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Microwave Assisted Synthesis of Pyromellitdiimide Bis Schiff Bases and Evaluation of Their Antimicrobial Activity

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Abstract

The present work involved synthesis a series of new pyromellitdiimide bearing two Schiff base components through performing several steps. Compound (1) was synthesized in first step, N, N`-bis[(4-acetophenyl)pyromellitamic acid] through reaction two moles of 4-amino acetophenone with pyromellitic anhydride in acetone solvent with stirring for two hours. Compound (1) was dehydrated in the second step by fusion process in sand bath for two hours affording compound (2), N, N-bis[(4-acetophenyl)pyromellitdiimide]. Third step involved adding compound (2) in acid_ catalyzed condensation reaction with various primary aromatic amines under the influence of microwave irradiation for (10-15) minutes producing the target bis Schiff bases (3-6), this technique has many advantages it is simple, safe, clean, very fast with high yields unlike traditional method that are costly and risky. Based on spectroscopic data FTIR, 1H-NMR and 13C-NMR, the structures of newly synthesized bisschiff bases were confirmed. Results of antimicrobial activity screening of compounds (3-6) indicated that most of them showed potent activity against gram positive bacteria (staphylococcus aureus), gram negative bacteria (E-Coli) and type of fungi (candida albicans), compounds (3) and (4) had strong inhibition against bacteria but weak inhibition against fungi since compounds (5) and (6) had strong inhibition against bacteria and moderate inhibition against fungi.

Keywords:

Pyromellitdiimide, Bis Schiff base, Fusion process, Microwave, Antimicrobial

Schiff bases the compounds that carrying azomethine functional group have attracted attention of researcher's duo to their extensive variety of biological activities such as analgesic(EL-Gammal et al., 2019), antituberculosis(Bandyopadhyay et al., 2017),anti-inflammatory(El-Gammal et al., 2021), antimicrobial, antioxidant activities(Saleem et al., 2021).

The presence of imine group is essential for exhibiting them this spectrum of biological activities (Rakesh et al., 2015). Schiff bases are also played vital role as important intermediates in organic synthesis and as ligands for metal complexation(EL-Gammal et al., 2019&Bandyopadhyay et al., 2017).

On the other hand, cyclic imides the compounds that possess bis amide linkages with common nitrogen represent very valuable group of bio active compounds with variety of biological activities including in anti-inflammatory, anticancer (Sondhi et al., 2010), analgesic (Borchhardt and Andricopulo, 2009), antimicrobial (Fadel and Al-Azzawi, 2021) and antibacterial activities (Fadel and Al-Azzawi, 2022).

Besides cyclic imides are important core structure present in many drugs and pharmaceuticals.

Based on the previously stated information we determined that it wasworthwhile to design and synthesis of new molecules by combining the two active pharmacophores (Schiff base and Imide)

together in single molecular frame and these definitely are expected to exhibit interesting biological activities.

Materials and Methods

All chemicals for this research were obtained from Merk, Fluka and BDH companies.Melting points of the prepared compounds were determined on Thomas Hoover apparatus.

FT-IR spectra were measured by SHIMADZU FT-IR-8400 spectrophotometer whereas1H-NMR and 13C-NMR were measured by BRUKER ultra-shield 400MHZ in University of Basrah and BRUKER BiospinGmbh in Tahran using DMSO-d6 and CDCl3 as solvent and TMS as internal standard

Synthesis of N, N`-bis (4-acetophenyl) pyromellitamic acid (1)

A soluation of 4- amino acetophenone (20 mmol, 2.70 gm) in (25 mL) acetone, added as small portion to the solution (10 mmol, 2.18 g) of pyromellitic anhydride dissolved in(30 mL) acetone with stirring at 25 °C (Fadel and Al-Azzawi, 2021).

The time of reaction was (2hr), the resulted solid product filtered, dried and the physical properties for compound (1) on Table(1)

Synthesis of N, N`-bis (4- acetophenyl) pyromellitdiimide (2)

Synthesis of the titled compound was performed via dehydration of amic acid (1) using fusion method. In sand bath compound (1) was heated until it completely melted and then the temperature was elevated for over the compound`s (1) melting point with keeping this condition for two hours(Fadel and Al-Azzawi, 2021). the resulted solid after cooling to room temperature was collected and all the physicalproperties for compound (2) on Table(1)

Synthesis of N,N`-bisschiff base pyromellitdiimide (3-6) by Microwave Technique

A mixture of compound (2) (1mmol, 0.45g), primary aromatic amine (2 mmol) was grinded and mixed thoroughly, then added to the mixture with stirring (2 mL) of ethanol absolute and acetic acid glacial (1 drop). The resulted homogenous mixture was irradiated by microwave for (10-15) minutes(Taha et al., 2018)(Al-Azzawi and Raheem, 2017), All the physical properties of compound (3-6) on Table (2)

Antimicrobial study

The antimicrobial study of the prepared compounds were tested against two types of bacteria staphylococcus aureus (as appositive bacteria type),E-coli (as a negative bacteria type) and one type of fungi (candidaalbicans).

The tested compounds solution were prepared at concentration (0.1g/mL) applied the cup plate technique, which used nutrient agar media, the petri dishes were incubated at 37°C for (48hr)(Al-Azzawi and Mahdi, 2013)(Al-Azzawi and Hassan, 2014).

The inhibition zone was measured in (mm) and summarized in Table (7)and Figure (1).

Results and Discussion

Considering that Schiff bases and cyclic imides are both significant compounds which exhibit various biological activities and having wide spectrum of important applications the aim of this work is directed towards synthesis of new compounds which their molecules comprising these two active components together as well as the predicted high biological activity.

Synthesis of the target compounds (bisimidyl Schiff base) in this work based on synthesis of bis cyclic imide already substituted with carbonyl groups via choosing 4-amino acetophenone as primary amine and introduce it in reaction with di anhydride (pyromellitic anhydride) producing bisamic acid (1) and this in turn was dehydrated by fusion producing compound (2) which is bis cyclic imide carrying two ketone carbonyl groups. In this work compound (2) is the key compound from which we can synthesized the target bis Schiff bases since compound (2) containing two ketone groups ready to introducing in condensation reaction with two moles of aromatic primary amines producing corresponding bisimidylschiff bases (3-6).

All steps are shown in scheme (1)while physical properties of compounds (1-2) and compounds (3-6) are listed on Tables (1) and Table (2) respectively.

Synthesis of compounds (3-6) was performed by depending on microwave irradiation since this technique has many advantages it is simple, safe, clean, very fast with high yields while performing synthesis of bis Schiff bases by conditional method need reflux for many hours for reaction completion with lower yields(Satyanarayana et al., 2008).

It is important to mention here that for comparison purpose we perform synthesis of new bisschiff bases (3-6) also by conventional method via heating one mole of compound (2) and two moles of aromatic primary amines with ethanol absolute and few drops of HOAc glacial under reflux with eight hours(Kadhim and

Khalaf, 2023)(Abdulrasool et al., 2017). The products are collected, dried and purified by suitable solvents. It is noticeable that the prepared compounds by the two methods (conventional and microwave) showed the same melting points and the same FT-IR spectra but the yield is lower and time for completion reaction is too long in conventional method, thus it is too preferable to apply synthesis by microwave method.

FT-IR, 1H-NMR and 13C-NMR data were used to confirm the chemical structure of the synthesized compounds.

FT-IR spectrum of compound (1) showed characteristic absorption bands at (3228-3454) cm-1 related to ν(OHcarboxyl) and ν (NH amide).

Other absorption bands appeared at (1700) cm-1, (1687) cm-1, (1635) cm-1, and (1591,1562) cm-1related tον(C=O) carboxyl, ν (C=O) ketone,ν(C=O)amide and ν(C=C) respectively.

FTIR spectrum of compound (2) showed disappearance of ν (OH) and ν (NH) absorption bands and appearance of clear absorption bands at (1785)cm-1 (1726)cm-1 and (1685)cm-1 which are related to asym.ν (C=O) imide, sym. ν(C=O) imide and ν(C=O) ketone respectively(Kumar et al., 2015).

FTIR spectra of compounds (3-6) displayed new absorption bands at (1622-1641) cm-1related to ν (C=N) imine proving the success of bis Schiff bases preparation. The spectra showed absorption band at (1776-1784) cm-1 and (1726) cm-1related to asym. and sym. ν (C=O) imide.

And other bands at (1396-1398)cm-1 and (1550-1602)cm-1related to ν (C-N)imide and ν (C=C) respectively(Azzawi and Al-Obiadi, 2016)(Shinde et al., 2014).

Tables (3) and (4) include all the details of FTIR spectral data of compound (1) and compounds (3-6) respectively.

whereas, 1H-NMR spectrum of compound (1) presented signals that belong to the proton of two methyl groups at (δ=2.37) ppm and signal at (δ=6.55-7.67) ppm belong to aromatic protons, while signals for protons that belong to (NH amide) and (OH carboxyl) appeared at (δ=7.93) and (δ=11.00) ppm.

Disappearance of signals that belong to (NH) and (OH) protons in 1H-NMR spectrum of compound (2), indicating success of dehydration reaction. The spectrum presented signals at (δ=2.51-2.56) ppm and (δ=6.63-7.82) ppm which related to methyl protons and aromatic protons respectively.

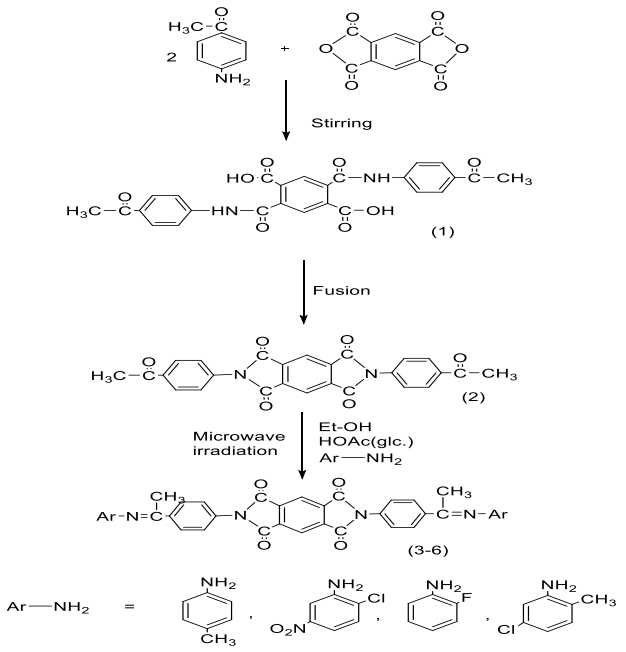
1H-NMR spectra of Schiff bases (3-5) presented signals at (δ=1.91-2.60) ppm related to protons of two CH3 and signals at (δ=6.37-8.11) ppm related to aromatic protons. Compound (3) presentedsignals at (δ=1.88) ppm related to protons of two CH3 group bonded to phenyl rings.

13C-NMR spectra of compounds (1-5) presented clear signals that belong to (CH3) and aromatic carbons. 13C-NMR spectrum of compounds (1) presented signals that related to (C=O) amide, (C=O) carboxyl and (C=O) ketone carbons, while 13C-NMR spectrum of compounds (2) presented signals related to (C=O) imide and (C=O) ketone carbons.

13C-NMR spectra of compounds (3-5) presented signals that related to (C=N) and (C=O) imide carbons(Al-Azzawi and Jassem, 2016).

All details of 1H-NMR and 13C-NMR spectral data of the prepared compounds are listed on Tables (5) and (6) respectively.

Antimicrobial activity study



Scheme (1) Synthetic steps for compounds (3-6)

The synthesized compounds (bis Schiff bases) were tested for antimicrobial activity against gram positive bacteria (staphylococcus aureus), gram negative bacteria (E-Coli) and type of fungi (candida albicans).

To investigate the antimicrobial property for bis Schiff bases compounds by measured the inhibition zone in (mm) unit and we used Methoprim and Amoxicillin as standard drugs against microbials while, DMSO as a control as shown in Figure (1). second group for compounds (5) and (6) had strong inhibition against bacteria and moderate inhibition against fungi as shown in Chart (2).

The prepared compounds were categorized in two groups, the first group for compounds (3) and (4) had strong inhibition against bacteria but weak inhibition against fungi as shown in Chart (1), The

Table (1) Physical properties of compounds (1-2)

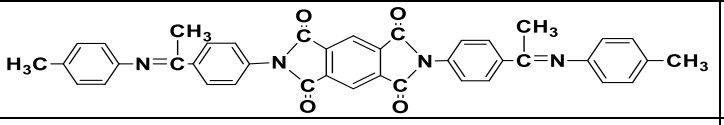
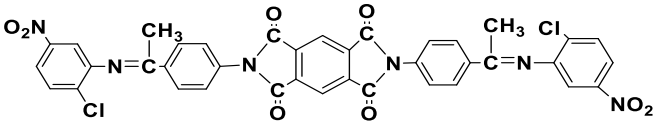
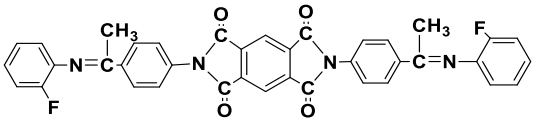
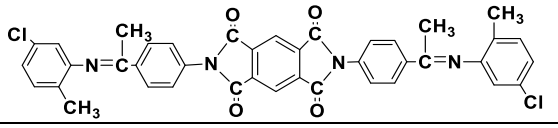
No. of Comp.	Compound	M.P (°C)	Color	Percent yield%	Purification solvent
3		>300	Gray	81	hexane
4		>300	brown	78	dioxane
5		>300	Pale-brown	85	dioxane
6		>300	brown	82	hexane

Table (2) Physical properties of compounds (3-6)

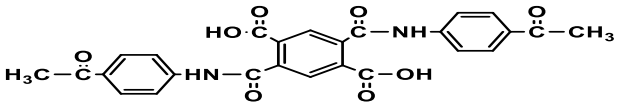
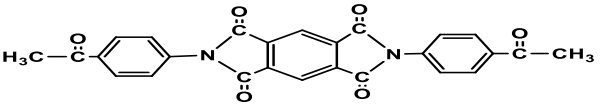
No.of Comp.	Compound	M.P (°C)	Color	Percent Yield%	Purification solvent
1		290-291.	Bright yellow	95	ethanol
2		260 dec.	Dark brown	60	acetone

Table (3) FTIR spectral data (cm-1) of compounds (1-2)

No. of Comp.	ν (O-H) carboxyl	ν (N-H) amide	ν (C-H) aromatic	ν (C-H) aliphatic	ν (C=O) carboxyl	ν(C=O) ketone	ν (C=O) amide	ν (C=C)
1	3454 3363	3228	3060 3024	2920 2815	1700	1687	1635	1591 1562

No. of Comp.	ν (C-H) aromatic	ν (C-H) aliphatic	ν (C=O) imide	ν (C=O) ketone	ν (C=C)	ν (C-N) imide
2	3060 3002	2977 2879	1785 1726	1685	1600 1575	1398

Tables (4) FTIR spectral data (cm-1) of compounds (3-6)

No. of Comp.	ν (C-H) aromatic	ν (C-H) aliphatic	ν (C=O) imide	ν (C=N) imine	ν (C=C)	ν (C-N) imide	Others
3	3076	2979 2885	1780 1726	1641	1602 1558	1398	-
4	3066	2952 2921 2852	1776 1726	1625	1585	1396	ν (NO2) 1488 1318
5	3066	2918 2848	1782 1726	1641	1598 1566	1396	-
6	3062	2918 2850	1784 1726	1622	1602 1550	1396	-

Table (5) 1H-NMR spectral data of compounds (1-5)

No. of Comp.	1H-NMR spectral data (ppm)
1	(δ=2.37)ppm (6H, protons of 2 CH3), (δ=6.55-7.67)ppm (10H,aromatic protons), (δ=7.93)ppm (2H, NH protons), (δ=11.0) ppm (2H, OH carboxyl protons).
2	(δ=2.51-2.56)ppm (6H, protons of 2CH3) , (δ=6.63-7.82)ppm (10H, aromatic protons).
3	(δ=1.88) ppm (6H, protons of 2 CH3 bonded to phenyl), (δ=2.55)ppm (6H, protons of 2 CH3 bonded to imine), (δ= 6.37-7.96)ppm (18H, aromatic protons).
4	(δ=1.91-1.92)ppm (6H, protons of 2 CH3), (δ=6.37-6.71)ppm (16H, aromatic protons)
5	(δ=2.60)ppm (6H, protons of 2 CH3), (6.70-8.11)ppm (18H, aromatic protons)

Table (6) 13C-NMR spectral data of compounds (1-5)

No. of Comp.	13C-NMR spectral data (ppm)
1	(δ=26.30)ppm (CH3 carbons), (δ=112.99-135.09)ppm (aromatic carbons), (δ=153.98)ppm (C=O)amid carbons, (δ=167.78)ppm (C=O) carboxyl carbons , (δ=195.43)ppm (C=O)ketone carbons
2	(δ=26.09)ppm (CH3 carbons), (δ=113.40-142.62)ppm (aromatic carbons), (δ=151.15)ppm (C=O)imide , (δ=162)ppm (δ=196.56)ppm (C=O)ketone carbons
3	(δ=29.14-31.24)ppm (CH3 carbons), (δ=112.47-152.46)ppm (aromatic carbons), (δ=162.0)ppm (C=N) imine carbons , (δ=178.0)ppm (C=O) imide carbons.
4	(δ=21.54)ppm (CH3 carbons), (δ=114.80-136.99)ppm (aromatic carbons), (δ=144.43)ppm (C=N), (δ=172.54)ppm (C=O) imide carbons.
5	(δ=29.39-29.40)ppm (CH3 carbons), (δ=133.20-159.22)ppm (aromatic carbons), (δ=164.16)ppm (C=N), (δ=175.78) ppm (C=O) imide carbons.

Table (7) The inhibition zone (mm) unit for bis Schiff bases compounds

	Staph.	E-Coli	Candida
DMSO	8	8	8
Amox.	34	35	22
Meth.	33	32	29
(3)	25	30	10
(4)	30	32	10
(5)	33	31	22
(6)	28	24	20

Strong (25-35 mm), Moderate (12-24 mm), Weak (8-11 mm)

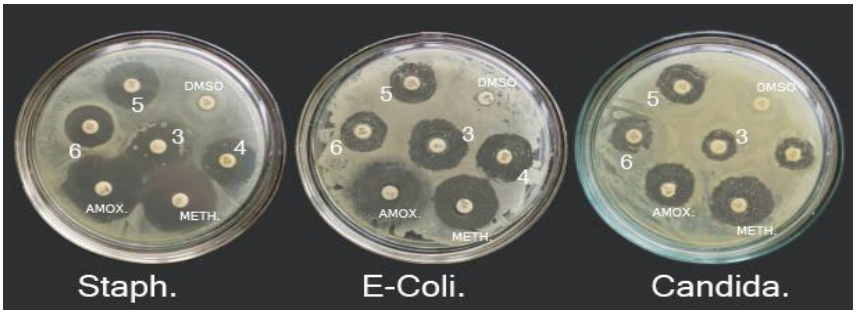


Figure (1) Antimicrobial Study for bis Schiff bases compounds (3,4,5,6)

Conclusion

The prepared compounds that bearing two Schiff bases components in addition two cyclic imides, confirm using spectral analysis FTIR, 1H-NMR and 13C-NMR showed perfect results against bacterial and fungi, that may able to discover in future new drugs treat microbial diseases or fight different types of bacterial.

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