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Synthesis, characterization and antioxidant activities of some novel oxime derivatives

Abstract

In this study, nine novel compounds were synthesized in the reaction of ω-chloro-isonitrosoacetophenone with 2-chloro-4-methylaniline, 2-chloro-5-methylaniline, 2-chloro-6-methylaniline, 3-chloro-2-methylaniline, 4-chloro-3-methylaniline, 5-chloro-2-methylaniline, 2,3-dichloroaniline, 2,4-dichloroaniline and 3,5-dichloroaniline resulting for *C1-C9*, respectively. Compounds *C1*, *C4-C7* and *C9* were handled in single crystalline forms, which the structures were also investigated by X-ray single crystal analysis. Compounds were evaluated for their nonenzymatic lipid peroxidation inhibition, antioxidant and antiradical activities and compared with standard agents at 5, 50, and 100μM concentrations. Compounds are exhibited good antioxidant activities and lipid peroxidation compared to standards (BHA, TBHQ, BHT and trolox). Due to the best of our knowledge for novel oxime compounds, this study is the first report of promising antioxidants to scavenge oxidative stress conditions.

Keywords: oximes, carbonyl-oxime, amide-oxime, amido-carbonyl oxime, antioxidant activity, lipid peroxidation inhibition

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Introduction

Reactive oxygen species (ROS) are produced in normal cellular oxygen metabolism, effective in some biological systems. The increase in ROS on the intracellular antioxidant capacity may result in a situation characterized by oxidative stress. ROS are free radicals such as hydroxyl radicals, superoxide anion radicals, and nonradical species such as singlet oxygen and hydrogen peroxide. ROS attack hepatic and extrahepatic organs and induce oxidative stress. Thus leading directly or indirectly causes degenerative diseases such as cancer, dementia, and aging.[1] Cells perform many repair and protection mechanisms to remove ROS. Intracellular defense systems occur in two forms, enzymatic and non-enzymatic mechanisms.[2]

Antioxidants are essential compounds that reduce or neutralize the ROS, thus protecting the organisms from ROS and preventing the cells from oxidative injury. Therefore, significant research has been directed toward the identification of newly synthesized antioxidants to prevent ROS-induced damage.[3,4] Recent studies exhibited that oximes and their derivatives are used for clinical, critical pharmaceutical and synthetic chemistry applications as chemical inhibitors of enzyme activities.[5,6]

Previous works reported that oxime derivatives possessed insecticidal, miticidal, nematocidal, antiradical, antioxidant, antiepileptic, antihyperglycemic, antimicrobial, antidote, anti-carcinogenic and anti-HIV activities.[7-18] We synthesized a series of novel phenylacetamidine based amido-carbonyl oximes (C1-C9). Structures of the compounds characterized by ^{1}H-NMR, IR spectroscopy, and X-ray crystallography. Furthermore, the goal of this work was to comparatively evaluate in vitro antioxidant properties, including total antioxidant activity, reducing power, inhibition of linoleic acid peroxidation, free radical scavenging, metal chelating, and hydrogen peroxide scavenging activity. Antioxidant activities of oxime compounds compared with standard antioxidants BHA, BHT, TBHQ, and Trolox commonly used by the food and pharmaceutical industry.

The general structure and the substitution pattern of the novel oximes are depicted in Table 1. The installation of active substituents in oxime moiety exhibits a preponderant role in the enhancement of the antioxidant activity.

Experimental

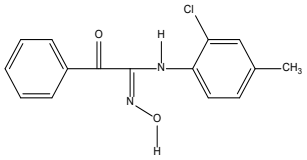
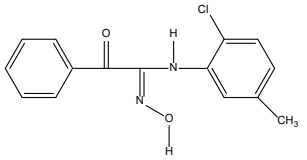
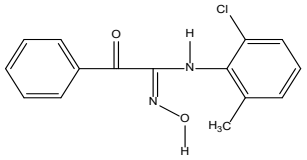
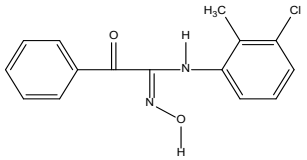
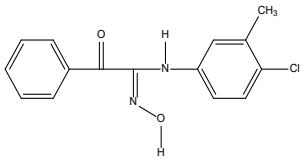
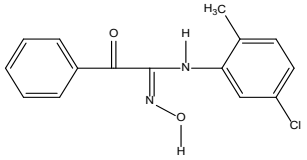
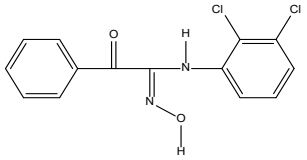
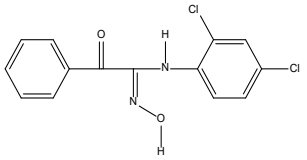
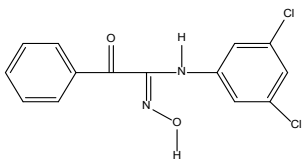
All starting materials were commercially available and were reagent grade. The ^{1}H NMR spectra were recorded on a Bruker 500 MHz NMR spectrometer, using deuterated chloroform as a solvent. IR spectra (4000–400 cm^{-1}) were recorded on a Bruker FT-IR spectrophotometer with a sample prepared as KBr pellets. To utilize antioxidant activities were done using Thermo Scientific Evolution Array UV-Vis spectrometer in ethanol solution.

Synthesis of the compounds

Compounds were prepared from the reaction of ω-chloro isonitroso acetophenone (ω)[19] with the corresponding amines by using previously reported methods.[7,9,20-25] A solution of 0.01 mol aniline derivatives (1.42 g 2-chloro-4-methylaniline for C1,1.42 g 2-chloro-5-methylaniline for C2, 1.42 g 2-chloro-6-methylaniline for C3, 1.42 g 3-chloro-2-methylaniline for C4, 1.42 g 4-chloro-3-methylaniline for C5, 1.42 g 5-chloro-2-methylaniline for C6, 1.62 g 2,3-dichloroaniline for C7, 1.62 g 2,4-dichloroaniline for C8, 1.62 g 3,5-dichloroaniline for C9 was dissolved in EtOH (10ml), then the solution was added dropwise to a solution of ω-chloro isonitroso acetophenone (0.03mol, 5.5g) in ETOH (10ml), and then solid $NaHCO_3$ (0.01mol, 0.84g) was added to the mixture. After 1 h, H_2O (10ml) was added dropwise to the mixture. The precipitated product was filtered, washed with water and then recrystallised from EtOH.

The IUPAC name, structures, yields, and melting point of the compounds are tabulated in Table 1.

Table 1 Structures of the oxime derivatives prepared in this work

Code	Compounds	Structure	Yield (%)	m.p. (°C)
1	N-Hydroxy-N'-(2-chloro-4-methylphenyl)-2-oxo-2-phenylacetamidine		20	125
2	N-Hydroxy-N'-(2-chloro-5-methylphenyl)-2-oxo-2-phenylacetamidine		58	112
3	N-Hydroxy-N'-(2-chloro-6-methylphenyl) -2-oxo-2-phenylacetamidine		25	78
4	N-Hydroxy-N'-(3-chloro-2-methylphenyl)-2-oxo-2-phenylacetamidine		20	172
5	N-Hydroxy-N'-(4-chloro-3-methylphenyl)-2-oxo-2-phenylacetamidine		53	139
6	N-Hydroxy-N'-(5-chloro-2-methylphenyl)-2-oxo-2-phenylacetamidine		42	148
7	N-Hydroxy-N'- (2,3-dichlorophenyl)-2-oxo-2-phenylacetamidine		42	170
8	N-Hydroxy-N'-(2,4-dichlorophenyl)-2-oxo-2-phenylacetamidine		68	84
9	N-Hydroxy-N'-(3-5-dichlorophenyl)-2-oxo-2-phenylacetamidine		72	164

X-ray crystallography

The crystal data were collected by using Mo Kα, λ=0.71073 Å radiation on a Bruker Smart Apex II diffractometer. On the diffractometer, Bruker APEX2 v2014.9-0[26] and Bruker SAINT v8.34A software programs were used; for data collection and data reduction, respectively.[27] Using OLEX2,[28] the structure was solved

with the Superflip[29] structure solution program using Charge Flipping Methods and all non-hydrogen atoms were refined anisotropically by full-matrix least-squares methods refined with the SHELXL[30] refinement package using Least Squares minimization. The hydrogen atoms were placed in geometrically idealized positions and refined as riding model (except OH proton of oxime group and the N–H protons adjacent to the oxime groups). All interaction in the solid-state was investigated by Platon analyses.[31]

Antioxidant and antiradical activity assays

The compounds were evaluated for their inhibition of nonenzymatic lipid peroxidation, antioxidant and antiradical activities and compared with BHA, BHT, TBHQ and Trolox at different concentrations. The evaluation of the total antioxidant activity,[32,33] reducing power,[34,35] Free radical scavenging activity,[36] metal chelating activity,[37] hydrogen peroxide scavenging activity[38] and inhibition of linoleic acid peroxidation[39] assays were done in 5-100 doses and compared with BHA, BHT, TBHQ and trolox at different concentrations, by lights of the literature methods. All the results are triplicates of mean ± SD.

Results and discussion

For the compounds suitable for X-Ray in single crystals analyses, the crystallographic data, the twisting angles for defined the planes, the selected bond lengths and angles and the hydrogen bond geometries are given in Table 2-5, respectively. The functional oxime group represented by carbon number 8, first nitrogen and the second oxygen atom (C8=N1-O2) is located in the molecule's centre. According to the X-Ray results, the oxime group and the adjacent amine nitrogen atom (N2) forms a plane which were marked as *P* to understand and compare the positions of the groups (Figure 1). The C1 to C6 carbon atoms represents the phenyl ring (R1) adjacent to the carbonyl group. In contrast, the C9 to C14 carbon atoms forms the second phenyl ring (R2) adjacent to the amine group of the molecule. The angles between the planes are given compared in Table 3.

Table 2 Crystal data and structure refinement

Identification code	*C1*	*C4*	*C5*	*C6*	*C7*	*C9*
Empirical formula	$C_{15}H_{13}ClN_2O_2$	$C_{15}H_{13}ClN_2O_2$	$2\times(C_{15}H_{13}ClN_2O_2)$	$C_{15}H_{13}ClN_2O_2$	$C_{14}H_{10}Cl_2N_2O_2$	$C_{14}H_{10}Cl_2N_2O_2$
Formula weight	288.72	288.72	577.45	288.72	309.14	309.14
Temperature/K	296.15	296.15	293(2)	296.15	296.15	296.15
Crystal system	triclinic	monoclinic	monoclinic	triclinic	monoclinic	triclinic
Space group	P-1	C2/c	$P2_1/n$	P-1	C2/c	P-1
a/Å	4.9223(2)	20.3709(8)	10.0345(2)	7.8097(2)	20.1424(7)	8.60120(10)
b/Å	9.3269(3)	14.4755(6)	10.4992(3)	8.4136(2)	14.4388(4)	8.99180(10)
c/Å	15.6760(4)	10.3947(5)	27.3026(6)	11.9910(3)	10.3241(3)	9.66030(10)
α/°	82.1470(10)	90.00	90.00	92.6740(10)	90.00	74.4730(10)
β/°	88.5200(10)	107.216(2)	96.0060(10)	90.7470(10)	106.0350(10)	83.0710(10)
γ/°	85.3720(10)	90.00	90.00	117.4000(10)	90.00	78.5010(10)
Volume/Å³	710.53(4)	2927.8(2)	2860.65(12)	698.22(3)	2885.76(15)	703.622(13)
Z	2	8	4	2	8	2
ρ_{calc}**g/cm³**	1.350	1.310	1.341	1.373	1.423	1.459
μ/mm⁻¹	0.271	0.263	0.269	0.276	0.451	0.463
F(000)	300.0	1200.0	1200.0	300.0	1264.0	316.0
Crystal size/mm³	0.45 × 0.23 × 0.13	0.32 × 0.29 × 0.18	0.45 × 0.45 × 0.37	0.45 × 0.37 × 0.15	0.45 × 0.33 × 0.24	0.29 × 0.28 × 0.14
Radiation	MoKα (λ = 0.71073)					
2Θ range /°	2.62 to 66.2	3.5 to 66.7	3 to 63.98	3.4 to 66.76	3.52 to 63.74	4.78 to 66.06
Index ranges	-7 ≤ h ≤ 7 -14 ≤ k ≤ 13 -23 ≤ l ≤ 23	-31 ≤ h ≤ 31 -22 ≤ k ≤ 21 -16 ≤ l ≤ 14	-14 ≤ h ≤ 14 -15 ≤ k ≤ 15 -40 ≤ l ≤ 38	-12 ≤ h ≤ 10 -12 ≤ k ≤ 13 -18 ≤ l ≤ 18	-29 ≤ h ≤ 19 -21 ≤ k ≤ 20 -15 ≤ l ≤ 14	-13 ≤ h ≤ 13 -13 ≤ k ≤ 13 -14 ≤ l ≤ 14
Reflections collected	20280	22777	37479	19447	19129	20172
Independent reflections	5349 [R_{int} = 0.0212 R_{sigma} = 0.0182]	5671 [R_{int} = 0.0181 R_{sigma} = 0.0162]	9805 [R_{int} = 0.0213 R_{sigma} = 0.0229]	5344 [R_{int} = 0.0167 R_{sigma} = 0.0161]	4922 [R_{int} = 0.0151 R_{sigma} = 0.0119]	5268 [R_{int} = 0.0221 R_{sigma} = 0.0186]
Data/restraints/ parameters	5349/0/184	5671/0/187	9805/0/367	5344/0/184	4922/0/186	5268/0/183
Goodness-of-fit on F^2	1.031	1.033	1.036	1.030	1.051	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0458 wR_2 = 0.1306	R_1 = 0.0507 wR_2 = 0.1384	R_1 = 0.0723 wR_2 = 0.1944	R_1 = 0.0434 wR_2 = 0.1163	R_1 = 0.0437 wR_2 = 0.1191	R_1 = 0.0446 wR_2 = 0.1230

Citation: Özen T, Bal A, Topcu S, et al. Synthesis, characterization and antioxidant activities of some novel oxime derivatives. *Pharm Pharmacol Int J.* 2021;9(5):176–192. DOI: 10.15406/ppij.2021.09.00343

Table Continued...

Identification code	*C1*	*C4*	*C5*	*C6*	*C7*	*C9*
Final R indexes [all data]	R_1 = 0.0647 wR_2 = 0.1474	R_1 = 0.0700 wR_2 = 0.1555	R_1 = 0.0984 wR_2 = 0.2142	R_1 = 0.0576 wR_2 = 0.1286	R_1 = 0.0539, wR_2 = 0.1286	R_1 = 0.0618 wR_2 = 0.1359
Largest diff. peak/ hole / e Å^{-3}	0.35/-0.27	0.29/-0.40	0.78/-0.32	0.43/-0.21	0.51/-0.45	0.59/-0.60

Table 3 The twisting angles between the oxime plane and phenyl ring planes

Compound	Twisting angles					
	R1-P	**R2-*P***	**R1-R2**	**C=O-R1**	**C=O-*P***	**C=O-R2**
C1	60.13(10)	36.56(9)	71.96(7)	9.79(9)	49.32(11)	50.30(9)
C4	63.36(9)	37.18(7)	89.53(8)	25.08(10)	37.10(9)	44.46(9)
C5	55.51(14)	46.49(12)	80.52(12)	11.32(18)	44.09(17)	45.37(16)
	58.97(13)*	44.49(11)*	71.67(12)*	7.72(13)	49.93(13)	45.40(11)
C6	59.69(8)	39.45(8)	83.27(7)	14.92(9)	44.42(10)	54.97(9)
C7	60.91(10)	34.66(9)	86.26(9)	23.42(11)	36.36(10)	45.40(10)
C9	63.10(10)	43.77(8)	86.63(9)	16.78(11)	46.32(10)	46.52(9)

(standard deviation for lengths and angles are given in parentheses)

Table 4 Selected bond lengths and angles

Comp.	*C1*	*C4*	*C5*	*C6*	*C7*	*C9*
Bond Atoms	**Bond Length/Å**					
O2-N1	1.4152(14)	1.4056(12)	1.4143(19) 1.4106(18)*	1.4134(11)	1.4050(14)	1.3994(13)
O1-C7	1.2101(15)	1.2131(14)	1.211(2) 1.214(2)*	1.2116(13)	1.2086(16)	1.2172(16)
N2-C8	1.3586(15)	1.3569(13)	1.355(2) 1.353(2)*	1.3554(12)	1.3571(16)	1.3687(15)
N2-C9	1.4048(14)	1.4062(13)	1.405(2) 1.407(2)*	1.4129(12)	1.3970(15)	1.3991(16)
N1-C8	1.2872(14)	1.2896(13)	1.287(2) 1.287(2)*	1.2921(12)	1.2872(15)	1.2859(15)
C7-C6	1.4779(17)	1.4810(17)	1.472(3) 1.479(2)*	1.4790(15)	1.483(2)	1.4744(17)
C8-C7	1.5167(16)	1.5052(15)	1.510(2) 1.513(2)*	1.5169(14)	1.5054(18)	1.5107(16)
N2-H2	0.8172(10)	0.8601(9)	0.9060(14) 0.8391(14)*	0.8200(9)	0.8405(11)	0.8003(10)
Cl1-Cx	1.7364(13)	1.7447(12)	1.7392(19) 1.7405(19)*	1.7409(13)	1.7212(14)	1.7351(13)
Cl2-Cy	-	-	-	-	1.7266(15)	1.7364(15)

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Table Continued...

Comp.	*C1*	*C4*	*C5*	*C6*	*C7*	*C9*
Bond Angle/°						
C10-C9-N2	119.73(11)	121.72(10)	118.39(16) 121.43(16)*	117.44(10)	117.39(11)	119.31(12)
C6-C7-C8	120.10(10)	118.23(9)	120.51(15) 120.36(15)*	117.96(9)	118.52(11)	119.62(10)
C8-N2-C9	126.48(10)	128.37(9)	126.56(14) 124.89(14)*	127.26(9)	128.79(11)	123.60(10)
C8-N1-O2	110.61(9)	110.80(9)	110.25(14) 111.13(13)*	110.98(8)	111.02(10)	111.54(10)
N1-C8-N2	123.76(11)	122.70(10)	124.14(15) 125.32(14)*	124.08(9)	122.30(12)	124.90(11)
N1-C8-C7	114.39(10)	112.94(9)	115.09(15) 114.15(14)*	113.52(8)	113.31(11)	113.52(10)
N2-C8-C7	120.92(9)	122.96(9)	119.63(15) 119.65(14)*	121.69(8)	122.88(11)	120.22(10)
O1-C7-C8	117.34(11)	118.68(11)	116.71(17) 116.33(15)*	118.72(10)	118.46(13)	117.06(11)
O1-C7-C6	122.54(11)	122.88(11)	122.73(17) 123.30(15)*	123.27(10)	122.84(13)	123.23(11)

(standard deviation for lengths and angles are given in parentheses)

*The asymmetric unit for C5 contains two molecules in the crystal form have different bond lengths and angles

Table 5 The hydrogen bond and interaction geometries

C1						
Donor	**Hydrogen**	**Acceptor**	**Bond length/Å**			**Angle/°**
D	**H**	**A**	**d(D-H)**	**d(H-A)**	**d(D-A)**	**D-H-A**
O2	H2	N1[1]	0.84	2.00	2.7786(14)	155.30(7)
C10	Cl1	R2[2]		3.5481(7)	4.0691(16)	94.44(5)
C7	O1	R1[2]		3.9582(12)	4.1818(16)	92.13(8)
[1]-X,1-Y,1-Z, -[2]1+X,Y,Z						
C4						
D	**H**	**A**	**d(D-H)**	**d(H-A)**	**d(D-A)**	**D-H-A**
O2	H2	N1[1]	0.85(2)	1.97(2)	2.7429(13)	150.8(19)
C2	H2A	R2[2]		2.93	3.699(2)	141
C15	H15A	R2[3]		2.85	3.7608(18)	159
[1]1-X,2-Y,1-Z, [2]1/2-X,1/2+Y,1/2-Z, [3]-X,Y,1/2-Z						

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C5

D	H	A	d(D-H)	d(H-A)	d(D-A)	D-H-A
O2	H2	N1A[1]	0.8675(14)	1.9405(15)	2.758(2)	156.54(10)
*O2A	H2B	N1[2]	0.8078(14)	2.0480(16)	2.802(2)	155.12(10)
R2		R2[3]			3.7269(11)	
*R2		*R2[4]			3.7700(11)	

[1]-1/2+X,1/2-Y,-1/2+Z; [2]1/2+X,1/2-Y,1/2+Z, [3]1-X,1-Y,-Z, [4]2-X,2-Y,-Z

C6

D	H	A	d(D-H)	d(H-A)	d(D-A)	D-H-A
O2	H2	N1[1]	0.80	2.04	2.7846(11)	154.83(6)
C15	H15A	R1		3.00	3.7799(16)	140
R2		R2[2]			3.8686(9)	0
R2		R2[3]			3.9546(9)	0

[1]-X,1-Y,1-Z, [2]-X,1-Y,-Z, [3]1-X,1-Y,-Z

C7

D	H	A	d(D-H)	d(H-A)	d(D-A)	D-H-A
O2	H2	N1[1]	0.82(2)	2.00(2)	2.7433(15)	150(2)
C2	H2A	R2[2]		2.99	3.721(3)	137
C10	Cl1	R2[3]		3.6464(9)	4.1206(16)	93.29(5)

[1]-X,1-Y,-Z, [2]1/2-X,1/2+Y,1/2-Z, [3]-X,Y,1/2-Z

C9

D	H	A	d(D-H)	d(H-A)	d(D-A)	D-H-A
O2	H2	N1[1]	0.86	2.0328(10)	2.8116(14)	150.31(7)
R2		R2[2]			3.7004(9)	0

[1]2-X,2-Y,-Z, [2]1-X,1-Y,2-Z

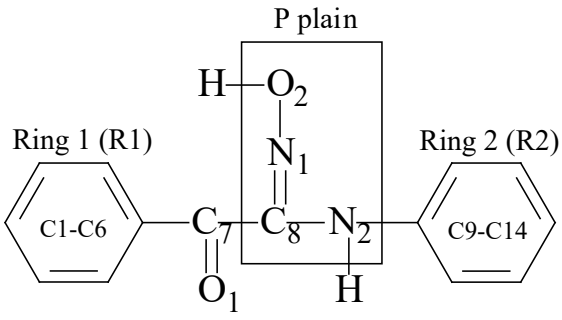

Figure 1 Reference P plain and phenyl groups rotating along the bond axis (R1 and R2).

Maximum deviation from the planes *P* was detected for compound ***C1*** (Table 3). These results indicated both phenyl rings and carbonyl group were twisted around the reference plane. The twisting was found on substituted phenyl rings (*R2*). The bond lengths and angels for all compounds (Table 4) were in good accord with literature analogs.[7,9,20-25]

The crystal structures of the crystallized compounds are given in Figure 2. The three crystals, which are ***C1***, ***C6*** and ***C9***, crystallized in triclinic space group P-1. The remaining three crystals, which are ***C4***, ***C5*** and ***C7*** crystallized in the monoclinic system and the space groups were found as C2/c, P21/n and C2/c, respectively.

No intra-molecular interactions were detected for the compounds in the solid-state. For all compounds, the oxime hydrogens (H2) formed intermolecular hydrogen bonds with the oxime nitrogen atoms (Figure 3, Table 5). In addition to the hydrogen bonds, the inter-molecular interactions were explained and shown in Figures 3-8.

The chlorine (Cl1) and carbonyl oxygen (O2) atoms of compound ***C1*** formed π interactions with the *R2* and *R1* phenyl rings, respectively (Figure 3, Table 5).

Citation: Özen T, Bal A, Topcu S, et al. Synthesis, characterization and antioxidant activities of some novel oxime derivatives. *Pharm Pharmacol Int J.* 2021;9(5):176–192. DOI: 10.15406/ppij.2021.09.00343

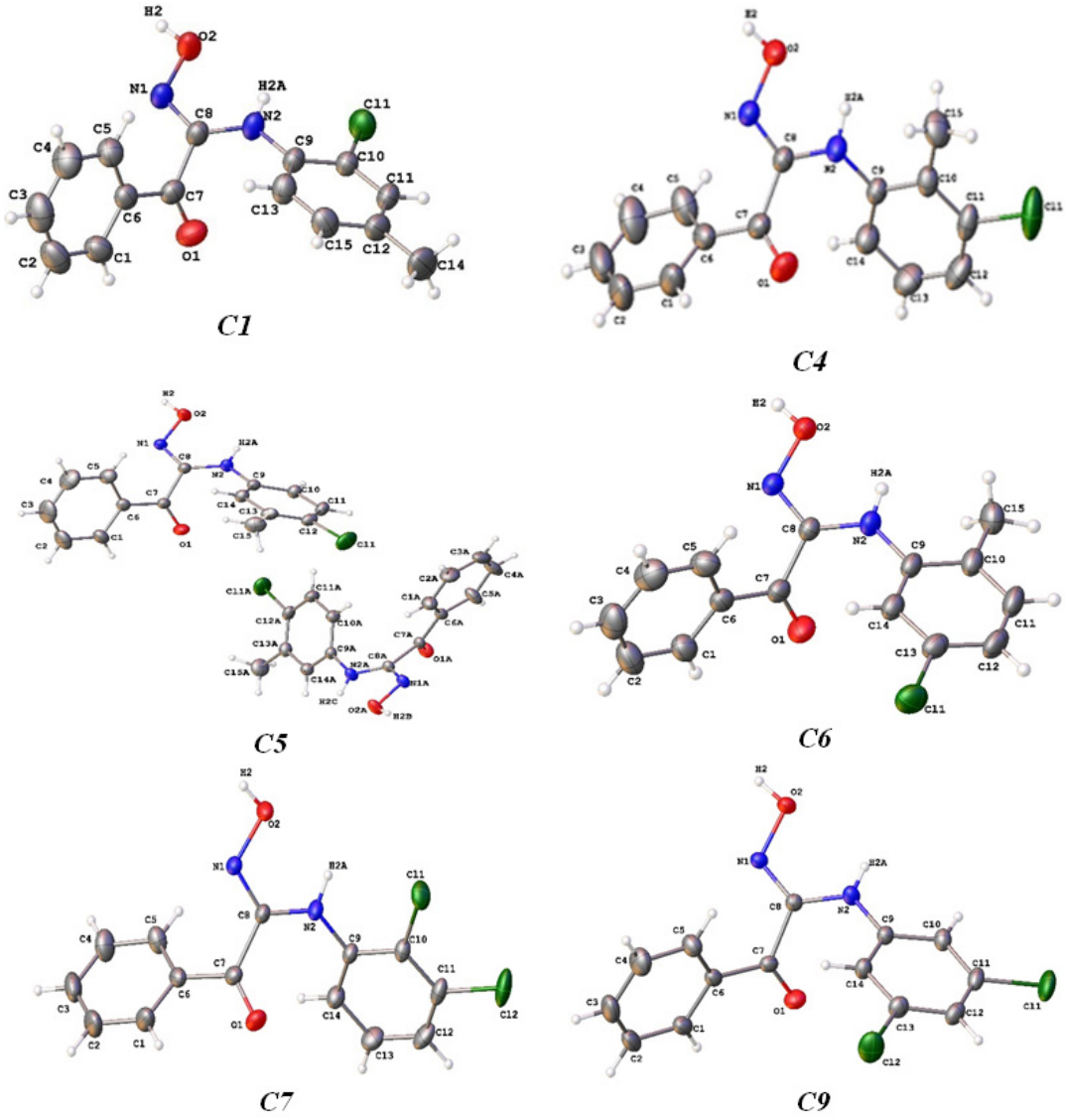

Figure 2 The structures of the crystallized oxime compounds.

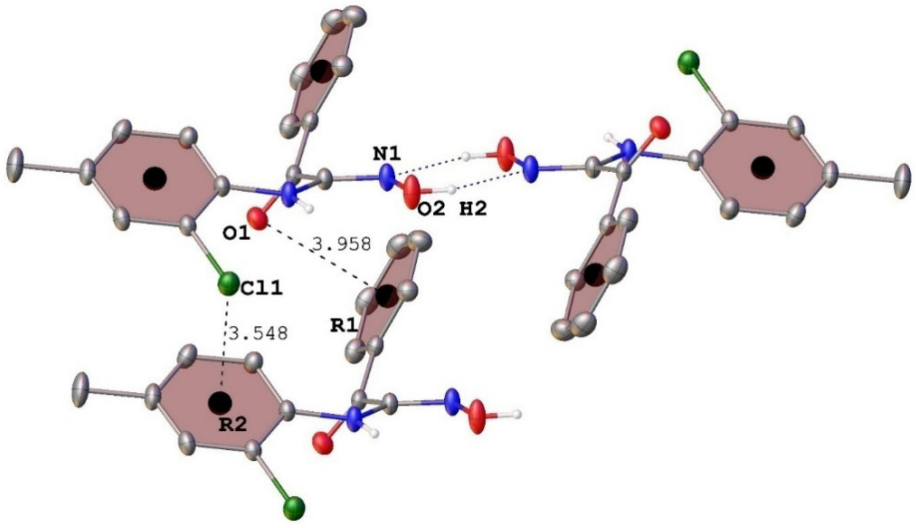

Figure 3 Interactions for compound ***C1***.

Citation: Özen T, Bal A, Topcu S, et al. Synthesis, characterization and antioxidant activities of some novel oxime derivatives. *Pharm Pharmacol Int J.* 2021;9(5):176–192. DOI: 10.15406/ppij.2021.09.00343

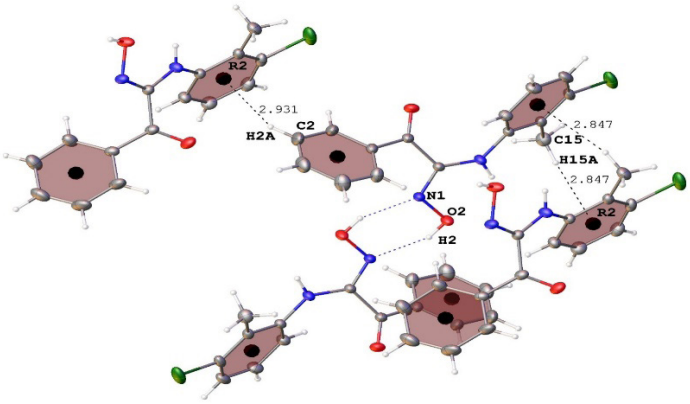

Figure 4 Interactions for compound ***C4***.

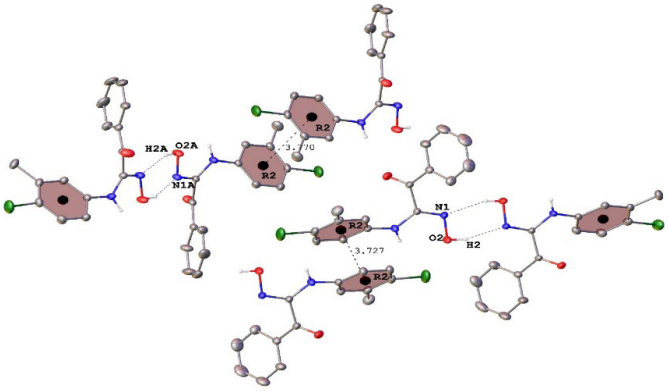

Figure 5 Interactions for compound ***C5***.

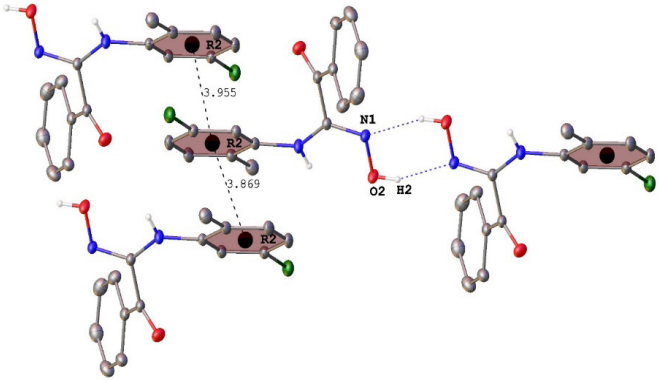

Figure 6 Interactions for compound ***C6***.

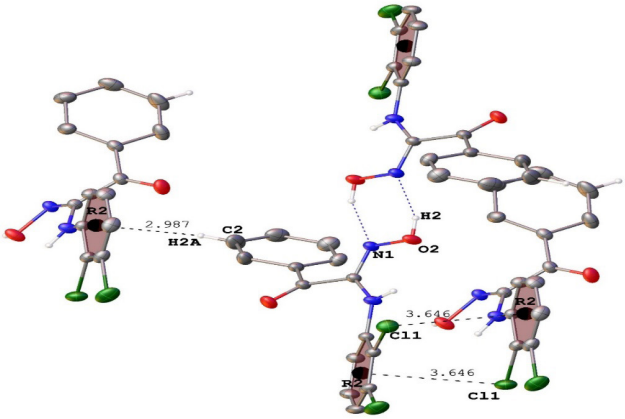

Figure 7 Interactions for compound ***C7***.

Citation: Özen T, Bal A, Topcu S, et al. Synthesis, characterization and antioxidant activities of some novel oxime derivatives. *Pharm Pharmacol Int J.* 2021;9(5):176–192. DOI: 10.15406/ppij.2021.09.00343

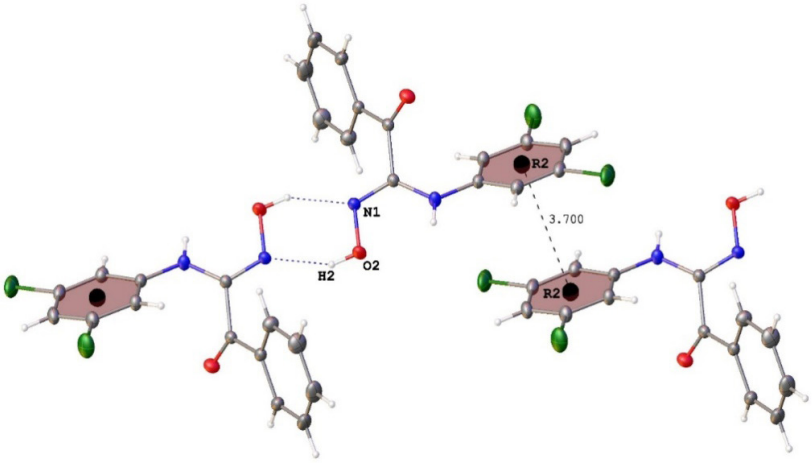

Figure 8 Interactions for compound ***C9***.

The C2 and C15 atoms of compound ***C4*** formed C-H···π interactions with the *R2* phenyl rings at 1/2-X,1/2+Y,1/2-Z and -X,Y,1/2-Z, respectively (Figure 4, Table 5).

The chlorine and methyl-substituted phenyl rings (*R2*) of compound ***C5*** formed π···π interactions with symmetry-related the *R2* phenyl rings at 1-X,1-Y,-Z, 2-X,2-Y,-Z, respectively (Figure 5., Table 5).

The chlorine and methyl-substituted phenyl rings (R2) of compound ***C6*** formed π···π interactions with symmetry-related the R2 phenyl rings at -X,1-Y,-Z, 1-X,1-Y,-Z, respectively (Figure 6., Table 5).

The Cl1 atom of compound ***C7*** formed π interactions with the *R2* phenyl ring. The C2 atom of the compound also formed C-H···π interactions with the *R2* phenyl ring at 1/2-X,1/2+Y,1/2-Z, via its H2A atom (Figure 7., Table 5).

The substituted phenyl rings (*R2*) of compound ***C9*** formed π···π interactions with symmetry-related the *R2* phenyl rings at 1-X,1-Y,2-Z (Figure 8., Table 5).

^{1}H NMR spectra of the compounds

A representative H-NMR spectrum of C8 is shown in Figure 9. In the ^{1}H NMR spectral data of the compounds given in Table 6, the OH proton of the oxime group and the N–H protons were seen very close to each other. While the peaks for the OH proton of oxime groups are observed at 8.05–8.02 ppm, the N–H protons adjacent to the oxime groups resonate at 8.00–8.18 ppm. The aromatic C–H protons resonate at 7.84–6.02 ppm while aliphatic C–H protons at 2.27–2.02 ppm. These results are in good agreement with those of known oximes[24,25,40-43] and coincide with handled structures by the single crystal data.[21-23,44-48]

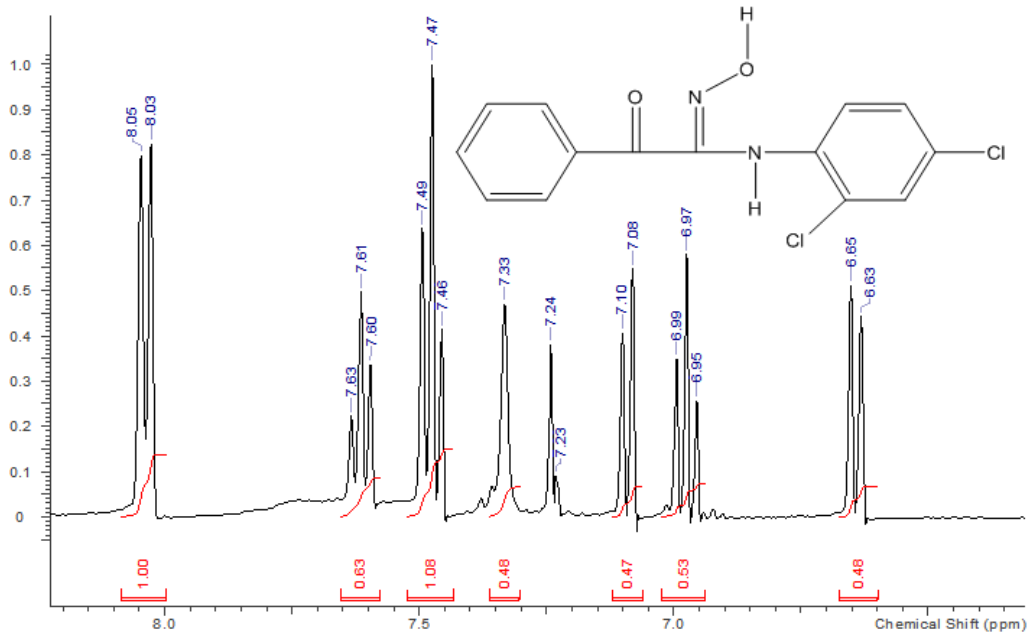

Figure 9 ^{1}H NMR spectral data of compound ***C8***.

Citation: Özen T, Bal A, Topcu S, et al. Synthesis, characterization and antioxidant activities of some novel oxime derivatives. *Pharm Pharmacol Int J.* 2021;9(5):176–192. DOI: 10.15406/ppij.2021.09.00343

Table 6 ^{1}H NMR spectra of the compounds in $CDCl_3$

Comp.	OH	NH	Aromatic						CH_3
C1	8.03	8.01	7.61	7.47	7.11	7.01	6.72	6.57	2.23
C2	8.02	8	7.59	7.45	7.07	6.91	6.83	6.68	2.37
C3	8.2	8.18	7.84	7.67	7.56	7.54	7.47	6.02	2.02
C4	8.02	8	7.59	7.46	7.06	6.94	6.78	6.73	2.27
C5	8.03	8	7.59	7.45	7.13	6.85	6.7	6.67	2.22
C6	8.02	8	7.58	7.45	7.18	7.18	6.72	6.6	2.14
C7	8.02	8	7.61	7.46	7.33	7.23	7.02	6.7	-
C8	8.05	8.03	7.61	7.47	7.33	7.1	6.97	6.65	-
C9	8.05	8.03	7.63	7.49	7.08	6.98	6.71	-	-

In the IR spectra of the compounds, bands at 3319-3392, 3123-3248, 1662-1682, 1603-1658, 1327-1385 and 950-999 cm^{-1} belong to N–H, O–H, C=O, C=N, –C–N– and N–O vibrations, respectively. These values are in accord with those of previously reported analogs of the compounds.[24,25] The IR spectra data of compounds are given in Table 7.

Table 7 The some IR spectra data of compounds

Comp.	N-H	O-H	C=O	C=N	-C-N-	N-O
ω	-	3277	1659		-	1036
C1	3392	3234	1678	1636	1374	950
C2	3385	3227	1682	1634	1379	964
C3	3319	3150s	1667	1613	1327	999
C4	3378	3180	1681	1603	1379	964
C5	3328	3153	1668	1622s	1367	969
C6	3380	3203	1680	1634	1376	956
C7	3358	3183	1679	1611	1371	969
C8	3345	3123	1672	1636	1385	953
C9	3367	3248	1662	1658s	1356	990

Total antioxidant activity

Total antioxidant activity assay is based on the reduction of phosphate-Mo (VI) to phosphate Mo (V) by the oximes and subsequent formation of a green-colored phosphate/Mo (V) complex and compared with those of BHA, TBHQ, BHT, and Trolox at 5-100μM as positive controls. This method is routinely applied in the samples to evaluate the total antioxidant capacity.[33,49] Generally, a strong electron-withdrawing substituent in the phenyl ring increase antioxidant activity.[9,50] The antioxidant capacities of the oximes were determined for 5-100μM concentrations and shown in Figure 10. The results showed that different substituents and concentrations affected the total antioxidant activities of newly synthesized oximes. The increasing of the chlorine and methyl groups to oxime benzene caused the exposure to show differences in antioxidant activities. The p-position of -methyl and -chlorine attached to the benzene ring exhibited the best total antioxidant activity in the ***C6*** and ***C2*** compounds. Compound ***C6*** exhibited better reduction from Mo(VI) to Mo(V) than standards due to the presence of -5 chloro and -2 methyl groups. Compounds ***C2*** and ***C4*** showed high activity according to BHA at 100 μM. The increase in the concentration of compounds and standards exhibited a significant increase in the antioxidant activities ($p < 0.05$). The trend observed in absorbance values at 695 nm were ***C6*** > TBHQ > trolox > BHT > ***C2*** > ***C4*** > BHA > ***C5*** > ***C9*** > ***C8*** > ***C7*** > ***C1*** >***C3*** at 100 μM.

Reducing power

The Fe^{3+} is the relatively biological inactive form of iron and reduced to the active Fe^{2+}.[51] Fe^{2+} can be oxidized back to Fenton Reaction with a production of ˙OH or Haber–Weiss Reaction with O_2^{-}. The presence of reductants causes the reduction of the Fe^{3+}-ferricyanide complex to the Fe^{2+} recorded by measuring Perl's Prussian blue at 700 nm.[52] The reducing power abilities of oximes were measured at concentrations (5-100 μM)[35] and compared standards (BHA, BHT, TBHQ, trolox). An increase in absorbance of the reaction mixture may indicate an increase in the reducing capacity due to an increase in the formation of the complex, $Fe_4[Fe(CN^{-})_6]_3$. The reducing power exerts antioxidant action by donating of a hydrogen atom to break the free radical chain.[53] All synthesized compounds and standards are depicted in Figure 11. The reducing power capacities were not significantly dose-dependent in the test. As shown in Table 2, compounds ***C5***, ***C6***, ***C8*** and ***C1*** have the most powerful ferric ion (Fe^{3+}) reducing power. The reducing power capacity of oxime compounds were in the following order: ***C5*** > ***C6*** > ***C8*** > ***C1*** > BHA > ***C4*** > BHT > ***C9*** > ***C2*** > ***C7*** > trolox > TBHQ > ***C3*** at higher concentration and showed moderate reducing power activity.

As can be seen in Figure 2, compound 5j and 5k has the most powerful ferric ion (Fe3þ) reducing capability.

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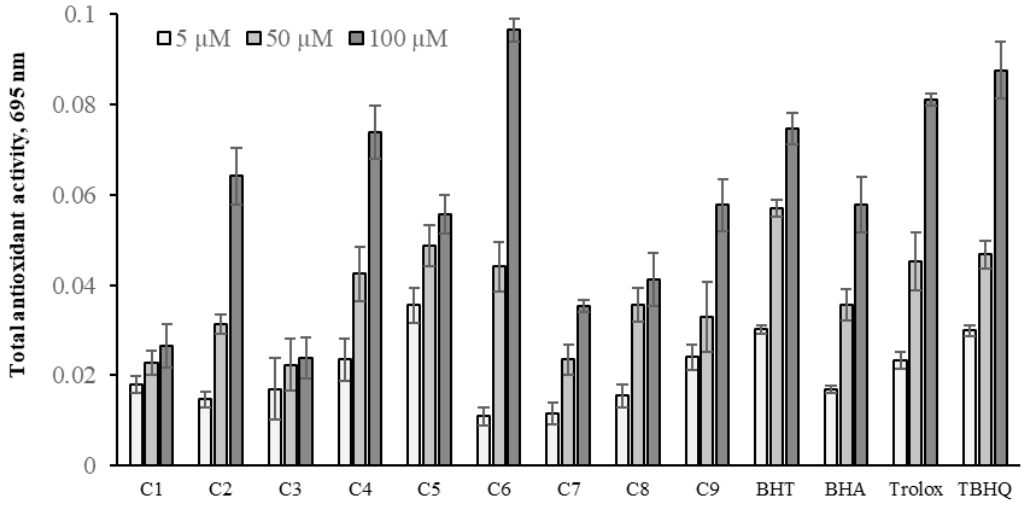

Figure 10 Total antioxidant activity of the oxime derivatives and standards at 5, 50 and 100µM. Where-corresponds to significant activity, p<0.05. Each value represents means±SD (*n*=3).

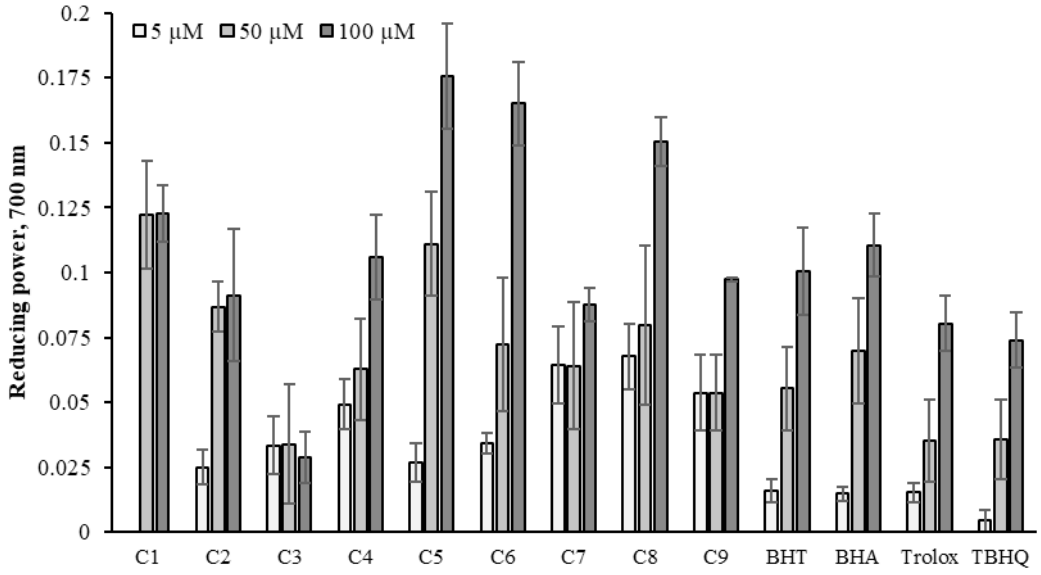

Figure 11 Reducing power of the oxime derivatives and standards at 5, 50 and 100µM. Where-corresponds to significant capacity, p<0.05. Each value represents means ± SD (*n* = 3).

Free radical scavenging activity

The DPPH free radical (DPPH˙) is a stable and well-known radical used in medicine, food, and health scientific research. DPPH˙ scavenging activity determination method is cheap, simple, and, fast and therefore, it is used to analyze of many synthetic and natural products. The free radical scavenging test determined the antiradical activities of the compounds. The action of antioxidant molecules causes this brilliant color. The antioxidant molecules convert the DPPH˙ to DPPH-H by transferring hydrogen source or electron. The active pink colored DPPH˙ will be removed with a light yellow color conversion and is measured at 517nm.[54] The novel compounds exhibited lower free radical scavenging activity than standards (Figure 12). Based on the observed results, ***C5*** compound exhibited a powerful free radical scavenger due to electron donor substituents (C5: 59.11%). ***C1***, ***C6*** and ***C2*** compounds have better free radical scavenging activity than BHT (56.14, 55.48 and 55.07 %, respectively). The effects of -methoxy and –hydroxyl groups on the phenyl ring of oximes in ascending order were found to be: trolox > TBHQ > BHA > ***C5*** > BHT > ***C1*** > ***C6*** > ***C2*** > ***C7*** > ***C4*** > ***C8*** > ***C9*** > ***C3*** at higher concentration, significantly ($p< 0.05$).

Metal chelating activity

Transition metals (iron, vanadium, nickel, copper, cobalt, chromium, arsenic, cadmium) play an important role in the decomposition reaction of H_2O_2 and lead to the formation of $O_2^{\cdot-}$ and ˙OH.[55] These free radicals may accelerate protein damage, lipid peroxidation, and DNA damage. Additionally, active transition metals transfer a single electron in oxidation reactions. Some antioxidant compounds inhibit oxidation by Fe^{2+} chelating activity, reduce redox potential and stabilize metal oxide. Chelating new agents are effective as synthetic antioxidants due to inhibiting the transition metal-dependent and process stabilizing the oxidized form of the active metal ion.[34,56] Chelating activities of oxime derivatives were compared to four chelating standards as BHT, BHA, TBHQ and trolox (Figure 13).

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The concentration of compounds and standards exhibited a significant increase in the metal chelating activities ($p<0.05$). ***C2*** exhibited higher metal-chelating activity than novel oximes and standards at 100µM. The increasing order of the metal chelating activity of the samples displayed in the following order of ***C2*** > BHT > ***C3*** > TBHQ > ***C4*** > ***C7*** > BHA > ***C9*** > trolox > ***C1*** > ***C6*** > ***C8*** > ***C5*** that were 24.45, 23.18, 20.95, 19.65, 18.99, 18.22, 16.24, 14.60, 12.05, 11.38, 11.34, 6.09, 4.96%, at 100µM, respectively.

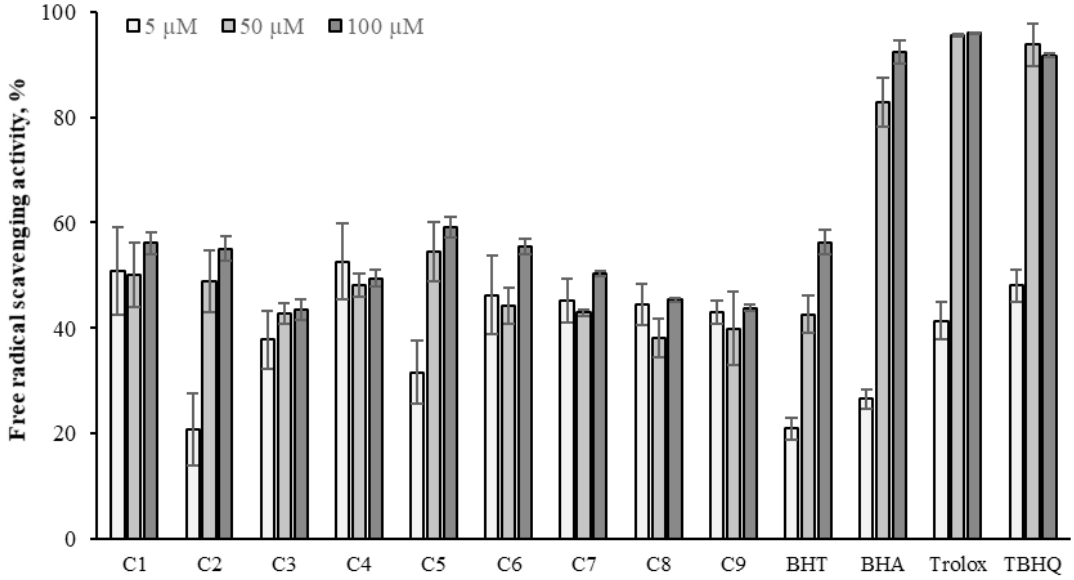

Figure 12 Free radical scavenging activity of the oximes derivatives and standards at 5, 50 and 100µM. Where-corresponds to significant activity, $p<0.05$. Each value represents means ± SD (n = 3).

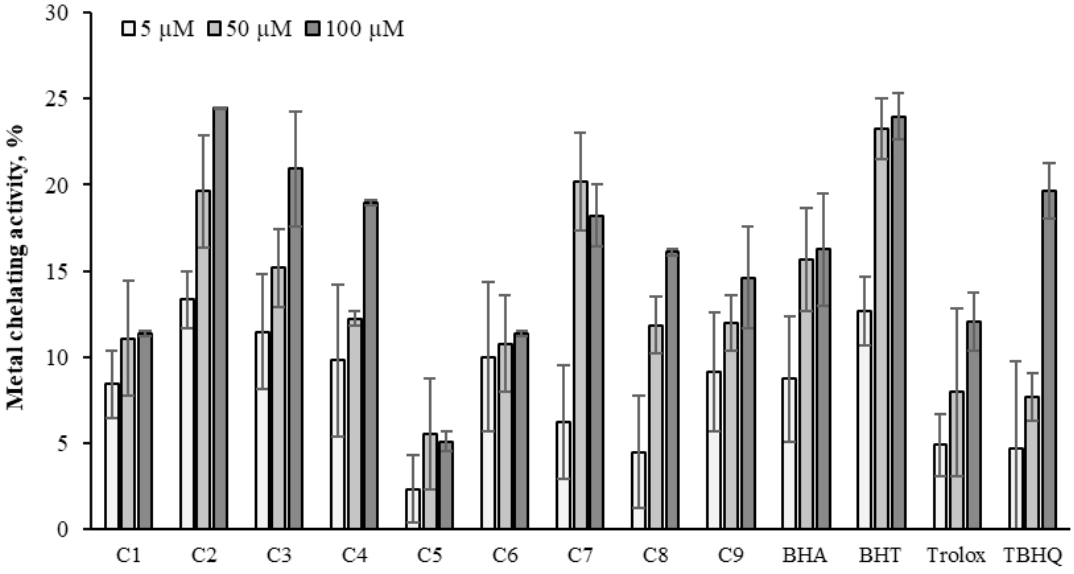

Figure 13 Metal chelating activity of the oximes derivatives and standards at 5, 50 and 100µM. Where-corresponds to significant activity, $p<0.05$. Each value represents means ± SD (n = 3).

Hydrogen peroxide scavenging activity

H_2O_2 forms in vivo by antioxidant enzymes in biological systems and indicates a precursor to producing the ·OH. The ·OH can cause tissue damage and react with most bimolecular cell death and cross cell membrane.[57] Thus, the scavenge of ·OH is crucial for the elimination of cells. Therefore, we investigated the hydrogen peroxide scavenging activity of the newly synthesized derivatives compared with standards (BHA, TBHQ, BHT and trolox) at the same dose (Figure 14). The hydrogen peroxide scavenging activities of the compounds and standards are strongly dependent on the concentration ($p<0.05$). ***C2*** and ***C5*** exhibited effective H_2O_2 scavenging activity higher than standards at the same dose. The scavenging activity values of H_2O_2 were as follows: ***C2*** > ***C5*** = TBHQ > ***C6*** > ***C8*** > ***C4*** > BHT > ***C9*** > ***C3*** > ***C1*** > Trolox > ***C7*** > BHA which were 64.81, 57.41, 57.41, 45.56, 42.59, 33.15, 31.48, 29.81, 26.85, 25.56, 24.07, 16.48 and 14.81% at 100 µM, respectively.

Citation: Özen T, Bal A, Topcu S, et al. Synthesis, characterization and antioxidant activities of some novel oxime derivatives. *Pharm Pharmacol Int J.* 2021;9(5):176–192. DOI: 10.15406/ppij.2021.09.00343

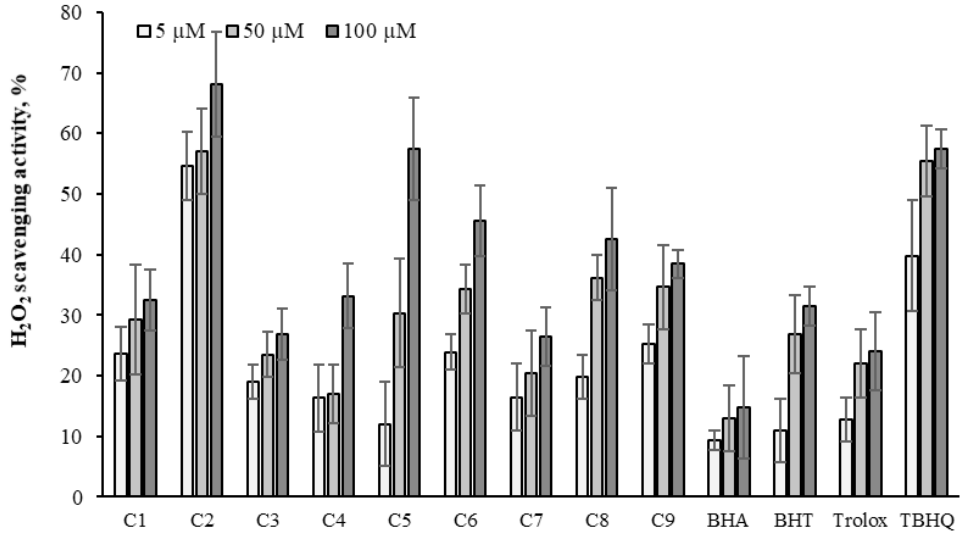

Figure 14 H_2O_2 scavenging activity of the oximes derivatives and standards at 5, 50 and 100µM. Where-corresponds to significant activity, $p<0.05$. Each value represents means ± SD (n = 3).

Inhibition of linoleic peroxidation assay

Several chemical and physical phenomena can initiate oxidation, which proceeds continuously in a suitable substrate(s) until a blocking defense mechanism occurs. Target substances include oxygen, polyunsaturated fatty acids, phospholipids, cholesterol, and DNA.[58] Lipids and lipid-containing materials are tending to peroxidation during processing and storage. Lipid peroxidation, a complex free radical chain process, involves an array of radicals and is measured by the amount of peroxide and the primary lipid oxidation product produced during the initial stages of oxidation.[59] The oxime derivatives tested the nonenzymatic linoleic peroxidation at 5-100µM. Oxime derivatives dose-dependently inhibited the linoleic peroxidation induced by Fe^{2+}. The activity extent of oximes and standards was in the comparable level at 5-100µM concentration and exhibited a significant increase in the inhibition of linoleic peroxidation ($p<0.05$) (Figure 15). ***C3*** (88.34%), ***C9*** (85.70%) and ***C6*** (74.93%) had the higher linoleic acid peroxidation inhibition activity at 100 µM than trolox and the results were found in order of TBHQ > ***C3*** > ***C9*** > ***C6*** > trolox > ***C8*** > BHA > BHT > ***C4*** > ***C7*** > ***C1*** > ***C5*** > ***C2***. Also, ***C3***, ***C9*** and ***C6*** compounds can inhibit free radical-induced chain reactions and biological damage-causing lipid peroxidation.

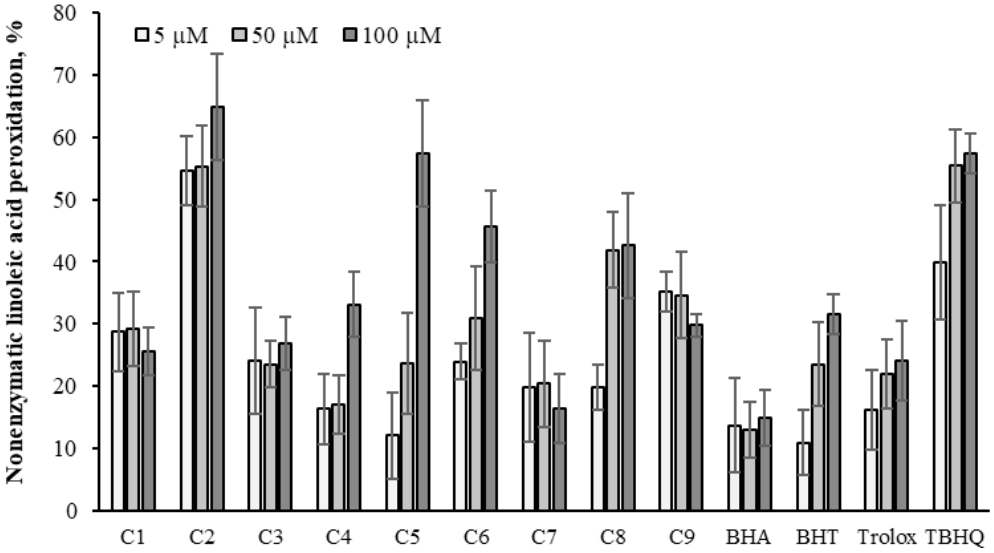

Figure 15 Nonenzymatic linoleic acid peroxidation level of the oximes derivatives and standards at 5, 50 and 100µM. Where-corresponds to significant activity, $p<0.05$. Each value represents means ± SD (n = 3).

Statistical analysis

The data were presented as the mean ± standard deviation (S.D.). Statistical analysis for antioxidant activities was analyzed using one-way ANOVA followed by Tukey's HSD test with α=0.05. These assessments were conducted using SPSS (20.0) software. All assays were performed in triplicate.

Table 8 Total antioxidant activity and reducing power of the oxime derivatives and standards at 5, 50 and 100μM. Where-corresponds to significant inhibition, p <0.05. Each value represents means ± SD (*n* = 3)

Samples	Antioxidant activity, 695 nm			Reducing Power, 700 nm		
	5μM	50μM	100μM	5μM	50μM	100μM
C1	0.0180±0.0019^{a}	0.0228±0.0027^{a}	0.0264±0.0048^{a}	0.0000±0.0000^{a}	0.1222±0.0207^{b}	0.1229±0.0108^{b}
C2	0.0147±0.0018^{a}	0.0314±0.0021^{b}	0.0742±0.0162^{c}	0.0250±0.0168^{a}	0.0868±0.0096^{b}	0.0913±0.0054^{b}
C3	0.0170±0.0068^{a}	0.0224±0.0059^{a}	0.0239±0.0045^{a}	0.0335±0.0111^{a}	0.0340±0.0229^{a}	0.0289±0.0097^{a}
C4	0.0180±0.0091^{a}	0.0425±0.0060^{b}	0.0738±0.0059^{c}	0.0492±0.0097^{a}	0.0627±0.0195^{a}	0.1060±0.0165^{b}
C5	0.0356±0.0039^{a}	0.0487±0.0045^{b}	0.0556±0.0044^{b}	0.0267±0.0075^{a}	0.1110±0.0210^{b}	0.1757±0.0202^{c}
C6	0.0110±0.0020^{a}	0.0541±0.0149^{b}	0.0965±0.0065^{c}	0.0343±0.0038^{a}	0.0722±0.0258^{a}	0.1650±0.0160^{b}
C7	0.0116±0.0025^{a}	0.0235±0.0034^{b}	0.0353±0.0014^{c}	0.0645±0.0150^{a}	0.0641±0.0246^{a}	0.0876±0.0063^{a}
C8	0.0155±0.0026^{a}	0.0356±0.0037^{b}	0.0413±0.0059^{b}	0.0677±0.0126^{a}	0.0795±0.0307^{a}	0.1505±0.0095^{b}
C9	0.0240±0.0029^{a}	0.0330±0.0078^{a}	0.0544±0.0116^{b}	0.0538±0.0146^{a}	0.0643±0.0304^{a}	0.0974±0.0007^{a}
BHA	0.0169±0.0007^{a}	0.0356±0.0036^{a}	0.0578±0.0062^{c}	0.0148±0.0027^{a}	0.0699±0.0204^{b}	0.1105±0.0120^{c}
BHT	0.0302±0.0010^{a}	0.0569±0.0019^{a}	0.0746±0.0034^{c}	0.0159±0.0044^{a}	0.0553±0.0159^{b}	0.1005±0.0168^{c}
TBHQ	0.0300±0.0012^{a}	0.0467±0.0029^{a}	0.0842±0.0120^{c}	0.0045±0.0042^{a}	0.0357±0.0152^{b}	0.0740±0.0107^{c}
TRX	0.0232±0.0019^{a}	0.0453±0.0063^{a}	0.0810±0.0013^{c}	0.0153±0.0037^{a}	0.0352±0.0160^{a}	0.0803±0.0107^{b}

Note: Different superscripts in the same column express significant differences (P <.05)

Abbreviations: BHT, butylated hydroxytoluene; BHA, butylated hydroxyanisol; TBHQ, t-butyl-hydroxyquinone; TRX, trolox

Table 9 Free radical scavenging and metal chelating activity of the oximes derivatives and standards at 5, 50 and 100μM. Where-corresponds to significant inhibition, p<0.05. Each value represents means ± SD (*n* = 3)

Samples		Free radical scavenging activity, %			Metal chelating activity, %		
		5 μM	50 μM	100 μM	5 μM	50 μM	100 μM
Compounds	***C1***	50.75±8.28^{a}	50.02±6.14^{a}	56.14±2.03^{a}	8.40±1.93^{a}	11.05±3.34^{a}	11.38±0.15^{a}
	C2	20.79±6.94^{a}	48.89±5.92^{b}	55.07±2.36^{b}	13.32±1.63^{a}	19.63±3.25^{ab}	24.45±0.04^{b}
	C3	37.86±5.47^{a}	42.76±1.88^{a}	43.48±1.98^{a}	11.47±3.35^{a}	15.16±4.24^{a}	20.95±6.54^{a}
	C4	52.57±7.21^{a}	48.15±2.21^{a}	49.41±1.60^{a}	9.80±4.41^{a}	12.21±0.42^{a}	18.99±0.16^{b}
	C5	31.61±5.91^{a}	54.52±5.66^{b}	59.11±1.88^{b}	2.32±1.98^{a}	5.53±3.25^{a}	5.09±0.58^{a}
	C6	46.27±7.38^{a}	44.26±3.47^{a}	55.48±1.44^{a}	10.01±4.32^{a}	10.76±2.81^{a}	11.34±0.16^{ab}
	C7	45.16±4.20^{ab}	42.91±0.60^{a}	50.34±0.59^{b}	6.21±3.29^{a}	20.21±5.83^{ab}	18.22±1.80^{b}
	C8	44.51±3.82^{a}	38.19±3.71^{a}	45.39±0.38^{a}	4.46±3.28^{a}	11.85±1.64^{a}	16.09±0.21^{b}
	C9	43.05±2.20^{a}	39.97±6.86^{a}	43.84±0.54^{a}	9.13±5.49^{a}	11.94±1.62^{a}	14.60±2.95^{a}
Standards	**BHA**	26.54±1.90^{a}	82.87±4.60^{b}	92.41±2.19^{c}	8.71±3.66^{a}	15.66±3.02^{a}	16.24±3.26^{a}
	BHT	20.93±2.14^{a}	42.55±3.56^{b}	56.33±2.23^{c}	12.66±1.99^{a}	23.25±1.79^{b}	23.98±4.33^{b}
	TBHQ	48.06±3.09^{a}	93.75±4.10^{b}	94.24±2.02^{b}	4.66±5.12^{a}	7.65±1.38^{a}	19.65±1.65^{b}
	TRX	41.34±3.54^{a}	95.51±0.25^{b}	95.95±0.08^{b}	4.88±1.82^{a}	7.96±4.87^{a}	12.05±1.67^{a}

Note: Different superscripts in the same column express significant differences (P <.05)

Abbreviations: BHT, butylated hydroxytoluene; BHA, butylated hydroxyanisol; TBHQ, t-butyl-hydroxyquinone; TRX, Trolox

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Table 10 H_2O_2 scavenging activity and nonenzymatic linoleic peroxidation of the oximes derivatives and standards at 5, 50 and 100μM. Where-corresponds to significant inhibition, p<0.05. Each value represents means ± SD (*n* = 3)

	Samples	H_2O_2 scavenging activity, %			Nonenzymatic linoleic peroxidation, %		
		5 μM	50 μM	100 μM	5 μM	50 μM	100 μM
Compounds	*C1*	23.70±4.46[a]	29.26±8.98[a]	32.56±5.01[a]	28.70±8.32[a]	29.26±8.98[a]	25.56±3.85b
	C2	54.63±5.59[a]	57.04±8.98[a]	68.15±8.63[a]	54.63±5.59[a]	55.30±10.56[b]	64.81±11.56c
	C3	19.07±2.85[a]	23.52±3.70[a]	26.85±4.24[a]	24.07±8.49[a]	23.52±3.70[b]	26.85±4.24c
	C4	16.30±5.59[a]	17.04±4.79[b]	33.15±5.28[b]	16.30±5.59[a]	17.04±4.79[a]	33.15±5.28b
	C5	12.04±6.99[a]	30.37±8.91[a]	57.41±8.49[b]	12.04±6.99[a]	23.70±14.07[b]	57.41±8.49c
	C6	23.89±2.89[a]	34.26±4.02[a]	45.56±5.77[b]	23.89±2.89[a]	30.93±8.36[a]	45.56±5.77b
	C7	16.48±5.56[a]	20.37±6.99[a]	26.48±4.85[a]	19.81±8.68[a]	20.37±6.99[b]	16.48±5.56c
	C8	19.81±3.70[a]	36.19±3.76[b]	42.59±8.49[b]	19.81±3.70[a]	41.85±6.12[b]	42.59±8.49c
	C9	25.19±3.21[a]	34.63±6.90[ab]	38.48±2.36[b]	35.19±3.21[a]	34.63±6.90[b]	29.81±1.79c
Standards	BHA	9.37±1.67[a]	12.96±8.49[a]	14.81±8.49[a]	13.70±7.56[a]	12.96±8.49[b]	14.81±8.49c
	BHT	10.93±5.28[a]	26.85±6.39[b]	31.48±3.21[b]	10.93±5.28[a]	23.52±11.71[b]	31.48±3.21c
	TBHQ	39.81±9.20[a]	55.37±5.84[ab]	57.41±3.21[b]	39.81±9.20[a]	55.37±5.84[b]	57.41±3.21c
	TRX	12.78±3.64[a]	22.04±5.56[a]	24.07±6.42[a]	16.11±6.41[a]	22.04±5.56[b]	24.07±6.42c

Note: Different superscripts in the same column express significant differences (P <.05)

Abbreviations: BHT, butylated hydroxytoluene; BHA, butylated hydroxyanisol; TBHQ, t-butyl-hydroxyquinone; TRX, trolox

Conclusion

In conclusion, the structures of the synthesized oxime compounds were confirmed by X-Ray crystallography, H-NMR spectrometry, and IR spectroscopy. It was observed that oxime hydrogens (H2) form intermolecular hydrogen bonds with nitrogen atoms in the oxime group of the neighboring molecule. In addition to hydrogen bonds, intermolecular interactions in the solid state were determined.

We have confirmed that the phenyl ring system containing chloro and methyl substitutions are found to exhibit good antioxidant activities and lipid peroxidation compared to standards effects (BHA, TBHQ, BHT and trolox). The interactions of -chloro and –methyl groups in the phenyl ring of ***C6*** compound make a reduction of improvement from Mo(VI) to Mo(V) in total antioxidant activity. ***C3***, ***C9***, and ***C6*** oximes were exhibited as the most potent inhibition of linoleic acid peroxidation. The results of reducing power, free radical scavenging, metal chelating and hydrogen peroxide scavenging activity at 5-100 μM concentrations showed significant reactive for all tested oxime compounds. The results obtained by testing of antioxidant activity purposed that the oxime derivatives might be useful as potential compounds for the new antioxidant agents preventing oxidation or a source for food and pharmaceutical with chemical structures.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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