ISSN: 0067-2904

Synthesis and Characterization of New Bis-Schiff Bases Linked to Various Imide Cycles

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Received: 8/9/2022 Accepted: 20/11/2022 Published: 30/3/2023

Abstract

This research includes the synthesis of new bis-Schiff bases linked to different imide cycles. There were some steps involved in the synthesis of the novel Schiff bases with succinimide, phthalimide, tetrachlorophthalimide, and tetrabromophthalimide cycles. The first step involved the preparation of 4,4`-bis[(4-aminophenyl) methyl benzylidene]tolidine (**1**) *via* the condensation reaction of 3,3'-dimethyl-(1,1'-biphenyl)-4,4'-diamine with 4-amino acetophenone. In the second step, compound **1** reacted with various cyclic anhydrides, affording bis-amic acid Schiff bases **2**-**5**. In the third step, the products 2-5 were dehydrated using the fusion method to produce the target bis-imidyl Schiff bases **6**-**9**. This work also involved the synthesis of bis-imidyl Schiff base **10** directly by fusion of compound **1** with 1,8-naphthalic anhydride. The prepared compounds were characterized depending on their FT-IR, ^{1}H NMR, and ^{13}C NMR spectra. The newly synthesized target compounds are expected to be very active biologically since their molecules are essential components of two active groups (imine and imide).

Keywords: Bis-Schiff bases, bis-imidyl Schiff bases, Bis-amic acid, cyclic imides, O-tolidine.

تحضير وتشخيص بعض ثنائي قواعد شيف جديده مرتبطة بحلقات أيمايد مختلفة

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الخلاصة

يتضمن هذا البحث تحضير ثنائي قواعد شيف جديدة مرتبطة مع أيمايدات حلقية مختلفة. تم تحضير ثنائي قواعد شيف الجديدة التي تحتوي على حلقات سكسن أيمايد,فثال أيمايد ,رباعي كلوروفثال أيمايد ورباعي بروموفثال أيمايد بعدة خطوات حيث تضمن الخطوه الاولى تحضير مركب **(1)** وهو 4,4`-ثنائي [(4-أمينو فنيل)مثيل بنزيليدين]توليدين وذلك من خلال تفاعل التكاثف بين المركبين 3,3-ثنائي مثيل(1,1- ثنائي فنيل)-4,4`-ثنائي امين و 4-امينو استوفينون. أما الخطوة الثانية فقد تم ادخال المركب **(1)** في تفاعل مع أنهدريدات حلقية مختلفة للحصول على مركبات ثنائي حامض الاميك قواعد شيف **(2-5)** وهذه بدورها تم سحب الماء منها في الخطوه الثالثه باستخدام تقنيه الصهر مما اسفر عن تكوين المركبات الهدف وهي ثنائي ايمايد قواعد شيف **(6-9)** . اضافه الى ذلك تضمن البحث ايظاً تحضير ثنائي قاعده شيف **(10)** المرتبطه مع 1, 8 -انهدريد النفثاليك . تم تشخيص المركبات المحضره اعتماداً على مطيافية الاشعة تحت الحمراء

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والرنين النووي المغناطيسي للبروتون والكاربون 13 . من المتوقع ان تظهر هذه المركبات الهدف المحضره في هذا البحث فعاليه بايولوجية سيما وان جزيئاتها قد بُنيت اساساً من مكونتين فعالتين بايولوجياً.

1. Introduction

A lot of interest has been paid to Schiff's base compounds that contain (carbon-nitrogen) double bonds because of their ease of synthesis and various applications [1-2]. These important compounds are usually formed *via* the condensation of primary amines with carbonyl compounds (aldehyde or ketone) [3]. The presence of imine linkage (-C=N-) in the Schiff base molecules is essential for exhibiting these compounds' wide spectrum of biological applications like analgesic, antimicrobial, antioxidant, antiviral, anticancer, and anti-inflammatory activities [4-8].[1] Besides, Schiff bases have various applications in many fields, including analytical chemistry, corrosion inhibitors, dyes, and ligands for metal complexes [9-11]. However, cyclic imides are organic compounds because they have biological activity, such as antibacterial, anticancer, analgesic, anti-inflammatory, and antimicrobial activities [12-15]. Moreover, cyclic imides are essential building blocks for the synthesis of pharmaceuticals, natural products, polymers, and drugs [16-17]. Depending on all the above facts, we believe it is very worthwhile to synthesize new molecules that combine these two active biological components (Schiff base and imide cycle) since they exhibit various biological activities.

2. Experimental part

The melting points of synthesized compounds were measured on the Thomas Hoover melting point apparatus and on the Shimadzu FTIR-8400 Fourier Transform Infrared spectrophotometer using KBr pellets. While their ^{1}H NMR and ^{13}C NMR were recorded in DMSO-d_6 on the Bruker 400MHZ instrument, the internal standard is TMS.

2.1. Synthesis of 4,4`-bis-[(4-aminophenyl)methylbenzylidene]tolidine (1)

A mixture of 3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diamine (2.12 g, 10 mmol) and 4-aminoacetophenone (2.7 g, 20 mmol) in ethanol absolute (35 mL) and glacial acetic acid (500 µL) was refluxed for 12 hours [18]. When the reflux had reached its completion, the reaction mixture was cooled to room temperature, and the solid-crude material was filtered, washed with ethanol, dried, and then recrystallized from acetone to give the title product **1**.

2.2. Synthesis of bis-(amic acid Schiff bases) 2-5

A solution of compound **1** (2.23 g, 5 mmol) in acetone was added dropwise through a dropping funnel to succinic, phthalic, tetrachlorophthalic, or tetrabromophthalic anhydride (10 mmol) in acetone (20 mL), with stirring and cooling [18]. After the completion of the addition, the reaction mixture was stirred for 2 hours. The solid-crude material was then filtered, dried, and recrystallized using a suitable solvent to afford the desired products **2-5**.

2.3. Synthesis of bis-imidyl Schiff bases 6-9

Bis-amic acid Schiff bases **2-5** were heated in a sand-bath until complete fusion, and then the temperature was raised to many degrees above the melting and held there for 2 hours [12]. The solid-crude material that resulted was recrystallized from a suitable solvent to yield the title products **6**-**9**.

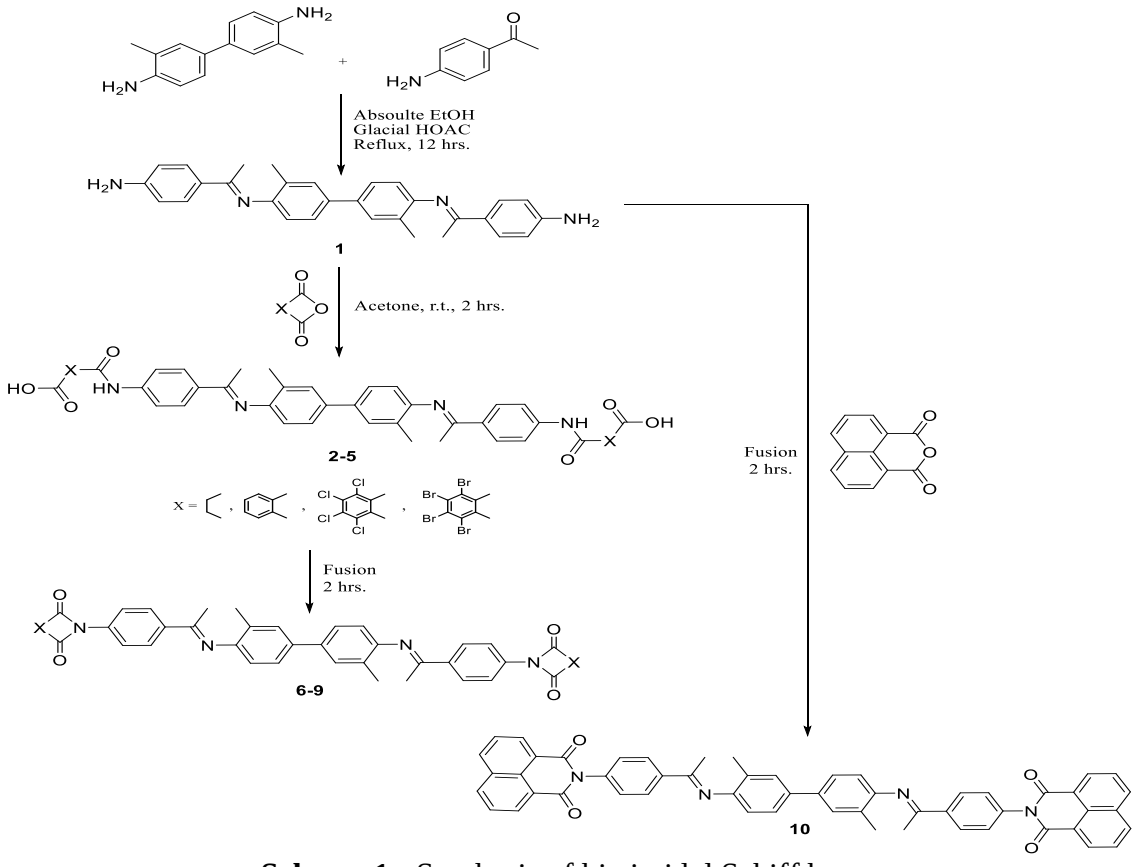
2.4. Synthesis of bis-naphthalimidyl Schiff base (10)

Following the same process employed in the synthesis of compounds **6**-**9**, a mixture of compound **1** (2.23 g, 5 mmol) and naphthalic anhydride (1.98 g, 10 mol) was grinded and

combined before being heated in a sand-bath for 2 hours. The resulting solid-crude material was recrystallized from ethanol to give the desired product **10**.

3. Result and discussion

The primary aim of this research is to develop novel compounds by combining these two active components (Schiff bases and cyclic imides) into a single molecule, followed by testing their antibacterial activity. Schiff bases and cyclic imides are both well-known, significant classes of organic compounds that exhibit various biological activities. Since the target compounds were just produced and have already been built with biologically active components, it is expected that they will have strong anti-bacterial activity. Many steps were performed to synthesize the target compounds, which are presented in Scheme 1. In the first step of preparing 4,4-bis[(4-aminophenyl)methylbenzylidene]tolidine (**1**), 3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diamine (one equivalent) and 4-aminoacetophenone (two equivalents) were combined in a condensation reaction with glacial acetic acid as a catalyst and absolute ethanol as a solvent for 12 hours [12]. Compound **1** represents the key material in our work since it contains two imine groups (Schiff bases) and two amino groups ready for introduction in subsequent reactions. Thus, in the second step, compound **1** was introduced in the reaction with different cyclic anhydrides, including succinic, phthalic, tetrachlorophthalic, and tetrabromophthalic anhydrides in acetone, producing the corresponding bis-amic acids **2-5** [18]. The third step includes the dehydration of compounds **2-5** using a fusion technique, giving the title products **6-9**. In addition, the fusion of compound **1** with 1,8-naphthalic anhydride affords bis-naphthalimidyl Schiff base **10**. The physical characteristics of compound **1** are reported in Table 1, whereas those of compounds **2-5** and **6-10** are shown in Tables 2 and 3**,** respectively.



Scheme 1 - Synthesis of bis-imidyl Schiff bases

Based on the data from their FT-IR, ^{13}C NMR, and ^{1}H NMR spectra, the chemical structure of the synthesized compounds was identified. The FT-IR spectral data of compound **1** showed absorption bands at 3463-3334 cm^{-1} related to $\nu(NH_2)$ and other absorption bands at 1645 cm^{-1}, and at 1591 and 1560 cm^{-1} belonging to ν(C=N) and ν(C=C) aromatic, respectively [19]. The ^{1}H NMR spectrum of compound **1** presented chemical shifts at 2.50 and 2.43 ppm attributed to the three protons of the two CH_3 groups. Other signals appeared at 4.75 ppm and from 6.03 to 7.69 ppm, which are due to NH_2 protons and aromatic protons, respectively [19]. Details of FT-IR and ^{1}H NMR spectral data for compound **1** are reported in Table 4. The FT-IR spectra of bis-amic acid Schiff bases **2-5** revealed distinct absorption bands at 3402-3463 cm^{-1} and 3228-3359 cm^{-1}, which correspond to ν(O-H) carboxylic and ν(N-H) amide, respectively. Other stretching bands are found at 1695-1720 cm^{-1}, 1650-1970 cm^{-1}, 1639-1656 cm^{-1} and 1554-1595 cm^{-1} for ν(C=O) carboxylic, ν(C=O) amide, ν(C=N) and ν(C=C), respectively [19]. On the other hand, FT-IR spectra of bis-imide Schiff base **6-10** showed the disappearance of ν(O-H) and ν(N-H) absorption bands and the appearance of two absorption bands at 1772-1782 cm^{-1} and 1701-1739 cm^{-1}, which are related to asymmetric ν(C=O) imides and symmetric ν(C=O) imides, respectively. These two points provide strong support for producing bis-imides **6-10**. Other absorption bands are associated with ν(C=N), ν(C=C), and ν(C-N) imides, which appear at 1604-1640 cm^{-1}, 1556-1575 cm^{-1}, and 1359-1390 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were used to confirm the structures of the prepared compounds. Thus, the ^{1}H NMR spectra of bis-amic acids **3** and **4** showed signals at 1.08-2.34 ppm, 6.07-7.72 ppm, 9.34-10.23 ppm and 10.32-10.49 ppm, which are related to CH_3 protons, aromatic protons, NH protons, and OH protons, respectively. It is noticeable that signals of NH and OH did not appear in the ^{1}H NMR spectra of bis-imides **6** and **7**, which proves the success of bis-imide formation. The ^{1}H NMR spectra of compounds **6**, **7**, and **10** showed clear signals at 2.08-2.38 ppm, 7.57-8.56 ppm, which are related to CH_3 protons and aromatic protons, respectively. Compound **6**'s 1H NMR spectrum revealed signals between 2.6 and 2.9 ppm related to -CH_2CH_2- protons in the succinimide ring. The ^{13}C NMR data of bis-amic acid Schiff bases **3** and **4** are 18.1-27.6 ppm and belong to the CH_3 groups, while signals at 115.2-138.5 ppm belong to the aromatic rings. Other signals appeared at 139.0-158.1 ppm, 162.1-163.9 ppm and 165.3-166.7 ppm, which are related to C=N imines, C=O amides, and C=O carboxylic acids, respectively. The ^{13}C NMR spectra of bis-imides **6** and **7** showed signals at 17.8-18.1 ppm, 112.9-137.4 ppm, 140.5-140.7 ppm, and 167.5-177.4 ppm, which are related to CH_3 groups, aromatic rings, C=N imines, and C=O imides [19]. Other signals in the 13C NMR spectrum of compound 6 range from 29.0 to 29.1 ppm, and are related to -CH_2CH_2- groups in succinimide rings. All details of FT-IR spectral data for compounds **2-5** and **6-10** are shown in Tables 5 and 6, while ^{1}H NMR and ^{13}C NMR spectral data for compounds **3**, **4**, **6**, **7**, and **10** are listed in Tables 7 and 8.

Table 1: Physical characteristics of compound **1**

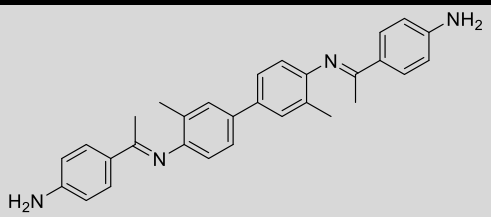
Compound	Structure	Colour	Yield (%)	m.p. (°C)	Purification solvent
1		Yellow	88	66-68	Acetone

Table 2: Physical characteristics of bis-amic acid Schiff bases **2-5**

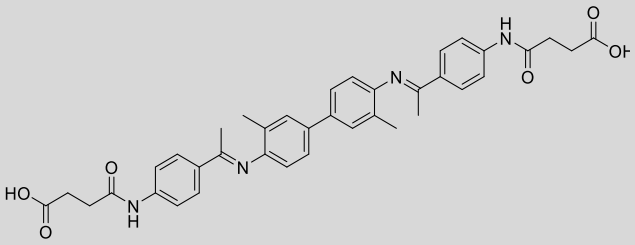
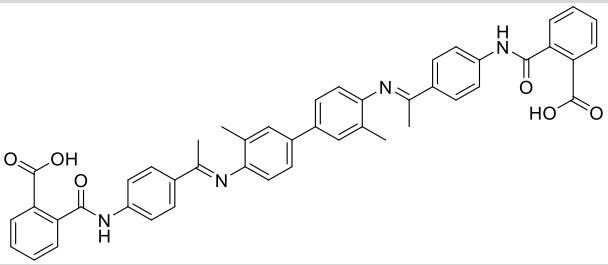
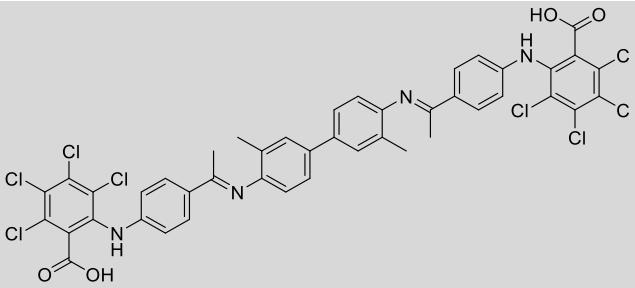
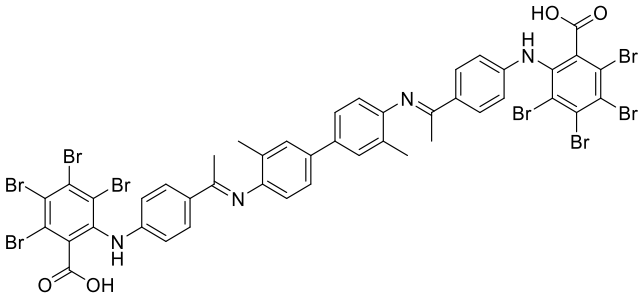
Compound	Structure	Colour	Yield (%)	m.p. (°C)	Purification solvent
2		White	85	100-102	Ethanol
3		White	87	120-124	Ethanol
4		Gray	81	Dec 250	Ethanol
5		Gray	90	>300	Acetone

Table 3: Physical characteristics of bis-imidyl Schiff bases **6-10**

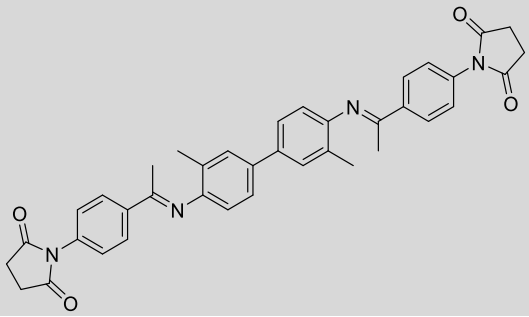
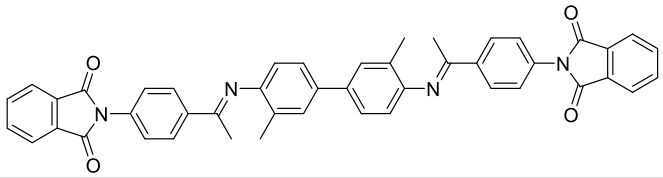
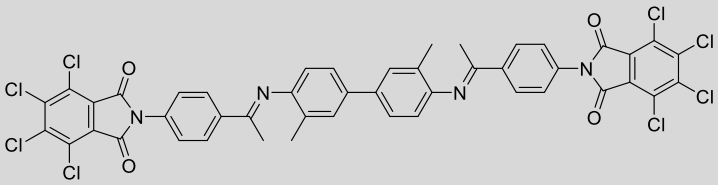
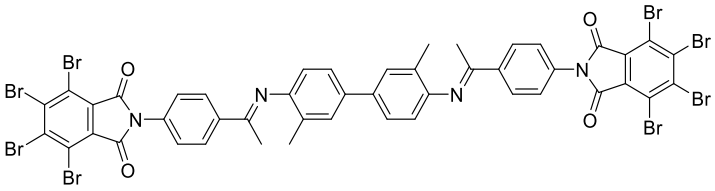
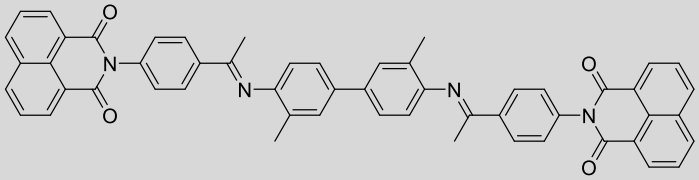
Compound	Structure	Colour	Yield (%)	m.p. (°C)	Purification solvent
6		Brown	80	118-120	Dioxane
7		Black	77	Dec. 128	Dioxane
8		Back	83	>300	Acetone
9		Red-brown	85	>300	Acetone
10		Off white	82	276-278	Ethanol

Table 4: FT-IR and ^{1}H NMR spectral data of compound **1**

Compound	ν (NH_2)	ν (C-H) Aromatic	ν (C-H) Aliphatic	ν (C=N) Imine	ν (C=C) Aromatic
1	3463 3402 3334	3030	2983	1645	1591 1560
	^{1}H NMR spectral data (δ, ppm)				
1	2.15, 2.43 (12H, $4CH_3$), 4.75 (4H, NH_2), 6.03-7.69 (14H, Ar-H)				

Table 5: Spectral data of FT-IR (ν, cm^{-1}) for bis-amic Schiff bases **2-5**

Compound	(OH) (NH)	(C-H) Aromatic	(C-H) Aliphatic	(C=O) Carboxylic	(C=O) Amide	(C=N) Imine	(C=C) Aromatic
2	3402 3336 3298 3228	3020	2987	1695	1650	1641	1589 1564
3	3438 3249	3028	2900 2875 2829	1703	1656	1656 (overlap)	1595 1585
4	3431 3288	3026	2975 2879	1699	1660	1639	1554
5	3463 3359 3230	3005	2975	1720	1670	1649	1591 1575

Table 6: Spectral data of FT-IR (ν, cm^{-1}) for bis-imidyl Schiff bases **6-10**

Compound	(C-H) Aromatic	(C-H) Aliphatic	(C=O) Imide	(C=N) Imine	(C=C) Aromatic	(C-N) Imide
6	3035	2977 2875	1772 1708	1637	1571	1390
7	3062	2979 2867	1782 1720	1625 1604	1556	1382
8	3004	2974 2885	1776 1718	1639	1558	1361
9	3010	2850 2981 2921	1774 1718	1640	1575	1380
10	3076	2977 2883	1772 1739 1701	1639	1558	1359

Table 7: ^{1}H NMR spectral data (δ, ppm) of compounds **3**, **4**, **6**, **7** and **10**

Compound	^{1}H NMR spectral data (δ, ppm)
3	10.49 (2H, OH), 9.34 (2H, NH), 7.40-6.71 (22H, Ar-H), 2.12-1.84 (12H, CH_3)
4	10.32 (2H, OH), 10.23 (2H, NH), 7.72-6.70 (14H, Ar-H), 2.34-2.09 (12H, CH_3)
6	8.08-6.57 (14H, Ar-H), 2.90-2.60 (8H, -CH_2CH_2-), 2.38-2.09 (12H, CH_3)
7	8.02-7.48 (22H, Ar-H), 2.22-2.08 (12H, CH_3)
10	8.56-7.90 (26H, Ar-H), 2.08 (12H, CH_3),

Table 8: ^{13}C NMR spectral data (δ, ppm) of compounds **3**, **4**, **6** and **7**

Compound	^{13}C NMR spectral data (δ, ppm)
3	166.7-166.6 (C=O), 158.1-154.5 (C=N), 138.5-115.6 (Ar-C), 27.6, 20.6 (CH_3)
4	165.3 (C=O) carboxyl, 162.2-162.1 (C=O) amide, 139.0 (C=N), 137.7-115.2 (Ar-C), 19.0-18.1 (CH_3)
6	177.4 (C=O) imide, 140.5 (C=N), 136.7-112.9 (Ar-C), 29.1-29.0 (-CH_2CH_2-), 17.8 (CH_3)
7	167.5 (C=O) imide, 140.7 (C=N), 137.4-124.1 (Ar-C), 18.1 (CH_3)

4. Conclusion

In this work, the changes in various physical characteristics of the prepared compounds were investigated. The obtained compounds were studied by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The prepared compounds **6**-**10**, which contain two biologically active components, may be able to lead to the discovery of new drugs that fight different bacterial infections or treat microbial diseases.

Acknowledgements

At the beginning, we give thanks to the great Allah, who gave me the power and health to complete my research. I would like to extend my gratitude and respect to the chemistry department for giving me the opportunity to complete this research. Also, I would like to thank my family and friends for their patience and support. I wish them all the best, and Allah bless them.

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