ChemSearch Journal 9(2): 1 – 7, December, 2018
Publication of Chemical Society of Nigeria, Kano Chapter

Received: 18/09/2018 Accepted: 26/11/2018

Liquid-assisted Mechanochemical Conversion of 2-hydroxy-3-methoxybenzaldehyde and Some Primary Aromatic Amines to Corresponding Schiff bases

[1*] Sani, S., [2]Kurawa, M. A., [2]Siraj, I. T., [3]Birniwa, A. H. and [1]Zauro, S. A.
[1]Department of Pure and Applied Chemistry, Usmanu Danfodiyo University, P.M.B. 2346, Sokoto, Nigeria
[2]Department of Pure and Industrial Chemistry, Faculty of Physical Sciences, Bayero University Kano, P.M.B 3011, BUK, Kano, Nigeria.
[3]Department of Polymer Technology, Hussaini Adamu Federal Polytechnic Kazaure, P.M.B 5004, Jigawa, Nigeria.
Email: salihu_sani2001@yahoo.com

ABSTRACT

In this paper, two Schiff bases of different solid primary aromatic amines were successfully synthesized using 1:1 and 2:1 molar ratio of 2-hydroxy-3-methoxybenzaldehyde to solid amine, by Liquid-assistant grinding. The Schiff-bases were investigated by analytical and spectroscopic techniques using FT-IR, Powder X-ray Diffraction Energy Dispersive X-ray (EDX) Melting point and CHN microanalysis. The Schiff bases were found to be soluble in polar solvent such as methanol and ethanol but insoluble in non-polar solvent such as hexane. Evidence from Infrared spectral study indicated that, the characteristics band attributed to aldehyde stretching disappeared on the final Schiff bases and the new absorption band at 1624 - 1644 cm^{-1} was due to the ν(C=N) stretching vibration, which is the characteristic band of Schiff base. The Powder-XRD analysis reveals that, the PXRD patterns of the Schiff bases were different from their respective starting materials which indicate the formation of new phase of the product. The elemental microanalysis of the Schiff base ligand is consistent with the calculated results from the empirical formula of the proposed structure of each compound. The antimicrobial activities of the synthesized Schiff base were tested using agar well diffusion method, against different strains of bacterial and fungal isolates. The antimicrobial results indicated that, the antibacterial activity of the (H_2L^1) Schiff base ligand was found to be more effective against *Escherichia coli*.

Keywords: Azomethine, Liquid-assistant grinding, Mechanochemistry, Powder x-ray, Schiff base

INTRODUCTION

Schiff bases are one of the important classes of organic compounds. Large number of metal complexes of Schiff base were reported with different ways in activation of small molecules, in addition to being as nano-precursors and with nice redox capability. In most recent studies, emphasis was made to their potential applications in the field of photosensitive material, (Bhat *et al.,* 1996) biology (Abd El-Halim *et. al*., 2011), catalysis, (Drozdzak *et al*., 2005), corrosion inhibition, (Emregul *et al*., 2006) as well as for thermal, magnetic and electrical purpose, (Mishra *et al*., 2012) etc. Due to their broad spectrum in utility, there are constantly growing interests in finding better and more convenient synthetic procedures to Schiff base.

Presently most procedures for the synthesis of Schiff bases are looking for optimization on reaction temperature, reaction time, (Abd El-Halim *et. al*., 2011) etc., the methods being environmentally stressful because of large use of volatile organic solvents (Zhang *et al.,* 2012). Also, as a society we are progressively aware of the environmental impact of human activity, and therefore the need to develop cleaner and more energy efficient technologies. It has been known that, the large-scale use of volatile organic solvents resulted in serious environmental contamination (Sheldon, 2005).

Schiff bases find various uses (Sheehan and Grenda 1962) some are active components in certain dyes, whereas some are used as liquid crystals. In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds. Schiff bases are also important intermediates in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate (Liimatainen *et. al.,* 2000). Schiff bases are used as starting materials for the synthesis of various bioactive heterocyclic compounds like 4-thiazolidinones, 2-azetidinones, benzoxazines and formazans. They possess diversified biological activities such as antibacterial (Nair and Bhattacharya 2009) and antifungal (Mishra and Soni 2008), Schiff bases are active against a wide

range of organisms, for example, *Candida albicans, Escherichia coli, Staphylococcus aureus, Bacillus polymxa, Trychophyton gypseum, Mycobacterium, Erysiphe graminis* and *Plasmopara viticola*. One of the important roles of Schiff bases is as an intermediate in the biologically important transamination reaction. They are used as a protective agent in natural rubber (George *et. al.,* 1993) and an amino protective group in organic synthesis.

To our knowledge, lots of organic compounds have been synthesized in solution so far, but up to now the corresponding synthesis in solid state is much less widespread. Recent progress has revealed on the mechanochemical method. James *et al*. reviewed solid-solid organic trans-formation and discussed the implication of the phase change during transformation (James *et. al.,* 2012). In a recent Chemical Society Review themed issue on mechanochemistry, Wang summarized various mechanochemical organic reactions realized by ball milling techniques (Wang, 2013)

As part of our investigation into the liquid-assisted mechanochemical path of solid aldehyde conversion to Schiff base, we felt that a greener, more versatile, and more convenient synthetic route to prepare Schiff bases are mandatory. Along this line, we noticed that 2-hydroxy-3-methoxybenzaldehyde is solid at room temperature, has an -OH group at *o*-position to carbonyl (-CH=O) to proceed to useful N,O-chelating Schiff base ligand, and has not been much used in the preparation of Schiff base before. Fortunately, this solid aromatic aldehyde, react with many solid primary aromatic amines, and this allowed us to see the broad spectrum of liquid-assisted mechanochemistry.

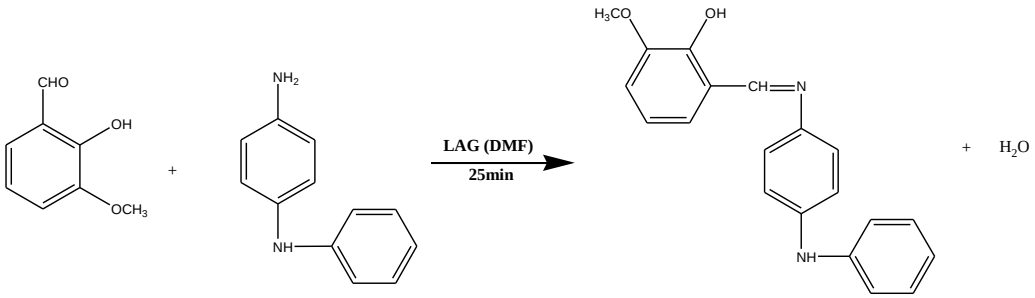
MATERIALS AND METHODS

Grinding in all the reactions was carried out in a mortar with pestle. Reagents used were obtained from Sigma Aldrich UK and were used without further purification. Solid state IR spectra were recorded on a Perkin-Elmer FTIR Spectrum-400. PXRD measurements were carried out on a PAN analytical EmpyreanX'Pert Pro X-ray diffractometer in the range 0-40^{o}C. Energy dispersive X-ray (EDX) were determined using FESEM/EDX Hitachi brand model SU8220. Elemental microanalysis of separated solid chelates for C, H and N were determined using Perkin-Elmer CHNS/O 2400 series II microanalyse, in the Department of Chemistry University of Malaya, Malaysia.

General Synthetic Procedure

2-methoxy-6-[(4-phenylamino-phenylimino)-methyl]-phenol; (H_2L^1) Schiff base

The solid reactants, 2-hydroxy-3-methoxybenzaldehyde (0.9129 g, 6 mmol) and N-Phenyl-benzene-1,4-diamine (1.910 g, 6 mmol) were grinded in 1:1 stoichiometric molar ratio in the presence of small amount of DMF (1.0 drop) for 25 min to obtained a gray powder. The compound was dried in air at room temperature. The dried product was further grinded for 3 min and weighed (Dominik and Branko 2011).

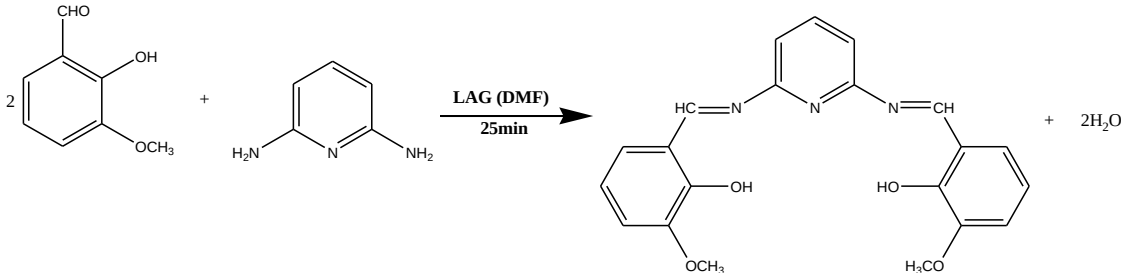


Scheme 1: Synthetic reaction of $H_2(L^1)$ Schiff base

Fig. 1: Showing the reactant and product of $H_2(L^1)$ Schiff base.

6,6'-Dimethoxy-2,2'-[1,3-Pyridinebis(nitrilomethylidyne)] bis-phenol; (H_2L^2) Schiff base

2-hydroxy-3-methoxybenzaldehyde (0.9129 g, 6 mmol) and 2,6-diaminopyridine (0.32739 g, 3 mmol) were grinded in 2:1 stoichiometric molar ratio in the presence of small amount of DMF (1.0 drop) for 25 min to obtained light brown powder. The compound was dried in an open air at room temperature. The dried product was further grinded for 3 min and weighed (Dominik and Branko 2011).



Scheme 2: Synthetic reaction of $H_2(L^2)$ Schiff base

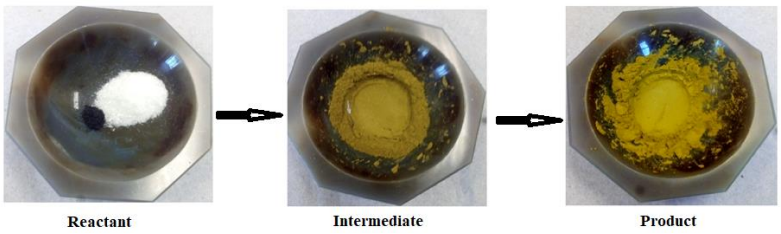


Fig. 2: Showing the reactant, intermediate and product of $H_2(L^2)$ Schiff base

Antimicrobial Sensitivity Test

The antimicrobial activities of the Schiff base ligands in Dimethylsulfoxide (DMSO) were performed *in vitro* by agar well diffusion method. The ligands were dissolved separately in dimethylsulfoxide to produce three different concentrations (60 μgml^{-1}, 30 μgml^{-1}, and 15 μgml^{-1}). Using inoculation loop, enough material from an overnight culture of the test organism was transferred into a test tube containing normal saline until the turbidity of the suspension matched the turbidity of the 0.5 Mcfarland standard (as a reference to adjust the turbidity of bacterial suspensions) as described by the national committee for clinical laboratory standard. The standard Inocula of the isolate were swabbed on to the surface area of the prepared and solidified agar plates. The prepared solution of the test compounds and the standard antibiotic concentration made Ciprofloxacin (bacterial standard) and Ketoconazole (fungal standard) were placed inside the agar well of the inoculated plates. The plates were incubated at 37°C for 24 hours before observation for the measurement of zone of inhibition (National Committee for Clinical Laboratory Standard, 2008).

RESULTS AND DISCUSSION

The characterization of mechanochemically prepared products has been reviewed (James *et. al.,* 2012), and the main emphasis in this report is on powder X-ray diffraction (PXRD). This can be used to identify known compounds. The present study focusses on the use of spectroscopic methods, specifically IR and powder X-ray diffraction.

The liquid-assisted mechanochemical method adopted produced Schiff bases ($H_2(L^1)$ and ($H_2(L^2)$ with good percentage yield of 85.7 and 90.1% respectively within a shorter reaction time of 25 minutes. The Schiff bases synthesized were coloured ranging from Gray for ($H_2(L^1)$ to light Brown colour for ($H_2(L^2)$ Schiff base. The Schiff bases are also non-hygroscopic crystalline solids with different melting point of 135 and 161°C respectively. The Schiff bases were found to be soluble in polar solvent such as methanol, ethanol, DMSO, DMF, Acetone and Acetonitrile but insoluble in non-polar solvent such as hexane. The solubility of the synthesized compounds in some common polar solvent was due to the polar nature the compounds (Table 2). The elemental analysis of the Schiff base ligands ($H_2(L^1)$ and ($H_2(L^2)$ for C, H, N (Table 1) are consistent with the calculated results from the empirical formula of the proposed structure of each compound.

Table 1: Physical properties and Elemental Microanalysis of the Schiff base Ligands

Compound	Molecular formula	Colour	Yield (%)	Melting point (^{O}C)	Found (Calculated) (%)		
					C	H	N
(H_2L^1)	$C_{20}H_{18}N_2O_2$	Gray	85.7	135	75.37(75.45)	5.93(5.70)	8.67(8.80)
(H_2L^2)	$C_{21}H_{18}N_3O_4$	Light Brown	90.1	161	67.14(66.83)	5.12(5.07)	11.21(11.13)

Table 2: Solubility Test of Schiff base Ligands

Compound	Methanol	Ethanol	DMSO	DMF	Hexane	Acetone	Acetonitrile
(H_2L^1)	S	S	S	S	IS	S	S
(H_2L^2)	S	S	S	S	SS	S	S

Key: $H_2(L^1)$ = Schiff base derived from 2-hydroxy-3-methoxybenzaldehyde and N-Phenyl-P- phenylenediamine.
$H_2(L^2)$ = Schiff base derived from 2-hydroxy-3-methoxybenzaldehyde and 2,6-diaminopyridine.
S = Soluble
SS = Slightly Soluble
IS = Insoluble

The significant feature of the infrared spectra of $H_2(L^1)$ and $H_2(L^2)$ Schiff bases were presence of bands at 1624 and 1644 cm^{-1} respectively which were assign to frequency of azomethine group (-C=N-). This suggested the formation of Schiff bases by reaction of 2-hydroxy-3-methoxybenzaldehyde with N-Phenyl-benzene-1,4-diamine and 2,6-diaminopyridine respectively. The spectra of two Schiff base ligands exhibit strong peak at 3416 and 3375 cm^{-1} which can be assigned to O-H stretching vibration. The band observed at 1076 and 1137cm^{-1} in the IR spectrum of $H_2(L^1)$ and $H_2(L^2)$ Schiff bases are characteristics of C-O-C symmetric stretching of methoxy (R-O-CH_3) (Vadivela, and Dhamodaranba 2015). The phenolic C-O stretching frequency of $H_2(L^1)$ and $H_2(L^2)$ ligands is seen at 1228 and 1153 cm^{-1} respectively. (Vadivela, and Dhamodaranba 2015). The spectra of Schiff base $H_2(L^1)$, and $H_2(L^2)$ shows bands corresponding to aromatic C-H stretching at 3073 and 3183cm^{-1}, and aromatic C-C stretching at 1535 and 1495cm^{-1} respectively (Fig. 3; Table 3).

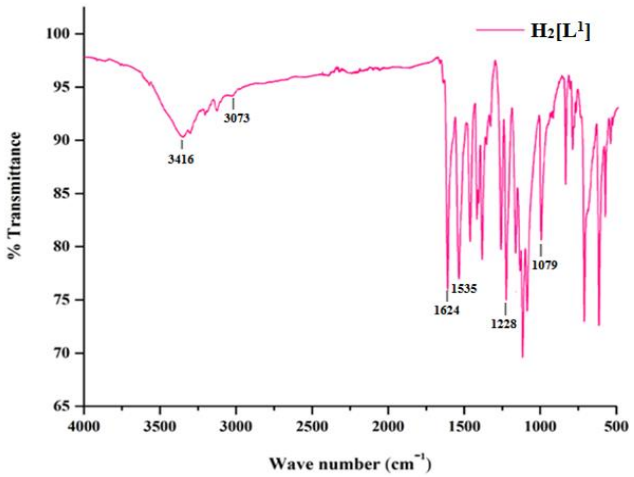


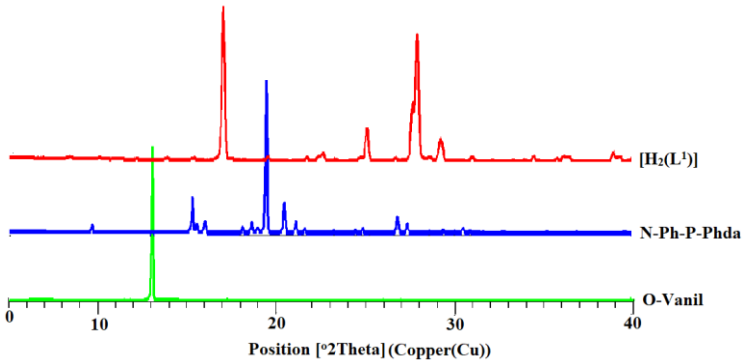
Fig. 3: FT-IR Spectra of $H_2(L^1)$ Schiff base

Table 3: Infrared spectral data of Schiff base Ligands (cm^{-1})

Compound	ν(C=N)	ν(O–H)	ν(C–O–C)	ν(C–O)	ν(C–C)
(H_2L^1)	1624	3416	1076	1228	1534
(H_2L^2)	1644	3375	1137	1153	1495

The sharp reflections in X-ray diffraction patterns of the synthesized Schiff base revels the crystalline nature of the compounds. The diffractogram and associated data depict the 2θ angle for each peak relative intensity and inter-planar spacing (d-value). Fig. 4 shows that, the powder X-ray diffraction patterns (PXRD) of the mechanochemical product was different from the PXRD of the reactants (3-

methoxy-2-hydroxybenzaldehyde and N-phenyl-P-phenylenediamine). New intense peaks corresponding to the mechanochemical ($H_2(L^1)$) Schiff base product were observed at 2θ = 17.26, 25.08, 27.85 and 29.42° with d-spacing 5.13, 3.55, 3.20 and 3.03Å respectively, which are absent in the reactants indicating formation of new phase (Atsushi *et al.*, 2016). Quantitative estimation of the 2θ PXRD patterns of the ($H_2(L^2)$) Schiff base were observed at 2θ= 14.51, 15.88, 17.76, 23.12 and 26.26° with d-spacing 6.10, 5.58, 4.99, 3.84 and 3.39Å respectively (Fig. 5)



Fig, 4: Comparison between PXRD Patterns of 2-Hydroxy-3-methoxy-benzaldehyde (O-Vanil), N-Phenyl-P-Phenylenediamine (N-Ph-P-Phda) and (H_2L^1) Schiff base

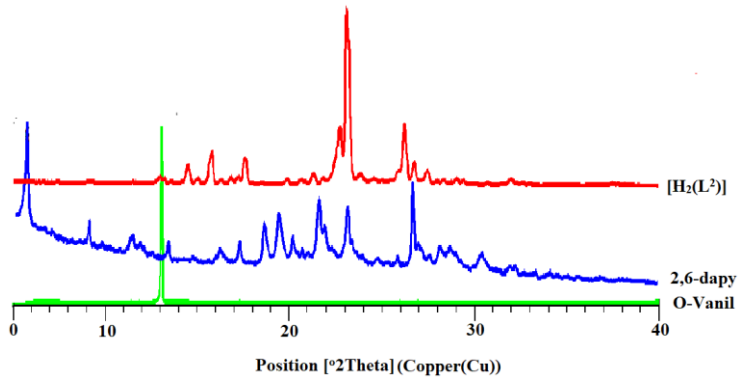


Fig. 5: Comparison between PXRD Patterns of 2-Hydroxy-3-methoxy-benzaldehyde (O-Vanil), 2,6-diaminopyridine (2,6-dapy) and (H_2L^2) Schiff base

Energy Dispersive X-ray referred to as EDX (Table 4) is an X-ray technique used to identify the elemental composition of materials or chemical characterization of a samples. EDX can be used to determine which chemical elements present in the sample and can be used to estimate their relative abundance. The data generated by EDX analysis consist of spectra showing peaks corresponding to the elements making up the true composition of the samples being analyzed. Elemental mapping of a sample and image analysis are also possible as showed in Fig. 6. EDX results of $H_2(L^1)$ Schiff base showed that, Carbon has the largest atomic percent 75.43%, followed by oxygen 16.30% and Nitrogen 12.27%. For $H_2(L^2)$ Schiff base, the atomic percent of carbon, oxygen and nitrogen were found to be 65.07, 22.50 and 12.43% respectively. The atomic percent of all the three component elements were compared in all the three-point analyzed and the result were found to be in agreement with each other indicating the uniform distribution of all the constituent elements in the sample compound.

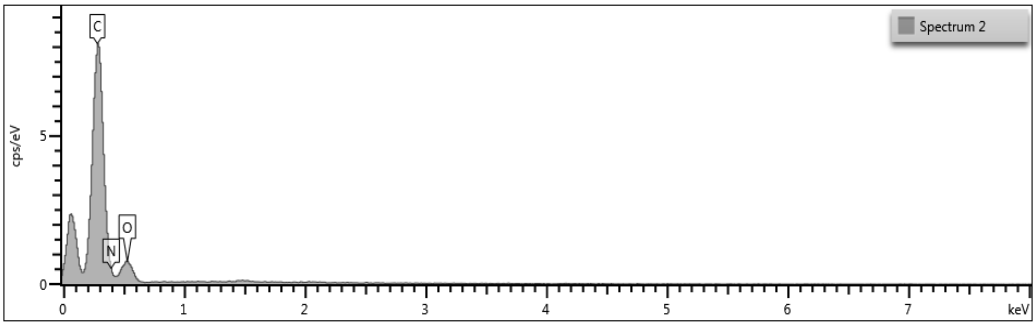


Fig. 6: EDX analysis of ($H_2(L^1)$) Schiff base showing peak due to Carbon, Nitrogen, and Oxygen in the Schiff base compound

Table 4: Energy Dispersive x-ray (EDX) of Schiff base Ligands

Compound	Element	Weight (%)	Atomic (%)	K Ratio	Line type
(H_2L^1)	C	66.89	75.43	0.07249	K Series
	N	15.77	12.27	0.00234	K Series
	O	17.34	16.30	0.00555	K Series
(H_2L^2)	C	60.49	65.07	0.07249	K Series
	N	16.41	12.43	0.00234	K Series
	O	23.10	22.50	0.00555	K Series

The antimicrobial activity of newly synthesized Schiff base ligands and the parent drugs (as standard) were investigated using agar well diffusion method. Different strains of bacteria which includes both gram positive (*Staphylococcus aureus*) and gram negative (*Escherichia coli*) and fungal isolates (*Candida albican* and *aspergillus Fumigatus*) were tested. The result indicates that, the highest inhibition of growth occurred on (H_2L^2) Schiff base against *Staphylococcus Aureus* especially at highest concentration (60 μgml^{-1}), however no significant activity was observed for (H_2L^2) Schiff base against *Escherichia coli* compared to the parent drug (Ciprofloxacin). (H_2L^1) Schiff base also show moderate activites against both *Escherichia coli* and *Staphylococcus aureus* as presented in Table 5.

Result of antifungal sensitivity test of (H_2L^1) Schiff base showed the best activity towards *Aspergillus Fumigatus* at nearly all concentration and moderate against *Candida albican* (Table 6). (H_2L^2) Schiff base showed moderate to good antifungal activities against *Aspergillus fumigatus* and *Candida albican*. The imine group present in the Schiff base compounds has been shown to be critical to their antimicrobial activities and therefore, the inhibition zone diameter results were mostly found to be dependent on the type of Schiff base (Bringmann *et al*., 2004; Souza *et al*., 2007; Guo *et al*., 2007).

Table 5: Antibacterial Sensitivity Test Showing the Inhibition Zones (mm) against the Bacterial Isolates

Compound	*Escherichia coli*			*Staphylococcus aureus*		
	60μgml^{-}	30μgml^{-1}	15μgml^{-1}	60μgml^{-1}	30μgml^{-1}	15μgml^{-1}
Ciprofloxacin(standard)		40			38	
DMSO (Control)	-	-	-	-	-	-
(H_2L^1)	14	11	10	12	10	-
(H_2L^2)	-	-	-	15	13	11

Table 6: Antifungal Sensitivity Test Showing the Inhibition Zones (mm) against the Fungal Isolates

Compound	*Candida albican*			*Aspergillus fumigatus*		
	60μgml^{-}	30μgml^{-1}	15μgml^{-1}	60μgml^{-1}	30μgml^{-1}	15μgml^{-1}
Ketoconazole (standard)		28			32	
DMSO (Control)	-	-	-	-	-	-
(H_2L^1)	13	12	-	15	13	10
(H_2L^2)	16	12	-	13	11	8

Key:: mm = Millimetre

- = Not Measurable or no activity

CONCLUSION

The Schiff bases were synthesized and characterized by FT-IR, Powder XRD, EDX, Melting point and CHN analysis. A yield of 85-90% was achieved after 25 min liquid-assistant grinding. The antimicrobial activity test of the synthesized compounds showed moderate to good activity against the organism tested. This technique involved simple experimental workup procedure, which makes it a convenient and attractive process, and is also consistent with the green Chemistry theme, which affords good yields.

ACKNOWLEDGEMENT

The authors thank Dr. Siti Nadiah Abdulhalim, Department of Chemistry, University of Malaya for her guidance toward characterization of the synthesized compounds.

REFERENCE

Abd El-Halim H. F., Mohamed M. O., Gehad G. M. and Mohsen A. S. (2011): Spectroscopic and Biological Activity Studies on Tridentate Schiff Base Ligands and their Transition Metal Complexes. *European Journal of Chemistry.* 2, 178–188.

Atsushi K., Tatsuya H., Masaki Y., and Masako K. (2016): Environmentally Friendly Mechanochemical Syntheses and Conversions of Highly Luminescent Cu(I) Dinuclear Complexes. *American chemical society(ACS) Inorganic. Chemistry*, 55, 1978 − 1985, DOI: 10.1021/acs.inorgchem.5b02160

Bhat K., Chang K. J., Aggarwal M. D., Wang W. S., Penn B. G. and Frazier D. O. (1996): Synthesis and Characterization of Various Schiff Bases for non-linear Optical Applications. *Material Chemistry and Physics.* 44, 261–266.

Bringmann G., Dreyer M., Faber J. H., Dalsgaard P. W., Staerk D. and Jaroszewski J. W. (2004): Ancistrotanzanine C and related 5,1'- and 7,3'-coupled naphthylisoquinoline Alkaloids from *Ancistrocladus tanzaniensis*. *Journal Natural Product* 67(5):743–8.

Dominik C. and Branko K. (2011). Schiff base Derived from 2-hydroxy-1-naphthaldehyde and liquid-assisted Mechanochemical Synthesis of its Isostructural Cu(II) and Co(II) Complexes. *Crystal Engineering Communication*, 13, 4351

Drozdzak, R., Allaert, B., Ledoux, N., Dragutan, I., Dragutan, V. and Verpoort, F. (2005): Synthesis of Schiff Base-Ruthenium Complexes and Their Applications in Catalytic Processes. *Advance Synthetic Catalysis.* 347, 1721–1743.

Emregul, K. C., Duzgun, E., Atakol, O. (2006): The application of Some Polydentate Schiff Base Compounds Containing Aminic Nitrogens as Corrosion Inhibitors for Mild Steel in Acidic Media. *Corrosion Science* 48, 3243–3260.

George, R. S., Joseph R. and George K. E. (1993). Study of Polyschiff's Base as a Protective Agent in Natural Rubber. *International Journal of Polymeric Materials and polymeric biomaterials.* 23, 17 – 26.

Guo, Z., Xing, R., Liu, S., Zhong, Z., Ji, X. and Wang, L. (2007): Antifungal Properties of Schiff Bases of Chitosan, N -substituted Chitosan and Quaternized Chitosan. *Carbohydrate Research* 342(10):1329–32

James, S. L., Adams, C. J., Bolm, C. and Waddell, D. C. (2012): Mechanochemistry: Opportunities for New and Cleaner Synthesis. *Chemical Society Reviews*, 41, 413-447.

Liimatainen, J., Lehtonen, A. and Sillanpaa R. **(**2000): *cis*-Dioxomolybdenum(VI) Complexes with Tridentate and Tetradentate Schiff Base Ligands. Preparation, Structures and Inhibition of Aerial Oxidation of Aldehydes. *Polyhedron.* 19, 1133–1138.

Mishra, A. P. and Soni, M. (2008): Synthesis Structural and Biological Studies of Some Schiff Base and Their Metal Complexes. *Metal-Based Drugs* II, 875410, 1 – 7.

Mishra, A. P., Tiwari, A. and Rajendra K. J. (2012): Microwave Induced Synthesis and Characterization of Semiconducting 2-thiophenecarboxaldehyde Metal Complexes. *Advance Material. Literature* 3, 213–219.

Nair, S. M. and Bhattacharya, I. R. A. (2009): Synthesis and Physiological Activities of Some Imines and Their Lactams. *Asian Journal Chemistry.* 2009, 21, 504 – 510.

National Committee for clinical Laboratory Standards (2008). Performance standards for antimicrobial susceptibility testing: ninth information supplement. NCCLS document M100-S9 national committee for laboratory standards, Wayne PA

Sheehan, J. C. and Grenda, V. *J.* (1962): The N-(2-Hydroxyarylidene) Protecting Group in Peptide Synthesis. *Journal of American Chemical Society.* 84, 2417–2420.

Sheldon, R. A. (2005). Green Solvents for Sustainable Organic Synthesis: State of the Art. *Green Chemistry* 7, 267–278.

Souza, A. O., Galetti F. C. S., Silva C. L., Bicalho, B., Parma, M. M. and Fonseca, S. F. (2007): Antimycobacterial and Cytotoxicity Activity of Synthetic and Natural Compounds. *Quim Nova* 30(7):1563–6.

Vadivela, T. and Dhamodaranba M. (2015): Synthesis, Characterization and Antibacterial Studies of Ruthenium (III) Complexes Derived from Chitosan Schiff Base. *International Journal of Biological Macromolecules.* biomac-5513; 9

Wang Guan-Wu, (2013): Mechanochemical Organic Synthesis. *Chemical Society Reviews* 42, 7668-7700. DOI 10.1039/C3CS35526H

Zhang, J., Zhao, F., Zhu, X., Wong, W.-K., Ma, D. and Wong, W.-Y (2012): New Phosphorescent Platinum(II) Schiff Base Complexes for PHOLED Applications. *Material Chemistry*. 22, 16448–16457