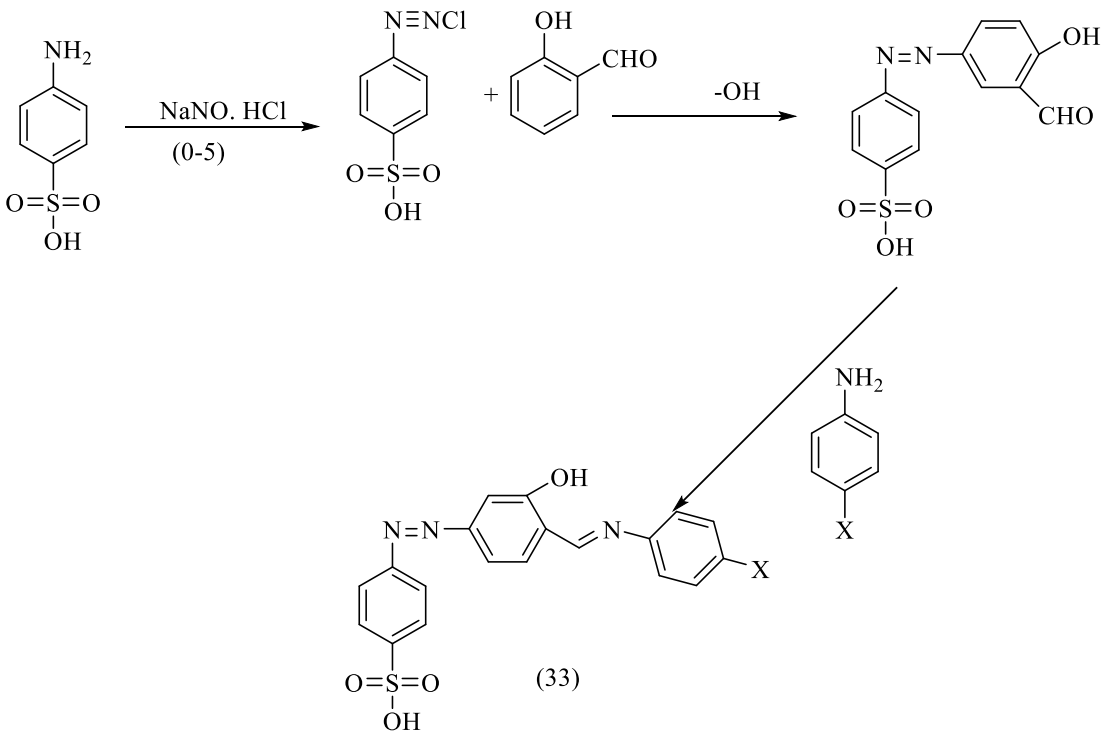
(31)

Kehman, W. et al. (2016) [45] prepared Schiff bases bioactive properties as shown:



(32)

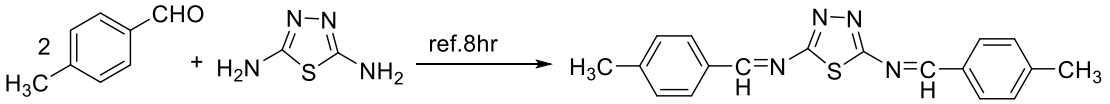
Hawaiz, F.E. et al. (2016) [46] were able to obtain Schiff bases containing azo compounds, as shown below:



X= -CH_3 ,Cl,-OCH_2CH_3 ,$COCH_3$,$NHCOCH_3$

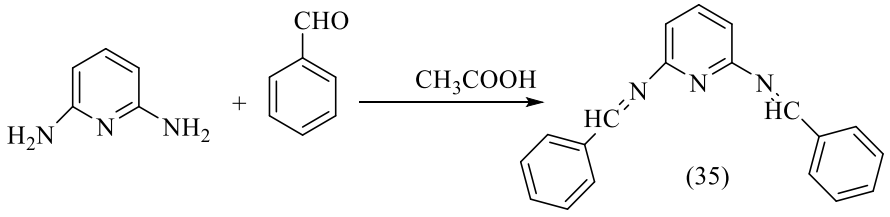
The azo compounds containing Schiff bases have important biological properties, such as antibacterial, antifungal, antispasmodic, malaria, and cancer. On the other hand, several compounds of azo Schiff bases have been used as catalysts for several organic reactions, such as oxidation or reduction [47]

Khaled, M. M and Duraid, A .A. (2016) [48] prepared new Schiff bases from the interaction of different aldehydes and amines, which in turn used them in the preparation of seven-membered ring heterocyclic compounds, as shown below:



(34)

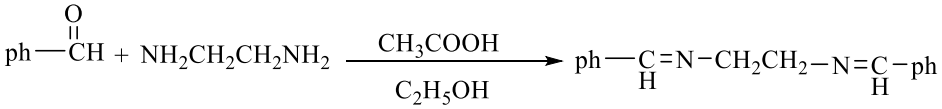
Al-salamy. A. M and Tah. N.A (2017)[49] were able to obtain bis-Schiff bases from the reaction of 2,6-diaminopyridine with various aromatic aldehydes and ketones in the presence of a small amount of glacial acetic acid as a catalyst and using microwave irradiation.



(35)

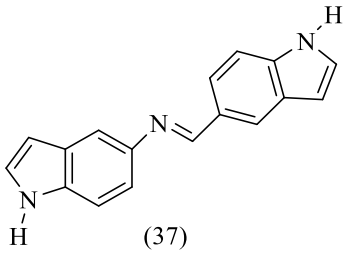
This, in turn, used these compounds to prepare the seven-membered rings of oxazapines.

Also, Abdulhussien. Z.R and Ali. M.A.M (2017) [50] prepared bis- Schiff bases by condensing ethylene diamine with some aldehydes, which they used later in the synthesis of seven heterocyclic rings, as shown below:



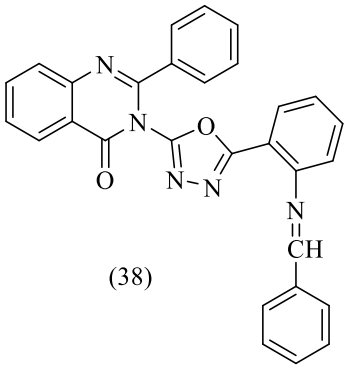
(36)

Ahmed. H.H. et al. (2017) [51] prepare bioactive Schiff bases by reflux as well as by microwave method, as shown in compound (37) below



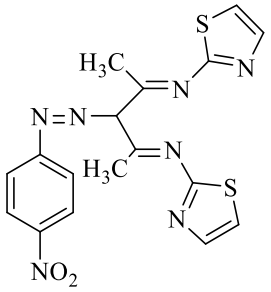
(37)

Dhansay, D. et al. (2017)[52] were able to synthesise Schiff bases as an anti-inflammatory and analgesic, as shown in compound(38) below :



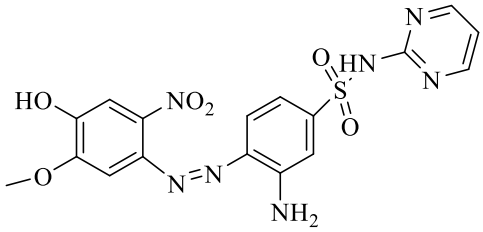
(38)

Nagham. M.A. et al. (2017) [53] were also able to prepare a new type of Schiff bases containing an azo group, which is considered an oral antibacterial compound, as shown in compound(39) below:



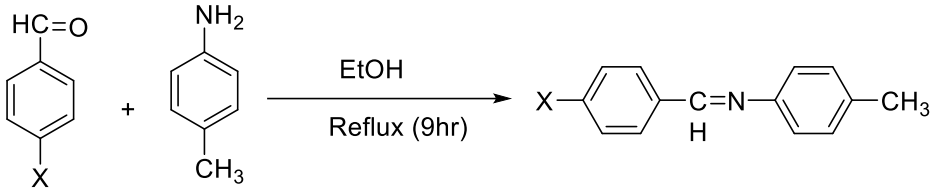
(39)

Kumar (2017) [54] prepared Schiff bases using some catalysts, as shown in compound (40) below:



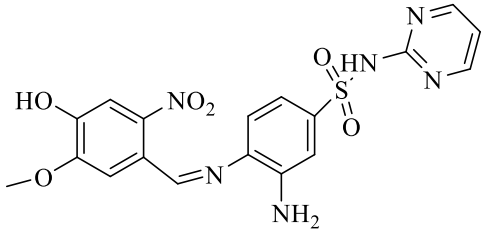
(40)

Abid. O.H. et al. (2018) [55] were also able to prepare Schiff bases by condensation of the aromatic amine 4-methylaniline with para-substituted benzaldehyde with reflux in the presence of absolute ethanol, which later used these bases to prepare heterocyclic compounds of oxazipines



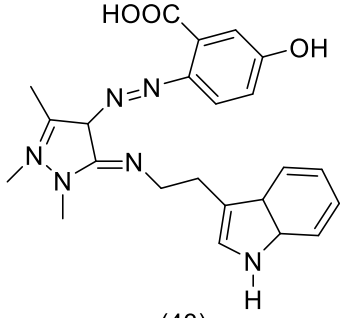
X =NO_2 ,Cl ,Br

Radhiyah. A.K. et al. (2018) [56] were able to obtain Schiff base compounds containing an imine group, as shown in compound (42) below:



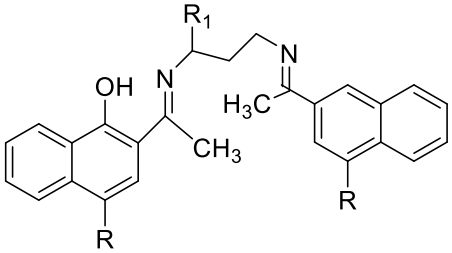
(42)

Wail.A. et al. (2018) [57] were able to prepare a bioactive Schiff base containing azo, as shown in compound (43) below:



(43)

Whereas Vanale et al. (2019) [58] were able to prepare new Schiff bases from the reflux of 1,3-propanediamine with 1-(4-substituted-1-hydroxynaphthalene-2-yl)ethane in the presence of drops of acetic acid in absolute ethanol, as shown in compound (44) below:

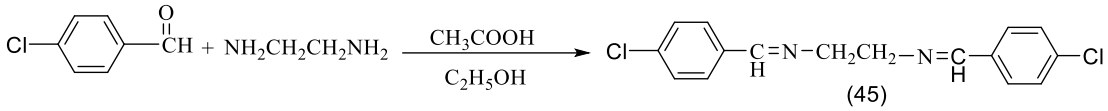


(44)

R= H,CL, Br
R1 = CH,- CH2,CH3

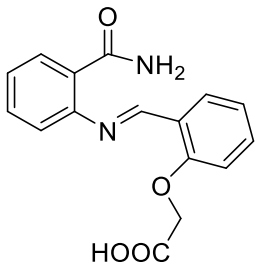
Roger and Kruse (2019) [59] also prepared Schiff bases from the reaction of aliphatic primary amines with acetylene in the presence of cadmium or zinc acetate.

Shahinur, M.D. et al. (2019) [60] obtained Schiff bases from the reaction of 4-chlorobenzaldehyde with ethylene diamine by reflux for 4 hours and in the presence of ethanol, as shown below:



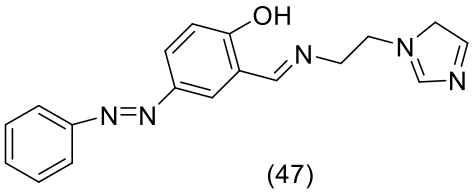
(45)

Shaabani, S.et.al (2019) [61] were also able to prepare Schiff bases, which were used in the preparation of seven-membered heterocyclic compounds, oxazapines, as shown below:



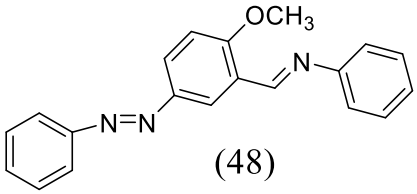
(46)

S. Siham et al. (2019) [62] prepared azo compounds containing a carbonyl group, then used them to prepare the azo Schiff, as shown in compound (47) below:



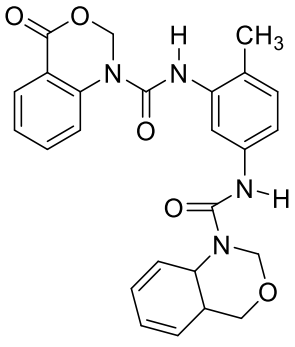
(47)

Ekhlas .Q. et al. (2020) [63] prepared the Azo-Schiff, where the Schiff bases were prepared firstly, then the Azo-Schiff secondly, as shown in compound (48) below:



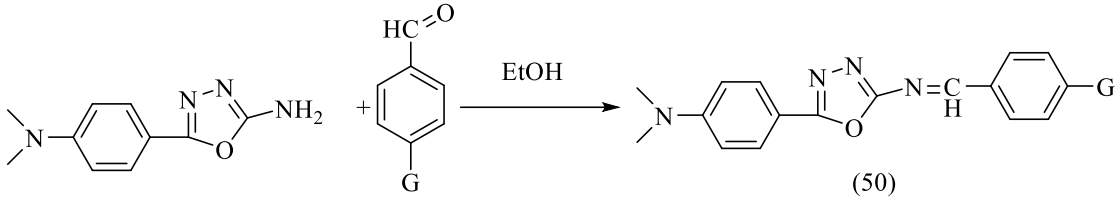
(48)

Ghufran T. S et al. (2020) [64] were able to prepare Schiff bases, which were reacted with methyl diisocyanates to obtain six-membered ring oxazines, as shown in the compound(49).



(49)

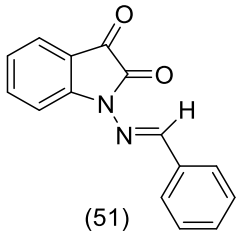
Abdulla. D.A. et al. (2020) [65] prepared Schiff bases from the reaction of 5-[4-(Dimethylamino) phenyl]-1, 3, 4-oxadiazol-2-amine, with substituted benzaldehyde



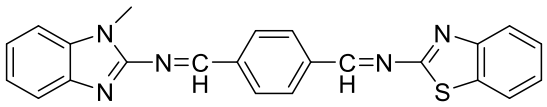
(50)

G = Cl, NO_2 ,2,4 OCH_3

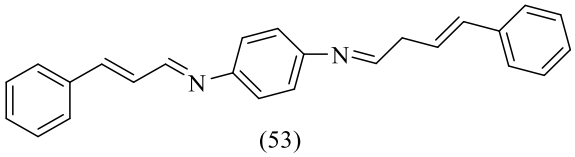
These bases were used to prepare the seven-membered rings (oxazepin, benzooxazepin,) [66], as shown in compounds (51, 52, and 53) below:



(51)

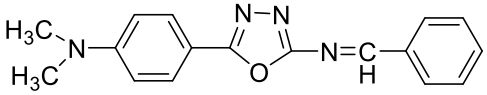


(52)



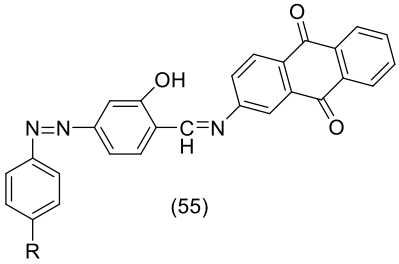
(53)

Abdullah. D.A. et al. (2020) [67] were able to prepare Schiff bases and use them in the preparation of five-membered heterocyclic compounds (oxadiazole), as shown in the compound (54) below:



(54)

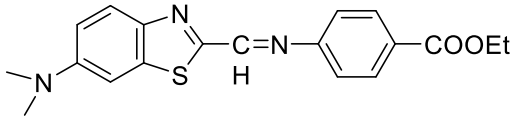
Organic compounds, including azo-Schiff were prepared by Nashwan . O.T. et al. (2021) [68] as shown in compound (55) below:



(55)

R= H,CH_3,Cl,NO_2

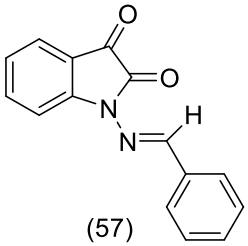
Sabrean F.J. &Nagham (2023) [69] was able to prepare Schiff bases and use them in the preparation of five-membered heterocyclic compounds (Tetrazole derivative), as shown in the compound (56) below:



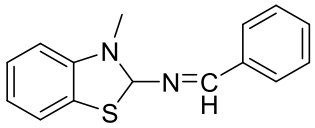
(56)

Biological activity

Through the literature review, it was noted that Schiff's bases have great biological importance as compounds (57) and (58)



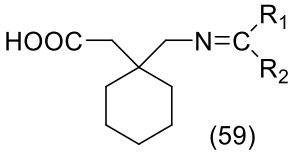
(57)



(58)

were used as antibiotics for different types of bacteria, Gram- positive and negative, such as B.sabtilis, S. aureus, S.marccscen E.COLi (Taresh,B.H) [(70)] .

Compound (59) showed activity for oxidative stress and spasms (Saleem et al., 2021) [(71)]

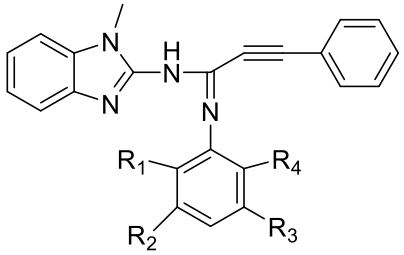


(59)

R1 = C6H5 , H

R2 = 3- OCH_3 C_6H_4, 4- OH C_6H_4

Compound (59) showed anti-malarial activity caused by P.flaciparum parasites and anti-trypanosomal activity, a human and animal disease caused by T.brucei parasites. In addition, the compound showed moderate toxicity against adenocarcinoma cells of the human cervix (Hela) (Fonkui et al., 2019) [(72)]

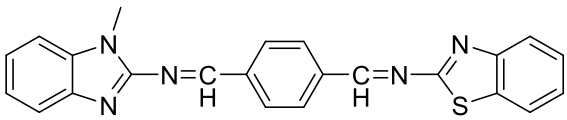


(59)

R1 = NO_2 ,OH ,H

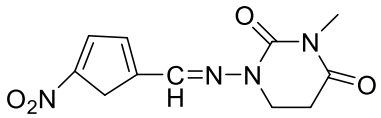
R2 = H,COOH ,R3= SO_3H ,R4 = H,X

Compound (60) also demonstrated distinct activity against two types of bacteria such as S.aureus, E.Coli, and fungi, such as A.niger and T.mentarophytes (Hassan et al. 2021) [(73)].



(60)

The compound (61), which is one of Schiff bases, contains heterocyclic rings and has pharmacological properties such as heart tonics and diuretics (Westlake et al., 1983) [(74).]



(61)

Conclusion:

This review provides an outlook and an introduction to synthesising Schiff-base compounds by different methods that achieve pharmaceutical applications. Our previous review covers the most essential Schiff compound precursors and investigates the pharmaceutical properties associated with these types of compounds. It aims to develop other methods by applying these compounds' lab results to drug programs. Moreover, this variety of methods was used to prepare many compounds that served as antibiotics and antibacterials. Additionally, it has been used to manufacture polymeric materials and cosmetic products.

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قواعد شف وتطبيقاتها الصيدلانية

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