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Synthesis and Identification of Some Imino Chalcone Derivatives with Evaluating their Anti-oxidant Activity

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Abstract

This work involves the preparation of high yield iminochalcon compounds (B1-B15) through two parts. The first part involves the preparation of 2,4-dihydroxy Chalcone (A1-A15) by the condensation of 2,4-dihydroxy acetophenone with aryl aldehyde in the presence of sodium hydroxide (40%) as a catalyst. The second part includes the preparation of iminochalcon from the condensation of p-hydroxy aniline with 2,4-dihydroxy chalcone derivatives (A1-A15) in the presence of some drops of conc. H_2SO_4. Thin-layer chromatography ((TLC) was used to control the chemical reaction . These new derivatives were characterized by using FT-IR and 1H-NMR spectroscopy. These synthesized compounds were also assessed by the DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) free radical method, through which the compounds (B1-B15) were evaluated for their antioxidant activity. The compound B3 was found to have the strongest antioxidant activity (IC50= 23.91 µg/mL) as compared to that of the common standard of ascorbic acid (IC50=31.95 µg/mL).

Keywords: iminochalcone, 2,4-dihydroxy chalcone , aniline, antioxidant activity.

تحضير وتشخيص بعض مشتقات الجالكون ايمين مع تقييم نشاطها المضاد للأكسدة

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الخلاصة

تضمن البحث تحضير منتوج عال من مشتقات الجالكون ايمين (B1–B15) من خلال جزئيين : تضمن الجزء الأول من الدراسة تحضير 2,4–ثنائي هيدروكسي جالكون من تكاثف 2,4–ثنائي هيدروكسي اسيتوفينون مع الالديهايدات الاورماتية بوجود هيدروكسيد الصوديوم(40%) كعامل مساعد. تضمن الجزء الثاني تحضير ايمينو جالكون من تكاثف بارا –هيدروكسي انيلين مع مشتقات2 ,4–ثنائي هيدروكسي جالكون (A1–A15) بوجود قطرات من حامض الكبريتيك المركز. تم استخدام كروماوغرافيا الطبقة الرقيقة للسيطرة على التفاعل الكيميائي. تم تشخيص المشتقات الجديدة من خلال تقنيات اطياف الاشعة تحت الحمراء FT–IR واطياف بروتون–الرنين النووي المغناطيسي ^{1}H–NMR.

تم فحص النشاط المضاد للأكسدة للمركبات المحضرة(B1–B15) بطريقة DPPH ، وأظهرت النتائج ان المركب B3 سجل اعلى نشاط مضاد للاكسدة (IC50= 23.91 µg/mL) مقارنة مع حامض الاسكوربيك(IC50=31.95 µg/mL) .

1. Introduction

Schiff bases are prepared through the condensation between equimolars of primary amine (aromatic , aliphatic, or related derivatives) and carbonyl compounds (aldehydes or ketones, aromatic ,

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aliphatic, or related derivatives) using basic or acidic media in alcoholic solvent [1]. They are characterized by the -N = CH- bond, which is essential in the process of transamination and racemization in biologic structures [2].They are used in various biochemical and biological activities, such as antitumor [3], anticancer and anti-tubercular [4], antimicrobial [5]antibacterial [6]and anti-biofilm formation in methicillin-resistant staphylococcus aureus [7]. Chalcones have a C^^(A)-CO-CH = CH-C^ (B) structure, where two aromatic rings (A and B) are bound by an aliphatic three carbon chain [8]. Chalcone condenses in ethanol with substituted aniline in the presence of 2,3 drops of H_2SO_4 to provide chalcone imine. Chalcones and their derivatives hold a special significance among pharmaceutical and synthetic compounds [9]. The chalcone nuclei are important components of several drugs [10]. The synthesis of imines from the condensation of carbonyl compounds (aldehydes or ketones) with amines as a nucleophile is typically used to prepare chalcones and Schiff bases [11]. Chalcone (1,3-diaryl-2-prapen-1-one) and Schiff bases (substituted benzylidene aniline) belong to the commonly used compounds in companies of natural intermediates. They have broad spectrums of biological activities, such as those of antioxidants [12], anti leshmanial [13], antifungal [14]and antimicrobial [15].α,β-Unsaturated ketimines, which are obtained from chalcone and amine condensation, possess different pharmacological properties [16]. Both chalcones and Schiff bases are essential for the synthesis of different active organic compounds, such as flavones [17], indazol-3-one and thioxo pyrimidines [18],pyrazoloins [19],β-lactams [20], sulfonamide derivatives [21], and metal complexes [22]. They are also used to minimize photosensitivity of photographic emulsions in color photography [23]and mesomorphic properties of dimer containing chalcone [24].

2. Materials and Methods

Chemicals used in this work are supplied from Sigma Fluka, MERCK, BDH and CDH and are used without further purification.

2.1Instruments

The melting points of the compounds prepared were determined using the SMP30 melting point instrument. The uncorrected FT- IR spectra were recorded on SHMADZU FT-IR 8400Series Japan)" using the KBr disk method . TLC was performed for silica gel G and spots were visualized by I_2 vapors. The H1- NMR spectra were obtained using DMSO as a solvent and TMS as an internal standard with NMR spectrometer (Bruker, Ultra Shield 400 MHZ, Switzerland).

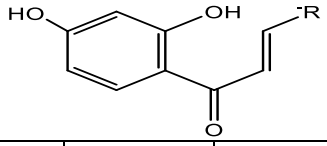
2.2 Synthesis of Chalcone Derivatives [25] (A1-A15)

A total of 40 % NaOH(10 mL) and 0.01mol of 2,4-dihydroxy acetophenone (1.52gm) were added to 15 ml absolute EtOH in 100ml round bottom flask with 30 minutes of stirring. The substituted aldehyde (0.01 mol) heated at 40-45 ^{0}C on water bath for 4-5 hours. The precipitate formed was left for overnight . The reaction mixture was completed by TLC using petroleum ether: ethylacetate (4:1), then washed with water and ethanol. Crushed ice was acidified with 45% (50ml) HCl and added . The precipitate was filtered and washed with 1% $NaHCO_3$ solution and water. The precipitate (yellow – orange product) was crystallized from EtOH . Its physical properties are shown in Table-1.

2.3 Synthesis of imino chalcone derivative [26] (B1-B15)

In a round bottom flask, equimolar quantities of substituted 2,4-dihydroxy chalcone (0.01 moles) and aromatic amines (p-hydroxy aniline, 1.091g, 0.01 moles) were dissolved in ethanol (20ml) and 2, 3 drops of Conc. H_2SO_4 was added . The mixture was heated at 70-80 ^{o}C in a water bath for 4-5 hours. TLC control (ethylacetate: methanol) (4:1) was used to complete the reaction. The reaction mixture was diluted with ice cold water. Solid substituted 2, 4-dihydroxy -N-hydroxy phenyl chalcone imines were obtained. These were purified, washed, and recrystallized from absolute ethanol. Their physical properties are shown in Table-2.

Table 1-Physical proprties of Chalcone compounds (A1-A15).



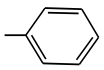
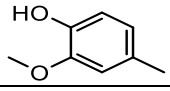
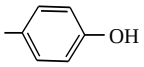
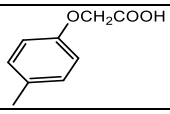
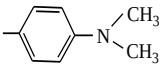
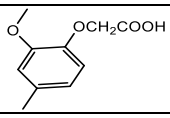
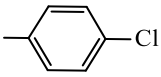
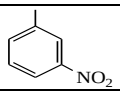
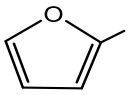
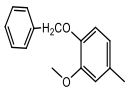
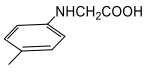
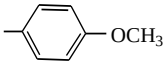
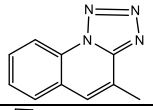
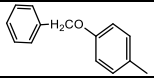
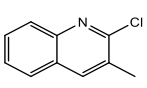
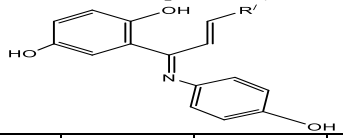
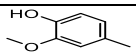
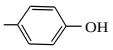
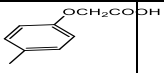
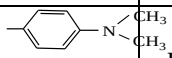
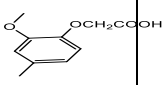
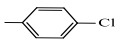
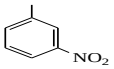
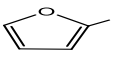
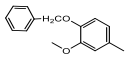
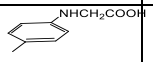
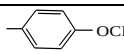
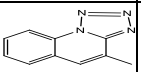
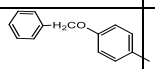
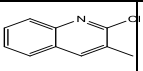
Com. NO.	Molecular Formula	R/	Color	Melting point. °C	Yield%	Retention factor	Petrolum ether: ethylacetate (TLC)
A1	$C_{15}H_{12}O_3$		Orange	148-150	92	0.94	(1:3)
A2	$C_{16}H_{14}O_4$		crystal orange	192–194	67	0.89	(1:4)
A3	$C_{15}H_{12}O_4$		Light brown	175-178	64	0.68	(2:3)
A4	C17H14O6		Light yellow	117-118	60	0.54	(1:9)
A5	$C_{17}H_{17}NO_3$		Wine red	180–182	62	0.59	(2:3)
A6	C18H16O7		Yellowish brown	135-137	65	0.71	(1:5)
A7	$C_{15}H_{11}ClO_3$		Light yellow	156–158	87	0.74	(2:3)
A8	$C_{15}H_{11}NO_5$		Brown	210-212	75	0.93	(2:3)
A9	$C_{13}H_{10}O_4$		White yellow crystals	71-74	73	0.93	(2:3)
A10	C23H20O5		Yellowish orange thick	186-187	82	0.77	(1:5)
A11	C17H15NO5		Pale yellow needles	113-114	67	0.65	(1:8)
A12	$C_{16}H_{14}O_4$		Orangish yellow	166-168	68	0.66	(2:3)
A13	C18H12N4O3		Yellow	178–180	58	0.73	(4 : 1)
A14	C22H18O4		Orange thick	188-189	81	0.66	(1:4)
A15	C18H12ClNO3		Pale yellow	312-314	78	0.51	(4 : 1)

Table 2-Physical properties of iminochalcone compounds (B1-B15).

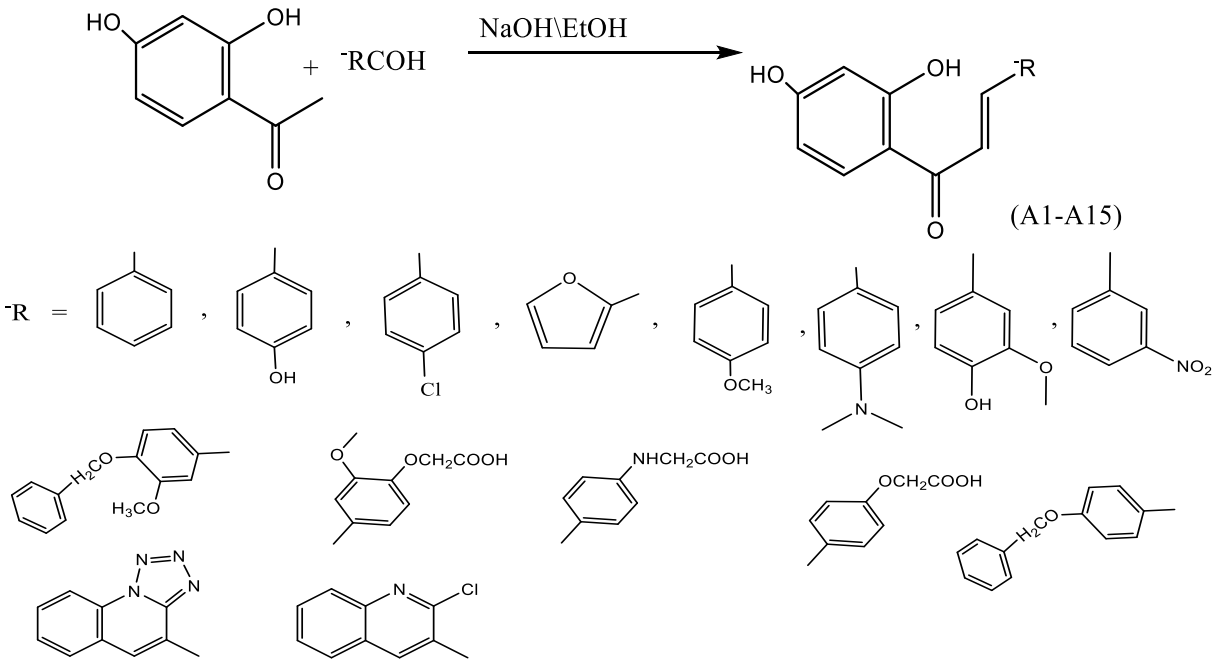


Compound	Molecular Formula	R/	Color	Melting point. °C	Yield %	Retention factor	ethylacetate :methanol (TLC)
B1	C21H17NO 3		Light brown	171-173	63	0.69	(4:1)
B2	$C_{22}H_{19}NO_4$		Pale yellow	208-206	57	0.77	(4:1)
B3	C21H17NO 4		Pale yellow	192-193	64	0.75	(4:1)
B4	C23H19NO 6		White shiny crystals	184-186	69	0.68	3:2
B5	$C_{23}H_{22}N_2O_3$		Dark brown	216-214	54	0.57	(4:1)
B6	C24H21NO 7		Light brown white	178-180	64	0.62	3:2
B7	$C_{21}H_{16}ClNO_3$		Dark orange	118 - 120	86	0.81	4:1
B8	$C_{21}H_{16}N2O_5$		Yellowish cream solid	184-186	90	0.66	4:1
B9	C19H15NO 4		Brown	131-132	73	0.74	4:1
B10	C29H25NO 5		Light yellow	162-163	76	0.67	3:2
B11	C23H20N2 O5		Red	126-128	60	0.57	3:2
B12	C22H19NO 4		Pale orange	152-150	68	0.78	(4:1)
B13	C24H17N5 O3		Pale green needles	261–263	66	0.53	n-hexane:CHCl3 1:1
B14	C28H23NO 4		White cream	156-158	75	0.73	4:1
B15	C24H17Cl N2O3		Dark yellow	237–239	82	0.70	n-hexane:CHCl3 1:1

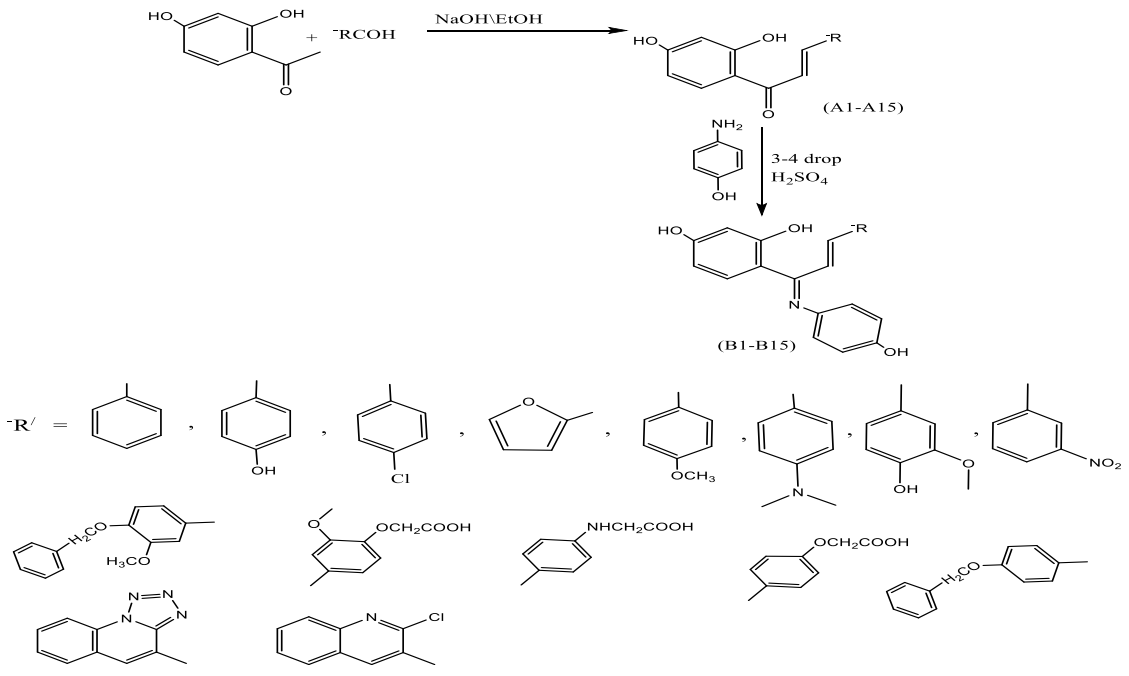
3. Results and Discussion

The formation of Schiff bases from an aldehyde (or) ketone is a reversible reaction and usually occurs under acid (or) base catalysis or heating. The formation is usually powered by the separation of

the liquid or water removal, or both, from the campsite. Replaced 2, 4-dihydroxychalcones imine (B1–B14) was synthesized from the substitution of 2,4-dihydroxy chalcone with p-hydroxy aniline, using H_2SO_4 as a catalyst, with a yield of 54-90 %. The reaction sequences are outlined in schemes 1.1 and 1.2.

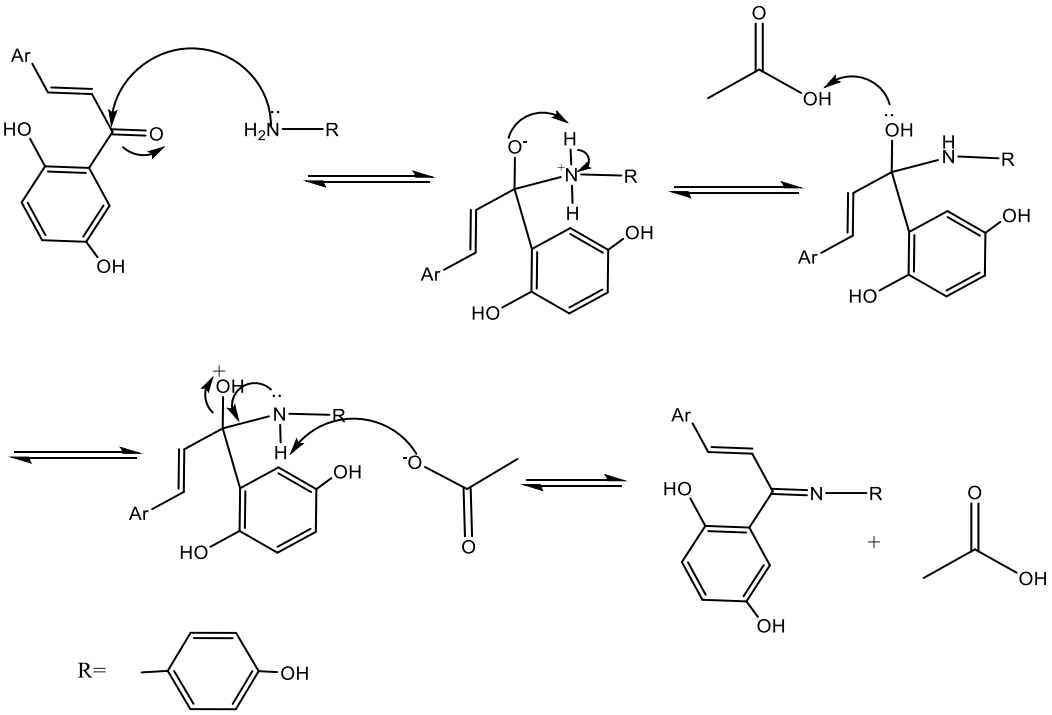


Scheme 1.1 - Synthesis of chalcone from 2,4-dihydroxy acetophenone (A1-A15).



Scheme 1.2 -Synthesis of imino chalcone derivatives from chalcone (B1-B15).

The mechanism of the preparation of α, β-unsaturated ketimines from aldehydes (or) ketones was developed in an acid-catalyzed process which begins with the addition of the primary amine to the carbonyl group by nucleophile [27], as shown in scheme 1.3.

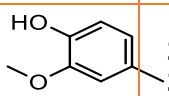
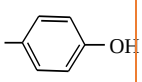


Scheme 1.3-Mechanism of Schiff's base synthesis (acid-catalyzed)

The FT-IR spectra of the prepared compounds (B1-B15), which are listed in Table-3 , did not show the band assigned to the υ (C=O) of chalcone derivative at (1674-1647) cm-1. The absorption bands of C=N at (1590-1630) cm-1 were observed. The stretching vibration of C=N was moved to low due to the conjugation of the C=N bond with the aromatic ring [28]. A wide band of the hydrogen-bonded phenolic hydroxyl group (bonding O-H) was observed at (3307-3417 cm-1). The C = C, aromatic two peaks at (1489-1586) cm-1 were also shown. Two bands of absorption appeared at (3050-2959) cm-1 belonging to (C-H, stretching) of the aromatic and aliphatic groups, respectively, and a (C-N) appeared at a stretching frequency of (1230-1020)cm-1, as shown in Figures-(1-6).

The ^{1}H-NMR data for some compounds (B8, B10,and B14) were recorded using DMSO as a solvent. The results showed : (δ 9.16 -9.92)ppm of (S,1H,OH at position C4), (δ (δ 13.22-11.99) ppm of (S,1H,OH at position C2) , (6.17-6.49)ppm of (α-H) , (6.73-6.99) ppm of (β-H) ,(7.22- 8.17)ppm of aromatic protons and (-OCH_3) at (3.97) ppm, as shown in Figures-(7-10).

Table 3 -Characterization of FT-IR absorption bands of compounds (B1-B15).

Compound	IR (KBr) ν cm^{-}							
	R/	**υ $CH_{ar.}$**	**υ $CH_{aliph.}$**	**υ C=N**	**υ OH**	υ C-O,C-N	**υC=C_{ar}**	others
B1		3005	2982	1634	3308	1229,1130 1257,1367	1574 1509	-
B2		3081 3004	2900	1623	3309	1236,1129 1264,1352	1577 1509	-
B3		3068	2996	1628	3355 3442	1213,1147 1254,1310	1587 1504	-

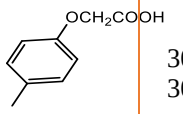
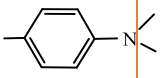
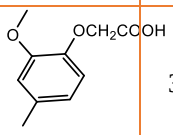
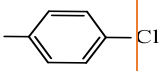
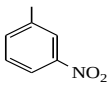
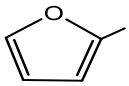
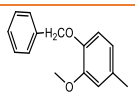
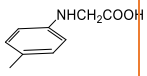
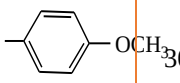
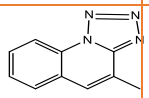
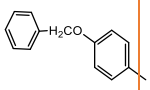
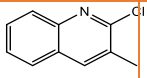
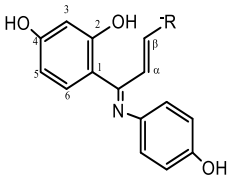
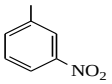
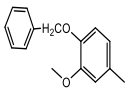
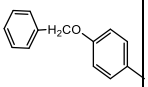
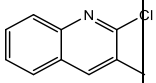
B4		3057 3025	2931 2833	1621	3310	1236,11 77 1283	1578 1600	**υ (OH)acid**(2583-3500)**υ C=O acid 1725**
B5		3042	2949 2842	1627	3432 3312	1215,11 76 1258,13 31	1587	-
B6		3069	2917 2806	1625	3427	1229,11 73 1262,13 06	1513 1571	**υ (OH)acid**(2498-3127)**υ C=O acid 1729**
B7		3070	-	1629	3308	1216,11 27 1228,13 67	1573 1508	**υ**C-Cl : 776
B8		3069	2910	1624	3337	1217,11 78 1256,13 94	1573 1600	m-NO2 (str.):1494 ,1337(N=O,symmetric)
B9		3068 3027	2896 2837	1633	3304	1212,12 88 1358	1597 1558	νC-O cyclic: 1026
B10		3082 3052	2907,280 0	1630	3483	1208,11 78 1294,13 33	1603 1572	-
B11		3033	2827	1621	3526	1233,11 50 1341	1567	**υ(OH)acid**(2487, 3500)**υ C=O acid 1716** **υ (NH) :3233**
B12		3013	2970 2945	1626	3460	1228,12 10 1265,13 67	1571 1610	-
B13		3006	2970,296 0 2868	1616	3307	1217,11 60 1368	1573	-
B14		3005	2970 2917	1626	3390 3307	1230,11 60 1254,13 27	1573 1505	-
B15		3047	2970	1633	3308	1256,11 30 1367	1574 1507	**υ**C-Cl : 616

Table 4-Chemical shift data of ^{1}H-NMR spectra of some chalcone imine derivatives



Compound	R/	^{1}H-NMR ppm)=(δ
B8		^{1}H-NMR(400MHz-DMSO-d6 ,solvent),(δ=ppm):6.44(d,1Hα),6.99(d,1Hβ),2.51(DMSOd6, solvent),13.22 (S,1H, OH at C2),9.16(S,1H,OHatC4),7.85- 8.17 (m, 11H, Ar -H), 8.39(S,1H, OH at C4$^{//}$)
B10		^{1}H-NMR(400MHz-DMSO-d6 ,solvent),(δ=ppm):6.17(d,1Hα),6.92(d,1Hβ),2.51(DMSOd6, solvent),4.97(S,2H,O-CH_2) 11.53 (S,1H, OH at C2) ,9.92 (S,1H, OH at C4), 3.97 (S,3H,OCH3),7.56-8.17 (m,15H,Ar -H),8.408(S,1H, OH at C4$^{//}$)
B14		^{1}H-NMR(400MHz-DMSO-d6 ,solvent),(δ=ppm):6.31(d,1Hα),6.92(d,1Hβ),2.51(DMSOd6, solvent), 5.29 (S , 2H ,O-CH_2) ,11.29 (S,1H, OH at C2) ,9.16 (S,1H, OH at C4) ,7.37-7.63(m,16H,Ar-H) 8.71(S,1H, OH at C4$^{//}$)
B15		^{1}H-NMR(400MHz-DMSO-d6 ,solvent),(δ=ppm):6.49(d,1Hα),6.73(d,1Hβ),2.51(DMSOd6, solvent), 11.99 (S,1H, OH at C2) ,9.57 (S,1H, OH at C4),7.22-8.15 (m,12H,Ar -H), 8.76(S,1H, OH at C4$^{//}$)

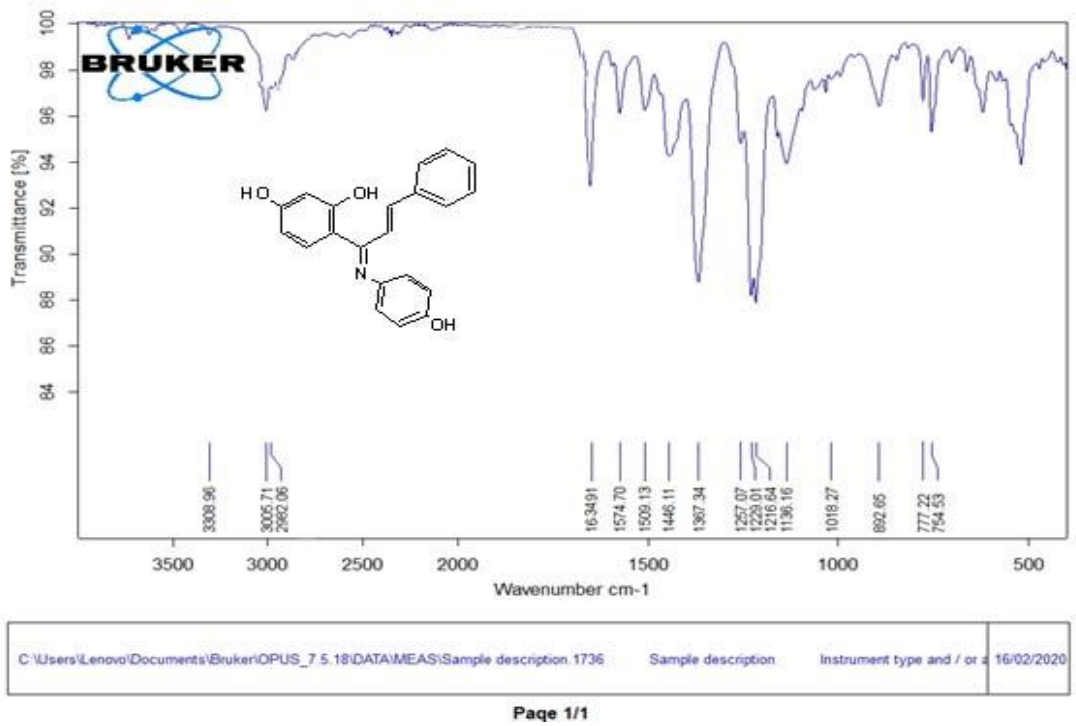


Figure 1- FT-IR spectrum of 2-((1E,2E)-1-((4-hydroxyphenyl)imino)-3-phenylallyl) benzene-1,3-diol (B1) .

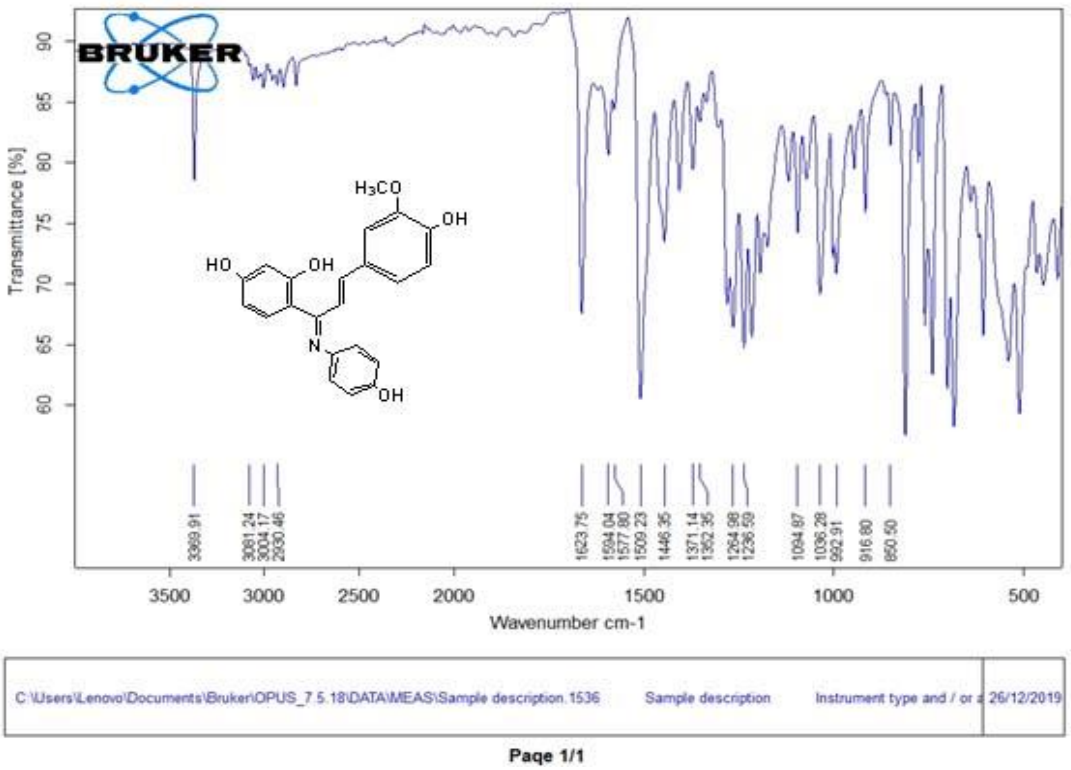


Figure 2-FT-IR spectrum of 2-((1E,2E)-3-(4-hydroxy-3-methoxyphenyl)-1-((4-hydroxyphenyl) imino)allyl)benzene-1,3-diol (B2) .

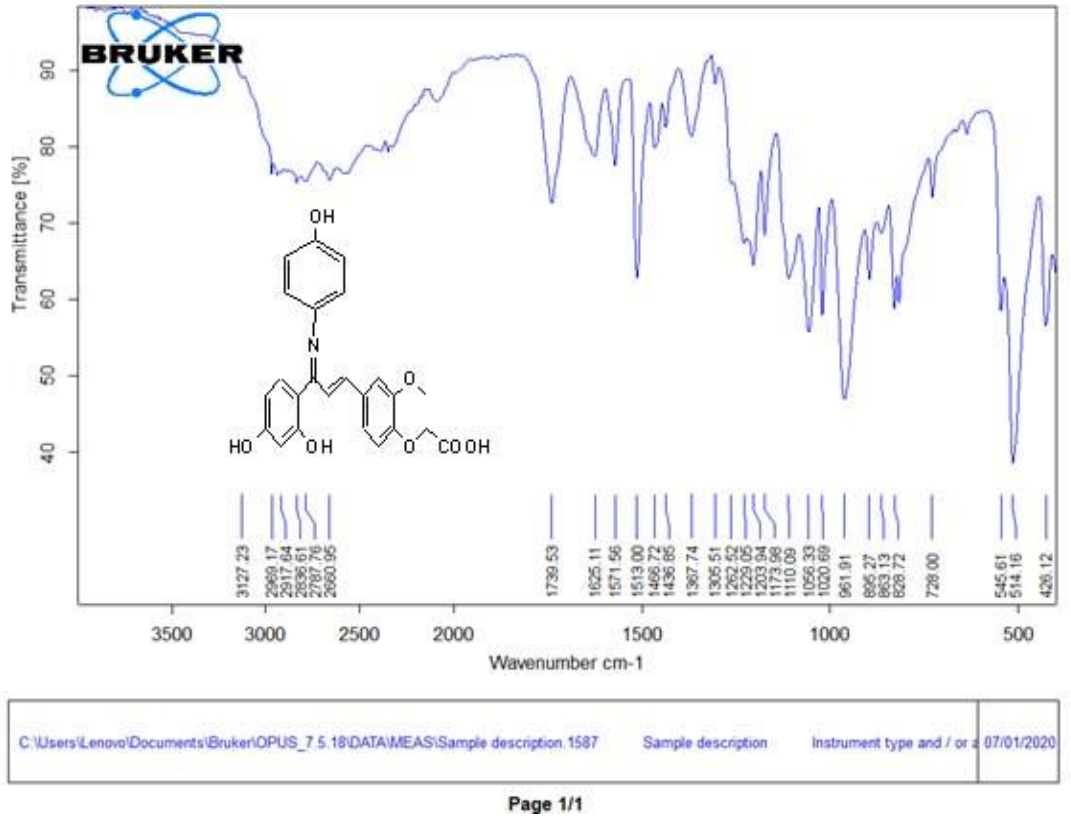


Figure 3-FT-IR spectrum of 2-(4-((1E)-3-(2,4-dihydroxyphenyl)-3-((4-hydroxyphenyl) imino)prop-1-en-1-yl)-2-methoxyphenoxy)acetic acid (B6) .

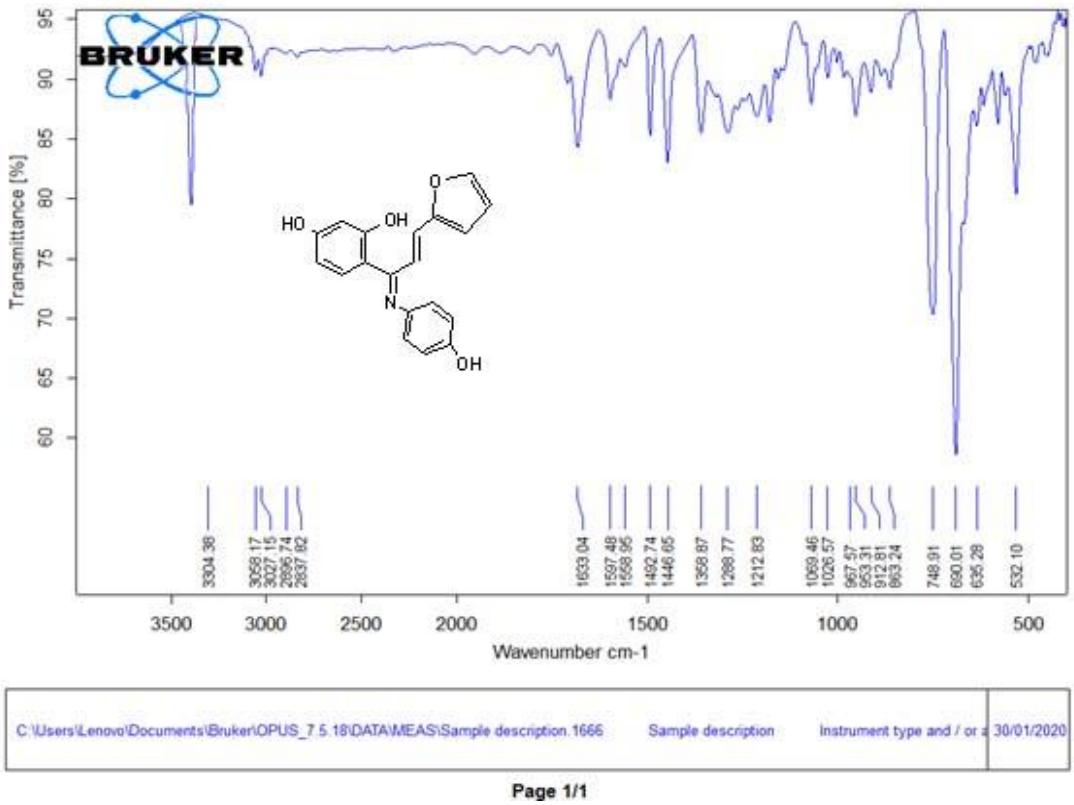


Figure 4-FT-IR spectrum of 4-((2E)-3-(4-(benzyloxy)-3-methoxyphenyl)-1-((4 hydroxyphenyl)imino) allyl)benzene-1,3-diol (B9) .

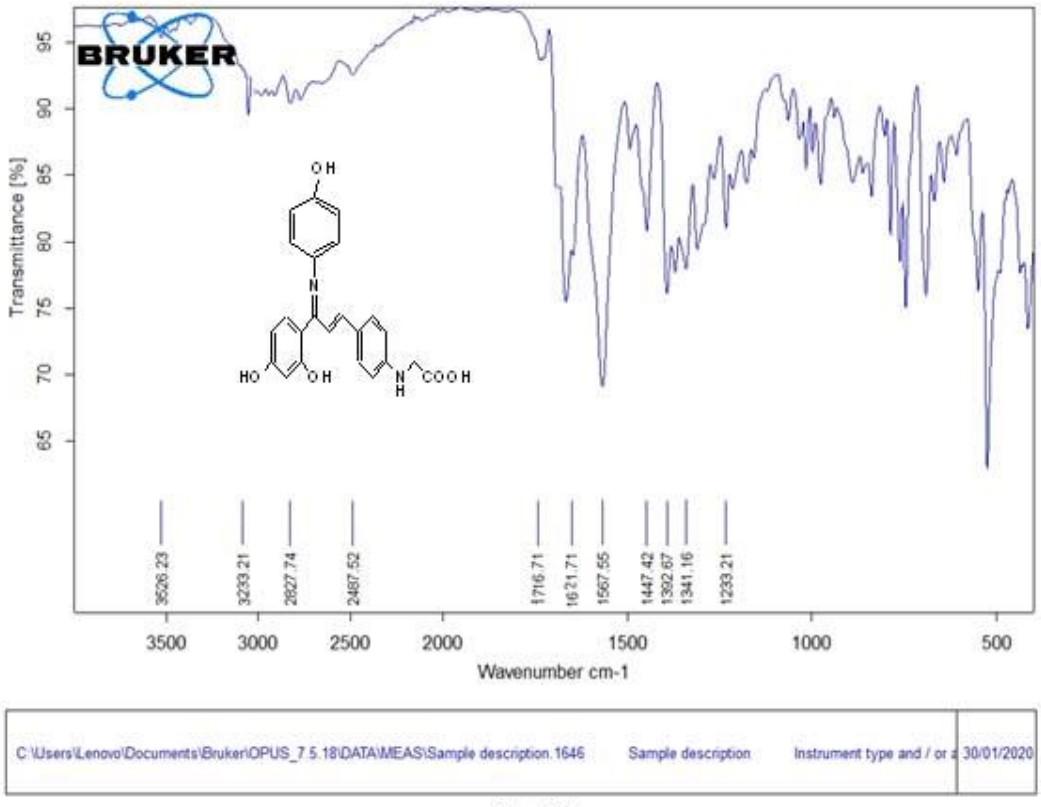


Figure 5-FT-IR spectrum of 2-((1E,2E)-1-((4-hydroxyphenyl)imino)-3-(4-methoxy phenyl) allyl) benzene-1,3-diol (B11) .

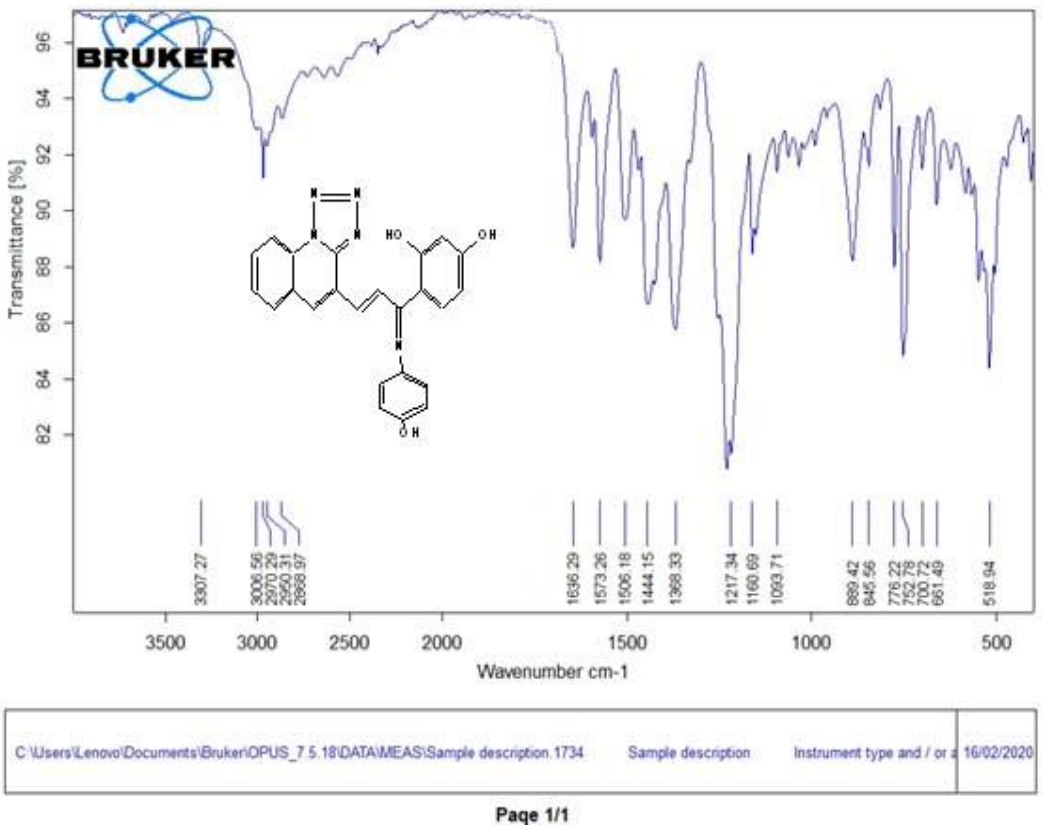


Figure 6-FT-IR spectrum of 4-((2E)-3-(4-(benzyloxy)phenyl)-1(4-hydroxyphenyl) iminoallylbenzene 1 ,3diol (B13) .

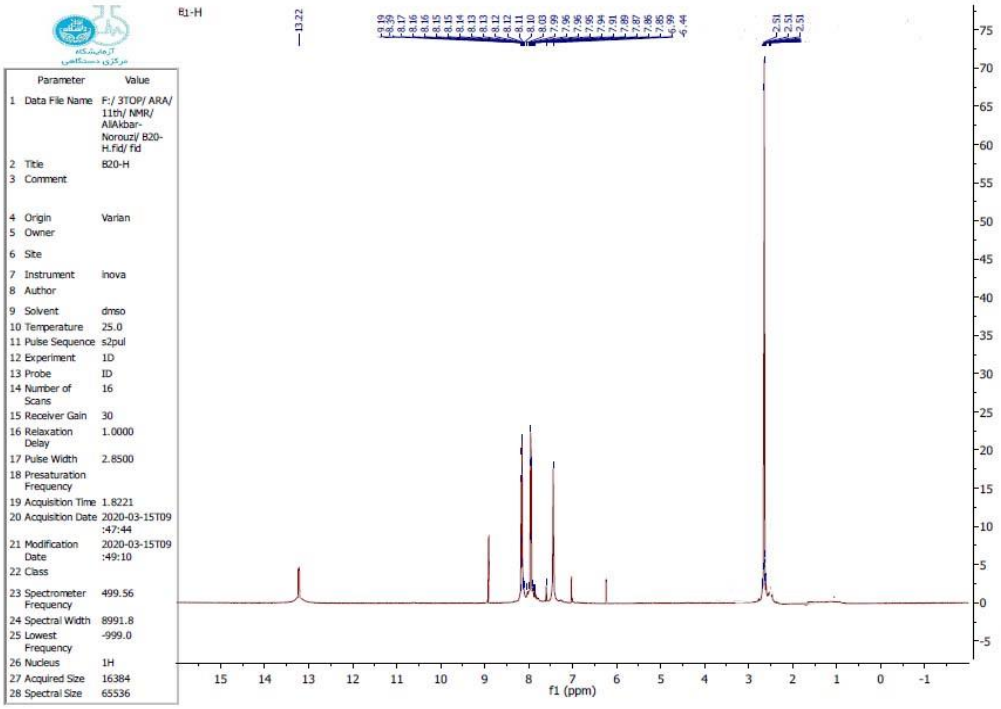


Figure 7- H^1-NMR spectrum of 2-((1E,2E)-1-((4-hydroxyphenyl)imino)-3-(3-nitrophenylallylbenzene 1, 3diol (B8) .

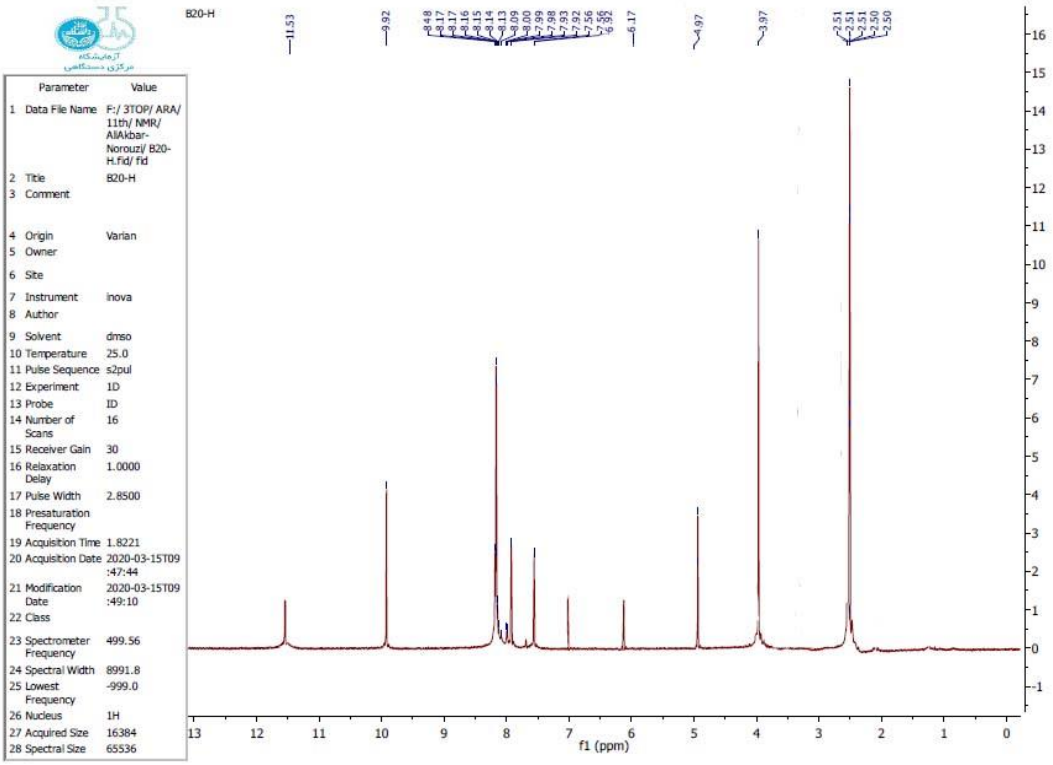


Figure 8-H[1]-NMR spectrum of (4-((1E)-3-(2,4-dihydroxyphenyl)-3-((4-hydroxy phenyl)imino)prop-1-en-1-yl)phenyl)glycine (B10) .

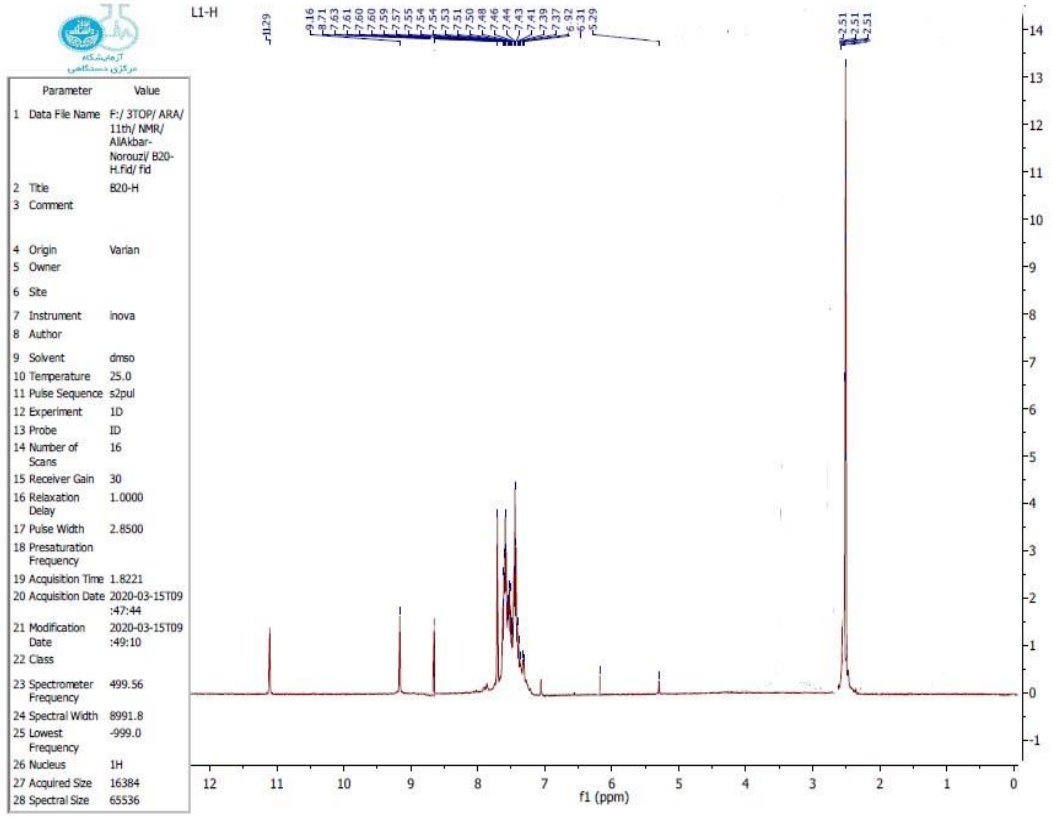


Figure 9-H[1]-NMR spectrum of 4-((2E)-3-(4-(benzyloxy)phenyl)-1(4-hydroxyphenyl) iminoallylbenzene1,3diol (B14) .

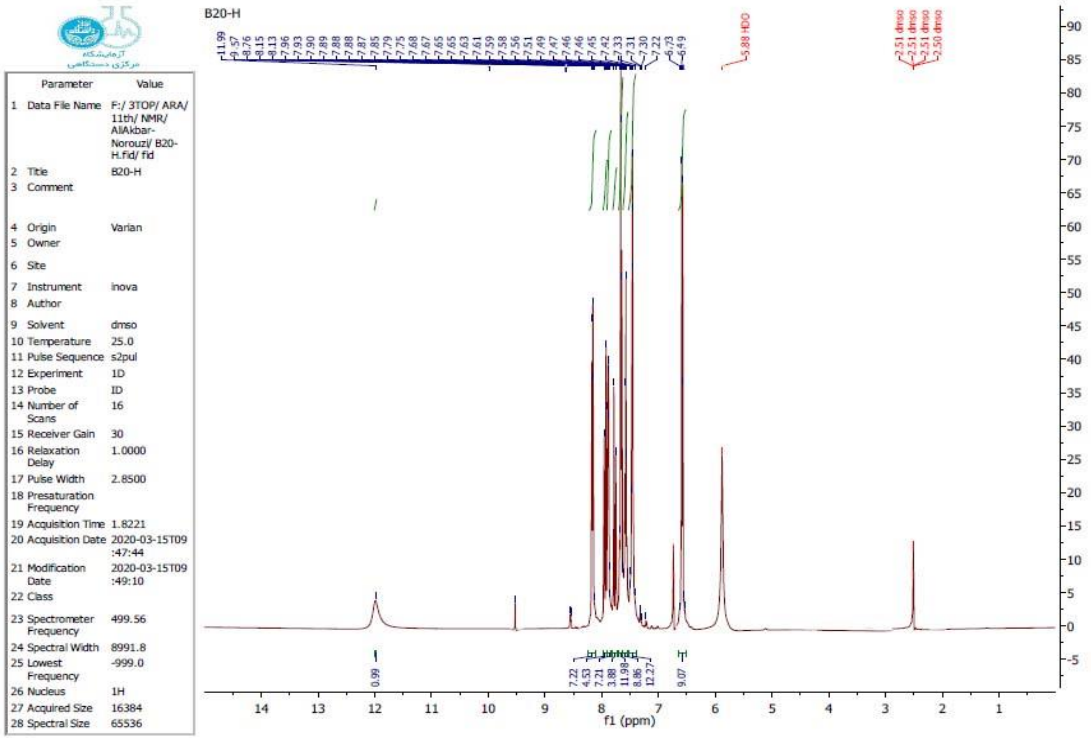


Figure 10-H^1-NMR spectrum of 4-((2E)-3-(2-chloroquinolin-3-yl)-1(4-hydroxyphenyl) iminoallylbenzene1,3diol (B15) .

3.1 Antioxidant Activities of the Prepared Compounds[29]

DPPH (1.3mg / ml) was prepared as a normal solution in methanol 100µl DPPH was added in 3ml of methanol and absorbance at 517 nm was noted. Various compound concentrations (25, 50, 75, and 100 µg / ml) were prepared. Sample (1 ml) was diluted to 3 ml and 100 µl of DPPH was applied. Test tubes were placed in light for 30 minutes to complete the reaction., Absorbance of each test tube was measured after 30min at 517 nm on UV-VIS spectrophotometer against methanol as a blank, as in Figures- (11, 12, 13).

The results of antioxidant activity are shown in Table-5 and indicate that the majority of the synthesized compounds displayed moderate to strong antioxidant activity in comparison to normal (ascorbic acid) activity (IC50=31.95 µg / mL). The highest activity was attributed to the p-OH group on the ring B in compounds B3 and B2 (IC50= 23.91 µg / ml and 28.82 µg / ml, respectively) . Conversely, compound B8 showed a low activity of m-NO_2 (IC50=123.87 µg / mL). For this reason, the (OH) ring in groups A and B confers high antioxidant activity. The p-OH group in B2 and B3 displayed greater free radical scavenging behavior than that of the m- NO_2 group of B8 compound. The standard reference made of ascorbic acid showed IC50 value of 31.95 µM. Compared to the reference, the strength of antioxidant functions of the tested compounds are in the following order: ascorbic acid >B3>B2>B6>B1>B11>B4>B10>B7>B9>B13>B12> B15> B14>B5>B8.

Table 5-Observation of in-vitro antioxidant activities of the synthesized compounds

conc. µg\ml	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15	STD (Ascorbic acid)
25	47.76	48.41	50.34	40.44	25.16	45.35	39.42	27.21	40.32	41.08	37.24	44.03	40.43	30.51	36.21	46.12
50	49.83	57.42	57.21	52.25	32.32	58.22	45.63	36.22	47.14	45.36	56.52	48.85	45.67	37.22	39.22	60.14
75	53.77	60.26	66.23	62.32	36.98	62.16	58.73	39.43	56.85	59.23	63.7	52.6	55.17	47.61	43.04	65.01

100	65.21	69.44	72.11	69.65	60.35	68.18	65.22	44.13	60.62	68.04	70.81	56.01	61.52	56.32	64.11	78.3
IC50 µg\ml	44.09	28.82	23.91	46.72	88.12	33.24	56.28	123.87	58.22	53.45	46.11	60.13	60.09	82.66	74.95	31.95

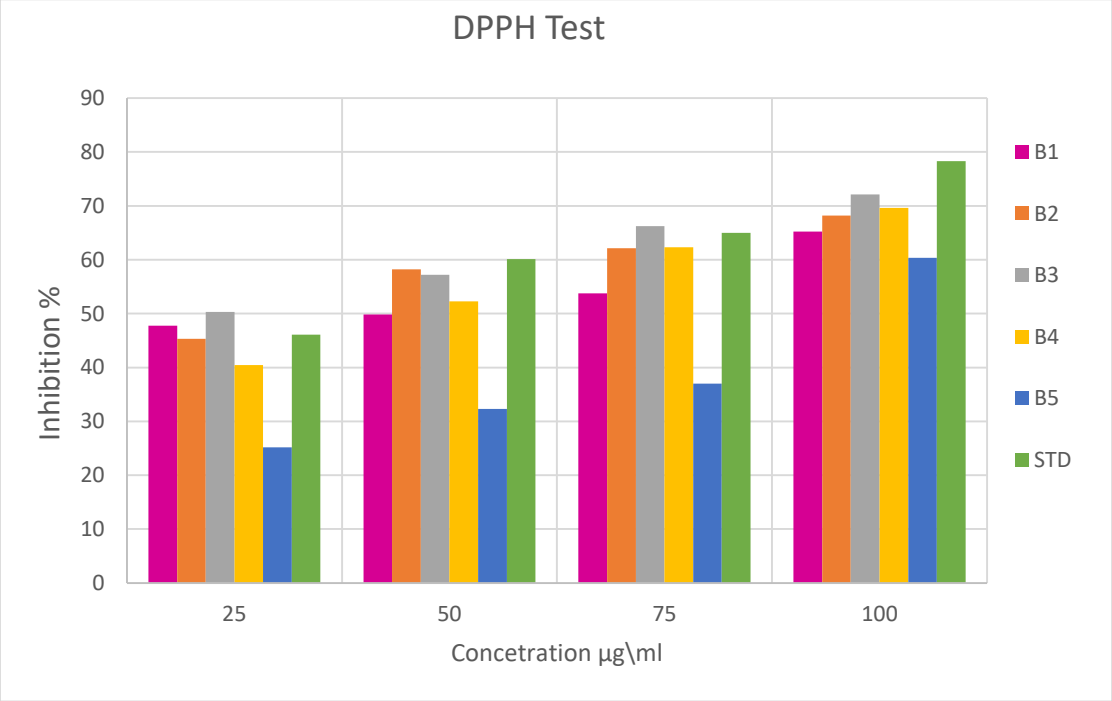


Figure 11- Graph showing DPPH scavenging activities of chalcones (B1-B5).

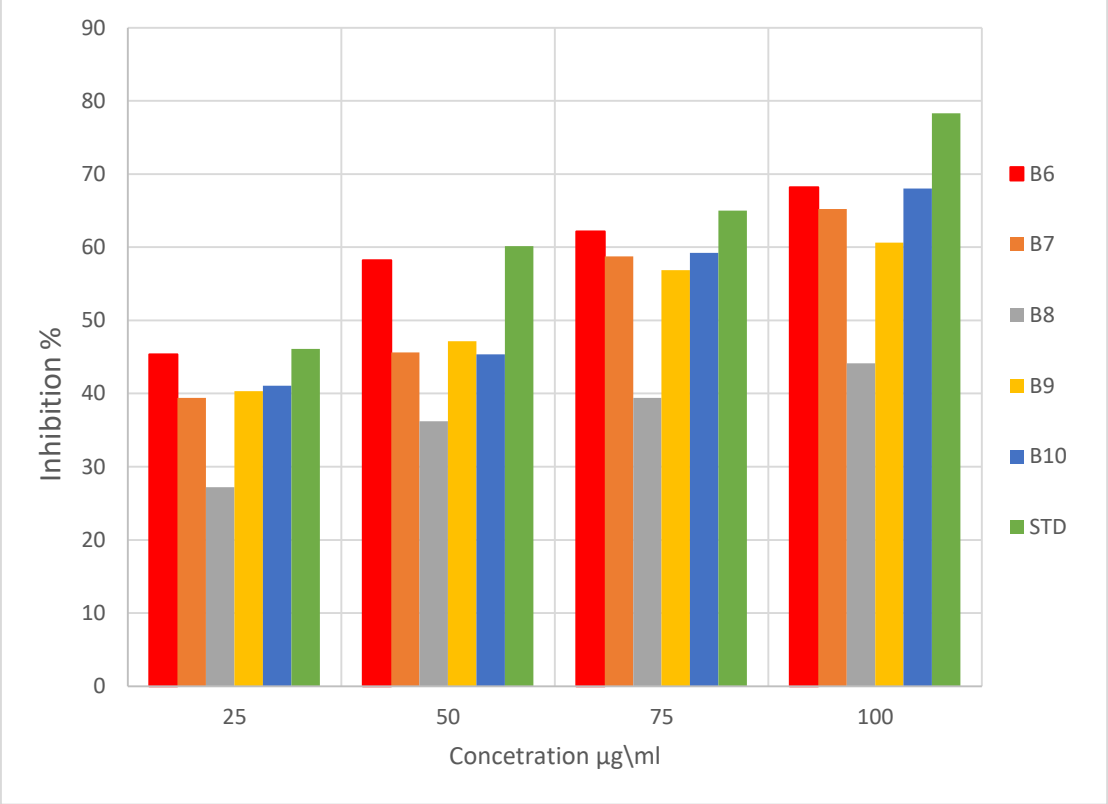


Figure 12- Graph showing DPPH scavenging activities of chalcones (B6-B10).

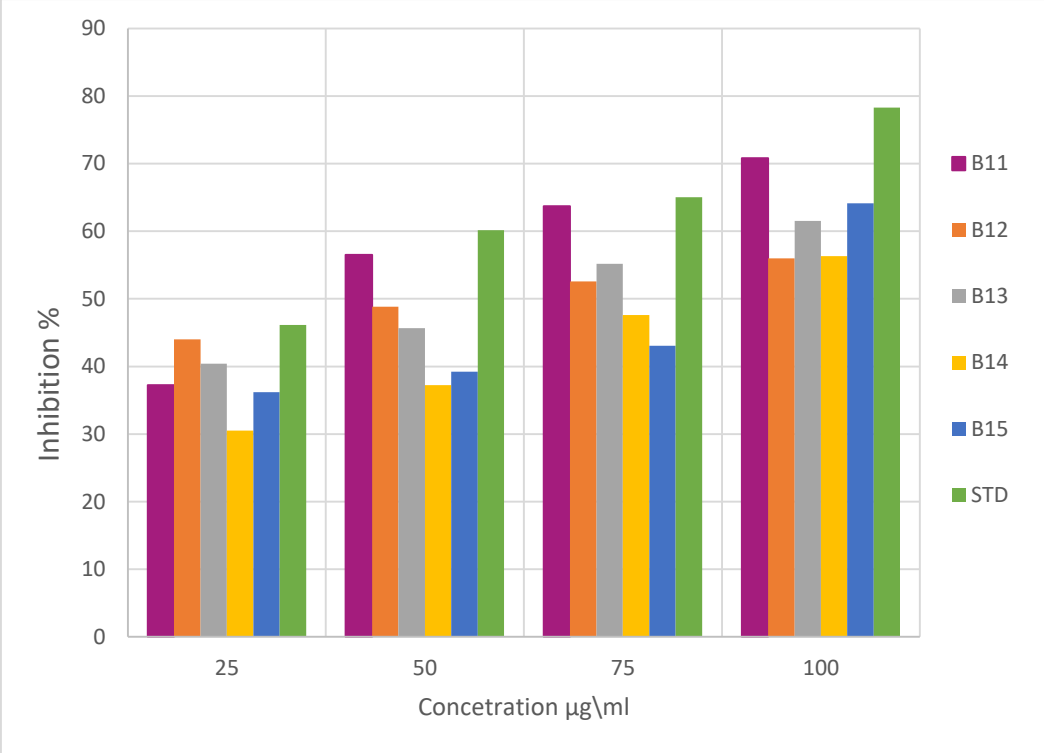


Figure 13-Graph showing DPPH scavenging activities of chalcones (B11-B15).

Conclusions

In the present study, substituted 2,4-dihydroxy–N- hydroxyl phenyl chalcone imines were synthesized with a percentage yield range of 54-90%. The structures of all these synthesized compounds were established on the basis of spectral data (FT-IR and ^{1}H-NMR). It is also interesting to note that the synthesized chalcone imines had strong antioxidant activities.

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