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Green Synthesis and *In vitro* Antioxidant Activity of 6-aryl-Quinazolin-4(3H)-ones via Suzuki Cross Coupling

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ABSTRACT

Suzuki cross coupling reaction based synthetic method for the preparation of 6-aryl-quinazolin-4(3*H*)-ones (3a-h) in ethylene glycol dimethyl ether is described by coupling of 6-iodo-2-phenyl-3-methyl-quinazolin-4(3*H*)-one (1) with various 6-aryl boronic acids 3 under microwave irradiation in between These compounds were screened for anti-oxidant activity.

Keywords: 6-aryl-Quinazolin-4(3*H*)-one, aryl boronic acid, $Pd(PPh_3)_4$, 1,1-diphenyl-2-picrylhydrazil(DPPH), ABTS*+ (2, 2'-azino-bis (3-ethylben - zthiazoline- 6-sulphonic acid), Suzuki coupling, Ethylene glycol dimethyl ether, Microwave irradiation, Antioxidant activity.

INTRODUCTION

The recent literature is enriched with progressive findings about quinazolin-4(3*H*)-one and its derivatives which exhibit a broad range of biological properties such as antioxidant[1], anti-tumour[2], anti-inflammatory[3], anti-malarial[4], anti-bacterial[5] and anticonvulsant activity[6]. Further, quinazolin-4(3*H*)-one have also been investigated scaffold for the synthesis of various drugs and their intermediates[7].

Cross coupling reaction is an significant method of generating carbon-carbon bonds in organic compounds, which is catalyzed by various transition metals. In the past three decades, carbon-carbon bond construction reaction has allowed chemists to produce complex molecular structures of various interests including total synthesis of natural products[8], medicinal chemistry and industrial process development[9].

In modern days, Microwave-Assisted Organic Synthesis (MAOS) has fascinated the interest of synthetic chemists. The rate of a reaction is speed up under microwave irradiation compared to conventional heating.

Insight of quinazolin-4(3*H*)-one moiety and cross coupling reaction, we have in the previous reported the successful use of Kumada cross-coupling reactions for the synthesis of 6-aryl-quinazolin-4(3*H*)-ones derivatives[10]. However, this coupling is related with extended

reaction times and with low yields. In search of our previous investigations toward developing more proficient protocol for the synthesis of 6-aryl-quinazolin-4(3*H*)-one derivatives, we optimized the Suzuki reaction conditions under microwave irradiation and conventional heating. It was envisaged that the microwave irradiation would enhance the rate of reaction, thereby reducing time.

Here in, we report the coupling of 6-iodo-3-methyl-2-phenyl-quinazolin-4(3*H*)-one (1) with aryl boronic acids in presence of $Pd(PPh_3)_4$ as catalyst derivatives under microwave irradiation as well as conventional heating conditions and evaluated their *in vitro* antioxidant property.

Experimental section

IR spectra for all the compounds were recorded in solid KBr on infra cold model 337 Perkin-Elmer instrument. Melting points were measured in open capillary tubes and are uncorrected. The ^1H NMR (400 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Varian Gemini 400 or Bruker 75 in $CDCl_3$ using tetramethylsilane as internal standard. The purity of all obtained compounds was checked by thin-layer chromatography. High resolution Mass spectra were recorded on Q-TOF mass spectrometer. Multisynth series microwave system (Milestone) were used for Suzuki reaction.

General procedure for the preparation of 3a-h via Suzuki cross coupling reaction

Microwave heating

The 6- iodoquinazolinone 1 (0.5 mmol) and boronic acid (0.55 mmol) were dissolved ethylene glycol dimethyl ether in a microwave vial. $Pd(PPh_3)_4$ (0.02 mmol) and Na_2CO_3 (1.25 mmol) were added, and the reaction mixture was irradiated in a microwave apparatus at 80°C, 250 W for 20 minute. After the reaction mixture was cooled to ambient temperature, the product was filtered, the filtrate was concentrated, and the crude mixture was purified by silica gel column chromatography using hexane/ ethyl acetate (88/12) as eluent.

Conventional heating

The 6-iodoquinazolinone 1 (0.5 mmol), boronic acid 2 (0.55 mmol) and Na_2CO_3 (1.25 mmol) were dissolved in ethylene glycol dimethyl ether in a seal tube. After degassing reaction mixture, $Pd(PPh_3)_4$ (0.02 mmol) and were added. And the reaction mixture was heated at 80°C, 250 W for overnight. After the reaction mixture was cooled to ambient temperature, the product was filtered, the filtrate was concentrated, and the crude mixture was purified by silica gel column chromatography using hexane/ethyl acetate (88/12) as eluent.

Assay of anti-oxidant property

Lipid peroxidation assay

In vitro lipid peroxidation of the compounds was determined by the described method[11,12]. Briefly, 1 mL of rat liver microsomal fraction was added to 1.0 mL of 150 mM Tris-HCl buffer (pH 7.4) containing various concentrations (50, 100 and 150 µg/ mL) of test compounds, 0.2 mL $FeCl_3$ (1 mM) and 0.2 mL ascorbic acid (0.5 mM) to induce lipid peroxidation. The mixtures were incubated at 37°C for 30 minutes. At the end of the incubation, 0.5 ml of glacial acetic acid and 0.5 ml of 0.33% TBA were added to each mixture. The mixtures were kept in a water bath at 97°C for 45 min. at cooling, the pink chromogen was extracted with 2 mL of butanol. The absorbance of the organic layer was measured at 535 nm, and the thiobarbituric acid reactive substances produced were estimated using the MDA standard curve. BHA was used as a control substance (20 µg/ml).

DPPH (1, 1-Diphenyl-2-picrylhydrazyl) radical Scavenging activity

The free radical scavenging activity of isolated compounds was measured by 1,1-diphenyl-2-picryl- hydrazyl (DPPH) method described by Blois 1958. 0.1 mM solution of DPPH in methanol was prepared and 1ml of this solution was added to 3 mL of various concentrations of (50, 100 and 150 µ g/ ml) test compounds and the reference compound (20 µ g/ml). After 30 min., absorbance was measured at 517 nm. BHA was used as the reference material. All the tests were performed in triplicate. The percentage of inhibition was calculated by comparing the absorbance values of the control and test samples.

% DPPH radical scavenging = [(Absorbance of control – Absorbance of test sample)/ (Absorbance of control)] ×100

ABTS*+ (2, 2'-azino-bis (3-ethylben - zthiazoline-6-sulphonic acid) radical cation decolourisation assay

This method was carried out by well described method[13]. ABTS*+ (54.8 mg) was dissolved in 50mL of distilled water to 2mM concentration and potassium persulphate (17 mM, 0.3 mL) was added. The reaction mixture was left to stand at room temperature overnight in dark before use. To 0.2 mL of various concentrations (50, 100 and 150 µ g/ mL) of test samples and reference standard BHA (20 µ g/mL) 1.0 mL of distilled DMSO and 0.16 mL of ABTS*+ solution was added to make a final volume of 1.36mL. Absorbance was measured spectro-photometrically, after 20 min. at 734 nm[14].

Spectral data

3-Methyl-2,6-diphenylquinazolin-4(3*H*)-one (3a): ^{1}H NMR (400MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.02 (d, 1H, *J* = 8.6 Hz), 7.82 (d, 1H, *J* = 8.6 Hz), 7.72 (d, 2H, *J* = 7.5 Hz), 7.47–7.60 (m, 7H), 7.38 (m, 1H), 3.53 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 162.7, 155.9, 146.4, 139.8, 139.6, 135.3, 133.1, 130.0, 128.9, 128.8, 127.9, 127.8, 127.1, 124.5, 120.7, 34.1; IR (KBr): 1680 cm^{-1}; ESI-HRMS: $[M+H]^+$ *m/z* calculated for $C_{21}H_{17}N_2O$: 313.1263; found at *m/z* 313.1343. m.p. 105–106°C.

3-Methyl-2-phenyl-6-(o-tolyl)quinazolin-4(3*H*)-one (3b) : ^{1}H NMR (400MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.73-7.80 (m, 2H), 7.55-7.60 (m, 5H), 7.31 (m, 4H), 3.52 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 162.8, 156.1, 146.1, 140.9, 140.5, 135.6, 135.4, 135.3, 130.0, 128.9, 128.0, 127.8, 127.2, 126.8, 125.9, 120.3, 34.3, 20.5; IR (KBr): 1674 cm^{-1}; ESI-HRMS: $[M+H]^+$ *m/z* calculated for $C_{22}H_{19}N_2O$: 327.1419; found at *m/z* 327.1481. m.p. 136 - 138°C.

6-(4-Methoxyphenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3c): ^{1}H NMR (400MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.99 (m, 2H), 7.57-7.65 (m, 7H), 7.02 (d, 2H, *J* = 7.9Hz), 3.87 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 162.7, 159.5, 155.7, 145.8, 139.4 ,135.2 132.8, 132.0, 130.0, 128.8, 128.2, 128.0, 127.8, 123.7, 120.6, 114.3, 55.3, 34.2; IR (KBr): 1674 cm^{-1}. ESI-HRMS: $[M+H]^+$ *m/z* calculated for $C_{22}H_{18}N_2O_2$: 343.13683; found at *m/z* 343.1448. m.p. 161 – 162°C.

6-(2-Chlorophenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3d): ^{1}H NMR (400MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.05 (d, 1H, *J* = 7.9 Hz), 7.91 (d, 1H, *J* = 7.9 Hz), 7.58-7.27 (m, 9H), 3.55 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 162.5, 156.4, 146.5, 139.2, 138.3, 135.7, 135.2, 132.5, 131.4, 130.17, 130.08, 129.07, 128.0, 127.34, 127.02, 127.4, 120.3, 34.3. ESI-HRMS: $[M+H]^+$ *m/z* calculated for $C_{21}H_{16}ClN_2O$: 347.0873; found at *m/z* 347.0959. m.p. 110 – 111°C.

6-(2,3-Dichlorophenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3e): ^{1}H NMR (400MHz, $CDCl_3$): δ 8.50 (d, 1H, *J* = 2.1Hz), 7.95 (dd, 1H, *J* = 8.5Hz), 7.82 (d, 1H, *J* = 8.3 Hz), 7.55-7.60 (m, 7H), 7.39 (m, 1H), 3.54 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 162.5, 156.6, 147.2, 136.9, 135.6, 135.5, 135.1, 132.8, 130.2, 128.9, 128.4, 127.9, 127.6, 125.6, 124.8, 34.4; IR (KBr): 1674 cm^{-1}. ESI-HRMS: $[M+H]^+$ *m/z* calculated for $C_{21}H_{15}Cl_2N_2O_2$: 381.0483; found at *m/z* 381.0549. m.p. 222-224°C.

6-(4-Fluorophenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3f): ^{1}H NMR (400MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.95 (d, 1H, *J* = 8.4Hz), 7.81 (d, 1H, *J* = 8.3Hz), 7.55-7.69 (m, 7H), 7.15-7.199 (m, 2H), 3.51 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 162.6, 156.4, 146.4, 138.7, 135.7, 135.2, 132.9, 130.0, 128.8, 127.9, 124.2, 120.6, 115.9, 115.6, 34.2; IR (KBr): 1680 cm^{-1}. ESI-HRMS: $[M+H]^+$ *m/z* calculated for $C_{21}H_{16}ClN_2O$: 347.0951; found at *m/z* 347.0959. m.p. 195 – 196°C.

6-(3-Fluoro-4-methoxyphenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3g): ^{1}HNMR (400MHz, $CDCl_3$) δ 8.49 s (s, 1H), 7.95 (m, 2H) 7.44-7.69 (m, 7H), 7.07 (m, 1H), 3.96 (s, 3H), 3.55 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 162.7, 155.9, 154.2, 150.9, 146.3, 138.2, 135.2, 132.6, 130.0, 128.8, 127.9, 123.9, 122.8, 120.6, 114.9, 114.6, 113.6, 56.3, 34.3; IR (KBr): 1679 cm^{-1}; ESI-HRMS: $[M+H]^+$ *m/z* calculated for $C_{21}H_{15}FN_2O$: 331.1168; found at *m/z* 331.1242. m.p. 159 – 160 °C.

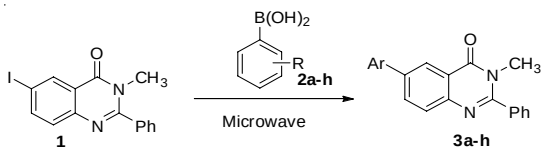
3-Methyl-6-(naphthalen-1-yl)-2-phenylquinazolin-4(3*H*)-one (3h): ^{1}H NMR (400MHz, $CDCl_3$) δ 8.49 (d, 1H, *J* = 1.7 Hz), 7.86-7.95 (m, 5H), 7.43-7.63 (m, 9H), 3.54 (s, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ162.7, 146.7, 146.5, 139.7, 138.7, 136.3, 133.8, 131.4, 130.1, 128.9, 128.4, 128.2, 128.0, 127.6, 127.4, 126.4, 125.5, 125.4, 120.5, 34.3;

IR (KBr): 1674 cm^{-1}; ESI-HRMS: $[M+H]^+$ *m/z* calculated for $C_{25}H_{18}N_2O$: 363.1419; found at *m/z* 363.1485. m.p. 111-113 °C.

RESULT AND DISCUSSION

6-Iodo-3-methyl-2-phenyl-quinazolin-4(3*H*)-one (1) was chosen as the scaffold which inturn was prepared in previous reported procedure. The compound 1 was characterized by ^{1}H NMR and HRMS spectral techniques[10].

Microwave-assisted Suzuki Cross-coupling reaction of 6-iodo-quinazolin-4-(3*H*)-one (1) is explored for the first time with a set of eight aryl boronic acid 2 to provide 6-aryl-quinazolin-4-(3*H*)-ones 3a. Primarily, the evaluation of solvent was studied using 6-iodo-quinazolin-4(3*H*)-one 1 (1.0 equiv) boronic acid 6a (1.1 equiv) and Na_2CO_3 7 (1.1equiv). Employing solvents (Entry 1, 2, 3, 4, 5, and 6) resulted in the required compound 3a with inferior yields. The reaction of **1** with aryl boronic acids 2a in presence of 10 mol% of $Pd(PPh_3)_4$ as catalyst for 20 min. in ethylene glycol dimethyl ether gave 3a with 95% yield (scheme-1). The same product 6a was also obtained (90%) under conventional heating (80°C) in toluene for 10 hours.



Scheme.1

(Table 1, entry 1).

The spectral identification of 3a has been discussed below. The IR (KBr) spectrum of 3a showed a strong absorption band at 1680 cm^{-1} corresponding to carbonyl group. The ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 3a showed a singlet at δ 8.56 for C-5 proton, a doublet at δ 8.02 corresponds to C-7 proton. A singlet peak at δ 3.53 integrating for three protons is due to N-CH_3 group. The peaks for the remaining eleven aromatic protons observed at δ 7.82 (d, *J* = 8.6 Hz, 1H), δ 7.72 (d, *J* = 7.50 Hz, 2H), δ 7.47-7.60 (m, 7H) and in the range δ 7.38-7.41(m, 1H). ^{13}C-NMR spectrum ($CDCl_3$, 100 MHz) of 3a showed signals at δ 162.7 due to carbonyl carbon, δ 155.9 for C-2 carbon, and a peak at δ 34.3 due to N-methyl carbon. Further ^{13}C NMR spectrum showed signals at δ 146.4, 139.8, 139.6, 135.3, 133.1, 130.0, 128.9, 128.8, 127.9, 127.8, 127.1, 124.5, 120.7 due to the remaining aromatic carbons. The structure was further confirmed by high resolution Mass spectrum of 3a indicates $[M+H]^+$ peak at m/z 313.1349 due to the molecular formulae $C_{21}H_{17}N_2O$.

This Suzuki coupling reaction of 1 was extended to remaining substituted phenyl boronic acids 2b-h and the corresponding 6-arylquinazolin-4(3H)-ones (3b-h) were isolated in 93-95% yield (Scheme-1, Table-2). These compounds **3b-h** were characterized based on their IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data

Table.1: Optimized conditions for 3a compound with different solvents

Entry	Solvent	Yield(%)	
		80°C	MW
1.	DMF	20	40
2.	DMF:Water (4:1)	40	60
3.	Toulene	37	40
4.	Toluene:Water	60	66
5.	1,4-Dioxane	33	43
6.	1,4-Dioxane:Water	62	71
7.	Ethylene glycol dimethyl ether	85	95

Assay of antioxidant property

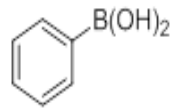
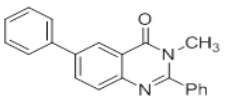
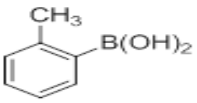
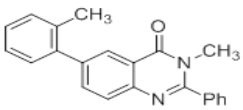
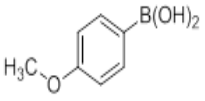
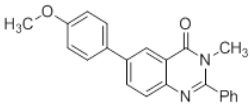
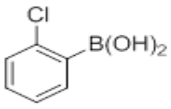
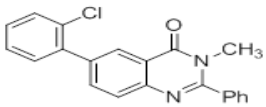
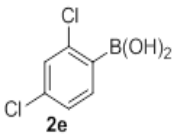
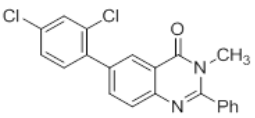
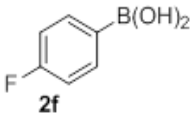
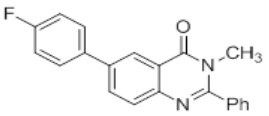
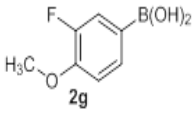
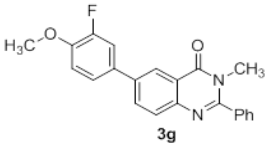
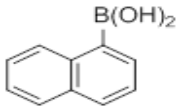
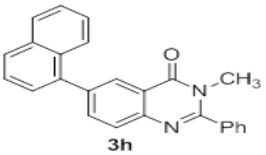
Lipid peroxidation assay

6-(2,3-Dichlorophenyl)-3-methyl-2-phenyl-quinazolin-4(3*H*)-one (3e) and 6-(3-Fluoro-4 methoxyphenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3g) exhibited concentration-dependent $FeSO_4$ induced lipid peroxidation and showed highest percentage of inhibition with that from other compounds and comparable to reference drug BHA. $P < 0.5$ (Table 4).

DPPH radical scavenging activity

Among the tested compounds 6-(2,3-Dichlorophenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3e) and 6-(3-Fluoro-4-methoxyphenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3g) are showed highest percentage of inhibition which was comparable with standard BHA. 3-Methyl-2,6-diphenylquinazolin-4(3*H*)-one (3a), 3-Methyl-2-phenyl-6-(o-tolyl)quinazolin-4(3*H*)-one (3b), 6-(4-

Table.2: Synthesis of 6-substituted quinazolinone using Suzuki cross coupling

$ArB(OH)_2$	Product[a]	Time[b]		Yield(%)	
		80°C	MW	80°C[d]	MW
 2a	 3a	(10 h)	20 min.	85	95
 2b	 3b	9 h	19 min.	89	93
 2c	 3c	10 h	16 min.	90	95
 2d	 3d	9 h	20 min.	80	94
 2e	 3e	10 h	20 min.	79	93
 2f	 3f	10 h	20 min.	82	94
 2g	 3g	8 h	20 min.	85	95
 2h	 3h	10 h	19 min.	90	95

a. The products were characterized by 1H NMR, mass and IR spectra
b. Time for conventional heating (80°C) reaction in mixture of toluene and water.
c. Isolated yields.
d. Yield after conventional heating (80°C) reaction in mixture of toluene and water

Table.3: *In vitro* antioxidant studies of synthesized compounds 3a-h

		3a			3b			3c			3d			3e			3f			3g			3h		
	50	10.0	15	50	100	150	50	100	150	50	100	150	50	100	150	50	100	150	50	100	150	50	10. 0	150
LPO	3.2	4	4.2	4.5	3.5	5	3	4.5	4	5.6	3	4.5	4.5	5	6.1	5.5	5.5	4.5	5	6	7	4.5	3.5	5
	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
	1.8	2.3	4.0*	2.6	2	2.9*	1.7	2.6	2.3*	3.2	1.7	2.6*	3.7	2.8	2.9*	3.1	3.2	2.6*	3.8	2.3	4.0*	2.6	2	2.9*
DPPH	5.5	8.6	11.5	3	4.5	6.1	5.5	7	12.5	4.5	8	7.1	4.5	8	14.1	8.0	8.1	9	8.0	11.1	13	3	4.5	6.1
	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±		±	±	±	±	±
	3.2	4.9	6.6*	1.7	2.6	3.5*	3.1	4	7.2*	2.6	4.6	8.1*	2.6	4.6	8.1*	4.6	6.4	7.5*	4.6	6.4	7.5*	1.7	2.6	3.5*
ABTS	5.5	2.5	5.5	5	6	7	6.1	7	8.5	5.5	2.5	5.5	3.5	4.5	6.5	7.5	11.5	13.5	7.5	10.5	12.5	5	9	9
	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
	3.1	1.4	3.2*	2.8	5.1	6.3*	3.5	4	4.9*	3.1	1.4	3.2*	2	2.6	3.7*	4.3	6.6	7.7*	4.3	5.6	7.7*	2.8	5.1	6.3*

L.P.O –Lipid Peroxidation assay, DPPH- DPPH free radical scavenging assay, ABTS- ABTS decolourising assay. n=3, * P < 0.5

Methoxyphenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3c), 6-(2-Chlorophenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3d), 6-(4 Fluorophenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3f) and 3-Methyl-6-(naphthalen-1-yl)-2-phenylquinazolin-4(3*H*)-one (3h) are also possessed considerable anti-oxidant properties P<0.5 (Table-3).

ABTS*+ radical cation decolourisation assay

Synthesized compounds showed good scavenging of ABTS*+ radical at all tested concentrations (Table-3). The highest inhibition was achieved with 6-(4-Fluorophenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3f) comparing to other compounds P<0.5. Whereas, 6-(3-Fluoro-4-methoxyphenyl)-3-methyl-2-phenylquinazolin-4(3*H*)-one (3g) was the next compound showed significant at 150 µ g/mL (Table-3).

CONCLUSION

A more efficient and novel C-C bond forming, Pd catalyzed Suzuki coupling reaction is developed as a new method for the preparation 6-aryl-quinazolin-4(3*H*)-ones (3a-h) under microwave irradiation conditions in ethylene glycol dimethyl ether has been achieved with good yields over conventional method. According to data obtained from the present study, these quinazolin-4(3*H*)-one derivatives could be considered as useful templates for further development to obtain *In vitro* antioxidant activity

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