Synthesis and Biological Activities of New 1,2,3,4-Tetrahydroquinoline Derivatives Using Imino Diels-Alder Reaction

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Abstract

This research contains the preparation of some novel derivatives of tetrahydro quinolone. First step, include prepared new Schiff's bases compounds (I_1-I_5) were prepared by the direct condensation between diamine compounds and aromatic aldehydes substituted by different groups. Tetrahydroquinoline derivatives compounds (I_6-I_{10}) were prepared through imino Diels-Alder reaction using the derivatives of Schiff base with cinnamic acid, and Boron tri fluoride ethyl etherate ($BF_3.Et_2O$) as a catalyst. The prepared compounds were identified by infrared spectra, ^{1}H-NMR, and ^{13}C-NMR. Antibacterial activity of the prepared compounds was measured by using three pathogenic microorganisms including *Staphyloccus haemolyticus, Klebsiella pneumonia,*and *Candida albicans.* Also, a comparative study was achieved to study the biological activity of these prepared compounds using Agar Diffusion method.

Keywords: *1,2,3,4-tetrahydroquinoline, cinnamic acid, Diels-Alder reaction, Antibacterial activity, Boron tri luoride ethyl etherate.*

Introduction

The 1,2,3,4-tetrahydroquinolines are relevant heterocycles that possess diverse biological activities and multiple applications. They are widely used as antimalarial [(1)], antibacterial[(2)], antiviral[(3)] and antitumor agents[(4)].Also, they are as inhibitors of thromboxane A2 synthase [(5)] and in other pharmaceutical applications[(6)]. For these reasons, the preparation of new tetrahydroquinolines remains of considerable interest. An active approach for the synthesis of tetrahydroquinolines is the acid-catalyzed Povarov reaction, which is classified as an imino Diels-Alder cycloaddition [(7)]. The primary goal of the current study is to seek novel molecules like the current compounds by synthesizing several 1,2,3,4 tetrahydroquinolines derivatives. Moreover, this methodology, tetrahydroquinolines of sulfonamides prepared through Imines- Diels- Alder reaction by using the derivatives of Schiff bases with cinnamic acid and Boron tri fluoride ethyl ether ($BF_3.Et_2O$) as catalyst. All the prepared compounds were characterized based on their melting point, IR, ^{13}C-NMR, and ^{1}H-NMR. The anti-microbial efficacy of the synthesized compounds has been estimated using Agar Diffusion method.

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Experimental Section:

The solvents, chemical materials and reagents utilized during this research were available bought from Romil, Sigma Aldrich and BDH are utilized as be given. Recorded infrared spectra were by using Shimadzu Infrared Spectrophotometer FT-IR model 8400s series spectrophotometer (KBr Pellet) in the region 400-4000 cm^{-1}. ^{1}H and ^{13}C-NMR spectral analysis were collected on NMR spectrometer 400 MHz, Bruker Biospin GmbH 400 MHz using DMSO-d_6 as the NMR solvent. Chemical shifts (δ) are expressed in ppm. Melting degrees were recorded on Sturat Scientific instrument SMPLU-K Model are uncorrected for the prepared compounds.

General procedure for the synthesis of Schiff bases (I_1-I_5):

Schiff base derivatives (I_1-I_5) under research were designed according to the method equimolar mixtures (0.002 mole) of 4,4'-thiodianiline and (0.002 mole) of substituted benzaldehyde were dissolved in 25 ml absolute ethanol. This mixture was refluxed for 3 hrs then cooled. The precipitate was obtained and then recrystallized from ethanol. The end reaction of the synthesized compounds was monitored by TLC using silica gel as stationary phase and ethanol cyclohexane (8:2) mobile phase (Scheme 1) and Table 1.

General procedure for the synthesis of Tetrahydroquinoline derivatives (I_6-I_{10}):

A mixture solution of cinnamic acid (0.0006 mole) in toluene in presence of 3ml of $BF_3.Et_2O$ was gradually added to the mixture, as a catalyst, was placed round bottom flask with condenser and stirred with heat for 15 minutes to completely dissolve the reactants, gradually add the solution of Schiff base [I_1-I_5] (0.0006 mole) dissolved in dry (30 mL) toluene to the mixture for another 15 minutes. Then, this mixture was refluxed for 5 hrs and then cooled. The end of the reaction was checked by TLC (EtOAc:Toluene, 2:3). The solvent was evaporated under reduced pressure for one-third of solvent and separated precipitation was filtered and re-crystallized from ethanol (Scheme 1) and Table 1.

Antibacterial activity of I_6-I_{10}

Antibacterial activity of these compounds was determined by the Ager Diffusion method against three pathogenic microorganisms involving two bacteria *Staphyloccus haemolyticus*, and *Klebsiella pneumonia*, and a yeast *Candida albicans*. All the synthesized compounds I6-I10 were used at the concentration of 25 mg/ml, on an agar seeded by bacteria. All the achieved plates were incubated in the incubator at the appropriate temperature at 37 °C for 24 hrs. After that, the diameter of the zone of inhibition was calculated by the ruler in millimeters (mm)[8].

Scheme 1: Step by step method for the preparation Tetrahydroquinoline derivatives

Table 1: Some physical properties of prepared compounds (I_1-I_{10})

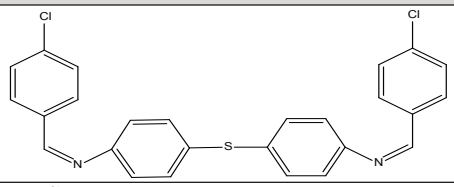
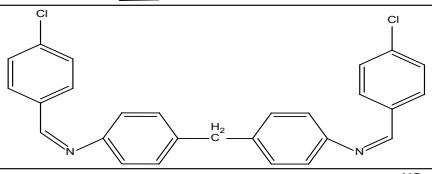
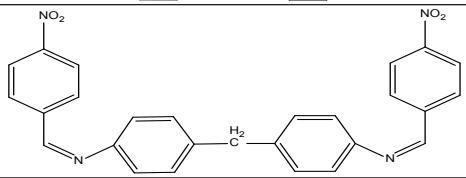
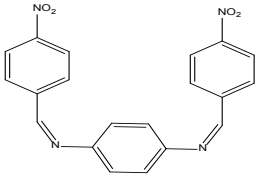
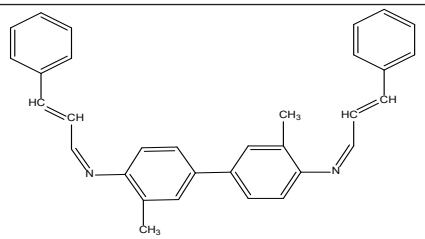
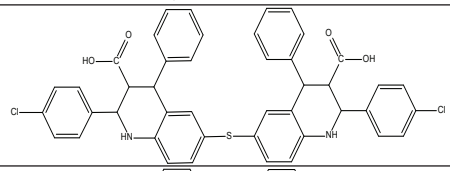
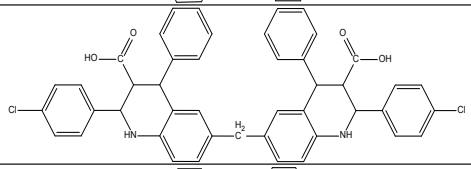
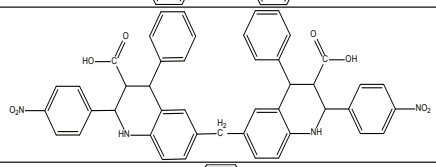
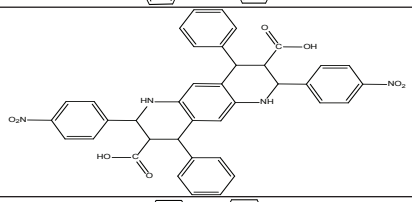
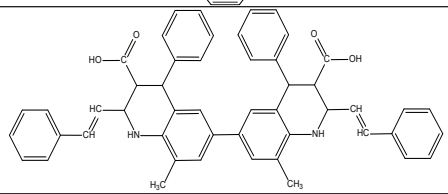
Comp. No.	Structures	Color	m.p. °C	Yield%	RF
I1		White	220-222	70	0.73
I2		White	170-172	60	0.97
I3		Yellow	230-232	55	0.23
I4		Brown	235-237	70	0.85

Table 1: Some physical properties of prepared compounds (I_1-I_{10})

I5		Green	200-202	68	0.89
I6		Orange	180-182	50	0.65
I7		Yellow	160-162	75	0.85
I8		Orange	90	73	0.86
I9		Brown	230-232	75	0.67
I10		Red	320-322	71	0.58

Results and Discussion

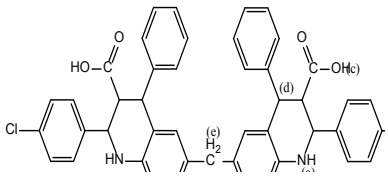
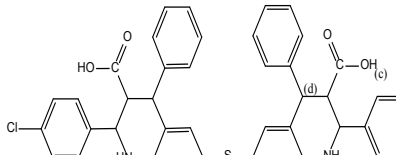
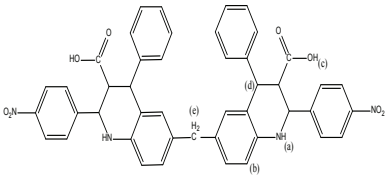
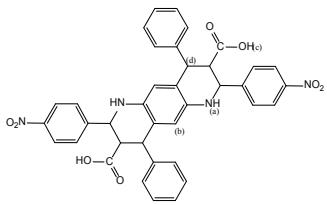
Scheme 1 appears the synthetic path for the new Tetrahydroquinoline derivatives. Stage 1and 2 are as notified in the step by step made method and includes condensation reaction of the substituted aromatic substituted aldehydes with the amines to result azomethine compounds I_1-I_5 follow by next reaction with solute cinnamic acid during toluene in presence of $BF_3.Et_2O$ to the corresponding wanted compounds I_6-I_{10}. The reaction methods in first and second steps were achieved utilizing FT- infrared spectroscopy. Manifestation of the band in the field 1597-1625 cm^{-1} in the infrared spectrum of the Schiff bases I_1-I_5 is suitable to C=N indicates condensation. The FT-IR spectra of I_1-I_5 exhibited the presence of the stretching absorption bands of (C=C) aromatic at (1586-1510) cm^{-1}, (C-H) aromatic at (3158-3009) cm^{-1}, (C-H) alphatic at (2922-2877) cm^{-1}, (C-Cl) at (721-717) cm^{-1} and (N=O) at (1369-1338) cm^{-1}.

The confirmed structures of the prepared compounds I_6-I_{10} were determined depending on the bases of their spectroscopy datum (FT- infrared, ^{1}H-NMR, & ^{13}C-NMR). The prepared Tetrahydroquinoline derivatives appeared suitable special signals needful to prove structures. FT- infrared spectrum of I_6-I_{10} exhibited the presence of the stretching absorption bands

of N-H group at (3500-3201) cm^{-1}, C=O group at (1708-1627) cm^{-1}, C-N group at (1083-1064) cm^{-1}, C-H alphatic at (2900-2835) cm^{-1},C-H aromatic at (3100-3008) cm^{-1}, C=C aromatic at (1593-1489) cm^{-1}, and O-H group at (3298-3116) cm^{-1}.

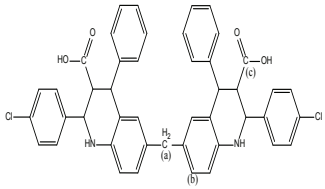
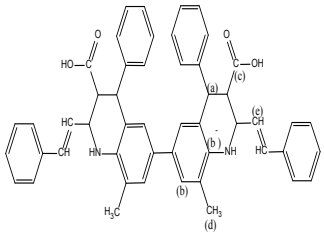
^{1}H-NMR spectrum for the prepared tetrahydroquinoline compounds presented appropriate for the aromatic proton with the proton shifts proper of the (H-N) and other groups are needful to emphasize the structure for tetrahydroquinoline membered system, also included in the table **2.**

Table 2: The ^{1}H-NMR Spectra of the compound $I_6 - I_9$

Comp. No.	Structure of prepared tetrahydroquinoline derivatives	(a)	(b)	(c)	(d)	(e)
I6		Singlet in 8.7	Multiplet in7.2	Singlet in 10.0	Singlet in 4.02	Singlet in 2.5
I7		Singlet in 8.6	Multiplet in7.3	Singlet in 10	Singlet in 2.4	--
I8		Singlet in 8.8	Multiplet in7.4	Singlet in 10.2	Singlet in 4.0	Singlet in 4.5
I9		Doublet in 8.4	Multiplet in 7.8	Doublet in 8.57	Singlet in 2.5	--

^{13}C-NMR for the prepared tetrahydroquinoline compounds proves the existence for chemical shifts of carbon identical the Major groups as included in the spectral data set as following in table 3.

Table 3: The ^{13}C-NMR Spectra of the compound I_6 and I_{10}

Comp. No.	Structure of prepared tetrahydroquinoline derivatives	(a)	(b)	(c)	(d)	(e)	(d)	
I6		41	128.06	192.6	--	--	--	
I10		40	129.5	153.6	178.3	18.2	131.7	

The biological activity

Antibacterial activity of the synthesized tetrahydroquinoline compounds were calculated using Ager Diffusion method against three pathogenic microorganisms involving *Staphyloccus haemolyticus, Klebsiella pneumonia,* and *Candida albicans.* All the synthesized compounds I_6-I_{10} were used at the concentration of 25 mg/ml. Table 4 showed the zones of inhibition against the pathogens. The best inhibition zone was 19.5 mm by the compound I_{10} against *K. pneumoniae*, followed 18 mm by the compound I_9 toward the same bacteria. While the compound I_6 recorded a zone of inhibition reached 7 mm against *K. pneumoniae and C. albicans*. Finally, the lowest inhibition zone was 10 mm by the compound I_{10} against *S. haemolyticus* and *C. albicans.*

Table 4: The biological activity of compounds I_6-I_{10} (Zone of inhibition, mm)

Compound Number	S. haemolyticus	K. pneumoniae	C. albicans
I6	15	17	17
I7	12.5	16	14
I8	15.5	16.5	16
I9	16	18	14
I10	10	19.5	10

Conclusion

We have successfully synthesized and characterized Schiff base compounds (I_1-I_5), and 1,2,3,4-Tetrahydroquinoline derivative(I_6-I_{10}) , The prepared compounds were identified by infrared spectra, H^1-NMR, and C^{13}-NMR, Antibacterial activity of the synthesized compounds was calculated using Ager Diffusion method against three pathogenic microorganisms involving *Staphyloccus haemolyticus, Klebsiella pneumonia,* and *Candida albicans*.where derivatives of tetrahydroquinoline showed varying results on the pathogenig microorganisms used ,Due to the presence of effective groups , The best inhibition zone was 19.5 mm by the compound I_{10} against *K. pneumoniae,* the lowest inhibition zone was 10 mm by the compound I_{10} against *S. haemolyticus* and *C. albicans*.the compound that gave the highest inhibition zone was due to the presence of effective functional groups and the large ring size .

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq

Conflict of Interest: Non

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