Egypt. J. Chem. **Vol. 68**, No. 8 pp. 425 - 449 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Schiff bases performance and challenge: Chemical synthesis and current state of biological activities

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Abstract

Several structure incorporating Schiff bases, found multiple applications in different field. Several therapeutic compounds in the anti-cancer, anti-hypertensive, anti-microbial, anti-fungal, and anti-ulcer segments have been produced using the moiety, which has become an essential anchor for the creation of novel pharmacologically active medicines. Since they are pharmacophoric and synthetically possible, Schiff bases have been actively sought after in the creation of novel derivatives and analogues. As a result, they have become one of the most sought-after and essential pharmacophores for drug development. A broad range of biological activities have been made possible by the different substituents and their varying patterns surrounding the Schiff base nucleus. Furthermore, theses moiety serves as a building block for the synthesis of several lead compounds, novel chemical entities, and therapeutic candidates.

Keywords: Synthesis, Schiff base, antibacterial activity, antioxidant, anticancer activity, antifungal, antimicrobial activity

1. Introduction

A fascinating class of organic compounds, Schiff bases offer a wide range of applications in analytical, biological, and coordination chemistry. Since they have an extensive variety of biological activities, compounds derived from Schiff base have become extremely important in the medical and pharmaceutical fields. These activities include antimicrobial [1, 2], antibacterial [3, 4], antifungal [5, 6], anti-ulcer [7, 8], anticonvulsant [9], antioxidant [10, 11], anti-inflammatory [12–14], analgesic [15–17], and anti-tubercular [18].

In fact, Schiff bases have a significant chelating capacity due to the unpaired electrons on the nitrogen atom of the azomethine moiety. Because of their chelating activity, ease of separation, and flexibility on the C=N group, Schiff bases are presently regarded as intriguing ligands for coordination chemistry [19].

Additionally, sensors employed to identify analytes in seized samples and test illegal narcotics may contain chemical processes involving Schiff bases [16]. The reason for Schiff bases extraordinary appeal in organic chemistry is their low-cost, straightforward synthesis methods. In actuality, the literature still describes a variety of synthetic pathways [17–19].

2. Chemistry

Schiff bases are named after Hugo Schiff, a German scientist and Nobel Prize laureate, who discovered them in 1864 [24]. These compounds **1** are produced by condensation of primary amines, aldehydes, or ketones. Aldehydes react quicker than ketones in condensation due to steric and electronic factors [25] (Scheme1). The most common method to generate Schiff bases by the condensation reaction of aliphatic or aromatic primary amines with aliphatic or aromatic aldehydes or ketones.

There are two key processes involved in the synthesis of Schiff bases, which are produced when carbonyl compounds react with primary amines. The carbonyl group condenses with the main amine in the first step to generate a carbinolamine intermediate which dehydrated in the second step resulting in a Schiff base [26].

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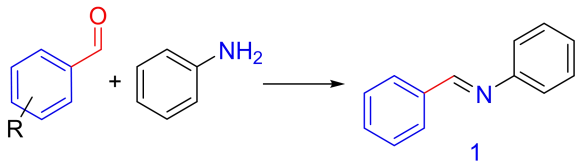
Received Date: 05 November 2024, Revised Date: 08 December 2024, Accepted Date: 15 December 2024

DOI: 10.21608/EJCHEM.2024.333199.10741

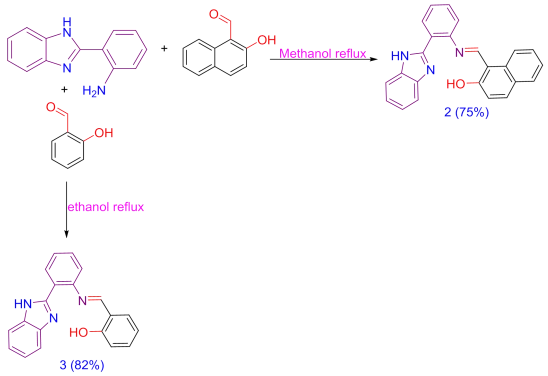


Scheme 1: General method for the synthesis of Schiff bases

Schiff bases, with a chemical structure of R'N=CR_2 (R' = H) [27], are typically produced by the chemical reaction of suitable alkyl/aryl aldehydes or ketones with primary amines [24]. Many believed they were equivalent as azomethines (RN=CR_2, R =H), a kind of imine (RN=CR_2, R = H, hydrocarbonyl) [27]. They are all carbonyl compound derivatives are formed by interacting with basic nucleophiles such as amines and their derivatives (hydroxylamine, hydrazine, N-acyl-hydrazine, and semi-carbazide). This class of compounds also comprises oximes (RR'C=NOH), hydrazones (R_1R_2C=N-NH_2), N-acyl-hydrazones (R_1R_2C=N-NH-CO-R), and semi carbazones (R_1R_2C=NNH-(CO)-NH_2) [28].

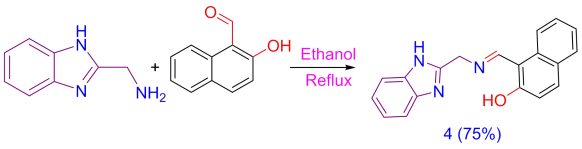
2.1 Schiff base from amines

Previously, we reported the synthesis of Schiff **2** and **3** base from benzimidazole aniline and salicylic aldehyde and 2-hydroxynaphthaldehyde according to the scheme 2 [29].



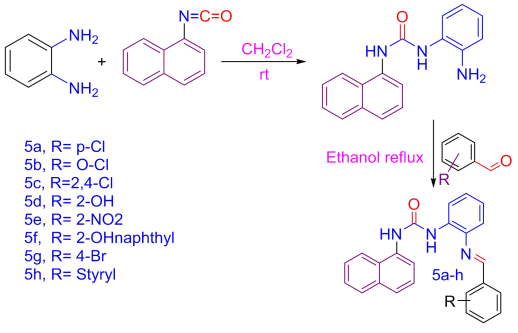
Scheme 2: Schiff base derived from benzimidazole aniline.

In the other hand, benzimidazole methylamine and 2-hydroxynaphtaldehyde was employed in the synthesis of Schiff base derivatives **4** following the scheme 3 [30,31].



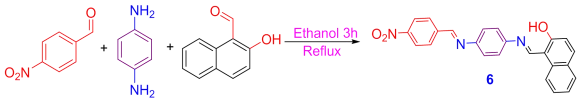
Scheme 3: Synthesis of Schiff base bearing benzimidazole methylamine.

Lately, o-phenylenediamine reacted readily with the suitable aldehydes and naphthyl isocyanate to produce the corresponding Schiff bases **5a-h** [32] (Scheme 4).



Scheme 4: Hybrid urea Schiff base synthesis

Furthermore, according to scheme 5, paraphenylenediamine was also mentioned in the literature as a starting material for the preparation of various Schiff bases **6** [33-37].

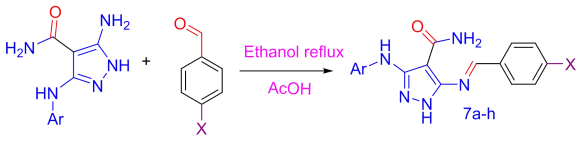


Scheme 5: Bis-Schiff base synthesized from *p*-phenylenediamine

2.2 From heterocyclic amines

It has been well documented that Schiff base exhibit potent bioactivity against a range of bacterial and fungal species. As an example, heterocyclic Schiff with halogen-saturated bases have dominated medicinal chemistry due to their many benefits [38,39]. Schiff Bases compound have garnered significant interest as broad-spectrum antiviral, antifungal, and antibacterial medications when combined with chemicals like pyrazole, 1,2,4-triazoles, benzoxazole, triazoles, coumarins, and 4-aminoantipyrine [40-42].

In addition, a multitude of heterocyclic amines was reviewed in the synthesis of Schiff bases derivatives. In this context, amino pyrazole condensed with arylaldehyde lead to the corresponding Schiff base **7a-h** (Scheme 6) [43].



Scheme 6: Synthesis of Pyrazole Schiff base

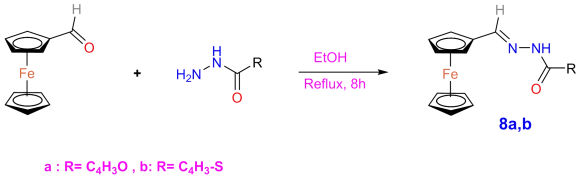
The potential activity of triazole Schiff bases as good DNA probes, antimicrobials, antioxidants, antivirals, anti-inflammatory, and analgesics is attributed to their other heterocyclic groups. Significant cytotoxic properties are also displayed by these compounds [44].

2.3 From hydrazides

Schiff bases are highly valued chemicals due to their propensity to form complexes with transition metal ions. Schiff base ligands are easily produced and form complexes with practically all metal ions. They coordinate with metal ions via azomethine nitrogen [26].

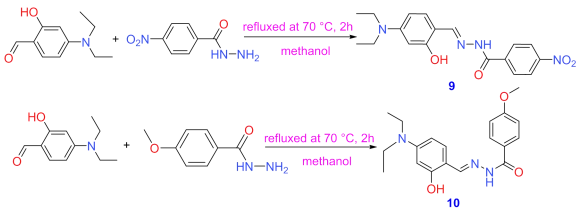
Since they are synthetic, they are used as flexible instruments in a variety of applications, such fluorescent turn-on/turn-off sensors for the identification of various analytes (like metallic components). Because of this, they may be used to distinguish harmful ions from their species in environmental media. The study encompasses a wide variety of Schiff bases that find use in the detection n of metallic cations and anions in diverse biological and environmental environments [27].

Ferrocene 2-carbaldehyde was combined with either furoic acid hydrazide or thiophene-2-carboxylic acid hydrazide to generate ferrocene hydrazone ligands **8a,b**, which were then refluxed in 100% ethanol for eight hours while according to scheme 7 [45]



Scheme 7: Synthesis of hydrazone.

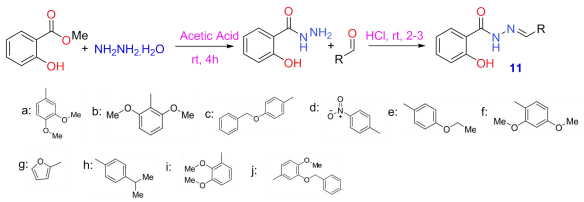
Stoichiometric quantities of the respective hydrazide and aldehyde were dissolved in methanol and refluxed for two hours at 70°C in a closed system to produce the Schiff bases **10**. (Scheme 8) [46].



Scheme 8: Synthetic pathway for Schiff base.

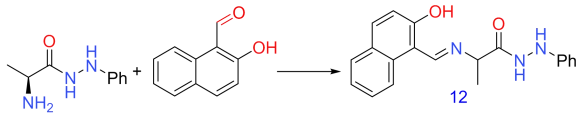
Two steps were involved in the synthesis of Schiff bases based **11** from hydrazides. The synthesis of hydrazide, was achieved from the condensation of methyl salicylate and hydrazine hydrate in methanol with three drops of acetic acid, and stirred constantly for four hours. Step 2 required the reaction of hydrazide during three hours of contact with various

aldehydes in EtOH in the presence of catalytic amount of HCl to produce the corresponding Schiff bases of hydrazones **11**. (Scheme 9) [47].



Scheme 9: The synthesis of Hydrazide based Schiff bases.

Under an argon-atmosphere, α-amino acid phenyl alanine hydrazide reacted with 2-hydroxy naphthaldehyde in methanol and heated for 4 hours at 50 °C leading to Schiff base **12** (Scheme 10) [48].



Scheme 10: Synthesis of the Schiff base from α-amino acid phenylalanine hydrazide.

The synthesis of Schiff base **13** was carried out by refluxing 3-Ketobutanehydrazide with salicylic hydrazide, in ethanol for 2 h with 90% yield (Scheme 11) [49].

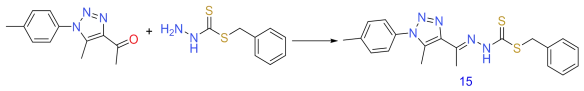
Scheme 11: Synthesis of the Schiff base from 3-Ketobutanehydrazide.

2.4 From hydrazines

The condensation of an equimolar of 2-(1-methylhydrazinyl) benzo[d]oxazole and salicylaldehyde leading to corresponding benzoxazole Schiff base **14** (Scheme 12) [50].

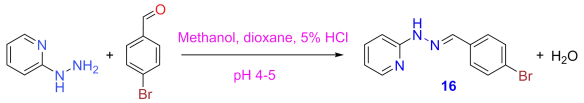
Scheme 12: Synthesis of benzoxazole Schiff base.

By refluxing 1-(5-methyl-1-(ptolyl)-*1H*-1,2,3-triazol-4-yl) ethanone with benzyl hydrazine carbo-dithioate in ethanol, Schiff base **15** was synthesized in 60% yield (Scheme 13) [51].



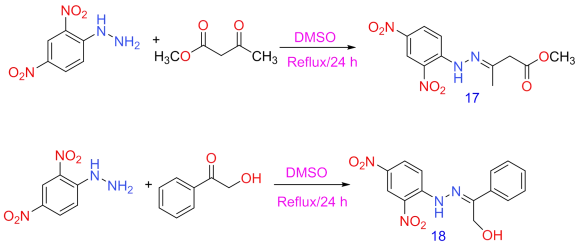
Scheme 13: Synthesis of Schiff base from 1-(5-methyl-1-(ptolyl)-*1H*-1,2,3-triazol-4-yl) ethanone with benzyl hydrazine carbodithioate.

In addition, (E)-2-(2-(4-bromobenzylidene) hydrazinyl) pyridine Schiff base **16** was elaborated from the reaction of 2-hydrazinopyridine with 4- bromobenzaldehyde in hot methanol in the presence of 5% HCl with constant stirring. The synthesis reaction of Schiff base was made at about pH 4–5 as shown in scheme14 [52].



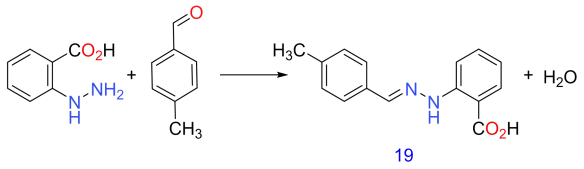
Scheme 14: Synthetic pathway for the synthesis of Schiff base.

Moreover, 2,4-dinitrophenylhydrazine was reacted with α-hydroxy acetophenone and methyl acetoacetate in DMSO during 24h generating the corresponding Schiff bases **17** in 70% and 85% for product **18** respectively (Scheme 15) [53].



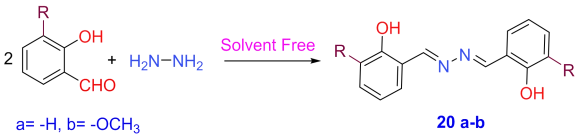
Scheme 15: Synthetic procedure for the preparation of hydrazine-based Schiff Bases **17** and **18**.

2-hydrazinobenzoic acid reacted with 4-methyl benzaldehyde in a hot methanol-dioxane in the presence catalytic amount of HCl (5%). The synthesis of Schiff base (E)-2-(2-(4-methylbenzylidene) hydrazinyl) benzoic acid **19** was achieved at pH of 4-5 following the scheme 16 [54].



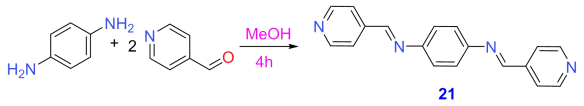
Scheme 16: Synthetic pathway for the synthesis of Schiff base.

Under free-solvent, the reaction of hydrazine with salicylaldehyde or *o*-vanillin at 40 °C for 4 hours lead to the corresponding Schiff bases **20a-b**. The new 2,2'-((1E,1'E)-hydrazine-1,2-diylidene bis (methanylylidene) diphenol products were obtained in yields respectively 88.4% and 89.7% (Scheme 17) [55].



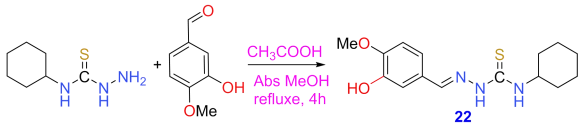
Scheme 17: Preparative route of Schiff bases under solvent-free condition.

The reaction of pyridine-4-carboxaldehyde and p-phenylenediamine in methanol over four hours at 45°C yielded the predicted Schiff base **21** with 82% yield. (Scheme 18) [56].



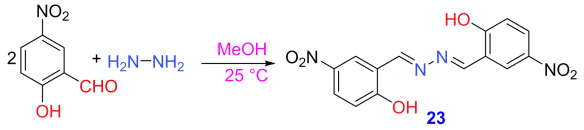
Scheme 18: Synthetic procedure of the Schiff base pyridine-4-carboxaldehyde and *p*-phenylenediamine

In boiling methanol, vanillin in the presence of calytic amount of glacial acetic acid for 30 min. The condensation of *N*-cyclohexyl hydrazine carbothioamide with vanillin was achieved for 4 hours of contact. The yield of the synthesized Schiff base **22** was 93%. (Scheme 19) [57].



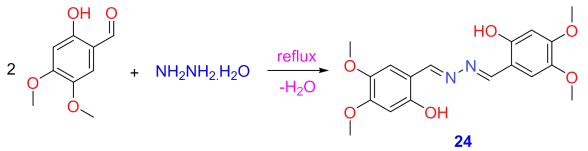
Scheme19: Schiff base synthesis from N-cyclohexyl hydrazine carbothioamide and vanillin.

In order to elaborate the 2,2'-((1E,1'E)-hydrazine-1,2-diylidenebis(methanylylidene)) bis(4-nitrophenol) Schiff base **23** according to scheme 20, hydrazine monohydrate reacted with 5-nitro-salicylaldehyde at 0 °C for one hour at room temperature. The synthetic Schiff base produced an 82% yield. [58].



Scheme 20: Synthesis of Schiff base.

Bis-Schiff base **24** was obtained by double condensation reaction 2 equivalent of hydroxy-4,5-dimethoxy benzaldehyde and hydrazine hydrate in ethanol under reflux. The reaction produced the targeted Schiff base **24** in 75% yield (Scheme 21) [59].

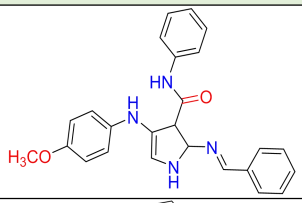
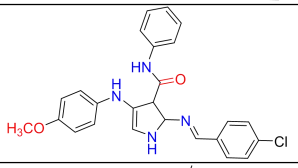
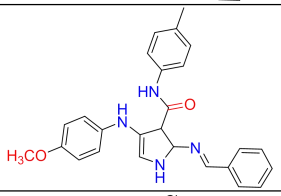
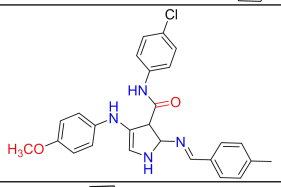
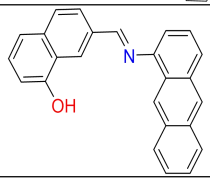


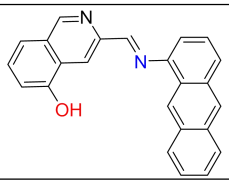
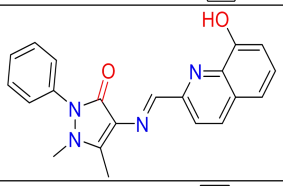
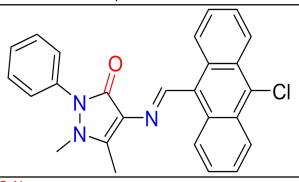
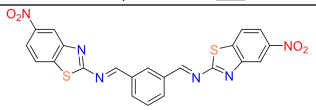
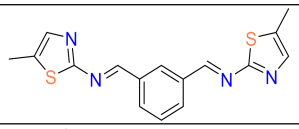
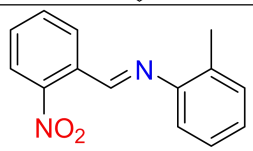
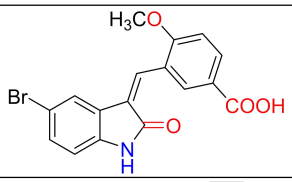
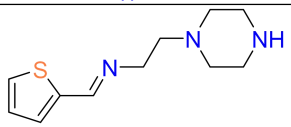
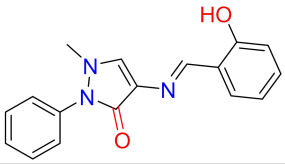
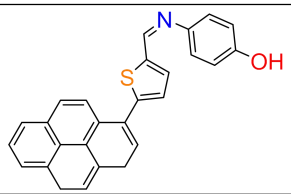
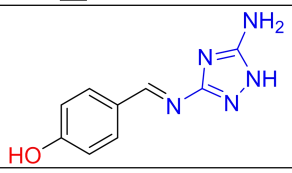
Scheme 21: Synthesis of targeted bis-Schiff base.

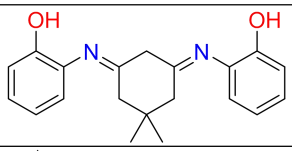
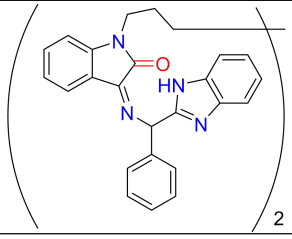
3. Biological activity

Schiff base displayed a wide range of biological actions [60-62], such as antimicrobial [63-65], antiproliferative [66], antimalarial [67,68], analgesic, anxiolytic [69], antidepressant [70], anti-inflammatory [71,72], antiviral [73], antipyretic, antibacterial [74], and antifungal [75]. Subsequent research on Schiff base-metal complexes also demonstrated their promise for managing diabetic mellitus [76] and their usage as anti-Alzheimer medications [77–79]. In contrast to other derivatives that were synthesized and employed as fluorescence sensors for the diabetes biomarker beta hydroxybutyrate [82], certain Schiff base derivatives demonstrated-glucosidase inhibition and antiglycation efficacy [80,81]. Furthermore, table 1 summarise some Schiff base as antibacterial activity [83-93]. One of the potential target chemicals used to treat cancer is Schiff base scaffolds [94,95]. Human breast MCF-7 [96,97], prostate cancer PC3 [98], ovarian cancer cell lines SKOV-3 [99], human kidney cell line HEK 293 [100], Vero cells (African green monkey kidney) [101], C6 cells (rat brain tumour cells) [102], HeLa cells (human uterus carcinoma) [103], and non-small cell lung cancer cell lines A549 [104] were among the human tumor cell lines used to test the anticancer properties of Schiff bases.

Table 1: Selected Schiff bases as antibacterial activity

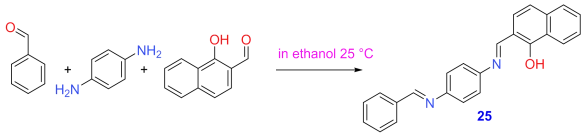
	Structure	Antibacterial Activity
1		MIC = 7.81 µg/ mL *(S.epidermidis)* Ref 84
2		MIC = 7.81 µg/ mL *(S.epidermidis)* MIC = 15.62 µg/ mL *(A.baumanni)* Ref 84
3		MIC = 7.81 µg/ mL *(S.epidermidis)* MIC = 15.62 µg/ mL *(A.baumanni)* Ref 84
4		MIC = 7.81 µg/ mL *(E. faecalis)* Ref 84
5		IZD = 13mm *(B. cereus)* **Ref 85**

6		IZD = 16 mm *(B. cereus)* IZD = 14 mm (*E. coli 10536*) **Ref 85**
7		MIC = 25 µg/ mL *(M. luteus)* MIC = 12.5 µg/ mL *(S. aureus)* **Ref 86**
8		MIC = 25 µg/ mL *(M. luteus* B1018*)* MIC = 12.5 µg/ mL *(S. aureus* 23235*)* MIC = 12.5 µg/ mL *(A. niger* 9642*)* **Ref 86**
9		IZD = 14 mm *(S. aureus MTCC 1144)* IZD = 15 mm (*P. acnes MTCC 1951*) **Ref 87**
10		IZD = 10 mm *(S. aureus MTCC 1144)* IZD = 14 mm (*P. acnes MTCC 1951*) **Ref 87**
11		MIC = 250 µg/ mL *(E.coli)* MIC = 125 µg/ mL *(S.thyphymurium)* **Ref 88**
12		MIC = 625 µg/ mL (*S. aureus* 25923) MIC = 78 µg/ mL *(P.aeruginosa clinical strain)* IZD = 10 mm *(P.aeruginosa clinical strain)* **Ref 88**
13		IZD = 12 mm *(S. aureus* 25923) IZD = 11 mm (*S. aureus* MRSA) IZD = 9 mm (*P.aeruginosa*) **Ref 89**
14		IZD = 32.5 mm *(S. aureus)* **Ref 90**
15		MIC and /or IZD not given
16		IZD = 12 mm *(C. salexigens* and H. salina) IZD = 10 mm (*H. halophila*) **Ref 91**

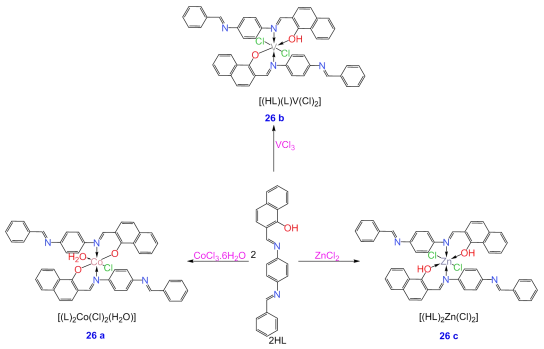
17		IZD =26mm (at 500µ/disc) **Ref 92**
18		IZD = 32 mm *(E coli)* IZD = 22 mm (*S. aureus*) **Ref 93**

3.1 Anticancer activity

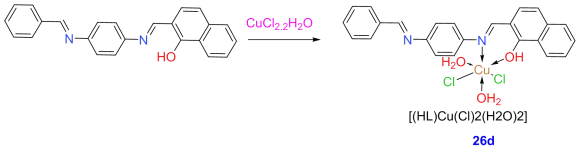
According to scheme 22, a novel Schiff base ligand, 2-((*E*)-((4-(((*E*)-benzylidene) amino) phenyl) imino) methyl)-naphthalene-1-ol, **25** was synthesized. The ligand and its metal complexes were investigated for in vitro anticancer activity against PC-3, SKOV3, and HeLa tumor cell lines, and they outperformed therapeutically utilized medicines such as cisplatin, estramustine, and etoposide. The Cu (II) complex **26d** was the most active of the investigated drugs against PC-3, SKOV3, and HeLa cells, with IC_{50} values of 0.161, 0.063, and 0.087 µg/mL, respectively (Scheme 23 and 24) [34].



Scheme 22: Synthesis of Schiff base ligand, 2-((E)-((4-((E)-benzylidene) amino) phenyl) imino) methyl)-naphthalene-1-ol.

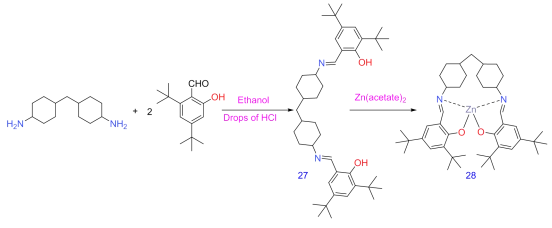


Scheme 23: Co (II), Zn (II) and V(III) complex synthesis from Schiff base



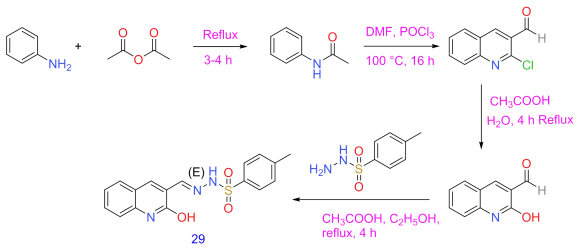
Scheme 24: Cu complex prepared from Schiff base.

A newly Schiff base ligand **27** and their complexes were prepared using 4,4'-methylene bis-cyclohexylamine and 2,4-*di-tert*-butyl-6-hydroxybenzaldehyde. At a 20 µM concentration, the most potent component, zinc metal complex 28, inhibits the A549 and H1299 lung cancer lines by 83.60 and 88.52%, respectively. The results provided clearly that zinc metal complex has more activity against the H1299 cell line in comparison to the H549 cell line. Additionally, it was found that the H1299 and A549 cell lines exhibited minimum inhibitory concentrations (IC_{50}) of 1.28 and 1.97 µM, respectively. (Scheme 25) [105].

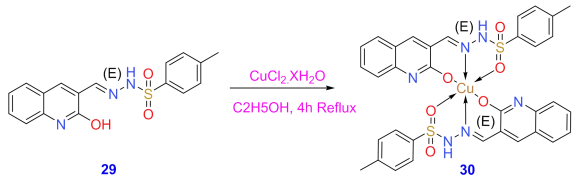


Scheme 25: zinc metal complex synthesized from 4,4'-methylenebis(cyclohexan-1-amine)

A new quinoline Schiff base **29** and its metal complexes were achieved. Among all synthesized compounds, Cu-complex **30** produced the best results with IC_{50} values of 37.03 and 39.43 µg/mL for A-549 and MCF-7 cancer cells, respectively (Scheme 26 and 27) [106].



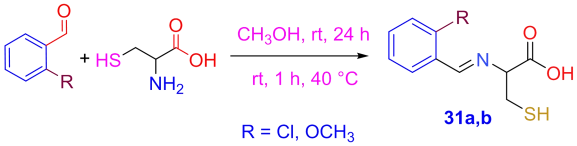
Scheme 26: Chemical synthesis of quinoline Schiff base



Scheme 27: Metal complexes derived from quinoline Schiff base**.**

3.2 Antimicrobial activity

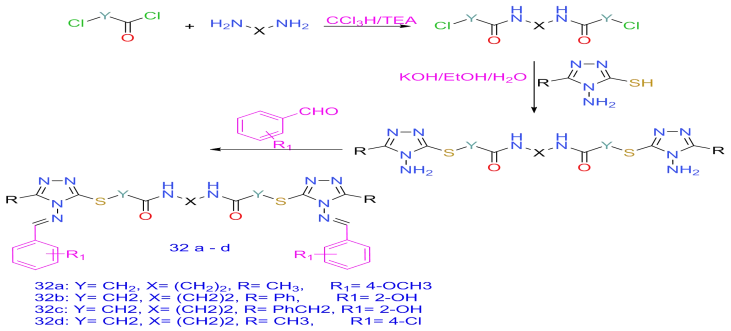
L-cysteine and substituted benzaldehyde were used to synthesized novel Schiff bases **31a, b.** The best antibacterial activity against a variety of Gram-positive bacteria is seen from Schiff base **31a** containing chlorine atom against *Staphylococcus aureus, Bacillus subtilis, Clostridium sporogenes, Micrococcus luteus* and *Micrococcus flavus*. The same results were described for Gram-negative bacteria including *Escherichia coli*, *Pseudomonas aeruginosa Proteus Hauser*, *Klebsiella pneumoniae*, *Salmonella enterica subsp. enterica serovar Enteritidis*. The results also mentioned that targeted Schiff bases **31a** displayed a strong activity against the following yeasts *Candida albicans*, *Saccharomyces cerevisiae* and fungal strain *Aspergillus brasilliensis* (Scheme 28) [107].



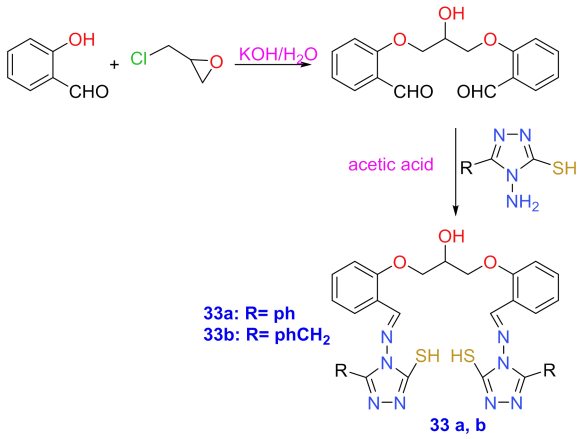
Scheme 28: Schiff base produced from L-cysteine.

Schiff bases **32a–d** (Scheme 29) and **33a, b** (Scheme 30) is formed in good amounts when bis-amino-triazoles react with the appropriate aldehydes. Synthesized compounds were evaluated for their *in vitro* antifungal and antibacterial activities with two different concentrations (10 and 50 mg/ml) against two fungal strains (*Aspergillus fumigatus*, *Candida albicans*), two Gram positive bacterial strains (*Staphylococcus aureus*, *Bacillus subtilis*) and two Gram-negative bacterial strains (*Escherichia coli* and *Proteus vulgaris*). The results demonstrated that compound **32b** have the highest inhibitory effect against *Aspergillus fumigatus* compared with the standard antibiotic Ketoconazole at both tested concentrations. Unfortunately, all tested compounds revealed no inhibitory effect against Gram positive bacterial strains (*Staphylococcus aureus*). On the other hand, compounds **32c, 32d, and 33b** present only moderate effect against (*Bacillus subtilis*) at a concentration of 50 µg/ mL.

Finally, the synthesized compounds were tested against Gram negative bacterial strains and indicated insignificant inhibitory effect against *Escherichia coli* at 10 µg/mL. Meanwhile, compound **32b** displayed moderate effect at 50 µg/ml. Finally, all compounds were also screened indicating a moderate inhibitory effect against *Proteus vulgaris* at both used concentrations [108].

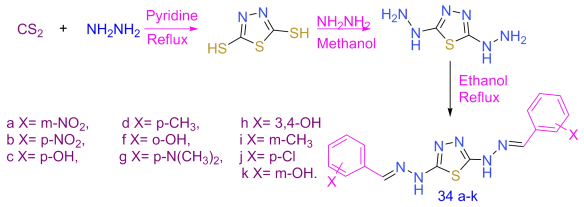


Scheme 29: Schiff bases produced via the reaction of bis amino triazoles with the suitable aldehydes



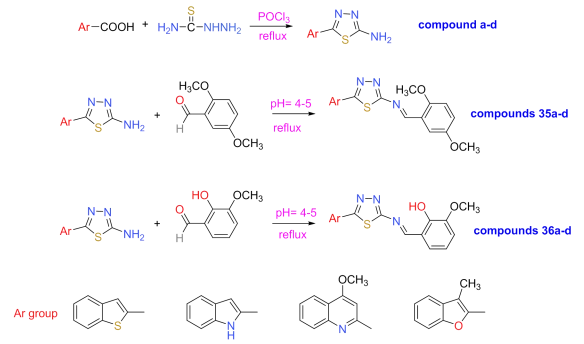
Scheme 30: Schiff bases produced via the reaction of bis amino triazoles with appropriate aldehydes

2,5-dimercapto-1,3,4-thiadiazole reacted with appropriate aldehydes affording the corresponding Schiff bases 2,5-bis(2-((E)-benzylidene) hydrazinyl)-1,3,4-thiadiazole **34a-k**. All the newly synthesized compounds were evaluated for their *in vitro* antibacterial activity against *Klebsiella pneumoniae*, *Staphyloccus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli*. Antibacterial data indicate that chemical compounds **34a-k** generated considerably impede the biological activity of the microorganisms under investigation (Scheme 31) [109].



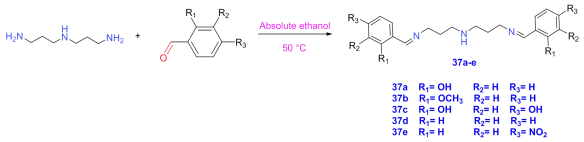
Scheme 31: Synthetic route to Schiff bases 2,5-bis(2-((E)-benzylidene) hydrazinyl)-1,3,4-thiadiazole**.**

5-substituted aromatic 1,3,4-thiadiazole-2-amine was used to design and synthesize a number of Schiff bases **35a-d** and **36a-d** using two arylaldehyde including 2,5-dimethoxy benzaldehyde and 2-hydroxy-3-methoxybenzaldehyde. Compounds **35c** and **35d** manifest strong DNA protection against the oxidative Fenton combination. Compound **35a** and **36b** demonstrated potent antibacterial action epidermidis (Scheme 32) [110].



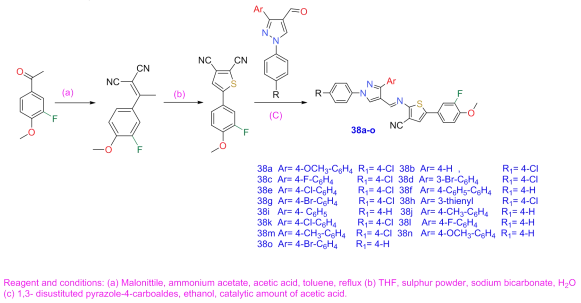
Scheme 32: Synthesized Schiff base from 5-substituted 1,3,4-thiadiazole-2-amine

Six Schiff bases **37a-e** were synthesized by reacting suitable benzaldehyde derivatives with N^1-(3-aminopropyl) propane-1,3-diamine. Tested against Gram positive and Gram-negative bacteria, the elaborated compounds demonstrated bacteriostatic rather than bactericidal effects. Furthermore, compound **37e** exhibited promise as a potential antibacterial medication by effectively suppressing the development of harmful bacteria including Candida. The results also indicated that compound **37c** anti-Candida activity was below average. (Scheme 33) [111].



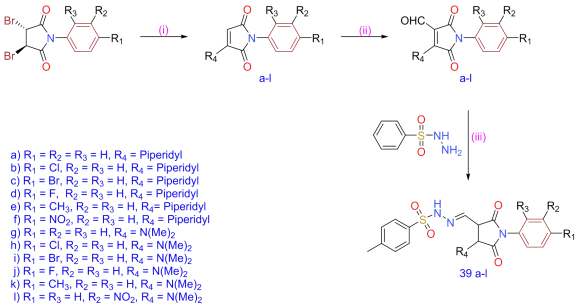
Scheme 33: Schiff bases derived from diamino-dipropyl amine and adequate aldehydes**.**

Schiff base **38a-o** bearing thiophene and pyrazole were designed and produced via the reaction of 5-(3-fluoro-4-methoxyphenyl) thiophene-2,3-dicarbonitrile with pyrazole aldehyde. The newly hybrid thiophene-pyrazole Schiff bases **38a-o** displayed considerable antifungal activity against *C. albicans* and presented a moderate antibacterial activity against *S. aureus*, *B. subtilis*, and *E. coli* (Scheme 34) [112].



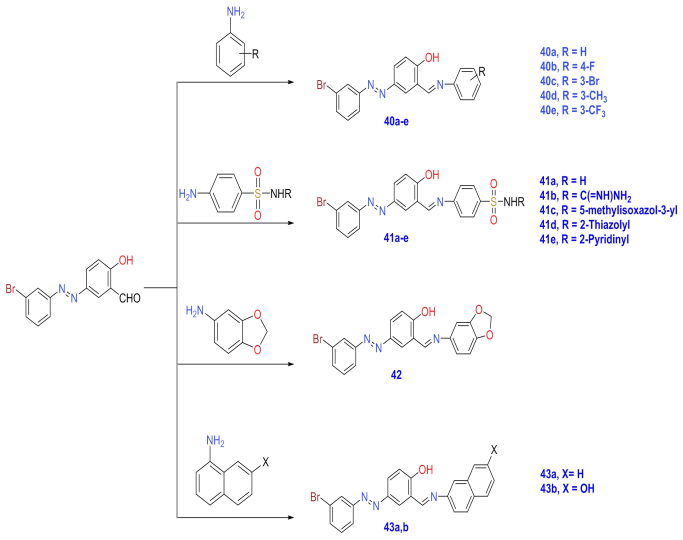
Scheme 34: Synthetic strategy of Schiff base bearing 2-amino-5-(3-fluoro-4-methoxyphenyl) thiophene-3-carbonitrile.

N-aryl 3- and 4-substituted maleimides were effectively used to synthesized a variety of new Schiff bases **39a-l**. The synthesized products were efficient against the pathogens *Escherichia coli* and *Staphylococcus aureus*. Additionally, they effectively bioactive against the fungus *Aspergillus niger* and *Candida albicans*. It is important to note that three derivatives **39a**, **39d**, and **39e** displayed antifungal activity comparable to standard drug normal fluconazole (Scheme 35) [113].

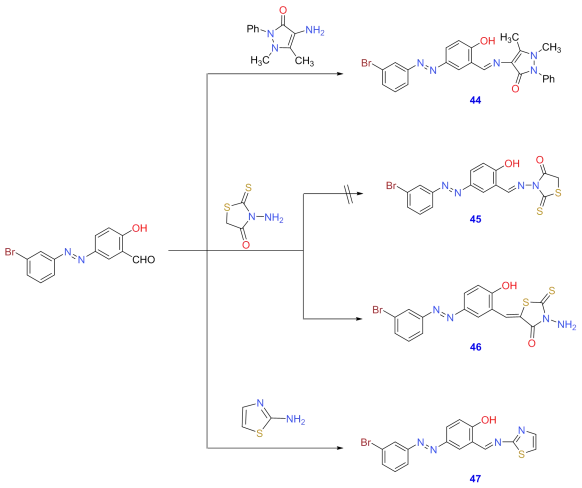


Scheme 35: N-aryl 3- and 4-substituted maleimides 39a-l synthesized using a variety of new Schiff bases.

According to schemes 36 and 37, two newly series of salicylaldehyde diazinyl Schiff bases was developed. First series, lead to Schiff bases **40a-e, 41a-e, 42 and 43a, b.** The second series generate also the Schiff bases **44-47**. The majority of the Schiff's bases appear to have strong antifungal activity against *Aspergillus fumigatus* and display a moderate activity against *Candida albicans* and *Bacillus subtilis* according to the mean values of the obtained inhibitory zone diameter for the synthesized compounds [114].

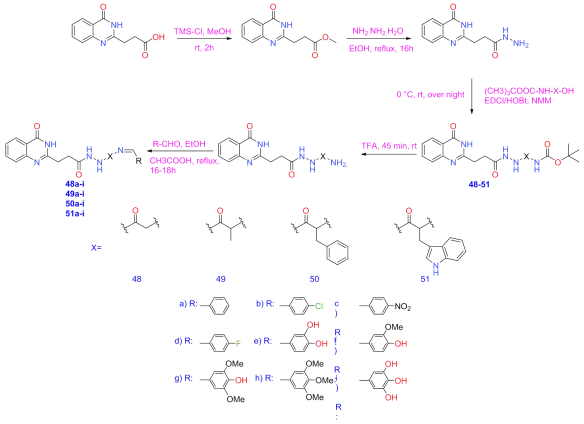


Scheme 36: First set of salicylaldehyde diazinyl Schiff bases



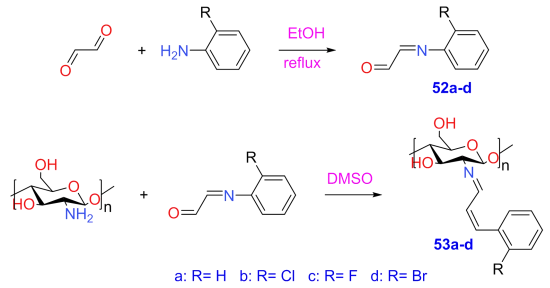
Scheme 37: Second series of salicylaldehyde diazinyl Schiff bases.

Quinazolinone Schiff bases **48-51a-i** were employed to generate a novel sequence of conjugated amino acids. Compounds **48e-i, 49e-i, 50e-i,** and **51e-i** present an excellent antibacterial activity, exceeding the standard drug Streptomycin in terms of antimicrobial activity. Compounds **48h, 49g-i, 50e-i, 51b,** and **51d-i** manifest also an excellent antifungal activity, exceeding the standard antifungal medicine Bavistin (Scheme 38) [115].



Scheme 38: Synthetic route to Quinazolinone Schiff bases.

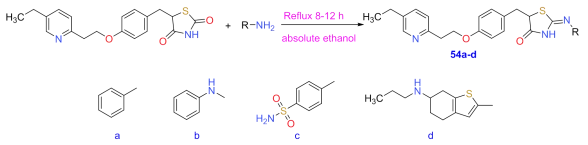
The antifungal activity of the Schiff bases **53a-d** derived from chitosan with halogenated aromatic rings was synthesized and evaluated *in vitro* against three common plant pathogens *Botrytis cinerea*, *Fusarium oxysporum* f. sp., *cucumerium,* and *Fusarium oxysporum* f. sp. *niveum*. The results revealed that, particularly at 1.0 mg/mL, the tested compounds exhibited stronger antifungal activity than chitosan (Scheme 39) [116].



Scheme 39: Synthesis of Schiff bases derived from chitosan with halogenated aromatic rings.

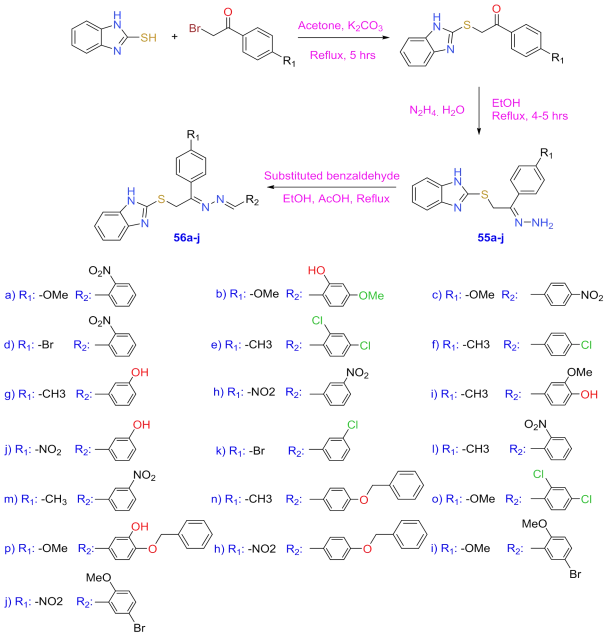
3.3 Antidiabetic activity

Following the scheme 40, a new set of pioglitazone Schiff base **54a-d** were synthesized**.** *In vitro* α-amylase inhibitory assay, compound **54c** exhibited potent effects as compared to other groups, that is, 93% inhibition, while pioglitazone showed 81% inhibition (Scheme 40) [117].



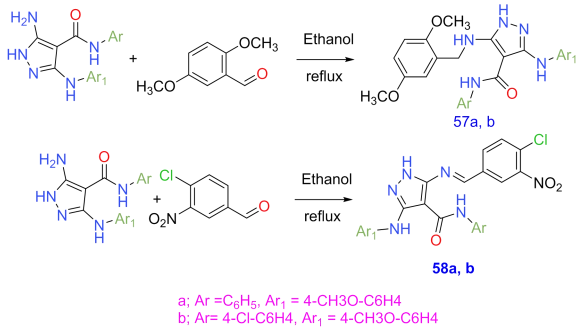
Scheme 40: Synthesis of pioglitazone Schiff bases **54a-d**.

Moreover, nineteen analogues of bis-Schiff bases **55a-j** and **56a-j** bearing benzimidazole were synthesized following the scheme 41. All analogues of the series displayed inhibition ranging between IC_{50} 2.20 ± 0.1 to 88.60 ± 1.70 µM when compared with the standard drug acarbose (IC_{50} = 38.45 ± 0.80 μM). Among the series, analogues **56a-m** and **56o** having IC_{50} values between 2.20 ± 0.1 to 36.80 ± 0.80 μM showed many folds greater α-glucosidase inhibitory potentials than standard drug acarbose [118].



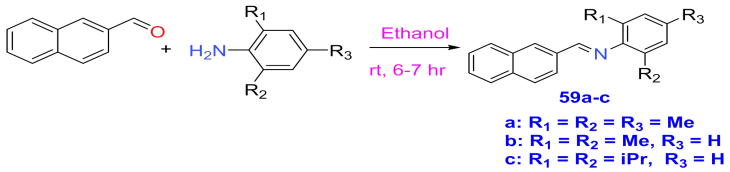
Scheme 41: Synthesis of benzimidazole bearing bis-Schiff bases

In addition, Schiff bases containing pyrazole scaffolds **57a, b**, and **58a, b** were easily produced via the reaction of 5-amino-*1H*-pyrazole-4-carboxamide and 2,5-dimethoxybenzaldehyde and 4-chloro-3-nitrobenzaldehyde respectively. Compound **57b** displayed considerable antioxidant, anti-diabetic (α-amylase% inhibition), and anti-Alzheimer's (ACE%) action, whereas compound **58a** manifest significant anti-arthritic activity (Scheme 42) [119].



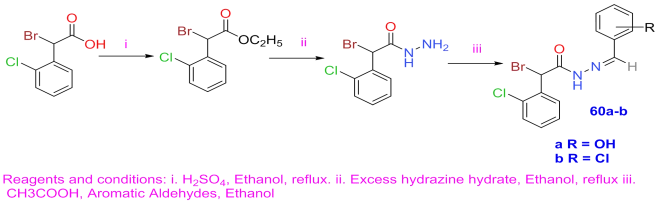
Scheme 42: Synthesis pathway of Schiff bases with pyrazole scaffolds **57a, b** and **58a, b.**

Three Schiff bases were synthesized by the condensation reaction of 2-napthaldehyde and aromatic amines**.** Compound **59a** showed very promising antidiabetic activities with IC_{50} values of 58.85 µg/mL and 57.60 µg/mL while the reference drug (Acarbose) had 405.84 µg/mL and 35.69 µg/mL for α-amylase and α-glucosidase respectively. The compounds exhibited good to excellent antioxidant properties with **59a** as well as **59c** having IC_{50} values of 70.91 and 91.21 µg/mL respectively for NO scavenging activities assay, which comparatively outshined acarbose (reference drug) with IC_{50} value of 109.95 µg/mL (Scheme 43) [120].



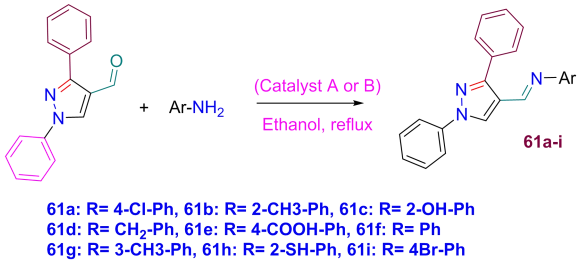
Scheme 43: Preparation of Schiff bases, **59a-c**.

Schiff base derived from 2-bromo-2-(2-chlorophenyl) acetic acid were synthesized**.** Compounds **60a** and **60b** showed strong α-glucosidase inhibitory activity, with IC_{50} values of 0.70 ± 0.11 and 10.29 ± 0.30 µM, respectively. These compounds were more effective than the standard drug, acarbose, which had an IC_{50} value of 873.34 ± 1.67 µM (Scheme 44) [121].



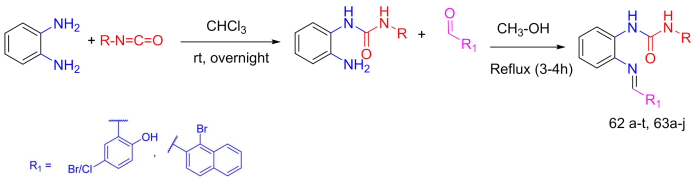
Scheme 44: Synthesis of Schiff bases of 2-bromo-2-(2-chlorophenyl) aceto-hydrazide **60a** and **60b**.

Recently, a series of pyrazole-Schiff base derivatives, were synthesized by reacting suitable arylamines with pyrazole aldehyde (Scheme 45). The most promising in vitro antidiabetic results were also observed with analogs **61c** (α-amylase IC_{50} = 19.57±0.07 μM, α-glucosidase IC_{50} = 17.13±0.28 μM) and **61h** (IC_{50} (α-amylase) =22.50±0.06 μM, IC_{50} (α-glucosidase) = 20.75±0.17 μM). Both compounds **61c** and **61h** exhibited relative activity comparable to the standard drug references acarbose (IC_{50} (α-amylase) =16.28±0.24 μM, IC_{50} (α-glucosidase) =13.19±0.26 μM). The higher antioxidant and antidiabetic activities of **61c** and **61h** compared to other compounds might be explained by the presence of a free phenolic hydroxy group in **61c** and a benzothiazole motif in **61h** [122].



Scheme 45: Synthesis of series pyrazole-Schiff base derivatives.

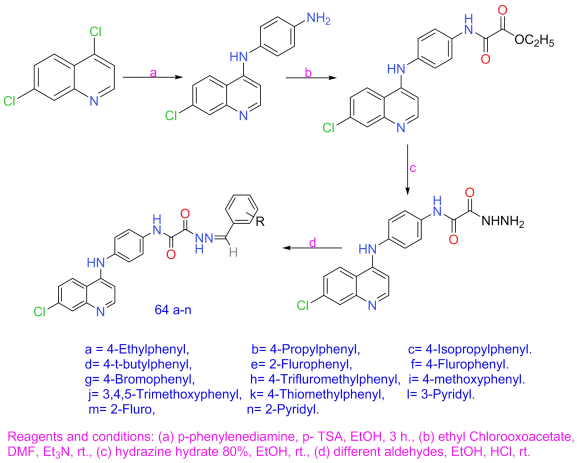
A series of Schiff base derivatives 1,3-diphenylurea was synthesized through the condensation of *O*-phenylenediamine, a variety of isocyanate and a suitable aldehyde. The anti-diabetic effect of thirty Schiff base derivatives was assessed by focusing on α-glucosidase. The compounds showed a strong ability to block α-glucosidase, with potencies ranging from 2.49 to 37.16 µM (Scheme 46) [123].



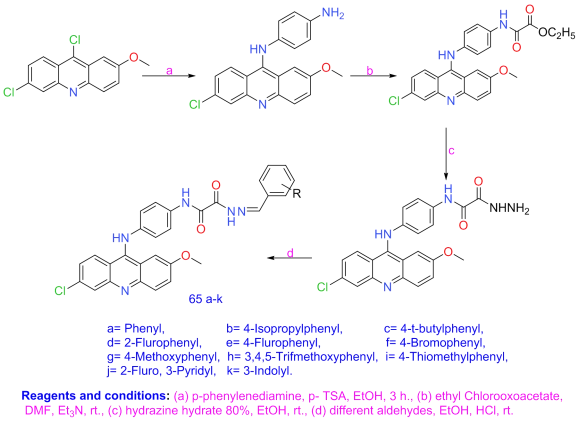
Scheme 46: Synthesis of series of Schiff base derivatives 1,3-diphenylurea.

3.4 Antimalarial activity

Two sets of new Schiff base hydrazones, 4-aminoquinolinyl and 9-anilinoacridinyl, have been elaborated and illustrated in schemes 47 and 48. The antimalarial activity of each drug was assessed in vitro against the chloroquine-resistant K1 strain of Plasmodium falciparum and the chloroquine-sensitive strain 3D7. The IC_{50} values for compounds **64d**, **64g**, and **64h** ranged from 19.69 to 25.38 µM, indicating excellent activity against the 3D7 strain. Additionally, compounds **64c, 64d, 64h, 64k, 64b,** and **64c** shown outstanding activity against the K1 strain (21.64-54.26 µM) [124].

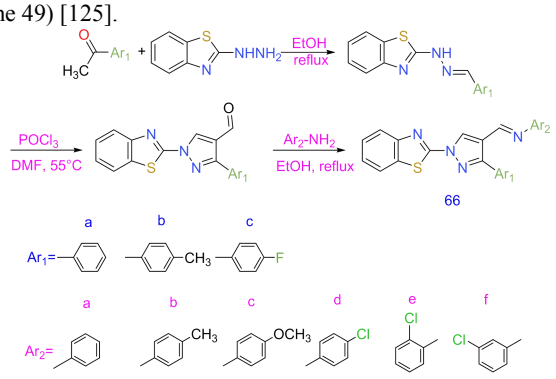


Scheme 47: Synthetic strategy of 4-aminoquinolinyl and 9-anilinoacridinyl Schiff base hydrazones



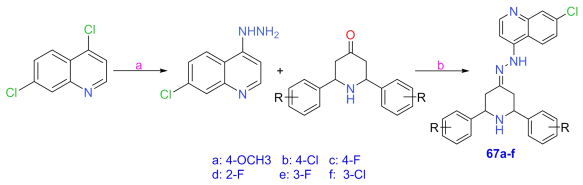
Scheme 48: Second series of 4-aminoquinolinyl and 9-anilinoacridinyl Schiff base hydrazones.

A variety of hybrid benzothiazole-pyrazole-Schiff bases with an extensive variety of substitution have been developed and investigated *in vitro* for its capacity to inhibit the asexual blood stages of the *Plasmodium falciparum* parasite responsible for malaria in humans. Regarding the compounds, it is emerged that compound **66bf** (methyl group at para position and 2-Chloro) and **66bd** (methyl and chlorine group at para position), with EC_{50} values of 1.95 µg/ml and 1.98 µg/ml, respectively, were promising molecules (Scheme 49) [125].



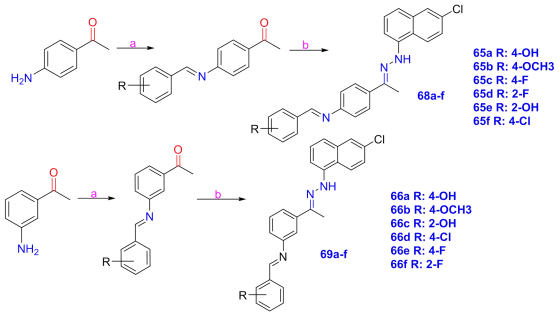
Scheme 49: Protocol synthesis of variety hybrid benzothiazole-pyrazole-Schiff bases.

Following the scheme 50, the synthesis of a series of new Schiff bases quinolinyl-hydrazones **67a-f** was accomplished by reacting 2,6-diphenylpiperidin-4-one with 7-chloro-4-hydrazinoquinoline. Additionally, novel quinolinyl-hydrazone Schiff bases **68a-f** and **69a-f** were generated by heating 7-chloro-4-hydrazinoquinoline with benzylideneaminophenylethan-1-one in ethanol under reflux (Scheme 51). The *in vitro* antimalarial properties of these synthesized hydrazones were evaluated in relation to *P. falciparum* strains that were resistant to chloroquine (K1) and susceptible to it (T96). One of the produced compounds, **66a**, displayed substantial antimalarial activity against both strains of *P. falciparum*, with IC_{50} values of 103.4 µg/mL and 18.76 µg/mL, respectively [126].



Reagents and conditions: (a) $N_2H_4.H_2O$ (80%), EtOH, 80°C, 2 h; (b) EtOH, reflux, CH_3COOH (2 drops), 24-36 h.

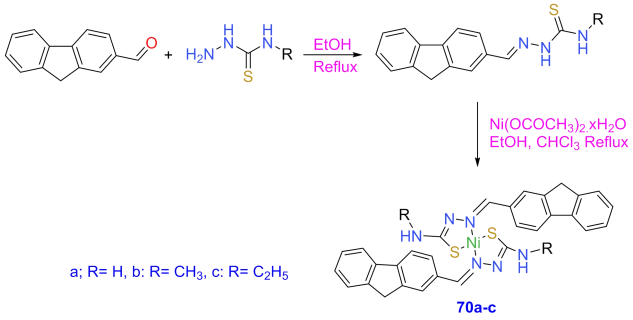
Scheme 50: Novel quinolinyl-hydrazones **67a-f** achieved via the reaction of 7-chloro-4-hydrazino-quinoline with 2,6-diphenylpiperidin-4-one.



Reagents and conditions: (a) EtOH, aldehydes, r.t, 2-11 h; (b) 7-chloro-4-hydrazinoquinoline, ethanol, reflux,CH3COOH (2drops), 6-8 h.

Scheme 51: Synthetic route of novel quinolinyl-hydrazone Schiff bases **68a-f** and **69a-f**.

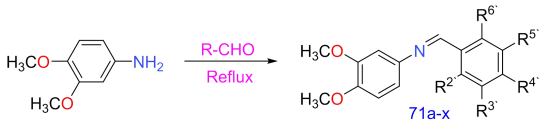
The analog of 9H-fluorene Schiff base is produced when 9H-fluorene-2-carbaldehyde reacts with substituted thiosemicarbazide in ethanol under reflux. Two nickel complexes, **70b** and **70c**, exhibited moderate antimalarial activity in vitro, with respective IC_{50} values of 23.79 and 2.29 µM. Complex **70c** revealed also the strongest antimalarial activity and produced the greatest results (Scheme 52) [127].



Scheme 52: Synthetic route of 9H-fluorene Schiff base.

3.5 Antioxidant activity

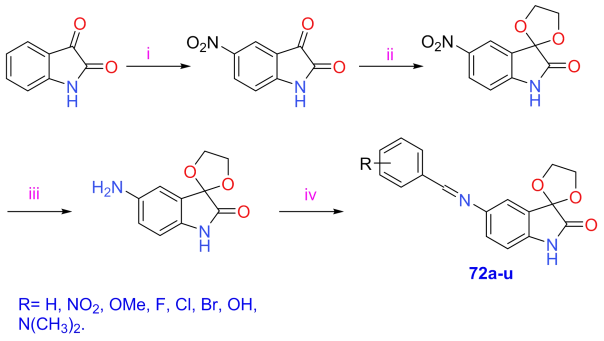
A series of Schiff Bases containing 3,4-Dimethoxybenzenamine was produced. Compounds **71a-d** and **71f** exhibited more activity than the standard *n*-propyl gallate, while all the compounds had high DPPH scavenging activity within the range of 10.12 to 84.34 µM. Compounds **71a-c** demonstrated higher activity in the superoxide anion radical test compared to the standard (Scheme 53) [128].



a: R3` = R4` = R5` = OH.
b: R2` = R4` = R6` = OH.
c: R2` = R5` = OH.
d: R3` = R4` = OH.
e: R2` = R4` = OH.
f: R2` = R3` = OH
g: R3` = R5` = OH.
h: R3` = $OCH_3$, R4` = OH.
i: R4` = OH.
j: R2` = OH.
k: R3` = OH, R4` = OCH3.
l: R3` = Br, R4` = OH.
m: R2` = OH, R5` = OCH3.
n: R2` = OH, R4` = OCH3.
o: R3` = OH.
p: R3` = OCH3, R5` = OCH3.
q: R4` = OCH3.
r: R3` = OCH3.
s: R2` = Cl.
t: R3` = Br, R4` = F.
u: R2` = NO2, R4` = COOCH3
v: R4` = CH3.
w: R4` = F.
x: R4` = NO2.
y: 4-Pyridine.

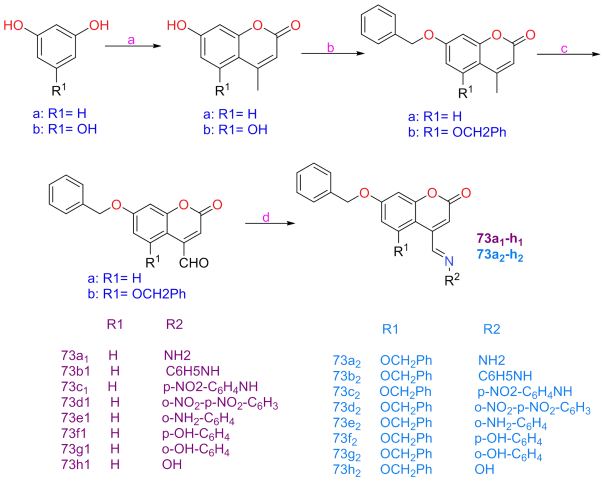
Scheme 53: Synthesis of 3,4-dimethoxybenzenamine Schiff bases.

A new set of Schiff bases based spiro-isatin **72a-u** was investigated for antioxidant activity by scavenging DPPH, CUPRAC, and ABTS cation radicals (Scheme 54). The results indicates that the majority of synthetic molecule exhibited higher antioxidant efficacy in each test. Compound **72c** displayed IC_{50} = 4.49 µM for DPPH; IC_{50} = 0.39 µM for $ABTS^+$ and IC_{50} = 0.42 µM for CUPRAC. The results revealed also significantly higher ability to scavenge radicals in DPPH, ABTS, and CUPRAC than the standard quercetin (IC_{50} = 8.69 µM for DPPH; IC_{50} = 15.49 µM for $ABTS^+$ and IC_{50} = 18.47µM for CUPRAC). Additionally, the compounds **72c** and **72d**, which possessed two hydroxyl groups, indicated the highest antioxidant activity for three mentioned tests (Scheme 54) [129].



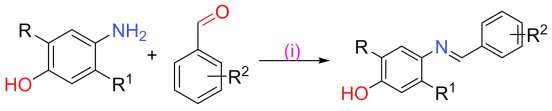
Scheme 54: Novel set Schiff bases-based spiro-isatin were studied for antioxidant activity.

In order to develop a broad structural core related two series of compounds **$73a_1$-h_1 and $73a_2$-h_2**, Zhang et *al* designed and synthesized many derivatives of 7-benzyloxy-coumarins with distinct salen groups that are formed at position 4 (Scheme 55). The DPPH assay revealed that compounds in first series **$73b_1$, $73d_1$, $73f_1$, $73f_2$, $73g_1$**, and **$73g_2$** present superior radical scavenging activities compared to BHT. Furthermore, compounds **$73a_1$, $73b_1$, $73c_1$, $73c_2$, $73d_1$, $73e_1$, $73e_2$, $73f_2$, $73g_1$, $73g_2$,** and **$73h_1$** manifest superior $ABTS^+$ radical scavenging activities compared to BHT. In addition, compounds **$73a_2$** and **$73g_2$** demonstrated stronger superoxide anion radical scavenging activities than BHA. Moreover, compound **$73e_1$** displayed more potent inhibition of hydroxyl radical than ascorbic acid. The aforementioned results indicate that it is possible to rationally construct 4-Schiff base-7-benzyloxy-coumarin derivatives as new antioxidants [130].



Scheme 55: design and synthesis of 7-benzyloxy-coumarins Schiff bases

A total of sixty-three Schiff bases were synthesized from various substituted amino-phenols. All of the compounds had greater activity than starting compounds. Compound **75r** was determined to have the greatest efficacy among the eight compounds **(74k, 74l, 74r, 75k, 75l, 75q, 76k, 76l, and 76r)**, with an IC_{50} of 7.55 µg/mL. The other compounds exceeded the reference drug (ascorbic acid) in terms of activity as well. Additionally, the ABTS technique was used to examine 24 of the most active compounds; the results revealed 60–90% inhibition at a concentration of 5 µg/mL. (Scheme 56) [131].

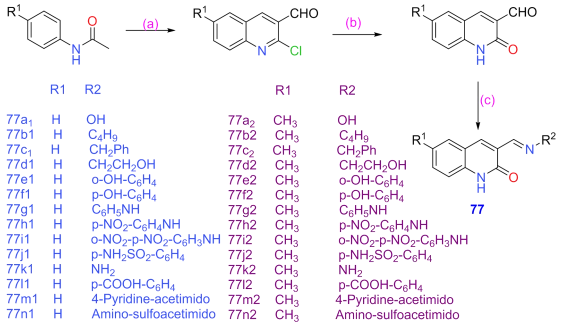


a, R2= H
b, R2= 4-Me
c, R2= 4-Et
d, R2= 4-n-Pr
e, R2= 4-i-Pr
f, R2= 4-t-Bu
g, R2= 4-F
h, R2= 4-Cl
i, R2= 4-Br
j, R2= 4-NO2
k, R2= 2-OH
l, R2= 4-OH
m, R2= 4-OMe
n, R2= 3,4-OMe
o, R2= 3,5-OMe
p, R2= 3,4,5-OMe
q, R2= 3,5-Br, 2-OH
r, R2= 3,5-Br, 4-OH
s, R2= 2,3-Methylenedioxy
t, R2= 2-Pyridyl
u, R2= 3-Pyridyl

Reagents and conditions: (i) dry MeOH, 30-35 °C, N2 atm, 3-4 h.

Scheme 56: Schiff bases from aminophenol.

A series of 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives were synthesized according the scheme 57. Among the all of targeted compounds, compounds **77b$_2$**, **77e$_1$**, **77e$_2$** and **77g$_2$** presented better radical scavenging activities than BHT in DPPH assay. The results indicated that compounds **77a$_1$**, **77e$_1$**, **77e$_2$**, **77f$_1$**, **77f$_2$**, **77g$_1$**, **77g$_2$**, **77h$_1$**, **77h$_2$**, **77k$_1$**, **77k$_2$**, **77n$_1$** and **77n$_2$** exhibited better ABTS$^+$ radical scavenging activities than BHT. Moreover, compounds **77b$_1$**, **77e$_1$**, **77f$_2$**, **77j$_1$**, **77k$_1$**, **77k$_2$**, **77m$_1$**, **77m$_2$**, and **77n$_2$** displayed stronger superoxide anion radical scavenging activities than BHT. Almost all the compounds, except **77f$_1$**, **77f$_2$**, **77l$_1$** and **77l$_2$** displayed more potent inhibition of hydroxyl radical than both of BHA and BHT [132].

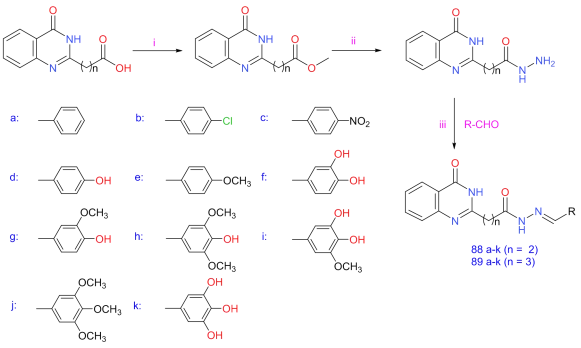


	R1	R2		R1	R2
77a$_1$	H	OH	77a$_2$	CH_3	OH
77b1	H	C_4H_9	77b2	CH_3	C_4H_9
77c$_1$	H	CH_2Ph	77c$_2$	CH_3	CH_2Ph
77d1	H	CH_2CH_2OH	77d2	CH_3	CH_2CH_2OH
77e1	H	o-OH-C_6H_4	77e2	CH_3	o-OH-C_6H_4
77f1	H	p-OH-C_6H_4	77f2	CH_3	p-OH-C_6H_4
77g1	H	C_6H_5NH	77g2	CH_3	C_6H_5NH
77h1	H	p-NO_2-C_6H_4NH	77h2	CH_3	p-NO_2-C_6H_4NH
77i1	H	o-NO_2-p-NO_2-C_6H_3NH	77i2	CH_3	o-NO_2-p-NO_2-C_6H_3NH
77j1	H	p-NH_2SO_2-C_6H_4	77j2	CH_3	p-NH_2SO_2-C_6H_4
77k1	H	NH_2	77k2	CH_3	NH_2
77l1	H	p-COOH-C_6H_4	77l2	CH_3	p-COOH-C_6H_4
77m1	H	4-Pyridine-acetimido	77m2	CH_3	4-Pyridine-acetimido
77n1	H	Amino-sulfoacetimido	77n2	CH_3	Amino-sulfoacetimido

Reagents and conditions: (a) DMF/$POCl_3$, 90 °C; 70% acetic acid aqueous solution, 95 °C; (c) R_2-NH_2, ethanol, 80 °C.

Scheme 57: Synthetic route of 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives.

A series of quinazolinone Schiff bases bearing substituted phenyl **78a-k** and **79a-k** were achieved following the scheme 58. Synthesized compounds **78f**, **79f**, **78i**, **79i**, **78j**, **78k** and **79k** containing electron donating OH and OCH_3 groups in benzene ring exhibited stronger radical scavenging activities than BHT, BHA, AA and GA in all the three assays performed [133].



Reagents and conditions: (i) TMS-Cl, MeOH, rt, 4 h, (ii) NH_2NH_2.H2O, EtOH, reflux, 16 h, (iii) EtOH, CH3COOH, reflux, 7-8 h.

Scheme 58: Synthesis of compounds **78a-k** and **79a-k**.

Conclusion

Schiff base pharmacophore diverse products produced from different substitutions and substructure entanglements through various synthesis methods have yielded molecules with a variety of pharmacological properties. A wide range of potential chemicals have been described, including antimicrobials, antivirals, anti-parasites, anti-cancer, anti-inflammatory,

antioxidants, antihypertensives, and anti-diabetics. Different structures derived from the Schiff bases nucleus have demonstrated the promise for future development into active molecules for drug discovery. Thus, Schiff base nucleus has the potential to speed the development of therapeutic candidates.

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