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Synthesis, Spectral Characterization and Biological Studies of Ethyl-4-(biphenyl-2-yl)-2-oxo-6-arylcyclohex-3-ene Carboxylates

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ABSTRACT

A new novel series Ethyl-4-(biphenyl-2-yl)-2-oxo-6-arylcyclohex-3-ene carboxylates are constructed by the reaction of ethylacetoacetate with biphenyl chalcones compounds under four step Michal addition reaction and ethanol used as a solvent and the chalcones synthesized by common Claisen-Schmidt condensation method. The reactions were monitored by Thin layer Chromatography (TLC). The characterization of the synthesized compounds by Infra-Red (IR), Proton Nuclear Magnetic Resonance (^{1}H-NMR), Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR), Correlation Spectroscopy (COSY), Heteronuclear Single Quantum Coherence (HSQC) and Mass spectral data's and elemental analysis. The synthesized compounds treated against Gram-positive and Gram-negative bacterial strains, the electron with-drawing group's particularly substituted derivatives (F) group shows greater inhibition against Gram-negative bacterial strain Escherichia coli and the electron donating (OCH_3) substitution derivative has shown excellent inhibition against Gram-positive bacterial strain Staphylococcus aureus using ciprofloxacin as a standard drug.

Keywords: 4-acetylbiphenyl chalcones, 4,6-Cyclo addition, Disc diffusion, Conventional

INTRODUCTION

Heterocyclic compounds are especially used in the field of pharmaceuticals, agrochemicals, fine chemicals and widely used as drugs [1]. The chiral cycloalkanones are generally synthesized from cycloalkanones by multi-step synthetic routes of chiral building blocks [2,3]. The 1,3-dipolar cycloaddition taken a prominent place in the synthesis of complex hetero cyclic systems [4]. The Mannich addition reaction is used in the synthesis of the enolic form cyclohexanone derivatives [5]. The asymmetric Diels-Alder mechanisms are also used to the synthesis of cyclohexanones by using ammine as a catalyst [6]. The most versatile methods are used in the formation of C-C bonds in the organic synthesis known as Michal addition [7,8]. The electronic properties of 2,6-bis(benzylidene)cyclohexanones are changes according to the substituents present in aryl rings [9]. The series of phenylcyclohexenes bind in to the colchicines site of tubulin shows significant potent towards plant than animal cell and the colchicines separately have high potent against animal cells [10]. The motive for the preparation of highly functionalized cyclohexanone ethyl carboxylates is due to fact that they are excellent carries of different types of biological activity [11,12]. Cyclohexanoic long chain fatty alcohols are used in the treatment of neurological disorders [13]. Ambuic acid has a highly functionalized antifungal activity [14]. The other important pharmaceutical applications are anticandidal activity [15-17], anti HIV [18], antimicrobial, antitumor, antifungal, etc., We already reported, the thiophenyl cyclohex-3-ene carboxylate derivatives which are obey the Lipinski's rule of five [19]. Nowadays we have to produce a large number of anti-microbial drugs because the micro-organisms (fungus and bacteria's) are the major problem to reduce immune system of humans. Moreover in the present work, the interesting stating material 4-acetylbiphenyl has a capacity to act against micro-organisms. Furthermore it designed as the cyclohexanone formation it have much more best cytotoxic effect towards micro-organisms. In this work, biphenyl chalcone prepared from the reaction of 4-acetyl biphenyl with various substituted ketone via Claisen-Schimidt condensation. The titled compound Ethyl-4-(biphenyl-2-yl)-2-oxo-6-arylcyclohex-3-ene carboxylates synthesized from the reaction of chalcone with Ethyl acetoacetate via addition reaction. Finally the synthesized compounds are characterized by Infra-Red (IR), Proton Nuclear Magnetic Resonance (^{1}H-NMR), Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR), Two-dimensional nuclear magnetic resonance spectroscopy (2D-NMR) like Correlation Spectroscopy (COSY) and Heteronuclear Single Quantum Coherence (HSQC) and also the compounds were tested against anti-bacterial strains.

MATERIALS AND METHODS

Physical measurements

The melting points were determined in the open capillaries and are uncorrected by using MEL-Temp apparatus. IR spectra were recorded on an SHIMADZU Fourier-transform infrared spectroscopy (FT-IR) spectrometer in KBr pellets. The ^{1}H-NMR spectra were recorded at 400MHz on

BRUKER 400MHz spectrometer using $CDCl_3$ as solvent and TMS as an internal standard and ^{13}C-NMR spectra, about 50 mg of the compound was dissolved in the same volume of the solvent.

General method for synthesis of (E)-1-(biphenyl-2-yl)-3-aryl prop-2-en-1-one

The solution of various substituted benzaldehyde (0.01 mol) and 4-acetylbiphenyl (0.01 mol) in ethyl alcohol cooled at 0-15ºC and was mixed with aqueous sodium hydroxide solution (10%, 5 ml) drop wise with continuous stirring for 3 hours, and the mixture was kept in the refrigerator for 24 h. The solid was filtered, dried and recrystallized from ethanol.

General method for Ethyl-4-(biphenyl-2-yl)-2-oxo-6-arylcyclohex-3-ene-carboxylates

The target compounds are synthesized by the reaction of (E)-1-(biphenyl-2-yl)-3-phenylprop-2-en-1-one with ethyl-3-oxobutanoate in the presence of sodium ethoxide under refluxing for 6 h. The completion of the reaction was checked by Thin Layer Chromatography. After completion of the reaction, the mixture was poured into crushed ice and kept aside overnight at room temperature. Finally the solid was filtered. Dried and recrystallized from ethanol.

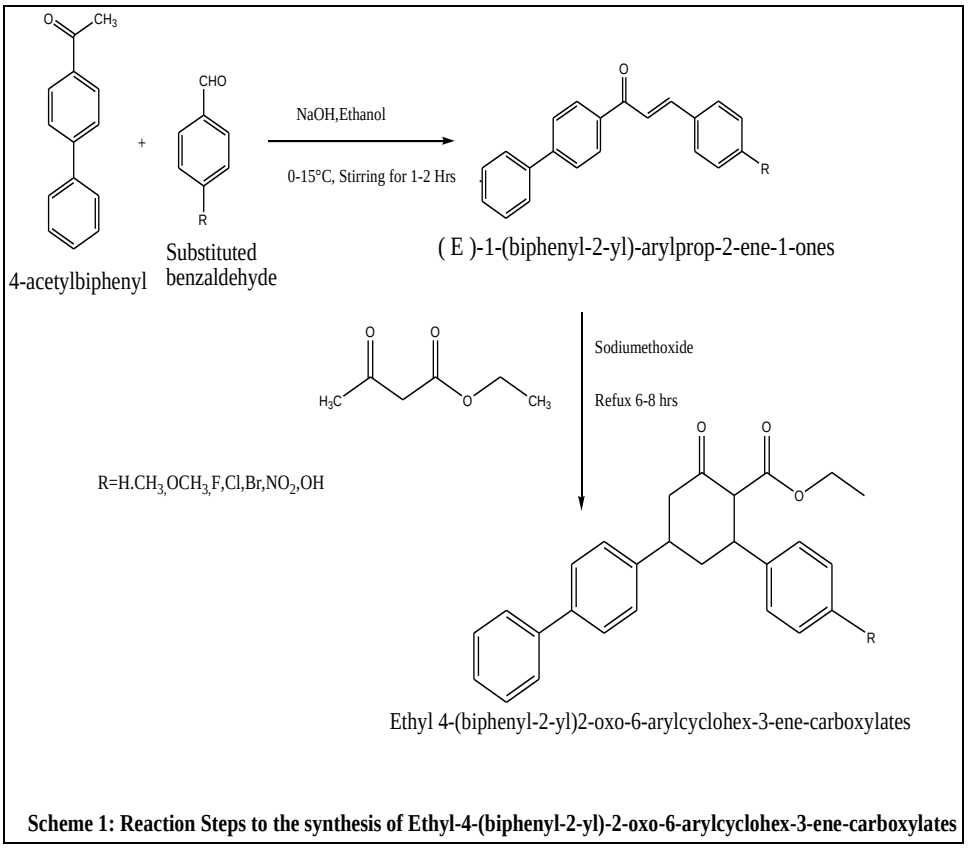
Antibacterial activity procedure

The standardized inoculums is inoculated in the plates prepared earlier (aseptically) by dipping a sterile in the inoculums removing the excess of inoculums by passing and rotating the swab firmly against the side of the culture tube above the level of the liquid and finally streaking the swab all over the surface of the medium 3 times rotating the plate through the angle of 60º after each application. Finally pass the swab round the edge of the agar surface. Leave the inoculums to dry at room temperature with the lid closed. Each Petri dish is divided into 8 parts, in each part sample discs [9(F), 10(H), 11(CH_3), 12(OCH_3), 13(Br), 14(Cl), 15(NO_2) and 80-100 µg/disc] are placed in each part and center of the plate for Standard antibiotic (Ciprofloxacin-5 µg/disc), are placed with the help of sterile forceps. Then Petri dishes are placed in the refrigerator at 4ºC or at room temperature for 1 h for diffusion and Incubated at 37ºC for 24 h. Observe the zone of inhibition produced by different samples. Measure it using a scale or divider or venire calipers and recorded the average of two diameters of each zone of inhibition.

RESULTS AND DISCUSSION

Chemistry

The conventional approach for the synthesis of Ethyl-4-(biphenyl-2-yl)-2-oxo-6-arylcyclohex-3-ene-carboxylates is follows: (E)-1-(biphenyl-2-yl)-arylprop-2-ene-1-ones are synthesized by the Claisen- Schmidt condensation and it react with ethylacetoacetate in the presence of sodium ethoxide in refluxing ethanol for 6-8 h to yield biologically important compound named as Ethyl-4-(biphenyl-2-yl)-2-oxo-6-arylcyclohex-3-ene carboxylates via simple four step Michal addition mechanism. The structure of the synthesized compounds is confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC spectral studies and elemental analysis. The possible reaction Scheme 1 and mechanism of titled compound displayed in Figures 1 and 2. The physical data's for the synthesized compounds are given in Table 1.



Scheme 1: Reaction Steps to the synthesis of Ethyl-4-(biphenyl-2-yl)-2-oxo-6-arylcyclohex-3-ene-carboxylates

Figure 1: Scheme of the synthesis

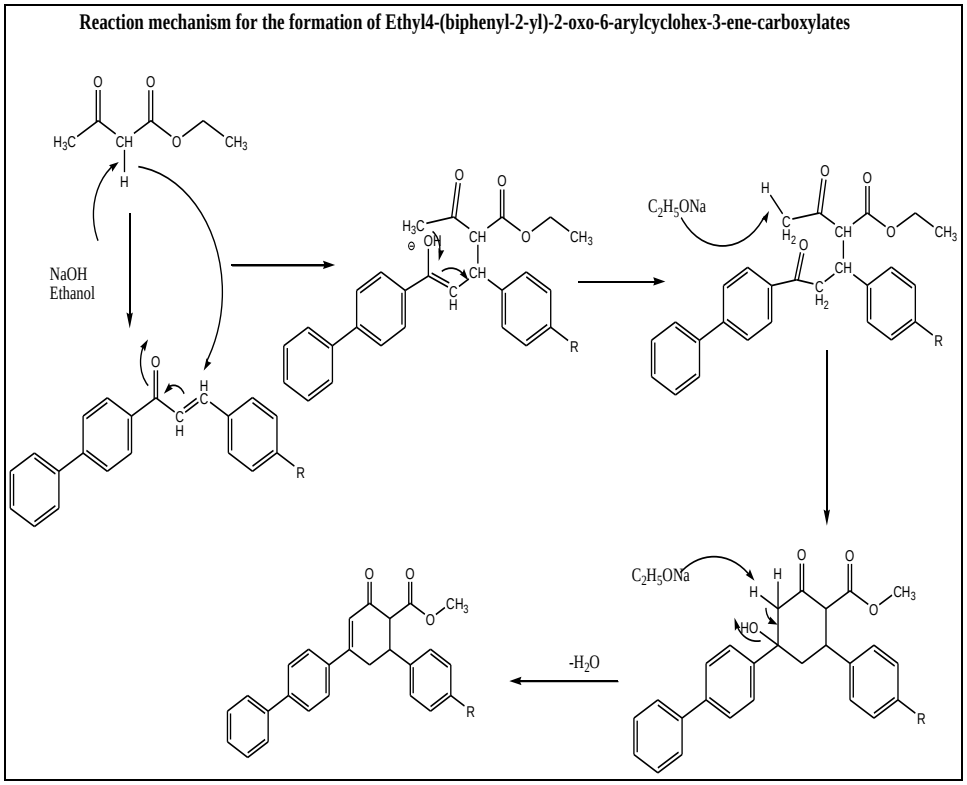


Figure 2: Mechanistic Pathway of the reaction Scheme

Table 1: Physical data's for synthesized compounds (1-16)

Entry	Molecular Formula	Molecular Weight	Melting Point in °C	FT-IR frequencies (cm^{-1})
1	$C_{21}H_{15}OF$	302	124	1662.71, 1425.40, 3026.31, 2899.01, 736.01, 824.56
2	$C_{21}H_{16}O$	284	98	1660.71, 1425.40, 3026.31, 2899.01, 756.01, 828.56
3	$C_{22}H_{18}O$	298	102	1668.75, 1426.40, 3026.45, 3000.01, 758.01, 838.56
4	$C_{22}H_{18}O_2$	314	123	1669.71, 1425.40, 3026.31, 2895.01, 726.01, 825.56
5	$C_{21}H_{15}OCl$	318	120	1670.71, 1425.40, 3026.31, 2899.01, 746.1, 823.56
6	$C_{21}H_{15}OBr$	363	143	1665.71, 1425.40, 3026.31, 2896.01, 756.01, 828.56
7	$C_{21}H_{15}NO_3$	329	92	1664.71,1425.40,3026.31,2896.01756.01,828.56
8	$C_{21}H_{16}O_2$	300	112	1668.75,1424.40,3026.45,2994.01,758.01,836.56
9	$C_{22}H_{23}O_3F$	414	86	1739.79, 1666.50, 1604.77, 3053.32, 2993.52, 2929.87, 835.18, 75.95, 692.44, 590.22
10	$C_{27}H_{24}O_3$	396	98	1735.93, 1662.64, 1589.34, 1521.84, 3051.39, 3001.24, 2974.23, 2908.65, 842.89, 738.74, 692.44, 601.79
11	$C_{28}H_{26}O_3$	410	105	1732.08, 1682.64, 1600.92, 3041.74, 2980.02, 2920.23, 835.18, 754.17, 698.23, 648.08, 619.55
12	$C_{28}H_{26}O_4$	426	122	1737.86, 1662.64, 1600.92, 1533.41, 3028.24, 2976.16, 2922.16, 825.53, 754.17, 700.16, 646.15, 626.87, 549.79
13	$C_{27}H_{23}O_3Cl$	430	94	1739.79, 1665.50, 1598.99, 3051.39, 2983.88, 833.25, 758.02, 692.44, 590.22
14	$C_{27}H_{23}O_3Br$	475	124	1720.50, 160.71, 1600.92, 3045.60,2924.09, 829.39, 752.24, 704.02, 650.01, 609.51, 543.93
15	$C_{27}H_{23}O_5N$	441	132	1734.01, 1662.64, 1598.98, 3053.32, 2976.16, 2953.02, 2931.80, 840.96, 752.24, 698.23, 642.30, 626.87, 545.85
16	$C_{27}H_{24}O_4$	412	142	1737.86, 1662.64, 1600.92, 1533.14, 3254.58, 3028.24, 2976.16, 2922.16, 825.53, 754.16, 700.16, 646.15, 626.87, 549.79

Analysis of ^{1}H-NMR spectrum of Ethyl-6-(4-fluorophenyl)-4-biphenyl-2-yl)-2-oxocyclohex-3-ene-carboxylate (9)

The ^{1}H-NMR spectrum of the compound (9) shows that the triplet appeared at 1.081 (J=7.0 Hz) ppm corresponding to six protons and this is assigned to the ester methyl proton at C-1. The doublet appeared at 4.08 (J =14.8 Hz) ppm has been assigned to the H-1. A multiplet observed at 3.85-3.81 ppm corresponding to the four protons and this signal is due to the presence of ester methylene protons at C-1. Three multiplets are obtained in the range from 3.01 to 2.94, 3.15-3.09 and 3.70-3.79 and they are due to H-5a, H-5e and H-6 protons. The singlet observed in the downfield region at 6.63 ppm is due to the H-3 Proton. The aromatic protons appeared as a multiplet in the range of 7.66-7.03 ppm. The ^{1}H-NMR Chemical shifts of compound (9-15) shown in Table 2.

Table 2: ^{1}H-NMR spectrum of compound (9-15)

Entry	^{1}H-NMR chemical shifts (δ (ppm))							
	H-1	H-3	H-5a	H-5e	H-6	Ester methylene proton	Ester methyl proton	Aromatic protons
9 (F)	4.08 (J=14.8 Hz)	6.63	3.01-2.94	3.15-3.09	3.79-3.74	3.85-3.81	1.08 (J=7Hz)	7.66-7.03
10(H)	4.11 (J=13.6 Hz)	6.54 (J=2.0 Hz)	2.99-2.95	3.14-3.00	3.68-3.61	3.95-3.87	0.93 (J=5.20 Hz)	7.72 - 7.37
11(CH_3)	4.09 (J=14.3 Hz)	6.52	2.99-2.95	3.13-3.04	3.69-3.57	3.92-3.89	0.92 (J=7.0 Hz)	7.63 -7.38
12(OCH_3)	4.06 (J=14.5 Hz)	6.51 (J=1.5 Hz)	3.02-2.94	3.09-3.03	3.64-3.60	3.92-3.90	0.94 (J=7.2 Hz)	7.71-6.69
13(Cl)	4.11 (J=15.6 Hz)	6.56	2.97-2.93	3.07-3.00	3.66-3.63	3.93-3.87	0.92 (J=7.0 Hz)	7.76-7.38
14(Br)	4.03 (J=14.35 Hz)	6.58	2.99-2.92	3.08-3.00	3.68-3.56	3.94-3.86	0.97–0.85	7.67–7.28
15 (NO_2)	4. 10 (J=15.2 Hz)	6.54	2.99-2.94	3.12-3.05	3.67-3.59	3.95-3.85	0.92 (J=7.2 Hz)	7.81–7.18

Analysis of ^{13}C-NMR spectrum of Ethyl-6-(4-fluorophenyl)-4-biphenyl-2-yl)-2-oxocyclohex-3-ene-carboxylate (9)

The ^{13}C-NMR spectrum of the compound (9) resonance at 193.81 ppm is assigned to the C-2 carbonyl carbon whereas the resonance at 169.22 ppm is assigned to the ester carbonyl carbon. The ^{13}C resonances at 61.09, 14.30 ppm are assigned to the ester methylene and methyl carbons at C-1 respectively. The signal observed at 59.77 ppm is assigned to C-1 carbon whereas the signal at 123.81 ppm is assigned to the C-3 carbon. The aromatic carbons are observed in the range of 128.99-126.75 ppm C-4 carbon resonance at 157.90 ppm. The remaining ^{13}C signals at 143.43, 139.81, 136.85, 136.82 and 136.25 ppm are due to the presence of ipso carbons. The ^{13}C chemical shifts values of compound (9-15) shown in Table 3 and Figures 3, 4.

Table 3: ^{13}C-NMR spectrum of compound (9-15)

Entry	^{13}C-NMR chemical shifts (δ (ppm))										
	C-1	C-2	C-3	C-4	C-5	C-6	Ester Carbonyl Carbon	Ester methylene carbon	Ester methyl Carbon	Aromatic Carbons	Ipso carbons
9 (F)	59.77	193.81	123.81	157.9	36.05	43.45	61.09	14.03	169.22	128.99-126.75	143.43,139.81, 136.85,136.82,136.25
10 (H)	58.67	194.27	122.89	159.29	35.28	43.46	169.31	59.89	13.79	130-124.16	140.28,139.86,138.00, 137.32
11(CH_3)	59.17	194.71	123.88	159.63	35.66	43.96	169.85	60.4	14.3	129.93-126.78	143.02,141.00,140.83, 140.53, 135.54,134.87
12(OCH_3)	59.17	194.5	121.53	159.11	35.4	43.95	169.78	60.34	14.3	128.70-114.68	140.88, 129.74
13 (Cl)	58.6	194.21	123.28	157.89	35.2	43.35	169.09	59.91		129.78-127.61	140.22,136.17,135.14
14(Br)	59.22	194.59	123.78	158.41	35.44	43.9	169.82	60.51	14.31	128.23-124.46	137.04, 132.22,129.07
15(NO_2)	58.59	194.19	122.84	158.07	35.27	43.39	169.15	59.89	13.79	128.91-115.64	142.5, 133.80, 129.00

Analysis of ^{1}H-^{1}H COSY spectrum of Ethyl-6-(4-fluorophenyl)-4-biphenyl-2-yl)-2-oxocyclohex-3-ene-carboxylate (9)

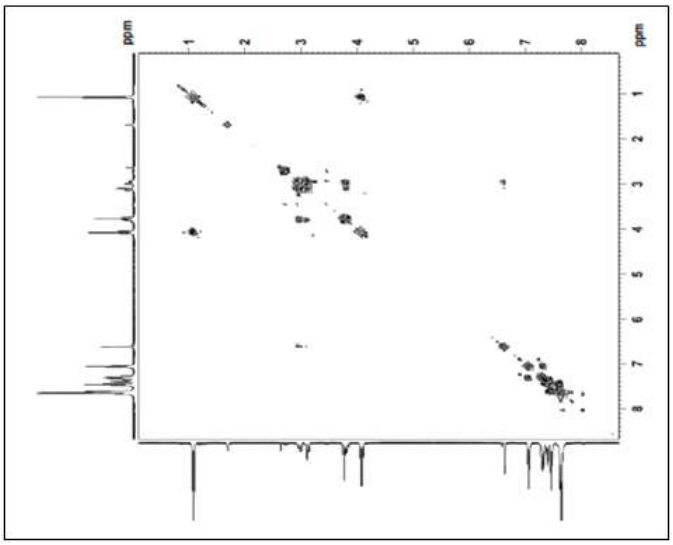


Figure 3: ^{1}H-^{1}H COSY Spectrum of the compound (9)

In the HOMO COSY spectrum of the compound (9) shows that the signal at 4.08 ppm shows correlation with the signal at 3.79- 3.74 ppm. Similarly, the signal at 3.79 -3.74 ppm have correlation with the signal at 4.09 ppm as well as with the signal at 3.01-2.94 and 3.15 -3.09 ppm. Likewise, the signal at 3.01- 2.94 ppm shows correlation with the signal at 3.15- 3.09 and 3.79-3.74 ppm. Moreover, the signal at 3.15-3.09 ppm shows correlation with the signal at 6.63 ppm, 3.01-2.94 ppm and 3.79- 3.74 ppm. Also the signal at 6.63 ppm shows correlation with the signal at 3.15-3.09 ppm. From the observed correlation, it reveals that three multiplets observed in the range 3.01-2.94, 3.15-3.09 and 3.79-3.74 ppm due to H-5a, H-5e and H-6 protons whereas the doublet at 4.08 ppm and the signal at 6.63 ppm are assigned to H-1 and H-3 proton. One multiplet at 3.85-3.81 ppm shows correlations with the triplet at 1.08 ppm and vice-versa. These mutual correlations reveal that the triplet observed at 1.08 ppm is due to ester methyl protons at C-1 and multiplet observed at 3.85-3.81 ppm is due to ester methylene protons at C-1.

Analysis of ^{1}H-^{13}C HSQC spectrum of Ethyl-6-(4-fluorophenyl)-4-biphenyl-2-yl)-2-oxocyclohex-3-ene-carboxylate (9)

In the HSQC spectrum for compound (9) shows that the one bond correlation 14.03/1.08 ppm is observed between ester methyl carbon at C-1 and also the ester methyl proton at C-1. The ^{13}C resonances at 61.09/3.85-3.81 ppm have correlation with ester methylene protons at C-1. Another one bond correlation 36.04/3.01-2.94 & 3.15-3.09 ppm is observed between C-5 and H-5a and H-5e. The ^{13}C resonance at 43.45 ppm has one bond correlation with a multiplet around 3.79-3.74 ppm. Hence the signal at 43.45 ppm corresponds to C-6 carbon whereas the multiplet at 3.79-3.74 ppm is assigned to H-6 proton. Another aliphatic carbon resonance at 59.77 ppm shows one bond correlation with a doublet at 4.08 ppm. From this correlation, it is revealed that the doublet at 4.08 ppm corresponds to H-1 proton of the cyclohexenone moiety and the ^{13}C signal at 59.77 ppm is assigned to the C-1 carbon. The ^{13}C resonance at 123.81 ppm has correlation with singlet at 6.63 ppm. So the signal at 6.63 ppm is assigned to the H-3 proton and the carbon signal at 123.81 ppm is assigned to C-3 carbon. In the HSQC, the ^{13}C resonance at 157.90, 169.22 and 193.81 has no correlations with protons and hence it is due to quaternary carbon C-4, ester carbonyl at C-1 and C-2 carbon respectively. Among the quaternary carbons, the ^{13}C resonances at 143, 43,139.81, 136.85,13625 ppm are due to ipso carbons.

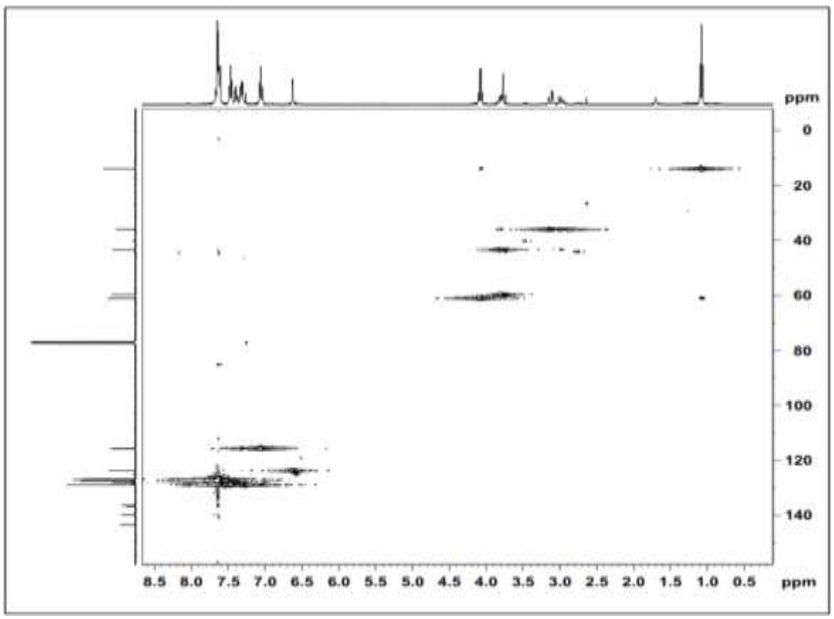


Figure 4: ^{1}H-^{13}C HSQC Spectrum of the compound (9)

Therefore with reference to ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC correlations in compound (9), the tentative assignments made for the protons and carbons are confirms. Based on the ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC correlations of the compound (9), the ^{1}H and ^{13}C chemical shifts are assigned unambiguously and are given in Tables 2 and 3.

Microbial Screening

The synthesized compounds are screened for their *in vitro* antibacterial activities against gram-positive, gram negative bacterial and fungal strains, according to disc diffusion method suggested by Maruzella et al., and two fold serial dilution method. The following clinically isolated bacterial strains are used to test the bacterial activity of all the newly synthesized compounds:

Gram-positive bacterial strain *Staphylococcus aureus* and Gram-negative bacterial strain *Escherichia coli.*

The inhibitory activities are compared with the standard drug under similar conditions. The zone of inhibition frame is measured in mm and they are represented by (-), (+) depending on the diameter and clarity.

From the Screening results, the Electron Withdrawing substituent 'F' has very good screening efficiency against Gram-negative organism *E. coli* at low concentration and the electron donating substituent'OCH_3' have a good inhibition property against Gram-positive organism *S. aureus* at lower concentration. The inhibition ability of all the synthesized compounds are noted in the Table 4.

Table 4: Anti-bactrial activity inhibition results of synthesized compounds (9-15)

S.No.	Compounds	Antibacterial activity of the compounds (Organisms)													
		E. Coli (Gram-Negative)							*S. aureus* (Gram-Positive)						
		500 µg/ml	250 µg/ml	125 µg/ml	65.5 µg/ml	31.25 µg/ml	15.625 µg/ml	7.812 µg/ml	500 µg/ml	250 µg/ml	125 µg/ml	65.5 µg/ml	31.25 µg/ml	15.625 µg/ml	7.812 µg/ml
1	9 (F)	-	-	+++++	+++++	+++++	+++++	+++++	-	-	+++	+++	+++	+++	+++
2	10(H)	-	-	++++	++++	++++	++++	++++	-	-	++	++	++	++	++
3	11(CH_3)	-	-	++	++	++	++	++	-	-	++	++	++	++	++
4	12(OCH_3)	-	-	+++	+++	+++	+++	+++	-	-	++++	++++	++++	++++	++++
5	13 (Cl)	-	-	++++	++++	++++	++++	++++	-	-	+++	+++	+++	+++	+++
6	14(Br)	-	-	+++	+++	+++	+++	+++	-	-	++	++	++	++	++
7	15(NO_2)	-	-	++++	++++	++++	++++	++++	-	-	+++	+++	+++	+++	+++

+ → Presence of growth, - → Absence of growth, +++++=Excellent, ++++=Very good, +++=Good, ++=Less

CONCLUSION

The simplest four step Michal-addition reaction mechanism is followed for the synthesis of the titled compound. It is also a low-cost and easy handling method of the cyclohexanone synthesis. The skeleton structure of the synthesized compounds are elucidated by using elemental analysis and FT-IR, ^{1}H-NMR, ^{13}C-NMR and 2D-NMR spectral analysis. The synthesized compounds are treated against the microbial strains. From the results, the electron-withdrawing group fluoro, chloro, bromo and nitro substituted derivatives are shows excellent inhibition against the *Gram-negative* organism of *E. coli*. And the electron-donating group particularly methoxy substitution derivative shows good inhibition ability against the *Gram-positive* organism of *S. aureus* at minimum concentration by disc diffusion method.

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