INTRODUCTION

The reactive oxygen species (ROS) and other related free radicals species are capable to react either directly or indirectly, to damage all biomolecules, such as proteins, lipids, DNA and carbohydrates resulting in cell damage and subsequently this damage can cause many diseases. Many researchers reported the implication of these free radicals will cause several diseases such as inflammatory, cancers, degenerative and chronic diseases. Phenolic antioxidant compounds are one of the most important antioxidant species which can inhibit the oxidative stress in biological system and prevent any damage. These compounds also show broad biological activity as anti inflammatory and anticancer.

Generally, antioxidants donate protons to become stable free radicals. This stability increases with the extent of delocalization and enhances antioxidant ability. As such, many synthesized compounds containing long chain resonance exhibited high antioxidant activity. Furthermore, the compounds which can be classified as a strong antioxidant usually shared common structure features. They often own multiple phenolic hydroxyl...
groups like flavonoids or which have full conjugation a system like carotenoids. Moreover, exhibited substituted groups might influence on the scavenging ability. This indicates the existence of a close relationship between the chemical structure and the ability to scavenge free radicals.

Derivatives of 1,3,4-oxadiazole are shown to exhibit various types of biological activities and antioxidant ability and compounds of Schiff base derivatives have even broader properties and applications such as liquid crystalline, nonlinear optical devices, dyes, biological and pharmaceutical applications. As for 2,6-dimethoxyphenol derivatives, there has been widespread interest during the last years as antioxidant materials. In this work we presented the synthesis of new 4-(((4-(5-((arylidene)amino)-1,3,4-oxadiazol-2-yl)benzyl)oxy)methyl)-2,6-dimethoxyphenol (7a-7e) as new antioxidant material.

**MATERIAL AND METHODS**

**Chemistry**

The IR spectra were obtained with a Perkin Elmer 400 Fourier Transform Infrared (FTIR) Spectrometer. 1H and 13C-NMR spectra were recorded at Joel Lambda and ECA DELTA spectrometers at 400 MHz) UM, Malaysia). CDCl3 and DMSO-d6 were used as solvents with TMS as the internal standard. The mass spectra were recorded using an Agilent 5975 system for EI/MS and a Finnigan TSQ7000 for HREIMS (NUS, Singapore). For UV spectroscopy, a Power Wave X340 (BIO-TEK Instruments, Inc., Winooski, VT, USA) was used to record the FRAP and DPPH. Melting points were measured on a Gallenkamp melting point apparatus in open-end capillary tubes. Flash column chromatography on silica gel 60 (230–400 mesh, E. Merck) was employed. General grade solvents and reagents were purchased from commercial suppliers and used without further purification.

**Synthesis of 3,5-dimethyl-4-((trimethylsilyl)oxy)benzaldehyde (1)**

4-Hydroxy-3,5-dimethylbenzaldehyde (3.64 g, 20 mmol) was dissolved in dry DMF (15 mL) containing anhydrous potassium carbonate (2.76 g, 25 mmol). The mixture stirred for 30 minutes at ambient temperature, then Chlorotrimethylsilane (3.25, 30 mmol) was added drop wise. The stirring mixture was heated under reflux (70-80 C) for 24 h. After cooling the resulting product was extracted from diethyl ether (3 x 50 mL) and dried under calcium chloride. The crude product was purified by column chromatography using hexane-ethylacitate (8:2) as eluent to obtain colorless oil, Yield: 74%, Bp 288-292 C at 760 mmHg, d=1.23 at 25 C. IR (liquid film) νmax 3033(CHAr), 2973, 2958(CH aliphatic), 1674(CO), 1595(C=C), 1190 (Ar-O-C), 842(Si-CH3) cm⁻¹, 1H-NMR(400MHz, CDCl3): δ 0.23(s, 9H, Si-(CH3)3), 3.84(s, 6H, 2×OCH3)7.13(s, 2H, H-3), 9.85(s, 1H, CHO). 13C-NMR (100 MHz, CDCl3): δ -0.08 (3C, Si-(CH3)3), 55.42(2C, OCH3), 108(2C, C-3), 131.63(1C,C-4), 134.17(1C, C-3), 151.83(1C, C-2), 192.07(1C, CO). HREIMS m/z = 254.0968 [M+H]⁺ (calc. for C12H18O4Si, 254.0974).

**Synthesis of 3,5-dimethyl-4-((trimethylsilyl)oxy)benzyl alcohol (2)**

Sodium borohydride (0.75 gm, 20 mmol) was added with small portion to a stirred solution of 3,5-dimethyl-4-((trimethylsilyl)oxy)benzaldehyde (3 g, 13.3 mmol) in THF-Methanol 4:1 (25 mL) and refluxed overnight. Upon cooling distill water (50 mL) was added and the mixture was stirred for further 10 minutes. The crude product was extracted from diethyl ether. The organic layer washed three times with saturated solution of Sodium hydrogen sulfate. After evaporating the solvent pale yellow oil was obtained. Yield 87%, Bp 314-317 C at 760 mmHg, d=1.12 at 25 C. IR (liquid film) νmax 3329(OH), 3067(CH Ar), 2943, 2877 (CH aliphatic), 1593(C=C), 1205 (Ar-O-C), 859(Si-CH3) cm⁻¹, 1H-NMR(400MHz, CDCl3): δ 0.20(s, 9H, Si-(CH3)3), 2.94 (bs, 1H, OH), 3.82 (s, 6H, 2×OCH3), 4.51(s, 2H, OCH2), 6.67(s, 2H, H-3). 13C-NMR (100 MHz, CDCl3): δ -0.05 (3C, Si-(CH3)3), 55.42(2C, OCH3), 62.34(1C, CH2OH), 107.52(2C, C-3), 128.44(1C, C-4), 135.68(1C, C-1), 152.08(1C, C-2), 192.07(1C, CO). HREIMS m/z = 256.1129 [M+H]+ (calc. for C12H20O4Si, 256.1131).

**Synthesis of 3,5-dimethyl-4-((trimethylsilyl)oxy)benzaldehyde (1)**

Small portions of 4-(bromomethyl)benzonitrile (2.3g, 11.6 mmol) was added to a stirring solution of 3,5-dimethyl-4-((trimethylsilyl)oxy)benzaldehyde (3 g, 13.3 mmol) in THF-Methanol 4:1 (25 mL) and refluxed overnight. Upon cooling distill water (50 mL) was added and the mixture was stirred for further 10 minutes. The crude product was extracted from diethyl ether. The organic layer washed three times with saturated solution of Sodium hydrogen sulfate. After evaporating the solvent pale yellow oil was obtained. Yield 87%, Bp 314-317 C at 760 mmHg, d=1.12 at 25 C. IR (liquid film) νmax 3329(OH), 3067(CH Ar), 2943, 2877 (CH aliphatic), 1593(C=C), 1205 (Ar-O-C), 859(Si-CH3) cm⁻¹, 1H-NMR(400MHz, CDCl3): δ 0.20(s, 9H, Si-(CH3)3), 2.94 (bs, 1H, OH), 3.82 (s, 6H, 2×OCH3), 4.51(s, 2H, OCH2), 6.67(s, 2H, H-3). 13C-NMR (100 MHz, CDCl3): δ -0.05 (3C, Si-(CH3)3), 55.42(2C, OCH3), 62.34(1C, CH2OH), 107.52(2C, C-3), 128.44(1C, C-4), 135.68(1C, C-1), 152.08(1C, C-2), 192.07(1C, CO). HREIMS m/z = 256.1129 [M+H]+ (calc. for C12H20O4Si, 256.1131).
((trimethylsilyl)oxy)benzyl alcohol (2.6 g, 11.6 mmol) in pyridine (15 mL) within 30 minutes. After complete the addition the mixture was refluxed for 6 h. Upon cooling the mixture poured into crushed water (100 mL) and acidified with 5% of hydrochloric acid. The product was extracted with diethyl ether (3 × 25 mL) and washed with water, then dried over magnesium sulfate. After evaporating the solvent, the crude material was purified by column chromatography using hexane-ethylacetate (9:1) as eluent to obtain colorless oil which is solidify after two days to obtain white powder. Yield 61%, Mp 36-38 °C, IR (KBr) vmax 3042 (CH Ar), 2962, 2890 (CH aliphatic), 2248 (Ca"N), 1595 (C=C), 1195 (Ar-O-C), 867 (Si-CH3) cm-1. 1H-NMR (400MHz, CDCl3): δ 0.18 (s, 9H, Si-(CH3)3), 3.89 (s, 6H, 2×OCH3), 4.31 (s, 2H, OCH2), 4.35 (s, 2H, OCH2), 6.62 (s, 2H, H-3), 7.41 (d, 2H, J 8.2, H-8), 7.49 (d, 2H, J 7.9, H-9).

Synthesis of 4-(((4-hydroxy-3,5-dimethoxybenzyl)oxy)methyl)benzoic acid (4)

4-(((3,5-dimethoxy-4-((trimethylsilyl)oxy)benzyl)oxy)methyl)benzonitrile (2.2 g, 6 mmol) was dissolved in ethanol (25 mL) and 5 mL of 4N KOH solution. The mixture was refluxed for 48 h. After evaporation the solvent the crude product extract with 20 mL ethyl acetate. The organic layer was ignored. The aqueous layer reduced to 5 mL by evaporation under reduced pressure. Acetic acid-THF 1:1 (10 mL) was added to the aqueous layer then refluxed overnight. The precipitated collected by filtration and washed with water. Recrystallized with ethanol to obtain white solid. Yield 84%, Mp 92-94 °C, IR (KBr) vmax 3418.2 (OH phenol), 3298, 3210 (NH, NH2), 3055 (CH Ar), 2958 - 2880 (CH aliphatic), 1665 (C=O), 1595 (C=C), 1197 (Ar-O-C), cm-1. 1H-NMR (400MHz, DMSO-d6): 3.68 (s, 6H, 2×OCH3), 4.33 (s, 2H, OCH2), 4.29 (s, 2H, OCH2), 4.74 (bs, 2H, NH2), 6.56 (s, 2H, H-3), 7.69 (d, 2H, J 8.2, H-8), 8.22 (d, 2H, J 7.88, H-9), 8.83 (bs, 1H, CONH), 9.14 (bs, 1H, OH). 13C-NMR (100 MHz, DMSO-d6): 56.1 (2C, OCH3), 71.11 (1C, CH2OCH2), 70.59 (1C, CH2OCH2), 70.59 (1C, CH2OCH2), 107.85 (2C, C-3), 129.01 (2C, C-8), 128.96 (1C, C-10), 133.33 (1C, C-4), 138.84 (1C, C-1), 138.84 (1C, C-1), 141.78 (1C, C-7) 152.08 (2C, C-2), 152.08 (2C, C-2), 166.11 (C=O). HREIMs m/z = 332.1368 [M+H]+ (calc. for C17H20N2O5, 332.1372).

Synthesis of 4-(((4-hydroxy-3,5-dimethoxybenzyl)oxy)methyl)benzohydrazide (5)

Thionyl chloride (4 mL) was added in small portions of 4-(((4-hydroxy-3,5-dimethoxybenzyl)oxy)methyl)benzoic acid (2 g, 6.2 mmol). The mixture was refluxed for 3 h, the excess of thionyl chloride was removed under reduced pressure. 0.1 moles of acid chloride (without further purification) were dissolved in dry benzene (15 mL), and it was transferred to an addition funnel hydrazine hydrate (3%). 5 mL in dried benzene (10 mL) was added into a two neck flask that equipped with a condenser. The addition funnel was then fixed onto the flask and secured firmly. The acid chloride was added dropwise at 0 °C. After that, the mixture was allowed to stand for 1 h at an ambient temperature. It was then stirred and refluxed for 3 h. The excess solvent was removed under reduced pressure and the crude solid was collected, wash with water and recrystallized from ethanol afforded white solid. Yield 84%, Mp 92-94 °C, IR (KBr) vmax 3418.2 (OH phenol), 3298, 3210 (NH, NH2), 3055 (CH Ar), 2958 - 2880 (CH aliphatic), 1665 (C=O), 1595 (C=C), 1197 (Ar-O-C), cm-1. 1H-NMR (400MHz, DMSO-d6): 3.68 (s, 6H, 2×OCH3), 4.33 (s, 2H, OCH2), 4.29 (s, 2H, OCH2), 4.74 (bs, 2H, NH2), 6.56 (s, 2H, H-3), 7.69 (d, 2H, J 8.2, H-8), 8.22 (d, 2H, J 7.88, H-9), 8.83 (bs, 1H, CONH), 9.14 (bs, 1H, OH). 13C-NMR (100 MHz, DMSO-d6): 56.1 (2C, OCH3), 71.11 (1C, CH2OCH2), 70.59 (1C, CH2OCH2), 107.85 (2C, C-3), 129.01 (2C, C-8), 128.96 (1C, C-10), 133.33 (1C, C-4), 138.84 (1C, C-1), 141.78 (1C, C-7) 152.08 (2C, C-2), 166.11 (C=O). HREIMs m/z = 332.1368 [M+H]+ (calc. for C17H20N2O5, 332.1372).

Synthesis of 4-(((4-hydroxy-3,5-dimethoxybenzyl)oxy)methyl)-2,6-dimethoxyphenol (6)

A solution of hydrazide, 5 (2 g, 6 mmol) in methanol (10 mL) and sodium bicarbonate (0.5, 6 mmol) was stirred in 50 mL round bottom flask, then cyanogen bromide (0.66 gm, 6.3 mmol) was added. The mixture was left stirring at ambient temperature overnight. After that, cold water (5 mL) was added to the mixture and the precipitate was collected and dried at 60 °C. The white solid was recrystallized from ethanol to give (62%) yield; Mp
Synthesis of 4-(((4-((5-(4-hydroxy-3-methoxybenzylidene) amino)-1,3,4-oxadiazol-2-yl)benzyl(oxymethyl))-2,6-dimethoxyphenol 7b

The crude mixture was purified by column chromatography using hexane- ethyl acetate (5:1) as eluent to give a white amorphous solid. Yield 69%. Mp 122-124°C. IR (KBr) ν<sub>max</sub> 3608(Oh phenol), 3083(CH<sub>3</sub>), 1621 (CH=N), 1605 (C=N<sub>oxadiazole</sub>), 1594, 1983(C=C), 1231(C=N), 1193(C=O), 1109 (C=O); cm<sup>-1</sup>. 1H NMR (DMSO-d<sub>6</sub>, δ): 3.67(s, 6H, 2×OCH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 4.43 (s, 2H, OCH<sub>2</sub>), 4.55 (s, 2H, OCH<sub>2</sub>), 6.62 (s, 2H, H-3), 6.83 (d, 1H, J 7.8, H-18), 6.86(2H,d, J 8.1, H-9), 8.59 (s, 1H, CH=N), 9.19(bs, 1H, OH), 9.96 (bs, 2H, OH). 13C-NMR (100 MHz, DMSO-d<sub>6</sub>): 56.11(2C, OCH<sub>3</sub>), 56.28(1C, OCH<sub>3</sub>), 71.21(1C, CH<sub>2</sub>OCH<sub>3</sub>), 69.91(1C, CH<sub>2</sub>OCH<sub>3</sub>), 107.85(2C, C-3), 110.32(1C,C-15), 115.85(1C,C-18), 122.44 (1C-C-10), 126.0(1C,C-19), 129.01(2C,C-9), 129.15(1C, C-14), 131.33(2C,C-8), 138.75(1C,C-1), 142.07(1C-C-4), 153.4(1C,C-16), 157(1C,C-17), 161.3(1C,C-13), 162.53 &164.22(C=N oxadiazole). HREIMs m/z = 491.1690 [M-] (calc. for C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>7</sub>), 491.1693.

Synthesis of 4-(((4-(4-hydroxy-3-ethoxybenzylidene)amino)-1,3,4-oxadiazol-2-yl)benzyl(oxymethyl))-2,6-dimethoxyphenol 7c

Crude product recrystallized from chloroform-methanol to afford off white precipitate. Yield 65%. Mp 148-150°C. IR (KBr) ν<sub>max</sub> 3595(Oh phenol), 3077(CH<sub>3</sub>), 2983, 2865 (CH<sub>2</sub><sub>phenyl</sub>) 1618 (CH=N), 1607 (C=N<sub>oxadiazole</sub>), 1595, 1986(C=C), 1225(C=N), 1203(C-O), 1111 (C=O-C); cm<sup>-1</sup>. 1H NMR (400MHz, DMSO-d<sub>6</sub>) 1.41 (t, 3H, J 6.9, O-CH<sub>2</sub>CH<sub>3</sub>), 3.71(s, 6H, 2×OCH<sub>3</sub>), 3.92 (q, 2H, J 7.0, O-CH<sub>2</sub>), 4.42 (s, 2H, OCH<sub>2</sub>), 4.45 (s, 2H, OCH<sub>2</sub>), 6.54 (s, 2H, H-3), 6.86 (d, 2H, J 8.2, H-18), 7.24 (dd, 1H, J 1.8, 2.7, H-19), 7.48 (s, 1H, H-15), 7.71 (2H, d, J 8.2, H-8), 8.21 (2H, d, J 8.2, H-9), 8.57 (s, 1H, CH=N), 9.16(bs, 1H, OH), 9.78 (bs, 1H, OH). 13C-NMR (100 MHz, DMSO-d<sub>6</sub>): 15.2 (1C, O-CH<sub>2</sub>CH<sub>3</sub>), 56.31(2C, OCH<sub>3</sub>), 64.2 (1C, OCH<sub>3</sub>), 69.91(1C, CH<sub>2</sub>OCH<sub>3</sub>), 107.85(2C, C-3), 110.19(1C, C-19), 116.25 (1C, C-15), 123.8 (1C,C-18), 126.44(1C,C-10), 129.01(2C,C-9), 129.15(1C,C-14), 131.33(2C,C-8), 133.04(1C,C-1), 138.75(1C,C-4), 142.07(1C,C-7), 147.26 C-10, 150.6 (1C,C-13).
17) 151.89 (2C, C-2), 161.01 (1C, C=N), 163.12 & 164.03 (C=N oxadiazole). HREIMS m/z = 505.1845 [M+1] (calc. for C_{27}H_{27}N_{3}O_{7}, 505.1849).

Synthesis of 4-(((4-(5-((4-hydroxy-3,5-dimethoxybenzylidene)amino)-1,3,4-oxadiazol-2-yl)benzyl)oxy)methyl)-2,6-dimethoxyphenol 7d

Crude product recrystallized from ethyl acetate-ethanol to afford pale yellow precipitate. Yield 62%. Mp 166-168 °C. IR (KBr) v_max, 3610 (OH phenol), 3082 (CH Ar), 2972, 2860 (CH aliphatic), 1614 (CH=N), 1605 (C=N oxadiazole), 1595, 1980 (C=C), 1221 (C-N), 1198 (C-O), 1135 (C-O-C); cm⁻¹. ¹H-NMR (400MHz, DMSO-d_{6}) δ: 3.71 (s, 6H, 2×OCH_{3}), 3.85 (s, 6H, 2×OCH_{3}), 4.42 (s, 2H, OCH₂), 4.45 (s, 2H, OCH₂), 6.57 (s, 2H, H-3), 7.19 (s, 2H, H-5, H-19), 7.75  (2H, d, J=8.2, H-8), 7.91 (s, 2H, H-15, H-19), 8.18 (2H, d, J=8.2, H-9), 8.59 (s, 1H, CH=N), 9.14 (bs, 2×OH), ¹³C-NMR (100 MHz, DMSO-d_{6}): 56.24 (2C, OCH_{3}), 56.36 (2C, OCH_{3}), 70.77 (1C, CH₂OCH₂), 69.91 (1C, CH₂OCH₂), 105.86 (2C, C-3), 107.98 (2C, C-15, C-19), 124.8 (1C, C-10), 129.21 (2C, C-9), 129.15 (1C, C-14), 131.33 (2C, C-8), 134.04 (1C, C-4), 138.75 (1C, C-7), 142.4 (2C, C-1, C-17) 151.89 (4C, C-2, C-16, C-18), 160.34 (1C, C=N), 162.44 & 165.11 (C=N oxadiazole). HREIMS m/z = 521.1793 [M+1] (calc. for C_{33}H_{39}N_{3}O_{6}, 521.1798).

Antioxidant DPPH assay

The assay was performed as reported by Gerhauser et al. ²⁷. Five microliters of the sample (dissolved in ethanol) was added into 195 µL of 100 µM DPPH reagent in ethanol (96%) and mixed in a 96-well plate. The intensity of the color was measured for 3 h at an interval of 20 min at 515 nm.

FRAP assay

The FRAP assay was performed according to the Benzie and Strain ²⁸ method. The FRAP reagent was prepared by combining 300 mM acetate buffer and 10 mM 2,4,6-tripyridyl-s-triazine (TPTZ) solution in 40 mM HCl and 20 mM FeCl₃·6H₂O, in a ratio of 10:1:1. The FRAP reagent was incubated at 37 °C prior to use. Ten microliters of the sample was reconstituted in the carrier (solvent or ultrapure water) and mixed with 300 µL of FRAP reagent. The mixture was incubated at 37 °C for 4 min in a microplate reader. The absorbance of the complex was 593 nm. The FRAP value can be calculated using the following equation²⁹:

\[
\text{FRAP} = \left(\frac{0-4 \text{ min } \text{ "A}_{593 \text{ nm of test sample}}}{0-4 \text{ min } \text{ "A}_{593 \text{ nm of standard}}}\right) \times \left(\text{[standard] (µM)} \times Y \times 1000\right)
\]

Where 

Y is the absorbance of the spectrophotometer.

RESULTS AND DISCUSSION

Chemistry

The new compounds (7a-7e) were synthesized from multi-steps. Scheme 1 displayed the synthesis of 5-dimethyl-4-(((trimethylsilyl)oxy) benzy alcohol (2) which is used as starting material to synthesis of 4-(((3,5-dimethoxy-4-((trimethylsilyl)oxy)benzylidene)amino)-1,3,4-oxadiazol-2-yl)benzyl)oxy)methyl)-2,6-dimethoxyphenol 7e

The crude products recrystallized from Chloroform afforded pale yellow precipitate. Yield 59.7%, mp 204-206, IR (KBr) v_max, 3633.7 (OH phenol), 3058 (CH Ar), 2960-2885 (CH aliphatic), 1621 (CH=N), 1601 (C=N oxadiazole), 1597-1589 (C=C) and 1262 (ArO-CH₂) 1152 (C-O-C). ¹H NMR, (400 MHz, CDCl₃), δ: 1.42 (s, 18H, 2×(t-Bu), 3.71 (s, 6H, 2×OCH₃), 4.42 (s, 2H, OCH₂), 4.45 (s, 2H, OCH₂), 5.62 (bs, 1H, OH), 6.57 (s, 2H, H-3), 7.72 (2H, d, J=8.2, H-8), 7.91 (s, 2H, H-15, H-19), 8.18 (2H, d, J=8.2, H-9), 8.59 (s, 1H, CH=N), 9.14 (bs, 1H, OH), ¹³C-NMR (100 MHz, DMSO-d₆): 30.32 (6C, 4(C(CH₃)₃)), 34.56 (2C, C(CH₃)₃), 56.12 (2C, OCH₃), 71.21 (1C, CH₂OCH₂), 69.91 (1C, CH₂OCH₂), 70.77 (1C, CH₂OCH₂), 105.86 (2C, C-3), 107.98 (2C, C-15, C-19), 124.8 (1C, C-10), 129.21 (2C, C-9), 129.15 (1C, C-14), 131.33 (2C, C-8), 134.04 (1C, C-4), 138.75 (1C, C-7), 142.4 (2C, C-1, C-17) 151.89 (2C, C-2), 157.25 (1C, C-17), 161.44 (1C, C=N), 162.44 & 165.11 (C=N oxadiazole). HREIMS m/z = 573.2833 [M+1] (calc. for C_{33}H_{39}N_{3}O_{6}, 573.2839).
corresponding hydrazide (5). The hydrazide cyclized to the 5-amino-1,3,4-oxadiazole 6. The 5-amino-1,3,4-oxadiazole were reacted with several substituted of 4-hydroxybenzylaldehyde (Table 1) as shown in Scheme 2.

All synthesized compounds were characterized from their IR, $^1$H-NMR, $^{13}$C-NMR spectrum beside the EIMS and HRMIS.

The IR spectrum of compound 3, showed an interesting peak at 2248 cm$^{-1}$ for $\text{C=NH}$ which is disappearing from compound 4 and a new peak of C=O was appeared at 1673 cm$^{-1}$, as well interesting peak of C=N of the oxadiazole ring for compound 6 was appearing at 1609 cm$^{-1}$. Moreover, the C=N of Schiff bases of compounds 7a-7e were appeared at 1614-1621 cm$^{-1}$beside the C=N of the oxadiazole ring. The $^1$H-NMR spectrum of compound 2 showed the disappearing of the proton of aldehyde from 9.85 ppm and appearing of two protons of CH$_2$ beside the OH which represents the successful reduction of aldehyde group. Furthermore, the new two doublets for compound 3 at 7.41 and 7.49 ppm (H-8, H-9) with coupling constant ($J$) 8.2 and 7.9 Hz respectively represented successfully of reaction compound 2 with 4-(bromo methyl)benzonitrile. As well $^1$H-NMR of compound 4 showed disappearing of trimethyl isilyl group from 0.18 ppm and appears of the broad singlet of OH for the converting the nitrile group to carboxylic acid. The $^1$H-NMR spectrum of compound 5 showed the disappearing of H of carboxylic and appeared of new two board singlet of NH$_2$ and NH at 4.74 and 8.83 ppm respectively, while compound 6 showed disappear these peaks and appeared new signal at 7.51 which is represented the NH$_2$ attached the oxadiazole ring. The $^1$H-NMR of compounds 7a-7e showed appearance of new peaks represented the Schiff base (imin proton) at 8.57-8.68 ppm. The peaks of the substituted 4-hydroxyphenol appeared in their expected areas (see the experimental section). The $^{13}$C-NMR spectrum of compound 2 showed the carbons of trimethylsilyl at -0.05 as well the carbon of CH$_2$-OH. While the $^{13}$C-NMR spectrum of compound 3 displayed two carbons of CH$_2$OH$_2$ at 70.76 & 71.14 beside the C=NH at 101.22 also the carbons of benzonitrile ring. Disappearing of carbon

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Scheme 1: Synthetic route of 3,5-dimethyl-4-((trimethylsilyloxy)benzyl alcohol
Scheme 2: Synthetic route of synthesis 4-(((4-(5-((aryidene) amino)-1,3,4-oxadiazol-2-yl)benzyl)oxy)methyl)-2,6-dimethoxyphenol

Fig. 1: DPPH inhibitions % of 7a-7e

Fig. 2: The possible resonance structure
the HREIMs value was confirmed the accurate mass and the molecular formula as depicted in Table 1.

Antioxidant activity
The synthesized compounds (7a-7e) were exhibited high antioxidant ability in both assays. Based on the type of substitute group of phenol. Compound 7e, which I possess 2,6-di-tert-butylphenol group shows antioxidant ability slightly higher than ascorbic acid in both assays (DPPH and FRAP) as shown in Figure 1.

While, compound 7d which is posses 2,6-di methoxy phenol group exhibited antioxidant ability higher than BHT also, all compounds showed antioxidant activity more than 2,6-dimethoxy phenol itself. The antioxidant of the substituted phenol followed the following sequence: 2,6-di-tert-butyl>2,6-dimethoxy>2-methoxyH"2-ethoxy> non substituted phenol. These results are in agreement with many articles xxx that the more hindered phenol increase the antioxidant stability. Furthermore, we assume that the long chain resonance between the substituted phenol and the main group (CH=N) attached the oxadiazole ring after donating a proton could enhance the free radical stability, which can enhance the free-radical scavenging ability. As shown in Figure 2.

The FRAP value was higher than DPPH when comparing the results with the references and this difference could be attributed to the different mechanisms for FRAP and DPPH. FRAP involves a single electron transfer mechanism, whereas DPPH assay depends on the H-atom transfer mechanism30 beside the hindrances around the phenol. Figure 3 displayed the FRAP value of the synthesized compound 7a-7e

CONCLUSIONS
A series of new Schiff base compounds from 5-amino-1,3,4-oxadizole incorporating hindered phenol moieties were successfully synthesized and characterized. All of the new compounds were screened for antioxidant activity using the FRAP and DPPH assays. The antioxidant ability of these compounds increases with increasing the hindered phenol.

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