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Synthesis, Characterization, and Anticancer Activity Study of New Curcumin Analogues against MDA-MB 231 Breast Cancer Cell Line

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RESEARCH ARTICLE

Synthesis, Characterization, and Anticancer Activity Study of New Curcumin Analogues against MDA-MB 231 Breast Cancer Cell Line

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ABSTRACT

Synthesis of six new curcumin analogues was performed through condensation reaction of 3-methyl-2, 4-pentandione with substituted aromatic aldehyde derivatives and boron oxide in the presence of trimethylborate and butylamine. The reaction was carried out under ultrasonic irradiation. The synthesized compounds were identified using ^{1}H-, ^{13}C-NMR, FT-IR spectroscopy, and electron impact mass spectrometry. The Swiss ADME website was used to predict the physicochemical properties of the new compounds using computational techniques like ADME studies. All produced compounds, according to this study, complies with the Lipinski rule of five. The microculture tetrazolium (MTT) assay was utilized to assess the investigated compounds, in vitro anticancer activity against the human breast cancer cell line MDA-MB 231. The results showed that compounds 6 and 2, with IC_{50} values of 47.78 and 111.8 μg/ml respectively, had potent anticancer activity compared to curcumin with IC_{50} value of 125.5 μg/ml.

Keywords: Anticancer activity, Curcumin, Lipinski rule, Microculture tetrazolium assay, Ultrasonic irradiation

Introduction

Natural Curcumin is a polyphenolic phytochemical compound derived from the root of rhizome *Curcuma longa*.[1,2] The three main curcuminiods found in turmeric are curcumin, demethoxycurcumin, and bisdemethoxycurcumin. It was first recognized by Vogel in 1815 as the main component of turmeric and it was further isolated in 1842.[3,4] Curcumin unsaturated α-β-diketones are generally found in nine distinct forms because of cis-trans isomerism and keto-enol tautomerism.[5] The Keto-enol tautomerism refers to the exchange of a proton between two constitutional isomers: keto and enol.[2]

Curcumin exhibits various pharmacological actions with different mechanisms of actions such as antibacterial,[6] anti-inflammatory,[7] antioxidant,[8] and anticancer.[9,10] Despite these benefits, it has many drawbacks when used as a drug; because it is poor drug properties such as poor aqueous solubility, instability (highly pH-dependent), poor absorption, low distribution, and rapid metabolism.[11,12] The traditional remedy curcumin has been studied for years for its potential as an anticancer and chemopreventive agent.[13]

Breast carcinoma is one of the most common types of the disease. With 23 percent of cancer cases occurring in women, it is a highly variable illness in terms of both histology and molecular levels.[14] Based on gene expression profiling, six different subtypes have been identified, the MDA-MB-231 is a particularly aggressive and invading breast cancer cell line that exhibits ER, PR, and HER2 negative expression. Furthermore, even though numerous new drugs have been introduced to the market, patient response to therapy remains low, and drug resistance develops. Consequently, there is an urgent need to develop anticancer drugs that are less likely to cause

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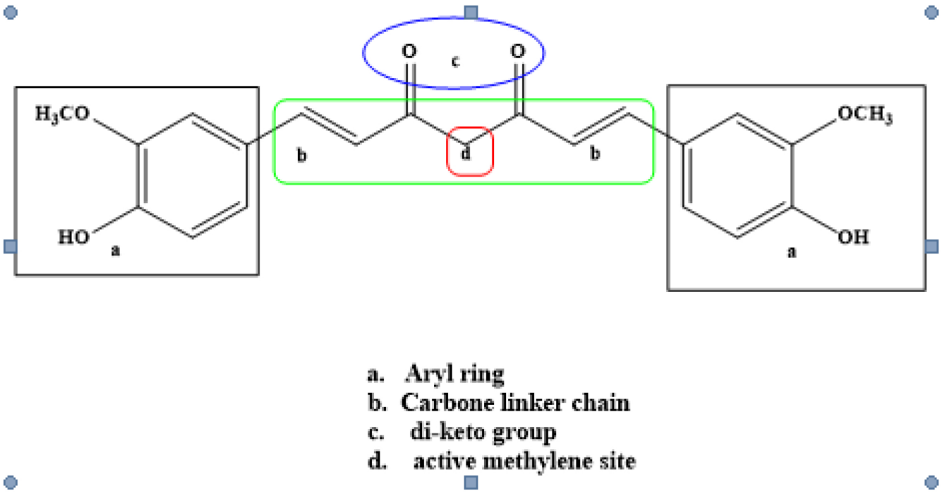


Fig. 1. Sites of modification and active functional groups of curcumin.

side effects and more effective.[15] To modify the molecule of curcumin it is important to study the structure of curcumin and identify the reactive sites in molecule Fig. 1.[9] For the heptadienedione series, the primary targets of the modifications were the aromatic ring. When the structure-activity relationship was first investigated, we focused on the substitution pattern of curcumin's aromatic ring's 3-OCH_3 and 4-OH groups. Removing the 4-OH groups or adding another group such as(OCH_3, OC_2H_5, OC_3H_7 and OC_4H_9) somewhat decreased or increase curcumin's anti-proliferative effects,[16] another modification employed active methylene position such as alpha methyl.

Materials and methods

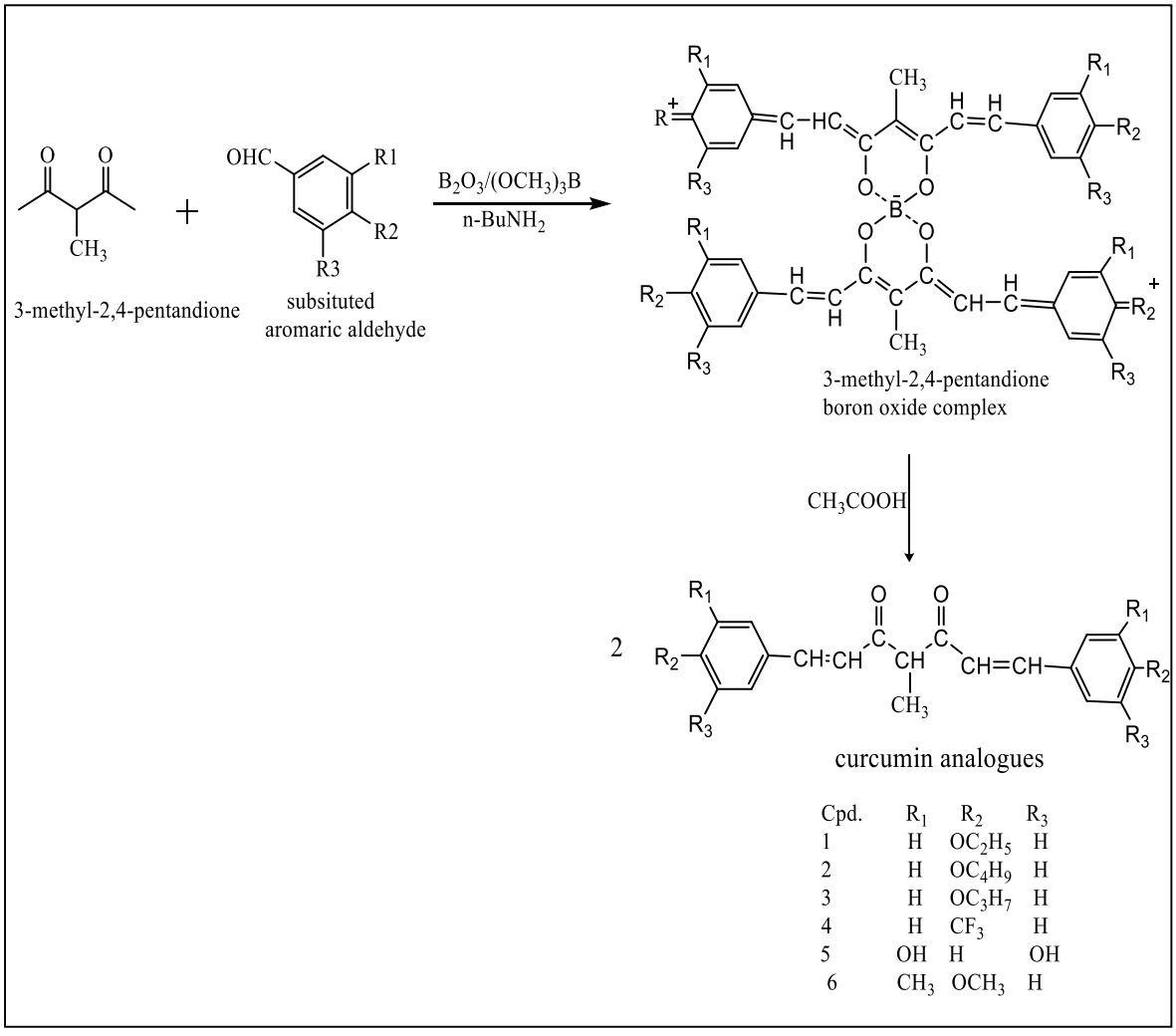
Chemical and instrument

All materials are used without further purification, straight from the typical source of the most excellent quality currently in use. The ultrasonic highest energy setting (40 kHz, 500 W) was used. The melting points of the prepared curcumin analogues were measured in capillary tube using electro thermal melting point apparatus model Stuart SMP30 apparatus. Thin-layer chromatography was performed on Merck's, TLC Silica Gel 60 F254, and measuring 20 by 20 cm and with a thickness of 0.2 mm. The spot visualized by UV light. The FTIR spectra using KBr discs and expressed in the range of 4000–500 cm^{-1} were recorded on FT-IR –84005 Shimadzu Corporation spectrophotometer at University of Basrah, College of Education for Pure Science, Department of Chemistry. Mass spectrometry of the studied compounds was done by using Agilent 5975c technologies at the University of Tehran, Iran. The synthesized compounds were subjected to ^{1}H-NMR and ^{13}C-NMR spectroscopy at the analytical laboratory of Tehran University, College of Sciences, Department of Chemistry. The Varian (INOVA500 MHz) spectroscopy was used in DMSO-d_6 as a solvent, the coupling constant was specified in Hz, and the chemical shift was in part per million (ppm). The anticancer activity of synthesized compounds were done in the Malaya University, Factuality of Medicine and Pharmacology Department,by using MTT assay.[17]

Experiment

Synthesis of curcumin analogues

The general method for synthesizing certain curcumin analogues.[18] It includes reacting 3-methyl-2, 4-pentanedione with substituted aromatic aldehydes under ultrasonic irradiation as shown in Scheme 1. 3-methyl-2, 4-pentanedione (1.48 ml, 0.013 mol) and substituted aromatic aldehyde (0.025 mol) were added to a round-bottom flask (100 ml) along with DMF (6 ml), tri-methyl borate (2 ml), and boron oxide (0.9 g, 0.013 mol) and the mixture were exposed to ultrasonication at 80°C for ten minutes then adding the butyl amine (0.6 ml) to the round. 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; after adding 100 mL of warm, five percent glacial acetic acid, the reaction was stirred continuously for an hour. We used the hot water to wash and filter it. Until neutralized pH was approximately 7. The product was left to dry overnight. Column chromatography was used to separate the



Scheme 1. Synthesis of curcumin analogues.

Table 1. Physical properties of curcumin analogues 1–6.

Compound No.	Weight(g)	color	Melting point (°C)	Yield%
1	2.86	Pale reddish- orange	165–170	58
2	3.86	Pale orange	147–150	68.68
3	3.038	Yellow	154–160	57.62
4	3.306	Pale yellow	156–159	59.94
5	0.33	Yellow	243–246	4.86
6	2.65	Yellow	166–171	54.19

dried products on silica (200–300 mesh) eluted with mixture of chloroform and ethanol, ethanol solvent was used for recrystallization.

Results and discussion

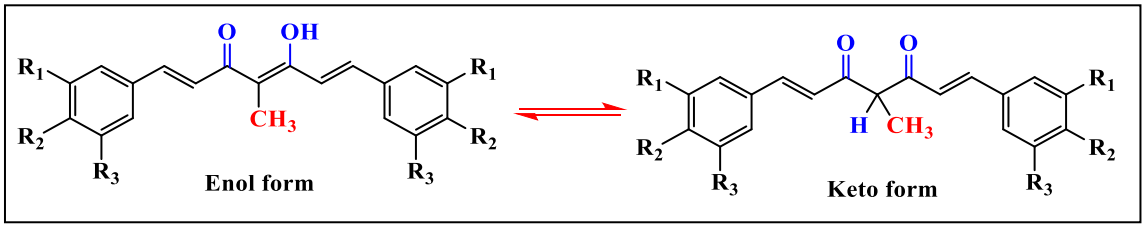
The physical properties of synthesized compounds are summarized in Table 1.

Mass spectrometry of curcumin analogues 1–6

The mass spectral data of the compounds (1–6), are gathered in Table 2, and the mass spectra are shown in (suppl. 1–6). Electron Ionization technique is used to record the spectra of the studied molecules. From these spectra the molecular ion peaks were determined for compounds, which are equal to molecular weight of synthesis compounds.

Table 2. Mass spectral data of the compounds (1–6).

Compound No.	Chemical formula	Molecular weight	Molecular ions (m/z)	IUPAC Name
1	$C_{24}H_{26}O_4$	378.47	378.3	(1E,6E)-1,7-bis(4-ethoxyphenyl)-4-methylhepta-1,6-diene-3,5-dione
2	$C_{28}H_{34}O_4$	434.58	435.4	(1E,6E)-1,7-bis(4-butoxyphenyl)-4-methylhepta-1,6-diene-3,5-dione
3	$C_{26}H_{30}O_4$	406.52	406.3	(1E,6E)-4-methyl-1,7-bis(4-propoxyphenyl) hepta-1,6-diene-3,5-dione
4	$C_{22}H_{16}F_6O_2$	426.36	426.3	1E,6E)-4-methyl-1,7-bis(4-(trifluoromethyl) phenyl)hepta-1,6-diene-3,5-dione
5	$C_{20}H_{18}O_6$	354.36	354.1	(1E,6E)-1,7-bis(3,5-dihydroxyphenyl)-4-methylhepta-1,6-diene-3,5-dione
6	$C_{24}H_{26}O_4$	378.47	378.3	(1E,6E)-1,7-bis(4-methoxy-3-methylphenyl)-4-methylhepta-1,6-diene-3,5-dione



Scheme 2. The keto-enol Tautomerization of curcumin analogue.

FT-IR spectroscopy of curcumin analogues 1–6

FTIR spectra of curcumin analogues which were prepared from appropriate benzaldehyde with absorption bands at 1687–1786 cm^{-1} are attributed to the carbonyl groups of aldehyde.[19] This band disappeared from the spectra of curcumin analogues, their carbonyl band appear at 1617–1629 cm^{-1} due to the formation of the intra-hydrogen bonded.[20,21] The aromatic(C-H) stretches are responsible for the bands in the infrared spectrum at 3074–3076.4 cm^{-1} weak band.[22] C=C stretching band appeared as strong band at 1600–1500 cm^{-1} which are attributed to the stretching vibrations of their C=C.[21] The weak broad band appeared in range 3200–2500 cm^{-1} for enolic ν(OH) this range is not very accurate due to overlapping with C-H stretching in this region.[22] The aliphatic C-H stretches bands have been observed as weak band in the infrared spectra (2800–3000) cm^{-1}. The FTIR spectrum of compound 5 showed very clear sharp bands in rang 3500–3200 cm^{-1} which are attributed to the stretching vibrations of their phenolic OH[23] (suppl.7–12).

^{1}H-NMR spectra of curcumin analogues 1–6

^{1}H-NMR spectra of compounds (1–6) (suppl. 13–18) had two peaks at 2.5 ppm and 3.3 ppm that were related to the solvent DMSO-d_6 and water respectively. The presence of both the β-diketone form and the keto-enol tautomer for curcumin analogs in solvent $DMSOd_6$ has been clearly established.[2] In solution, both tautomers are present at the same time as shown in Scheme 2.

^{1}H-NMR spectra of curcumin analogs require the tautomerism of molecules in keto-enol form. This spectrum shows singlet signal at 17.66 ppm corresponding mainly to the enolic proton. Its position downfield has been attributed to the combined effect of strong intramolecular hydrogen bonds and the conjugation through the system.[24] The phenolic protons (OH) which can be observed at 9–9.5 ppm disappear in all compounds with the exception of compounds 5, while the signals at 4.58 ppm as quartet refer to the methine (CH) keto form. The spectrum showed triplet and quartet signals at 4.07 ppm and 1.33 ppm referred to the 2 methyl and 2 methylene proton of the alkoxy group .The aromatic and olefinic protons signals developed as multiplet near 6.87–7.74 ppm. At 2.18 ppm, the α-methyl proton of enol form can be observed as a singlet, while the α-methyl proton of keto form signals appeared as doublet at 1.28 ppm with J coupling constant 7 Hz. The interaction of keto and enolic protons determined how its integrates are challenging.[25]

^{13}C-NMR spectra of compounds 1–6

^{13}C-NMR spectra of compounds 1–6 were shown in Figs. 2 to 7. Using ^{13}C-NMR the presence of both the β-diketone form and the keto-enol tautomer for curcumin analogs in solvent $DMSOd_6$ has been clearly established as shown in Scheme 3.[25]

These spectra had signals at 40 ppm that related to the solvent DMSO-d_6. The ^{13}C-NMR spectra for the β-diketone tautomer suggest that carbonyl carbon in the keto-enol form is slightly less deshielded than in the β-diketone form.[26] In ^{13}C-NMR

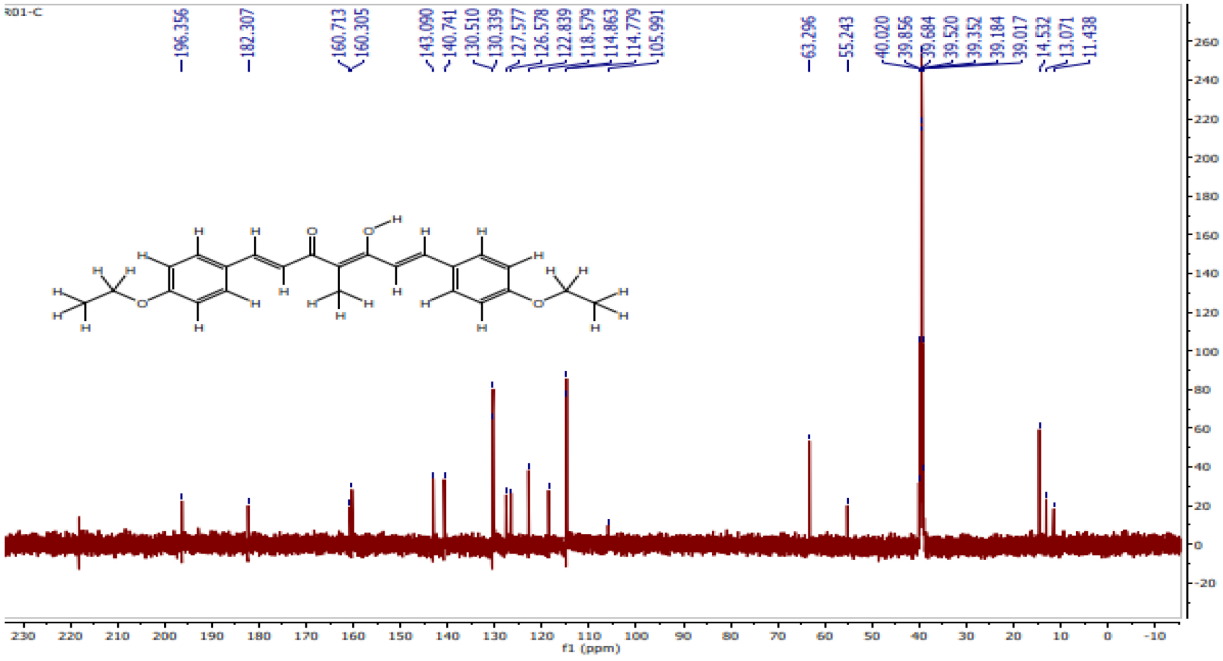


Fig. 2. The ^{13}C-NMR spectrum of compound (1).

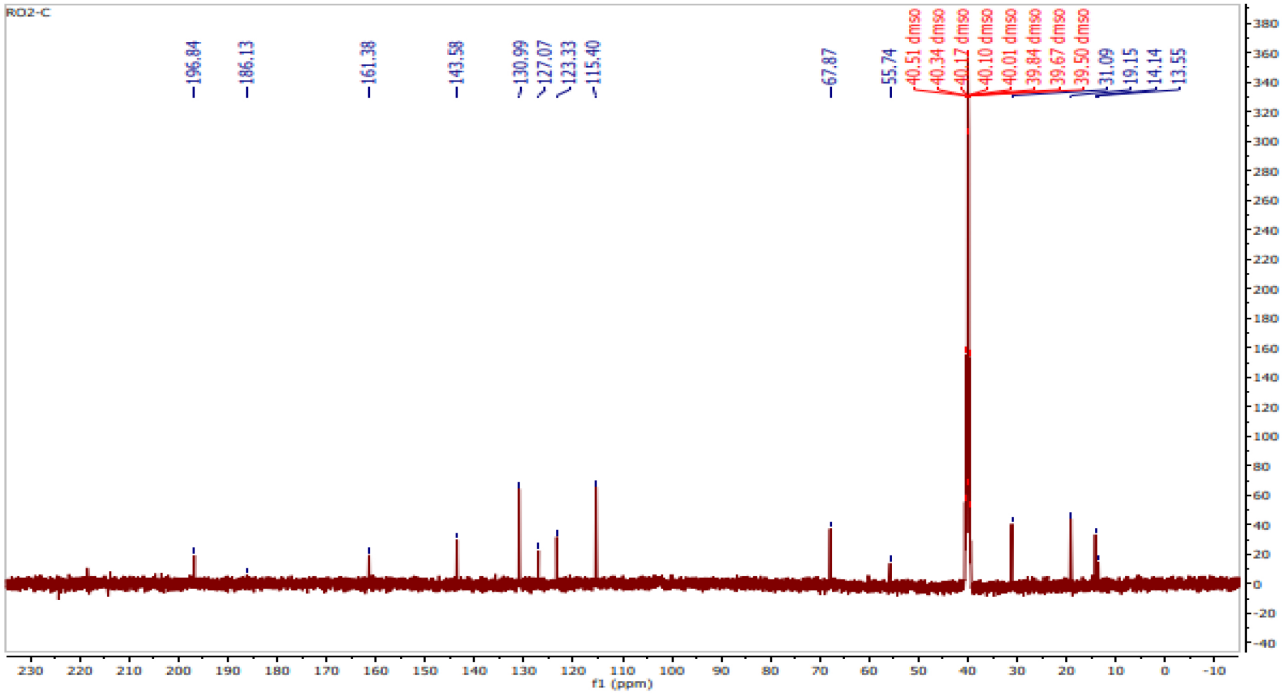


Fig. 3. The ^{13}C-NMR spectrum of compound (2).

spectra we can observed the distinctive signals as following:

- The keto carbon (C5) signal appear at 196.2–197.3 ppm while the enol carbon (C3) at 180.2–186.1ppm.[25,27]
- The signal at 160.3–161.4 ppm referred to aromatic carbon (C4) attached to alkoxy group,[28] shielded of the signal to up field when attached to trifluoromethyl group.
- The signals at 140.1–144.3 ppm referred to heptadienedione carbon (C1, C7). The signals at

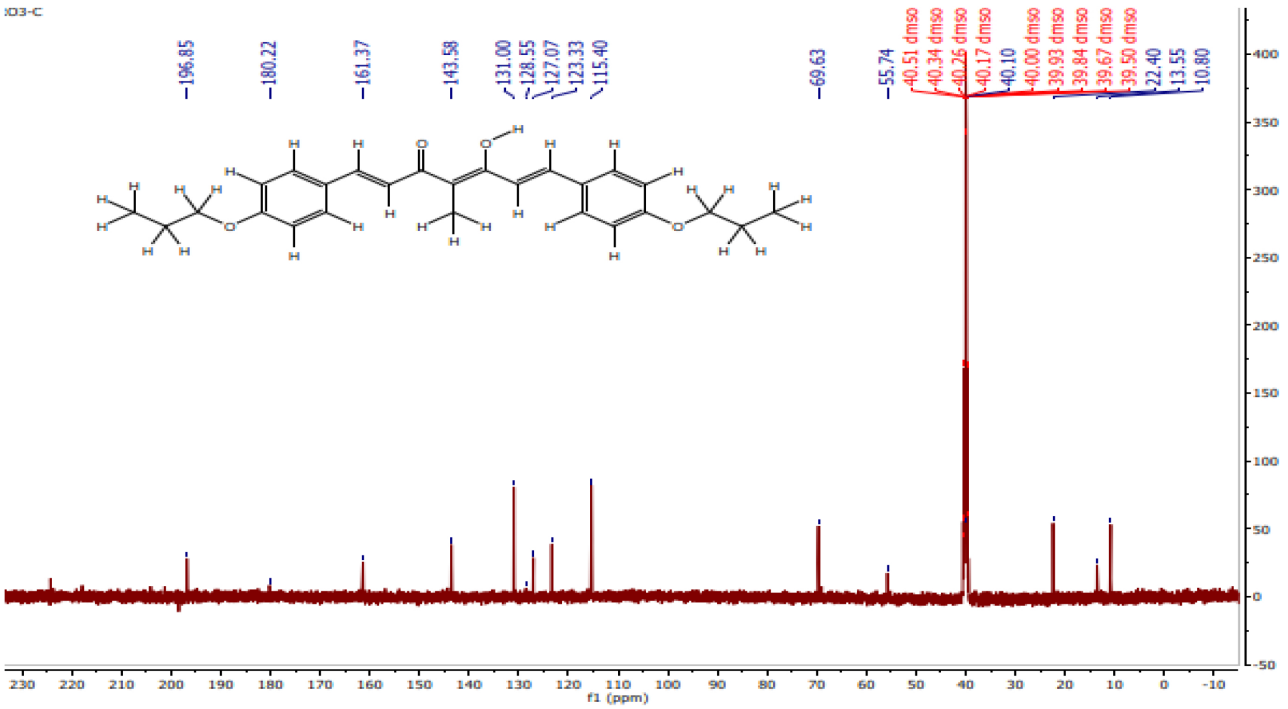


Fig. 4. The ^{13}C-NMR spectrum of compound (3).

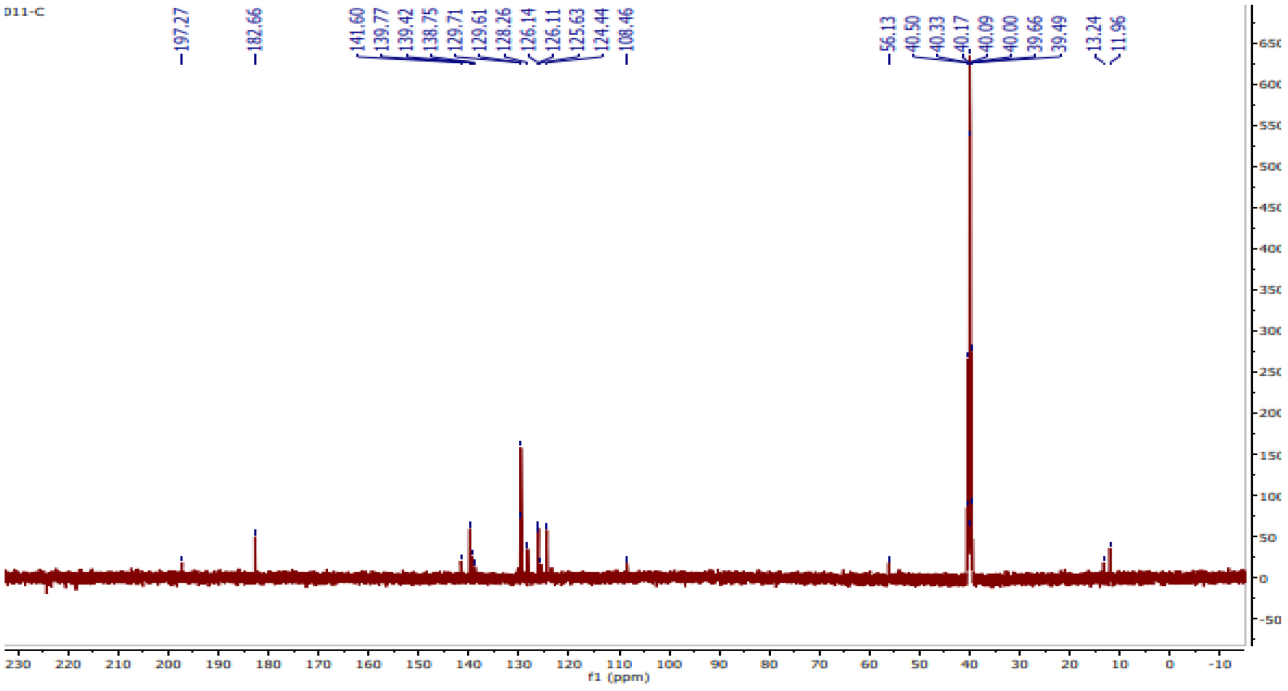


Fig. 5. The ^{13}C-NMR spectrum of compound (4).

118.6–124.4 ppm referred to heptadienedione carbon (C2, C6).[25]

- The alpha methyl carbon (CH_3) signal appeared at 10.80–13.55 ppm.[25]
- The carbon CH of keto form C4 signals appeared at 69.6–55.5 ppm, while the enol form signal appeared within the range 105.25–115.4 ppm. The aliphatic methyl carbon signal at 14.5 ppm and 13.1 ppm referred to keto and enol form respectively[25].
- The aromatic ring carbon (C3) signal appeared at 114.9 ppm and (C5) signal at 114.8 ppm.

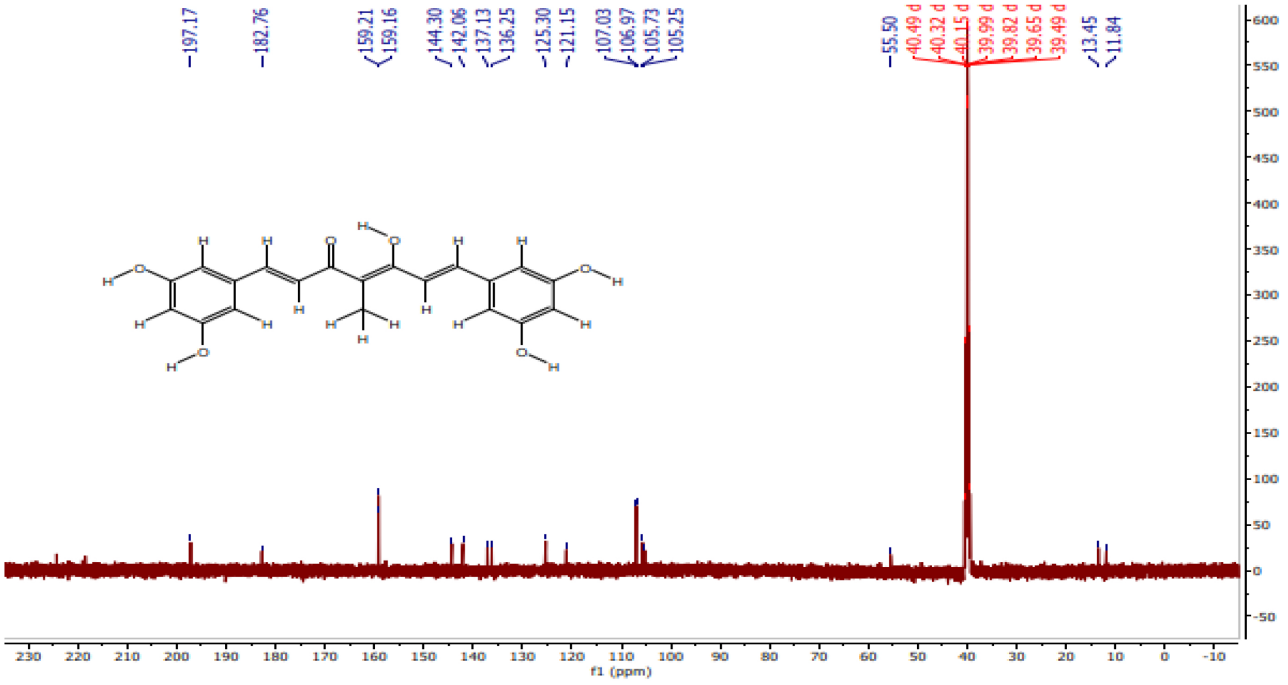


Fig. 6. The ^{13}C-NMR spectrum of compound (5).

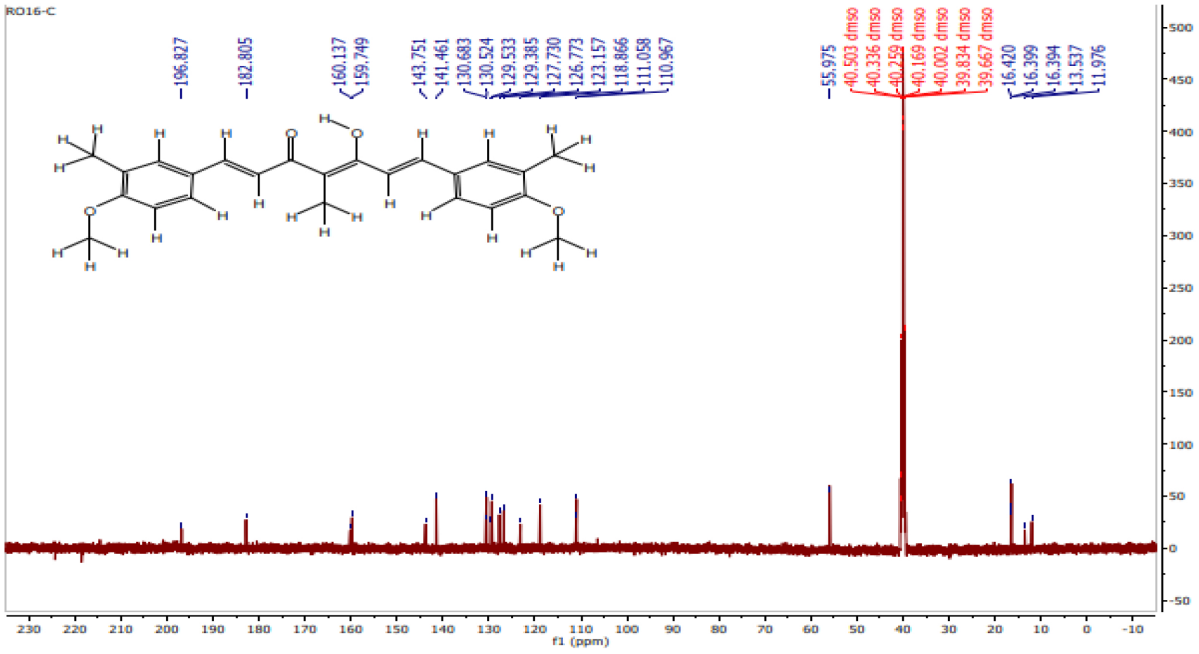
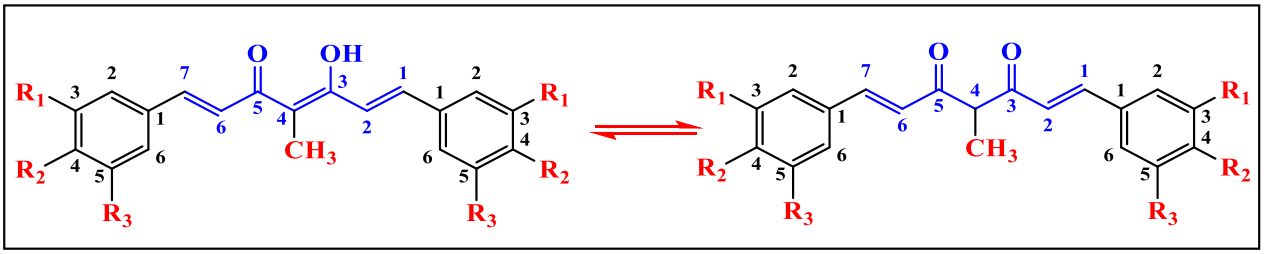


Fig. 7. The ^{13}C-NMR spectrum of compound (6).

and (C2,C6) signal at 130.5 ppm. The carbon aromatic (C1) signal appeared at 127.5 ppm.[25] For the compounds (4) the multiplet signal at 126.1 ppm referred to fluorinated carbon.[25,29]

The physicochemical properties of curcumin analogues 1–6 by lipinski's rule of five

The physicochemical properties of the studies compounds were computed by the Swiss ADME website.



Scheme 3. The keto-enol Tautomerization of curcumin analogue.

Table 3. Lipinski properties obtained for the curcumin analogues.

Compound No.	Mol.wt.(g/mol)	NRB	NHBD	NHBA	TPSA(Å^2)	Log p	Lipinski's Rule of Five Violation
1	378.46	9	1	4	55.76	4.21	0
2	434.57	13	1	4	55.76	5.19	0
3	406.51	11	1	4	55.76	4.49	0
4	426.35	7	1	8	37.30	3.43	1
5	354.35	5	5	6	118.22	1.74	0
6	378.46	7	1	4	55.76	4.02	0

Mol. wt.: molecular weight, NRB: number of rotatable bonds, NHBA: number of hydrogen bond acceptors, NHBD: number of hydrogen bond donors, TPSA: topological polar surface area, Log P: logarithm partitioning coefficient.

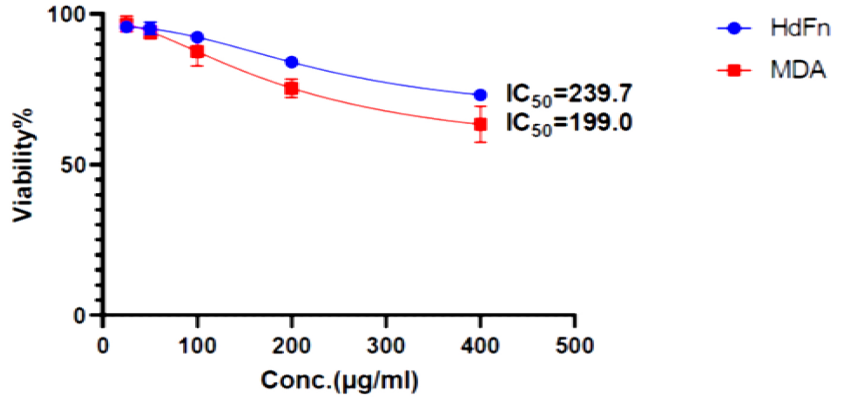


Fig. 8. Impact of compound (1) at various concentrations on the cell viability percentage.

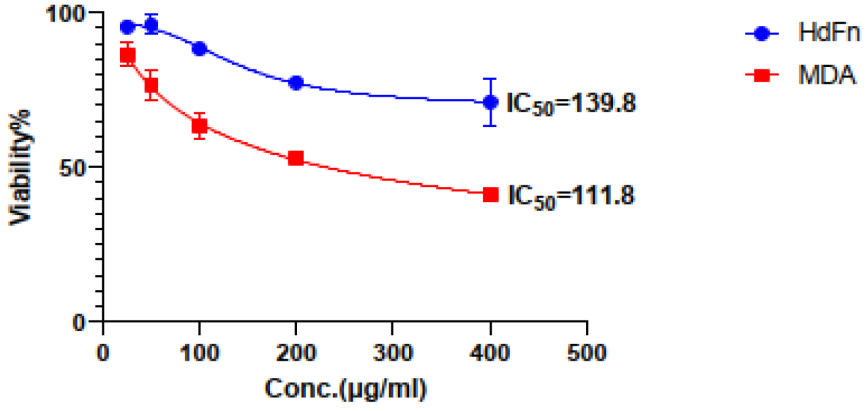


Fig. 9. Impact of compound (2) at various concentrations on the cell viability percentage.

It is freely available URL (http://www.swissadme.ch/) was applied to computed ADME, the pharmacokinetic, and other drug-like properties by drawing the chemical structure and entering SMILE.[30] All the results for Lipinski properties obtained for curcumin analogues are shown in Table 3. According to the rule

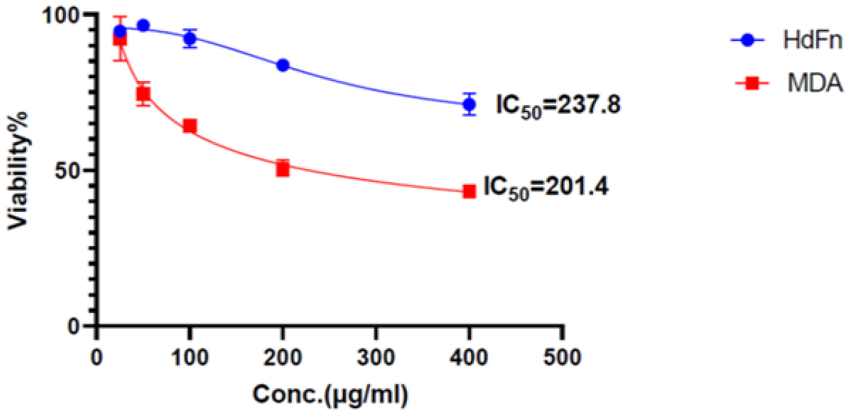


Fig. 10. Impact of compound (3) at various concentrations on the cell viability percentage.

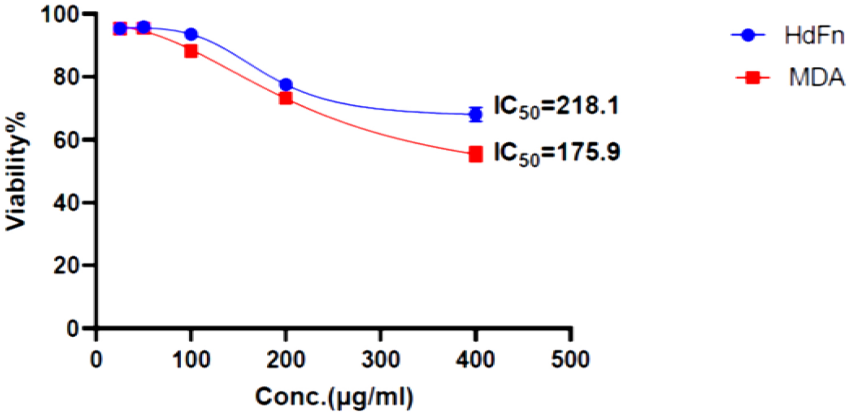


Fig. 11. Impact of compound (4) at various concentrations on the cell viability percentage.

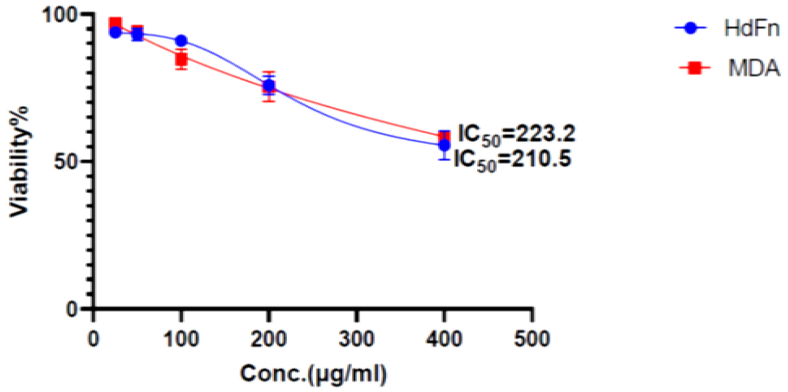


Fig. 12. Impact of compound (5) at various concentrations on the cell viability percentage.

of five, there should be equal or fewer than five hydrogen bond donors, fewer than ten Hydrogen bond acceptors, a molecular weight (M.wt.) of below 500, and a logarithm partitioning coefficient (Log p) of equal or less than five for there to be good absorption or penetration.[31] The results showed that the computed molecular weight for compounds ranges from 354.35 to 434.57 g/mol. The results showed the number of hydrogen bond donors for compounds in the range 1–5 and the number of hydrogen bond acceptors for compounds in the range 1–8. The recently developed PSA calculating method is known as TPSA (topological PSA).[32] For a molecule to penetrate a cell membrane, its PSA must be <140 A^2 and must be less than 90 A^2 to pass through the blood-brain barrier[32,33] The results that show the polar

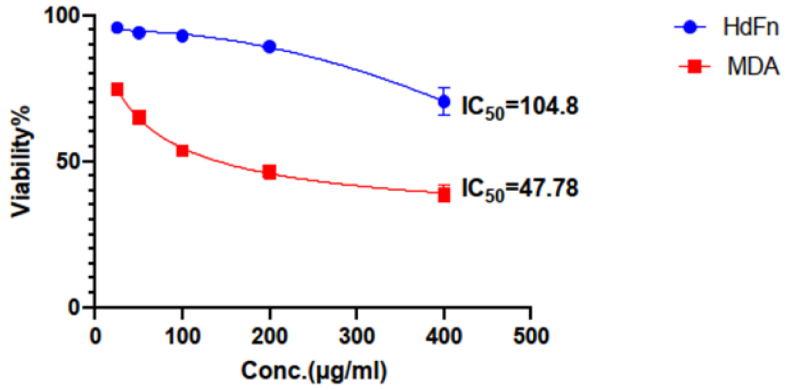


Fig. 13. Impact of compound (6) at various concentrations on the cell viability percentage.

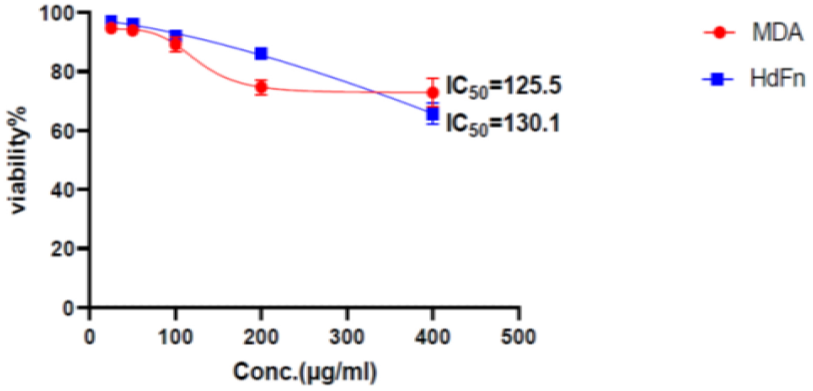


Fig. 14. Impact of compound (7) at various concentrations on the cell viability percentage.

Table 4. The IC_{50} and SI of curcumin and it is analogues.

Compound No.	HdFn (IC50)μg/ml	MDA-MB231(IC50)μg/ml	selectivity index (SI)
1	239.7	199.0	1.2
2	139.8	111.8	1.3
3	237.8	201.4	1.2
4	218.1	175.9	1.2
5	223.2	210.5	1.06
6	104.8	47.78	2.2
curcumin	130.1	125.5	1.03

surface area of compounds in ranges from 37.3–55.76 except compound 5 have TPSA 118.22 A^2. The compound is not considered orally active if two or more of these characteristics do not match the requirements of rule five. If a molecule fits Lipinski's rule of five, it is classified as a drug.[34]

In vitro anticancer assay of curcumin analogues

The studies compounds were preliminary tested for their in vitro anticancer activity against the human breast cancer cell line MDA-MB231 using the MTT assay. This assay is widely used to screen for cytotoxic compounds during the development of chemotherapy.[35] That uses colorimetric techniques based on mitochondrial dehydrogenase activity measurement to estimate the amount of viable cells. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide yellow colored is reduced by dehydrogenase in living cells to produce a crystals purple colored formazan dye, and subsequent solvation of the crystals with a suitable solvent and measuring their absorbance of light at 570 nm. The cytotoxic activity of curcumin derivatives 1–6 were estimated in vitro via MTT assay against breast cancer cell lines MDA-MB231. The half maximal Inhibitory Concentration (IC_{50}) was determined based on the dose–response curve created after finding the percent of the cell death at several concentrations of the composites as shown in Figs. 8

to 14. The anticancer activity of compounds is categorized into three groups based on their cell growth inhibition; active $IC_{50} < 20\mu g$ /ml, moderate activity IC_{50} 20–100μg/ml and inactive $IC_{50} > 100\mu g$ /ml.[36]

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} MDA-MB231). Compounds with anticancer specificity indicated by SI values higher than 1.0, while compounds with significantly higher SI values than 1.0 are highly selective.[37] All synthesized compounds exhibited cytotoxicity with IC_{50} assumed in a range of 47.78–210.5μg/mL as shown in Table 4.

The cytotoxic activity of curcumin derivatives was estimated and it was found that compound 6 with IC_{50} 47.78 μg/ml and with SI 2.2 which have moderate anticancer activity and highly selectivity against MDA-MB231 and more potent anticancer activity in comparison to curcumin whereas compound 2 with IC_{50} 111.8 μg/ml and SI 1.3 was considered as specific anticancer activity against MDA-MB231 and has more anticancer activity in comparison to curcumin with IC_{50} equal to 125.5μg/ml and SI 1.03.

Conclusion

Curcumin analogues 6 was characterized by highly selective anticancer activity against MDA-MB-231, the most potent anticancer agent observed, with IC_{50} of 47.78 μg/mL and SI of 2.2, the methoxy group at the para position of the aromatic ring and a methyl group at the meta position led to increase in the lipophilicity of compound 6 and increase in cytotoxicity. Compound 2 with IC_{50} of 111.8 μg/mL and SI of 1.3 has specific anticancer activity against MDA-MB231 and has higher anticancer activity and selectivity against MDA-MB231 compared to curcumin with IC_{50} of 125.5 μg/mL and SI of 1.03.

Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that all the figures and tables in the manuscript are ours. Furthermore, figures and images, that are not ours, have been included with the necessary permission for republication, which is appended to the manuscript.
- No animal studies are present in the manuscript.
- Authors signed on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Basrah.

Authors' contribution statement

The present study's topic was suggested and organized by R. S. E. and S. A. N. while O. A. O developed and carried out the experiments and wrote the manuscript. All authors participated in the analysis, discussion and contributed to the final manuscript.

Supplementary materials

Supplementary materials are available at https://bsj.uobaghdad.edu.iq/cgi/viewcontent.cgi?filename=0&article=5204&context=home&type=additional&preview_mode=1.

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تحضير, تشخيص ودراسة الفعالية المضادة للسرطان لنظائر الكركمين الجديدة ضد خلايا سرطان الثديMDA-MB231

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الخلاصة

تحضير ستة نظائر جديدة للكركمين من خلال تفاعل التكثيف لـ 3-ميثيل-2،4-بنتانديون مع مشتقات الألدهايد المعوضة وأوكسيد البورون وبوجود ثلاثي ميثيل بورات و بيوتيل أمين. تم تنفيذ التفاعل تحت إشعاع بالموجات فوق الصوتية باستعمال جهاز الرنين الصوتي. المركبات المحضرة تم التعرف عليها باستخدام مطيافية الرنين النووي المغناطيسي للبروتون (^{1}HNMR) والرنين النووي المغناطيسي للكاربون(^{13}CNMR) وطيف الاشعة تحت الحمراء(FTIR) ومطيافية الكتلة التصادمية للإلكترون(MS) . تم استخدام موقع (ADME) السويسري للتنبؤ بالخصائص الفيزيائية والكيميائية للمركبات الجديدة باستخدام التقنيات الحسابية مثل دراساتADME. حيث وجد ان كل المركبات التي تم انتاجها وفقا لهذه الدراسة تخضع لقاعدة ليبنسكي .تم استخدام مقياس التترازوليوم للزراعة الدقيقة (MTT) لتقييم فعالية المركبات المفحوصة مختبريا ضد خلايا سرطان الثدي البشري MDA-MB231. واظهرت نتائج الاختبار ان المركبين 6،2 بقيم IC_{50} تبلغ 47.78 و111.8ميكروغرام/مل على التوالي، كان لهما فعالية قوية مضادة للسرطان مقارنة مع الكركمين بقيمة IC_{50} تبلغ125.5 ميكروغرام/ مل.

الكلمات المفتاحية: الفعالية المضادة للسرطان، كركمين، قاعدة ليبنسكي، مقياس التترازوليوم للزراعة الدقيقة، الرنين الصوتي.