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Synthesis of new compounds of (5E,5'E)-5,5'-([1,1'-biphenyl]-4,4'-diylbis(azanylylidene))bis (3,3-dimethylcyclohexan-1-one) in new laboratory methods

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Abstract

Six new Schiff bases were synthesized via reaction of benzidine, [1,1'-biphenyl]-4,4'-diyldimethanamine, 3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diamine, 2,2'-dimethyl-[1,1'-biphenyl]-4,4'-diamine, ethane-1,2-diamine and propane-1,3-diamine with 5,5-dimethylcyclohexane-1,3-dione in acidic medium of acetic acid. The structures of new compounds were elucidated with NMR, FTIR, UV and elemental analysis and antimicrobial activity of them were applied. Three different methods were used Conventional, microwave and grinding methods, and concluded that the grinding and clicking method is the best in terms of the quantity of the product and the time required for the reaction to be very fast, As well as protecting the health of workers and the environment.

Keywords: Bis-Schiff bases, Ecofriendly method, antimicrobial activity.

1. Introduction

Schiff bases were synthesized via reaction of carbonyl compounds with amine compounds. Schiff bases has a wide variety of biological activities such as antimicrobial, [1] antitumor [2]anti-inflammatory with pharmacological activity[3].

It is well known that Schiff bases derived from different β-diketones and diamines are in ketimine-enolimine-ketamine tautomer, where the former appears to predominate [4-6]. However, some β-diketone Schiff bases were found to be tautomerized predominately into the enolimine tautomer [7]. On the other hand, UV spectral studies on Schiff bases derived from dimedone and monoamines have indicated that these Schiff bases exist almost entirely in the ketamine form[8].

There are many methods that used to synthesize Schiff base such as traditional, microwave, and click methods, the former depends on refluxing with stirring while microwave or click methods depend on ecofriendly steps such as grinding in mortar, microwave radiation that affects reactants through wavelength to afford products in pure form with less time. [9, 10]

Therefore, all the present work is aiming to synthesize a new series of Schiff bases via ecofriendly green method, that derived from reaction of benzidine, [1,1'-biphenyl]-4,4'-diyldimethanamine, 3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diamine, 2,2'-dimethyl-[1,1'-biphenyl]-4,4'-diamine, ethane-1,2-diamine and propane-1,3-diamine with 5,5-dimethylcyclohexane-1,3-dione and also the *in vitro* antimicrobial potency of the new compounds against the panel pathogenic bacteria and fungi strains were studied.

2. Experimental

UV spectra were measured on a PyeUnicam SP8- 200 UV- visible spectrophotometer. NMR spectra were measured on a Bruker 90 and 220 MHz NMR spectrometer, respectively, using TMS as reference in $CDCl_3$ at room temperature and Kenwood Mw 596 microwave oven is used in the chemistry department, Faculty of Applied Sciences, Hit, University of Anbar.

Synthetic methods of new compounds

A. Conventional method (intensive) [11]

In a Florence flask, 5,5-dimethylcyclohexane-1,3-dione 1 (0.02 mol , 2.1 g) in 20 mL absolute ethanol with continuous stirring and 0.5 mL acetic acid were added dropwise. Then diamine derivatives **2a-f** (0.01 mol) in absolute ethanol was added. The mixture was refluxed for 9h (TLC). The reaction was evaporated to afford a precipitate, recrystallized with ethanol. Yield: 66%, reddish-brown, m.p.295-296ºC.

B. Microwave method [12]

In a 250 ml flask, 5,5-dimethylcyclohexane-1,3-dione 1 (**0.02 mol**, 2.1 g) in 20 mL absolute ethanol with continuous stirring and 5 mL acetic acid were added dropwise. Then diamine derivatives **2a-f** (0.01 mol) in absolute ethanol was added. Shake the mixture using a microwave oven for one minute 300 W. Cool the

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mixture and the crystallization was made using ethanol. Yield: 75%, reddish-brown, m.p.295-296°C.

C. Click method [13]

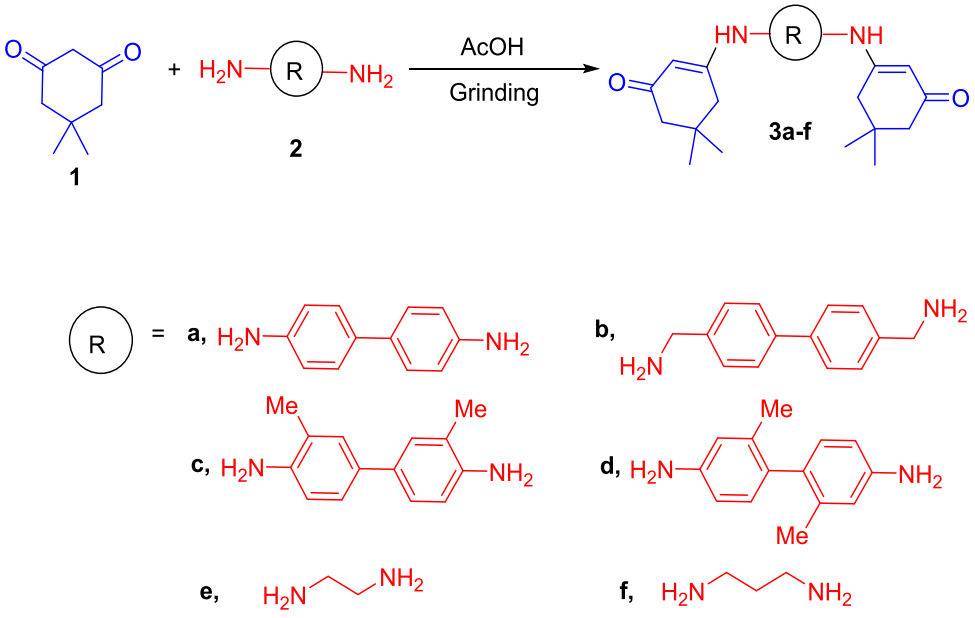
In the ceramic mortar, 5,5-dimethylcyclohexane-1,3-dione (**1**, 2.1 g) and 5 mL acetic acid were added dropwise. Then diamine derivatives **2a-f** (0.01 mol) was added. Then we grind the mixture with the pestle for a period ranging between two and three hours until the reaction is complete (TLC) by used Ethanol : water. Then we leave the precipitate to dry in the laboratory atmosphere, to get rid of the ethanol and water molecules, Yield: 95%, reddish-brown, m.p.295-296°C.

3. Antibacterial Activity

The microbial activities were carried out using the diffusion plate method[14-16]. A filter paper sterilized disk saturated with the measured quantity (25 μL) of the sample (1 mg/mL) was placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar) or a fungal medium (potato dextrose agar) that was seeded with the spore suspension of the test organism. After incubation at 37°C for 24 h for bacteria (in case of fungi, at 25°C for 72 h), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter × 100). All measurements were done in methanol as a solvent that has zero inhibition activity. The antimicrobial activity of the new compounds was examined against Gram positive bacteria *Bacillus subtilis*, and *Staphylococcus aureus*, as well as Gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginose*, *Acinetobacter baumannii* and two fungi *Aureobasiduim Pullans and Trichodermaviride*.

4. Results and Discussion

Herein, we utilized 5,5-dimethylcyclohexane-1,3-dione (**1)** of a simple manner in the synthesis of various derivatives of the corresponding bis-imino **3a-f** derivatives (Scheme 1). Compounds **3a-f** are proven according to full sets of analytical and spectroscopic data (*cf. Experimental*)[17].



Scheme 1: Synthesis of Schiff bases 3a-f

The most important features of structures **3a-f** are the presence of imino group around 3200 cm^{-1} in IR spectrum, while signals of cyclohexane H-2 at 5.38 ppm and imino proton (D_2O exchangeable) at 7.64 ppm in ^1H NMR spectra, aromatic protons at 7.44 (d, J = 7.5 Hz, 2H), 6.79 (d, J = 7.5 Hz, 2H), while cyclohexane CH_2 at 2.56 as singlet, and at 1.93 as doublet (*cf. Experimental*).

Table 1 has IUPAC names of new compounds while Table 2 and Scheme 2 represent the UV absorption bands dimedone amine in ethanol which are in good agreement with the previous UV spectral data [18, 20]. The bands of dimedone ethane-1,2-diamine and dimedone propane-1,3-diamine at 290 nm could be attributed to the dimedone part of the Schiff base molecule since the other parts are transparent in this region. Measurements of these bands in different polar and non-polar solvent showed negligible effect on the intensity which means that these compounds exist mainly in on form.[16]

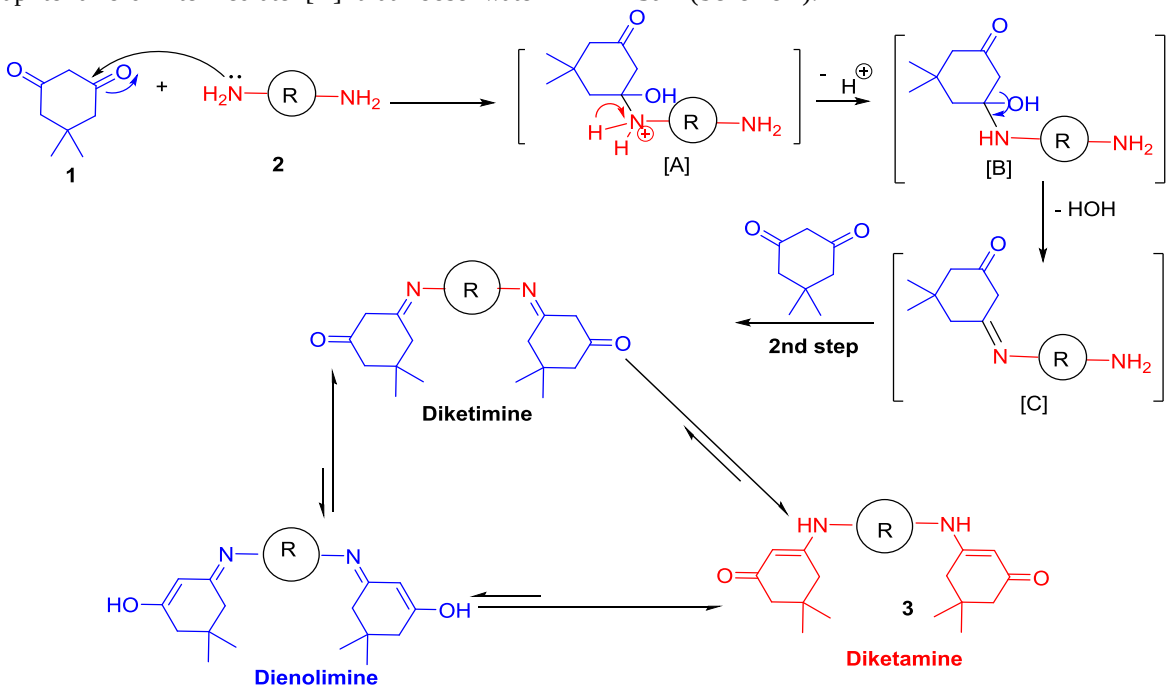
Table 1: IUPAC names of new compounds 3a-f [21]

No	IUPAC names
3a	3,3'-([1,1'-biphenyl]-4,4'-diylbis(azanediyl))bis(5,5-dimethylcyclohex-2-en-1-one)
3b	3,3'-(([1,1'-biphenyl]-4,4'-diylbis(methylene))bis(azanediyl))bis(5,5-dimethylcyclohex-2-en-1-one)
3c	3,3'-((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(azanediyl))bis(5,5-dimethylcyclohex-2-en-1-one)
3d	3,3'-((2,2'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(azanediyl))bis(5,5-dimethylcyclohex-2-en-1-one)
3e	3,3'-(ethane-1,2-diylbis(azanediyl))bis(5,5-dimethylcyclohex-2-en-1-one)
3f	3,3'-(propane-1,3-diylbis(azanediyl))bis(5,5-dimethylcyclohex-2-en-1-one)

Table 2: UV spectrum and physical properties of new compounds

	R	Elemental analyses			M.p	Color	Yield %	λmax, nm (£m²mol)
		C theoretical experimental	H theoretical experimental	N theoretical experimental				
3a	$C_{28}H_{32}N_2O_2$	78.47 77.56	7.53 7.21	6.54 6.49	295	Brownish Red	98	310 (2830), 225 (1050)
3b	$C_{30}H_{36}N_2O_2$	78.91 78.24	7.95 7.44	6.13 5.33	286	Brown pale	87	292 (2880), 280 (550)
3c	$C_{30}H_{36}N_2O_2$	78.91 78.57	7.95 7.46	6.13 5.92	288	Reddish Yellow	90	294 (2050), 208 (300)
3d	$C_{30}H_{36}N_2O_2$	78.91 78.55	7.95 7.42	6.13 5.88	279	Brown	93	308 (2100), 230 (660)
3e	$C_{19}H_{30}N_2O_2$	71.66 71.21	9.50 9.34	8.80 7.89	289	Yellow	98	290 (2800)
3f	$C_{18}H_{28}N_2O_2$	71.02 70.57	9.27 9.12	9.20 9.04	291	Pale white	94	290 (2600)

Mechanism of formation of new Schiff bases **3a-f** was depicted in Scheme 2, at which nucleophilic attack via lone pair of amino group to the carbon of carbonyl group to afford intermediate [A] that loose water molecule to afford intermediate [C] which under presence of another mole of 5,5-dimethylcyclohexane-1,3-dione (**1**), it reacts to afford diketimine derivatives **3a-f** (Scheme 2).



Scheme 2: Mechanism & synthetic rout of formation of 3a-f derivatives

Mainly in the ketamine form. The sharp signal, which appeared at about 1.06 ppm in the spectra of all compounds is due to the methyl groups of the dimedone part of the molecule, since both groups have the same chemical environments. The complete assignment of the proton NMR spectra is illustrated in tabl.3.

The ketoamine tautomer of dimedone amines appears to have a greater stability than the enolimine or ketiminetautomers, although the possibility of forming intermolecular hydrogen bonding is ruled out since the NMR spectra were measured in dilute CDCI3 solutions and there is no possibility of forming intramolecular hydrogen bonding between N-H and C=O groups since they are too far to form such bonding.

Spectra when R=n- propyl and biphenyl determines the position of carbon atoms of (- $CH_2CH_2CH_2$-) and biphenyl groups, whereas the comparison be- tween the spectra when R=biphenyl and R=(m or p -bitolyl) indicates the position of CH_3 signal. The signal, which lies at low field in the carbon- 13 NMR spectra of all our compounds is attributed to C-3 (fig.3), namely the carbon of the carbonyl group.

The infrared spectra also confirms the confirmation of prepared compounds. For example, there is a single-phase bundle (N-H) in the 3285 cm^{-1} range. And the absence of the package (N =C) in the range 1700 - 1800 cm^{-1} and the carbonyl beam (C=O) 1583, 1612 cm^{-1} double pack[22]. Add the other packages to each composite. As shown in table 5 and fig. 6.

Table 3: ^{1}H NMR

	No. of H atom				δ, i.m	Proton of R δ,i,m
	2	4	6	7	8	
3a	5.56 (2.s)	2.33 (2.s)	2.19 (2.s)	1.08 (12.s)	7.09 (2.s)	7.13(2.s), 7.15(2.s), 722(2.s), 7.28(2.s).
3b	5.10 (2.s)	2.24 (4.s)	2.10 (4.s)	1.03 (12,s)	5.79 (2.s)	4.20(4.d), for 2CH_2, 7.28(10.s) biphenyl.
3c	4.94 (2.s)	2.33 (4.s)	2.13 (4.s)	1.05 (12.s)	6.74 (2.sb)	2.15(6.s) for 2o-CH_3, 7.18(4.s)-7.10(4.s)for ph.
3d	4.56 (2.s)	2.33 (4.s)	2.18 (4.s)	1.05 (12.s)	6.90 (2.sb)	2.29(6.s),for 2m-CH_3, 6.98-7.18 (8,mu)for ph.
3e	5.11 (2.s)	2.19 (4.s)	2.18 (4.s)	1.03 (12.s)	4.56 (2.sb)	3.03(2.q), 1.62(mu), 0.95 (6,t).
3f	5.11 (2.s)	2.20 (4.s)	2.18 (4.s)	1.07 (12.s)	5.00 (2.sb)	3.04(2,mu), 1.54(4,mu), 0.92(6,t), 1.18(2,mu).

δ, Chemical shift in ppm relative to TMS. i, Intensity. m, Multiplicity. s, Singlet. sb, Singlet broad. d, Doublet. t, Triplet. q, Quartet. mu, Multiplet.

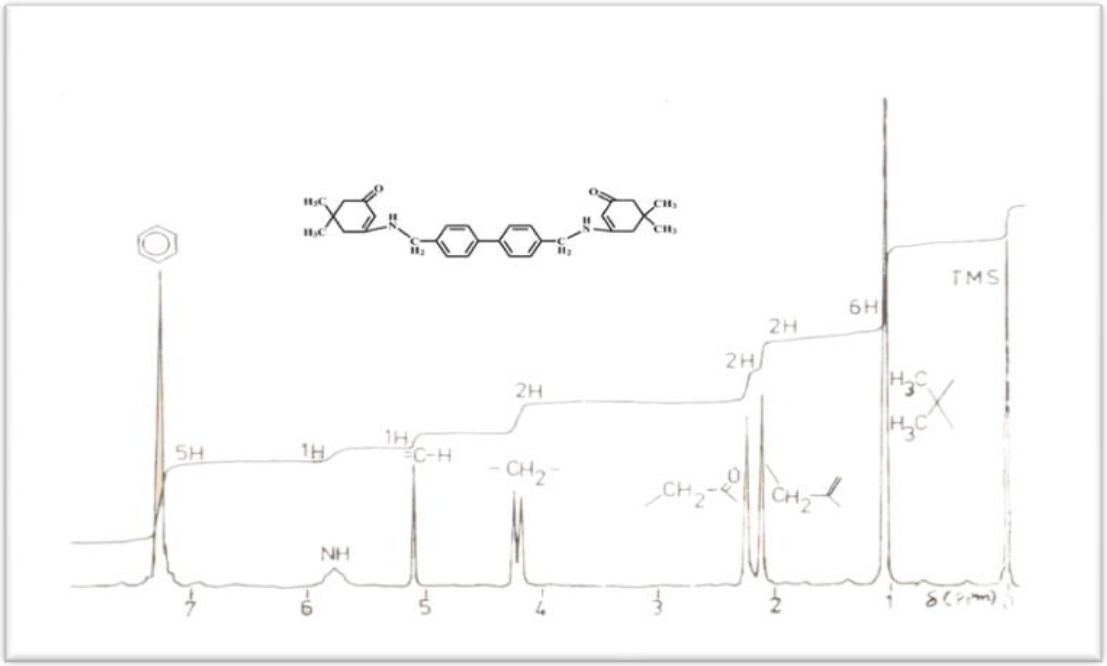


Figure (4).1H NMR spectrum of 3a

Table 4: ^{13}C –NMR of new compounds 3a-f

N. co.	No. of C atom							Carbon atom of R δ Ar
	1	2	3	4	5	6	7	
	δ. Ppm							
3a	161.79	97.81	197.96	50.43	32.69	43.21	28.20	123.93, 125.30,129.20, 138.63
3b	163.77	95.53	196.76	50.36	32.69	43.08	28.20	46.85, 127.32, 128.68, 137.19
3c	163.64	96.96	197.24	50.36	32.75	42.63	28.14	17.61, 127.66, 127.56, 130.95, 134.66, 136.60
3d	161.43	98.20	197.96	50.56	32.75	47.42	28.27	21.31, 121.07, 138.55, 139.20, 124.58, 129.09
3e	163.19	94.62	196.27	50.36	32.69	49.84	28.92	10.39, 19.49, 44.71, 43.47
3f	162.99	95.40	196.72	50.30	32.75	43.61	28.87	11.43, 21.83,

δ, Chemical shift in ppm relative to TMS.

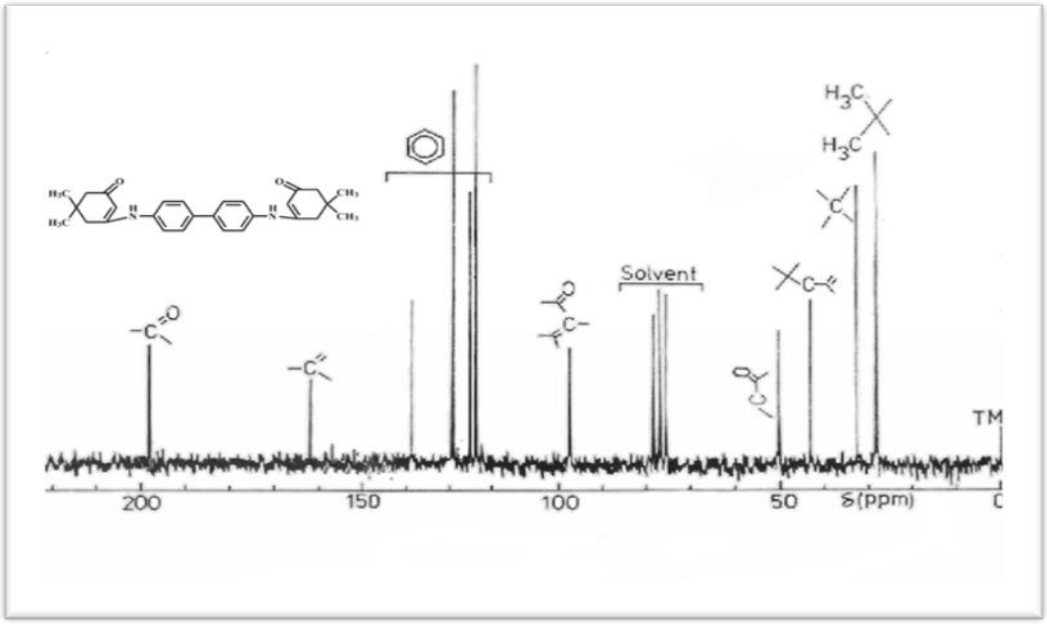


Figure 5: 13C NMR spectrum of 3a

Table (5).IR spectrum of new compounds 3a-f

No.co.	Spctro. IR. Cm^{-1}								
	Di-β-Kataimine							R	
	N-H	N-C	C=O	C=C	CH_2	CH_3	CH	Other	cm^{-1}
3a	3285	1313	1612	1583	1421	1223	3092	Ph-Ph, C-H	1507,938
3b	3288	1347	1625	1574	1432	1220	3084	Ph-Ph,Ph-CH_2 C-H	1611,1370 1389
3c	3421	1354	1633	1577	1457	1237	3088	Ph-Ph O-CH_3,C-H	1620 1375,1385
3d	3427	1344	1628	1586	1402	1248	3121	Ph-Ph,m-CH_3 C-H	1590,1377 1361
3e	3358	1349	1654	1612	1489	1268	3057	CH_2-CH_2,C-H	1374,1485
3f	3388	1351	1658	1627	1458	1279	3098	CH_2-CH_2,C-H	1380,1250

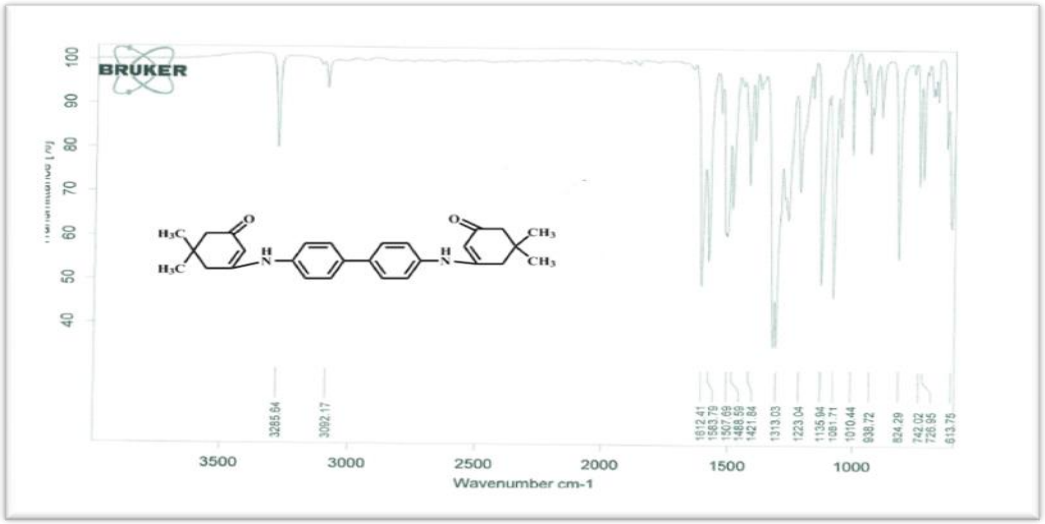


Figure 5: IR spectrum of 3a

5. Antimicrobial activity

The antimicrobial activity of the new compounds was examined against Gram positive bacteria[23] *Bacillus subtilis*, and *Staphylococcus aureus*, as well as Gram negative bacteria[24] *Escherichia coli*, *Pseudomonas aeruginose*, *Acinetobacter baumannii* and two fungi *Aureobasiduim Pullans and Trichodermaviride* (Table 6 and Table 7).

Table 6: Antibacterial activity

No. Co.	Con. ppm	*Bacillus Subtilis*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Acinetobacter*	*Escherichia coli*
3a	100	4	9	11	10	14
	250	10	13	12	14	12
	500	5	12	---	16	10
	1000	16	19	18	9	8
3b	100	8	7	12	7	9
	250	12	8	15	15	20
	500	5	16	11	--	
	1000	8	--	18	16	16
3c	100	--	--	7	8	--
	250	12	--	10	--	11
	500	7	8	--	17	9
	1000	--	5	9	14	6
3d	100	11	20	17	16	22
	250	17	19	--	22	15
	500	16	15	21	13	16
	1000	20	16	18	19	9
3e	100	--	1	-	10	13
	250	10	--	9	9	--
	500	--	13	--	7	14
	1000	5	8	11	12	--
3f	100	7	15	12	9	11
	250	12	4	45	--	9
	500	8	11	8	13	10
	1000	4	12	9	10	8
Con.DMSO		-	-	-	-	-

Table 7: Antifungal activity

Com.	Con. mg/ml	Fungi	
		Aureobasidium	Trichoderma
3a	50	12	15
	100	13	17
	200	12	9
3b	50	27	11
	100	25	18
	200	14	22
3c	50	10	14
	100	15	29
	200	27	17
3d	50	26	28
	100	16	28
	200	25	10
3e	50	13	13
	100	27	21
	200	18	19
3f	50	10	10
	100	14	23
	200	15	27

The tested compounds showed various activity from moderate to higher activity (Table 6). The selectivity and safety profile of the tested compounds requires further studies.

6. Conclusion

From above results, we can conclude that Schiff bases that prepared via various methods can be prepared with ecofriendly methods of grinding with higher product ratio than the previous method, After comparing it with traditional and microwave methods, and concluded that the grinding and clicking method is the best in terms of the quantity of the product and the time required for the reaction to be very fast, As well as protecting the health of workers and the environment.

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