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Synthesis, Characterization of Ethyl Dioxoisoindolinyl Cyclohexenone Carboxylate Derivatives from Some Chalcones and its Biological Activity Assessment

Mohammad M. Al-Tufah[1,*], Shakhawan Beebaeny[2], Saad Salem Jasim[2], Bari Lateef Mohammed[3]

[1]*Directorate of Education, Kirkuk, Ministry of Education, Iraq*
[2] *Chemistry Department, College of Sciences, University of Kirkuk, Kirkuk, Iraq*
[3]*Biology Department, College of Sciences, University of Kirkuk, Kirkuk, Iraq*

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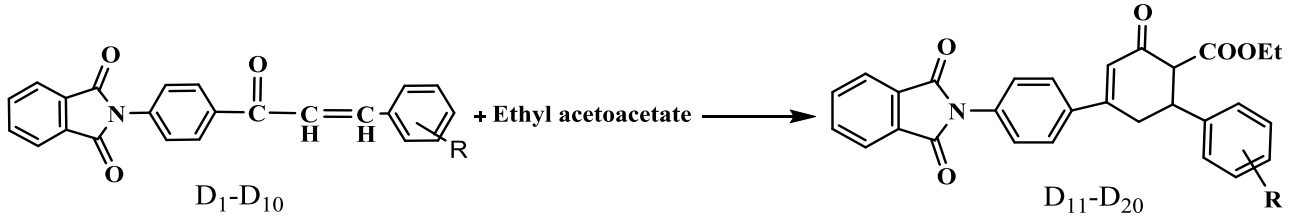
ABSTRACT

In this study, new ethyl dioxoisoindolinyl cyclohexenone carboxylate derivatives have been synthesized via addition and cyclocondensation reactions when ethylacetoacetate added to chalcone compounds in a strong alkaline media. Ethylacetoacetate was added to chalcone compounds (D_1-D_{10}) in ethanol as solvent to produce cyclohexenone compounds (D_{11}-D_{20}), using sodium hydroxide as catalyst. The prepared compounds structures have been identified using the infrared spectroscopy (FT-IR) and some of them by ^{1}H-NMR and ^{13}C-NMR spectroscopy. The chalcones were prepared from our earliest published work. These new cyclohexenones have been applied as antibacterial agent towards *Staphylococcus aureus*, *Staphylococcus* epidermidis (gram-positive bacteria), and *Escherichia coli* (gram-negative bacteria). The results exhibited good antibacterial activity of the synthesized compounds against *Staphylococcus aureus* and *Staphylococcus* epidermidis at high concentrations (0.01 and 0.001) mg/mL compared to low concentration (0.001 mg/mL) because of high concentration effect.

GRAPHICAL ABSTRACT



R= 4-Br, 4-Cl , H, 4- OH, 4-OCH_3, 2,4-diCl, 4-NO_2, 4-$N(CH_3)_2$, 2-Br, 3,4-di OCH_3

* Corresponding author: Mohammad M. Al-Tufah
✉ E-mail: sh.beebany@uokirkuk.edu.iq

Introduction

Cyclohexenone compounds have been classified as cyclic compounds. Cyclohexenone and its derivatives were considered as one of the important synthetic chemistry methods because they are utilized as starting materials in the formation of plenty natural products as well as other interesting chemical derivatives such as antibiotics and steroids [1]. Cyclohexenone derivatives have been widely applied in biological field such as antitumor [2], anti-bacterial [3], and antimicrobial [4]. In addition, cyclohexenone compounds can be used in the synthesis of natural products with a wide spectrum of biological functions, functionalized chiral cyclohexenone has been given a lot of interest academically [5].

Cyclohexenones were synthesized from chalcones using ethyl acetate through based catalyzed cyclization reaction [6]. It was reported that benzothiazolyl chalcones [7], benzodioxolyl chalcones [8], methoxphenyl chalcones [9], benzochalcones [10], thiolyl chalcones [11], nitro phenyl, and naphthyl chalcones [12] have been converted into cyclohexenone derivatives, using ethylacetoacetate in strong alkaline media via cyclization reaction based on Michael addition and Aldol condensation reactions. Robinson annulation is well-known as a critical step in the formation of six-membered ring compounds. It is consisted of two steps as Michael addition reaction followed by Aldol condensation reaction to form cyclohexenone [8]. This is involved in utilizing sodium hydroxide or sodium ethoxide as a catalyst in a cyclo-condensation process between, unsaturated carbonyl and the β-keto ester (ethyl acetoacetate) [12]. According to this literature review none of these published works contain dioxoisoindolinyl cyclohexenone carboxylate derivatives for biological efficacy assessment. Therefore, synthesis and biological activity evaluation of novel dioxoisoindolinyl cyclohexenone carboxylate are considered to have additional scientific value in academic research field.

The aim of this work was to synthesis new cyclohexenone series including dioxoisoindolinyl part and evaluate their antibacterial effect against some gram-positive and negative bacteria. In addition to see the difference in biological activity for the prepared cyclohexenones with earliest published works containing pyrazoline [13] and bis pyrazoline derivatives [14]. Synthesis of novel cyclohexenone derivatives along with evaluation of their antibacterial effect are of significant interest academically. Development, synthesis, and biological activity evaluation for new organic compounds will continue as an academic topic for investigation.

Materials and Methods

Chalcones (D_1-D_{10}) compounds have been already prepared from previous published work [15] and used for this research directly. Chemicals (sodium hydroxide, ethanol, hydrochloride acid, and ethylacetoacetate) are all provided by Aldrich and Fluka, and also used without further purification. A Stuart SMP II melting point device was used to determine melting points for the prepared compounds. A Shimadzu FTIR-8400 Fourier Transform Infrared Spectrophotometer was run on the prepared chemicals using KBr disc to obtain the IR spectra. An ultra-shielded magnet 300 MHz apparatus was employed to record ^{1}H-NMR and ^{13}C-NMR spectra using TMS as an internal standard and DMSO-d_6 as the solvent.

Synthesis of ethyl dioxoisoindolinyl cyclohexenone carboxylate derivatives (D_{11}-D_{20})

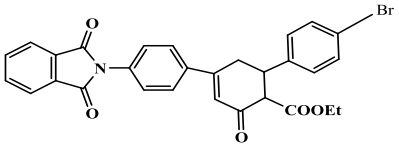
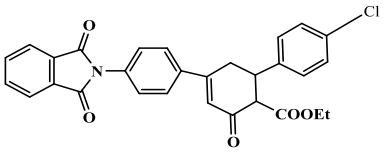
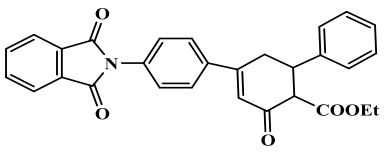
Chalcone compounds (D_1-D_{10}) (0.01 mol), and Ethylacetoacetate (0.01 mol, 1.30 g) were dissolved in (5 mL) of ethanol. After NaOH solution (0.5 mL, 10%) addition, the mixture was refluxed for 6-8 hrs, and then diluted by cold water (100 mL) and acidified using hydrochloric acid to form the precipitant. The precipitated matter was filtered, washed by cold water, and dried. The product recrystallized from ethanol. The details about this cyclization procedure is available in [16]. Physical properties of ethyl dioxoisoindolinyl cyclohexenone carboxylate derivatives (D_{11}-D_{20}) are presented in Table 1. Note that used weights of chalcones (D_1-D_{10})

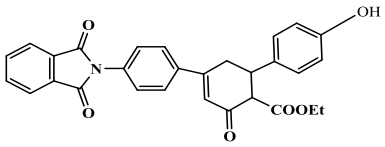
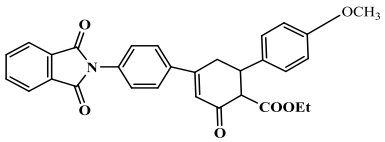
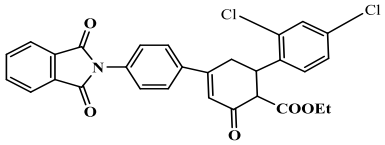
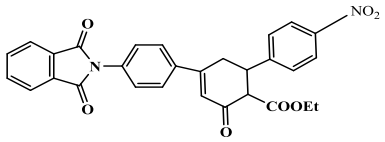
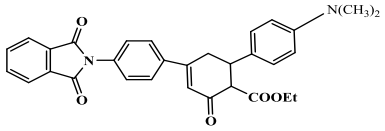
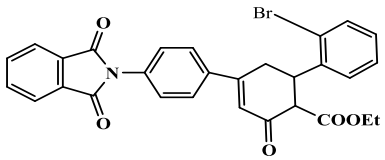
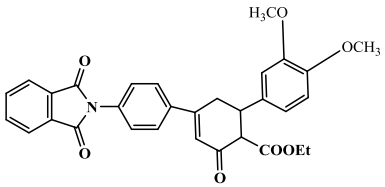
were (4.32, 3.87, 3.53, 3.69, 3.83, 4.22, 3.98, 3.96, and 4.32, 4.13) g, respectively.

Antibacterial effect study

This section involved in applying the synthesized compounds (D_{11}-D_{20}) against two types of bacteria; gram-positive bacteria (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and gram-negative bacteria (*Escherichia coli*). For information about the procedure see [17, 18]. The concentrations of the prepared compounds were (0.0001, 0.001, and 0.01) mg/mL, and DMSO used as solvent. The micro-organisms were separated and diagnosed in microbiology laboratories in the Biology Department, Science College in Kirkuk University. The single protectorate has been located into a test tube including 5 mL nutrition and the broth brooded maintained at 37 °C for 24 hours. The suspended bacterial solution has been collected and compared with tube number 0.5 of McFarland-standards, was given a cell with density of (1.5×108 cell/mL). A piece of sterilized cotton has been immersed into the bacterial solution with wiping on a Muller-Hinton agar plate surface in equal manner. The plate surfaces have been incubated at 37 °C for 30 minutes. The saturated disks were set up from Whatman number 1 and kept for 24 hours with the tested compounds (0.0001, 0.001, and 0.01) mg/mL. This was employed on the agar surface by Kirby-Bauer disc spread procedure. Forceps have to be compressed strongly to verify the contact with agar. Furthermore, the plates should be turned upside down and kept at 37 °C for 14-18 hours. It is worthy to be mentioned that all the disks have been soaked with a DMSO solvent, and then dried in an incubator for two days. The maximum inhibition zone diameter (IZD) was determined for analysis against each type of microorganism. Ciprofloxacin and gentamicin have been used as blank and control samples at three concentrations (0.0001, 0.001, and 0.01) mg/mL.

Table 1: Physical properties of the synthesized compounds (D_{11}-D_{20})

Compound No.	Structural formula	Nomenclature	Mp (°C)	Yield (%)	Color
D_{11}		ethyl 4''-bromo-4-(1,3-dioxoisoindolin-2-yl)-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	140-142	55	Yellow Light
D_{12}		ethyl 4''-chloro-4-(1,3-dioxoisoindolin-2-yl)-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	105-107	56	Yellow Light
D_{13}		ethyl 4-(1,3-dioxoisoindolin-2-yl)-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	122-124	58	Reddish Orang

D_{14}		ethyl 4-(1,3-dioxoisoindolin-2-yl)-4''-hydroxy-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	221-223	55	Yellow
D_{15}		ethyl 4-(1,3-dioxoisoindolin-2-yl)-4''-methoxy-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	138-140	47	Yellow
D_{16}		ethyl 2'',4''-dichloro-4-(1,3-dioxoisoindolin-2-yl)-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	117-120	66	Yellow Light
D_{17}		ethyl 4-(1,3-dioxoisoindolin-2-yl)-4''-nitro-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	138-140	63	Brown
D_{18}		ethyl 4''-(dimethylamino)-4-(1,3-dioxoisoindolin-2-yl)-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	115-117	73	Orang
D_{19}		ethyl 2''-bromo-4-(1,3-dioxoisoindolin-2-yl)-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	91-93	62	Yellow
D_{20}		ethyl 4-(1,3-dioxoisoindolin-2-yl)-3'',4''-dimethoxy-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate	87-90	54	Orang

Results and Discussion

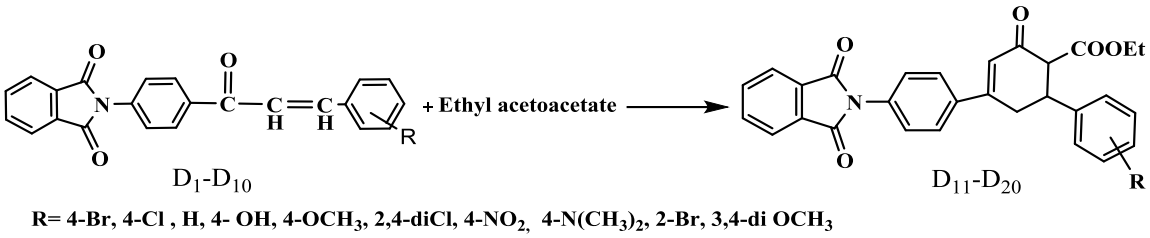
In this research, chalcones (D_1-D_{10}) have been converted into cyclohexenones compounds attached with ethyl carboxylate through cyclocondensation reaction between ethylacetoacetate and chalcones, as displayed in Scheme 1. The above cyclization reaction is an example of the Robinson mechanism to synthesize ethyl dioxoisoindolinyl cyclohexenone carboxylate compounds [19]. This involved in the

Michael addition reaction step following by aldol condensation step, as depicted in Scheme 2.

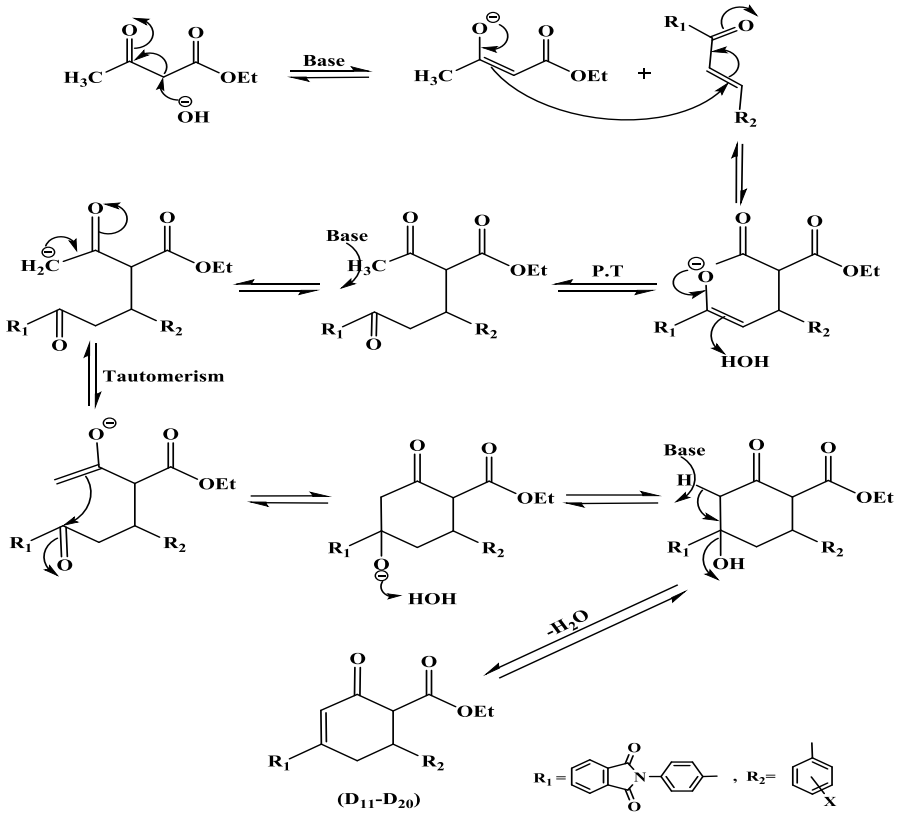
Characterization of ethyl cyclohexenone carboxylate derivatives (D_{11} – D_{20})

The discussion of characterization will be focused on only the part of new prepared cyclohexenones not chalcones as the latter has been already discussed in [15]. The cyclohexenones (D_{11}-D_{20}) were synthesized according to the reaction between compounds (D_1-D_{10}) with Ethyl acetoacetate in absolute ethanol solution of aqueous sodium hydroxide (5%), as displayed in Scheme 1. To discuss the spectral data, D_{14} and D_{20} will be discussed as sample for the whole series of D_{11}-D_{20}.

The FT-IR spectra of compounds (D_{14} and D_{20}) shows asymmetry and symmetry absorbance bands for the alkyl groups at the aliphatic range vibrational stretching 2923 cm^{-1}, 2852 cm^{-1}, 2918, and 2837 cm^{-1}, respectively. This is referred to the present of ethyl carboxylate attached to the cyclohexenones. Furthermore, the interesting change was the existence of ester carbonyl bands at 1714 cm^{-1}, 1716 cm^{-1} for compounds (D_{14} and D_{20}), respectively, as shown in Figures 1 and 2.



Scheme 1: Scheme of cyclization reaction to synthesis ethyl dioxoisoindolinyl cyclohexenone carboxylates (D_{11}-D_{20})



Scheme 2: Scheme of cyclization reaction mechanism to synthesis ethyl dioxoisoindolinyl cyclohexenone carboxylates (D_{11}-D_{20})

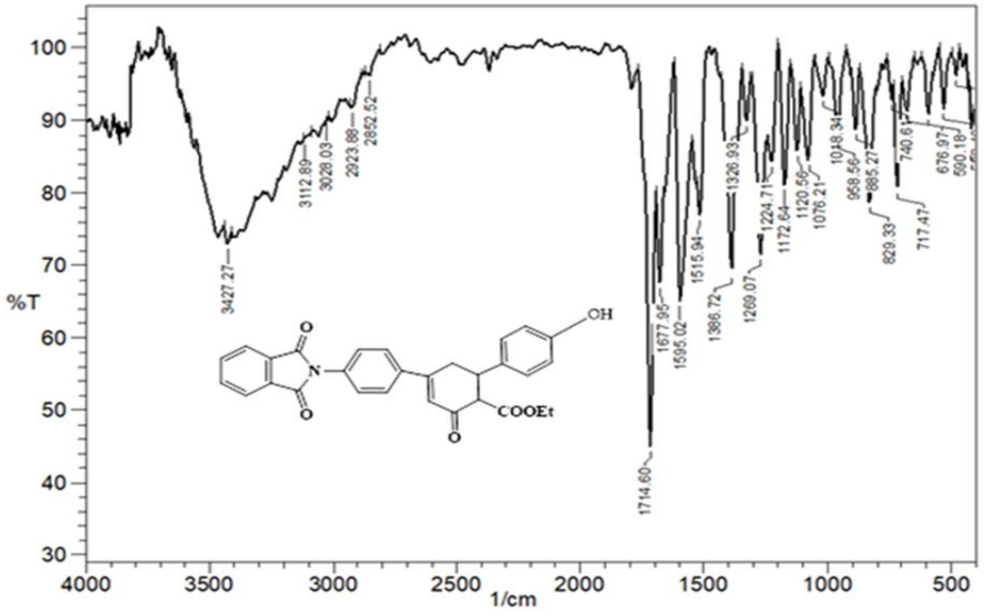


Figure 1: IR spectrum of D_{14}

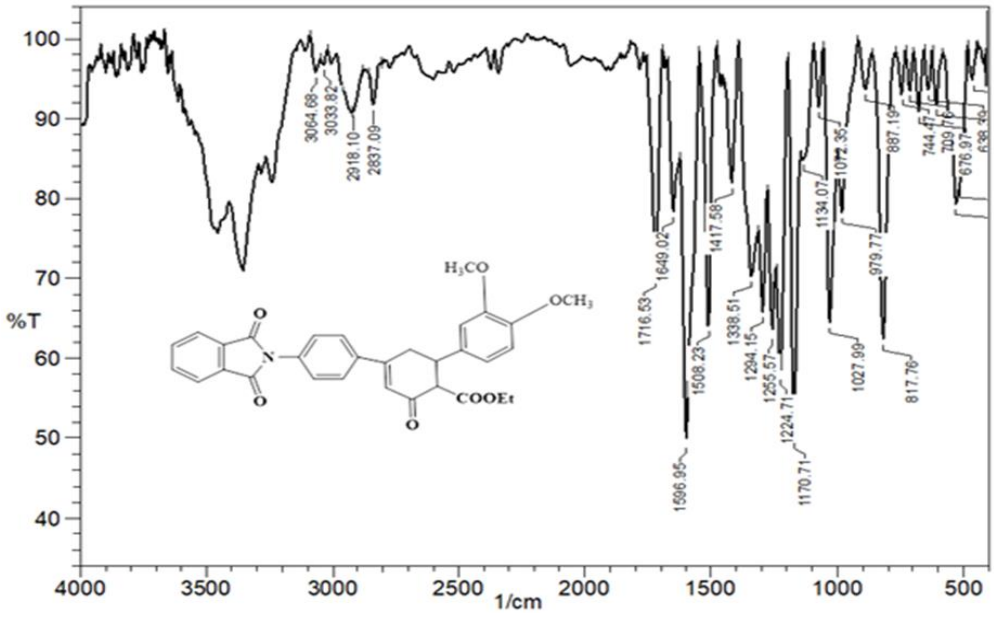


Figure 2: IR spectrum of D_{20}

This proves that a change has been occurred to the olefinic bond in chalcones [20]. The remaining absorbance bands were observed at their predictable regions; see Table 2 for whole IR data (D_{11}-D_{20}).

The ^{1}H-NMR spectrum of compound (D_{14}) gave the aromatic proton signals at δ 7.69-8.30, with singlet at δ 10.80 for hydroxyl proton. The interesting signals are δ 1.07-1.35 for the methyl protons with signals at δ 4.09-5.08 for methylene protons linked to ester group. This is ascribed to electronic changes for olefinic bond in chalcone to ethyl cyclohexenone carboxylate compound. The remaining proton signals observed in their expected regions, as demonstrated in Figure 3.

Table 2: FT-IR data of synthesized ethyl cyclohexenone carboxylate derivatives (D_{11}-D_{20})

IR (KBr) cm^{-1}							
Compound No.	R	υ (C=C) Ar	υ (C=O) Ketone	υ (C=O) Ester	υ (C-H) Alip.	υ (C=C) Alip.	Other
D_{11}	4-Br	1519-1488	1657	1728	2926,2867	1587	υ (C-Br) 665
D_{12}	4-Cl	1515-1409	1656	1726	2924,2866	1589	υ (C-Cl) 827
D_{13}	H	1543-1466	1668	1737	2944,2867	1610	-
D_{14}	4-OH	1595-1515	1677	1714	2923,2852	1602	υ (C-OH) 3427
D_{15}	4-OCH_3	1516-1406	1671	1724	2929,2840	1605	υ CH_3 2929,2840 C-O,1108
D_{16}	2,4-diCl	1519-1487	1660	1730	2981,2898	1602	υ C-Cl 825
D_{17}	4-NO_2	1517-1444	1668	1714	2926,2866	1606	υ (NO_2) 1409, 1373
D_{18}	4-$N(CH_3)_2$	1520-1407	1656	1730	2925,2850	1593	υ CH_3 2925,2850
D_{19}	2-Br	1525-1465	1667	1714	2923,2875	1595	υ (C-Br) 611
D_{20}	3,4-diOCH_3	1508-1417	1649	1716	2918,2837	1597	υ CH_3 2918,2837 C-O,1089

The ^{1}H-NMR spectrum of D_{20} exhibited the aromatic proton signals at δ 7.69-8.30. The interesting signals are δ 1.14-1.28 for the methyl protons with signals at δ 6.12-6.58 for methylene protons attached to carboxylate group. This is attributed to achieve ethyl cyclohexenone carboxylate formation. The remaining signals appeared in their expected locations, as illustrated in Figure 4 and Table 3. The ^{13}C-NMR spectrum (Figure 5) of D_{14} clearly shows a carbon signal at δ 173.43 corresponding to the carbonyl for ester group of the cyclization olefinic bond. This is strong evidence for achieving the cyclization reaction. Moreover, it gives two carbon atom signals for ethyl carboxylate carbon atoms at δ 15.24 and 61.06 referring to the methyl and methylene groups, respectively, in addition to the present cyclic carbon signals for cyclohexenone ring at δ 39.85 and 63.74 instead of olefinic carbon atoms of chalcones. This is clear evidence for the change in electronic environment caused by cyclization of the olefinic bond [14]. The combined spectroscopic data suggest cyclization reaction of chalcone to form cyclohexenone ethyl carboxylate [20]. The ^{13}C-NMR spectrum of D_{20} clearly shows a carbon signal at δ 172.14 corresponding to the carbonyl for ester group of the cyclization olefinic bond. This suggests achieving the cyclization reaction for olefinic bond carbons. Furthermore, it gives two carbon atom signals at δ 14.24 and 63.74 representing to the methyl and methylene

groups, respectively, in ethyl carboxylate attached to cyclohexenone, as indicated in Figure 6. In addition, cyclic carbon signals are observed at δ 39.85 and 63.74 instead of olefinic carbon atoms for chalcones. This is related to the change in electronic environment caused by cyclization of the olefinic bond [14]. The combined spectroscopic data support cyclohexenone derivatives formation [20]. Details about carbon spectral data are summarized in Table 4.

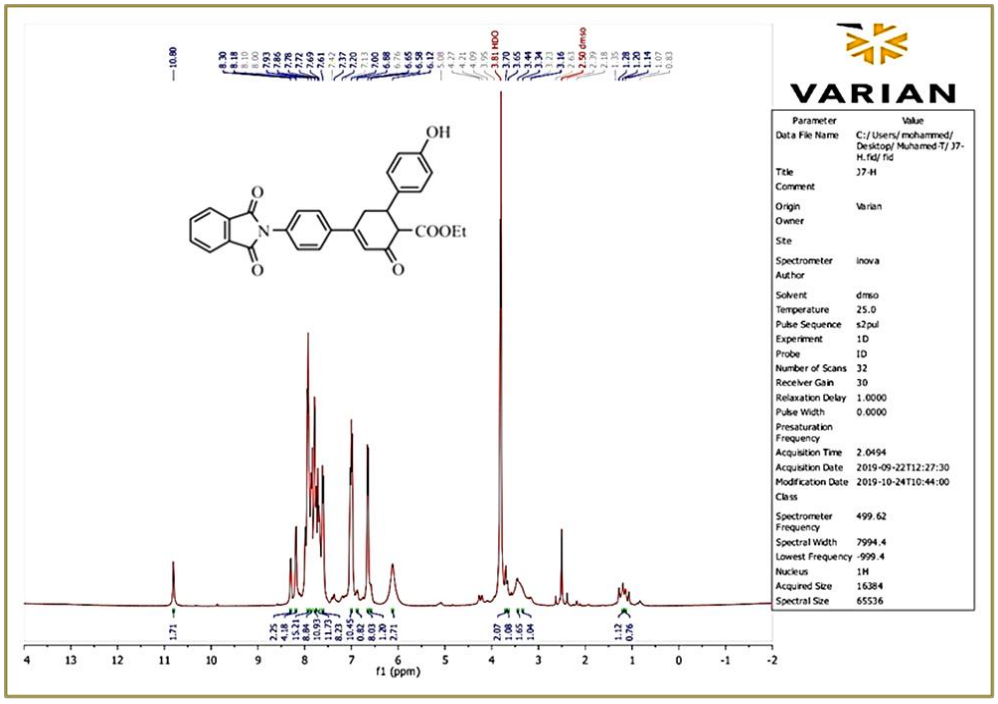


Figure 3: ^{1}H-NMR spectrum of D_{14}

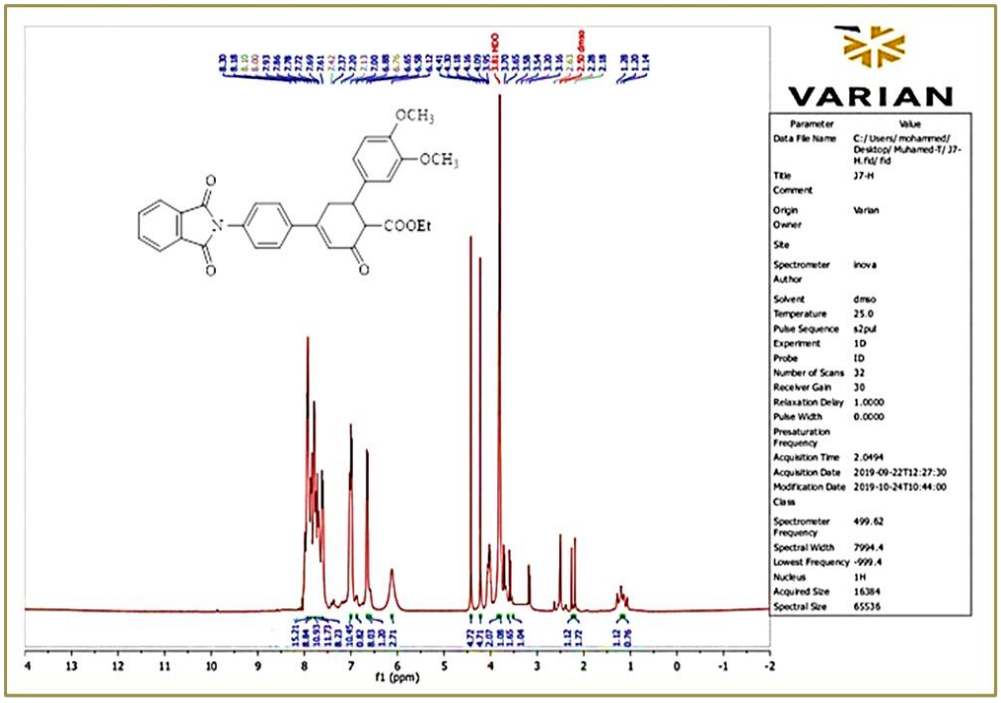
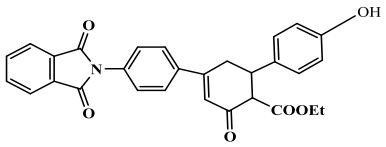
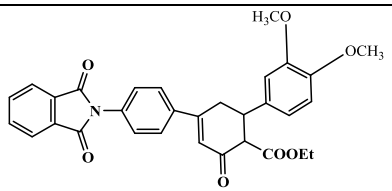


Figure 4: ^{1}H-NMR spectrum of D_{20}

Table 3: ^{1}H-NMR spectra data for some newly synthesized compounds

Compound No.	Compound structure	^{1}H-NMR data of (δ-H) in ppm
D14		*δ* 1.07-1.35 (3H, t, -Et), 2.18-2.13 (2H, dd, H_2 cyclohex), 3.23-3.44 (1H, d, H_4 cyclohex), 3.65-3.95 (1H, q, H_3 cyclohex), 4.09-5.08 (2H, q, -Et), 6.12-6.65 (1H, s, H_6 cyclohex), 7.00-8.30 (11H, m, Ar-H), and 10.80 (s, H, OH).
D_{20}		*δ* 1.14-1.28 (3H, t, Et), 2.18-2.63 (2H, dd, H_2 cyclohex), 3.16-3.58 (1H, d, H_4 cyclohex), 3.65-3.95 (1H, q, H_3 cyclohex), 4.30-4.41 (3H, s, m-OCH_3), 4.41 (3H, s, p-OCH_3), 6.12-6.58 (2H, q, Et), 6.65-6.88 (1H, s, H_6 cyclohex), and 7.61- 8.30 (11H, m, Ar-H).

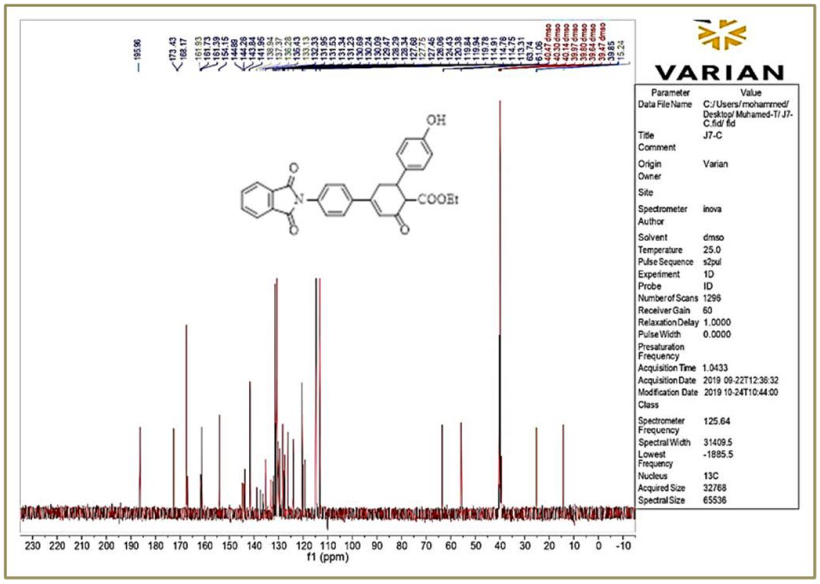


Figure 5: ^{13}C-NMR spectrum of D_{14}

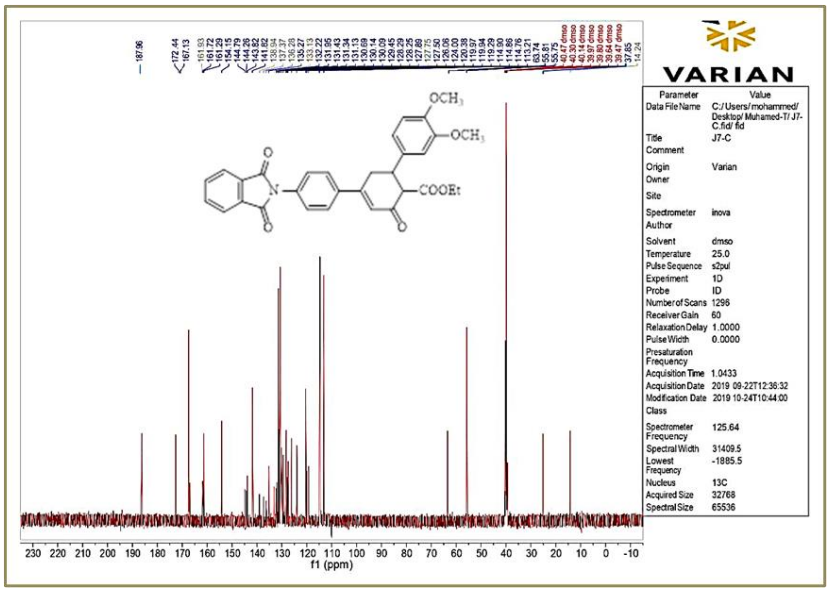
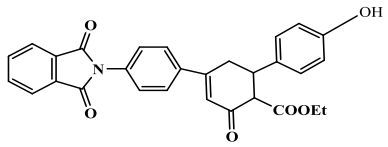
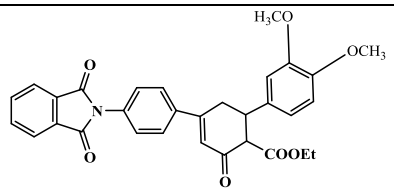


Figure 6: ^{13}C-NMR spectrum of D_{20}

Table 4: ^{13}C-NMR spectra data of some newly synthesized compounds

Compound No.	Compound structure	^{13}C-NMR data of (δ-C) in ppm
D_{14}		*δ* 1.07-1.35 (3H, t, Et), 2.18-2.13 (2H, dd, H_2 cyclohex), 3.23-3.44 (1H, d, H_4 cyclohex), 3.65-3.95 (1H, q, H_3 cyclohex), 4.09-5.08 (2H, q, -Et), 6.12-6.65 (1H, s, H_6 cyclohex), 7.00-8.30 (11H, m, Ar-H), and 10.80 (s, H, OH).
D_{20}		*δ* 14.24 (CH_3) Acyle, 37.85 (C2 cyclohex), 55.75 ($2OCH_3$), 55.81 (CH_2) Acyle, 63.74 (C4 cyclohex), 113.93-161.93 (Ar-Cs and C1 cyclohex, C6 cyclohex), 167.13 (C=O) imide, 172.14 (C=O) estare, and 187.96 (C=O) ketone.

Antibacterial activity

The antibacterial effect of the newly synthesized derivatives was assessed towards *Staphylococcus aureus* and *Staphylococcus* epidermidis (gram-positive bacteria) and *Escherichia coli* (gram-negative bacteria). The results showed that whole prepared compounds gave good antibacterial activity against *Staphylococcus aureus* and *Staphylococcus* epidermidis at high concentrations with (0.01 and 0.001) mg/mL compared to low concentration (0.001 mg/mL) due to the high concentration effect. However, there was no activity (zero effect) for the all prepared compounds against *Escherichia coli*. This is ascribed to the difference in the structure of cell wall and having some virulence agents such as capsule and biofilm agents for the gram-positive bacteria compared to gram-negative bacteria leading to increase bacteria resistivity towards the tested materials [21].

Table 5: Antibacterial effect results of compounds (D_{11}-D_{20}) on the growth of used bacteria

Compound No.	Growth inhibition zone (mm)			
	Conc. (mg/mL)	Staphylococcus aureus	Staphylococcus Epidermidis	*E. coli*
D_{11}	0.01	24	13	0.0
	0.001	13	12	0.0
	0.0001	8	4	0.0
D_{12}	0.01	26	24	0.0
	0.001	16	16	0.0
	0.0001	8	5	0.0
D_{13}	0.01	0.0	4	0.0
	0.001	0.0	0.0	0.0
	0.0001	0.0	0.0	0.0
D_{14}	0.01	4	5	0.0
	0.001	0.0	0.0	0.0
	0.0001	0.0	0.0	0.0
D_{15}	0.01	22	26	0.0
	0.001	15	17	0.0
	0.0001	8	14	0.0
D_{16}	0.01	20	22	0.0
	0.001	18	10	0.0
	0.0001	12	12	0.0
D_{17}	0.01	25	25	0.0

	0.001	14	18	0.0
	0.0001	8	5	0.0
D_{18}	0.01	8	5	0.0
	0.001	0.0	0.0	0.0
	0.0001	0.0	0.0	0.0
D_{19}	0.01	6	4	0.0
	0.001	0.0	0.0	0.0
	0.0001	0.0	0.0	0.0
D_{20}	0.01	18	14	0.0
	0.001	12	10	0.0
	0.0001	0.0	0.0	0.0
Ciprofloxacin	0.01	24	28	26
Gentamicin	0.01	18	20	20

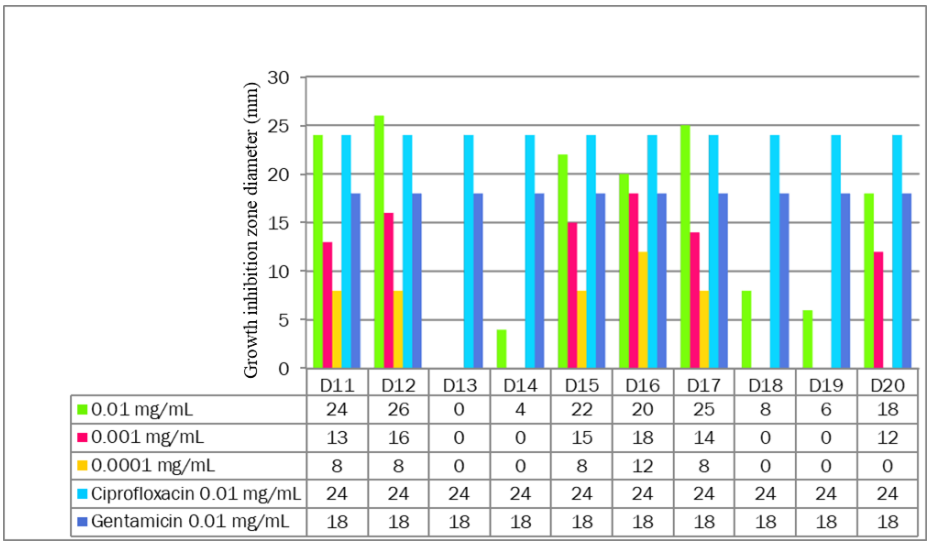


Figure 7: Differential effects and concentrations of the applied new derivatives towards Staphylococcus aureus

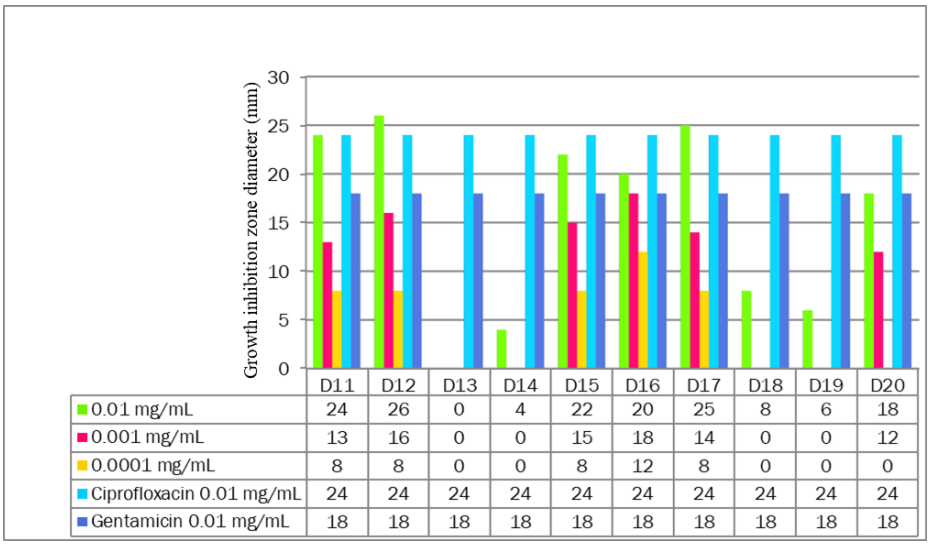


Figure 8: Differential effects and concentrations of the applied new derivatives towards staphylococcus epidermidis

Furthermore, at concentration of 0.001 mg/mL and 0.0001 mg/mL the tested materials exhibited a similar effect with low inhibition zone diameter compared to both used antibiotics as a result of the concentration effect. Nevertheless, the highest effect has been obtained for D_{12} and D_{17}. This is could be explained as the availability of NO_2 and Cl withdrawal groups according to the literature [22]. The results of the newly synthesized derivatives effect on all used bacteria are available in Table 5 and Figures 7 and 8.

Conclusion

Cyclohexenone derivatives have a good biological activity and significant academic interest for pharmaceutical applications. New ethyl dioxoisoindolinyl cyclohexenone carboxylate derivatives have been successfully synthesized via addition and cyclocondensation reactions when ethylacetoacetate added to chalcone compounds in a strong alkaline media. The identification results were consistent with structures of the cyclohexenone carboxylates. The results clearly verified that new compounds behaved as good antibacterial material towards *staphylococcus aureus* and *staphylococcus* epidermidis at high concentrations with (0.01 and 0.001) mg/mL compared to low concentration (0.001 mg/mL) because of the high concentration effect. D_{12} and D_{17} compounds possess a high antibacterial effect on *staphylococcus aureus* and *staphylococcus epidermidis* with concentrations of (0.01 and 0.001) mg/mL. This can be described as the role of withdrawal groups (NO_2 and Cl) availability in new derivatives structure compared to the others. However, there was no antibacterial effect for all the tested compounds against *Escherichia coli* due to the difference in the structure of cell wall and having some virulence agents such as capsule and biofilm agents for the gram-positive bacteria compared with gram-negative bacteria protecting bacteria towards the applied materials as antibacterial agents. As a result, cyclohexenone derivatives should be considered as antibacterial agents for pharmaceutical industrial applications.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Orcid

Mohammad M. Al-Tufah
https://orcid.org/0000-0002-0797-4882
Shakhawan Beebaeny
https://orcid.org/0000-0002-8231-5481
Saad Salem Jasim
https://orcid.org/0000-0003-3893-8769
Bari Lateef Mohammed
https://orcid.org/0000-0002-2031-3747

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