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Review Article

Ease to Challenges in Achieving Successful Synthesized Schiff Base, Chirality, and Application as Antibacterial Agent

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This study reports how to overcome the challenges experienced in achieving successful synthesized Schiff base via types of Schiff base (chiral and achiral), synthesis, nature of products, and its antibacterial applications. Schiff base is a versatile ligand which is useful in asymmetric reactions to prepare chiral catalysts. It is also used in symmetric reactions to prepare achiral compounds. In line with the achiral compounds, conventional (room temperature and refluxing) and microwave irradiation methods are the two main types of methods to synthesize achiral Schiff base as reported in this review. Among various experimental approaches, this study supports the green chemistry microwave approach to synthesize Schiff base because of its benefits environmental sustainability. Problems relating to the nature of products formed from the synthesized Schiff bases were examined and resolved. Herein, the products could either be solid (crystals, powder, and precipitate), oily, or viscous (sticky) products. Some familiar characterization techniques used to identify and confirm the successful syntheses of Schiff bases, such as solubility test, melting point (MP), Fourier transform infrared (FTIR), ultraviolet-visible (UV-Vis), and nuclear magnetic resonance (NMR, ^{1}H NMR, and ^{13}C NMR), were discussed. In addition, the antibacterial studies on Schiff base and corresponding metal complexes confirmed their biological relevance to the human.

1. Introduction

1.1. Schiff Base Definition, General Synthesis, and Versatile Uses. In 1864, Hugo Schiff discovered Schiff base by condensation reaction of alkanal or alkanone and primary in azeotropic distillation, which was named after him [1–8]. Schiff bases are characterized with azomethine (imine) groups [2, 4, 5, 7, 9, 10]. Sangle regarded Schiff base as a subclass of imines [6], while Ceramella et al. posited the imine or azomethine group (>C=N–) as being essential for the Schiff base biological activities [9]. The azomethine group (C=N) makes Schiff bases active and functional [11, 12].

Based on successful synthesis, Schiff base is referred to as "privileged base," because of the ease of its preparation from the condensation of amines and aldehydes [13]. Schiff bases are versatile compounds synthesized from the condensation reaction of a primary aliphatic or aromatic amine group and a carbonyl (alkanal (aldehyde) or alkanone (ketone) group under certain conditions [8, 9, 11, 14–16].

Two groups of researchers reported that aromatic alkanals with efficient conjugated systems were more stable than aliphatic alkanals because aliphatic alkanals are unstable and polymerize freely [7, 8]. In support of both group of researchers, Sadi et al. stated that aromatic alkanals made syntheses of Schiff bases easy [7, 8, 17]. Sadi et al. further compared both alkanals and alkanones in condensation reaction and stated that alkanals' reactivities are usually faster than those of alkanones [17].

The general structural formula for Schiff bases is $R^1R^2C{=}NR^3$ where R^1R^2 and R^3 are either alkyl, aryl, cycloalkyl or heterocyclic group [2, 4, 5]. The general structural formula and general synthesis are shown in Figure 1 and Scheme 1, respectively.

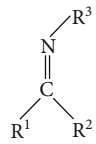
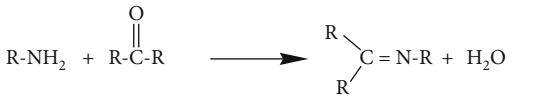


Figure 1: General structural formula for Schiff bases.



Scheme 1: General synthesis of Schiff base.

Among several ligands, this study recognizes the versatility of Schiff base ligand because of its wide spectrum of biological properties, such as analgesic, anticancer, antidepressant, antidiabetic, anti-inflammatory, antiepileptic, antimalarial, antimicrobial (antibacterial, antifungal, and antiviral), antioxidant, antiplatelet, antiproliferative, antitubercular, and herbicidal [4, 5, 9, 11, 14, 17–19]. Schiff bases can also be incorporated with other ligands like dithiocarbamates [20] which make them have diverse and multipurpose applications.

This study is a mini review which reports the ease to challenges of achieving a successful synthesized Schiff base via types of Schiff base synthesis (achirality and chirality), nature of products formed, chirality, chemical characterization of Schiff base products, and the antibacterial activities.

2. Schiff Base Synthesis

Recently, research focused on the Schiff base synthesis, as well as the coordination compounds because of its numerous applications in different Chemistry fields [21]. They further stated that because of Schiff base's versatile applications, there was extraordinary interest to improve effective methods for the synthesis. Various research groups developed different methods to synthesize Schiff bases, but these methods experienced drawbacks, such as long reaction time and small yields [21]. In line with this, different researchers considered ways to reduce the reaction time and obtained very high yields for Schiff bases syntheses [21]. This section reports four chiral Schiff base syntheses and their reactions.

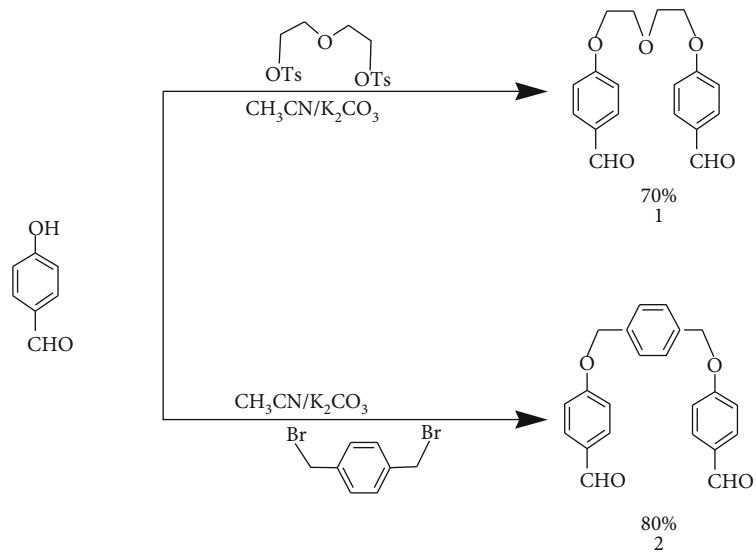
2.1. Synthesis of Chiral Schiff Base and Its Usefulness in Asymmetric Reactions. Chiral Schiff base is useful to produce catalysts and chiral drugs. The chiral nature of Schiff base contributes to their being termed "privileged ligands" or "chiral ligands." The chirality helps in asymmetric synthesis and catalysis [8, 16]. Chiral Schiff base applications are very relevant in catalysis, mainly in asymmetric cyclopropanation [22], the first asymmetric Henry reaction (nitro aldol) to be catalyzed by chiral copper Schiff base complexes [22]. Subsequently, interests in this area expanded, and diverse chiral catalysts were developed, such as those built upon BINOL by Shibasaki, bis (oxazoline) by Evans and Jørgensen, cinchoma alkaloids by Corey, dinuclear zinc complexes by Trost, Salen complexes by Yamada, and amino alcohols by Palomo [22]. This section further observes how five groups of researchers synthesized their chiral Schiff bases and the conclusions they arrived at.

2.1.1. Henry or Nitro Aldol Reaction. Among the numerous carbon-carbon (C-C) bond forming reactions, the Henry or nitro aldol reaction is one of the conventionally called reactions in organic synthesis [22]. Since its finding in 1895, the nucleophile coupling made from a nitroalkane with a carbonyl electrophile has been an extensively used transformation [22]. The subsequent reaction product was a β-nitroalcohol, which is a multipurpose intermediary in synthetic organic chemistry. Çolak et al.'s experiment used Zhou and Fang's experimentation as basis for their experiments, with modifications [22]. They and Gan et al. supported Zhou and Feng-described reaction conditions for their synthesized chiral Schiff base-copper-catalyzed Henry reaction conducted firstly at room temperature in ethanol using 10 mol % catalyst and triflate as the metal ion source for 40 h [22, 23]. The reaction conditions were used for all entries [22, 23].

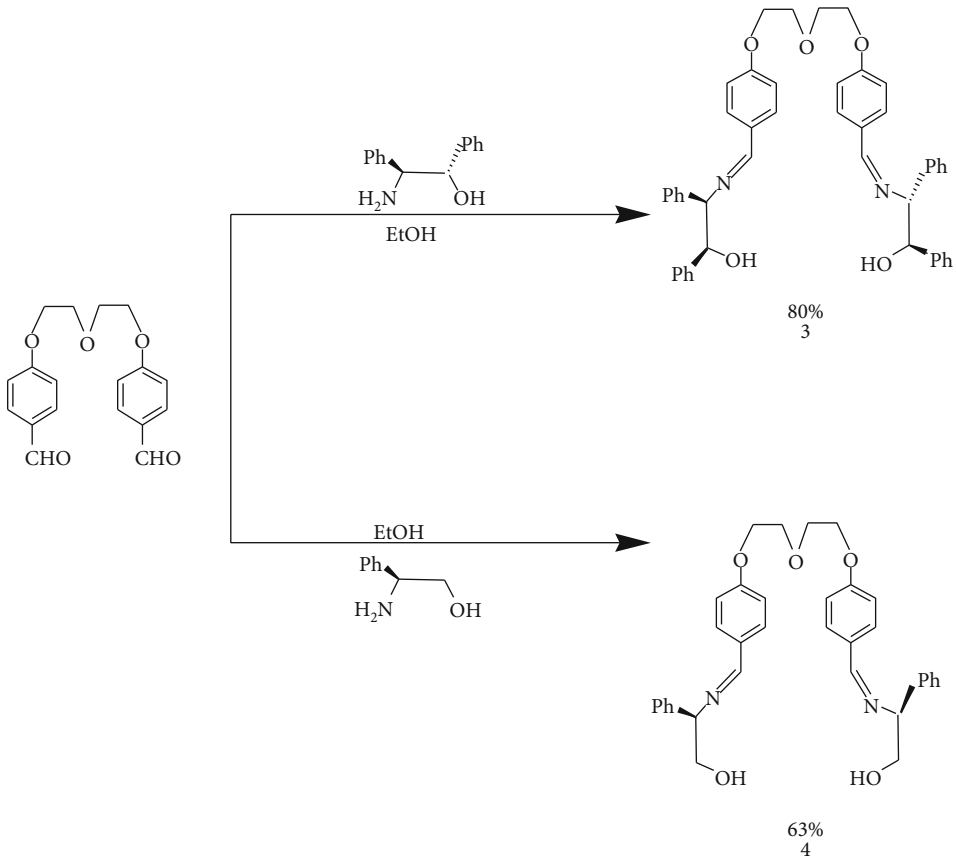
With the aim to form a distinct chiral Schiff base, *p*-hydroxybenzaldehyde was used to react with diethyleneglycolditosylate and 1,4-bis(bromomethyl) benzene in acetonitrile/potassium trioxocarbonate(IV) (CH_3CN/K_2CO_3) (Scheme 2) to yield two chiral amino alcohols [(1S, 2R)-2-amino-1, 2-diphenylethanol and (R)-(-)-phenylglycinol]. The two chiral amino alcohols ((1S, 2R)-2-amino-1, 2-diphenylethanol and (R)-(-)-phenylglycinol) were applied as chiral sources to synthesize the desired chiral Schiff base ligand (Schemes 3 and 4). The dialdehyde reaction with the two chiral amino alcohols in ethanol (EtOH) generated chiral Schiff base compounds. The chiral Schiff base was used to catalyze the enantioselective Henry (nitro aldol) reaction between nitromethane and *p*-nitrobenzaldehyde in the presence of $Cu(OTf)_2$ and $Zn(OTf)_2$ (Scheme 5, Table 1).

Çolak et al.'s conclusions from their experimental results were (i) the Zn(II) triflate used for the reaction gave higher yield than copper(II) triflate, although there were reduced enantiomeric excesses (e.e), and (ii) copper(II) triflate was the best promoter as evident with ligands 3 and 5 being superior because of higher enantiomeric excesses when compared with other tested ligands where the superiority might be due to steric hindrance of the two phenyl groups present on the two ligands and configuration of adducts (R) as evident in Table 1 [22]. In summary, $Zn(OTf)_2$ improved the reaction yield, while the $Cu(OTf)_2$ improved the excess. The highest enantioselectivities were observed with ligand 3 (44% e.e) and ligand 5 (47% e.e). However, recently, the extensive applicability of this transformation was reduced due to the unobtainability of appropriate catalysts for assigning a certain stereochemistry to the newly made stereogenic centers [22].

2.1.2. Jaworska et al.'s Reaction. In the case of Jaworska et al., they synthesized nine bidentate Schiff bases from pure enantiomerically (S)-α-methylbenzylamine as chiral ligands in the electronically controlled asymmetric addition of

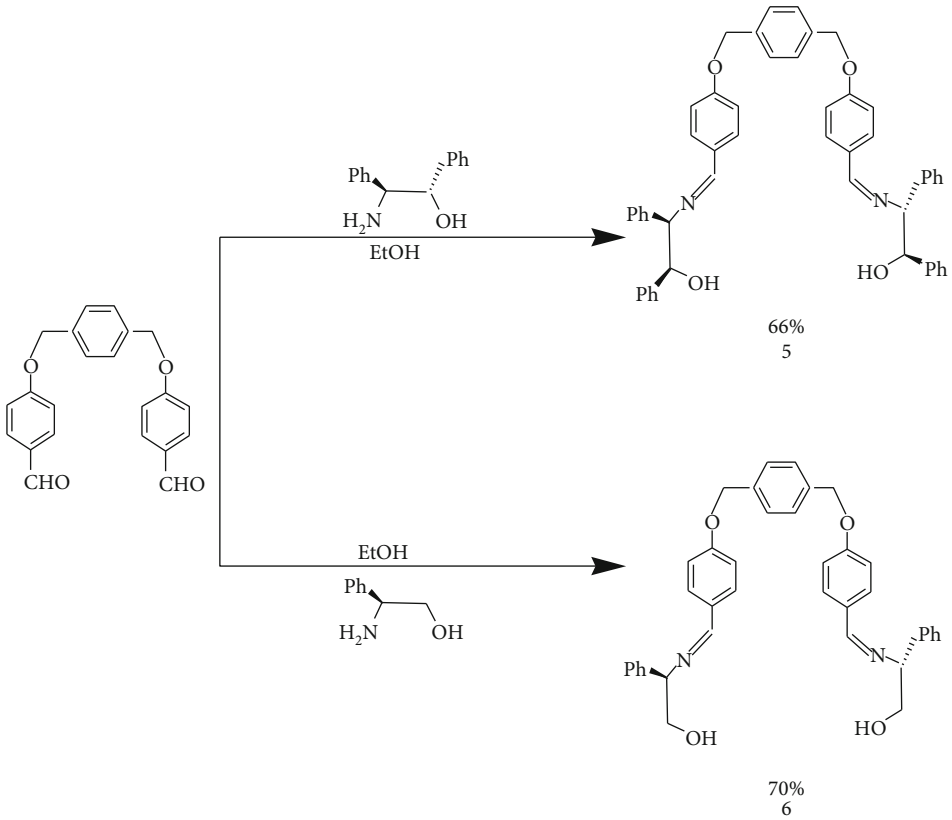


Scheme 2: The reaction of *p*-hydroxybenzaldehyde with diethyleneglycolditosylate and 1, 4- bis(bromomethyl) benzene in acetonitrile/potassium trioxocarbonate(IV) (CH_3CN/K_2CO_3) [22].

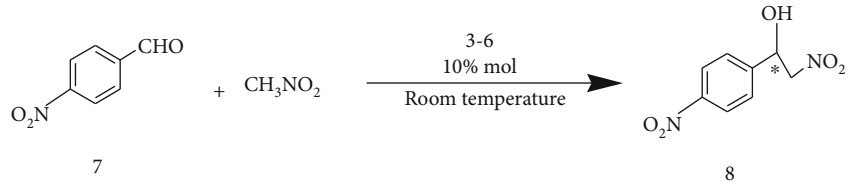


Scheme 3: Synthesis of chiral amino alcohols [(1S, 2R)-2-amino-1, 2-diphenylethanol [22].

diethylzinc to aldehyde as shown in Scheme 6 [24]. They achieved an enantiomer excess (e.e) of 8 to 94% based on the substrate, and the finest was observed for (S, e)-2-(1-(1-phenylethylimino)-ethyl) phenol [24]. Additionally, chiral Schiff bases with substituent were reported to have strong influence on a catalyst's effectiveness, enantioselectivities, and reactivities [14, 25]. The increased enantioselectivinsty was linked to the substituent-induced electronic effects in the substrates as shown in Table 2 [24]. The use of *o*-, *m*-, *p*-methoxy, *o*-chloro-, *o*-bromobenzaldehyde, and *p*-dimethylaminobenzaldehyde, cyclohexanecarbaldehyde (Table 2; entries 1-5, 9, 10) gave lower enantiomeric excesses. On the other side, the



Scheme 4: Synthesis of chiral amino alcohols [(R)-(-)-phenylglycinol] [22].

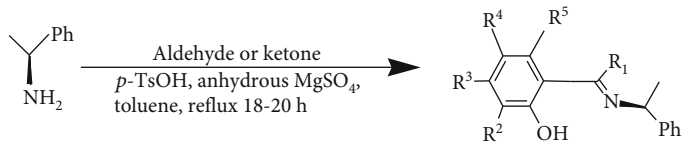


Scheme 5: Asymmetric Henry (nitro aldol) reaction between *p*-nitrobenzaldehyde and nitromethane [22].

Table 1: Asymmetric nitro aldol (Henry) reaction between nitromethane and *p*-nitrobenzaldehyde catalyzed by chiral Schiff base [22].

Entry	Cat.	$M(OTf)_2$	Time (h)	Yield[b] (%)	e.e[c] (%)	Config.[d]
1	3	$Cu(OTf)_2$	40	56	44	(R)
2	3	$Zn(OTf)_2$	40	62	8	(S)
3	4	$Cu(OTf)_2$	40	45	30	(S)
4	4	$Zn(OTf)_2$	40	57	18	(S)
5	5	$Cu(OTf)_2$	40	56	47	(R)
6	5	$Zn(OTf)_2$	40	63	11	(S)
7	6	$Cu(OTf)_2$	40	54	27	(S)
8	6	$Zn(OTf)_2$	40	64	17	(S)

[a]All reactions were performed on a 0.2 mmol scale of 4-nitrobenzaldehyde in the mixture of 0.8 ml of ethanol and 0.6 ml of nitromethane. [b]After purification with thin layer chromatography (TLC), ethyl acetate/petroleum ether (30 : 70) R_f: 0.36, while literature gave 0.34. [c]Determined by chiral high-performance liquid chromatography (HPLC) using an OD column. [d]Determined by comparing HPLC elution order of the enantiomers with a genuine sample according to the literature and that by HP chiral detectors [22]. OTf is the triflate group, identified by the systematic name trifluoromethanesulfonate.



1:$R^1 = CH_3$, $R^2 = R^3 = R^4 = R^5 = H$;
2:$R^1 = R^2 = R^3 = R^4 = R^5 = H$;
3:$R^1 = R^3 = R^4 = R^5 = H$, $R^2 = OH$;
4:$R^1 = R^3 = R^5 = H$, $R^2 = R^4 =$ *tert*-butyl;
5:$R^1 = R^3 = R^4 = H$, $R^2 = Me$;
6:$R^1 = R^3 = R^5 = H$, $R^2 =$ t.Bu, $R^4 = Me$;
7:$R^1 = R^3 = R^5 = R^4 = H$, $R^2 =$ *isoproyl*;
8:$R^1 = R^2 = R^3 = H$, $R^4 = R^5 = C_6H_4$ (naphthalene);
9:$R^1 = R^2 = R^3 = R^5 = H$, $R^4 = Br$

Scheme 6: Jaworska et al.'s synthesis of nine chiral Schiff bases [24].

Table 2: Schiff base 1 catalytic reaction of the asymmetric addition of diethylzinc to aldehydes [24].

Entry	Ligand	Aldehyde	Time (h)	Yield (%)	e.e (%)[b]/config.[c]
1	1	*o*-Methoxybenzaldehyde	72	38	16 (R)
2	1	*m*-Methoxybenzaldehyde	72	78	23 (R)
3	1	*p*-Methoxybenzaldehyde	72	61	39 (R)
4	1	*o*-Chlorobenzaldehyde	72	80	24 (R)
5	1	*o*-Bromobenzaldehyde	72	52	15 (R)
6	1	*m*-Chlorobenzaldehyde	72	92	94 (S)
7	1	*p*-Chlorobenzaldehyde	72	75	53 (S)
8	1	*p*-Bromobenzaldehyde	72	90	96 (S)
9	1	*p*-Dimethylaminobenzaldehyde	72	89	—
10	1	Cyclohexanecarboaldehyde	72	94	30 (S)

use of *m*-chloro, *p*-chlorobenzaldehyde, and *p*-bromobenzaldehyde gave very considerable higher enantiomeric excesses of addition products (e.e. = 94%, 53%, and 96%, respectively, in Table 2: entries 6-8). They observed that the presence of electron-withdrawing substituent in the substrates which initiated an increased Lewis acidity on the carbon atom of the carbonyl group was accountable for increased substrate's reactivity [24].

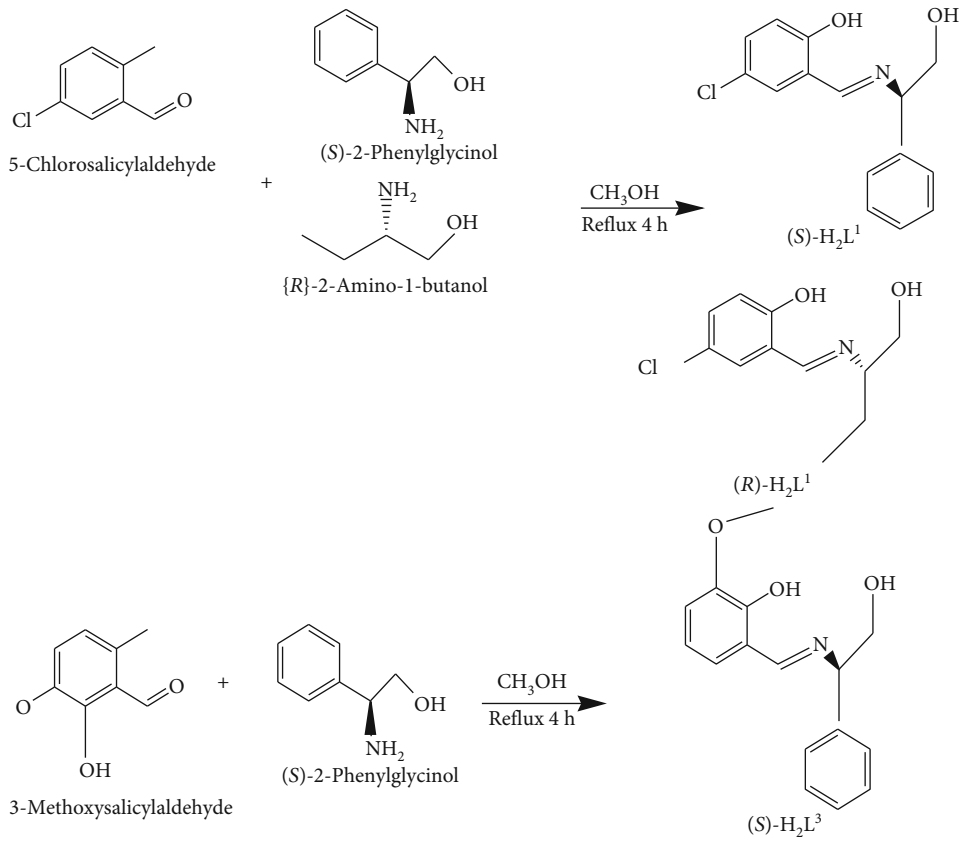
2.1.3. Chang et al.'s Reaction. Four researchers synthesized three Schiff base ligands and coordinated them to coordinate manganese (II) and coper(II) ions (Scheme 7). The three Schiff base ligands are (i) H_2L^1-(*S*)-2-phenyl-2-(2-hydroxy-5-chlorobenzylideneamino)ethane-1-ol], (ii) H_2L^2-(*R*)-2-(2-hydroxy-5-chlorobenzylideneamino)butane-1-ol], and (iii) H_2L^3-(*S*)-2-phenyl-2-(2-hydroxy-3methoxybenzylideneamino)ethane-1-ol]. Contrary to antibacterial studies, Chang et al. applied their metal Schiff base complexes research to anticancer activities. In vitro cytotoxicity screening revealed that the metal complexes had substantial cytotoxic results higher than that of cisplatin, against three cancer cell lines breast (HepG2), cervical carcinoma (MDA-MB231), and lung (A549) cancer cell lines.

2.1.4. Yang's Chiral Schiff Base Synthesis. Yang compared three methods of synthesizing chiral Schiff base [16]. These three methods are microwave irradiation, refluxing, and stirring at room temperature. Microwave irradiation is becoming an increasing recognized heating method of synthesizing Schiff base to replace the other two because it is an affordable, clean, convenient, efficient, and environmental friendly method to support green chemistry [16, 27, 28]. Additionally, it gives very high yield in a very short period. Yang et al. synthesized Schiff base called ((*E*) -4-methyl-N-(3, 4, 5-trimethoxybenzylidene)) benzenamine from 3, 4, 5-trimethoxybenzaldehyde and para-toluidine as shown in Scheme 8 [16]. They concluded that microwave irradiation was the best among the three methods. Justification for their conclusion is evident in the results in Table 3.

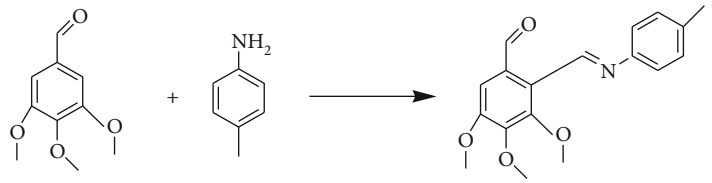
(1) Yang's Characterization Techniques Used and Their Obtained Results. Yang et al. used three characterization techniques.

(1) Melting point: 91-93°C

(2) Infrared (IR; KBr cm^{-1}): 2954, 2934, 2835, 1624, 1558, 1506, 1460, 1330, 1127, and 1003



Scheme 7: Synthesis of three Schiff base ligands (H_2L^1-(*S*)-2-phenyl-2-(2-hydroxy-5-chlorobenzylideneamino)ethane-1-ol], H_2L^2-(*R*)-2-(2-hydroxy-5-chlorobenzylideneamino)butane-1-ol], and H_2L^3-(*S*)-2-phenyl-2-(2-hydroxy-3methoxybenzylideneamino)ethane-1-ol] [26].



Scheme 8: Synthesis of ((*E*) -4-methyl-N-(3, 4, 5-trimethoxybenzylidene) benzenamine [16].

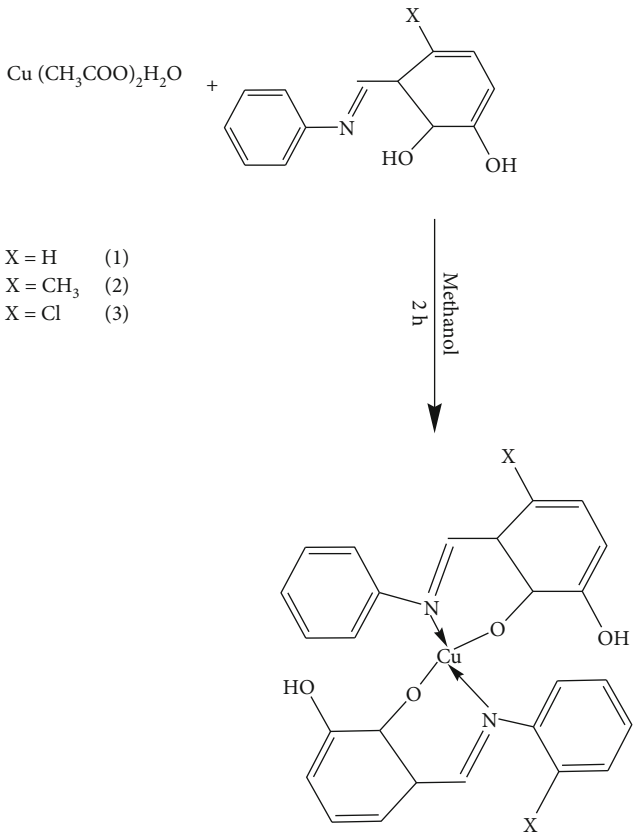
Table 3: Comparison of Yang's three methods used to synthesize Schiff base [16].

Method	Reaction condition	Time	Yield
1	Microwave irradiation	4 min	85%
2	Refluxing	Over 7 h	72%
3	Rt stirring	4 h	75%

rt: room temperature.

(3) Proton nuclear magnetic resonance (^{1}H NMR; 300 MHz, $CoCl_3$): δ 2.35 (s, 3H, -CH_3), 3.90 (S, 9H, -$(OCH_3)_3$), 7.11 (S, 6H, PhH), and 8.31 (S, 1H, N=CH)

2.1.5. Yusuf et al.'s Designed Three Schiff Base Copper(II) Complexes. Yusuf et al. synthesized three ligands (i) HL^1-(*E*)-3-((phenylimino)methyl)benzene1,2-diol, (ii) HL^2-(*E*)-3-((o-tolylimino)methyl)benzene-1,2-diol, and (iii) HL^3-(*E*)-3-(((2-chlorophenyl)imino)methyl)benzene1,2-diol in excellent yields with Yusuf et al.'s (Scheme 9) [29]. Hence, an equimolar ratio of the suitable primary amine and the aldehyde was ground in a poly top vial for 5 min with a glass rod to give yellow solids [30]. Subsequently, Yusuf et al. designed three Schiff base copper(II) complexes via the synthesis and studied the crystal structures, density functional theory (DFT), and binding potency toward cytochrome P450 3A4 for their druglikeness [29]. Results from study confirmed successful copper(II) complexes' synthesis via elemental analysis, Fourier transform infrared (FTIR) with UV-visible spectroscopy, X-ray diffraction (XRD), and DFT method to explore the quantum chemical properties of these complexes. Biological activity result to confirm druglikeness via the in silico showed that the copper Schiff base complexes served as permeability-glycoprotein (P-gp) and various cytochrome P450 substrates. Furthermore, the copper(II) complexes bind to cytochrome P450 3A4 to confirm



Scheme 9: Syntheses of the three copper(II) complexes [29].

their druglikeness abilities. The copper Schiff base complexes as the abridged scheme are shown in Scheme 9.

3. Synthesis of Achiral Schiff Base

Some Schiff bases are achiral and are very useful in different areas of life. Right synthesis is important for the application of the synthesized product in various fields, such as agriculture, biology, biosensors, industry, materials science, medicine, and pharmacy. This section observes how six groups of researchers synthesized their achiral Schiff bases and the conclusions they arrived at.

3.1. Bhagat et al.'s Achiral Schiff Base Synthesis. On a similar note, Bhagat et al. synthesized five salicyaldehyde-based Schiff bases in aqueous media, using both microwave irradiation and refluxing methods [27]. They observed that the thoughtful choice of solvent and reaction conditions led to the excellent yield of the final products in a one-step process. They cited advantages of microwave irradiation method as reduced reaction time, conversion increase, reduced wastes, and very high yields, while for the conventional method, it was a tedious work-up and gave lower yields [27]. The results obtained are shown in Table 4 [27].

3.2. Rao et al.'s Schiff Base Synthesis. Rao et al. agreed with Bhagat et al. that conventional methods used to synthesize Schiff bases required long reaction times and the use of organic solvents [21, 27]. In this approach, both of them used water as solvent in the aqueous solution to promote green synthesis. On the other hand, Rao et al. did not use microwave irradiation, but a benign condensation reaction method, where they stirred 1, 2-diamobenzene with various aromatic aldehydes in water (Scheme 10). In addition, they used aqueous media to prepare eighteen Schiff bases and obtained high yields within short periods as evident in their results shown in Tables 5 and 6 [21]. They used neither acid catalysts nor any aromatic solvent for azeotropic water separation [21]. Condensation reactions took place efficiently in the presence of water, and the products were isolated by filtration [21]. They reported a clean, green, simple, green, high yield, and less reaction duration [21]. The synthesized products of Schiff bases were obtained by simple filtration processes, washed with water, and dried [21].

3.3. Hussain et al. Achiral Schiff Base Synthesis. Hussain et al. synthesis based on conventional method resulted to five Schiff bases with the general formula, $RHC = N - R_1$, where R_1 is sulfamethoxazole (Figure 2) and R is benzaldehyde 4-bromobenzahyde, 2-hydroxybenzaldehyde (salicylaldehyde), 4-N, N-dimethylbenzaldehyde, and 3-nitrobenzaldehyde [2]. The five Schiff bases were synthesized by the reaction of R and individual R_1 in ethanol using glacial acetic acid as catalyst are shown in Schemes 11(a)–11(e) [2]. Glacial acetic acid is a natural acid, therefore eco-friendly [31]. Its use helps to drive Schiff base formation and enhances reactivity [2]. Furthermore, [32, 33] stated that the addition of acid as a catalyst was to remove water molecules and accelerate the reaction [32, 33]. However, removal of water via mild dehydrating agents, such as sodium tetraoxosulphate(VI) acid helps to prevent the conversion of aminal into imine because it could be reversible [32, 33].

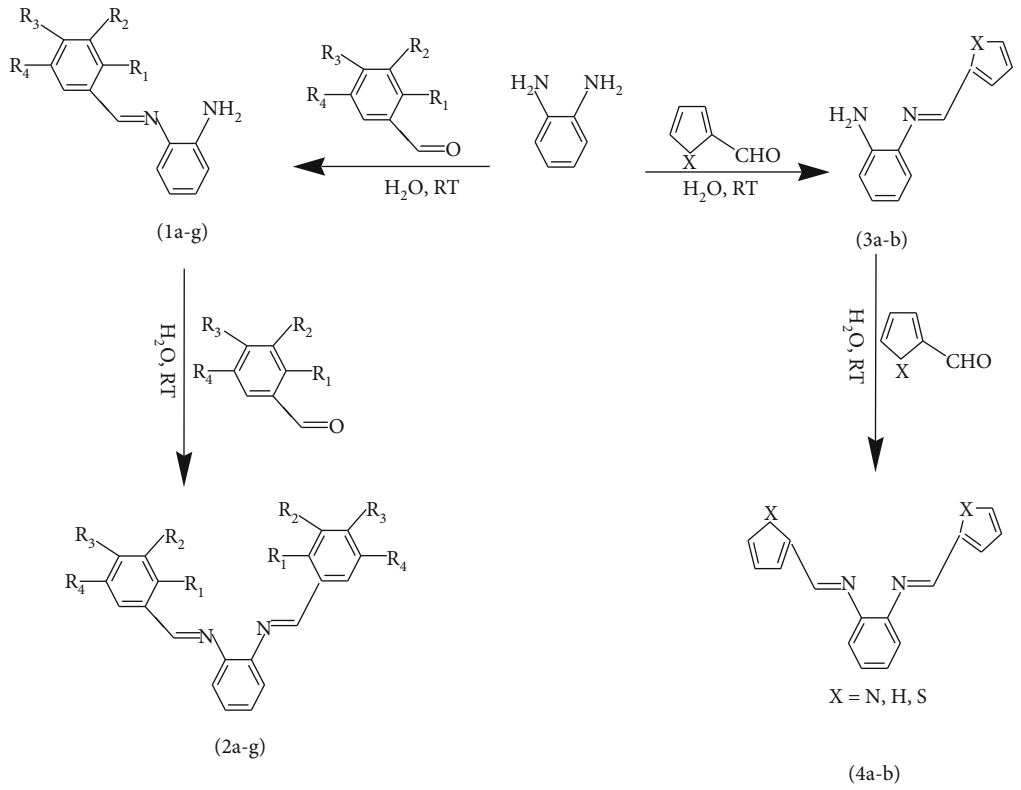
Hussain et al.'s synthesis reported no yield, but results on the physical data (color, melting point and elemental analysis), infrared spectroscopy, ultraviolet-visible spectroscopy, and nuclear magnetic resonance are shown in Tables 7–10, respectively [2].

3.4. Kumar et al.'s Achiral Schiff Base Synthesis. Kumar et al. synthesized Schiff base by reacting 3-ketobutanehydrazide (a ketone) and salicylhydrazide in ethanol by refluxing method (Scheme 12) [34]. On the same note of conventional method, Kumar et al.'s research was also able to give a high yield of 90%, which might be due to an alkanone (ketone) used instead of an alkanal (aldehyde) [34].

3.5. Uyar et al.'s Synthesis of Schiff Base with their Corresponding Copper(II) and Manganese(II) Complexes. Uyar et al. synthesized Schiff base by dissolving 2-hydroxy-6-methoxybenzaldehyde (0.31 g; 2.04 mmol) in 15 ml of ethanol in a 100 ml round-bottom flask equipped with a magnetic stirring bar [35]. To this solution, 4, 4′-oxydianiline (0.204 g; 1.02 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. The excess solvent was removed with a rotary evaporator, and Schiff base was obtained as a yellowish solid. Yellowish solid Schiff base (0.158 mmol) and the respective metal chloride salt, MCl_2

Table 4: Five Schiff bases synthesized from microwave irradiation and conventional methods [27].

Compound	Power	Microwave method			Conventional method		
		Temp	Time	Yield	Temp	Time	Yield
3a	200 W	70°C	60 sec	95%	Ambient	2 h	70%
3b	200 W	70°C	30 sec	92%	Ambient	1.5 h	75%
3c	200 W	70°C	60 sec	96%	Ambient	1.5 h	75%
3d	200 W	70°C	30 sec	94%	Ambient	1 h	72%
3e	200 W	70°C	120 sec	90%	Ambient	1.5 h	70%



Scheme 10: Syntheses of Schiff bases from 1, 2-diamobenzene with various aromatic aldehydes in water at room temperature [21].

(0.158 mmol), were added to a round-bottom flask equipped with a water condenser and magnetic stirring bar. Methanol (20 ml) was added to dissolve the refluxed reaction mixture, for 24 h, and the reaction mixture was permitted to cool to room temperature. The reaction mixture was filtered with a Number1 Whatman filter paper, and the residue was washed first with methanol and second with ether to subsequently obtain brown copper(II) and dark orange manganese(IIII) complexes, which were both dried under vacuum [35]. The color changed from yellow to brown, and dark orange indicated the metal complex (coordination compound) formation because transition metal complexes are colored [36].

3.6. Jabbi et al.'s Achiral Schiff Base Synthetic Reaction. Jabbi et al. used 0.01 mol of 2-aminophenol and 0.01 mol of 3-formyl-2-hydroxy-6-methoxyquinolinecarboxaldehyde in aqueous hydrochloric acid (35 ml, 4 mol). Subsequent solution was heated under reflux on water bath for merely 1 hour. The subsequent mixture was cooled to room temperature, where 2-hydroxy-6-methoxy-3-quinlinecarboxaldehyde was filtered, washed meticulously with cold ethanol, and further washed with diethyl ether to yield a yellow cotton-like solid as shown in Scheme 13 [3]. The Schiff base ligand was synthesized by condensation reaction of 0.01 mol of 3-formyl-2-hydroxy-6-methoxyquinoline with 0.01 mol of 2-aminophenol in ethanol and refluxed on water bath for six to seven hours (6-7 h) with three to four drops of acetic acid. Subsequently, the reaction mixture was cooled to room temperature, filtered, and washed meticulously with cold ethanol followed by diethylether to get a pure sample. The chemical reaction is shown in (Scheme 14).

The synthesized Schiff base was ligated with Mn(II) and Fe(II) ions to form respective Mn(II) and Fe(II) complexes. Successful synthesis of each complex was confirmed with characterization techniques, such as atomic absorption

Table 5: Fourteen Schiff bases synthesized from aromatic aldehydes using green and conventional methods [21].

Compound	R_1	R_2	R_3	R_4	Reaction time		Yields (%)	
					Green	Conv.	Green	Conv.
1a	OH	H	H	H	8 min	2 h	95	65
1b	H	H	OH	H	5 min	4 h	98	54
1c	OH	H	H	H	10 min	2 h	96	66
1d	H	H	H	H	20 min	4 h	96	71
1e	H	H	Cl	H	22 min	4 h	97	90
1f	OH	H	H	Cl	10 min	2 h	95	74
1 g	OH	H	H	Br	8 min	1 h	94	52
2a	OH	H	H	H	8 min	4 h	97	48
2b	H	OH	H	H	5 min	5 h	98	55
2c	H	H	OH	H	10 min	1 h	96	62
2d	H	H	H	H	20 min	3 h	95	64
2e	H	H	Cl	H	22 min	2 h	96	55
2f	OH	H	H	Cl	10 min	1 h	95	58
2 g	OH	H	H	H	8 min	2 h	97	52

Note: Conv.: conventional method.

Table 6: Four Schiff bases synthesized from heterogeneous aromatic aldehydes using green and conventional methods [21].

Compound	X	Reaction time		Yields (%)	
		Green	Conv.	Green	Conv.
3a	N-H	12 min	2 h	95	65
3b	S	12 min	4 h	98	54
4a	N-H	10 min	2 h	96	66
4b	S	10 min	4 h	96	71

Note: Conv.: conventional method.

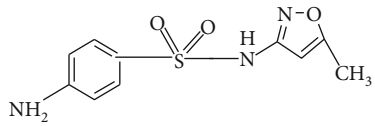


Figure 2: Chemical structure of sulfamethoxazole.

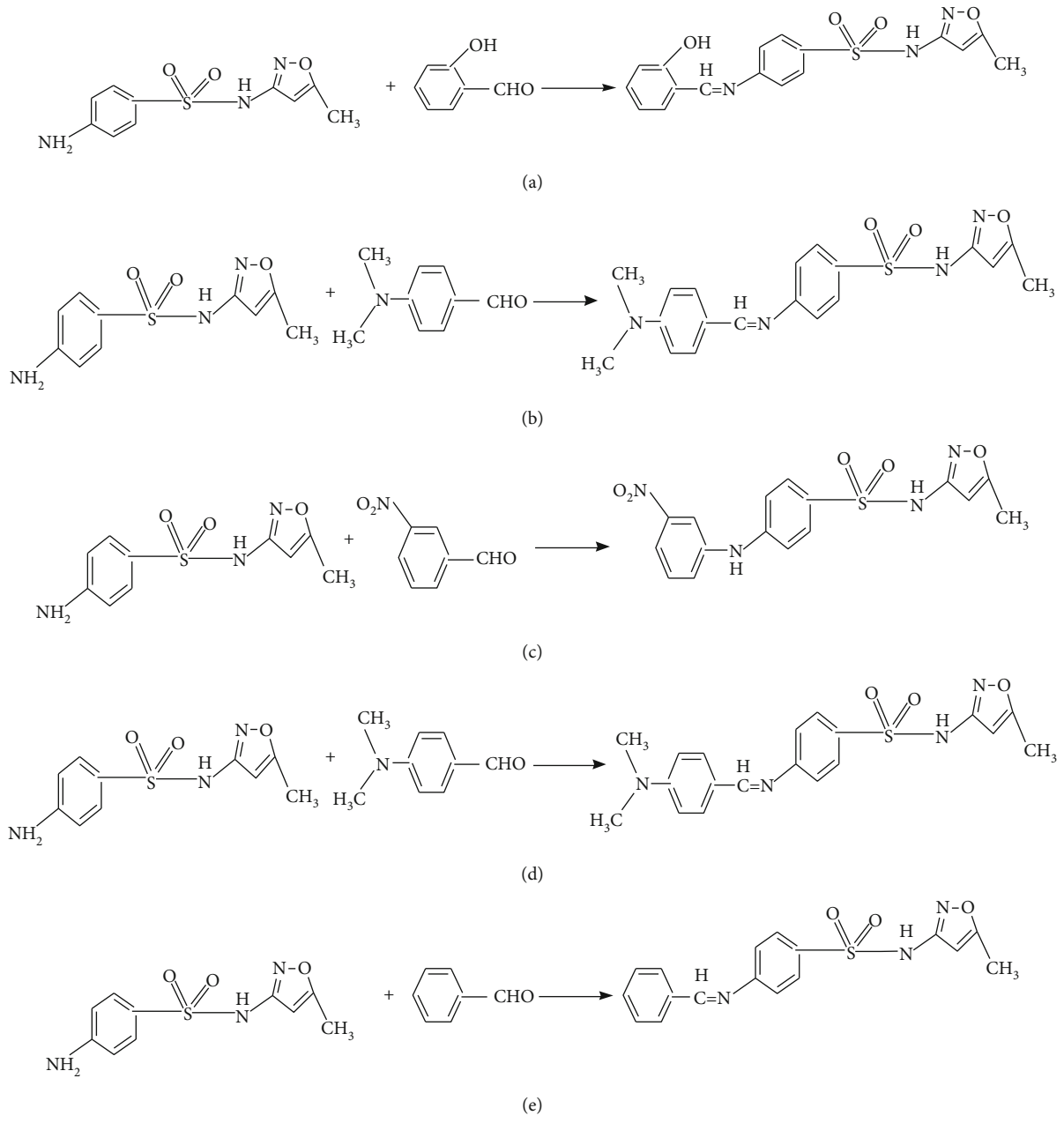
spectroscopy (AAS) analysis, decomposition temperature, elemental analysis, magnetic susceptibility, melting point, molar conductivity, infrared (IR) spectral analysis, and solubility test. Antimicrobial studies' results showed that the Mn(II) and Fe(II) complexes possessed better antibacterial and antifungal activity than the corresponding parent Schiff base ligand.

4. Microwave Method

In 1986, the first application of microwave irradiation in chemical synthesis was published [37]. Microwave-supported synthesis has transformed chemical synthesis, where microwave irradiation is generally used as a heat source in chemical synthesis [38]. The fundamental mechanisms observed in microwave-supported syntheses were conduction and dipolar polarization [38]. Microwave-supported synthesis offers better selectivity, cleaner synthesis with improved reaction rates, higher yields, and more economical for synthesis of large quantity of organic molecules, when compared with conventional heating [37, 38].

Numerous materials have diverse responses when subjected to microwave radiation; therefore, not all the materials are liable to microwave heating [37, 38]. In line with this, materials liable to microwaves (i) absorb microwaves, such as water, (ii) reflect microwaves, such as copper, or (iii) are transparent to microwave, such as sulfur [38]. The three core different mechanisms involved for heating in microwave chemistry are conduction mechanism, dipolar polarization, and interfacial polarization [38].

4.1. Conduction Mechanism. In the conduction mechanism, heat is produced through resistance to an electric current [38]. In a case when the irradiated sample is an electrical conductor, the charge carriers (electrons, ions, etc.) are relocated through the material under the effect of the electric field, ensuing in polarization [38]. The induced heating causes sample heating because of any electrical resistance [38]. The main disadvantage of conduction mechanism is its inability to be applicable for high conductivity materials, because such materials reflect maximum energy which falls on them [38].



Scheme 11: (a–e) Syntheses of five Schiff bases from sulfamethoxazole (R) and five different aldehydes (R_1) [2].

Table 7: Physical data of the five synthesized Schiff bases [2].

Samples	Color	Melting point (O°C)	Elemental analysis theoretical/found (actual)				
			%C	%H	%N	%O	%S
1	Yellow	190-192	57.13(57.23)	4.23(4.88)	11.76(10.39)	17.91(16.88)	8.97(9.11)
2	Brown	148-150	60.85(59.82)	6.23(6.43)	13.52(13.63)	11.58(12.09)	7.74(8.10)
3	Orange	122-124	52.84(53.88)	3.65 (3.22)	14.50(13.91)	20.70(19.33)	8.30(8.21)
4	Light yellow	142-143	48.58(49.59)	3.36(3.51)	10.00(9.33)	11.42(10.21)	7.62(8.33)
5	Orange	110-112	59.81(69.88)	4.83(3.89)	12.31(12.49)	14.06(14.63)	9.31(10.21)

4.2. Dipolar Polarization. Dipolar polarization can produce heat by either interaction between polar solvent molecules, such as ethanol, methanol, and water, or interaction between polar solute molecules, such as ammonia and formic acid [38]. The major requirement for dipolar polarization is that the oscillating field's frequency range should be correct to

Table 8: Infrared (IR) data of the five synthesized Schiff bases [2].

Samples	v (NH_2) (cm^{-1})	v (N-H) (cm^{-1})	v (C=N) imine (cm^{-1})	v (C=N) ring (cm^{-1})
Sulfamethoxazole	3298	—	—	1620
1	—	3250	1650	1616
2	—	3266	1603	1620
3	—	3290	1650	1620
4	—	3270	1650	1630
5	—	3287	1633	1615

Table 9: Ultraviolet (UV) data of the five synthesized Schiff bases [2].

Samples	Absorption bands (nm)	Assigned transitions
Sulfamethoxazole	280	$\pi \rightarrow \pi^*$
1	283, 310	$\pi \longrightarrow \pi^*$, $\pi \longrightarrow \pi^*$
2	250, 360	$\pi \longrightarrow \pi^*$, $\pi \longrightarrow \pi^*$
3	270	$\pi \longrightarrow \pi^*$
4	271	$\pi \longrightarrow \pi^*$
5	270	$\pi \longrightarrow \pi^*$

allow sufficient interparticle interaction [38]. Microwave radiation has the proper frequency (0.3-30 GHz) to oscillate polar particles and allows sufficient interparticle interaction [38].

4.3. Interfacial Polarization. Interfacial polarization method could be regarded a combination of conduction mechanism and dipolar polarization [38]. It is essential for heating systems comprising a conducting material distributed in a nonconducting material [38], for instance, a distribution of metal particles in sulfur powdered form [38]. The metal powder is a good radiation absorber when heated by a mechanism like dipolar polarization [38].

4.4. Microwave Synthesis Apparatus (Microwave Reactor). Microwave synthesis apparatus is also referred to as microwave reactor [37, 38]. Microwave synthesis apparatus entails a single-mode microwave oven and multimode microwave oven [37, 38].

4.4.1. Single-Mode Microwave Apparatus. The distinguishing feature of a single-mode microwave apparatus is its capability to generate a vertical wave pattern [38]. This interface produces a collection of nodes with zero microwave energy intensity, and a collection of antinodes with maximum microwave energy magnitude [38]. This apparatus could process volumes extending from 0.2 ml to around 50 ml in closed-vessel conditions and volumes around 150 ml under open-vessel conditions [38]. A disadvantage of single-mode microwave apparatus is one vessel irradiation once, while an advantage is its high heating rate [37, 38]. However, the apparatus is user-friendly [38]. The single-mode microwave ovens are used presently for automation, combinational chemical applications, and small-scale drug delivery [38].

4.4.2. Multimode Microwave Apparatus. A major feature of a multimode microwave apparatus is the thoughtful prevention of producing a vertical wave pattern [38]. The aim was to produce as much disorderliness as possible in the apparatus [38]. The greater the disorderliness, the higher the radiation distribution, which increases the region which could cause efficient heating in the apparatus, resulting in accommodating a number of samples simultaneously for heating, unlike single-mode microwave apparatus [38]. Due to this feature, a multimode heating apparatus is used for bulk heating and conducting chemical analysis processes, such as ashing and extraction [38]. The disadvantage is that heating samples are uncontrollably efficient because of lack of temperature conformity [38]. The advantage is that several reaction mixtures could be processed in both open- and closed-vessel conditions [37, 38].

4.5. Enhanced Microwave Synthesis. In recent times, a substitution method for carrying out microwave-supported organic reactions, called enhanced microwave synthesis (EMS), was examined [38]. The reaction vessel was cooled outwardly with compressed air, while controlling microwave irradiation concurrently, more energy could be applied directly to the reaction mixture [38]. The EMS ensures that a high, continuous level of microwave is applied [38]. Concurrent cooling allows a greater quantity of microwave energy to be introduced into the reaction, while keeping low the reaction temperature [38]. The significant outcomes are cleaner chemistry and greater yields [38].

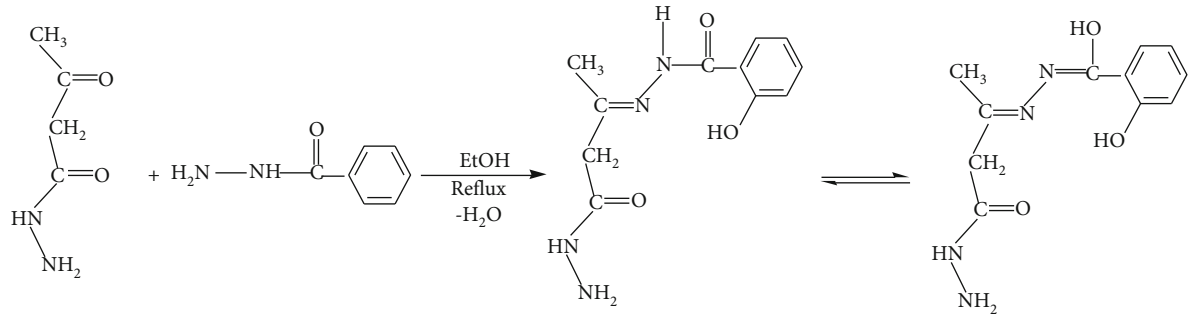
5. Type of Color and Nature of the Product of Schiff Base Ligand

Among researchers is the contention that a Schiff base ligand must be yellow in color and the nature of the product must be solid. This contention has prevented further research in Schiff base applications. On another note based on products' colors when compared with compounds of dithiocarbamate ligands, colors of dithiocarbamates' products with pink, red, yellow, and white (colorless) signify complete syntheses of dithiocarbamate ligands, while that of Schiff base could be of any color [20, 39].

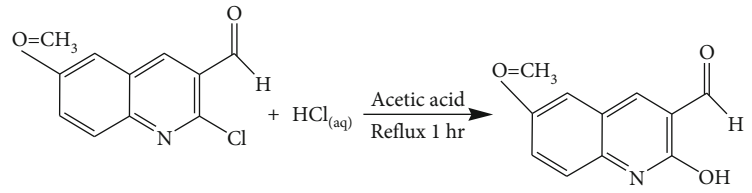
5.1. Type of Color of Schiff Base Ligand. Schiff bases' products devoid of coordination with metal ions form different colors, such as brown (light and dark brown) [1, 40, 41], cream [42], greenish yellow [12], grey [43], light coffee [42], orange [44], orange-yellow [40], pinkish cream [42],

Table 10: Proton nuclear magnetic resonance of sulfamethoxazole and compound 5 [2].

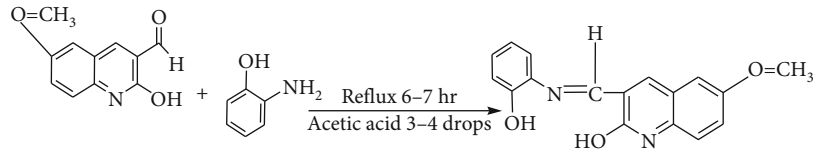
Samples	CH_3 (ppm)	C-H isoxazole rings (ppm)	Aromatic benzene rings (ppm)	Azomethine/imine (ppm)	N-H (ppm)	-OH (ppm)
Sulfamethoxazole	2.212	6.029	6-743-7.768	8.764	9.352	10.525
Compound 5	2.200	5.833	6.789-7.749	8.698	9.602	—



Scheme 12: Synthesis of the Schiff base from 3-ketobutanehydrazide and salicylhydrazide in ethanol [34].



Scheme 13: Synthesis of 3-formyl-2-hydroxy-6-methoxyquinolinecarboxaldehyde [3].



Scheme 14: Preparation of the Schiff base of 3-[(2-hydroxy-phenylimino)-methyl]-6-methoxy-quinolin2-ol [3].

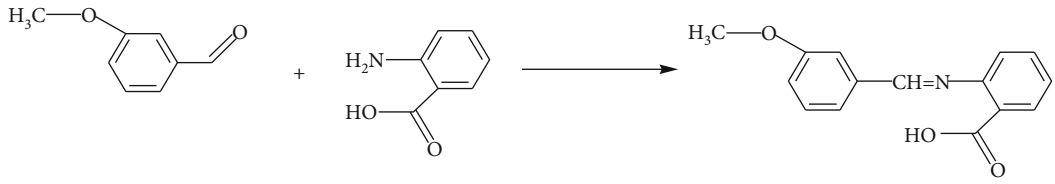
red [43], white [45], and yellow (light and deep yellow) [2, 13, 40, 46–48] are typical colors for complete syntheses of Schiff bases. In summary, Schiff bases are not color subjective, that is, any color could be observed.

5.2. Nature of Product of Schiff Base Ligand. The usual and normal state of synthesized product of Schiff base is a precipitate (solid), while the anomalous (atypical) nature of products of Schiff bases are rare cases of gelatinous (sticky/viscous) and oily products which are sometimes produced among researchers. How eight researchers resolved issues on gelatinous and oily products are subsequently explained.

5.2.1. Prakash et al.'s Synthesis. Prakash et al. synthesized vanillin anthranilic acid Schiff base from ethanolic solution of vanillin and ethanolic solution of anthranilic acid and stirred continuously for 10 min (Scheme 15) [49]. The reaction was refluxed on a water bath between 4 and 5 h, cooled with ice blocks to obtain an oily liquid product. Prakash et al. allowed the liquid product to stay aside for a certain period, where it was able to form crystals of the Schiff base [49]. A bit of sodium tetraoxosulphate(VI) was used to wash the crystals to remove unreacted aldehydes [49].

5.2.2. Hajrezaie et al.'s Synthesis. Hajrezaie et al. synthesized Schiff base from 2-hydroacetophenone in absolute ethanol and an ethanolic solution of N, N' dimethylethyldiamine as shown in Figure 3(a) and 3(b) and refluxed for 3 h at room temperature [50]. They obtained a clear yellow oily product after evaporation process and isolated the product in liquid form by adding few drops of diethyl ether or n-heptane [50]. The purity was confirmed by thin layer chromatography (TLC) [50].

5.2.3. Dehghani and Firoumandi's Synthesis. Dehghani and Firoumandi synthesized a Schiff base called 2-(2-(pyridine-2-ylmethyleneamino)ethylthio)-N-(thiophene-2-ylmethylene) aniline from an ethanoic solution of 2-(2-aminoethylthio)-N-(thiophene-2-ylmethylene) aniline and an ethanoic solution of pyridine-2-carbaldehyde (Scheme 16)



Scheme 15: Synthesis of vanillin anthranilic acid Schiff base [49].

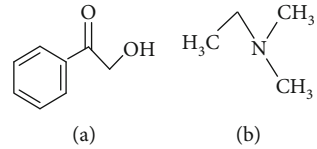
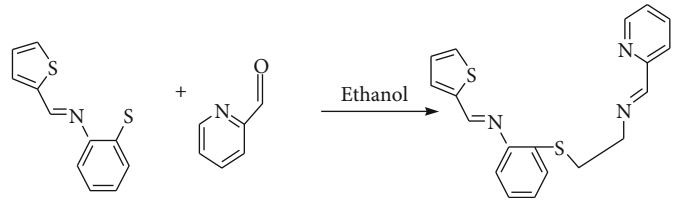


Figure 3: (a, b) Chemical structures of 2-hydroacetophenone and N, N' dimethylethyldiamine [50]. (a) 2-hydroacetophenone. (b) N, N' dimethylethyldiamine.



Scheme 16: Synthesis of 2-(2-(pyridine-2-ylmethyleneamino)ethythio)-N-(thiophene-2-ylmethylene) aniline [51].

[51]. Refluxing process took 3 h, and the obtained solution was vacuum evaporated to yield yellow oil product [51]. Petroleum ether was used to wash the yellow oil, and the product remained as yellow oil [51].

5.2.4. Jaworska et al.'s Synthesis. Jaworska et al. synthesized nine Schiff bases from (S)-α-methylbenzylamine and either aromatic aldehydes or ketones in toluene, which gave 46 to 99% yields. Four were obtained as yellow oil products and were purified by distillation under pressure [24].

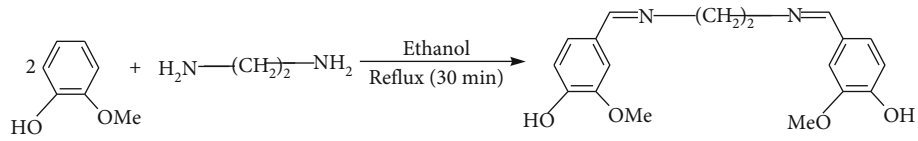
5.2.5. Yang's Synthesis. Yang's type of Schiff base synthesis involved 3, 4, 5-trimethoxybenzaldehyde, para-toluidine in dichloromethane (DCM) solvent and anhydrous magnesium tetraoxosulphate(VI) [16]. The reaction mixture was stirred for 2 h at room temperature, filtered through a sintered glass funnel with DCM, and the filtrate was concentrated under reduced pressure with a rotary evaporator to obtain yellow oil. The yellow oil was dissolved in ethanol and heated in 80°C water bath. Hot water was added while stirring. The solution was cooled to room temperature and in an ice-bath for 2 h [16]. The product was filtered to obtain white lamellar crystals [16].

5.2.6. Amarasekara and Razzaq's Synthesis. Amarasekara and Razzaq synthesized a Schiff called N, N'-bis(vanillidene)-1, 3-propanediamine from a mixture of vanillin and 1, 3-propanediamine in ethanol and refluxed for 30 min (Scheme 17) [52]. The solution was cooled to room temperature and stood overnight at room temperature. The solution was evaporated to yield a yellow viscous oil of 99% [52].

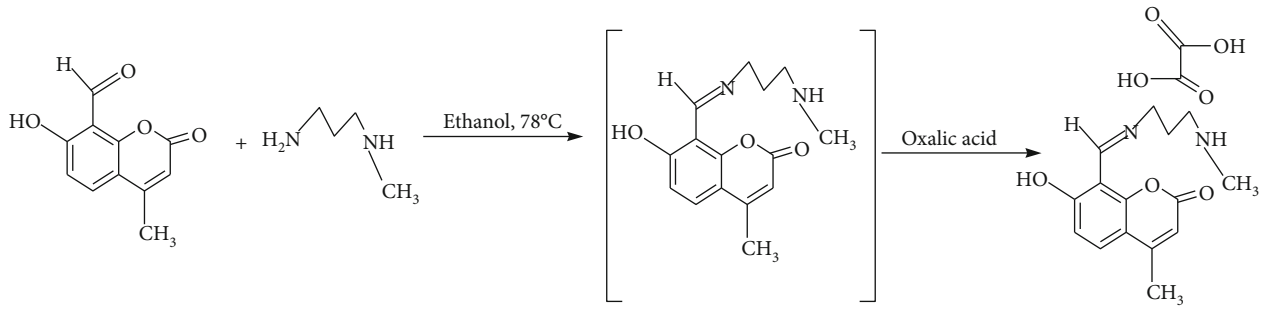
5.2.7. Yamgar et al.'s Synthesis. Yamgar et al. prepared a Schiff base called 7-hydroxy-4-methyl-8-[(Z)-{[3-(methylamino)propyl]imino}methyl]-2-H-chromen-2-one oxalate salt by the condensation reaction of 7-hydroxy-4-methyl-2H-chromen-2-one-8-carbaldehyde and N-methyl propane-1, 3-diamine in ethanol with few drops of concentrated hydrochloric acid (Scheme 18) [53]. The reaction mixture was refluxed for 1 h. The product was cooled and isolated as yellowish brown oil. Yamgar et al. indicated that the oily Schiff base was unstable in nature for the compound to be characterized [53]. They formed the oxalate salt for its distinctive characterization [53].

5.2.8. Gwaram et al.'s Synthesis. Gwaram et al. synthesized a Schiff base called 2-morpholino-N-(1-pyridin-2-yl) ethylidene) ethanamine (Figure 4) from a mixture of 4-(2-aminoethyl)-morpholine and 2-acetylpyridine in ethanol [54]. The mixture was refluxed for 2 h, and few drops of glacial acetic acid were added as a catalyst. The resulted orange oil stood for 12 h at 55°C in an oven, and it formed a solid. The solid was recrystallized in methanol with a yield of 61.5% [54].

In summary, all the eight researchers justified the efforts devoted to the syntheses of Schiff bases, regardless of oily product. With the exceptions of Yamgar et al. who obtained yellowish brown oil product and Gwaram et al. who obtained orange oil product, the other six researchers obtained yellow oily product. Additionally, Yamgar et al. indicated that characterization is better with nonoily products, which are stable product in nature than unstable oily products [53, 54].



Scheme 17: Synthesis of N, N'-bis(vanillidene)-1, 3-propanediamine [52].



Scheme 18: Synthesis of 7-hydroxy-4-methyl-8-[(Z)-{[3-(methylamino)propyl]imino}methyl]-2-H-chromen-2-one oxalate salt [53].

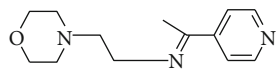


Figure 4: Chemical structure of 2-morpholino-N-(1-pyridin-2-yl) ethylidene) ethanamine [54].

5.3. Eight Researchers Resolved Issues on Gelatinous and Oily Products. Prakash et al. cooled the yellow oily product for an unspecified duration to obtain crystals, while Hajrezaie et al. purified yellow oily product with few drops of diethyl ether or n-heptane using the phenomenon of decontaminator factor and confirmed purity with TLC [49, 50]. Dehghani-Firouzabadi et al. was also able to purify the yellow oil with petroleum ether but still had yellow oil, but Jaworska et al. purified yellow oil product with distillation under pressure [24, 51]. Yang et al. used the process of solvent extraction and heating in water bath, cooling on ice-bath, and filtration on their yellow oily product to obtain white lamellar crystals, while Amarasekara et al. only reported the 99% yield of their yellow viscous oily product [16, 52]. Yamgar et al. formed an oxalate salt of the yellowish brown oil, while Gwaram et al.'s orange oil product was solidified by standing for 12 h at 55°C in an oven [53, 54].

5.3.1. Factors Responsible for Oily Products and How to Control them. There could be factors responsible for obtaining an oily product rather than a solid (crystals, powder, or precipitates) product. The Amarasekara et al.'s Schiff base synthesis shall be looked into, as well as other factors [52].

Two moles of vanillin used by Amarasekara and Razzaq might have contributed to the oily product because aldehydes are susceptible to self-condensation, where they act as both electrophile and nucleophile giving rise to oily products [55]. In several cases, self-condensation is an undesirable side-reaction. As a result, chemists approved numerous methods to avoid this from taking place when performing crossed aldol reaction Three of the several methods to avoid self-condensation are (i) the use of a better reactive electrophile and non-enolizable partner, (ii) generating enolate quantitatively, and (iii) silyl enol ether formation. Self-condensation is an organic reaction, where a chemical compound consisting of a carbonyl group acts as both the electrophile and the nucleophile in an aldol condensation. It is also called symmetrical aldol condensation in contrast to a mixed aldol condensation, whereby the electrophile and nucleophile are different species [56]. Other factors which might be responsible for oily products are (i) heating instead of allowing synthesis to be carried out at room temperature, (ii) moisture, (iii) presence of impurities which could be removed by purification techniques, such as solvent extraction, column chromatography, thin layer chromatography (TLC), and vacuum distillation, and (iv) incomplete reaction, where reaction duration could be increased, and cases, where Schiff base might be naturally oily. Either oily or viscous (sticky) product could be solidified with several times washing of either product with diethyl ether or petroleum ether. However, a glass rod is used for stirring in both cases.

6. Characterization Techniques

Confirmation of successful synthesis of Schiff base ligand could be achieved with some familiar characterization techniques among several others, such as solubility test, melting point (MP), elemental analysis (EA), Fourier transform infrared (FTIR), UV-Vis, and nuclear magnetic resonance (NMR).

6.1. Solubility Test. Solubility test is usually done at room temperature and devoid of a unit [47]. Aliyu et al. synthesized a Schiff base from the addition of ethanoic solution of ethylenediamine and ethanoic solution of 2-hydroxy-1-naphtaldehyde by refluxing for 1 h [57]. The yellow crystalline solid product was filtered, washed with ethanol, and dried over phosphorus (V) oxide for 7 d. The solubility test done on the Schiff base showed that it was insoluble in

water, ether, carbon tetrachloromethane (CCl_4), slightly soluble in nitrobenzene, and acetonitrile but soluble in methanol, ethanol, and dimethyl sulfoxide (DMSO) [57]. Abood synthesized Schiff base was insoluble in acetone, alcohols, and chloroform but soluble in dimethylformamide (DMF), DMSO, and tetrahydrofuran (THF) [45]. Jabbi et al.'s study confirmed that the Schiff base ligand and the respective its metal (II) complexes were insoluble in n-hexane and water and slightly soluble in methanol and tetrachloromenthane, but soluble in DMF and DMSO [3]. Yusuf et al.'s metal Schiff base complexes were insoluble in ether, methanol, ethanol, and heptane, but very soluble in chloroform, dichloromethane, acetonitrile, DMF, toluene, and dimethyl sulfoxide (DMSO). However, it is. Concisely, regardless of factors affecting solubility, the study supports the four groups of researchers' results. As a result, DMF, DMSO, and THF are the most relevant solvents for a worthy Schiff base solubility test.

Additionally, among all solvents, DMSO is widely used to carry out liquid state analyses for characterization techniques, such as FTIR, NMR, UV-Vis, and biological activities because of it its highest solubility gradient status.

6.2. Melting Point. Some researchers reported the melting points of Schiff base ligands [3, 8, 29, 54, 57, 58]. The seven groups of researchers' results from melting point apparatus were uncorrected and directly reported. Melting point is expressed in degree Celsius (°C). Higher melting points are possible with coordination of ligands with metals and transition metals. In line with this, a change in melting point between ligand and metal complex indicates a chemical reaction has taken place [36].

6.3. Elemental Analysis (EA). The elemental analysis of Schiff bases confirms the excellent synthesis in support of qualitative and quantitative determination of elements present in the synthesized Schiff base. The unit is expressed as a percentage. A less than or equal to 0.5% difference between the found (actual/observed) from analysis and the calculated (theoretical) signifies correct elemental analysis [3, 57]. Some elemental analysis results by Hussain et al. shown in Table 7 were above 0.5% difference between the actual and theoretical, which might be due to experimental error [2]. However, Jabbi et al.'s EA results confirm successful metal Schiff base complexes' syntheses, where less than 0.5% difference was observed between the found and calculated results as shown in Table 11 [3]. The EA helps to confirm successful synthesis of Schiff base ligand with the corresponding complex and determine the stoichiometry of a metal Schiff base [3].

6.4. Infrared (IR) Spectroscopy. The IR spectra for Schiff bases or any other compound are usually recorded on an infrared spectrophotometer within a 4000-400 cm^{-1} range. All IR values are expressed in wavenumbers (cm^{-1}). The Schiff base sample is analyzed either in a solid state or oily state. Surve et al. stated that a strong absorption band between 1600 and 1700 cm^{-1} was due to azomethine group stretching vibration frequency [7]. In line with this, Aliyu et al. observed strong stretching frequency at 1631-1642 cm^{-1} in the FTIR spectra and ascribed them to the azomethine group [57]. Jabbi et al. reported that the FTIR spectral details of their Schiff base showed a band at 1622 cm^{-1} for the Schiff base ligand's azomethine group: ν(C=N), [3].

Joshi et al. synthesized two new Schiff base ligands (2-((2,4-Dimethylphenylimino)methyl)-6-methoxy-4-nitrophenol (MPM) shown in Figure 5 and 2-((3, 4-difluorophenylimino)methyl)-6-methoxy-4-nitrophenol (FPM) shown in Figure 6. They observed a strong band at 1614 cm^{-1} and assigned it to the stretching vibrations of azomethine groups in Figures 5 and 6 [59]. Patel et al. reported that stretching frequency for azomethine υ(C=N) obtained for synthesized Schiff base was assigned 1679 cm^{-1}, while the complexation of azomethine nitrogen to the vanadium υ(C=N) bands was assigned 1615 cm^{-1} [46]. Sobola et al. reported strong absorption band for the azomethine from 1612 to 1615 cm^{-1} [60]. Abood, Hussain et al., [3, 46, 59]; Sobola et al., and Uddin et al.'s IR values for their synthesized Schiff bases are within Surve et al.'s range, as sharp absorption bands [2, 7, 45, 60, 61].

Contrary to Surve et al.'s IR range, some researchers reported the azomethine IR values below 1600 cm^{-1}, especially for metal Schiff base complexes. Jabbi et al. stated that when their Schiff base ligand was coordinated with metals, there was a shift to lower frequencies of 1573 and 1614 cm^{-1} for the metal Schiff base complexes [3]. Reddy et al. reported the range for the infrared vibrational frequencies for azomethine groups to be between 1550 and 1650 cm^{-1}, and Sadi et al. stated the infrared vibrational frequency for the synthesized Schiff base as 1561 cm^{-1}, while Xavier et al. confirmed the formation of azomethine (-C=N-) with a medium to strong stretching frequency range between 1587 and 1620 cm^{-1} [8, 17, 62].

In summary, going by the two ranges, the infrared vibrational frequency of azomethine group (-C=N-) could be found between 1550 and 1700 cm^{-1}, where factors of attached substituent might be responsible for differences in the IR of the Schiff bases.

6.5. UV-Vis Spectroscopy. Electronic spectra of both liquid and solid states' Schiff bases and corresponding metal complexes are usually done and recorded at room temperature with ultraviolet-visible (UV-Vis) spectrophotometer, and units of results obtained are expressed in wavelength (nm). Most researchers who did liquid state UV-Vis analyses for Schiff bases used DMSO as solvent [8, 46]. The solvent used for dissolution serves as the blank solution, which is tested before the sample solution, that is, the Schiff base solution. Gwaram et al. stated that the absorption bands typical of Schiff bases were in three distinct regions [54]. The first region ranges from 200 to 250 nm, which is a characteristic of the electronic interligand $\pi \longrightarrow \pi^*$, while the second characteristic wavelength in the region of 250-400 nm is the second inter ligand $n \longrightarrow \pi^*$ transition [2, 60, 63]. The wavelength maxima always have signals below 400 nm [8, 58]. Possibility of higher wavelengths can occur when they are coordinated with metals. The third region ranges from 400 to 1000 nm, which is a characteristic of ligand transfer

Table 11: Elemental analysis data of the Schiff base and its metal (II) complexes [3].

Compound	Found/(calculated) %			
	% N	% C	% H	% M
L (ligand)	8.90	64.39	4.18	—
$[MnL(H_2O)_3]\bullet H_2O$	6.34 (6.68)	49.02 (48.70)	4.73 (4.81)	13.10
$[FeL(H_2O)_3]\bullet H_2O$	7.02 (6.67)	48.09 (48.59)	5.10 (4.81)	13.29

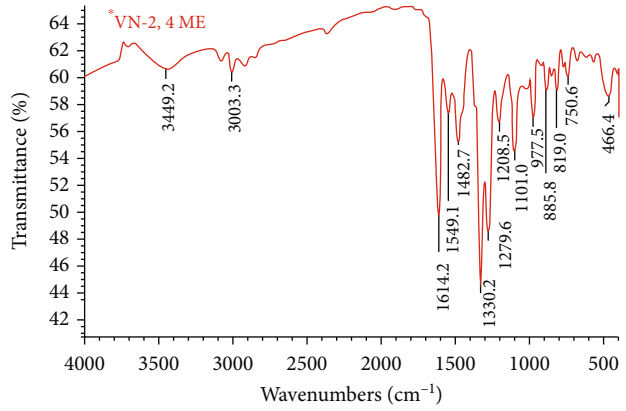


Figure 5: The IR spectrum of 2-((2, 4-dimethylphenylimino)methyl)-6-methoxy-4-nitrophenol (MPM) [59].

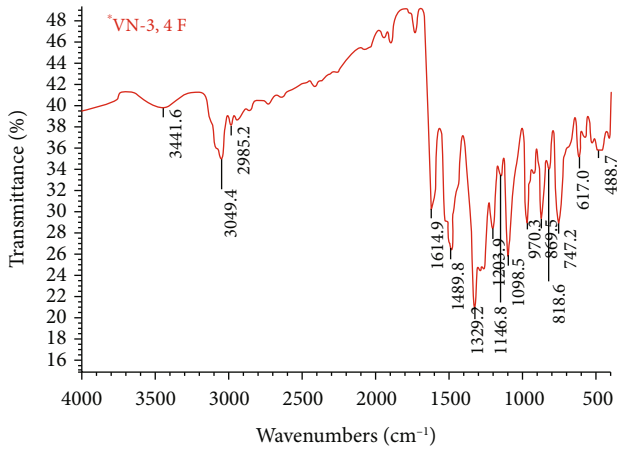


Figure 6: The IR spectrum of 2-((3, 4-difluorophenylimino)methyl)-6-methoxy-4-nitrophenol (FPM) [59].

between functional groups [45], ligand to metal charge transfer (LMCT) from the nitrogen atom to the central transition metal (coordination compounds $d \longrightarrow d^*$), and metal to ligand charge transfer (MLCT) [46, 60, 64]. Joshi et al. reported the copper and nickel coordination compounds of (2-(2, 4-dimethylphenylimino)methyl)-6-methoxy-4-nitrophenol (MPM) and 2-((3, 4-difluorophenylimino)methyl)-6-methoxy-4-nitrophenol (DPM) [59] as shown in Figure 7.

According to Uyar et al., the electronic spectra of their synthesized Schiff ligand with the corresponding copper(II) and manganese (III) complexes were recorded in DMSO between 250 and 500 nm [35]. Here, the UV-Vis spectra of both ligand and m4etal complexes showed an absorption assigned to the $\pi \longrightarrow \pi^*$ transition of the aromatic rings,

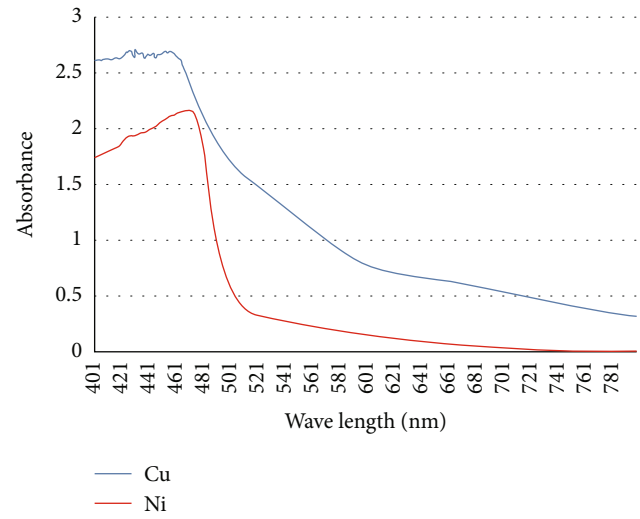


Figure 7: The reported UV-Vis of the copper and nickel coordination compounds of (2-(2,4-dimethylphenylimino)methyl)-6-methoxy-4-nitrophenol) (MPM) and 2-(3, 4-difluorophenylimino)methyl)-6-methoxy-4-nitrophenol) (DPM) [59].

while a second absorption peak at 332 nm was assigned to the $\pi \longrightarrow \pi^*$ transition of the azomethine group. In the visible region, the band around 360-400 nm was assigned to 2B1 g →2Eg transition [35], while the bands observed above 400 nm for both metal complexes were assigned to the charge transfer transitions from the filled π orbital of the bridging phenolic oxygen atoms to the vacant d-orbital of metal ions [35].

6.6. Nuclear Magnetic Resonance (NMR) Spectroscopy. Nuclear magnetic resonance (NMR) as a characterization technique is a diagnostic tool to confirm synthesized compound from an instrument called the NMR spectrometer. The NMR could also be used to detect unreacted aldehydes or ketones, with their chemical shifts being signaled in the NMR spectra. The NMR as a characterization technique is used to identify the Schiff base ligand and metal complexes [4]. It could be done as a solid state or in a solution form. The solution form entails deuterated solvents. Nondeuterated solvents give nothing in the spectrum except a big signal from the solvent in hydrogen NMR. As a result, NMR spectrometers use deuterium to retain magnetic field constant. Deuterated solvents are compounds where one or more hydrogen atoms are replaced with deuterium atoms. They are used in NMR spectroscopy. Examples of deuterated solvents commonly used are deuterated acetone, deuterated

benzene, deuterated chloroform, deuterated dichloromethane, deuterated dimethylformamide (DMF), deuterated dimethyl sulfoxide (DMSO), deuterated ethanol, deuterated methanol, deuterated tetrahydrofuran (THF), and heavy water. The NMR analyses are mostly proton NMR (^{1}H NMR) and carbon13 (^{13}C NMR).

6.6.1. Proton NMR (^{1}H NMR). Iqbal et al. reported that chemical shifts for azomethine (-HC=N-) could have signals between 8.0 and 8.7 ppm [58]. Their synthesized Schiff base gave 8.1 ppm for the presence of azomethine group, which fell in the range they reported [58]. Hussain et al. reported a chemical shift of 8.698 ppm for their synthesized Schiff base, as shown in Table 10 and Figure 8 [2]. Sharma et al. reported a chemical shift of 8.39 ppm for the azomethine group in their synthesized Schiff base [66]. Sobola et al. also reported a chemical shift in the range of 8.64 to 8.68 ppm for the azomethine group in their synthesized Schiff bases [60]. In contrary to previous proton NMR results, Abood et al. and Ashraf et al. gave different resonances [1, 45], while Abood et al. reported higher NMR signals at 9.31 and 9.90 ppm. Ashraf reported NMR signals at 9.218, 9.22, 9.36, 9.40, 9.50, 10.26, and 10.39 ppm were attributed to the (-C=N-) protons in their seven synthesized Schiff bases [1, 45]. Issa et al. and Kumaran et al.'s proton NMR results for azomethine (Figure 8) were in line with Abood et al. and Ashraf et al. [1, 45, 65, 67]. Issa et al. also reported 8.90-9.35 ppm for the NMR proton signal for azomethine, while Kumaran reported 9.66 ppm for the chemical shift of azomethine [65, 67]. In the case of Gwaram et al., they did not report the ^{1}H NMR for their synthesized Schiff bases, except for ^{13}C NMR [54]. In summary, different NMR proton signals ranging from 8.1 to 10.39 ppm for azomethine group (-C=N-) might be due to the impacts of substituents' attachments on the Schiff bases.

6.6.2. Carbon 13 NMR (^{13}C NMR). Ashraf et al. stated that ^{13}C NMR offered additional support for the structural characterization of Schiff bases [1]. Gwaram et al. assigned a range of 160-170 ppm to the azomethine (-C=N-) they obtained from metal complexes of Schiff bases [54]. Cinarli et al., Issa et al., Kumaran et al. (Figure 9), and Oguntoye et al. carbon 13 NMR signals for azomethine group were in the Gwaram et al.'s assignment range [54, 65, 67–69]. On contrary to Gwaram et al.'s ^{13}C NMR range, Yousif et al. reported a chemical shift of 111.12 ppm for the azomethine functional group of the synthesized Schiff base [47, 54]. It could be concluded that Gwaram et al.'s assignment range for azomethine group was justified.

6.7. Characterization Technique of Single X-Ray Crystallography for Recrystallization. Some of the techniques used to purify Schiff base products are chromatography, distillation, *recrystallization*, and sublimation. The opinion of doing a solubility test before recrystallization will help to determine the dissolving properties of the Schiff base, whether it is insoluble, partially soluble, or soluble. The X-ray crystallography is a technique excellent for structural determination of Schiff base and its metal complexes. It gives elucidation to determine the atomic numbering scheme, bond angles, bond distances, geometry, and goodness of fit.

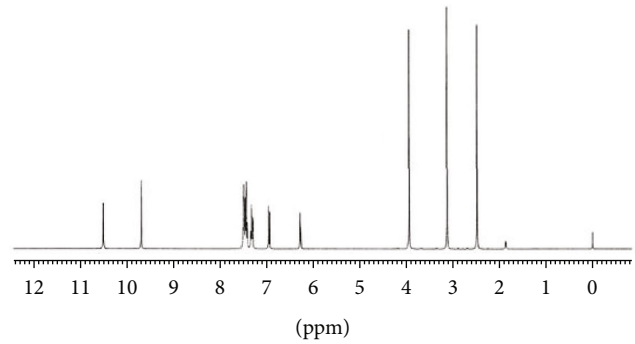


Figure 8: Kumaran et al.'s proton NMR structure for HL [65].

According to Ani et al., 4-methoxybenzylamine (230 mg; 1.70 mmol) was added to 4-nitrocinnamaldehyde (300 mg; 1.70 mmol) in ethanol solution (15 ml) [70]. The mixture was stirred for 48 h in a 100 ml round-bottom flask at room temperature. The subsequent precipitates were filtered, washed with cold ethanol, and then dissolved in hot ethanol to grow crystals. Single rod-shaped orange crystals of the Schiff base compound 1 suitable for single-crystal X-ray diffraction study were obtained with slow evaporation of the ethanolic solution. The (*E*)-N-((*E*)-3-(4-nitrophenyl)allylidene)-2-phenylethanamine as Schiff base compound 2 was synthesized under the same experimental condition as Schiff base compound 1, and single plank-shaped orange crystals were obtained by recrystallization from methanol [70].

Chang et al. used single-crystal X-ray diffraction to determine three crystal structures of their three metal (II) Schiff base complexes [26]. Complex 1 mononuclear manganese structure showed a six-coordinate octahedral geometry around the manganese ion. Complex 2 tetranuclear copper structure showed a five-coordinate distorted square pyramidal geometry around the central copper ion [26]. Complex 3 trinuclear manganese structure showed a six-coordinate octahedral geometry around the manganese ion surrounded by four L_3 ligands and acetate ions [26].

Yusuf et al. reported the synthesis and crystal structures of three new copper(II) Schiff base complexes [29]. Hence, the X-ray diffraction (XRD) analysis revealed a monoclinic space group C2/c in the first and third metal Schiff base complexes, while a triclinic space group P1 in the second metal Schiff base complex. Each metal Schiff base complex adopted a square planar geometry around the metal center [29]. Concisely, from the two groups of researchers, Schiff base compounds were characterized with X-ray diffraction, while the geometry is either five-coordinate square planar geometry or six-coordinate octahedral geometry around the metal center.

However, in case of inability to grow crystals of Schiff base and its corresponding metal complex, characterization techniques of powdered X-ray diffraction and molecular modelling could be used as alternatives for structure determination [71].

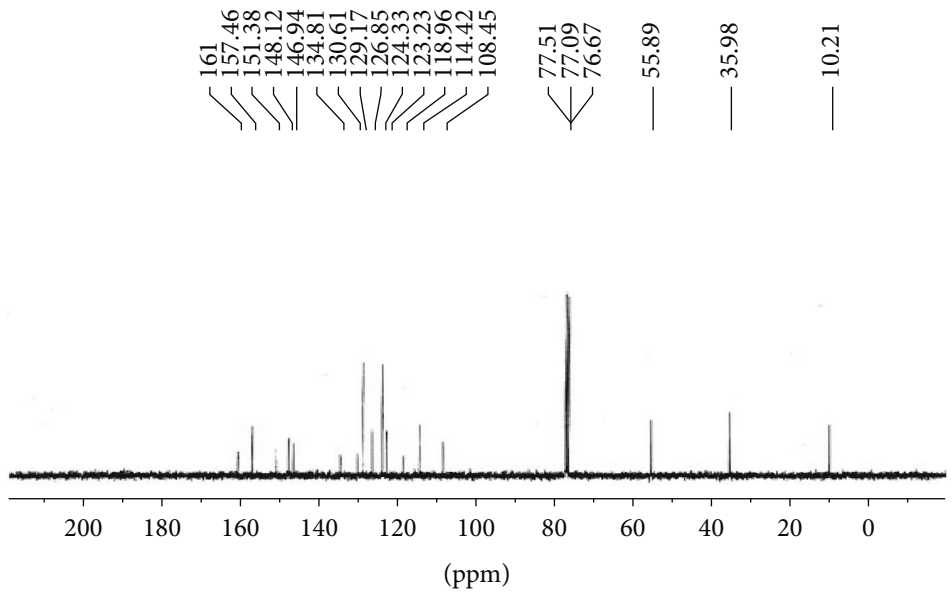


Figure 9: Kumaran et al.'s carbon 13 NMR structure for HL [65].

7. Antibacterial Studies

Contemporary challenges involve aiming at the microbicidal potentials and potencies of novel Schiff base ligands and coordination compounds (metal complexes) to combat multidrug-resistant pathogens. The azomethine group is essential in Schiff base's biological activities [6]. The incorporation of heterocycles in the Schiff base ligands make available additional donor sites for their successive metalation and, therefore, widened the increase of bioinorganic, clinical, and their industrial applications [6].

According to Sangle, additional study is needed for biological activities of Schiff base compounds, which could warrant design of antibacterial agents [6].

Hassan and Said, Hussain et al., Shaheen et al., and Vinusha et al. ligated different Schiff bases with different metal ions to form Schiff base metal complexes applicable as antibacterial agents [72–76].

Jabbi et al. screened their synthesized Schiff base ligands with their metal Schiff base complexes for their antibacterial activities against three bacteria strains of *Escherichia coli*, *Salmonella typhi*, and *Staphylococcus aureus* by disc diffusion method (Table 12). They observed that the metal (II) Schiff base complexes possessed more antibacterial inhibiting effects than the Schiff base ligand [3]. The metal (II) Schiff base complexes enhanced antibacterial inhibiting effect is due to the interaction of the metal (II) complexes with the bacterial cell lipoproteins, resulting in restriction in the bacterial cell usual functioning abilities [3]. In addition, the metal Schiff base complexes' higher stabilities at higher temperature could also allow them to be applied as a potential antibacterial agent [3].

While Jabbi et al. focused on using the zone of inhibition (ZOI) to obtain results for antibacterial activities of their Schiff base compounds, Nazirkar et al. used minimum inhibitory concentration (MIC) [3, 74]. Nazirkar et al. synthesized five Schiff base ligands (6a-e) with corresponding ten copper(II) and zinc (II) Schiff base complexes (7a-j) [74]. All synthesized compounds were screened for their antibacterial activities by *in vitro* analysis against three bacterial strains of *Staphylococcus. Aureus* (*S. Aureus*), *Escherichia coli* (*E. coli*), and *Bacillus Subtilis* (*B. Subtilis*) using minimum inhibitory concentration (MIC) with the preliminary disc diffusion method.

The disc diffusion method is usually used to assess the sensitivity of drugs and to determine the zone of inhibition (ZOI), minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) of studied compounds, which are compared to standard positive controls, such as ampicillin, cephalothin, gentamicin, penicillin, and tetracycline [77]. The dimethylsulphoxide (DMSO) is mostly used as the negative control for a culture without a dissolving solvent [78]. The penicillin and streptomycin are two of the several positive controls (standard drugs).

For Nazirkar et al.'s study, the resulting minimum inhibitory concentration (MIC) in μg/ml for the fifteen tested compounds (samples) two standard drugs as positive controls are shown in Table 13. Metal complexes showed enhanced antibacterial activities as compared with parent Schiff base ligands because of the higher lipophilicity of the complexes via ligand field theory (LFT). The LFT states that the overlapping of metal orbitals with orbitals of ligands minimizes the positive charge on central metal with electrons gain from donor groups of the Schiff base ligands and the delocalized electrons from ligand to metal enhance of the metal complex lipophilicity. With increased lipophilic character, metal complex can easily pass across the bacterial cell wall; therefore, it can prevent several bacterial enzymes. Comparing both metal complexes, antibacterial activities of Cu (II) complexes are higher than Zn(II) complexes, which might be due to stronger affinity of Cu (II) for biomolecules via enhanced permeability of the Cu (II) complexes through the bacterial cell membrane [74]. According to Hassan and Said,

Table 12: Antibacterial activity on the Schiff base Ligand and its metal (II) complexes [3].

Compound	Concentration ($\mu g\,cm^{-3}$)	Bacterial inhibition zones in mm		
		Staphylococcus aureus	*Escherichia coli*	*Salmonella typhi*
L (Ligand)	1000	07	09	08
	2000	06	08	10
	3000	09	07	09
$[MnL(H_2O)_3]\bullet H_2O$	1000	09	10	11
	2000	11	13	13
	3000	13	18	16
$[FeL(H_2O)_3]\bullet H_2O$	1000	11	11	10
	2000	12	15	15
	3000	16	18	14

Table 13: Minimum inhibitory concentration (MIC) of the antibacterial activities of Schiff bases (6a–6e) and metal complexes (7a–7j) [74].

Sr No.	Sample	*E. aureus*		*E. coli*		*B. subtilis*	
		200 μg/ml	100 μg/ml	200 μg/ml	100 μg/ml	200 μg/ml	100 μg/ml
1	6a	1.10	0.95	1.20	1.00	1.00	0.90
2	6b	1.20	1.00	1.10	1.00	1.10	0.90
3	6c	1.10	1.00	1.20	1.00	1.20	1.00
4	6d	1.20	1.00	0.95	0.80	0.95	0.85
5	6e	0.90	0.70	0.80	0.70	1.00	0.90
6	7a	1.20	1.00	0.95	0.80	0.95	0.85
7	7b	0.90	0.90	0.95	0.90	0.90	0.80
8	7c	0.95	0.85	0.95	0.90	1.00	0.90
9	7d	1.00	0.80	1.00	0.90	0.90	0.85
10	7e	1.00	0.90	0.85	0.80	0.85	0.75
11	7f	1.50	1.20	1.00	0.90	0.95	0.90
12	7g	0.90	0.90	1.10	0.90	1.20	0.90
13	7h	1.00	0.80	1.20	1.00	1.00	0.90
14	7i	0.95	0.85	1.20	1.10	1.20	1.00
15	7j	1.10	1.00	1.50	1.50	1.30	1.10
16	Penicillin	—	2.00	—	0.80	—	1.00
17	Streptomycin	—	0.70	—	0.70	—	3.00

Sr No.: serial number; 6a: (*E*)-ethyl5-(2-hydroxybenzylideneamino) benzofuran-2-carboxylate; 6b: (*E*)-ethyl5-(5-chloro-2-hydroxybenzylideneamino)benzofuran-2-carboxylate; 6c: (*E*)-ethyl5-(5-bromo-2-hydroxybenzylideneamino)benzofuran-2-carboxylate; 6d: (*E*)-ethyl5-(2-hydroxy-5-nitrobenzylideneamino)benzofuran-2-carboxylate; 6e: (*E*)-ethyl5-((1-hydroxynaphthalen-2yl)methyleneamino)benzofuran-2-carboxylate; 7a-7e: copper(II) complexes; and 7f-7j: zinc (II) complexes [74].

increased antibacterial activity might also be considered as factor of Overtone's concept and the Tweedy's chelation theory [77].

Concisely, the study supports Sangle for more studies on Schiff base compounds incorporating designs to alleviate global bacterial diseases. The lipophilic character from LFT, as well as factor of Overtone's concept and the Tweedy's chelation theory, indicate that Schiff base synthesis should progress to their coordination with metals to apply the inherent metal Schiff base complexes' potentials.

8. Conclusion and Recommendation

Schiff bases are versatile ligands in terms of chiral and achiral Schiff bases. This study delved into five asymmetric reactions of preparing chiral Schiff base ligands. For achiral Schiff bases, six different syntheses from conventional and microwave irradiation were considered for this study. The affordable, clean, convenient, efficient, environmentally friendly, and high yield qualities of microwave irradiation make it a better and green method than conventional method. The nature of products synthesized is important. As a result, eight different oily Schiff base products were examined with reasons for their anomalous nature being different from the usual solid solids (crystals, powder, or precipitate). In essence, oily product would not indicate that the synthesized compound should be discarded, but rather be refined. Some very familiar characterization techniques, such as MP, EA, FTIR, UV-Vis, and NMR (^{1}H NMR and ^{13}C NMR), and single-crystal

X-ray crystallography are used to characterize and determine successful synthesis of Schiff base ligands for innovative applications as antibacterial agents. This study recommends the use of microwave to synthesize Schiff base and its complexes because it supports green chemistry and it benefits environmental sustainability.

9. Future Research

Future work will entail a review on the comparative studies on Schiff bases complexes as trio antibacterial, anticancer, and antioxidant agents.

Data Availability

The data in the document and figures used to support the findings on this study are included within the research article.

Conflicts of Interest

Author declares no conflict of interest.

Acknowledgments

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