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RESEARCH ARTICLE

SYNTHESIS AND ANTI-OXIDANT ACTIVITY OF 1-SUBSTITUTED BIPHENYL DERIVATIVES

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ABSTRACT:

A series of [1,1'-biphenyl]-4-yl)-3-substitued 2-en-1-one derivatives (4a-h) were synthesized by general acylation methods and [1,1'-biphenyl]-4-yl)2-oxyethyl substituted derivatives were synthesized by Friedal-crafts acylation and then followed by cyclization of respective derivatives afforded targeted compounds (5a-d). The newly synthesized derivative compounds were characterized by IR, H1NMR,13C NMR, Mass analyses and screened for their invitro antioxidant activity (scavenging of hydrogen peroxide, scavenging of superoxide radical methods).

Keywords: Biphenyl, Freidal-Crafts acylation and Antioxidant activity.

INTRODUCTION

Biphenyl compounds having more than one aromatic nucleus, the both aromatic nuclei attached to each other at only one point. The biphenyl derivatives have been found to be effective against many therapeutic diseases as anti-inflammatory agents[1], analgesic[2], antipyretic[3], antiarthretis[4], antirheumatoid[5], anti hypertensive[6] and antifungal[7] activities. In continuation of new antioxidant activity we designed and synthesized novel 1-substitued biphenyl derivatives. The structures of products were characterized by H^1NMR, IR and LCMS. The results of biological activity indicate that some of the compounds possess moderate antioxidant activity.

EXPERIMENTAL PROCEDURE

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected.IR spectra were recorded on BRUKER FT-IR spectrometer using ATR. ^{1}HNMR spectra of the compounds in deuteriated dimethyl sulfoxide and $CDCl_3$ was recorded on BRUKER Av 400 spectrometer. Mass spectra were recorded on LCMS QP 5000 Schimadzu.Thin layer Chromatography was performed using pre-coated aluminium plates, coated with silica gel GF_{254}[E.Merck].Ethyl acetate:Methanol in the ratio of 3:2 was used as the eluent. The spots were visualized in the UV/Iodine chamber.

MATERIALS AND METHODS

Synthesis of 1-([1,1'-biphenyl]-4-yl)ethan-1-one (2)

In a 100 ml conical flask placed 5gm (0.03mol) biphenyl, 35ml (0.3mol) of dry benzene and 12ml (0.1mol) of acetyl chloride were added. Shake the flask thoroughly to ensure thorough mixing and then kept it in an ice bath with continuous stirring and in portions 7.5gms (0.05mol) of anhydrous aluminium chloride was added and maintain the temperature does not rise above 0^0C during the addition. Stir the mixture for 30 minutes and the temperature was allowed to rise 10^0C. Filter the precipitated solid and wash with benzene. Transfer the solid into a 100ml beaker containing 30gm

of crushed ice and 3ml of concentrated hydrochloric acid and filtered. Dissolve the solid in ethanol and reflux for 10 minutes and filtered. Cool the filtrate in ice and collect crystals of 1- acetyl biphenyl.

Synthesis of [(1,1'-Biphenyl)-4-yl] substituted compounds (4a-h):

A equimolar mixture of **(2)** and substituted aldehydes (0.01 mol) were mixed and dissolved in ethanol (25ml) and 40% NaOH solution (8ml) was added gradually. The reaction mixture was stirred at room temperature for a required period. Completion of the reaction was identified by TLC using Silica gel-G. After that the sodium salt of chalcone was decomposed by ice cold 2N HCL (2-3 ml). The separated Chalcone was filtered, washed with water (250ml) and recrystallised from ethanol to afforded analytical samples of compounds (4a-h).

Synthesis of 1-biphenyl-4-yl-2-chloroethanone (3)

In a 250 ml three necked flask provided with a dropping funnel, a mechanical stirrer and a reflux condenser, 1.54 g (0.01mol) of biphenyl (**1)**, 1.33 g (0.01mol) of finely powdered anhydrous aluminum chloride and 35 ml of anhydrous carbon disulphide was placed. The dropping funnel was charged with 0.8 ml (0.01mol) of pure chloroacetyl chloride and closed with a calcium chloride guard tube. The mixture was heated on a water bath until gentle reflux commenced and chloroacetyl chloride was added drop wise, the addition product made its appearance as a curdy mass when about three quarters of the chloroacetyl chloride was added, the reaction mixture was refluxed gently for an hour. The reaction mixture was cooled and poured slowly and with stirring on to crushed ice to which hydrochloric acid had been added. The product was filtered and washed with water to remove traces of hydrochloric acid and dried.

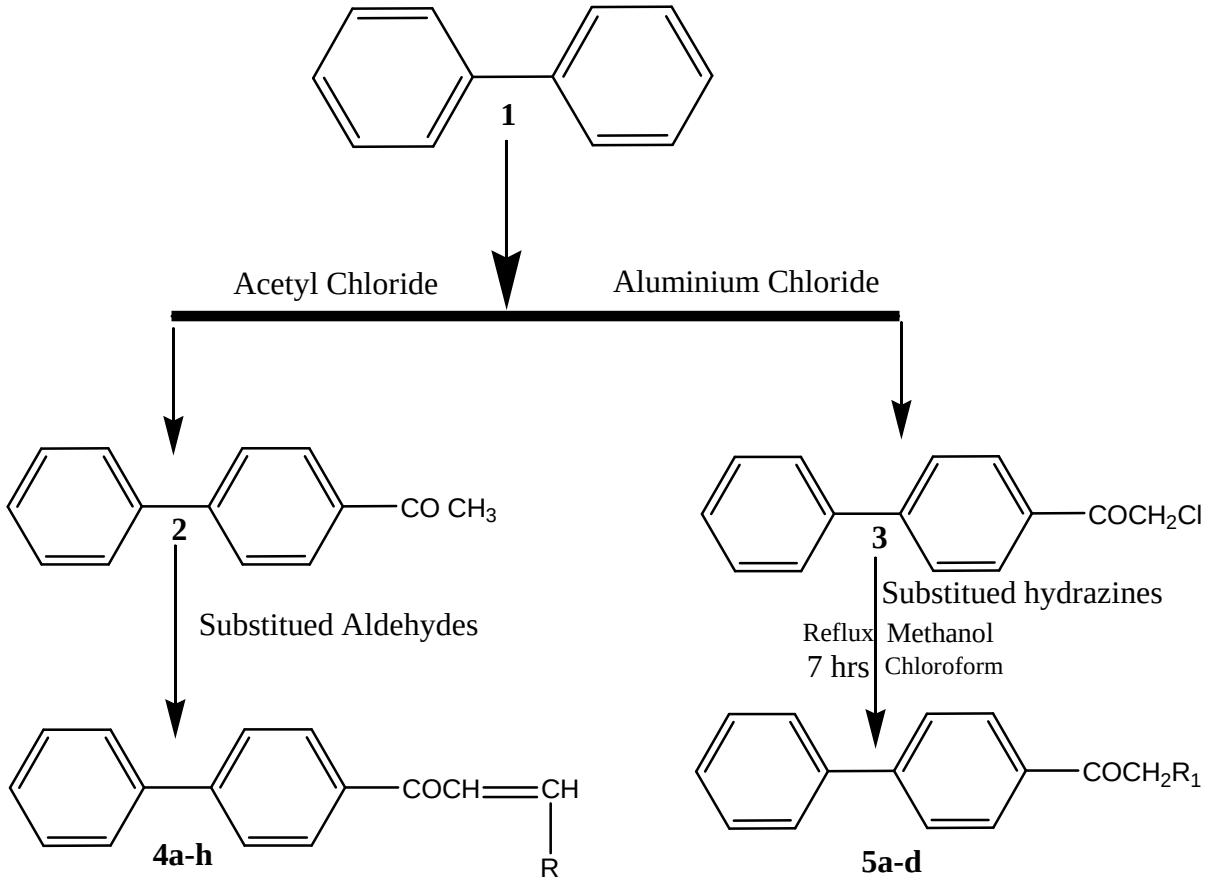
Synthesis of 2-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one/ (5a) and 2-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)-5-methyl-1-phenyl -pyrazolidin-3-one/1-([1,1'-biphenyl]-4-yl)-2-(5-amino-3-mercapto-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one/1-([1,1'-biphenyl]-4-yl)-2-(2-amino-4,5-dihydro-1H-imidazol-1-yl)ethan-1-one (5a-d)

The equimolar mixture of a compound (**2)** (0.1mol) and the Hydrazine hydrate/ phenyl hydrazine/thiosemi carbazide/ guanidine hydrochloride (0.1mol) in ethanol (40ml) was reflexued for 8 hrs. Which on cooling to room temperature yielded a product which was filtered, washed with water and recrystallised with ethanol. The afforded four compounds cyclized in presence of methanol and chloroform under reflux for 7 hrs yielded targeted compounds **(5a-d)**.

RESULTS AND DISCUSSION:

[1,1'-biphenyl]-4-yl)-3-substitued 2-en-1-one derivatives (4a-h) were synthesized by general acylation method and [1,1'-biphenyl]-4-yl)2-oxyethyl substituted derivatives were synthesized by Friedal-crafts acylation and then followed by cyclisation of respective derivatives(5a-d). 1-biphenyl-4-yl-2-ethanone derivatives.The structures of synthesized compounds were confirmed by chromatographic and spectral analysis. The physicochemical characteristics of synthesized compounds are summarized in **Table 1**.

Scheme-1



1- ([1,1'biphenyl] -4 -yl) -3-(4- (dimethylamino) phenyl) prop -2 - en-1- one (4a)**:** m.p:90-95^{0}C; Yield:79.45%w/w; Time: 7hrs R_f : 0.72; IR ν_{max} ATR in (cm^{-1}): 3395.56 (NH; str), 2918.68 (Aromatic C-H; str), 2851.04 (Aliphatic-CH;str),1432.97 (Ar-C=C; str), 1672 (Aliphatic C=C; str),1739.35 (C=O; str), 765.48 (Ar-CH; Bend). ^{1}HNMR(δ in $CDCl_3$ ppm) : 8.107 (d,2H,-Ar-H), 7.835 (d, 2HAr-H), 7.732 (d,2H,-Ar-H), 7.679 (t,3H,-Ar-H), 7.513-7.410 (m,4H,-CH=CH,Ar-H) 6.95 (d,2H,Ar-H) 3.084 {s,6H,N$(CH_3)_2$}.

1-([1,1'biphenyl]-4-yl-4-yl)-3-(2-chlorophenyl)prop-2-en-1-one (4b): m.p:75-80^{0}C**;** Yield: 77.76%w/w; Time: 7hrs; R_f : 0.94 (Ethyl acetate: Benzene,4:1); IR ν_{max} ATR (cm^{-1}): 3030.56 (Ar-CH; str), 1439.11(Ar-C=C; str),1601.35 (Aliphatic-C=C; str),1737.91(C=O; str), 748.44 (Ar-CH; Bend), 695.16 (C-Cl; str). ^{1}HNMR(δ in$CDCl_3$ ppm): 7.934(d,2H,-Ar-H),7.682(d, 2H Ar-H), 7.473(t,3H,-Ar-H), 7.25-7.14(m,4H,-Ar-H,CH=CH), 7.45(m,4H,-CH=CH,Ar-H) 6.95(d,2H,Ar-H).

1-([1,1'-biphenyl]-4-yl)-3-(3-nitrophenyl)prop-2-en-1-one (4c): m.p:135-140^{0}C; Yield: 69.16%w/w; Time: 6hrs; R_f: 0.93(Ethyl acetate: Benzene,4:1); IR ν_{max} ATR (cm^{-1}): 2918.50 (Ar-CH;str), 1655.72 (AliphaticC=C ; Str), 1596.45 (ArC=C ; Str), 1523.21 (N-O ; str), 739.44 (Ar-CH Bend), 1739.20 (C=O;str); ^{1}HNMR (δ in $CDCl_3$ ppm): 8.52 (s,1H,-Ar-H), 8.23 (d, 1H Ar-H), 7.957(d,3H,-Ar-H), 7.77 (t,3H,-Ar-H), 7.68 (t,3H,Ar-H), 7.134 (s,1H,Ar-H) 7.261-7.606 (m,5H-CH=CH,Ar-H).

1-([1,1'-biphenyl]-4-yl)-3-(4-nitrophenyl)prop-2-en-1-one(4d): m.p:172-175^{0}C; Yield: 67.42%w/w Time: 9hrs R_f : 0.86 (Ethyl acetate: Benzene, 4:1); IR ν_{max} ATR (cm^{-1}): 2918.98 (Ar-CH;str), 1655.72 (ArC=C; Str), 1455.90 (Aliphatic CH=CH; Str), 690.83 (Ar-CH,Bend), 1678 (C=O;str),1002.63 (C-N; str) ^{1}HNMR(δ in DMSO ppm): 8.14(d,2H,-Ar-H),8.084(d, 2H Ar-H), 7.67 (d,2H,-Ar-H), 7.48-7.369 (m,4H,-Ar-H, CH=CH), 7.583 (d,2H,Ar-H) 7.32 (t,3H,Ar-H).

1-([1,1'-biphenyl]-4-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one(4e): m.p:118-120^{0}C; Yield: 78.64%w/w Time: 7hrs R_f: 0.79(Ethyl acetate: Benzene,4:1) IR ν_{max} ATR (cm^{-1}) : 3031.24 (Ar-CH; str), 1739.16 (C=O;str), 1657.38 (Aliphatic C=C; str),1485.07 (Ar-C=C; str), 2920.75 (Aliphatic CH; str). ^{1}H NMR(δ inCDCl$_3$,ppm) : 8.107 (d,2H,-Ar-H),7.835 (d, 2HAr-H), 7.732 (d,2H,-Ar-H), 7.679 (t,3H,-Ar-H), 7.513-7.410 (m,4H,-CH=CH,Ar-H) 6.95 (d,2H,Ar-H) 3.79 (s,3H,OCH$_3$). ^{13}C NMR (δ in CDCl$_3$,ppm): C=O (189.99), CH (29.69), COCH (114.47), OCH$_3$ (26.69),Ar-C (127.23-145.32).Mass(m/z): 314.

1-([1,1'-biphenyl]-4-yl)-3-(4-(chlorophenyl)prop-2-en-1-one(4f): m.p: 170-175^{0}C; Yield**:** 61.35%w/w Time: 9hrs R_f : 0.87 (Ethyl acetate: Benzene,4:1); IR ν_{max} ATR (cm^{-1}): 3031.01(Ar-CH; str), 1402.99(Ar-C=C; str),1653.77 (Aliphatic-C=C; str), 1738.73(C=O; str), 732.44 (Ar-CH; Bend), 817.71 (C-Cl; str). ^{1}HNMR (δCDCl$_3$ppm): 7.934 (d,2H,-Ar-H), 7.682 (d, 2H Ar-H), 7.473 (t,3H,-Ar-H), 7.395-7.674 (m,9H,-Ar-H,CH=CH).^{13}C NMR (δ in CDCl$_3$,ppm): C=O (189.62), CH (29.69), COCH (122.50), OCH$_3$ (26.69),Ar-C (127.50-145.70). Mass (m/z): 318

1-([1,1'-biphenyl]-4-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one(4g): m.p:275-280^{0}C; Yield: 65.13%w/w; Time **:**10hrs; R_f : 0.86 (Ethyl acetate: Benzene,4:1); IR ν_{max} ATR (cm^{-1}): 2920.14 (Ar-CH; str), 1452.92 (Ar-C=C; str), 1677.33 (Aliphatic-C=C; str), 1739.08 (C=O; str), 694.32 (Ar-CH; Bend), 1231.27 (Assymetric C-O-C; str),1003.14 (Symmetric C-O-C; str), 2850 (Aliphatic-CH; str).^{1}HNMR(δ in CDCl$_3$ ppm): 7.87(d,2H,-Ar-H),7.62(d, 2H Ar-H), 7.34(d,2H,-Ar-H), 7.23-7.13(m,3H,-Ar-H,CH=CH), 6.23(d,Ar-H),3.73(s,OCH$_3$).

1-([1,1'-biphenyl]-4-yl)-3-(3-ethoxy-4-hydroxyphenyl)prop-2-en-1-one(4h): m.p:225-;Yield: **:** 73.94%w/w**;**Rf:0.78;Time:90hrs; IR ν_{max} in ATR (cm^{-1}) **:** 3744 (OH; str), 2920.84 (Ar-CH; str), 1485.51 (Ar-C=C; str),1678.12 (Aliphatic-C=C; str), 1739.31 (C=O; str) , 1120.37 (C-O; str) 762.64 (Ar-CH; Bend).^{1}HNMR(δin DMSO ppm):8.107 (d,2H,-Ar-H), 7.835 (d, 2HAr-H), (d, 2HAr-H), 7.732 (d,2H,-Ar-H), 7.679 (t,3H,-Ar-H), 7.513-7.410 (m,4H,-CH=CH,Ar-H) 6.95 (d,2H,Ar-H) 3.79 (s,3H,OC2H5).

2-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)5-methyl-2,4dihydro-3H-pyrazol-3-one(5a):m.p:110-115^{0}C;Yield:77.17%w/w Time:10Hrs R_f:0.71(Ethyl acetate: Benzene,4:1) IR ν_{max} ATR (cm^{-1}): .3030.27(Ar-CH;str),1655.72 (ArC=C ; Str),,690.83(Ar-CH,Bend), 1678(C=O;str),1155.29(C-N; str).^{1}HNMR(δ in CDCl$_3$ppm): 8.177 (d,2H,Ar-H), 7.821 (d,2H,Ar-H), 7.508 (d,2H,Ar-H),7.23 (t,1H,Ar-H), 6.56-6.77 (m,3H,Ar-H), 3.86(s,2H,CH$_2$), 3.02 (m,1H,NH), 2.49 (m,1H,CH$_2$), 2.24 (1H,CH$_2$), 1.25 (d,3H,CH$_3$).

2-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)5-methyl-1-phenylpyrazolidin3-one (5b):m.p:125-130^{0}C; Yield: 82.72%w/w Time:10hrs R_f : 0.96(Ethyl acetate: Benzene,4:1) IR ν_{max} ATR (cm^{-1}):3029.39(Ar-CH;str),1655.72(ArC=C;Str),738.83(Ar-CH,Bend), 1596(C=O;str),1218.63(C-N; str).^{1}HNMR(δin CDCl$_3$ppm): 8.177 (d,2H,Ar-H),7.821 (d,2H,Ar-H), 7.508 (d,2H,Ar-H),7.23 (t,1H,Ar-H), 6.56-6.77 (m,3H,Ar-H), 3.86 (s,2H,CH$_2$), 2.49 (m,1H,CH$_2$), 2.24 (1H,CH$_2$), 1.25 (d,3H,CH$_3$).

1-([1,1'-biphenyl]-4-yl)-2-(5-amino-3-mercapto-4,5-dihydro-1h-pyrazol-1-yl)ethan-1-one (5c): m.p:160-165^{0}C Yield:72.67%w/w Time:5hrs R_f : 0.86(Ethyl acetate: Benzene,4:1) IR ν_{max} ATR (cm^{-1}): 3029.61 (Ar-CH;str),3245.09 (NH; str)1478.78 (ArC=C ; Str),757.86 (Ar-CH,Bend), 1609 (C=O;str),1111.63 (C-N; str).^{1}HNMR(δ in CDCl$_3$ppm): 7.958 (d,2H,Ar-H), 7.69 (d,2H,Ar-H), 7.46 (d,2H,Ar-H), 7.37 (m,3H,Ar-H), 3.62 (m,4H,CH$_2$,), 2.25 (s,2H, NH$_2$), 1.25 (s,1H,SH).

1-([1,1'-biphenyl]-4-yl)-2-(2-amino-4,5-dihydro-4,5-dihydro-1H-imidazol-1-yl)ethan-1-one (5d): m.p:270-275^{0}C Yield:84.96%w/w Time:6hrs R_f :0.88(Ethyl acetate: Benzene,4:1)IR ν_{max} ATR (cm^{-1}): 3029.21(Ar-CH;str),3393.35(NH; str)1478.78 (ArC=C ; Str), ,754.62(Ar-CH,Bend), 1673(C=O;str),1392.98(C-N; str).^{1}HNMR(δ in CDCl$_3$ppm): 7.95 (d,2H,-Ar-H),7.62 (d, 2H,Ar-H), 7.43 (d,2H,-Ar-H), 7.37 (t,3H,-Ar-H), 3.62 (s,2H,CH$_2$),1.92 (s,2H,NH$_2$) ,2.25 (s,2H,CH$_2$).^{13}CNMR(δin CDCl$_3$):141(C=O),15.31(CH$_2$), 140(C=S), C$_3$(66), C$_5$(56), Ar-C(126-130)Mass(m/z):310

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Antioxidant Activity[8]

All the synthesized compounds (4a-4h), (5a-5d) were screened for their invitro antioxidant activity by various methods scavenging of hydrogen peroxide and superoxide radical method. Invitro antioxidant activity of all synthesized compounds was summarized in **Table 2** and **Table 3.**

Table. 1

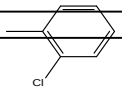
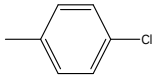
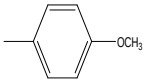
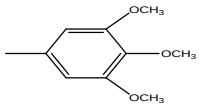
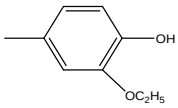
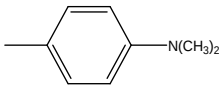
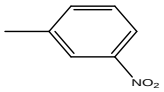
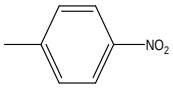
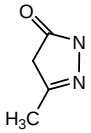
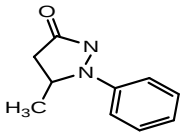
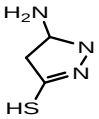
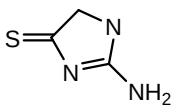
Entry	Product	R	R_1	M.f	M.w
1	4a		_	$C_{23}H_{21}NO$	327
2	4b		_	$C_{21}H_{15}OCl$	318
3	4c		_	$C_{21}H_{15}NO_2$	313
4	4d		_	$C_{21}H_{15}NO_2$	313
5	4e		_	$C_{22}H_{18}O_2$	314
6	4f		_	$C_{21}H_{15}OCl$	318
7	4g		_	$C_{24}H_{22}O_4$	374
8	4h		_	$C_{23}H_{20}O_3$	344
9	5a	_		$C_{18}H_{16}N_2O_2$	292
10	5b	_		$C_{28}H_{21}O_2N_2$	417
11	5c	_		$C_{16}H_{14}OSN_3$	296
12	5d	_		$C_{17}H_{15}ON_3S$	309

Table.2 Antioxidant activity (IC50 values) of compounds(4a-h) and (5a-d)

Compound Code	% Scavenging Activity ± S.E.M*					
	100µg/ml	200µg/ml	500µg/ml	1000µg/ml	2000µg/ml	IC_{50}
4-a	11.89±0.34	13.11±0.38	16.58±0.25	19.81±0.60	28.42±0.68	1.08
4-b	18.92±0.41	29.56±0.55	50.13±0.48	60.07±0.35	65.43±0.50	1.56
4-c	3.67±0.20	11.51±0.34	17.51±0.34	29.9±0.41	37.54±0.22	1.90
4-d	10.23±0.45	13.3±0.29	24.89±0.46	38.34±0.47	49.76±0.10	1.80
4-e	14.56±0.55	19.72±0.44	26.56±0.54	31.23±0.18	39.59±0.36	1.27
4-f	18.82±0.23	25.12±0.32	31.7±0.37	42.64±0.44	53.23±0.20	1.35
4-g	14.9±0.33	21.26±0.25	29.3±0.30	35.8±0.29	47.28±0.45	1.43
4-h	20.24±0.36	27.9±0.54	38.53±0.31	46.4±0.02	57.64±0.41	1.33
5-a	23.6±0.21	32.17±0.48	47.5±0.65	56.7±0.45	62.37±0.42	1.24
5-b	29.5±0.29	32.61±0.31	46.34±0.36	58.38±0.39	67.54±0.48	1.15
5-c	21.9±0.43	39.87±0.28	47.76±0.71	59.94±0.42	79.01±0.35	1.44
5-d	32.62±0.20	47.2±0.32	55.6±0.21	63.7±0.48	70.39±0.26	0.94
STANDARD	59.29±0.64	67.43±0.37	79.97±0.56	87.76±0.74	99.3±0.56	0.82

S.D.=standard deviation (Average of three determination); Standard=Ascorbic acid.

Table.3. Antioxidant activity (IC50 values) of compounds (4a-h) and (5a-d)

Compound code	%Scavenging Activity ± S.E.M					
	100µg/ml	200 µg/ml	500 µg/ml	1000 µg/ml	2000 µg/ml	IC50
4-a	33.18±0.25	46.68±0.36	53.35±0.29	67.47±0.32	76.41±0.25	0.99
4-b	32.31±0.41	45.87±0.47	51.09±0.18	66.8±0.44	72.25±0.29	0.90
4-c	34.98±0.31	55.76±0.18	62.98±0.32	70.12±0.39	76.89±0.26	0.65
4-d	30.12±0.22	52.87±0.50	60.67±0.34	67.87±0.68	77.98±0.34	0.94
4-e	39.76±0.17	54.87±0.33	62.76±0.17	71.56±0.29	78.98±0.45	0.53
4-f	40.76±0.34	53.63±0.35	62.76±0.20	72.87±0.29	79.87±0.08	0.57
4-g	43.25±0.46	56.78±0.54	67.65±0.37	75.56±0.30	81.54±0.31	0.43
4-h	39.87±0.20	47.98±0.45	56.78±0.34	63.98±0.41	79.67±0.55	0.67
5-a	37.28±0.41	48.65±0.45	57.80±0.20	65.34±0.44	78.77±0.36	0.76
5-b	45.26±0.22	52.76±0.28	60.09±0.36	69.54±0.29	75.74±0.32	0.098
5-c	44.65±0.36	50.07±0.38	62.98±0.28	68.54±0.51	76.89±0.32	0.27
5-d	47.77±0.52	52.89±0.45	59.64±0.41	69.99±0.39	77.22±0.25	0.019
STANDARD	59.29±0.67	67.43±0.45	79.97±0.29	87.76±0.79	99.3±0.23	0.084

S.D.=standard deviation (Average of three determination); Standard=Ascorbic acid.

CONCLUSION:

In conclusion, we have described simple and efficient protocol for the synthesis of novel 1-substituted biphenyl derivatives (4a-4h) and (5a-5d) with good yields. All the synthesized compounds have been investigated for their anti-oxidant activity by Hydrogen peroxide scavenging method, Superoxide radical method. Among the synthesized compounds some of the compounds possess moderate to promising activity when compared with standard

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