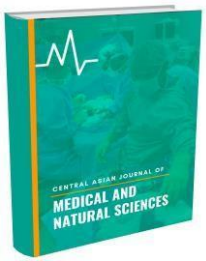

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Article

Synthesis, Characterization, Anticancer Activity Study of Novel Curcumin Analogues Against A549 Lung Cancer Cell Line

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Abstract: A series of new curcumin analogues were synthesized using the ultrasonic irradiation method, which involved the condensation reaction of 3-ethyl-2,4-pentandione and substituted aromatic aldehydes in the presence of boric oxide, trimethylborate, and butylamine. The synthesized compounds were identified using electron impact mass spectrometry (EI), 1HNMR,13CNMR and FTIR spectroscopy, which confirmed the proposed structure of the synthesized compounds. The in vitro anticancer activity study of synthesized compounds against the A549 lung cancer cell line was examined employing the microculture tetrazolium (MTT) assay. The results showed that compound 1 (IC50 10.8 µg/ml, SI of 17.56) has the most potent cytotoxic activity and high selectivity compared to curcumin (IC50 94.4 µg/ml, SI of 3.20). On the other hand, compound 7 (IC50 88.5 µg/ml, SI of 1.15) exhibits more anticancer activity against A549 lung cancer but has less selectivity than curcumin.

Keywords: A549, Anticancer, Lung Cancer, Selectivity, Ultrasonic Irradiation

1. Introduction

Curcumin was previously believed to be the primary component responsible for the active medicinal potential of turmeric [1]. People often consume turmeric, which has been used for many years as a food additive to give meals a spicy flavor and a yellow color [2]. In the subsequent years, attention began to study the curcumin molecule and curcumin-related compounds and their role in biological activities. Curcumin exhibits various pharmacological actions through different mechanisms, such as antibacterial [3], antifungal [4], anti-inflammatory [5], antioxidant [6], and anticancer [7]. Despite these benefits, curcumin has many drawbacks when used as a drug because of its poor drug properties, such as poor aqueous solubility, instability (highly pH-dependent), poor absorption, low distribution, and rapid metabolism [8].

Lung cancer is a deadly tumor with high morbidity and death rate, its mortality and incidence have increased dramatically on a worldwide level [9].

Despite the fact that chemotherapy is presently regarded as a useful cancer treatment approach, its effectiveness in treating patients with advanced lung cancer is severely limited due to drug resistance and toxicity [10]. Researchers have studied the traditional remedy curcumin for years due to its potential as an anticancer and chemopreventive agent [11]. Curcumin displays antiproliferative activity against human lung cancer A549 cells. Its chemical structures have three active functional moieties: two ortho-methoxy phenolic groups, two enone moieties, and 1,3-diketone moieties. Because

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of cis-trans isomerism and keto-enol tautomerism, unsaturated alpha-beta-diketones are typically found in nine distinct forms [12]. The aromatic rings were the primary targets of the modifications.

The structure-activity relationship was first investigated by focusing on the substitution pattern of curcumin's aromatic ring's 3-OCH3 and 4-OH groups [13]. Curcumin's anti-proliferative activities were either somewhat reduced or enhanced by removing the 4-OH groups or by adding another group, such as CH3, OC2H5, OC3H7, OC4H9, and CF3. Another modification employed active methylene positions, such as the alpha-ethyl group.

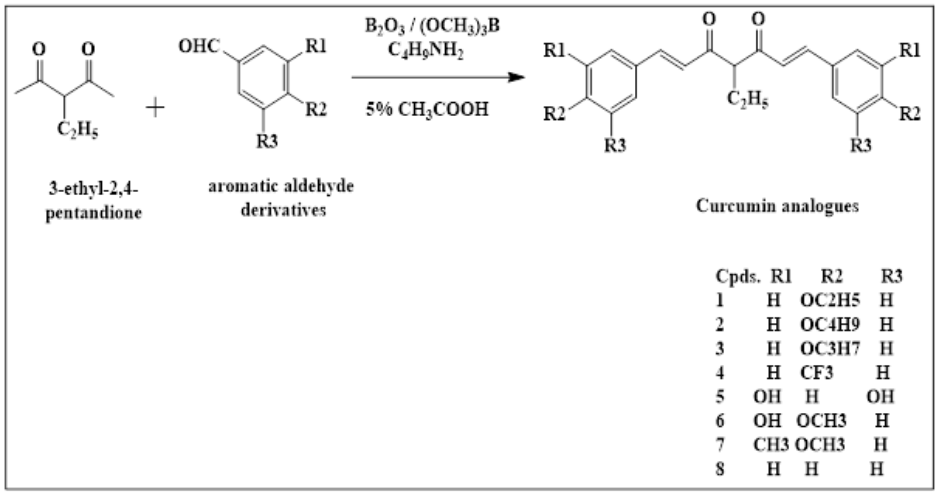
2. Materials and Methods

2.1 Materials and instruments:

All materials were utilized without further purification, straight from the typical source of the most excellent quality currently in use. The ultrasonic high-energy setting (40 kHz, 500 W) was employed. The melting points of the synthesized compounds were measured in a capillary tube using an electro thermal melting point apparatus model Stuart SMP30. Thin-layer chromatography was performed on Merck's TLC Silica Gel 60 F254, measuring 20 by 20 cm and with a thickness of 0.2 mm. The spot is visualized by UV light. The FTIR spectra using KBr discs and expressed in the range of 4000–500 cm-1 were recorded on the FT-IR-84005 Shimadzu Corporation spectrophotometer at the University of Basrah, College of Education for Pure Sciences, Department of Chemistry. Mass spectrometry of the studied compounds were done using Agilent 5975c technologies at the University of Tehran, Iran. The synthesized compounds were subjected to 1HNMR and 13CNMR spectroscopy at the analytical laboratory of Tehran University, College of Sciences, Department of Chemistry. The Varian (INOVA500 MHz) spectroscopy was used in DMSO-d6 as a solvent, the coupling constant was specified in Hz, and the chemical shift was in parts per million (ppm). The anticancer activity of synthesized compounds was determined in the Malaya University Faculty of Medicine and Pharmacology Department by using the MTT assay [14].

2.2. Synthesis of curcumin analogues (1-8) [15]

The general procedure for synthesizing certain curcumin analogues involved reacting of 3-ethyl-2,4-pentanedione with substituted aromatic aldehydes under ultrasonic irradiation, as shown in Scheme 1. 3-ethyl-2,4-pentanedione (3.49 ml, 0.026 mol) and substituted aromatic aldehyde (0.05 mol) were added to a round-bottom flask (250 ml) along with DMF (12 ml), tri-methyl borate (4 ml), and boron oxide (1.8 g, 0.026 mol). The mixture was exposed to ultrasonication at 80 °C for ten minutes before adding the butyl amine (1.2 ml, 0.012 mol) to the mixture in a round-bottom flask. The reaction process was monitored using TLC, and the reaction persisted for 45 minutes. After the reaction was complete, the round-bottom flask was heated in a hot water bath at 80 °C. After an addition of 200 mL of warm, glacial acetic acid (5%), the reaction was stirred continuously for an hour. The crude product was filtrated and washed with hot distilled water until the neutralized pH was approximately 7. Let the product dry overnight. The dried products were separated on silica (200 –300 mesh) using column chromatography after being eluted with a mixture of chloroform and ethanol (96:4) and then recrystallized by using an ethanol solvent.



Scheme (1): Synthesis of curcumin analouges

3. Results and Discussion

Some physical properties of synthesized compounds were summarized in Table (1).

Table (1): Physical properties of curcumin analogues 1-8.

Compound No.	color	Weight(g)	Yield%	Melting point (°C)
1	yellow	2.247	44.20	131-137
2	yellow	3.670	63.16	130-135
3	yellow	2.950	54.20	150-157
4	pale yellow	2.900	50.87	178-183
5	yellow	0.110	2.30	230-235
6	reddish – orange	1.900	37.00	173-179
7	orange	2.857	56.24	172-180
8	yellow	0.942	19.95	150-157

3.1 Mass spectra of the compounds (1-8)

The mass spectral data of the compounds (1 – 8), were gathered in Table (2) and the mass spectra were shown in Figures 1 – 8. Electron ionization technique is used to record the spectra of the studied molecules. From these spectra the molecular ion peaks were determined for compounds (1-8), which are equal to molecular weight of synthesis compounds. In the mass spectra of compound 5, a weak molecular ion peak was observed at m/z 368.1 and the base peak at m/z 163.1, which corresponds to the fragment ion of this compound and the possible fragmentation [16].

Table (2): Mass spectral data of the compounds 1-8.

Compound No.	Chemical formula	Molecular weight	Molecular ions (M^{+})	IUPAC Name

1	$C_{25}H_{28}O_4$	392.49	392.1	(1E,6E)-1,7-bis(4-ethoxyphenyl)-4-ethylhepta-1,6-diene-3,5-dione
2	$C_{29}H_{36}O_4$	448.6	448.2	(1E,6E)-1,7-bis(4-butoxyphenyl)-4-ethylhepta-1,6-diene-3,5-dione
3	$C_{27}H_{32}O_4$	420.55	420.2	(1E,6E)-4-ethyl-1,7-bis(4-propoxyphenyl)hepta-1,6-diene-3,5-dione
4	$C_{23}H_{18}F_6O_2$	440.39	440.3	(1E,6E)-4-ethyl-1,7-bis(4-(trifluoromethyl)phenyl) hepta-1,6-diene-3,5-dione
5	$C_{21}H_{20}O_6$	368.38	368.4	(1E,6E)-1,7-bis(3,5-dihydroxyphenyl)-4-ethylhepta-1,6-diene-3,5-dione
6	$C_{23}H_{24}O_6$	396.44	396.1	(1E,6E)-4-ethyl-1,7-bis(3-hydroxy-4-methoxyphenyl) hepta-1,6-diene-3,5-dione
7	$C_{25}H_{28}O_4$	392.49	392.1	(1E,6E)-4-ethyl-1,7-bis(4-methoxy-3-methylphenyl)hepta-1,6-diene-3,5-dione
8	$C_{21}H_{20}O_2$	304.39	304.4	(1E,6E)-4-ethyl-1,7-diphenylhepta-1,6-diene-3,5-dione

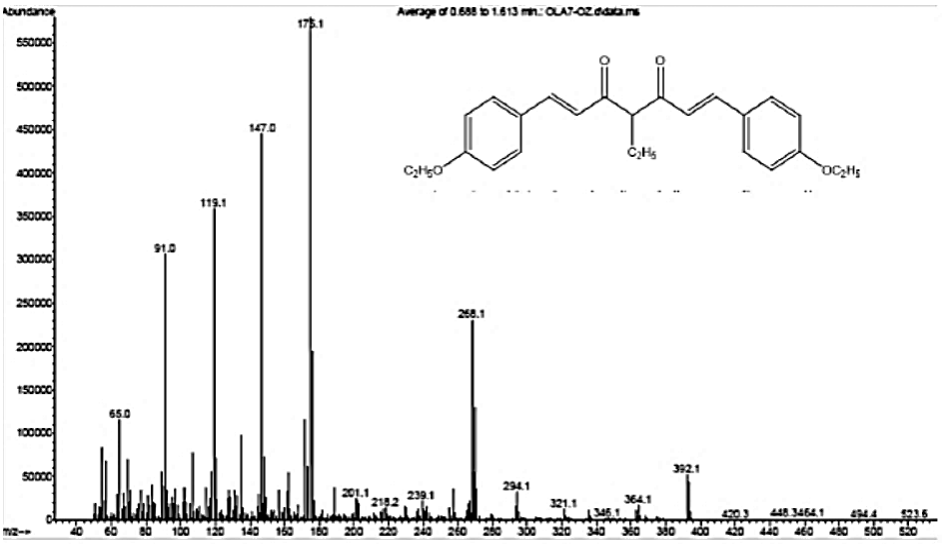


Figure (1): The EI mass spectrum of compound (1).

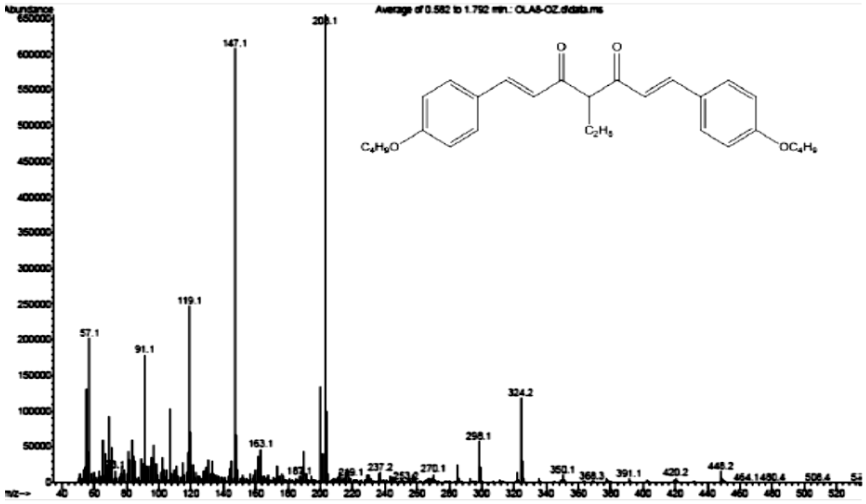


Figure (2): The EI mass spectrum of compound (2).

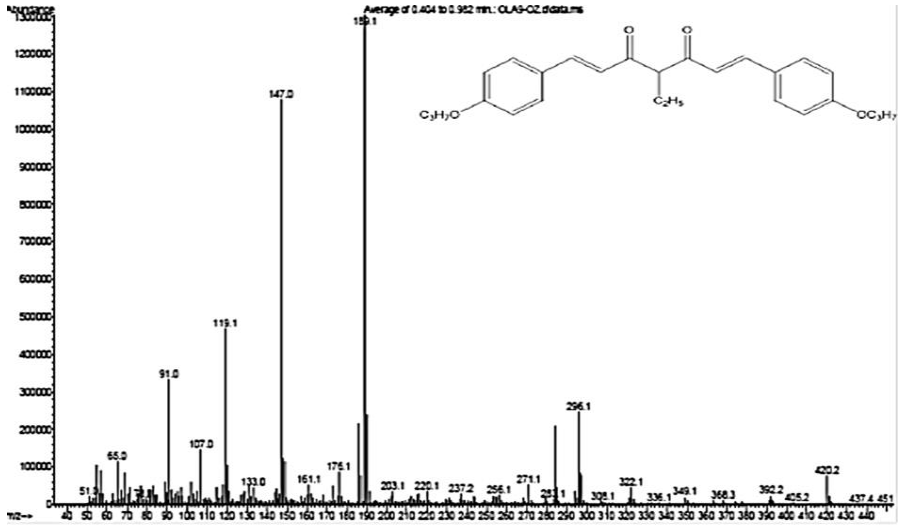


Figure (3): The EI mass spectrum of compound (3).

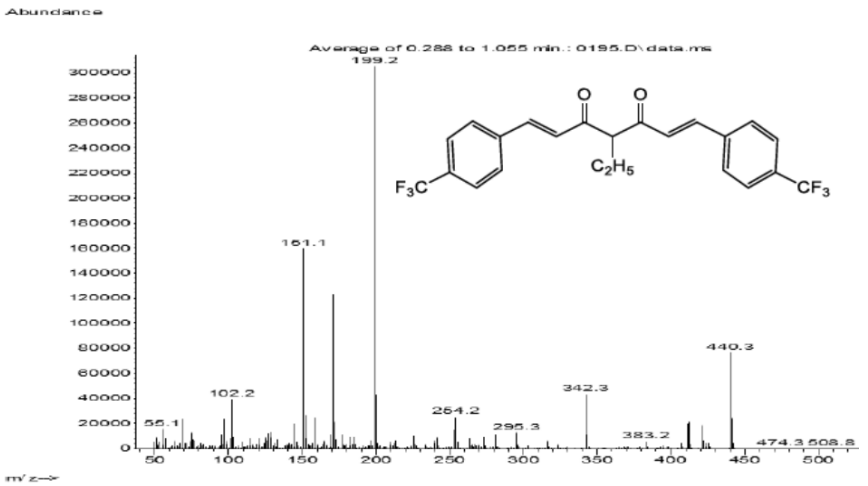


Figure (4): The EI mass spectrum of compound (4).

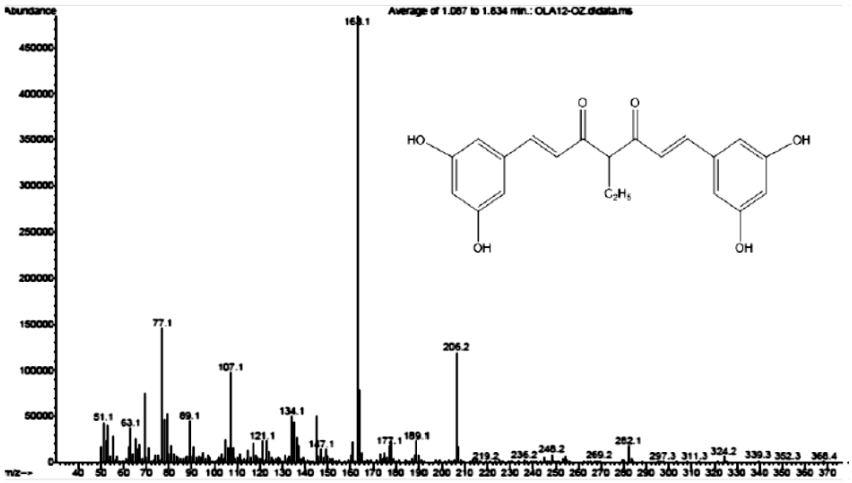


Figure (5): The EI mass spectrum of compound (5).

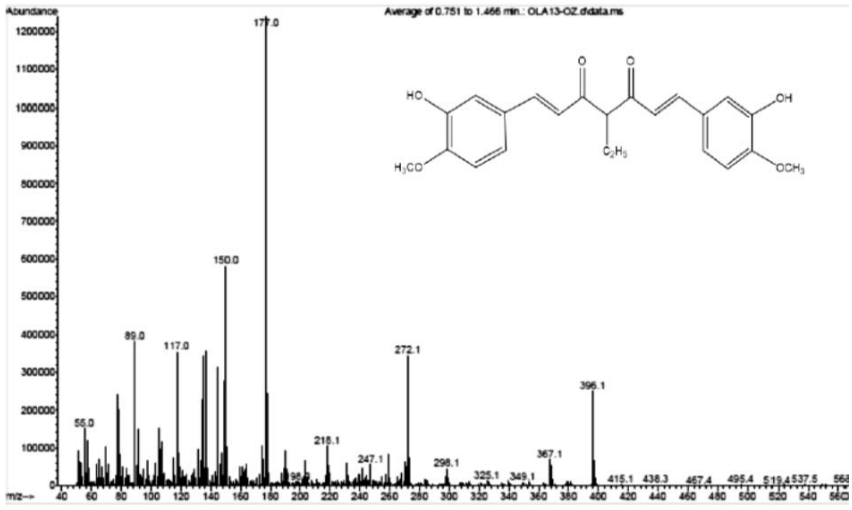


Figure (6): The EI mass spectrum of compound (6).

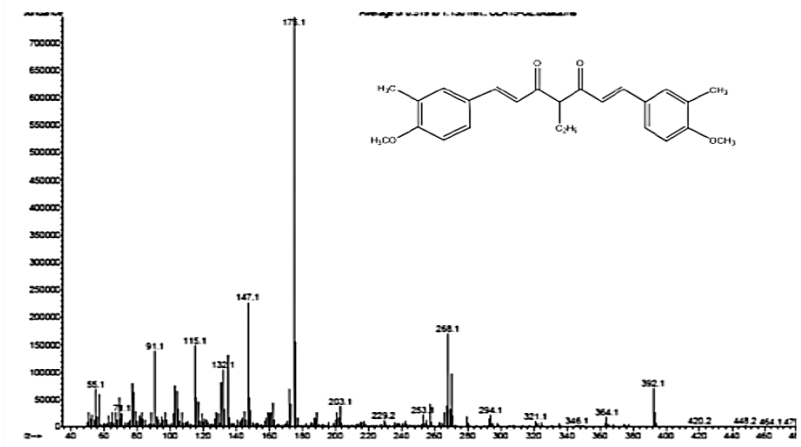


Figure (7): The EI mass spectrum of compound (7).

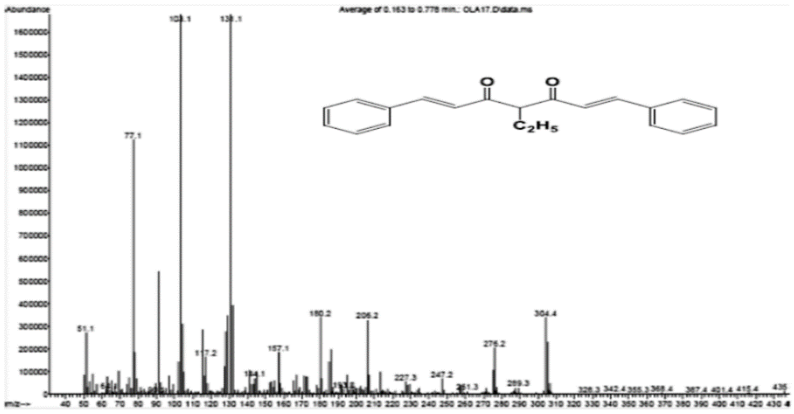
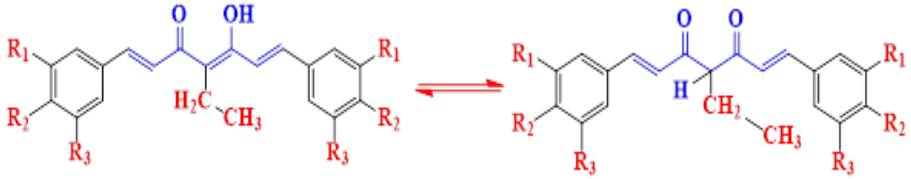


Figure (8): The EI mass spectrum of compound (8).

3.2 1H NMR spectra of synthesized compounds (1-8)

The 1HNMR spectra of compounds 1–8 were shown in Figures 9–16. They may have two peaks at 2.5 ppm and 3.3 ppm that are related to the solvents DMSO-d6 and water, respectively.

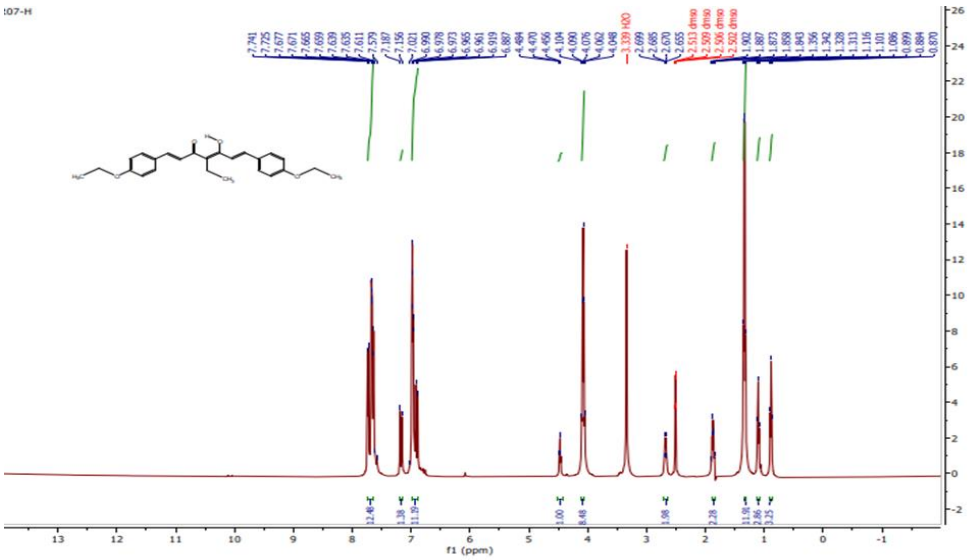
The studied compounds (1–8) exist mainly as an equilibrium between keto-enol and diketo tautomerism, as shown in Scheme (2). The separated signals of protons resonance are always detected for the different groups in the keto-enol and diketo forms [17].



Scheme (2): The keto-enol tautomerism of compounds (1-8).

Their 1HNMR spectra are identical and differ only in substitutions on the aromatic rings. Generally, their spectra consist of three main groups of signals: the signals of aromatic and olefinic protons as a multiplet within the range (6.30–8.05 ppm), the enolic OH signal of the keto-enol form appearing as a singlet signal within the range (17.40–17.86 ppm) as a results of intramolecular hydrogen bonding within the central chelating ring [18], and the aliphatic protons signals, which are divided into two main groups: the signals of alpha CH2CH3 groups of protons for diketo forms of CH3 appear as a triplet within the range (0.87–0.93

ppm), and a pentate signal at the range (1.49–1.93 ppm) refers to CH2, while the keto-enol forms signals of alpha-ethyl appear as a triplet within the range (1.10–1.15) ppm refers mainly to CH3, and a quartat signal at the range 2.64–2.76 ppm refers to CH2, respectively. In addition, the signal of the α-CH proton in the



diketo form appears as a triplet within the range of 4.44–4.60 ppm.

Figure (9): ^{1}HNMR spectrum of compound (1) at 500 MHz.

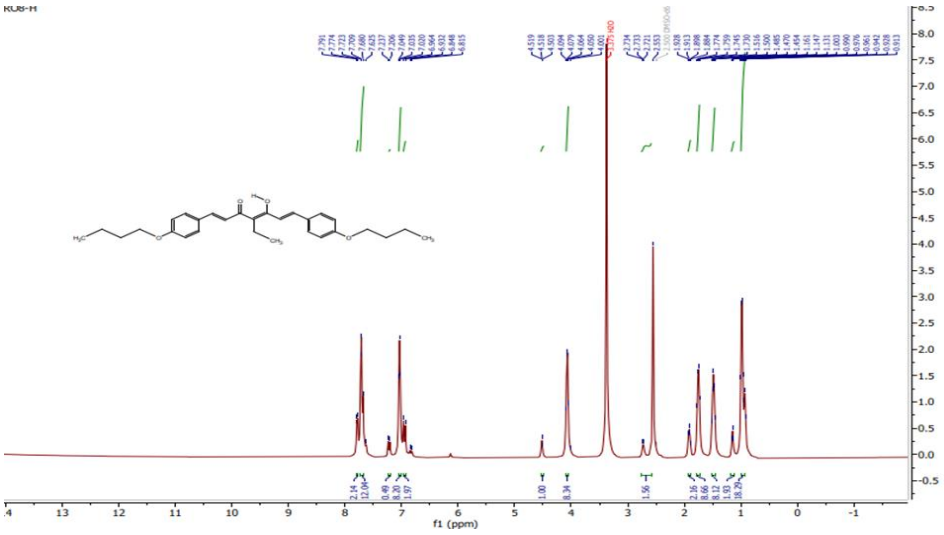


Figure (10): ^{1}HNMR spectrum of compound (2) at 500 MH

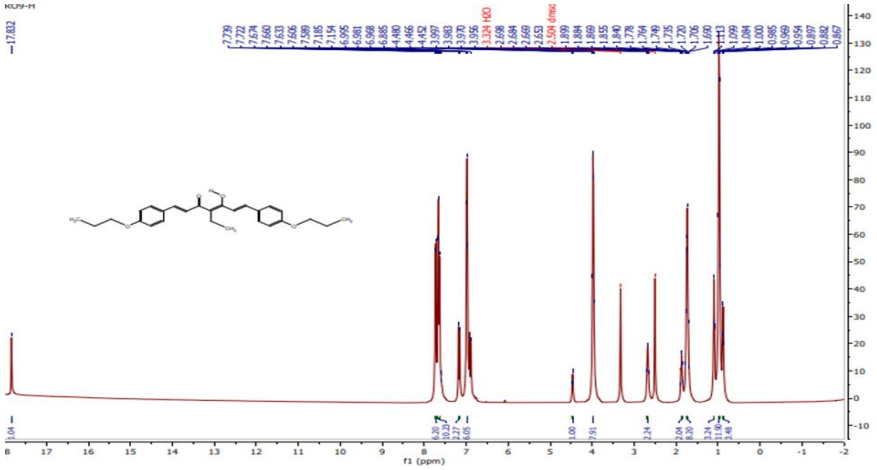


Figure (11): ^{1}HNMR spectrum of compound (3) at 500 MHz.

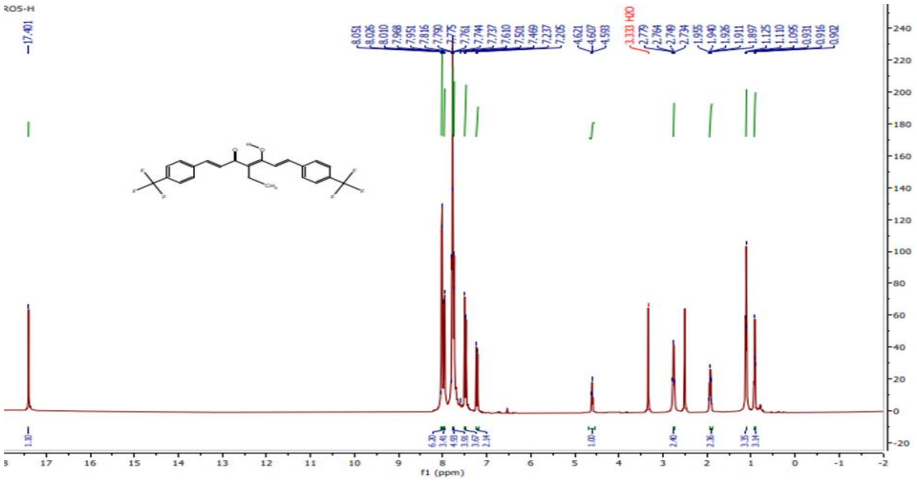


Figure (12): ^{1}HNMR spectrum of compound (4) at 500 MHz.

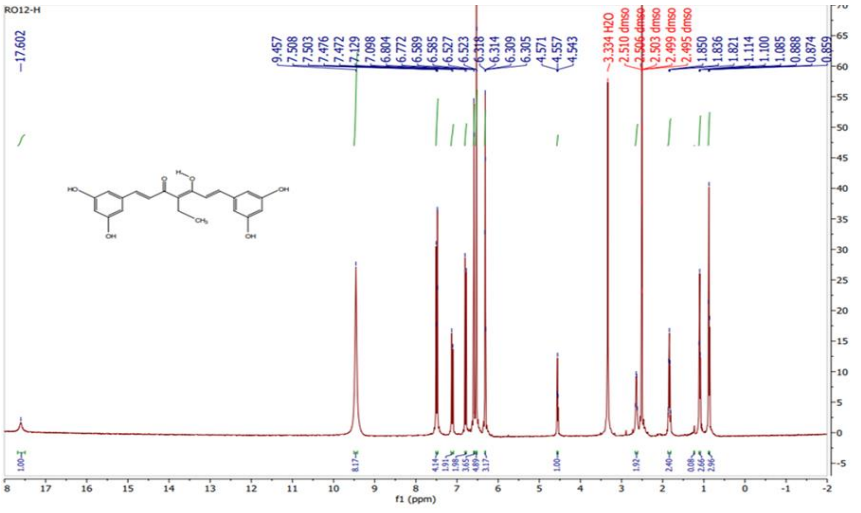


Figure (13): ^{1}HNMR spectrum of compound (5) at 500 MHz.

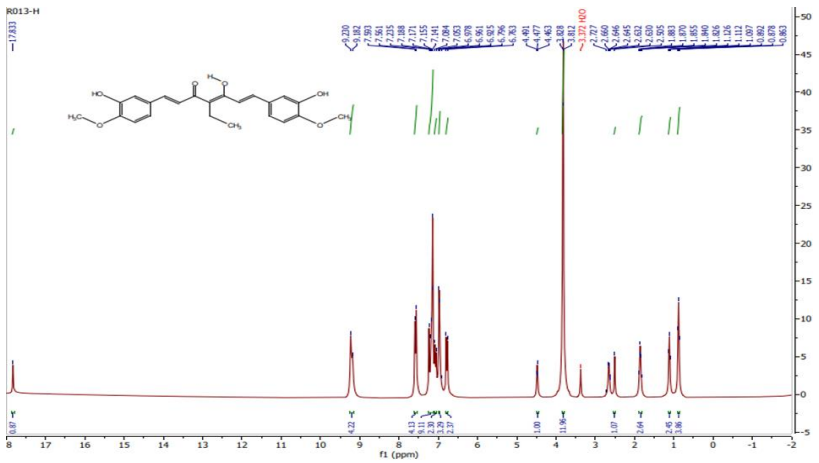


Figure (14): ^{1}HNMR spectrum of compound (6) at 500 MHz.

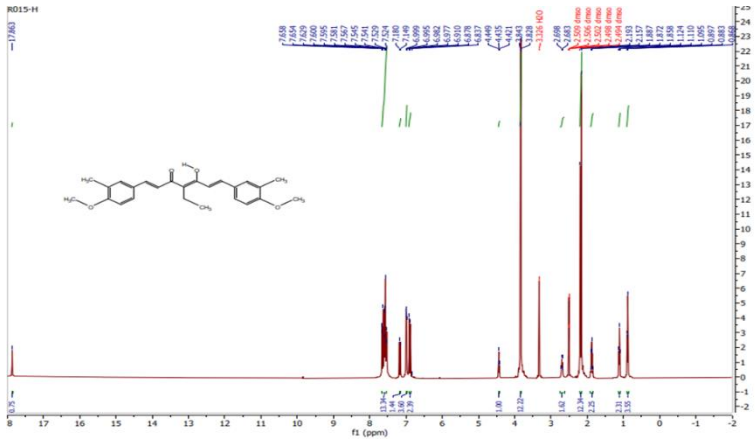


Figure (15): 1HNMR spectrum of compound (7) at 500 MHz.

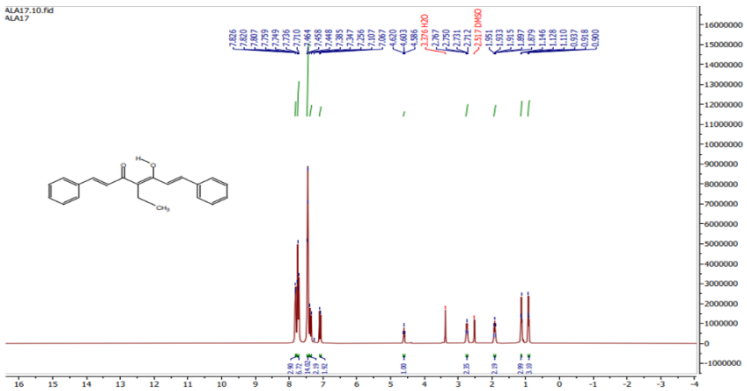


Figure (16): 1HNMR spectrum of compound (8) at 500 MHz

3.3 13 CNMR spectra of compounds (1-8)

The 13CNMR spectra of compounds (1-8) were shown in Figures (17-24). These spectra have a multiplete signals at 40 ppm that related to the solvent DMSO-d6. The studied compounds exist mainly as a mixture of the diketone and keto-enol forms as shown in scheme (3). The 13C-NMR spectra for the β-diketone tautomer suggest that carbonyl carbon in the keto-enol form is slightly less deshielded than in the beta-diketone form [19]. All of the compounds (1–8) are structurally and chemically identical, with the exception of substitution on the

aromatic rings. Thus, their spectrum are roughly similar; they have identical signals, and they differ only in the signals of substitution on the aromatic rings.

Scheme (3): The keto-enol tautomerism of compounds (1-8).

The keto carbon (C11) signals appear within the range (195.8–196.3 ppm), while the enol carbon (C9) signals are within the range (182.9–183.1 ppm) [18]. The signals that appear at 63.1–67.9 ppm and 105.3–115.3 ppm belong to the diketo and keto-enol forms, respectively, of the heptadien chain carbon10 [19]. The alpha-ethyl carbon (CH2CH3) signals appear at 12.4–12.5 ppm and 15.0–17.8 ppm, respectively, attributed mainly to CH3 for diketo and keto-enol forms, while CH2 signals appear at 18.6-22.0 ppm and 18.6-24.1 ppm for diketo and keto-enol forms, respectively [19]. The signals that appear within the range of 118.4–123.9 ppm and 120.6–127 ppm refer to heptadienedione carbon (C8 and C12), respectively [19].

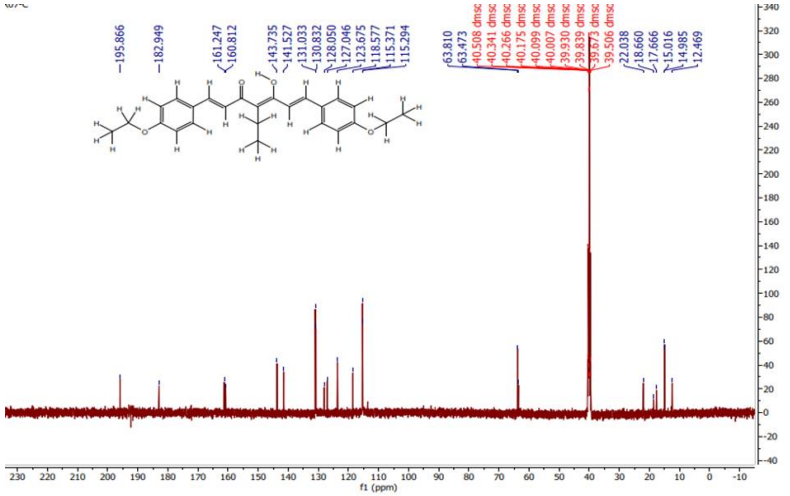


Figure (17): ^{13}CNMR spectrum of compound (1)

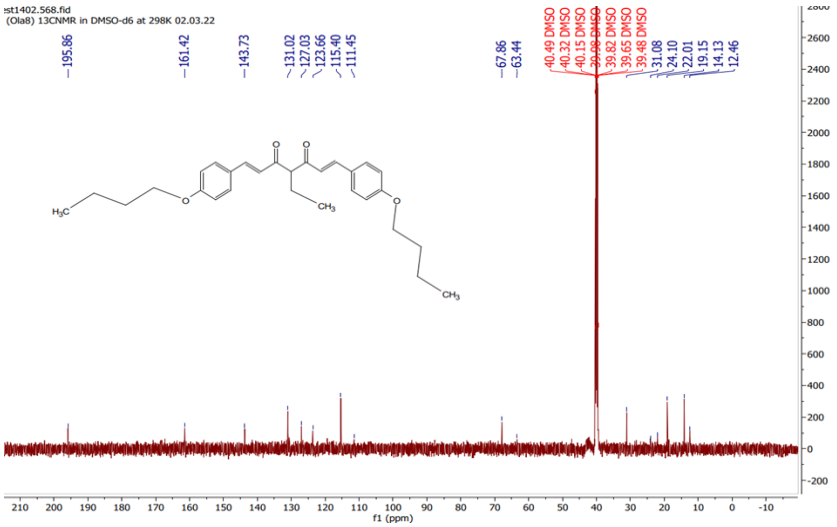


Figure (18): ^{13}CNMR spectrum of compound (2).

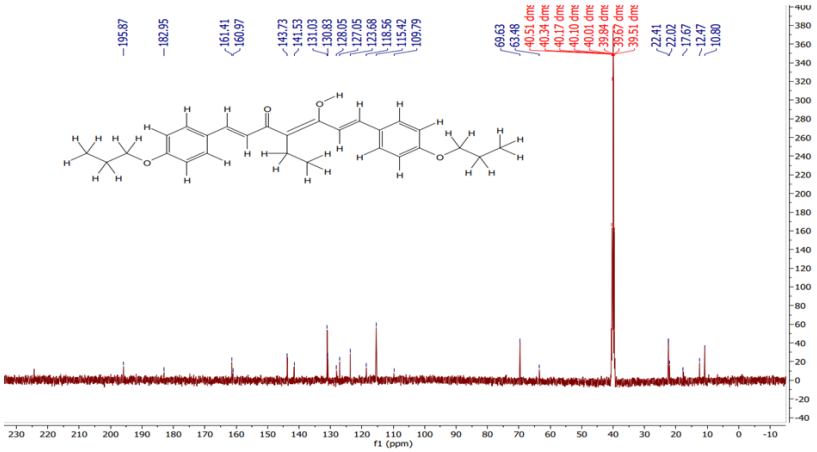


Figure (19): ^{13}CNMR spectrum of compound (3).

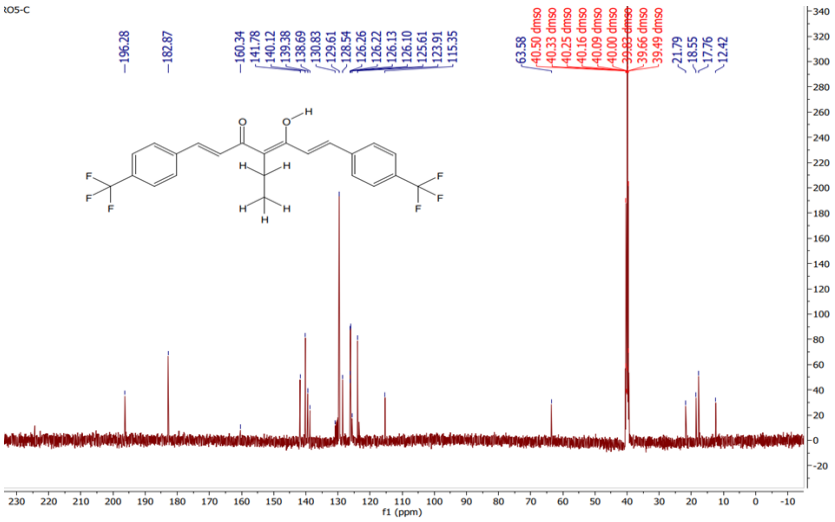


Figure (20): ^{13}CNMR spectrum of compound (4).

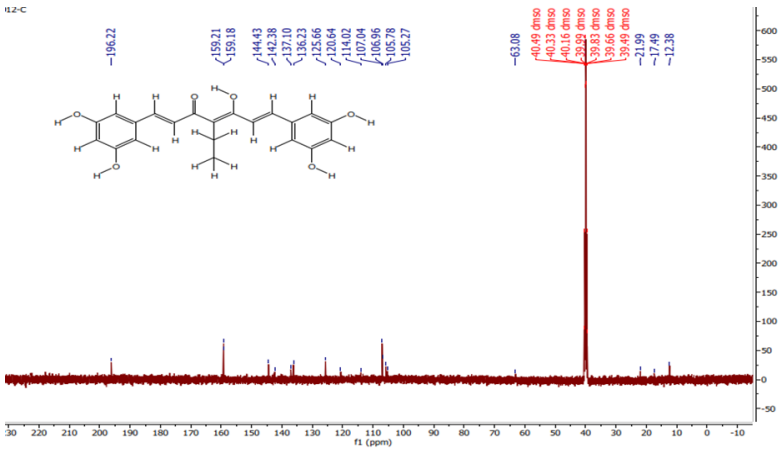


Figure (21): 13CNMR spectrum of compound (5).

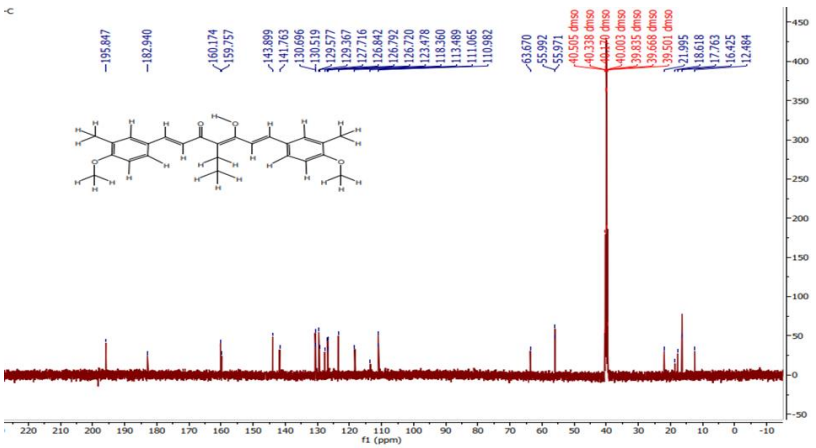


Figure (22): ^{13}CNMR spectrum of compound (6).

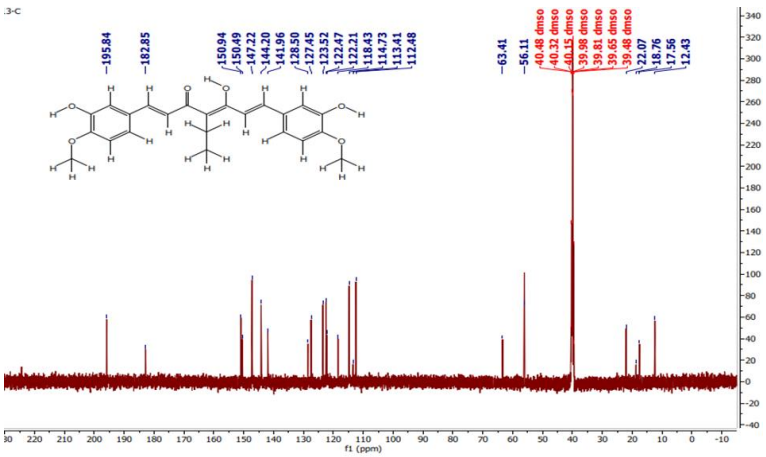


Figure (23): ^{13}CNMR spectrum of compound (7).

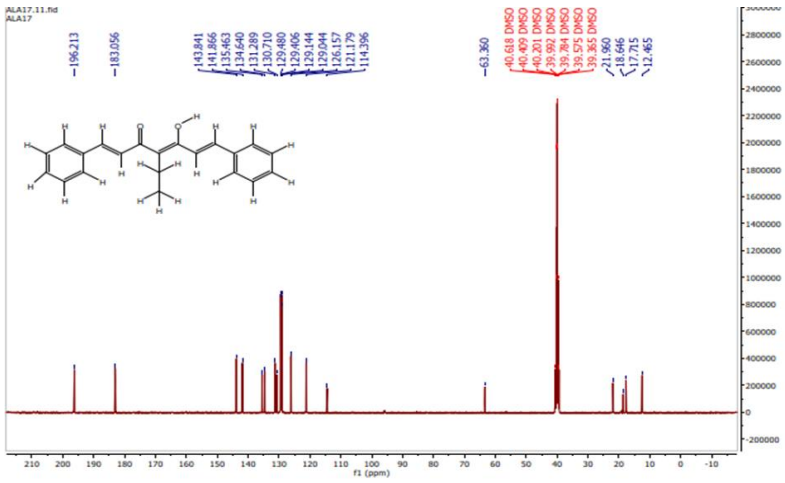


Figure (24): ^{13}CNMR spectrum of compound (8).

3.4 The FTIR spectra of the compounds (1-8)

In the FTIR spectra of compounds (1-8), which were prepared from appropriate benzaldehyde with absorption bands at 1687 -1786 cm^{-1} attributed to the carbonyl groups of aldehyde [20], this band disappeared from the spectra of synthesized compounds, which in turn their carbonyl band appear at 1575-1624 cm^{-1} due to the formation of the intramolecular hydrogen bond [21, 22]. The aromatic (C-H) stretches are responsible for the weak bands in the infrared spectrum in the range

3057-3130 cm^{-1} weak band [23]. The C=C stretching band were appeared as a strong band at 1471- 1579 cm^{-1} attributed to the stretching vibrations of their C=C [23, 24]. The weak broad band in the range 3200-2500 cm^{-1} for enolic υ(OH) is not very accurate due to overlapping with C-H stretching in this region [25, 26]. The aliphatic C-H stretching bands have been observed as weak bands in the infrared spectra (2839-2968) cm^{-1}. The FTIR spectra of compounds 5 and 6 show very clear, sharp bands in the range 3529-3255 cm^{-1} attributed to the stretching vibrations of their phenolic OH [24].

3.5 In vitro anticancer activity study of the compounds (1-8)

The studies compounds were preliminary examined for their in vitro anticancer activity against the human lung cancer cell line A549 and HdFn as normal cell using the MTT assay. That uses colorimetric techniques based on mitochondrial dehydrogenase activity measurement to estimate the number of viable cells. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide is yellow-colored and is reduced by dehydrogenase in living cells to produce a purple-colored formazan dye, followed by the solvation of the crystals with a suitable solvent and measuring their absorbance of light at 570 nm [27]. The half maximal inhibitory concentration (IC_{50}) was determined based on the dose response curve generated after finding the percent of survival cells at various concentrations of the compounds, as displayed in Figures (25–26). The anticancer activity of compounds is categorized into three groups based on their cell growth inhibition: active IC_{50} < 20 μg/ml, moderate activity IC_{50} 20–100 μg/ml, and inactive IC_{50} > 100 μg/ml [28].

The selectivity index (SI) is known as the ratio of the tested compounds cytotoxicity in normal cells (IC_{50} HdFn μg/ml) versus cancer cells (IC_{50} A549). Compounds with anticancer specificity are indicated by SI values higher than 1.0, while compounds with significantly higher SI values than 1.0 are highly selective [27].

The synthesized compounds exhibited cytotoxicity, with an assumed IC_{50} range of 10.39–234.3 μg/ml, as shown in Table 3. The results show that compound 1 with an IC_{50} of 10.39 μg/ml and SI of 17.56 is the most potent agent and very highly selective against A549 lung cancer compared to curcumin (IC_{50} of 94.25 μg/ml and SI of 3.20) and the other studied compounds. Whereas compound 7 with (IC_{50} 88.5 μg/ml and SI 1.15), has more potent activity but less selectivity than curcumin.

The structure-activity relationship study indicated that the presence of the various substituted groups on the aromatic rings mainly affected the cytotoxic activity of the studied compounds, as seen in compound 1, with the ethyl group at the alpha position and the ethoxy group at the para position of the aromatic rings, which has more anticancer activity and high selectivity against A549 lung cancer compared to curcumin. Therefore, the presence of the methyl group at the meta-position and para-methoxy group on the aromatic ring, as shown in compound 7, has moderate anticancer activity; other compounds 2–6 and 8 are inactive anticancer agents against A549 lung cancer.

Table (4.3): The IC_{50} of curcumin and its derivatives 1-8 against lung cancer

Compound NO.	HdFn IC_{50}μg/ml	A549 IC_{50} μg/ml	SI
1	182.5	10.39	17.56
2	122.8	110.1	1.12
3	261.6	222.4	1.18
4	192.5	186.4	1.03

5	193.4	182.3	1.06
6	144.4	115.0	1.25
7	102.5	88.82	1.15
8	301.8	234.3	1.29
curcumin	**301.8**	**94.25**	**3.20**

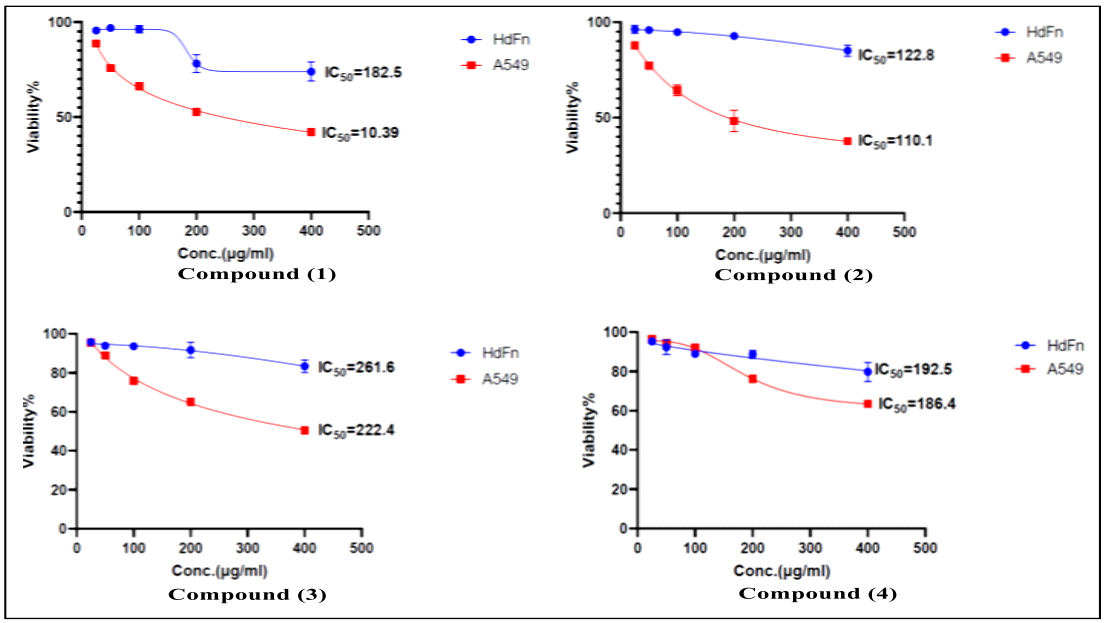


Figure (25): Impact of compounds 1-4 at various concentration on the percentage of cell viability

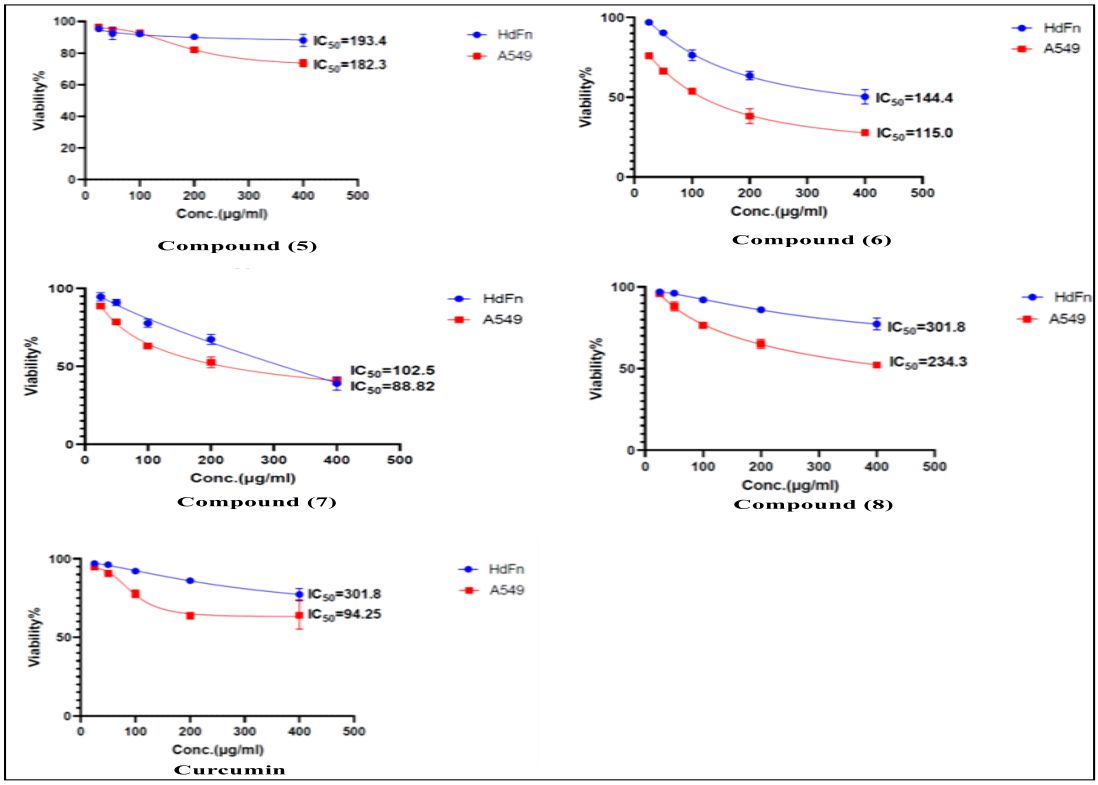


Figure (26): Impact of compounds 5-8 and curcumin at various concentration on the percentage of cell viability

4. Conclusion

Eight novel compounds (1–8) were prepared and designed as anticancer agents. The structures of these compounds were specified by mass, 1HNMR, 13CNMR, and FTIR techniques. The results show that curcumin analogues are characterized by highly selective anticancer activity against the A549, and the compound with the most potent anticancer activity and high selectivity observed is compound 1, with an IC50 equal to 10.39 μg/ml and SI equal to 17.56. An increase in cytotoxicity is caused by the presence of an ethoxy group at the para-position of the aromatic rings and an alpha-ethyl group at the active methylene positions. Followed by compound 7 with an IC50 of 88.8 μg/ml and a SI of 1.15, which is considered to have moderate anticancer activity against A549 and has less selectivity in comparison to curcumin with an IC50 of 94.25 μg/ml and a SI of 3.20.

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