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Stereoselective photochemistry of heteroaryl chalcones in solution and the antioxidant activities

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Abstract

Two new δ-truxinic type dimers; compound **1**, rel-(1β,2α)-di-(2-thienoyl)-rel-(3β,4α)-di-(4-methoxy)phenylcyclobutane and compound **2**, rel-(1β,2α)-di-(2-thienoyl)-rel-(3β,4α)-di-(3,4-dimethoxy)phenylcyclobutane were synthesized stereoselectively in solution by the dimerization of two known methoxy derivatives of heteroaryl chalcones (2*E*)-1-(2-thienyl)-3-(4-methoxy)-phenylpropen-1-one (**3**) and (2*E*)-1-(2-thienyl)-3-(3,4-dimethoxy)-phenylpropen-1-one (**4**). Precursor chalcones and the dimeric products showed antioxidant activities of different extents with respect to individual compounds as well as to the antioxidant methods.
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Keywords: Heteroaryl chalcone; Photodimerisation; Solution; Antioxidant; Radical scavenging

1. Introduction

Intramolecular photocycloaddition of chalcones, heteroaryl chalcones and their derivatives to give cyclobutane has proven to be a fast and simple method to shrink a cyclophane ring to a tricyclic system. A fast method to obtain cyclobutane rings is the photochemical dimerization of α,β-unsaturated carbonyl compounds and in particular of 1,3-diaryl-2-propene-1-one (chalcones) [1–6]. These reactions can be carried out in solid state, molten state and solution by UV–vis irradiation, with variable results in terms of product composition and yield [1–8]. Although photodimerisations of chalcones have been studied especially in solid state [1–8], not many work found for the photodimerisations of chalcones in solution. Therefore, the need is still high for unstudied photodimerisations of heteroaryl chalcones, stereoselectively in solution.

The cycloaddition of trans-chalcones may give four possible stereoisomers, namely *syn*, *anti*, head-to-head, and head-to-tail (Scheme 1). The formation of different stereoisomers in the dimerization of chalcones and related compounds may be dependent on the physical state of the substrate (solution, solid and molten state) and glass [1–8]. In these cases, a regiospecific ring closure is undoubtedly favoured by structures of the precursors. In the literature, various cyclobutane containing chalcones have been reported to be synthesized [1–8] and isolated from various plants [9–11]. Analogous to these dimers of chalcones, two new dimers of heteroaryl chalcones were synthesized stereoselectively in the current study.

Chalcones belong to the largest class of plant secondary metabolites, which, in many cases, serve in plant defense mechanisms to counteract reactive oxygen species (ROS) in order to survive and prevent molecular damage and damage by microorganisms, insects, and herbivores [12]. They are known to possess antioxidant character at various extents [13,14]. The antioxidant activity of natural compounds like chalconoids is related to a number of different mechanisms such as free radical scavenging, hydrogen donation,

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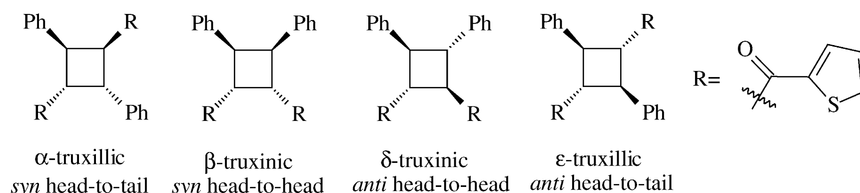
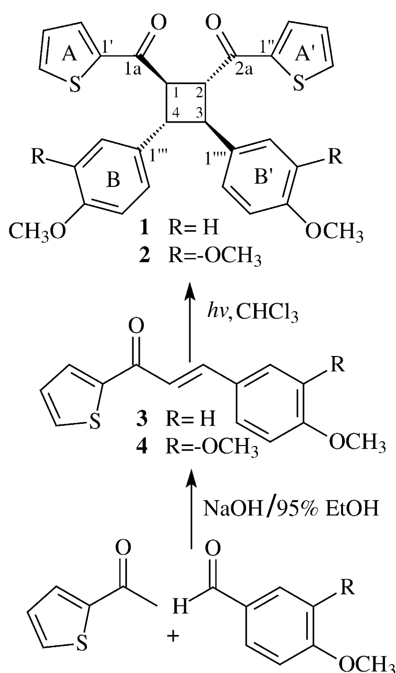


Scheme 1.

singlet oxygen quenching, metal ion chelation, and acting as a substrate for radicals such as superoxide and hydroxide [15]. Because oxidative stress is well-known to cause many diseases, scientists have become more interested in natural sources to fight it, looking for active components of plants in this respect in the recent years. Antioxidants, which can inhibit or delay the oxidation of an oxidizable substrate in a chain reaction, therefore appear to be very important in the prevention of these diseases. Several methods have been developed in recent years to evaluate the total antioxidant capacity of synthesized compounds and biological samples. The basis of most of these methods relies on a substrate that is oxidized in the procedures, and oxygen consumption, oxidation products, or substrate loss is monitored in different manners by various methods [16].

In our work, known heteroaryl chalcones (**3**, **4**) [17,18] have been prepared with the known procedure [19] according to the route indicated in Scheme 2. These heteroaryl chalcones, when exposed to UV light (400 W high-pressure Hg lamp), are converted to the respective cyclobutanes **1** and **2** as major products, with the yields (chromatographated products, PTLC) of 45% (**1**) and 32% (**2**). The minor products of these reactions were less than 5% which were not characterized.



Scheme 2.

In the literature, antiviral and antimicrobial activities of chalcones were studied [20–25] but, antioxidant activity of the hetero chalcones **3** and **4** was not reported. Thus, the antioxidant activity of the chalcones **3** and **4** and their dimerization products **1** and **2** were tested by using two antioxidant assays. First, their antioxidant activity was measured according to a basic method that utilizes linoleic acid as the substrate of oxidation and measures the fluorescence persistence time of each spot placed on a fluorescent-silica coated TLC plate [26,27]. The longer the fluorescence persisted, the higher the antioxidant activity was. The second method was used to determine radical scavenging activity of the compounds in reducing the amount of DPPH radical present in the medium, which was monitored spectrophotometrically [28].

2. Experimental

2.1. General and instrumentation

NMR spectra were recorded on a Varian Mercury NMR at 200 MHz instrument in $CDCl_3$. The mass spectral analyses were carried out on a Micromass Quattro LC–MS/MS spectrophotometer. Infrared spectrum was measured on a Perkin-Elmer 1600 FT-IR (4000–400 cm^{-1}) spectrometer. The optical rotation was measured with an Optical Activity Limited AA-5 series polarimeter. Melting points were obtained using a Gallenkamp apparatus and are uncorrected. UV–vis spectra were obtained with a Unicam UV2-100, at 25 °C. Thin-layer chromatography (TLC) and fluorescence persistence time measurements were carried out on Merck precoated 60 Kieselgel F_{254} analytical aluminum plates. PTLC was carried out on Merck precoated 60 Kieselgel F_{254} (20 mm × 20 mm × 0.2 mm) silica gel plates. A Camag UV source at 254 nm was used for antioxidant activity measurements.

3. Materials and methods

2-Acetylthiophene, 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde were purchased from Aldrich and used without further purification. The solvents (chloroform, *n*-hexane, ethanol and diethyl ether) used were either of analytical grade or bulk solvents distilled before use.

Table 1
NMR data of compounds **1** and **2** in $CDCl_3$

Position	1[a]		2[a]	
	δ_H	δ_C	δ_H	δ_C
1, 2	4,38, AA′BB′, J = 9.2, 5.6, nd, 8,8 Hz	48.54	4.39, AA′BB′, J = 9.0, 5.6, nd, 8.8 Hz	48.48
3, 4	3.84, AA′BB′, J = 9.2, 5.6, nd, 8.8 Hz	47.63	3.85, AA′BB′, J = 9.0, 5.6, nd, 8.8 Hz	47.87
1a, 2a	-	191.44	-	191.43
1′/1″	-	143.28	-	143.21
2′/2″	7.43, d, J = 4.0 Hz	134.68	7.45, d, J = 4.0 Hz	134.77
3′/3″	6.97, dd, J = 4.0, 5.0 Hz	128.32	6.99, dd, J = 5.0, 4.0 Hz	128.35
4′/4″	7.60, d, J = 5.0 Hz	133.48	7.63, d, J = 5.0 Hz	133.53
1‴/1⁗	–	133.22	–	133.64
2‴/2⁗	7.24, AX, J = 8.6 Hz	128.48	6.84, s	111.05
3‴/3⁗	6.84, AX, J = 8.6 Hz	113.96	–	148.08
4‴/4⁗	-	158.66	-	148.86
5‴/5⁗	6.84, AX, J = 8.6 Hz	113.96	6.82, d, J = 7.8 Hz	110.34
6‴/6⁗	7.24, AX, J = 8.6 Hz	128.48	6.90, d, J = 7.8 Hz	119.36
$2xOCH_3$	3.78, s	55.22	3.87, s	55.82
$2xOCH_3$	–	–	3.82, s	55.77

nd: AB′ coupling constant was not detected.
[a] Assignment based on ^{1}H, APT, ^{1}H–^{1}H COSY, NOESY, HETCOR and. ACD NMR program.

3.1.1. Photodimerisation of **3** *in solution*

A solution of compound **3** (60 mg, 0.160 mmol) in 30 mL of chloroform, kept in a Pyrex flask, was exposed to UV light (400 W high-pressure Hg lamp). The progress of the reaction was followed by silica gel TLC (*n*-hexane–diethyl ether (1:1)). The reaction was stopped after 4 h. The solution was evaporated and the residue purified by PTLC (0.5 mm, 20 mm × 20 mm, two plates) to give compound **1** (27 mg, 45% yield, R_f = 0.6, *n*-hexane–diethyl ether (1:1)).

3.1.2. Photodimerisation of **4** *in solution*

A solution of compound **4** (62 mg, 0.160 mmol) in 30 mL of chloroform, kept in a Pyrex flask, was exposed to UV light (400 W high-pressure Hg lamp). The progress of the reaction was followed by silica gel TLC (*n*-hexane–diethyl ether (1:1)). The reaction was stopped after 6 h. The solution was evaporated and the residue purified by PTLC (0.5 mm, 20 mm × 20 mm, two plates) to give compound **2** (20 mg, 32% yield, R_f = 0.5, *n*-hexane–diethyl ether (1:1)).

*3.1.3. rel-(1β,2α)-di-(2-thienoyl)-rel-(3β,4α)-di-(4-methoxy)phenylcyclobutane (***1***)*

Yellowish amorphous solid, mp 53–55 °C; $[\alpha]^D$ +23° ($CHCl_3$; c 1.74 × 10^{-3}); UV $\lambda_{max}^{CHCl_3}$ (nm): 240, 268, 286; ^{1}H NMR ($CDCl_3$, 200 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) see Table 1; positive LC–MS/MS m/z (%); m/z = 511(100) $[M + Na]^+$, 512(37) $[M + 1 + Na]^+$, 513(16) $[M + 2 + Na]^+$, 475(20), 328(38), 248(17), 244(7), 240(3), 164(22), 161(5), 134(6), 111(38); FT-IR (cm^{-1}): 3087, 2931, 2836, 1800–1680, 1650, 1513, 1414, 1248, 1178.

*3.1.4. rel-(1β,2α)-di-(2-thienoyl)-rel-(3β,4α)-di-(3,4-dimethoxy)phenylcyclobutane (***2***)*

White amorphous solid, mp 64–66 °C; $[\alpha]^D$ +12° ($CHCl_3$; c 2.50 × 10^{-3}); UV $\lambda_{max}^{CHCl_3}$ (nm): 242, 268, 289; ^{1}H NMR ($CDCl_3$, 200 MHz) and ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) see Table 1; positive LC–MS/MS *m/z* (%); *m/z* = 571(100) $[M + Na]^+$, 572(36) $[M + 1 + Na]^+$, 573(15) $[M + 2 + Na]^+$, 475(22), 300(8), 274(5), 248(17), 240(3), 191(4), 164(12), 161(5), 134(6), 111(13); FT-IR (cm^{-1}): 3087, 2929, 2835, 1800–1680, 1645, 1515, 1414, 1241, 1026.

The spectral data (^{1}H, ^{13}C, FT-IR, UV and MS) of compounds **3** and **4** are reported here for comparison [18].

*3.1.5. (2E)-1-(2-thienyl)-3-(4-methoxy)phenylpropen-1-one (***3***)*

mp 102–104 °C; R_f: 0.39, *n*-hexane–diethyl ether (1:2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.3, [AB, J = 15.4 Hz, *H*-2], 7.8 [AB, J = 15.4 Hz, *H*-3], 7.72 [dd, J = 1.0, 5.4 Hz, *H*-3′], 7.20 [m, *H*-4′], 7.90 [dd, J = 1.0, 5.4 Hz, *H*-5′], 7.15 [s, *H*-2″], 6.86 [d, J = 7.63 Hz, *H*-5″], 7.18 [m, *H*-6″], 3.93 [s, $-OCH_3$], 3.96 [s, $-OCH_3$]; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 181.76 [*C*-1], 127.99 [*C*-2], 143.93 [*C*-3], 145.48 [*C*-2′], 131.40 [*C*-3′], 123.00 [*C*-4′], 133.44 [*C*-5′], 127.33 [*C*-1″], 109.86 [*C*-2″], 148.88 [*C*-3″], 151.15 [*C*-4″], 110.81 [*C*-5″], 119.07 [*C*-6″], 55.69 [2x $-OCH_3$]. GC–MS *m/z* (%); *m/z* = 274(100) $[M]^+$, 243(51.2) $[M–31]^+$, 207(50) $[M – 67]^+$, 111(76) $[M – 163]^+$; FT-IR (cm^{-1}): 3089, 1800–1650, 1643, 1510, 1463, 1414, 1261, 1241.

3.1.6. (2E)-1-(2-thienyl)-3-(3,4-dimethoxy)phenylpropen-1-one (**4**)

mp 80–81 °C; R_f: 0.67, *n*-hexane–diethyl ether (1:2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 7.34 [AB, J = 15.3 Hz, *H*-2], 7.88 [AB, J = 15.3 Hz, *H*-3], 7.68 [m, H-3′], 7.18 [t, J = 3.05 Hz, *H*-4′], 7.86 [m, H-5′], 7.58 [d, J = 8.54 Hz, *H*-2′′/6′′], 6.94 [d, J = 8.54 Hz, *H*-3′′/5′′], 3.84 [s, –OCH_3]; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 180.00 [*C*-1], 126.13 [*C*-2], 143.82 [*C*-3], 145.708 [*C*-2′], 130.22 [*C*-3′], 128.14 [*C*-4′], 133.51 [*C*-5′], 127.30 [*C*-1′′], 119.10 [*C*-2′′], 161.62 [*C*-3′′], 114.33 [*C*-4′′], 131.44 [*C*-5′′], 121.91 [*C*-6′′], 55.34 [–OCH_3]. GC–MS *m/z* (%); *m/z* = 244(100) $[M]^+$, 243(40) $[M-1]^+$, 108(42) $[M-136]^+$; FT-IR (cm^{-1}): 3082, 1800–1650, 1646, 1511, 1461, 1414, 1256, 1219.

3.2. The antioxidant activity measurements

The antioxidant capacity of the compounds was examined by comparing to that of known antioxidants BHT and Trolox® by employing the following two in vitro assays: TLC plate fluorescence persistence time method [26] and DPPH free radical scavenging assay [28].

3.2.1. Antioxidant activity by fluorescence persistence time

The TLC plate method [26] was used for the determination of antioxidant activity. A fluorescent-labeled silica TLC plate (silica gel 60 F254) was dried at 105 °C for 30 min, and a 5 μL aliquot from each sample and from reference standard butylated hydroxytoluene (BHT) (1.0 mg/mL) was spotted on the plate twice with a 5 μL semiautomatic pipet, drying in between. The plate was then plunged into 3% α-linoleic acid solution in hexane twice, drying in between and at the end. The dried plate was then placed 2.5 cm below a UV (254 nm) light source and the background of the spots appeared within the first 10–15 min under continuous irradiation. The TLC plate was observed every 15 min under continuous irradiation, and the time each fluorescent spot disappeared was considered to be the induction period for lipid peroxidation. The antioxidant activities of the samples and Trolox® were evaluated by comparing their fluorescence disappearance times with those of the reference standard BHT and given as per cent of the activity of BHT.

3.2.2. Free radical scavenging activity assay

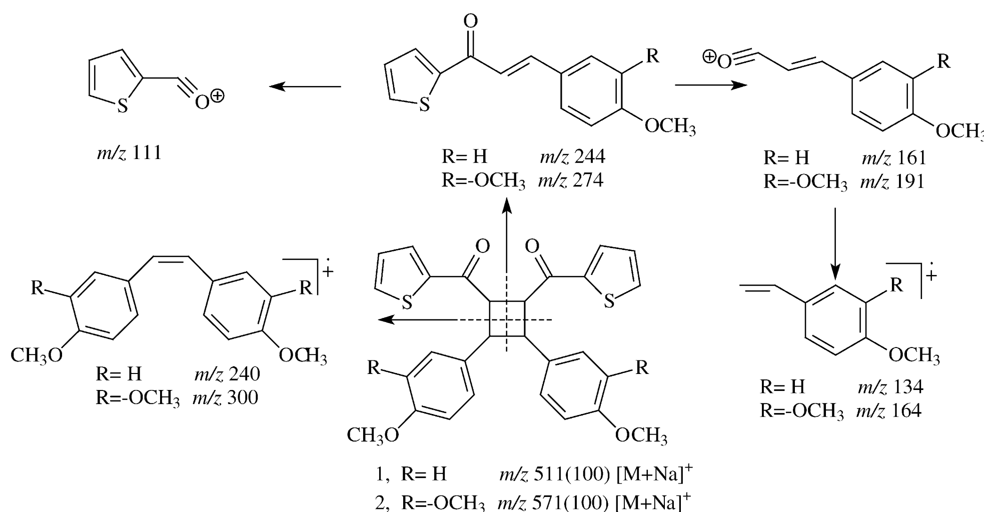
The free radical scavenging activity of the compounds was tested by utilizing DPPH scavenging [28]. Briefly, 50 μl sample of various concentrations was added to 5 ml 0.004% ethanolic DPPH solution. After a 30 min incubation period at room temperature, the absorbance was read against a blank at 517 nm. Lower absorbance of the reaction mixture indicates higher DPPH radical scavenging activity. The results were compared with those of BHT and Trolox®.

4. Results and discussion

In this study, we found that [2 + 2] photodimerisations of heteroaryl chalcone derivatives **3** and **4** proceed efficiently and stereoselectively in the solution and gave the corresponding rel-*anti*-head-to-head dimmers **1** and **2** in relatively good yields. This cyclization allows the formation of the most stable δ-truxinic type isomers. Irradiation of two polymorphic crystals of heteroaryl chalcones **3** and **4** were done at room temperature for 6 h using a 400 W high-pressure Hg lamp.

The structures of the cyclobutyl rings of products **1** and **2** were elucidated from their ^{1}H NMR spectra which show highly shielded CH protons signals at δ_H 4.38/3.84 and δ_H 4.39/3.85, respectively [1–11].

Stereochemistry of the compounds **1** and **2** were determined from NMR spectrometry information. Two symmetrical multiplets (AA′BB′) at δ_H 4.38 (δ_C 48.54)/δ_H 3.84 (δ_C 47.63) for compound **1** and at δ_H 4.39 (δ_C 48.48)/δ_H 3.85



Scheme 3.

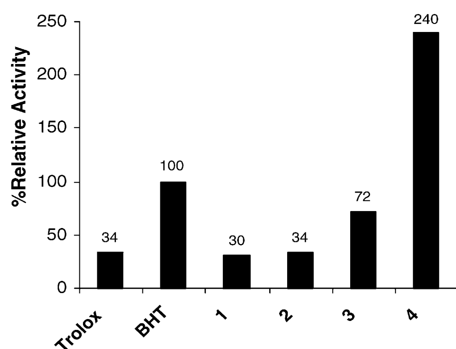


Fig. 1. The antioxidant activities of the reference standards and the chalcone monomers and dimers. The activities are expressed as percentage of the fluorescence persistence times with the test compounds compared to that of BHT, taking the activity of BHT as 100%.

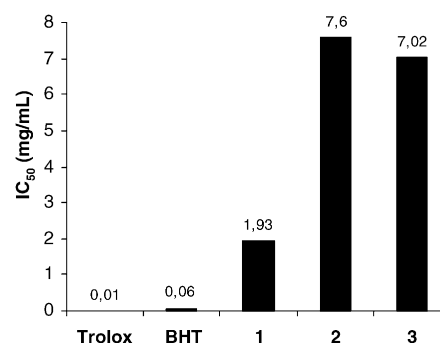


Fig. 2. DPPH radical scavenging activities of the reference standards and the chalcone monomers and dimers. IC_{50} value for each compound refers to its mg/mL concentration providing 50% scavenging of DPPH radicals present in the test medium. Compound **4** was prooxidant and, thus, is not shown in the graph.

(δ_C 47.87) for compound **2** were observed for the cyclobutyl protons in ^{1}H NMR spectra. Simulation of these NMR patterns has allowed the calculation of the coupling constants of the cyclobutyl protons ($J_{AA'}$ = 9.2/9.0, J_{AB} = 5.6, J_{AB} = not detected, J_{BB} = 8.8). The values of these coupling constants suggest that **1** and **2** were formed by the head-to-head coupling, but they do not allow a certain assignment with respect to *syn*/*anti* stereochemistry. A more accurate structural determination was attained by ^{1}H, ^{1}H–COSY, ^{1}H, ^{13}C–COSY and NOESY spectra and literature data [1–12]. The close similarity of the ^{1}H and ^{13}C NMR patterns of the cyclobutyl moieties with δ-truxinic structure strongly suggests that the formation of cyclobutane ring occurs by *anti* head-to-head junction in compounds **1** and **2** [1–6].

The structural connectivities of compounds **1** and **2** were established, in part from ^{1}H–^{1}H COSY. It was found that for the most down field for the cyclobutyl ring, methines designated H-1/H-2 at δ_H 4.38 (δ_C 48.48) was connected to H-3/H-4 at δ_H 3.84 (δ_C 47.63) for **1** and H-1/H-2 at δ_H 4.39 (δ_C 48.5) was connected to H-3/H-4 at δ_H 3.85 (δ_C 47.87) for **2**. The important NOESY interactions in compounds **1** and **2** were seen between H-1 and H-3 and between H-2 and H-4. Thus, the presence of cyclobutane ring was established. The chemical shifts of compounds **1** and **2** are in total agreement with those of similar structures in the literature with δ-truxinic structure [1–6].

Further connectivities for the thiophenyl part of the compound **1** were observed from H-4′ (δ_H 7.60) to H-3′ (δ_H 6.97) and from H-3′ (δ_H 6.97) to H-2′ (δ_H 7.43). These data clearly show thiophenyl part of the compound **1**. The ^{1}H NMR spectra of compound **1** also shows AX spin system for phenyl group at δ_H 7.24 (H-2′′′/6′′′, J = 8.6 Hz) and δ_H 6.84 (H-3′′′/5′′′, J = 8.6 Hz). Similar correlations were also seen in the ^{1}H–^{1}H COSY NMR spectra of compound **2**.

The positive LC–MS/MS gave M + Na at *m*/*z* 511(100) for **1** and at *m*/*z* 571(100) for **2**, which were consistent with the molecular formulas to be $C_{28}H_{24}O_4S_2$ for **1** and $C_{30}H_{28}O_6S_2$ for **2** requiring dimeric structures (Scheme 3). LC–MS/MS showed a typical chalcone fragmentation [1–12,27] with a fragment ions for **1** at *m*/*z* 244 (chalcone monomer, $C_{14}H_{12}O_2S$) and for **2** at *m*/*z* 274 (chalcone monomer, $C_{15}H_{14}O_3S$). Further fragments were observed at *m*/*z* 240, 161, 134 (one methoxyl on the B and B′ rings) for **1** and *m*/*z* 300, 191, 164 (two methoxyl on the B and B’ rings) for **2**. Although, theoretically the products of such dimerization reactions of chalcones are expected to give racemic mixtures, compounds **1** and **2** showed optical rotations of +23° and +12°, respectively.

Based upon the above observations, the complete chemical shift assignments for **1** and **2** were deduced and are shown in Table 1. Compound **1** and **2** were thus shown to be rel-(1β,2α)-di-(2-thienoyl)-rel-(3β,4α)-di-(4-methoxy) phenylcyclobutane and rel-(1β,2α)-di-(2-thienoyl)-rel-(3β,4α)-di-(3,4-dimethoxy)phenylcyclobutane, respectively. These two chiral compounds **1** and **2** were synthesized and characterized first time in this work.

The antioxidant activities of the compounds synthesized were evaluated according to the two antioxidant assays. In the first method, the comparison of percent antioxidant activities relative to that of BHT revealed that the monomeric starting compounds were more active than the dimers and Trolox® (Fig. 1). The antioxidant activities of the dimers were similar to that of Trolox®. DPPH radical scavenging activity assay results were inconsistent with those of the first method. The concentrations of the dimers required to scavenge 50% of the radicals present were less than those of the monomer **3** (Fig. 2). The monomeric compound **4** was prooxidant. The DPPH scavenging activities of Trolox® and BHT were incomparably high. The inconsistency among the results of two different antioxidant activity methods is not uncommon in literature and results from many different factors, including sample preparation, mechanism of antioxidant action, and the behavior of individual compounds toward test mixture components.

Acknowledgements

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