http://dx.doi.org/10.5012/bkcs.2012.33.8.2585

Synthesis of Heterocyclic Chalcone Derivatives and Their Radical Scavenging Ability Toward 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) Free Radicals

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Received April 24, 2012, Accepted May 7, 2012

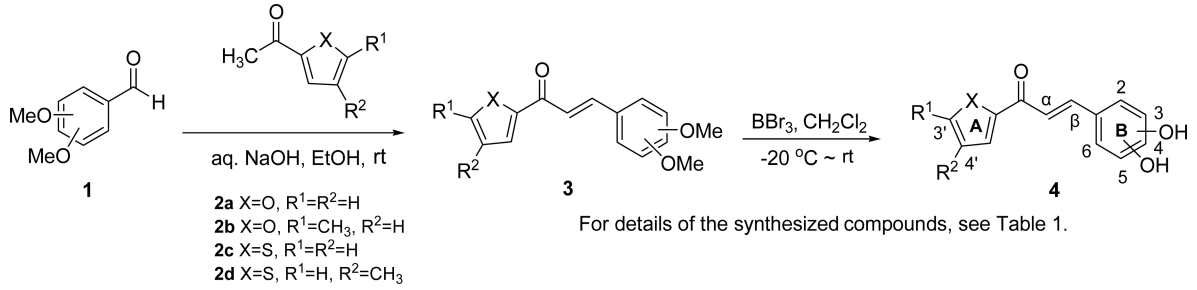
A series of heterocyclic chalcone derivatives bearing heterocycles such as thiophene or furan ring as an isostere of benzene ring were carefully prepared, and the influence of heterocycles on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activities was systematically investigated. Structure-activity relationships (SAR) analysis showed that the activities of thiophene ring-containing chalcones were higher than those of furan ring-containing chalcones, and the presence of methyl substituent of heterocyclic ring distinctly affected the activities compared with non-substituted heterocycles in an opposite manner, with the 4'-methyl group of thiophene ring increasing activity and the 3'-methyl group of the furan ring decreasing activity. The distinct isosteric effect of heterocycles (*i.e.*, thiophene or furan ring) on radical scavenging activities of heterocyclic chalones was distinctly demonstrated in our work.

Key Words : Heterocyclic chalcones, Anti-oxidant, DPPH free radical, Furane, Thiophene

Introduction

Chalcones (1,3-diaryl-2-propen-1-ones) are a major class of natural products belonging to the flavonoid family. Interesting pharmacological activities attributed to chalcones include anti-bacterial, anti-fungal, anti-inflammatory, anti-microbial, anti-tumor, insect anti-feedant and anti-mutagenic.[1] The biological activities of chalcones could be closely correlated to their anti-oxidant potential.[2] The versatility of chalcones has spurred synthesis-based efforts to develop diverse chalcone derivatives with improved activities and physiological stability. Because the anti-oxidant property of chalcones are markedly influenced by the two aryl structures of the chalcone molecule, their structural modification has mainly focused on the variation of the two aryl structures, *i.e.*, the substituents on the two aryl rings and their substitution patterns.[3,4] Accordingly, we previously performed a synthetic-based study on a series of dihydroxylated chalcone derivatives with diverse substitution patterns including a phenyl ring at the 3-position of chalcone and the *para*-substituents on a phenyl ring at 1-position, which included a structure-activity relationship (SAR) analysis.[5] The data demonstrated that the substitution patterns of two hydroxyl groups on ring B are very important structural factors in the enhancement of radical scavenging activity.

These positive results encouraged us to extend the synthetic spectrum of chalcone derivatives. In the present work, we prepared heterocyclic chalcone derivatives bearing heterocycles at the 1-position of chalcone, such as thiophene or the furan ring as an isostere of benzene ring, which have the same dihydroxylated substitution patterns on a phenyl ring at the 3-position as in our previous work,[5] and then systematically investigated their SAR. The isosteric equivalent to the benzene ring, such as thiophene or furan ring, could influence the electronic distribution through the chalcone molecule, which consequently could change its polarities, while the aromaticity of heterocycles would be conserved, with the size-difference between heterocycles and benzene being ignored. The change of the electronic and structural environments in the chalcone skeleton due to the heterocycle could influence their anti-oxidant activities in terms of radical quenching properties. In fact, some intermittent SAR of some heterocyclic chalcone derivatives has been reported in the recent literature.[6] However, the systematic study on the synthesis and the analysis of their SAR is fairly rare. Herein, we report synthetic details of the preparation of the



Scheme 1. General procedure for the formation of heterocyclic chalcones (**3a-3t**, **4a-4t**).

heterocyclic chalcone derivatives bearing heterocycles such as thiophene or furan ring as an isostere of benzene ring at 1-position of chalcone (Scheme 1), and the analysis of the structure-activity relationships in terms of their anti-oxidant activities. The anti-oxidant activity of the heterocyclic chalcone derivatives was measured by standard free radical scavenging assay (2,2-diphenyl-1-picrylhydrazyl (DPPH) test) as a primary tool.

Experimental Section

Chemistry. Melting points were recorded on Electro-thermal melting point apparatus and were uncorrected. ^{1}H- and ^{13}C- NMR spectra were recorded on Jeol 400 MHz or 600 MHz spectrometer. Chemical shifts are shown in δ values (ppm) with tetramethylsilane (TMS) as internal standard. All chemicals were purchased from Sigma-Aldrich (USA). All solvents for column chromatography were of reagent grade and were purchased from commercial sources. Methylene chloride used as a reaction solvent was distilled from commercial analytical grade after being refluxed in the present of CaH_2.

General Synthetic Procedure for the Preparation of Heterocyclic Dimethoxy Chalcone Derivatives (3a-3t, Scheme 1 and Table 1). Aqueous NaOH (53 mg in 0.5 mL water, 1.32 mmol) was added dropwise to a solution of appropriate dimethoxybenzaldehyde (3.0 mmol) and 2-acetylthiophene **2c** (356 μL, 3.3 mmol) in absolute ethanol (3 mL). The resulting mixture was stirred at room temperature for 1-2 h. The reaction mixture was diluted with water (100 mL) and adjusted to neutral pH with 10% aqueous HCl, and then extracted with ethyl acetate (50 mL × 2). The combined organic layer was washed with water, saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to yield crude residue. The desired product was purified by flash column chromatography eluted with hexane-ethyl acetate co-solvent to afford a solid (**3a-3t**, Table 1).

3a: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, 1H, *J* = 15.6 Hz), 7.82 (d, 1H, *J* = 2.4 Hz), 7.62 (d, 1H, *J* = 4.8 Hz), 7.55 (d, 1H, *J* = 8.4 Hz), 7.45 (d, 1H, *J* = 15.6 Hz), 7.15 (dd, 1H, *J* = 4.8, 3.6 Hz), 6.53 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.47 (d, 1H, *J* = 2.4 Hz), 3.89 (s, 3H), 3.84 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 182.65, 163.04, 160.45, 146.10, 139.71, 132.99, 131.71, 131.08, 128.00, 119.98, 116.94, 105.43, 98.43, 55.50, 55.44.

3b: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.86 (d, 1H, *J* = 15.6 Hz), 7.63 (s, 1H), 7.55 (d, 1H, *J* = 8.8 Hz), 7.41(d, 1H, *J* = 15.6 Hz), 7.22 (s, 1H), 6.52 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.46 (d, 1H, *J* = 2.4 Hz), 3.90 (s, 3H), 3.84 (s, 3H), 2.31 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 182.56, 162.97, 160.39, 145.55, 139.45, 138.77, 133.21, 130.97, 128.89, 119.92, 116.96, 105.37, 98.37, 55.49, 55.44, 15.63.

3c: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, 1H, *J* = 15.6 Hz), 7.62 (d, 1H, *J* = 1.6 Hz), 7.58 (d, 1H, *J* = 8.8 Hz), 7.44 (d, 1H, *J* = 15.6 Hz), 7.27 (d, 1H, *J* = 3.2 Hz), 6.56 (t, 1H, *J* = 2.0 Hz), 6.53 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.46 (d, 1H, *J* = 2.4 Hz), 3.90 (s, 3H), 3.85(s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 178.67, 163.10, 160.48, 154.08, 146.03, 139.51, 130.89, 119.36, 116.97, 116.73, 112.22, 105.43, 98.38, 55.50, 55.45.

3d: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, 1H, *J* = 15.6 Hz), 7.57 (d, 1H, *J* = 8.40 Hz), 7.37 (d, 1H, *J* = 15.6 Hz), 7.19 (d, 1H, *J* = 3.2 Hz), 6.52 (dd, 1H, *J* = 8.4, 2.4 Hz), 6.47 (d, 1H, *J* = 2.4 Hz), 6.19 (d, 1H, *J* = 2.4 Hz), 3.89 (s, 3H), 3.85 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 178.00, 162.91, 160.34, 157.53, 152.85, 138.74, 130.70, 119.59, 118.76, 117.12, 108.96, 105.37, 98.38, 55.49, 55.45, 14.12.

3e: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 1H, *J* = 4.4 Hz), δ 7.81 (d, 1H, *J* = 15.6 Hz), δ 7.67 (d, 1H, *J* = 4.4 Hz), δ 7.29 (d, 1H, *J* = 15.6 Hz), δ 7.25 (d, 1H, *J* = 8.4 Hz), δ 7.18 (t, 1H, *J* = 4.4 Hz), 7.15 (s, 1H), δ 6.90 (d, 1H, *J* = 8.4 Hz), 3.95 (s, 3H), δ 3.93 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 181.99, 151.48, 149.24, 145.71, 144.17, 133.50, 131.46, 128.12, 127.68, 123.12, 119.50, 111.14, 110.25, 77.31, 77.00, 76.67, 55.97.

3f: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, 1H, *J* = 15.6 Hz), 7.67 (s, 1H), 7.26 (d, 1H, *J* = 15.6 Hz), 7.24 (s, 1H), 7.22 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.14 (d, 1H, *J* = 2.0 Hz), 6.88 (d, 1H, *J* = 8.4 Hz), 3.94 (s, 3H), 3.91 (s, 3H), 2.30 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 181.78, 151.26, 149.06, 145.07, 143.77, 138.81, 133.41, 129.33, 127.58, 123.02, 119.32, 110.97, 110.04, 55.82, 15.50.

3g: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, 1H, *J* = 15.6 Hz), 7.65 (s, 1H), 7.33 (d, 1H, *J* = 3.6 Hz), 7.32 (d, 1H, *J* = 15.6 Hz), 7.24 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.17 (d, 1H, *J* = 2.0 Hz), 6.90 (d, 1H, *J* = 8.4 Hz), 6.59 (dd, 1H, *J* = 3.6, 2.0 Hz), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 178.04, 153.84, 151.50, 149.23, 146.22, 144.08, 127.73, 123.31, 119.01, 117.08, 112.45, 111.10, 110.13, 55.97, 55.94.

3h: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, 1H, *J* = 15.6 Hz), 7.26 (d, 1H, *J* = 4.4 Hz), 7.25 (d, 1H, *J* = 15.6 Hz), 7.24 (d, 1H, *J* = 6.0 Hz), 7.15 (d, 1H, *J* = 2.4 Hz), 6.90 (d, 1H, *J* = 8.8 Hz), 6.22 (dd, 1H, *J* = 3.4, 1.2), 3.95 (s, 3H), 3.93 (s, 3H), 2.45 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 177.32, 157.87, 152.59, 151.30, 149.17, 143.41, 127.86, 123.05, 119.17, 111.09, 110.21, 109.22, 77.31, 77.00, 76.67, 55.96, 14.16.

3i: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, 1H, *J* = 4.0 Hz), 7.76 (d, 1H, *J* = 15.6 Hz), 7.68 (d, 1H, *J* = 4.0 Hz), 7.37 (d, 1H, *J* = 15.6 Hz), 7.18 (t, 1H, *J* = 4.0 Hz), 6.77 (d, 2H, *J* = 2.0 Hz), 6.53 (t, 1H, *J* = 2.0 Hz), 3.38 (s, 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 181.95, 161.03, 145.43, 144.03, 136.56, 133.91, 131.84, 128.21, 122.07, 106.39, 102.71, 55.44.

3j: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, 1H, *J* = 15.6 Hz), 7.67 (s, 1H), 7.33 (d, 1H, *J* = 15.6 Hz), 7.27 (s, 1H), 6.77 (d, 2H, *J* = 2.4 Hz), 6.52 (t, 1H, *J* = 2.4 Hz), 3.84 (s, 6H), 2.32 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 181.89, 161.05, 144.91, 143.78, 139.02, 136.66, 133.85, 129.81, 122.89, 106.37, 102.67, 55.46, 15.60.

3k: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 1H, *J* = 15.6 Hz), 7.66 (s, 1H), 7.40 (d, 1H, *J* = 15.6 Hz), 7.34 (d, 1H, *J* =

4.0 Hz), 6.79 (d, 2H, J = 2.0 Hz), 6.60 (dd, 1H, J = 4.0, 1.6 Hz), 6.53 (t, 1H, J = 2.0 Hz), 3.84 (s, 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 177.93, 161.03, 153.66, 146.52, 143.98, 136.59, 121.63, 117.54, 112.54, 106.41, 102.85, 55.45.

3l: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 1H, J = 15.6 Hz), 7.33 (d, 1H, J = 15.6 Hz), 7.26 (d, 1H, J = 3.6 Hz), 6.78 (d, 2H, J = 2.0 Hz), 6.51 (t, 1H, J = 2.0 Hz), 6.22 (d, 1H, J = 3.6 Hz), 3.83 (s, 6H), 2.44 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 177.14, 161.01, 158.19, 152.46, 143.24, 136.76, 121.82, 119.61, 109.32, 106.36, 102.56, 55.44, 14.16.

3m: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, 1H, J = 16.0 Hz), 7.86 (d, 1H, J = 4.0 Hz), 7.67 (d, 1H, J = 5.2 Hz), 7.51 (d, 1H, J = 16.0 Hz), 7.26 (d, 1H, J = 8.0 Hz), 7.17 (t, 1H, J = 4.0 Hz), 7.09 (t, 1H, J = 8.0 Hz), 6.97 (d, 1H, J = 8.0 Hz), 3.89 (s, 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 182.36, 153.21, 148.99, 145.61, 138.95, 133.69, 131.71, 128.89, 128.16, 124.15, 123.27, 119.78, 114.22, 61.25, 55.87.

3n: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, 1H, J = 15.6 Hz), 7.66 (s, 1H), 7.47 (d, 1H, J = 15.6 Hz), 7.27~7.25 (m, 2H), 7.09 (t, 1H, J = 8.0 Hz), 6.97 (d, 1H, J = 8.0 Hz), 3.89 (s, 6H), 2.32 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 182.32, 153.24, 149.00, 145.10, 138.98, 138.72, 133.78, 129.59, 129.02, 124.15, 123.37, 119.77, 114.17, 61.30. 55.90, 15.62.

3o: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, 1H, J = 15.6 Hz), 7.65 (d, 1H, J = 1.2 Hz), 7.50 (d, 1H, J = 15.6 Hz), 7.32 (d, 1H, J = 3.6 Hz), 7.28 (dd, 1H, J = 8.0, 1.2 Hz), 7.09 (t, 1H, J = 8.0 Hz), 6.97 (dd, 1H, J = 8.0 Hz), 6.59 (dd, 1H, J = 3.6, 2.0 Hz), 3.89 (s, 6H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 178.24, 153.76, 153.18, 149.02, 146.42, 138.75, 128.91, 124.11, 122.67, 119.61, 117.39, 114.24, 112.41, 61.30, 55.85.

3p: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, 1H, J = 16.0 Hz), 7.44 (d, 1H, J = 16.0 Hz), 7.27 (d, 1H, J = 8.4 Hz), 7.24 (d, 1H, J = 3.6 Hz), 7.08 (t, 1H, J = 8.0 Hz), 6.96 (dd, 1H, J = 8.4, 0.8 Hz), 6.21 (d, 1H, J = 3.6 Hz), 3.89 (s, 3H), 3.88 (s, 3H), 2.44 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 177.58, 158.01, 153.21, 152.62, 148.95, 138.07, 129.14, 124.10, 123.03, 119.67, 119.44, 114.05, 109.21, 61.30, 55.89, 14.15.

3q: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, 1H, J = 16.0 Hz), 7.85 (d, 1H, J = 3.6, 1.2 Hz), 7.67 (dd, 1H, J = 5.2, 1.2 Hz), 7.50 (d, 1H, J = 16.0 Hz), 7.17 (dd, 1H, J = 4.4, 4.0 Hz), 7.15 (d, 1H, J = 2.8 Hz), 6.94 (dd, 1H, J = 9.2, 2.8 Hz), 6.88 (d, 1H, J = 9.2 Hz), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 182.55, 153.49, 153.43, 145.76, 139.45, 133.53, 131.64, 128.13, 124.37, 122.77, 117.16, 114.07, 112.48, 56.11, 55.85.

3r: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, 1H, J = 16.0 Hz), 7.65 (s, 1H), 7.46 (d, 1H, J = 16.0 Hz), 7.25 (s, 1H), 7.15 (d, 1H, J = 3.2 Hz), 6.94 (dd, 1H, J = 9.2, 3.2 Hz), 6.87 (d, 1H, J = 9.2 Hz), 3.87 (s, 3H), 3.82 (s, 3H), 2.32 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 182.43, 153.49, 153.39, 145.21, 139.16, 138.91, 133.64, 129.41, 124.43, 122.74, 117.08, 113.97, 122.47, 56.12, 55.84, 15.63.

3s: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, 1H, J = 16.0 Hz), 7.65 (d, 1H, J = 2.0 Hz), 7.49 (d, 1H, J = 16.0 Hz), 7.31 (d, 1H, J = 3.6 Hz), 7.18 (d, 1H, J = 2.8 Hz), 6.94 (dd, 1H, J = 8.4 Hz), 6.58 (dd, 1H, J = 3.6, 2.0 Hz), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 176.76, 153.20, 152.97, 152.69, 148.27, 137.01, 123.19, 121.93, 119.37, 118.03, 113.02, 112.68, 112.63, 56.10, 55.64.

3t: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, 1H, J = 15.6 Hz), 7.42 (d, 1H, J = 15.6 Hz), 7.23 (d, 1H, J = 3.2 Hz), 7.17 (d, 1H, J = 2.8 Hz), 6.93 (dd, 1H, J = 8.8, 2.8 Hz), 6.86 (d, 1H, J = 8.8 Hz), 6.20 (dd, 1H, J = 3.2, 1.2 Hz), 3.86 (s, 3H), 3.81 (s, 3H), 2.44 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 177.68, 157.92, 153.46, 153.33, 152.65, 138.46, 124.54, 122.30, 119.33, 116.96, 113.77, 112.44, 109.13, 56.09, 55.84, 14.15.

General Synthetic Procedure for the Preparation of Heterocyclic Dihydroxychalcones (4a-4t except 4k, Scheme 1 and Table 1). Compound **3a** (350 mg, 1.27 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) under an argon (Ar) atmosphere and cooled in ice bath for 10 min. To this solution was added pre-cooled BBr_3 (1 M in CH_2Cl_2, 7.7 mL, 7.65 mmol) in dropwise fashion. The color of the solution was changed from yellow to dark violet. Then, the ice-bath was removed and the reaction mixture was stirred for 1-2 h at ambient temperature. After checking the completeness of the reaction by thin layer chromatography (TLC), the reaction mixture was diluted with ice-water (50 mL) and adjusted to pH 6 by adding ice-cooled 5% aqueous K_2HPO_4. The mixture was extracted with ethyl acetate (50 mL × 2), and the combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated to dryness to yield crude red crystal. The desired product was purified by flash silica gel column chromatography with the elution of CH_2Cl_2-MeOH co-solvent (v/v = 95:5) to give analytically pure demethylated heterocyclic chalcones **4a**. In the preparation of **4k**, 2 equivalents of $AlCl_3$ to **3k** and 4 equivalents of Me_2S were sequentially added to the solution of **3k**,[7] and the reaction mixture was stirred for 12 h at 0 °C. The same work-up procedure was adopted.

4a: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 10.18 (s, 1H), 9.95 (s, 1H), 8.11 (d, 1H, J = 3.2 Hz), 7.95 (d, 1H, J = 15.6 Hz), 7.94 (d, 1H, J = 10.8 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 15.6 Hz), 7.26 (t, 1H, J = 4.4 Hz), 6.37 (s, 1H), 6.31 (d, 1H, J = 8.4 Hz); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 182.81, 160.99, 159.22, 146.30, 141.00, 132.53, 131.32, 130.85, 127.86, 118.22, 114.12, 108.16, 103.26.

4b: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 10.15 (s, 1H), 9.96 (s, 1H), 7.95 (s, 1H), 7.93 (d, 1H, J = 15.6 Hz), 7.67 (d, 1H, J = 8.8 Hz), 7.56 (s, 1H), 7.52 (d, 1H, J = 15.6 Hz), 6.37 (d, 1H, J = 2.4 Hz), 6.30 (dd, 1H, J = 8.8, 2.0 Hz), 2.26 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 181.50, 161.45, 159.09, 145.62, 138.92, 138.72, 134.08, 130.11, 129.78, 116.78, 113.13, 107.95, 102.43.

4c: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 10.26 (s, 1H), 10.02 (s, 1H), 8.05 (s, 1H), 8.01 (d, 1H, J = 15.6 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.63 (d, 1H, J = 3.6 Hz), 7.50 (d, 1H, J = 15.6 Hz), 6.80 (d, 1H, J = 2.0 Hz), 6.44 (d, 1H, J = 2.0), 6.37 (dd, 1H, J = 8.0, 2.0 Hz); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 177.19, 161.51, 159.18, 153.47, 147.41, 138.96, 130.33, 117.68, 116.88, 113.11, 112.54, 108.02, 102,50.

4d: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 10.14 (s, 1H), 9.91 (s, 1H), 7.90 (d, 1H, J = 15.6 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 2.8 Hz), 7.37 (d, 1H, J = 15.6 Hz), 6.36 (s, 2H), 6.29 (d, 1H, J = 8.4 Hz), 2.37 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 176.40, 161.27, 158.94, 157.39, 152.32, 138.15, 130.01, 119.45, 116.92, 113.13, 109.18, 107.89, 102.45.

4e: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.71 (s, 1H), 9.09 (s, 1H), 8.23 (d, 1H, J = 4.4 Hz), 7.99 (d, 1H, J = 4.4 Hz), 7.58 (d, 1H, J = 15.6 Hz), 7.53 (d, 1H, J = 15.6 Hz), 7.27 (t, 1H, J = 4.4 Hz), 7.25 (d, 1H, J = 2.0 Hz), 7.17 (dd, 1H, J = 8.0, 2.0 Hz), 6.80 (d, 1H, J = 8.0 Hz); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 181.42, 148.77, 145.85, 145.57, 144.04, 134.80, 132.84, 128.78, 126.08, 122.21, 118.22, 115.70, 115.61.

4f: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.68 (s, 1H), 9.10 (s, 1H), 8.07 (s, 1H), 7.58 (s, 1H), 7.54-7.51 (d, 2H, J = 15.6 Hz), 7.24 (s, 1H), 7.16 (dd, 1H, J = 8.4, 1.2 Hz), 6.79 (d, 1H, J = 8.4 Hz), 2.27 (s, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 181.34, 148.73, 145.60, 145.33, 143.83, 138.86, 134.87, 130.35, 126.14, 122.18, 118.25, 115.69, 115.59, 15.34.

4g: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.76 (s, 1H), 9.18 (s, 1H), 8.08 (d, 1H, J = 2.0 Hz), 7.76 (d, 1H, J = 4.0 Hz), 7.64 (d, 1H, J = 15.6 Hz), 7.44 (d, 1H, J = 15.6 Hz), 7.28 (d, 1H, J = 2.0 Hz), 7.20 (dd, 1H, J = 8.4, 2.0 Hz), 6.86 (d, 1H, J = 8.4 Hz), 6.81 (dd, 1H, J = 3.4, 2.0 Hz); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 176.69, 153.15, 148.75, 147.80, 145.59, 143.66, 126.00, 122.12, 118.46, 118.19, 115.73, 115.35, 112.59.

4h: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.68 (s, 1H), 9.12 (s, 1H), 7.62 (d, 1H, J = 3.6 Hz), 7.53 (d, 1H, J = 15.6 Hz), 7.33 (d, 1H, J = 15.6 Hz), 7.20 (d, 1H, J = 2.0 Hz), 7.12 (dd, 1H, J = 8.4, 2.0 Hz), 6.78 (d, 1H, J = 8.4 Hz), 6.39 (d, 1H, J = 3.6 Hz), 2.38 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 175.94, 157.86, 152.09, 148.58, 145.58, 143.01, 126.10, 121.97, 120.27, 118.27, 115.71, 115.27, 109.33, 13.69.

4i: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.46 (s, 2H), 8.29 (d, 1H, J = 4.0 Hz), 8.03 (dd, 1H, J = 4.0, 1.2 Hz), 7.66 (d, 1H, J = 15.6 Hz), 7.50 (d, 1H, J = 15.6 Hz), 7.28 (td, 1H, J = 4.0, 1.2 Hz), 6.68 (d, 2H, J = 2.0 Hz), 6.35 (s, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 181.59, 158.64, 145.42, 143.80, 136.17, 135.38, 133.54, 128.91, 121.49, 106.94, 105.18.

4j: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.45 (s, 2H), 8.12 (s, 1H), 7.62 (d, 1H, J = 15.6 Hz), 7.61 (s, 1H), 7.48 (d, 1H, J = 15.6 Hz), 6.67 (d, 1H, J = 2.0 Hz), 6.35 (s, 1H), 2.26 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 181.48, 158.66, 144.88, 143.57, 139.00, 136.18, 135.50, 130.87, 121.52, 106.90, 105.13, 15.27.

4k: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.47 (s, 2H), 8.04 (s, 1H), 7.79 (d, 1H, J = 3.6 Hz), 7.51+7.49 (AB, 2H, J = 15.6 Hz), 6.76 (dd, 1H, J = 3.6, 2.0 Hz), 6.64 (d, 2H, J = 1.6 Hz), 6.33 (s, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 176.66, 158.66, 152.90, 148.26, 143.42, 136.04, 121.44, 119.31, 112.73, 106.79, 105.14.

4l: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.44 (s, 2H), 7.70 (d, 1H, J = 3.6 Hz), 7.47-7.43 (d, 2H, J = 15.6 Hz), 6.64 (d, 2H, J = 2.0 Hz), 6.40 (d, 1H, J = 3.6 Hz), 6.33 (s, 1H), 2.38 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 175.85, 158.66, 158.38, 151.89, 142.80, 136.17, 121.51, 121.10, 109.50, 106.72, 105.02, 13.69.

4m: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.33 (br, 2H,), 8.20 (dd, 1H, J = 4.0; 1.2 Hz), 8.06 (d, 1H, J = 15.6 Hz), 8.02 (dd, 1H, J = 4.0, 1.2 Hz), 7.71 (d, 1H, J = 15.6 Hz), 7.33 (dd, 1H, J = 8.0, 1.2 Hz), 7.28 (dd, 1H, J = 5.0, 4.0 Hz), 6.85 (dd, 1H, J = 8.0, 1.2 Hz), 6.69 (t, 1H, J = 8.0 Hz); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 181.76, 145.99, 145.72, 145.67, 138.82, 135.03, 132.94, 128.83, 121.80, 120.49, 119.11, 118.45, 117.16.

4n: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.68 (s, 1H), 9.15 (s, 1H), 8.04 (d, 1H, J = 15.6 Hz), 8.03 (s, 1H), 7.68 (d, 1H, J = 15.6 Hz), 7.60 (s, 1H), 7.32 (d, 1H, J = 8.0 Hz), 6.86 (d, 1H, J = 8.0 Hz), 6.70 (t, 1H, J = 8.0 Hz), 2.27 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 181.67, 145.94, 145.74, 145.18, 138.91, 138.63, 134.86, 130.53, 121.88, 120.55, 119.16, 118.45, 117.16, 15.30.

4o: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.68 (s, 1H), 9.18 (s, 1H), 8.04 (d, 1H, J = 15.6 Hz), 8.02 (s, 1H), 7.67 (d, 1H, J = 3.6 Hz), 7.59 (d, 1H, J = 15.6 Hz), 7.26 (d, 1H, J = 8.0 Hz), 6.85 (dd, 1H, J = 8.0, 1.2 Hz), 6.75 (dd, 1H, J = 3.6, 1.6 Hz), 6.69 (t, 1H, J = 8.0 Hz); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 177.11, 153.17, 147.95, 145.98, 145.73, 138.63, 121.76, 120.63, 119.17, 118.62, 117.19, 112.69, 48.59.

4p: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.65 (s, 1H), 9.12 (s, 1H), 8.01 (d, 1H, J = 15.6 Hz), 7.60 (d, 1H, J = 3.6 Hz), 7.52 (d, 1H, J = 15.6 Hz), 7.25 (d, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 8.0 Hz), 6.68 (t, 1H, J = 8.0 Hz), 6.40 (d, 1H, J = 2.8 Hz), 2.85 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 176.22, 158.05, 152.08, 145.78, 145.71, 137.84, 121.87, 120.63, 120.48, 119.12, 118.36, 117.00, 109.39, 13.70.

4q: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.58 (s, 1H), 8.92 (s, 1H), 8.21 (d, 1H, J = 3.2 Hz), 8.01 (dd, 1H, J = 4.8, 1.2 Hz), 7.97 (d, 1H, J = 15.6 Hz), 7.65 (d, 1H, J = 15.6 Hz), 7.28 (dd, 1H, J = 4.8, 3.6 Hz), 7.20 (s, 1H), 6.75 (s, 2H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 181.73, 150.33, 149.94, 145.66, 138.77, 134.97, 132.94, 128.86, 121.44, 120.33, 119.90, 116.97, 113.35.

4r: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.57 (s, 1H), 8.91 (s, 1H), 8.04 (s, 1H), 7.96 (d, 1H, J = 15.6 Hz), 7.62 (d, 1H, J = 15.6 Hz), 7.59 (s, 1H), 7.21 (s, 1H), 6.75 (s, 2H), 2.26 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 181.62, 150.31, 149.97, 145.15, 138.94, 138.53, 134.90, 130.46, 121.52, 120.35, 119.85, 116.97, 113.32, 15.29.

4s: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.57 (s, 1H), 8.90 (s, 1H), 8.02 (s, 1H), 7.96 (s, 1H, J = 15.6 Hz), 7.67 (d, 1H, J = 3.2 Hz), 7.51 (d, 1H, J = 15.6 Hz), 7.14 (s, 1H), 6.75 (m, 1H), 6.74 (s, 2H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 177.02, 153.15, 150.30, 149.93, 147.91, 138.44, 121.35, 120.30, 119.85, 118.58, 117.01, 113.25, 112.68.

4t: ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.54 (s, 1H), 8.90 (s, 1H), 7.92 (d, 1H, J = 15.6 Hz), 7.60 (d, 1H, J = 3.6 Hz), 7.45 (d, 1H, J = 15.6 Hz), 7.13 (d, 1H, J = 2.8 Hz), 6.73 (m, 2H), 6.40 (d, 1H, J = 3.6 Hz), 2.49 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 176.21, 157.97, 152.09, 150.15, 149.92, 137.75, 121.46, 120.37, 120.32, 119.63, 116.97, 113.11, 109.42, 13.69.

DPPH Free Radical Scavenging Assay. The DPPH assay was based on the reported methods.[7] Briefly, the ethanolic sample solution of 100 μL at several concentrations was added to 100 μL of 100 μM of 1,1-diphenyl-2picryl-hydrazyl (DPPH) solution in ethanol in 96 well plates. The mixed solution was incubated at room temperature for 30 min. The absorbance of reaction mixture was read at 517 nm using a VERSA max microplate reader (Molecular Devices, USA) and the remaining DPPH was calculated. The free radical scavenging activity was expressed as follows:

$$\text{DPPH scavenging activity (\%)} = \left(\frac{Ac-As}{Ac-Ab}\right) \times 100,$$

, where *Ac* was the absorbance of the control, *As* was the the sample and *Ab* was the blank (EtOH). Each sample was assayed at five concentrations (12, 25, 50, 100, and 200 μM) and four wells for each concentration. All experiments were carried out in triplicate. The IC_{50} values were defined as the concentration that could scavenge 50% DPPH free radical. Ascorbic acid and α-tocopherol were used as positive control.

Statistical Analysis. Determination of all samples was carried out in triplicate for DPPA assays. All results were calculated as mean standard deviation (S.D.).

Results and Discussion

The diversely substituted heterocyclic chalcone derivatives **3** were easily prepared in good yield (74-99%, Table 1) through base-catalyzed Claisen-Schmidt condensation of five kinds of dimethoxybenzaldehydes **1** with four kinds of heterocyclic ketones **2** (Scheme 1). The heterocyclic ketones **2** used in the reaction include 2-acetylthiophene, 2-acetyl-4-methylthiophene, 2-acetylfuran, and 2-acetyl-5-methylfuran. As a next step, the heterocyclic dihydroxychalcones **4** were prepared in acceptable but various yields (50-90%, Table 1) by applying a usual demethylation reaction condition (boron tribromide,[7] ambient temperature, 1-2 h) to the corresponding compound **3**. But, the demethylation of compound **3k** was an exceptional case; the application of the same demethylation condition to **3k** gave no desired product. After several demethylation conditions were attempted, the desired product **4k** was obtained with the condition, $AlCl_3$/Me_2S[8] at 0 °C but in fairly poor yield (14%). The double bond geometry of all chalcones was determined as *E* from the characteristic coupling constants between α and β protons, 15-16 Hz. With the synthetic heterocyclic chalcone compounds in hand, the anti-oxidant activity was measured by DPPH free radical scavenging assay as a primary tool to investigate systematic SAR. The structures of the synthetic compounds and their inhibitory activity (IC_{50} (μM)) values are listed in Table 1. The statistically analyzed results of scavenging activity of DPPH radicals of each compound are shown in Figure 1.

Most compounds show the increase of DPPH radical scavenging activities in concentration-dependent manner. The first notable observation is that three groups of heterocyclic chalcone compounds (3,4-dihydroxyl: **4e**-**4h**, 2,3-dihydroxyl: **4m**-**4p**, and 2,5-dihydroxyl: **4q**-**4t**) show much higher DPPH radical scavenging activities than those of two

Table 1. The specifications of synthesized heterocyclic chalcones **3** and **4**

Compound	R_1	R_2	X	Substituents on ring B	Yield (%)[a]	mp (°C)	IC_{50} (μM)	Compound	R_1	R_2	X	Substituents on ring B	Yield (%)	mp (°C)	IC_{50} (μM)
3a	H	H	S	2,4-diOCH_3	96	102-103	>200	**4a**	H	H	S	2,4-diOH	76	118	>200
3b	H	CH_3	S	2,4-diOCH_3	92	oily	>200	**4b**	H	CH_3	S	2,4-diOH	75	121-122	>200
3c	H	H	O	2,4-diOCH_3	88	oily	>200	**4c**	H	H	O	2,4-diOH	60	162(dec.)	>200
3d	CH_3	H	O	2,4-diOCH_3	99	96.5	>200	**4d**	CH_3	H	O	2,4-diOH	97	157(dec.)	>200
3e	H	H	S	3,4-diOCH_3	84	160	>200	**4e**	H	H	S	3,4-diOH	90	181	35
3f	H	CH_3	S	3,4-diOCH_3	85	oily	>200	**4f**	H	CH_3	S	3,4-diOH	60	172.8	20
3g	H	H	O	3,4-diOCH_3	86	109	>200	**4g**	H	H	O	3,4-diOH	73	168.5	67
3h	CH_3	H	O	3,4-diOCH_3	87	119	>200	**4h**	CH_3	H	O	3,4-diOH	68	198(dec.)	>200
3i	H	H	S	3,5-diOCH_3	83	95	>200	**4i**	H	H	S	3,5-diOH	70	157(dec.)	>200
3j	H	CH_3	S	3,5-diOCH_3	96	117-118	>200	**4j**	H	CH_3	S	3,5-diOH	74	198-200	>200
3k	H	H	O	3,5-diOCH_3	44	114	>200	**4k**	H	H	O	3,5-diOH	16	184(dec.)	>200
3l	CH_3	H	O	3,5-diOCH_3	87	102	>200	**4l**	CH_3	H	O	3,5-diOH	99	206	>200
3m	H	H	S	2,3-diOCH_3	90	oily	>200	**4m**	H	H	S	2,3-diOH	84	140(dec.)	106
3n	H	CH_3	S	2,3-diOCH_3	77	73	>200	**4n**	H	CH_3	S	2,3-diOH	44	107(dec.)	85
3o	H	H	O	2,3-diOCH_3	84	oily	>200	**4o**	H	H	O	2,3-diOH	53	141(dec.)	126
3p	CH_3	H	O	2,3-diOCH_3	91	142	>200	**4p**	CH_3	H	O	2,3-diOH	85	156(dec.)	>200
3q	H	H	S	2,5-diOCH_3	74	113	>200	**4q**	H	H	S	2,5-diOH	90	173(dec.)	>200
3r	H	CH_3	S	2,5-diOCH_3	89	oily	>200	**4r**	H	CH_3	S	2,5-diOH	78	175(dec.)	62
3s	H	H	O	2,5-diOCH_3	77	69-70	>200	**4s**	H	H	O	2,5-diOH	66	165(dec.)	89
3t	CH_3	H	O	2,5-diOCH_3	87	85-86	>200	**4t**	CH_3	H	O	2,5-diOH	60	186(dec.)	107
Ascorbic acid							18	α-Tocopherol							4

[a]Isolated yields.

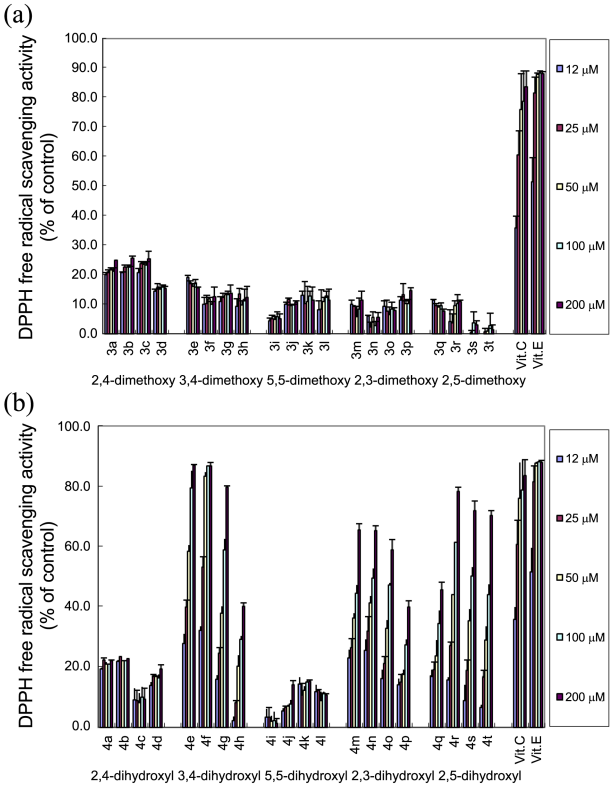


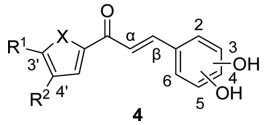
Figure 1. The DPPH radical scavenging rates of heterocyclic dimethoxychalcones (a) and their demethylated heterocyclic chalcones (b).

groups (2,4-dihydroxyl: **4a-4d** and 3,5-dihydroxyl: **4i-4l**) (Figure 1). Namely, the *ortho*- (*i.e.* 2,3- and 3,4-) and *para*- (*i.e.* 2,5-) substitution patterns on ring B of heterocyclic chalcones show much stronger anti-oxidant potentials than *meta*- (*i.e.* 2,4- and 3,5-) substitution pattern. Additionally, the former groups showed distinctly higher DPPH radical scavenging activities than those of the corresponding dimethoxy ones (**3e-3h**, **3m-3p**, and **3q-3t**), while in contrast, the latter groups showed no apparent enhancement in activities compared with the corresponding dimethoxy ones (**3a-3d** and **3i-3l**). This observation is consistent with the analysis mentioned above; only *ortho*- or *para*- substitution patterns of two hydroxyl groups on ring B of heterocyclic chalcones play a crucial role in the anti-oxidant activities, but *meta*-substitution pattern does not. These results were also consistent with those from our earlier work[5] on the SAR of dihydroxylated chalcone derivatives with diverse substitution patterns on a phenyl ring B. So, it is obvious that the substitution patterns of two hydroxyl groups on ring B of heterocyclic chalcones are very important structural devices for their radical scavenging activity enhancement.

The main issue in the present work was to investigate the isosteric effect of heterocycles (*i.e.*, thiophene or furan ring) on radical scavenging activities of heterocyclic chalones. This isosterism was distinctly demonstrated from the analysis of the next intriguing observations. For a clear comparison, the heterocyclic chalcones bearing the *ortho*- (*i.e.* 2,3- and 3,4-) and *para*- (*i.e.* 2,5-) substitution patterns of two hydroxyl groups on ring B (**4e-4h**, **4m-4p**, and **4q-4t**) and their IC_{50} values are shown in separate Table 2. The activities of thiophene ring-containing chalcones as heterocycle were higher than those of furan ring-containing chalcones. The difference in activity was larger at lower concentrations (< 25 μM). Another noteworthy observation to be worth to mention here is that the methyl substituent of heterocycle interestingly makes distinct differences in radical scavenging activities compared with non-substituted heterocycles. Namely, the chalcones bearing 4'-methylthiophene ring show higher activities than those of chalcones with non-substituted thiophene ring (35 μM for **4e** and 20 μM for **4f**, 106 μM for **4m** and 85 μM for **4n**, > 200 μM for **4q** and 62 μM for **4r**, Table 2), in contrast, the chalcones bearing the at 3'-methylfuran ring show lower activities than those of non-substituted furan ring (IC_{50}: 67 μM for **4g** and > 200 μM for **4h**; 126 μM for **4o**, > 200 μM for **4p**; 89 μM for **4s**, 107 μM for **4t**, Table 2).

Another noteworthy observation is that the influences of the methyl group on the activities were evident in an opposite way according to which heterocycle the methyl group was substituted (*i.e.*, the positive influence of 4'-methyl group of thiophene ring on the activity and negative one of 3'-methyl group of furan ring). This caused a marked difference in activities especially between the three sets of compounds: 4'-

Table 2. The DPPH radical scavenging activities (IC_{50} (μM)) of heterocyclic chalcones (**4e-4h**, **4m-4p**, and **4q-4t**)



4

Compound	R^1	R^2	X	Substituents on ring B	IC_{50} (μM)	Compound	R^1	R^2	X	Substituents on ring B	IC_{50} (μM)
4e	H	H	S	3,4-diOH	35	**4g**	H	H	O	3,4-diOH	67
4f	H	CH_3	S	3,4-diOH	20	**4h**	CH_3	H	O	3,4-diOH	>200
4m	H	H	S	2,3-diOH	106	**4o**	H	H	O	2,3-diOH	126
4n	H	CH_3	S	2,3-diOH	85	**4p**	CH_3	H	O	2,3-diOH	>200
4q	H	H	S	2,5-diOH	>200	**4s**	H	H	O	2,5-diOH	89
4r	H	CH_3	S	2,5-diOH	62	**4t**	CH_3	H	O	2,5-diOH	107

methylthiophenyl chalcones and 3'-methylfurany ones (IC_{50}: 20 μM for **4f** and > 200 μM for **4h**, 85 μM for **4n** and > 200 μM for **4p**, 62 μM for **4r** and 107 μM for **4k**, Table 2).

Conclusion

In summary, we carefully designed and prepared a series of heterocyclic chalcone derivatives bearing heterocycles such as thiophene or furan ring as an isostere of benzene ring, and investigated the influence of heterocycles on DPPH radical scavenging activities in more systematic manner. The SAR analysis shows several notable results. Namely, the activities of thiophene ring-containing chalcones are higher than those of furan ring-containing chalcones, and the presence of methyl substituent of heterocyclic ring is manifest as distinct differences in the activities compared with non-substituted heterocycles. More interestingly, the influences of methyl group of heterocycle on the activities are exhibited in an opposite way; the 4'-methyl group of the thiophene ring increased the activity and the 3'-methyl group of furan ring decreased the activity. Presently, the isosteric effect of heterocycles (*i.e.*, thiophene or furan ring) on radical scavenging activities of heterocyclic chalones was distinctly demonstrated.

Acknowledgments. This research was supported by the Bio-industry Technology Development Program, Ministry for Food, Agriculture, Forestry and Fisheries, Republic of Korea, and in part by the grant from Duk-myung, Huh Jin-Kyu Memorial Fund of Chonbuk National University.

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