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RESEARCH ARTICLE

Synthesis, Identification, and Biological Evaluation of New Coumarin-Pyrazoline Derivatives as Anti-oxidant Agents

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ABSTRACT

The coumarin scaffold was combined with nitrogen containing heteroatom molecule known as pyrazoline to increase its biological activity, and it demonstrated a wide range of activity. The study involved the synthesis of a new compound by condensation method, and the structural structures of the prepared compounds were characterized using spectroscopic and analytical studies FT-IR, 1H-NMR,13CNMR, and mass spectrometry, through which it was proven that pyrazoline ring through the appearance of protons of the methylene group in different coupling constants. On the other hand, the proton of C11', adapts to two different adjacent angles for the two protons of the methylene group, so the coupling constant of the protons adjacent to each other is different, and the bidirectional angle between the protons can be related to the karplus relationship with the adjacent proton coupling constant. The biological activity of the prepared compounds was studied using the principle of ABTS•+ assay depended on the generation of the blue/green ABTS•+ chromophore by the reaction between ABTS and potassium persulfate at about 734 nm, as the results of its effectiveness showed the results show that coumarin-pyrazoline derivatives are characterized by high antioxidant activity that is superior to ascorbic acid, especially the dimethylamine derivative.

Keywords: ABTS assay, Antioxidants compounds, Ascorbic acid, Coumarin- pyrazoline derivatives, Hybrid coumarin

Introduction

From the Dipteryx Odorata (tonka bean), Voleg extracted and refined coumarin in the **year** 1822.[1] It was first prepared by Perkin in **year** 1868.[2,3] Because coumarin includes a π-π conjugate system as shown in Fig. 1, it has strong charge-transfer characteristics,[4] and it is well dissolved in oils, ethanol and chloroform, instead dissolving in boiling water and not so much in ice water under 20°C,[2] whereas coumarin compounds have been extracted through over 800 plant species (including Rutaceae, Clusiaceae, Guttiferae, Umbelliferae and Oleaceae).[5,6] Coumarins are abundant throughout the natural world and can be identified as metabolites in a broad variety of plant tissues, including root, flower, leaflets, peel, seed, & fruit,[7,8] with found over than a thousand coumarin compounds have been identified by researchers.[9,10]

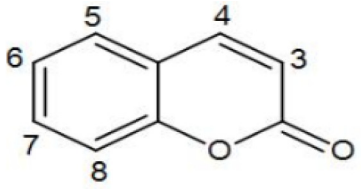

Fig. 1. Chemical structure of coumarin.

The "one-disease, one-target, one-drug" model has discovered drugs for decades. But in complicated

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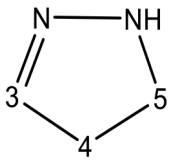


Fig. 2. Chemical structure of pyrazoline ring.

multifactorial cases, this model fails and Physicians treated resistant patients with pharmacological combination treatment[11,12] hooked up coumarin-chalcone with nitrogen-containing heterocyclic compounds; Azoles that are a significant group of N-heterocycles that may be found in a variety of medicinal medications.[13] Pyrazoline in Fig. 2, a ring with five members, the basic structure of which consists of three carbons and two neighboring nitrogen atoms,[14] pyrazoline has a wide range of pharmacological effects, including pain relief, fever reduction, blood sugar regulation, mood enhancement, infection prevention, antioxidant protection, and cancer prevention.[14,15]

Thus, the molecular hybridization technique is crucial in the discovery of new medicines for treating a wide range of multifactorial disorders.[5,16] Coumarin–Pyrazoline derivatives, which have a strong antioxidative potential, are a popular substitute for natural antioxidant supplies because of their ability to mimic the effects of vitamin E.[17] Moreover, the amine derivative from coumarin-pyrazoline derivatives showed remarkable radical-scavenging action. The presence of oxygen plus amine functional groups, as well as the hydrogen bond created across them, may be essential for the efficient scavenging action.[2]

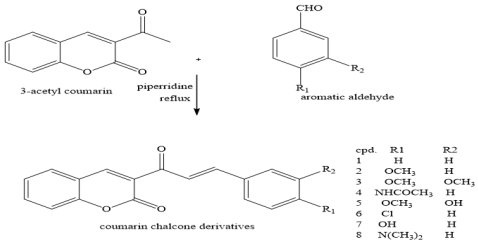
Materials and methods

All the applied chemicals were supplied by Merck AG and Sigma-Aldrich.

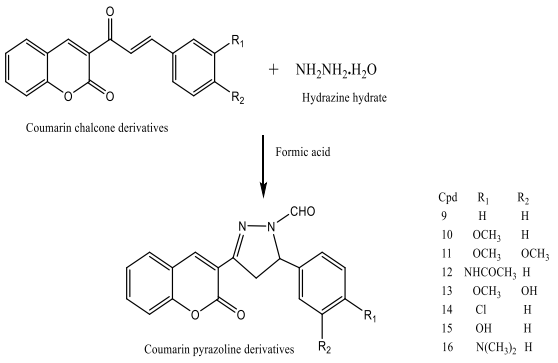
General methods for preparations of Coumarin Chalcone Derivatives (1–8)

Preparing of coumarin-chalcone derivatives were prepared by mixing in a 50 mL round-bottom flask equipped with a magnetic stirrer, (1.9 g, 0.001 mol.) of 3-Acetylcoumarin with (0.01mol.) appropriate aromatic aldehyde was dissolved in 3mL ethanol and refluxed for 2–12 hours in the presence of piperidine (7 drops) as a catalyst. The end point of the reaction was detected using a TLC plate, eluent containing Ethyl acetate: n-hexane 2:8, with a UV light chamber.

The reaction mixture was filtered off after cooling. The precipitated solid was formed, washed with water, recrystallized from appropriate solvents, and dried for 24 hours at room temperature. Scheme 1 shows synthesis of coumarin chalcone derivatives.



Scheme 1. Synthesis of coumarin chalcone derivatives.



Scheme 2. Synthesis Coumarin Pyrazoline derivatives.

General methods for preparation of Coumarin Pyrazoline Derivatives (9–16)

0.01mol. appropriate coumarin-chalcone derivatives, with 20 mL of formic acid, in a 50 mL round-bottom flask equipped and 0.02 mol. hydrazine hydrate was refluxed for 2 - 8 hours. The end point of the reaction was detected by using a TLC plate, using eluents containing Ethyl acetate: n-hexane 2:8, ethyl acetate: petroleum ether 1:1, and ethyl acetate, depending on compounds, with UV light chamber as shown in Table 1. The reaction mixture was filtered off after cooling. The precipitated solid was formed, washed with water, recrystallized from suitable solvents, and dried at room temperature for 24 hours. Scheme 2 shows the synthesis of coumarin pyrazoline derivatives.

Results and discussion

Analysis of coumarin pyrazoline derivatives 9–16 and some of their physical properties is one of the results as shown in Table 1, other methods were used to identify including the infrared spectrum, a mass spectrum, and the ^{1}H NMR and ^{13}C NMR spectroscopy.

Table 1. Physical properties of coumarin pyrazoline derivatives 9–16.

Cpd.	Molecular formula	Molecular weight (g/mol)	Yield%	Melting point (°C)	Physical appearance	Time of reaction (hours)	eluent	Rf
9	$C_{19}H_{14}N_2O_3$	318.33	28.9	229–231	Yellow Fluorescent crystal	6	(1)	0.5
10	$C_{20}H_{16}N_2O_4$	348.36	27.9	172–174	Yellow crystal	6	(2)	0.21
11	$C_{21}H_{18}N_2O_5$	378.38	48.44	255–256	yellow crystal	2	(2)	0.18
12	$C_{21}H_{17}N_3O_4$	375.12	14.04	184–187	Orange-yellow crystal	8	(3)	0.40
13	$C_{20}H_{16}N_2O_5$	364.36	63.8	215–218	Pale yellow crystal	4	(2)	0.20
14	$C_{19}H_{13}N_2CI\ O_3$	352.77	23.8	150–153	Light yellow crystal	5	(2)	0.27
15	$C_{19}H_{14}N_2O_4$	334.33	28.9	264–268	Orange-yellow crystal	6	(2)	0.16
16	$C_{22}H_{23}N_3O_3$	361.17	43.43	212–214	Yellow crystal	2.5	(2)	0.52

Eluent :(1) = Ethyl acetate: n-hexane 2:8, (2) = ethyl acetate: petroleum ether 1:1, (3) = ethyl acetate

FT-IR spectroscopy of coumarin pyrazoline derivatives 9–16

The compounds 9–16 were discovered using an FT-IR spectrum, which revealed a strong band at 1724–1732 cm^{-1} attributed to carbonyl groups of coumarin part, [18] while the absorption band at 1649–1674 cm^{-1} related to carbonyl groups at pyrazoline ring. [19,20]

All synthetic compounds with Pyrazoline derivatives show absorption bands in the regions 1608–1618 cm^{-1} corresponding to the C=N stretching bands of pyrazoline ring. [19,21] In addition, the absorption bands at regions around 1415–1481 cm^{-1} were attributed to the (N–N) stretch vibrations. [22] As shown in Figs. 3 to 10.

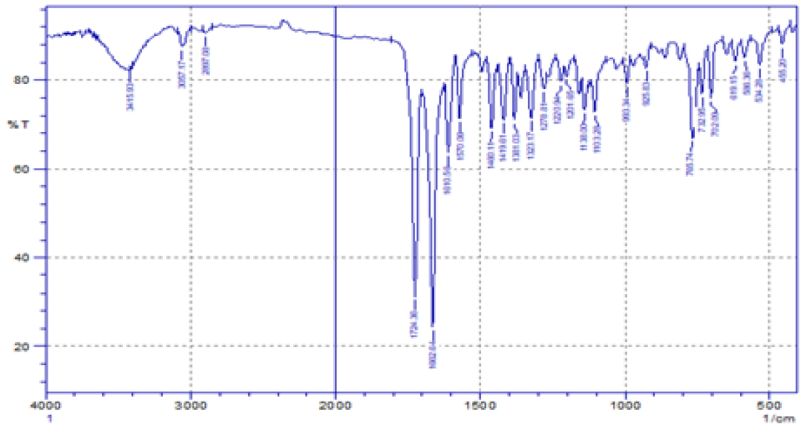


Fig. 3. IR-spectrum of compound 9.

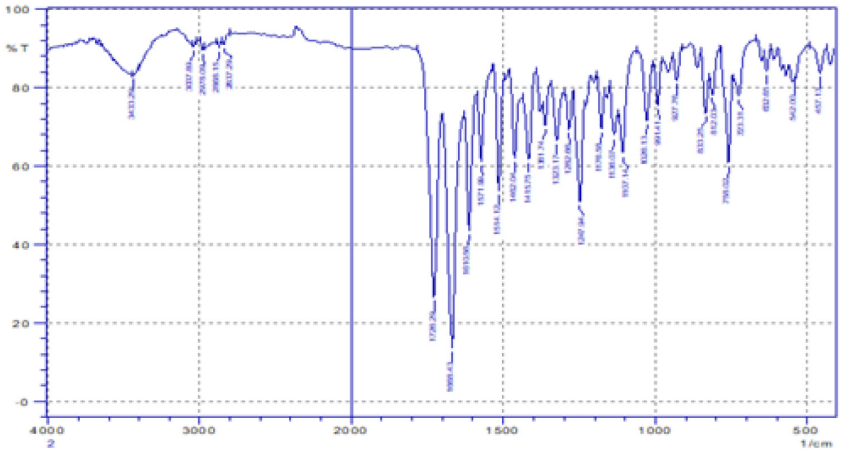


Fig. 4. IR-spectrum of compound 10.

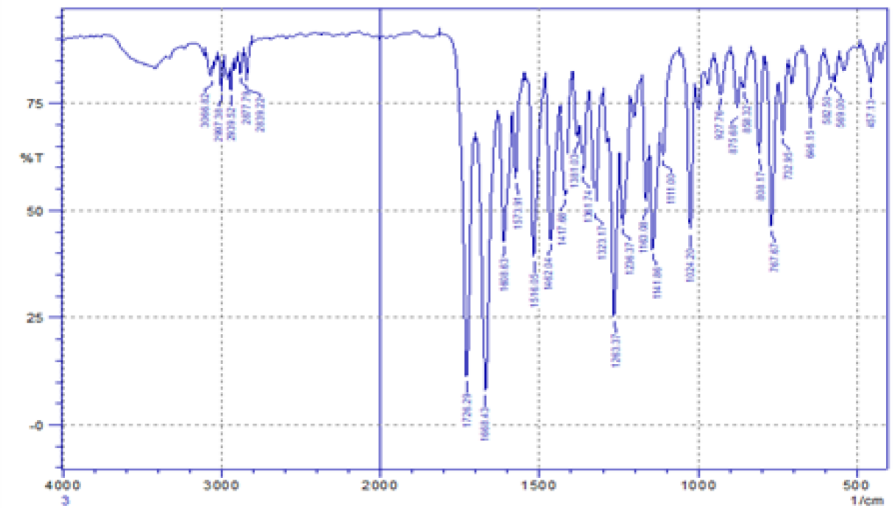


Fig. 5. IR-spectrum of compound 11.

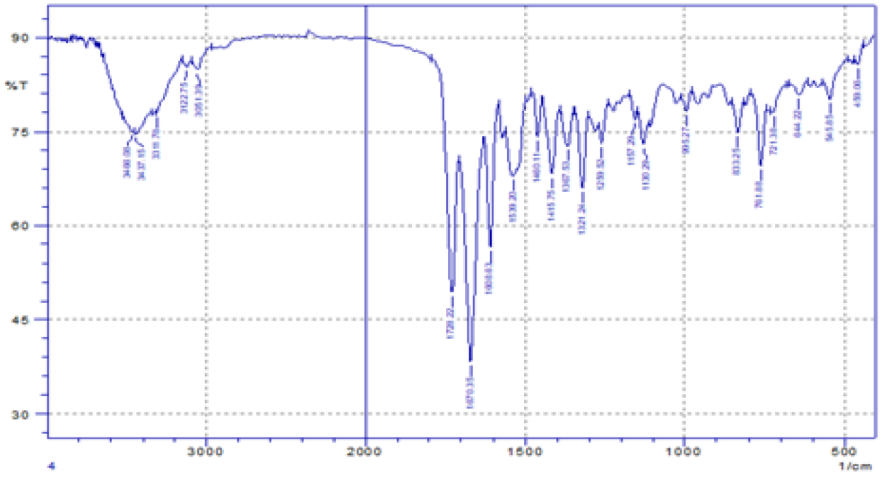


Fig. 6. IR-spectrum of compound 12.

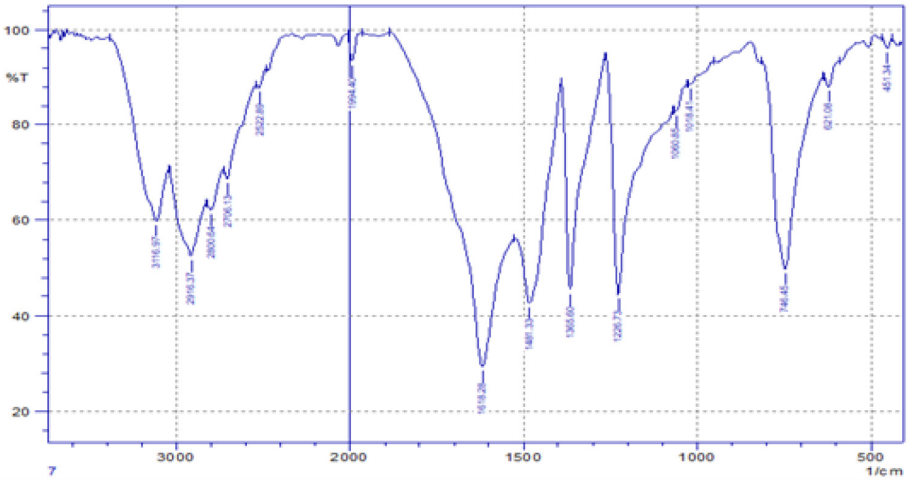


Fig. 7. IR-spectrum of compound 13.

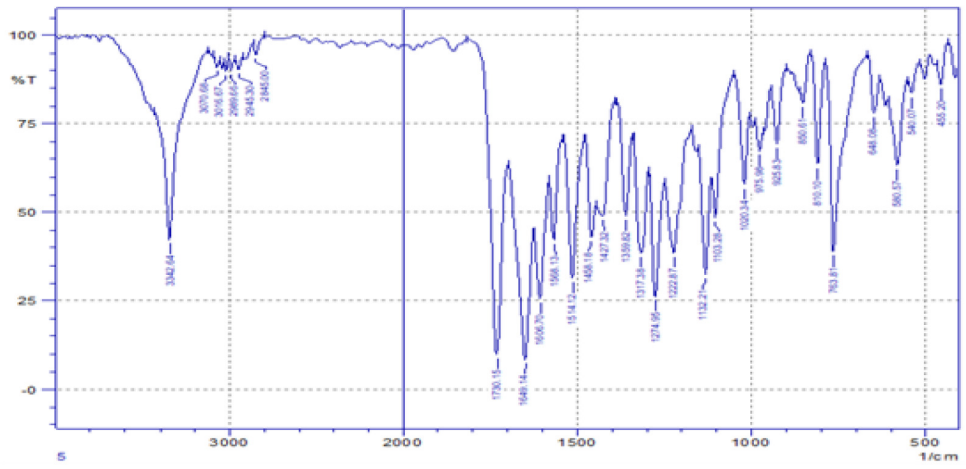


Fig. 8. IR-spectrum of compound 14.

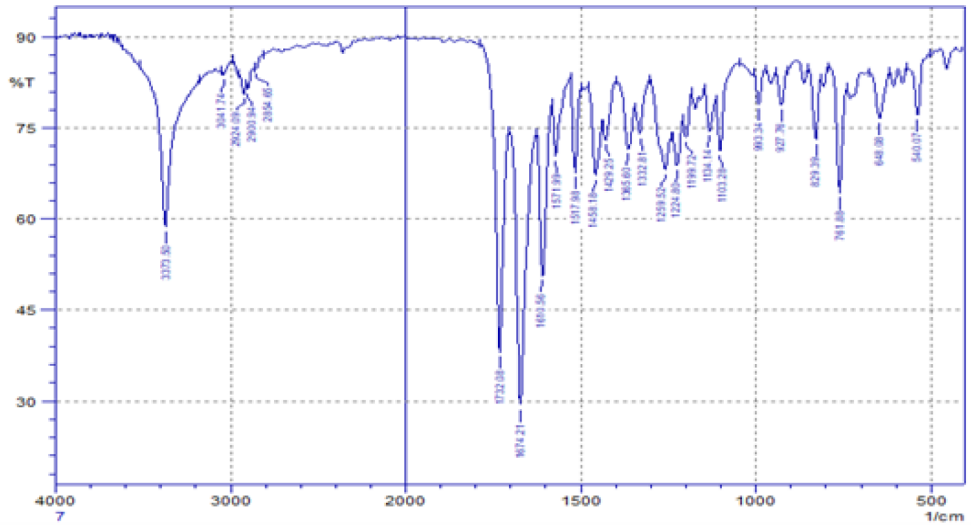


Fig. 9. IR-spectrum of compound 15.

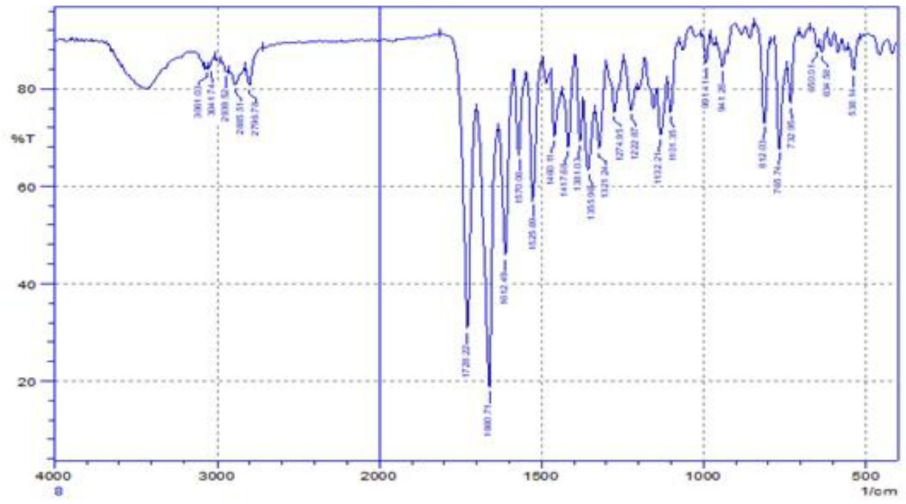


Fig. 10. IR-spectrum of compound 16.

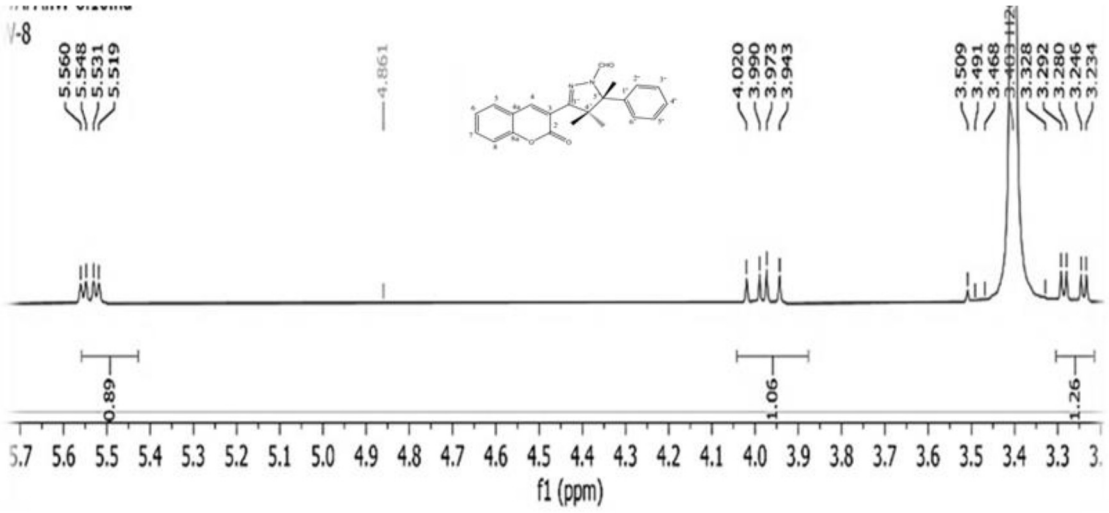


Fig. 11. ^{1}H NMR spectrum of compound 9.

^{1}H-NMR spectroscopy of coumarin pyrazoline derivatives 9–16

In general, the spectra of the compounds 9–16 tell something essentially different:[23]

1. One singlet signal within the chemical shift of the aldehyde (–CHO) proton at the region of about 8.9 ppm with the integration of one proton.[19]
2. A doublet of doublets signals with coupling constants about 18 Hz and 4.8 Hz, as geminal coupling and vicinal coupling, respectively, at about 3.25 ppm has one proton integration, which refers to (Ha) proton of carbon 4".
3. A doublet of doublets signals with coupling constant about 18 Hz and 11.8Hz as geminal coupling and vicinal coupling, respectively, at about 3.9 ppm has one proton integration, which refers to (Hb) proton of carbon 4".
4. A doublet of doublets signals with coupling constants about 11.8 Hz and 4.8 Hz as vicinal coupling, at about 5.5 ppm has one proton integration, refers to a proton of carbon 5".[24,25] Figs. 11 to 18 show the H NMR of compound 9–16.

The ^{13}C NMR spectra of compounds 9 to 16 were shown in (Figs. 19 to 26)

In general, the spectrum supports the proposed structures of the compounds 9–16 by the following notes:

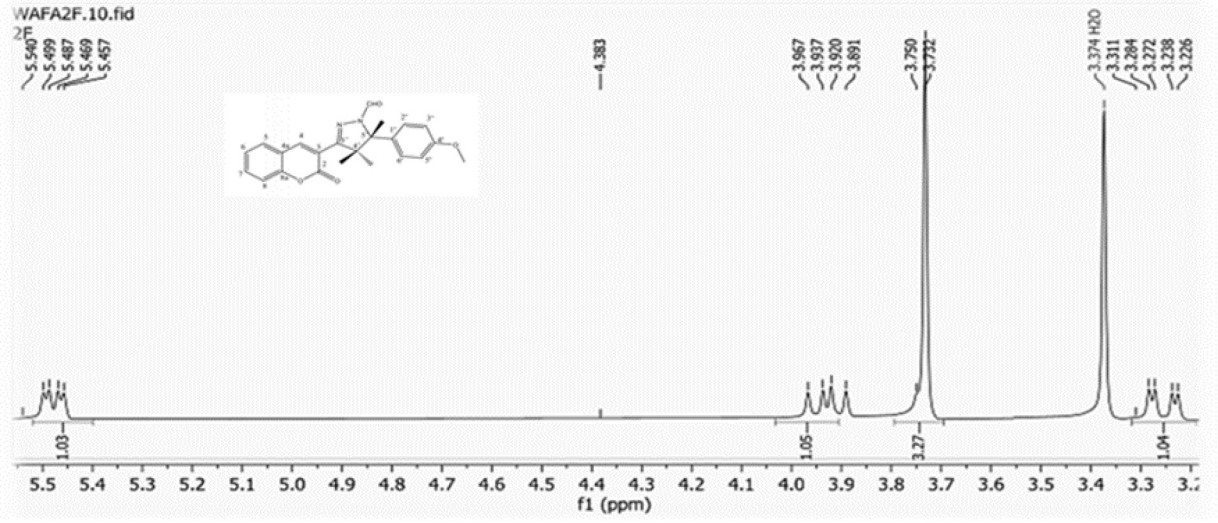


Fig. 12. ^{1}H NMR spectrum of compound 10.

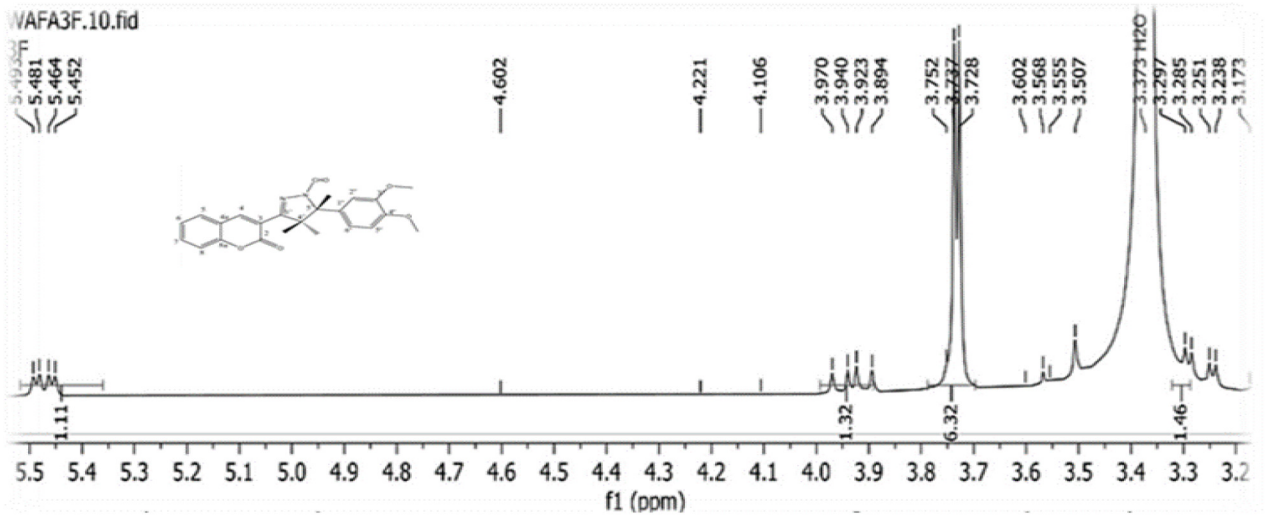


Fig. 13. ^{1}H NMR spectrum of compound 11.

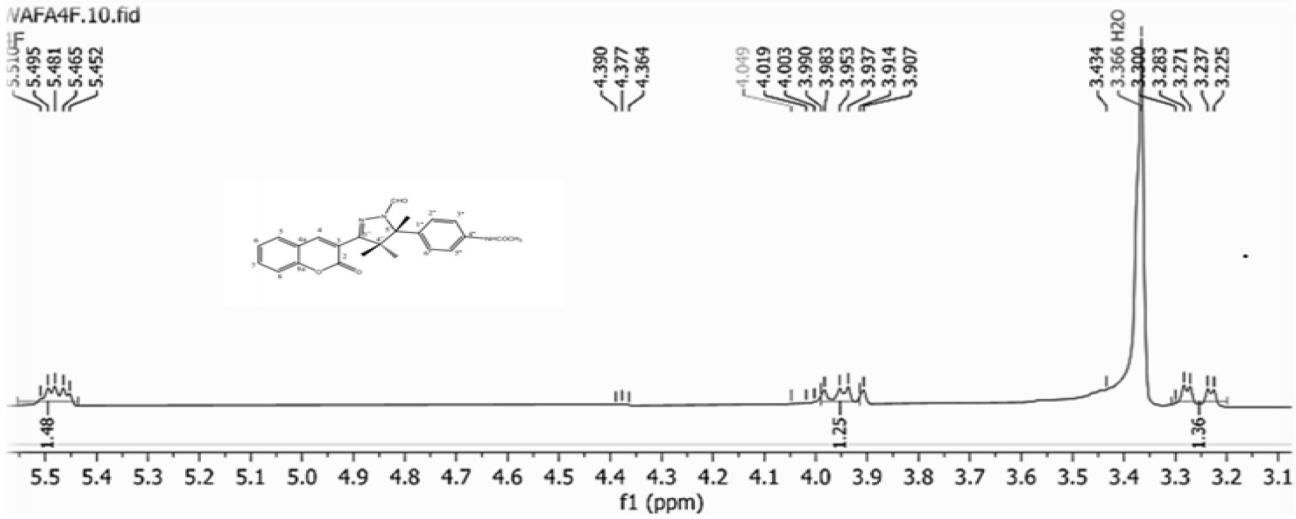


Fig. 14. ^{1}H NMR spectrum of compound 12.

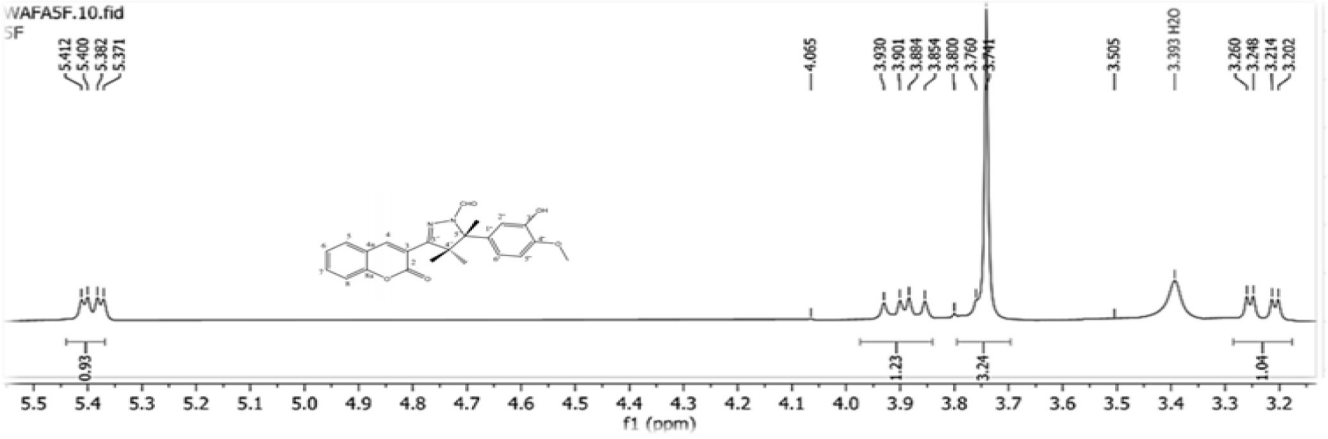


Fig. 15. ^{1}H NMR spectrum of compound 13.

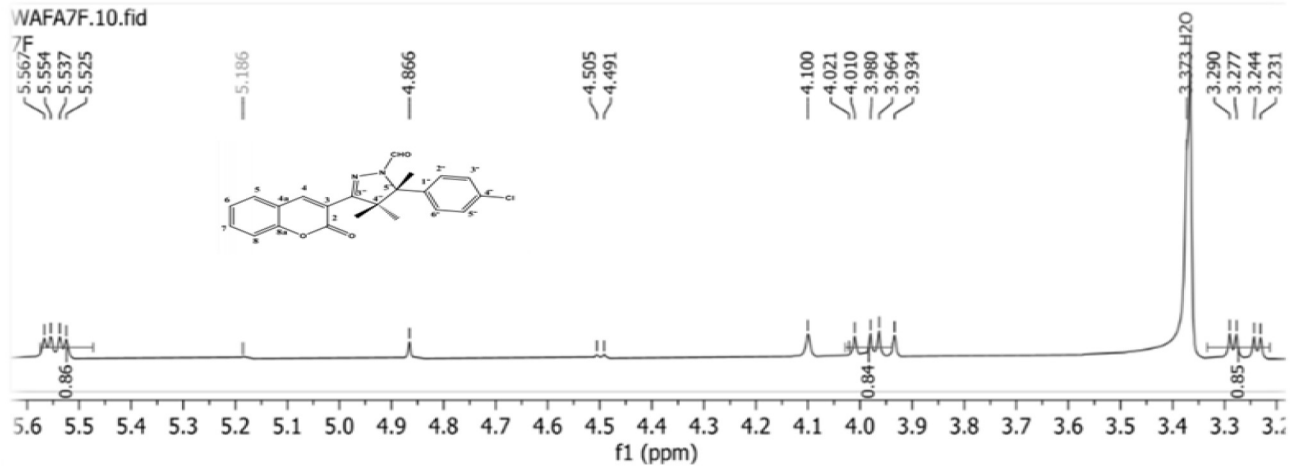


Fig. 16. ^{1}H NMR spectrum of compound 14.

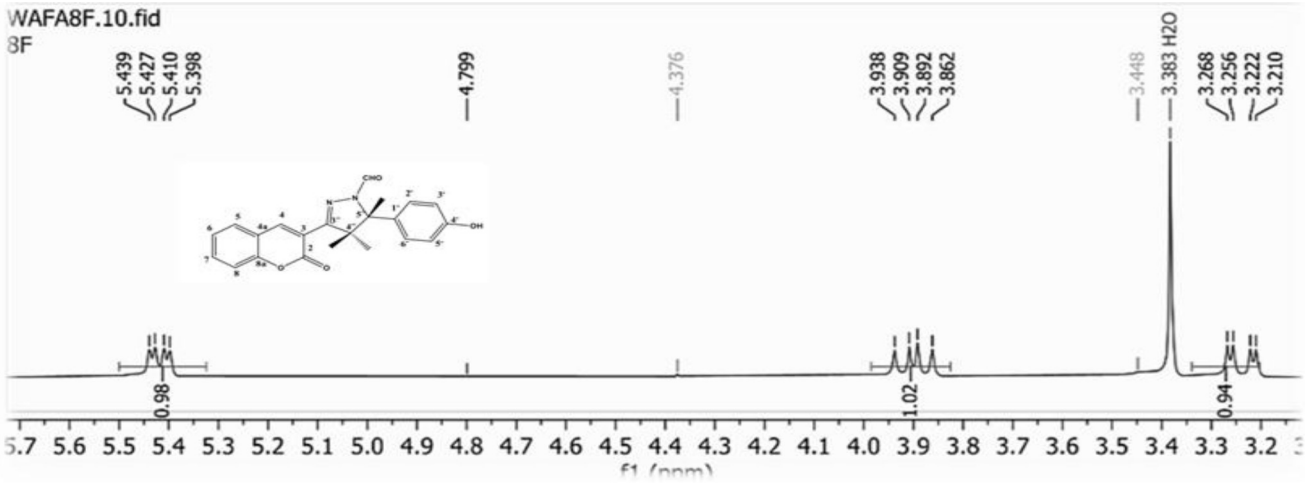


Fig. 17. ^{1}H NMR spectrum of compound 15.

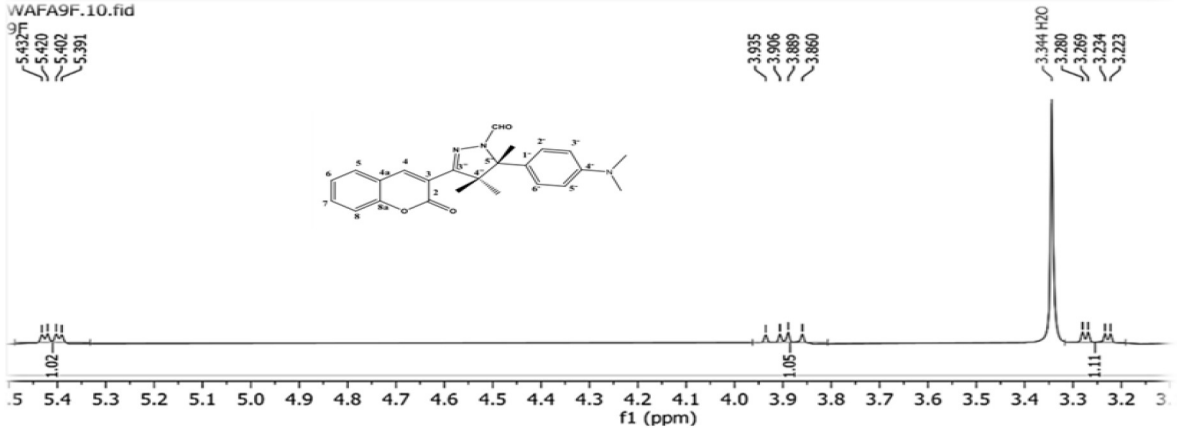


Fig. 18. ^{1}H NMR spectrum of compound 16.

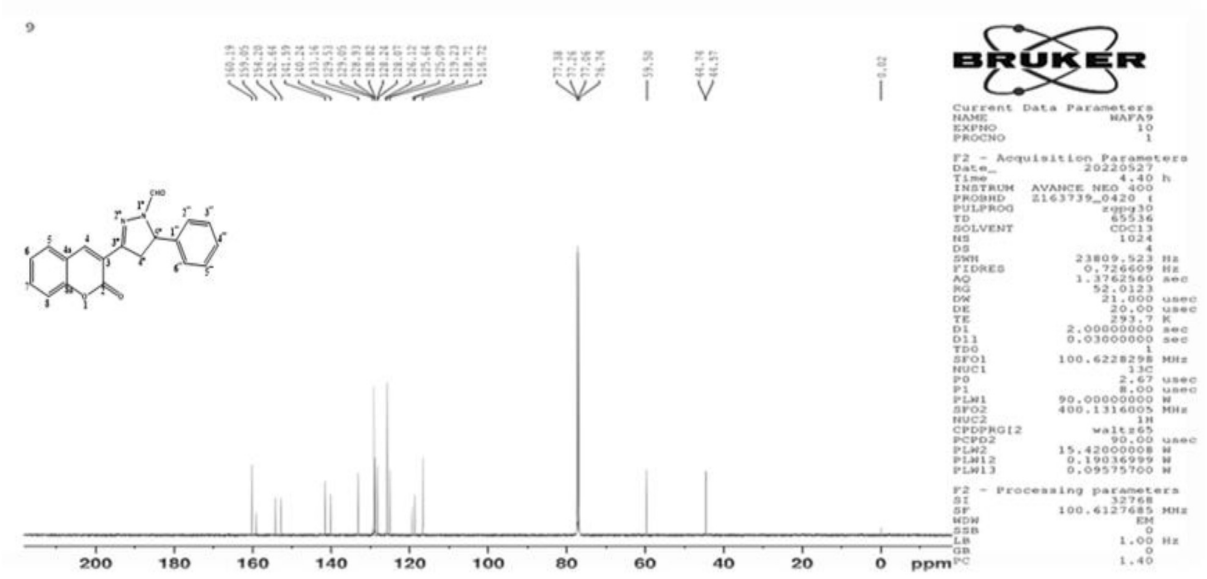


Fig. 19. ^{13}C NMR spectrum of compound 9.

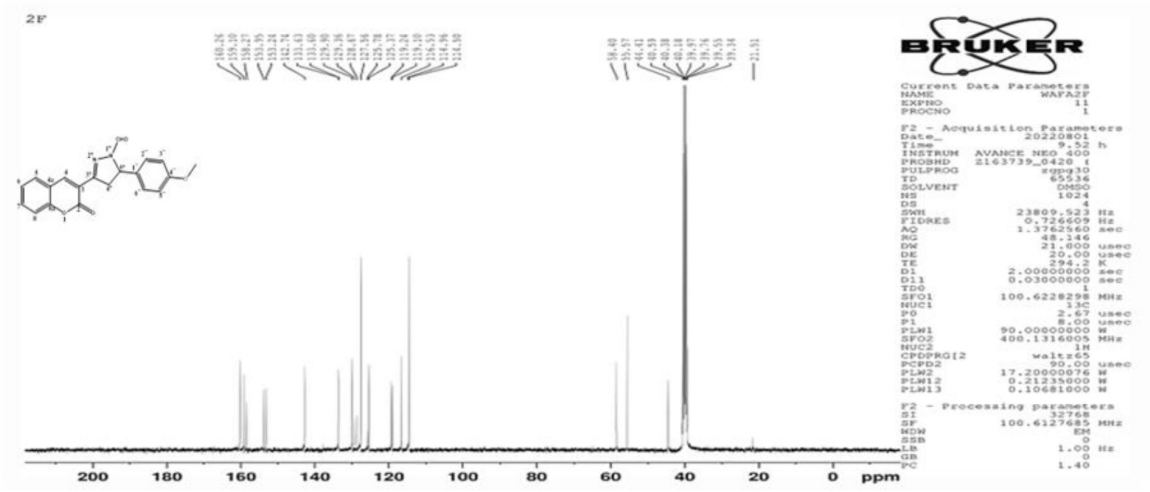


Fig. 20. ^{13}C NMR spectrum of compound 10.

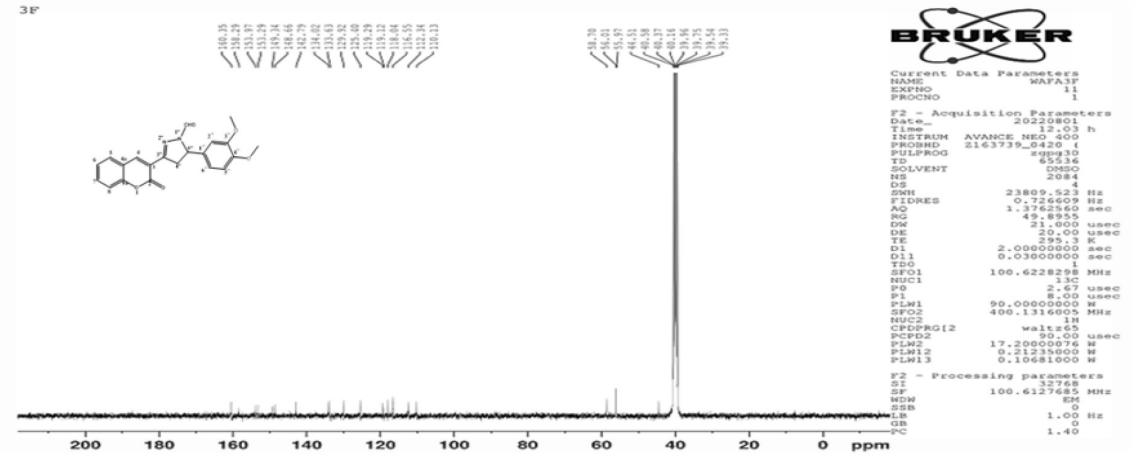


Fig. 21. ^{13}C NMR spectrum of compound 11.

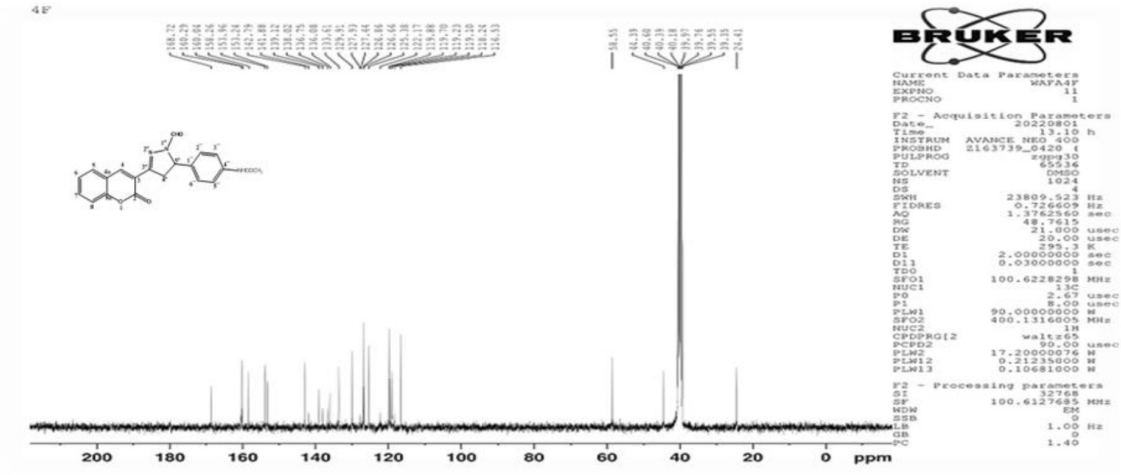


Fig. 22. ^{13}C NMR spectrum of compound 12.

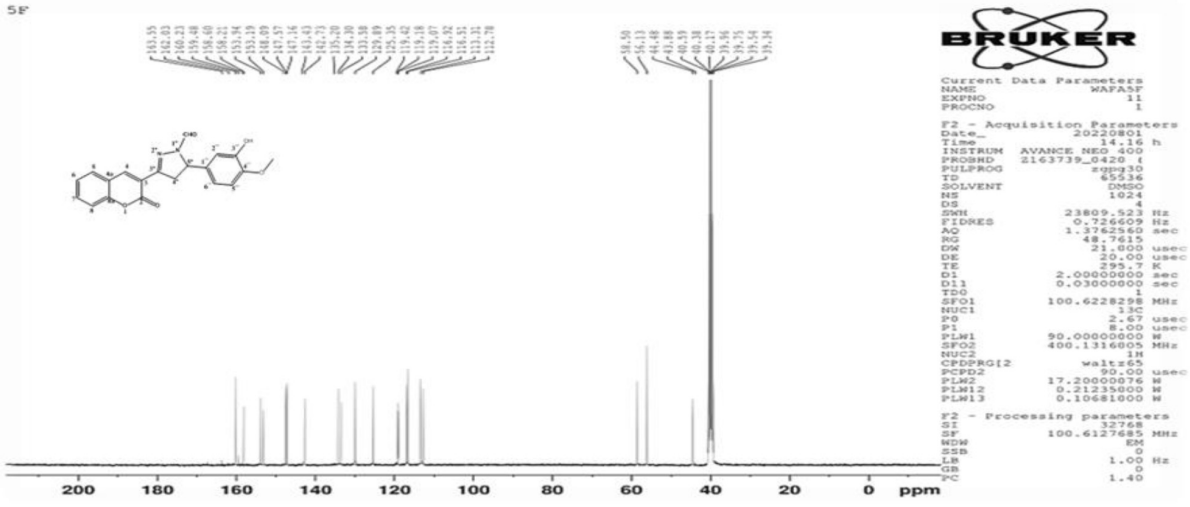


Fig. 23. ^{13}C NMR spectrum of compound 13.

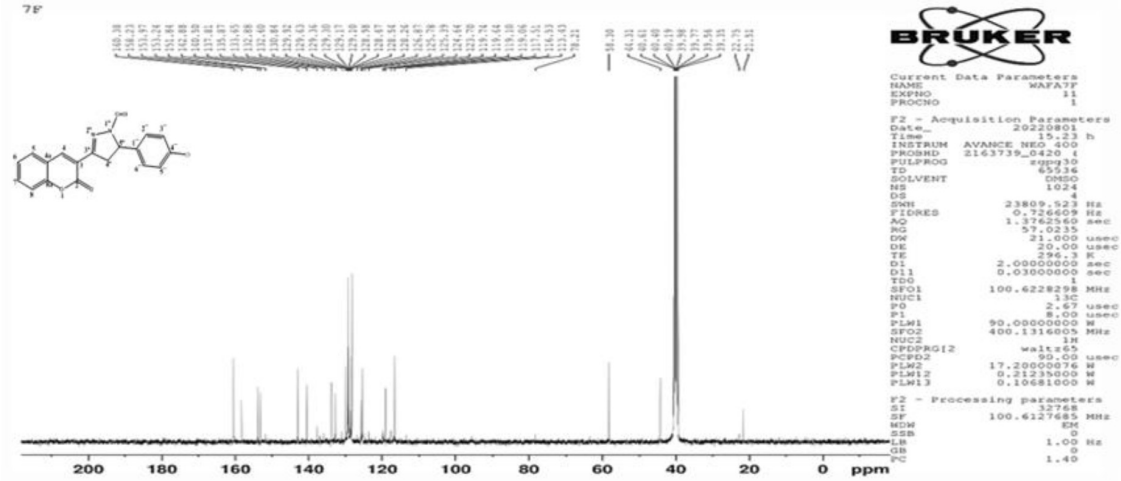


Fig. 24. ^{13}C NMR spectrum of compound 14.

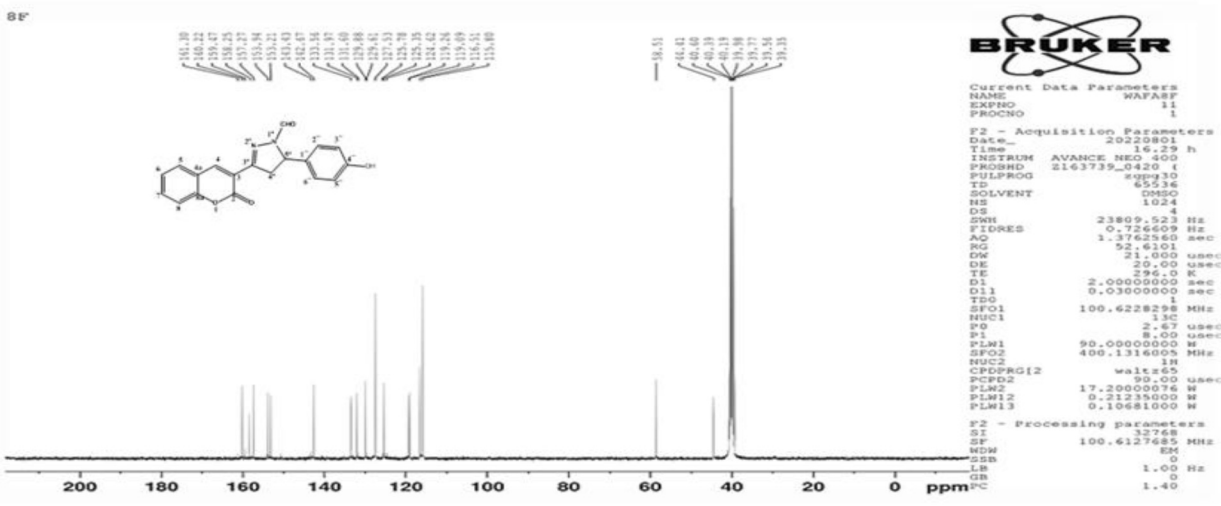


Fig. 25. ^{13}C NMR spectrum of compound 15.

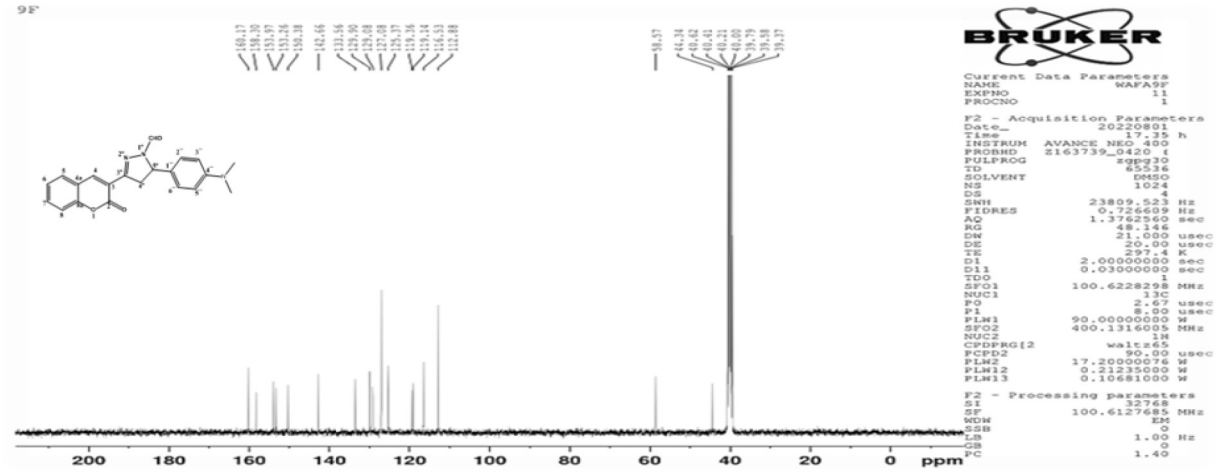


Fig. 26. ^{13}C NMR spectrum of compound 16.

1. The disappearance of the α, β-unsaturated ketone signal within positions 10' and 11' in coumarin-chalcone compounds, with the appearance of a pyrazoline ring that distinguishes with signals around 44 ppm and 59 ppm [20,25] respectively, referred to conform coumarin-pyrazoline compounds 9 to 16.
2) The carbonyl of chalcone seems around 186 ppm, and generally disappears after the formation of the pyrazoline ring, with an appearing signal at about 153 ppm, [23] refers to the C=N group as a part of the pyrazoline ring, which agrees with the previous literature. [20,24]
3) The strongest downfield signal appeared at 160 ppm, indicating the formation of an aldehyde group on the pyrazoline ring. [20,24]
4) The aromatic carbons appeared between 116.5–158.6 ppm. [24]

Mass spectrometry of coumarin pyrazoline derivatives 9–16

The mass spectrum is as shown in Figs. 27 to 34, while all values found in Table 2, agreed extremely well with the estimated values of compounds synthesis. To explain the mass spectrum, compound 9 is taken as an example; the mass spectrum showed a molecular ion peak at 318 m/z corresponding to the molecular formula $C_{19}H_{14}N_2O_3$. The molecular ion underwent fragmentation to produce a peak at 289 m/z referred to as the molecular formula $C_{18}H_{13}N_2O_2$, while the peak at 263 m/z referred to

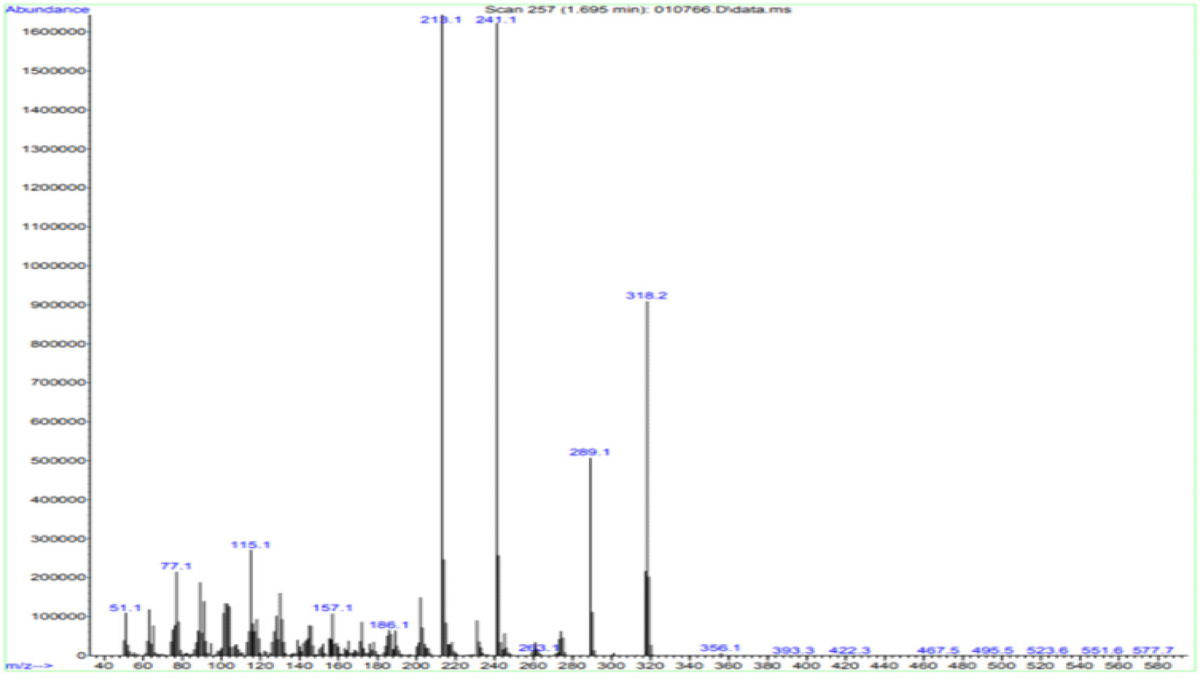


Fig. 27. Mass spectra of compound 9.

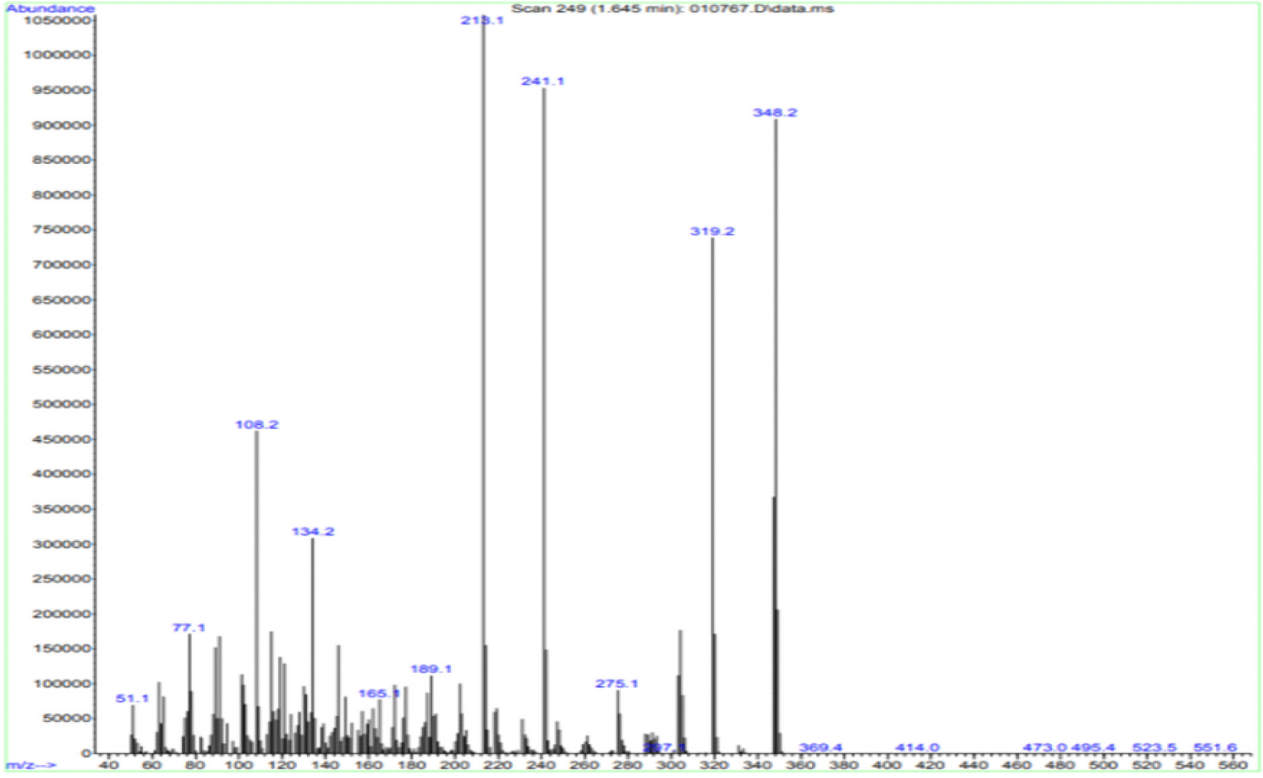


Fig. 28. Mass spectra of compound 10.

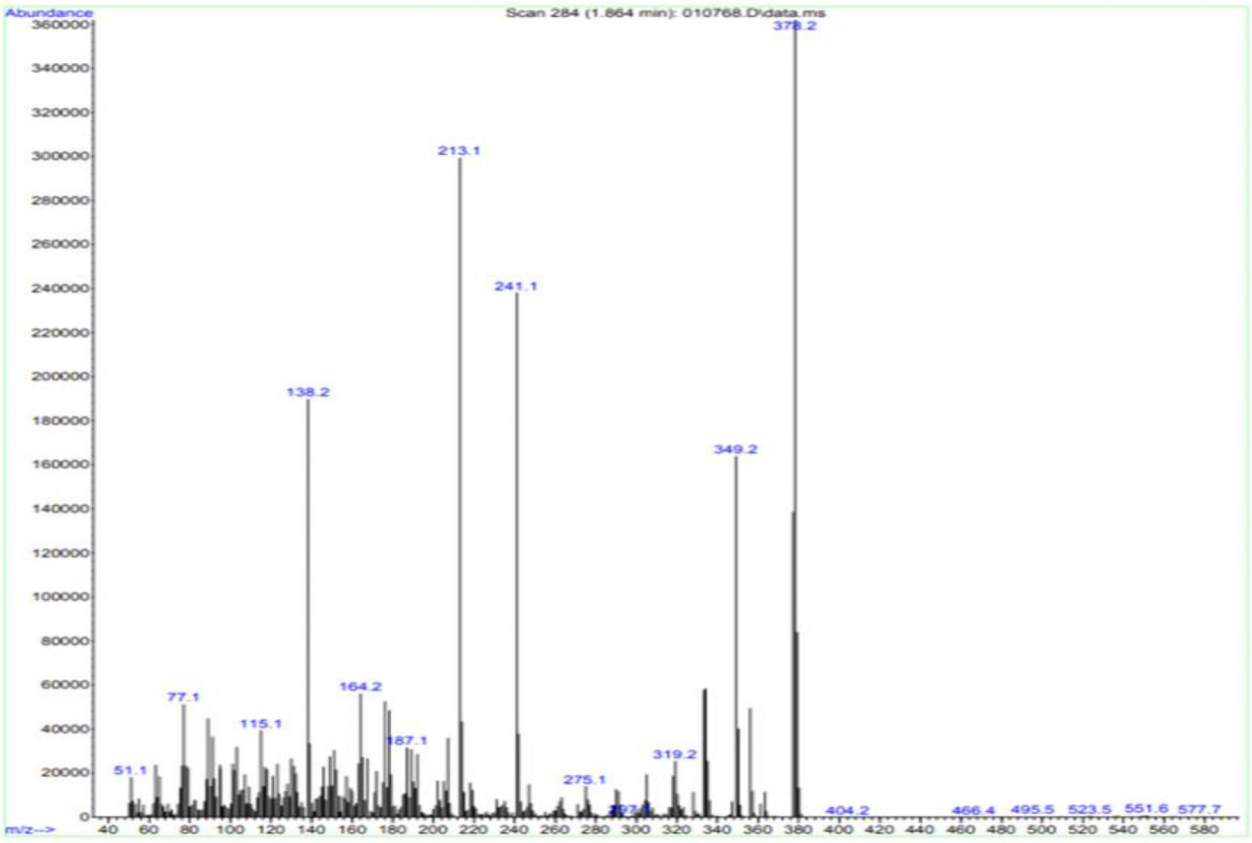


Fig. 29. Mass spectra of compound 11.

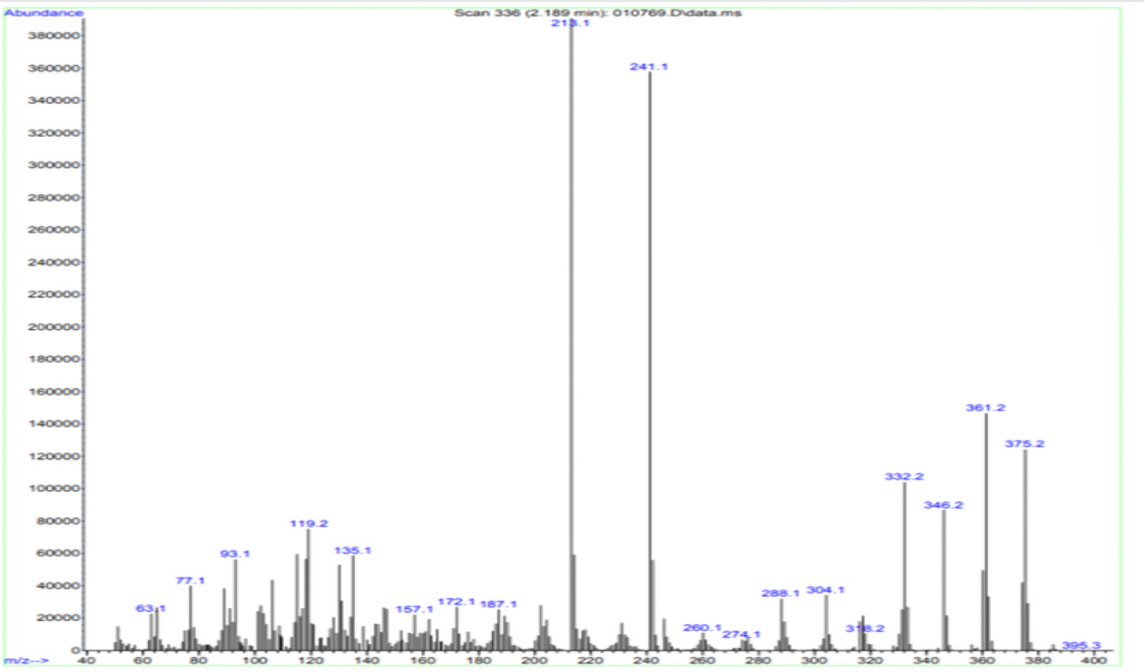


Fig. 30. Mass spectra of compound 12.

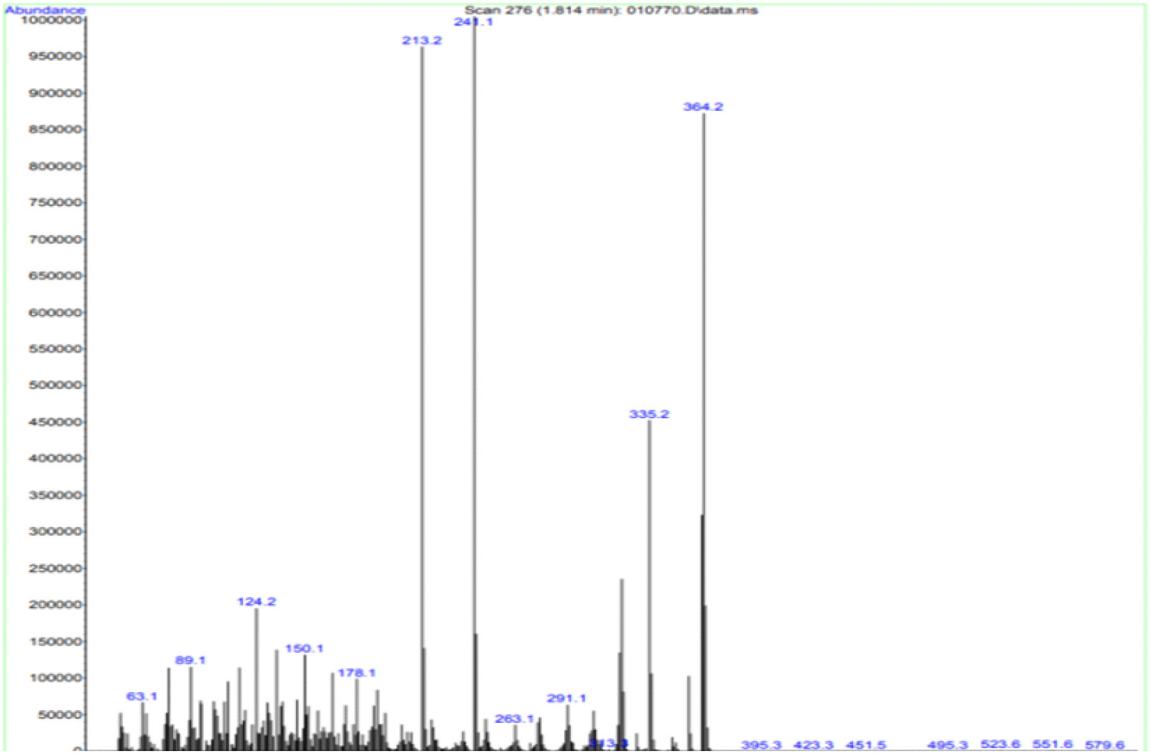


Fig. 31. Mass spectra of compound 13.

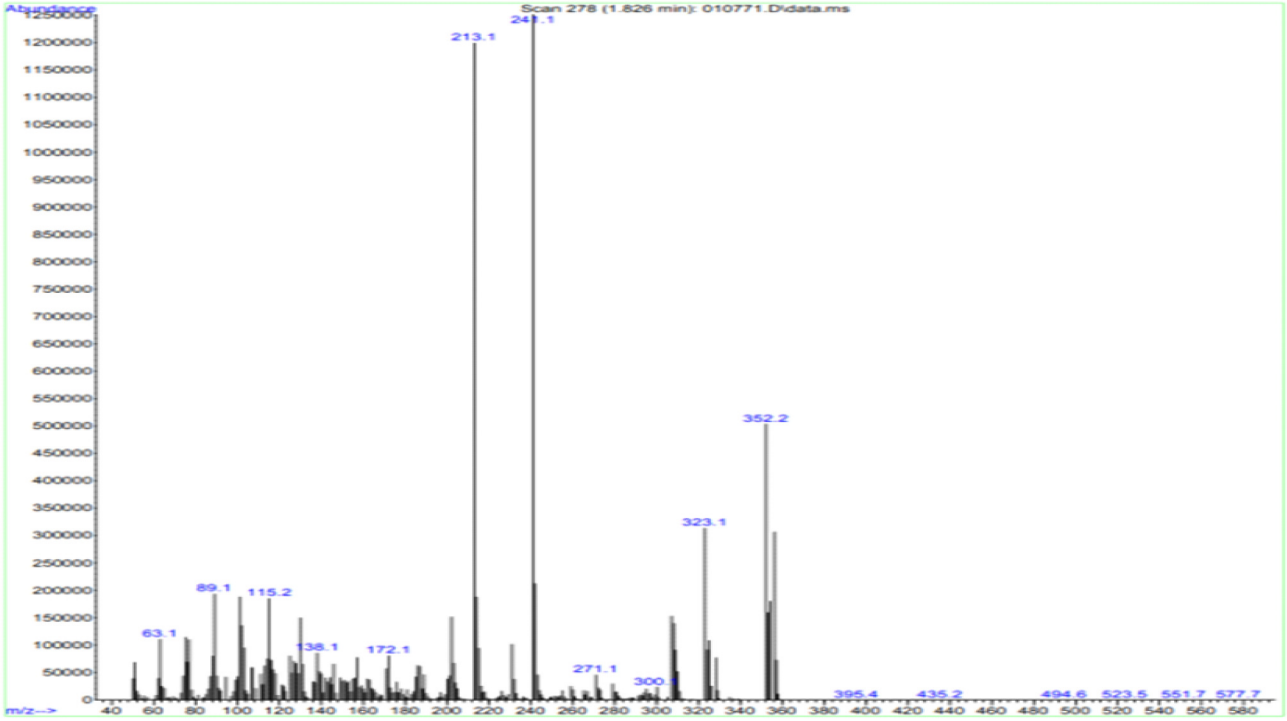


Fig. 32. Mass spectra of compound 14.

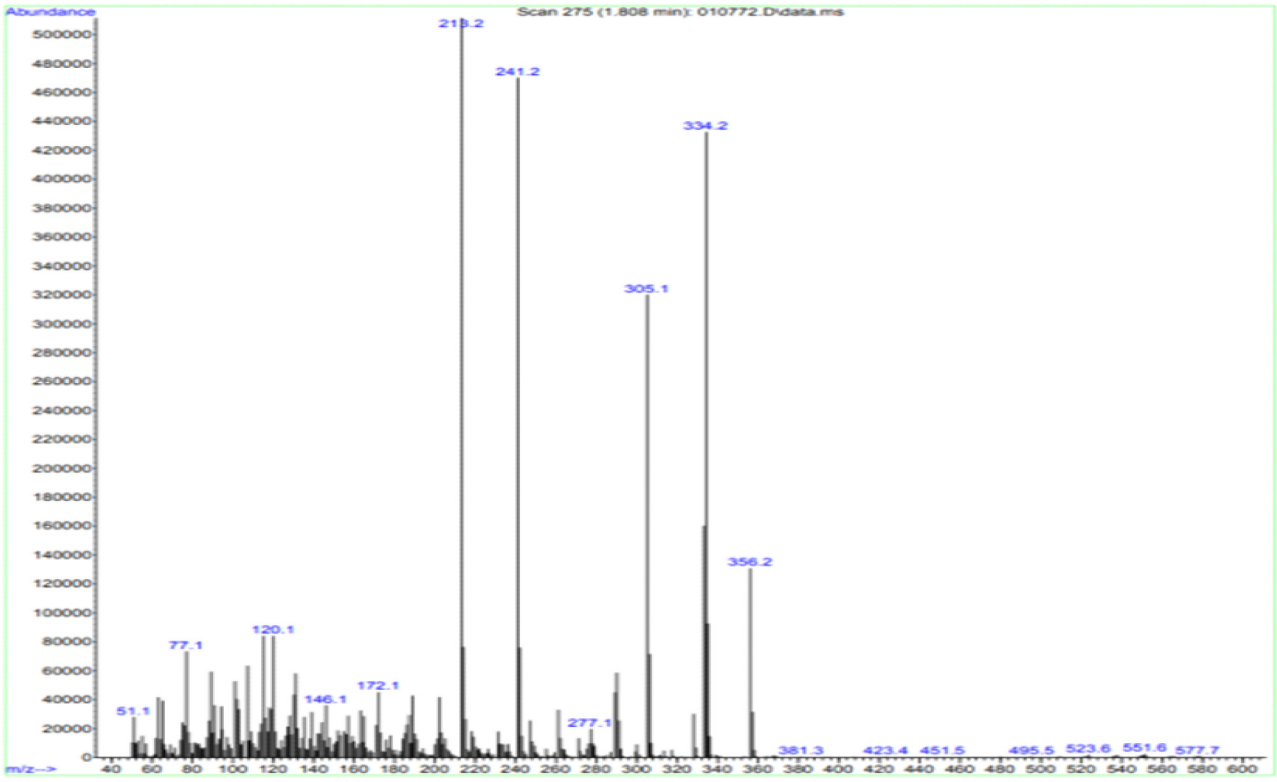


Fig. 33. Mass spectra of compound 15.

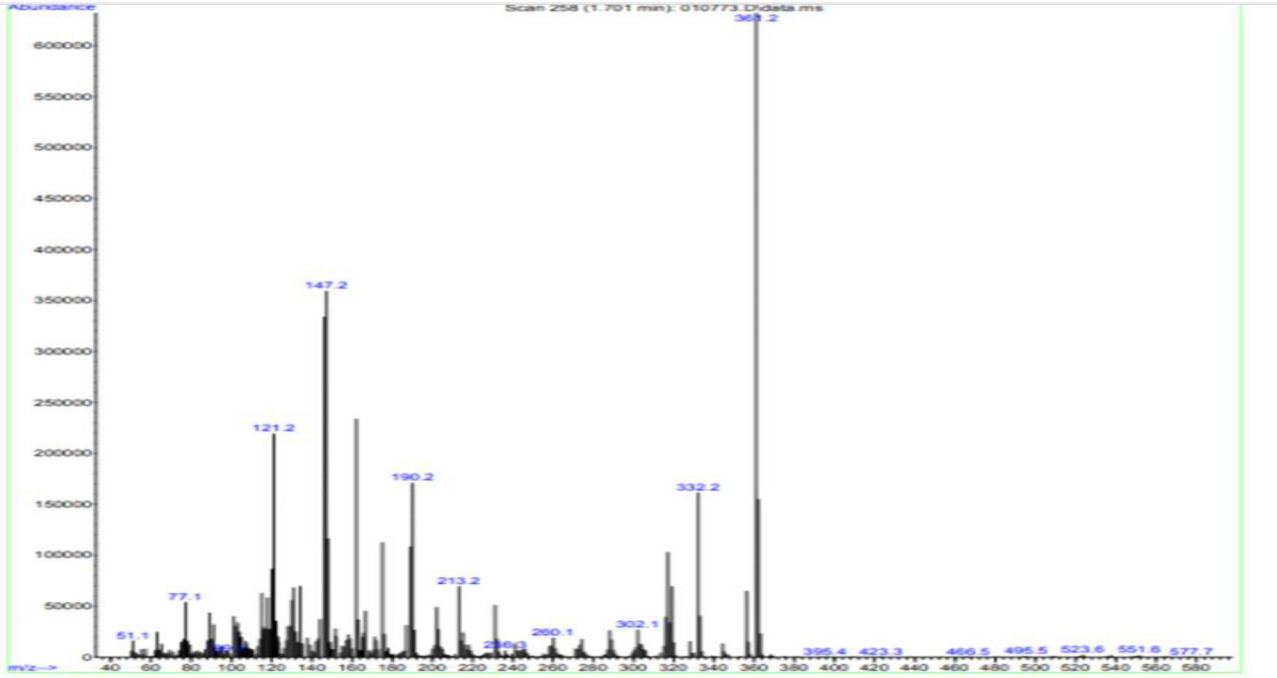


Fig. 34. Mass spectra of compound 16.

Table 2. Mass spectrum of coumarin pyrazoline derivatives 9–16.

Cpd.	Molecular weight	Molecular ions $M^{\cdot+}$
9	318	318.2
10	348	348.2
11	378	378.2
12	375	375.2
13	364	364.2
14	352	352.2
15	334	334.2
16	361	361.2

molecular formula $C_{17}H_{13}NO_2$. The peaks at 157 and 77 m/z referred to structures of the coumarin part and phenyl ring respectively.

Antioxidant evaluation of coumarin pyrazoline derivatives 9–16

Studying the in vitro antioxidant activity of the coumarin pyrazoline derivatives (9–16) by monitoring their effect on the absorbance of the stable free radical ABTS (2,2^{-}-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)). In this assay, the absorption at 734 nm with Trolox as the standard material.[26] $ABTS^{\cdot+}$ was created by mixing a newly manufactured 2.45 mM potassium persulfate solution with a 7 mM ABTS stock solution (1:1), then incubating the mixture for 12 to 16 hours at room temperature in the dark until the absorbance stabilized and the reaction was complete. By adding the necessary quantity of water, the UV-vis absorbance of the ABTS solution was diluted to 0.70, and after 6 minutes, 1 mL of this solution was combined with 1 mL of the test sample, in this time, the absorbance was measured at 734 nm,[17] by using Eq. (1)

$$\% \text{ of antioxidant activity} = ((A - A_{6\min.})/A) * 100\%^{27} \quad (1)$$

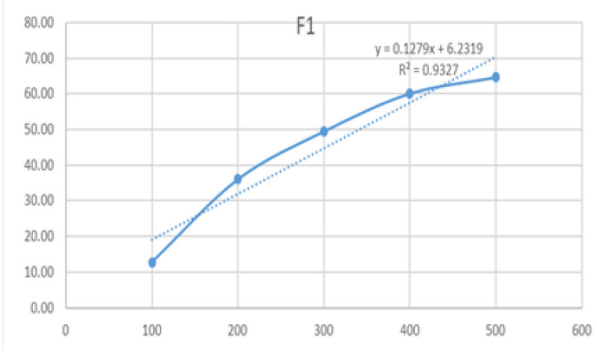


Fig. 35. The effect of different concentrations of compound (9) on the percentage of ABTS remaining.

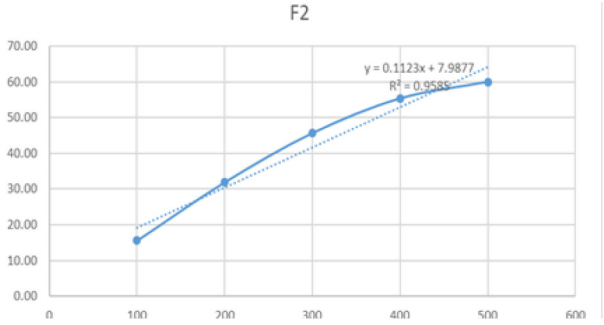


Fig. 36. The effect of different concentrations of compound (10) on the percentage of ABTS remaining.

were A account for the absorption of ABTS solution.

$A_{6\ min}$ absorption of ABTS after 6 minutes of antioxidant addition. Preparation of numerous Trolox solutions at concentrations ranging from 12.5 to 400 µM by using ammonium persulfate in Eppendorf tubes. The next step was to dilute the samples to the desired concentrations, generally using 2.000, 1.000, 0.500, and 0.250 mg/mL. The results for the compounds are shown in Table 3 and Figs. 35 to 42).

Table 3. The percentage of antioxidant activity and IC50 values of coumarin pyrazoline derivatives (9–16) against ABTS.

	Mean of Antioxidant activity % ± standard deviation							
Conc. (µg/mL)	Comp. 9	Comp. 10	Comp. 11	Comp. 12	Comp. 13	Comp. 14	Comp. 15	Comp. 16
100	12.76 ± 0.007	15.55 ± 0.013	8.25 ± 0.028	5.69 ± 0.026	37.9 ± 0.008	6.08 ± 0.028	37.51 ± 0.023	49.39 ± 0.001
200	36.01 ± 0.007	31.88 ± 0.008	25.98 ±0.47	17.78 ± 0.024	70.07 ± 0.007	14.1 ± 0.024	59.03 ± 0.024	61.04 ± 0.025
300	49.44 ± 0.015	45.65 ± 0.004	43.92 ± 0.028	39.13 ± 0.003	89.3 ± 0.003	31.72 ± 0.018	85.28 ± 0.010	90.19 ± 0.014
400	60.09 ± 0.006	55.35 ± 0.007	55.07 ± 0.021	41.81 ± 0.001	91.97 ± 0.001	50.61 ± 0.010	91.08 ± 0.006	94.04 ± 0.007
500	64.66 ± 0.11	59.98 ± 0.006	65.22 ± 0.47	59.31 ± 0.048	91.92 ± 0.002	60.09 ± 0.015	94.20 ± 0.008	97.99 ± 0.001
IC 50	342.20	374.10	327.1	431.40	98.10	421.00	139.27	80.90

Comp. = compound

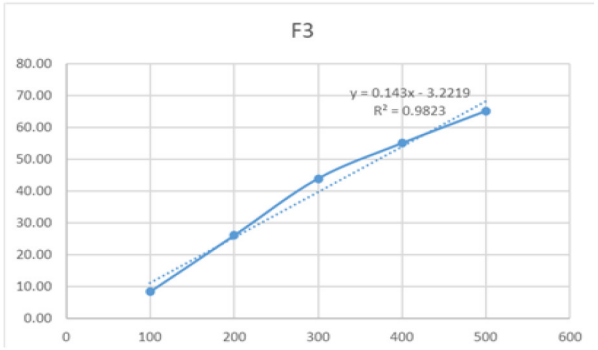


Fig. 37. The effect of different concentrations of compound (11) on the percentage of ABTS remaining.

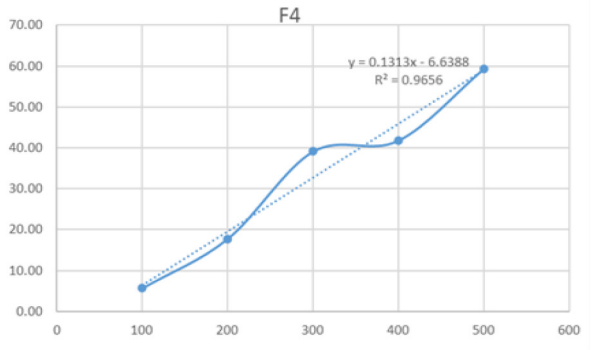


Fig. 38. The effect of different concentrations of compound (12) on the percentage of ABTS remaining.

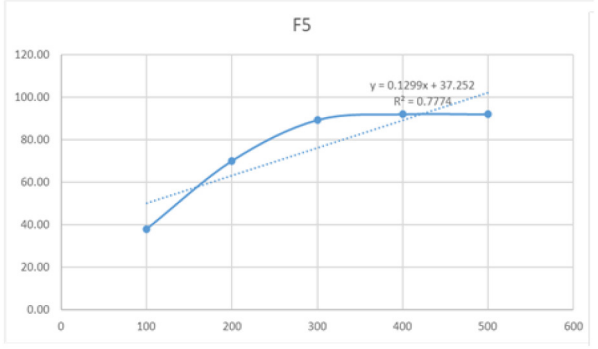


Fig. 39. The effect of different concentrations of compound (13) on the percentage of ABTS remaining.

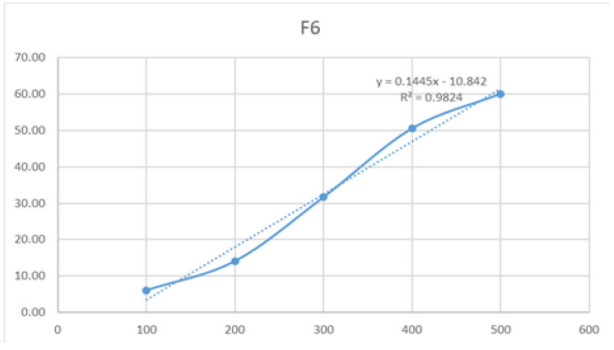


Fig. 40. The effect of different concentrations of compound (14) on the percentage of ABTS remaining.

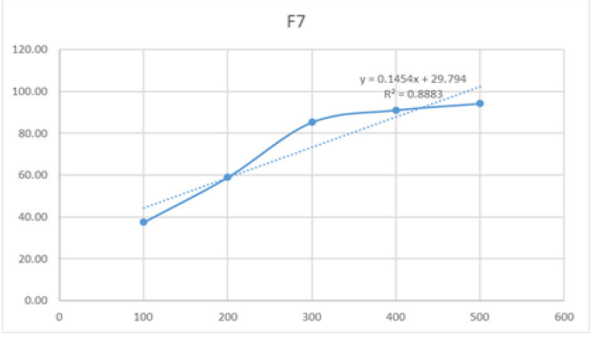


Fig. 41. The effect of different concentrations of compound (15) on the percentage of ABTS remaining.

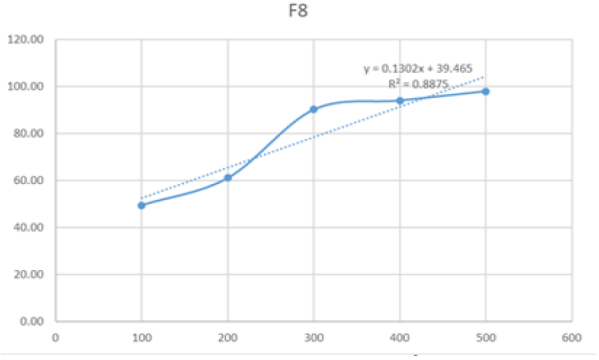


Fig. 42. The effect of different concentrations of compound (16) on the percentage of ABTS remaining.

Conclusion

In this study, novel coumarin pyrazoline derivatives (9–16) were synthesized and designed as antioxidants. The structures were confirmed by FTIR, ^{1}H-NMR, and MS techniques. The results show that coumarin-pyrazoline derivatives are characterized by high antioxidant activity that is superior to ascorbic acid (antioxidant activity is 59.8% and IC50 is 323.6 µg/ml). The more potent antioxidant activity noticed is compound 16 with antioxidant activity equal to 97.99% and IC_{50} equal to 80.90 µg/mL, the presence of dimethyl amine led to an evaluation of the polarity of the compound and an increase in the oxidation activity. Followed by compounds 15 and 13 that have antioxidant activity as 94.20% and 91.92% with IC 50 equal to 139.27 µg/mL and 98.10 µg/mL, respectively.

Acknowledgment

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Author's declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and Images, which are not ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at University of Basrah.
- No animal studies are present in the manuscript.
- No human studies are present in the manuscript.
- No potentially identified images or data are present in the manuscript.

Author's contribution statement

L.A. and R.S. conceived this idea, based on the expressions of W.Y., L.A and R.S. supervised the project. W.Y. carried out the experiment, wrote the manuscript, and performed the analysis. All authors discussed the results and contributed to the final manuscript.

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تحضير وتشخيص لمشتقات جديدة من الكومارين- بيرازولين وتقييمها بيولوجيا كعوامل مضادة للأكسدة

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الخلاصة

تم تهجين مركب الكومارين مع جزيء غير متجانس يحتوي على النيتروجين يعرف باسم بيرازولين وذلك لزيادة نشاطه البيولوجي، وأظهر نطاقا واسعا من النشاط. تضمنت الدراسة تحضير مركب جديد بطريقة التكثيف، وتم تشخيصها وأثبات الهياكل التركيبية للمركبات المحضرة بمطيافية الاشعة تحت الحمراء، بروتون ن م ر ومطيافية كاربون-13 بالاضافة الى مطيافية الكتلة (MS, ^{13}CNMR, FT-IR, ^{1}HNMR) والتي اثبت من خلالهما تكون حلقة البيرلزوين من خلال ظهور بروتونات مجموعة المثيلين في ثوابت ازدواج مختلفة. من ناحية اخرى بروتون C11' يتكيف مع زاويتين متجاورتين مختلفتين لبروتوني مجموعة المثيلين , فعليه ان ثابت ازدواج البروتونات المتجاورة مع بعضها البعض اعلى منها لبروتونات المجاورة لبعضها البعض ويمكن للزاوية الثنائية الاتجاه بين البروتونات ترتبط بعلاقة كاربلس مع ثابت ازدواج البروتونات المتجاورة. كما تمت دراسة النشاط الحيوي للمركبات المحضرة باستخدام مبدأ مقايسة $ABTS^{\bullet+}$ والذي اعتمد على توليد كروموفور الاخضر/ المزرق من خلال التفاعل بين ABTS وبيرسلفات البوتاسيوم عند حوالي 734 نانومتر، حيث أظهرت النتائج أن مشتقات الكومارين- بيرازولين تتميز بنشاط مضاد للأكسدة عالي يتفوق على نشاط حامض الأسكوربيك، وخاصة مشتق ثنائي مثيل أمين.

الكلمات المفتاحية: تحليل مضاد الاكسدة، مركبات مضادة للتأكسد، حامض الاسكوربك، مشتقات الكيومارين، البيرازولين، تهجين الكيومارين.