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The Synthesis and Spectral Properties of Benzofuran Derivative Bis-Chalcone

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ABSTRACT

Khellin, a natural furanochromone, was isolated from the fruits of *Ammi visnaga* L. by using a rapid and easy technique. It was then hydrolyzed with 10% KOH to obtain khellinone. From the Claisen-Schmidt condensation of khellinone with terephthalaldehyde, a new benzofuran derivative bis-chalcone was synthesized and its spectroscopic properties were investigated in details.

Keywords:
Khellin, Khellinone, *Ammi visnaga* L., Claisen Schmidt condensation, Bis-chalcone

INTRODUCTION

Chalcones, a class of compounds naturally occuring in various plants, are precursors of flavonoids and they consist of two aromatic rings connected by an α,β-unsaturated carbonyl group (Figure 1). They can be obtained by the Claisen-Schmidt condensation reaction between acetophenone and benzaldehyde derivatives in the presence of acid or base catalysts [1].

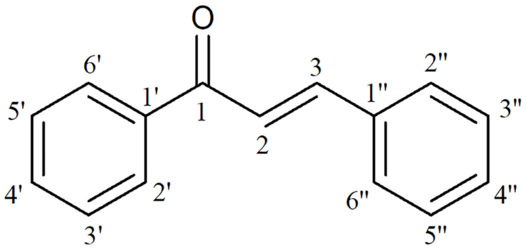


Figure 1. The general structure and numbering of chalcones.

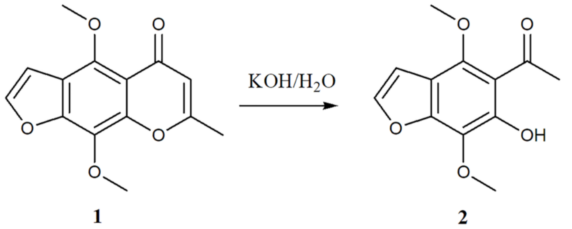
Khellinone, the compound containing an acetophenone group, is a valuable starting material for the synthesis of new chalcone derivatives. It is essentially prepared via alkaline hydrolysis of khellin, a natural furanochromone isolated from Ammi visnaga L. (Scheme 1) [2]. In the literature, there are few studies on the synthesis of khellinone derivative chalcone compounds. Due to the presence of benzofuran moiety, they have a great potential for biological activities and pharmaceutical utilities [3-5].

Hitherto, many studies have been focused on synthetic and natural chalcone derivatives and their biological activities such as antibacterial, anticancer, antifungal, anti-inflammatory, antitubercular and antioxidant activity [6]. Also they have been extensively studied in optoelectronic fields due to their interesting photopysical and photochemical properties [7-10]. Recently, in situ generated copper (II) complexes of chalcone ligands have been found to catalyze the oxidation reaction of catechol to the corresponding o-quinone, a procedure known as catecholase activity [11].

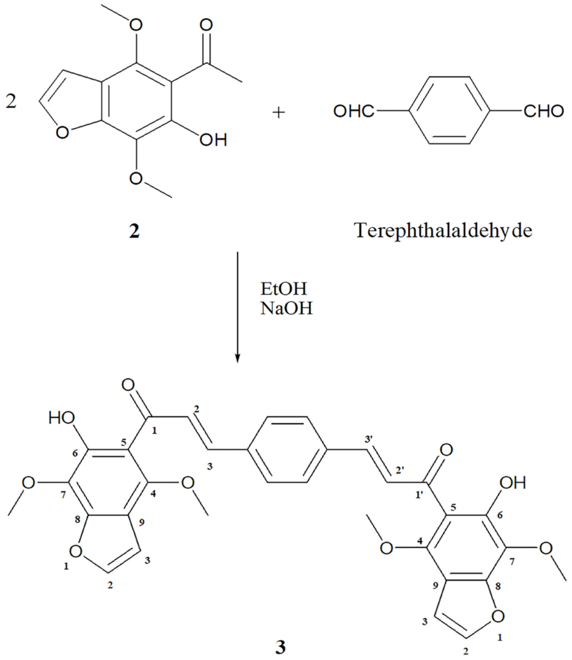
In the present study, we report the isolation of khellin from Ammi visnaga L. growing in Hatay region and its basic hydrolysis to khellinone which is a benzofuran derivative and a starting material for the synthesis of chalcone. Then, a new bis-chalcone containing benzofuran moiety was synthesized from Claisen Schmidt condensation reaction of khellinone with terephthalaldehyde and its spectral properties was described in details.

MATERIALS AND METHODS

Terephthalaldehyde, Sodium hydroxide (NaOH) and the organic solvents were analytical grade and used without further purification. The plant material was harvested in September 2014 near Hatay region of Turkey and a voucher specimen have been deposited in the Herbarium of Biology Department, Mustafa Kemal University. The melting points were determined with a Thermo Scientific 9100 melting point apparatus and are not corrected. Elemental analyses were performed with a LECO CHNS-932 (USA) elemental analyzer. The electronic spectra were



Scheme 1. Alkaline hydrolysis of khellin to khellinone.



Scheme 2. The synthetic route of bis-chalcone.

measured on a OPTIZENα UV-Vis Spectrometer (South Korea). The mass spectra have been obtained by Agilent (USA) LC/MSD spectrometer using the ESI technique. The FT-IR spectra (4000-400 cm^{-1}) were recorded by Perkin Elmer (USA) Spectrum Two with U-ATR FTIR spectrometer. ^{1}HNMR (600 MHz) and ^{13}C NMR (600 MHz) spectra were recorded on a Bruker Advance III HD (USA) spectrometer using $CDCl_3$ and tetramethylsilane (TMS) was used as an internal reference. Thin-layer chromatography (TLC) was performed on Merck silicagel plates (60F$_{254}$), and visualized with ultraviolet light (366 and 254 nm).

Isolation of Khellin, 1

The ripe fruits (500 g) of *Ammi visnaga* L. were dried, grounded and extracted with 1 L hot water by a Soxhlet apparatus for 30h and the extract was concentrated by rotary evaporator to its half-volume. It was then extracted with 150 mL hexane many times, dried over Na_2SO_4 and concentrated to dryness under vacuum. The presence of khellin in the hexane residue was detected by thin layer chromatography. Khellin gave yellowish brown fluorescence under 254 nm UV light with R_f value 0.56 in solvent system EtOAc:$CHCl_3$ (60:40) [12]. The hexane residue was purified by column chromatography on silica gel G 60. The fraction eluted with dichloromethane-ethyl acetate (90:10) were concentrated and recrystallized from MeOH-water to obtain 0.9 g khellin. The structure of khellin (4,9-dimethoxy-7-methylfuro[3,2-g]chromen-5-one) was confirmed by comparing its melting point with the value reported as 154-155°C [13, 14].

Synthesis of Khellinone, 2

Khellinone (4,7-Dimethoxy-5-acetyl-6-hydroxybenzofuran) was prepared by alkaline hydrolysis of khellin according to the literature [2, 15]. 1.00 g of khellin (3.84 mmol) was dissolved in 15 mL of hot 10% KOH solution while the temperature was maintained at 70-80°C. At the end of the 2h reflux period, the reaction mixture was allowed to cool to room temperature and 3 mL of concentrated HCl was added dropwisely. The resulting precipitate was filtered off, recrystallized from hot MeOH and dried under vacuum to obtain 0.81 g (3.43 mmol) of khellinone with a yield of 89% (m.p. 99-100°C) [2, 15].

Synthesis of Bis-Chalcone, 3

Khellinone (4.23 mmol) was dissolved with terephthalaldehyde (2.15 mmol) in 30 mL of ethanol. The solution was treated with 5 mL of 50% sodium hydroxide solution and left overnight. The reaction mixture was neutralized with dilute acetic acid (10%) and the separated product was collected, washed with water and recrystallized from hot MeOH.

3.(2E,2'E)-3,3'-(1,4-phenylene)bis[1-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)]prop-2-en-1-one. Dark yellow powder, yield: 0.77g, 63%. m.p.: 229-230°C. Molecular formula $C_{32}H_{26}O_{10}$. Elemental Analysis Calc. (%): C = 67.36; H = 4.59. Found. (%): C = 67.03; H = 4.77. Selected IR data (ν, cm^{-1}) 3137 (Ar-H), 2940 (C-H), 2835 (C-H), 1621 (C=O), 1551 (C=C). UV-Vis: λ_{max} (nm) (Ethanol): 270, 362. ^{1}H NMR (600 MHz; $CDCl_3$): δ, ppm 12.68 (s, 2H, 2xAr-OH), 7.94 (d, 2H, *J*=15.6 Hz, 2xC=CH), 7.85 (d, 2H, *J*=15.6 Hz, 2xCO=CH), 7.70 (s, 4H, Ar-H), 7.54 (d, 2H, *J*=2.3 Hz, 2xfuran-H), 6.90 (d, 2H, *J*=2.3Hz, 2xfuran-H), 4.10 (s, 6H, 2xOCH_3), 4.07 (s, 6H, 2xOCH_3). ^{13}C NMR (150 MHz; $CDCl_3$): δ, ppm 194.52 (C), 153.27 (C), 152.07 (C), 150.77 (C), 144.30 (CH), 142.19(CH), 137.13 (C), 129.07 (CH), 129.00 (CH), 128.84 (CH), 128.08 (CH), 112.76 (C), 111.87 (C), 105.25 (CH), 62.03 (OCH_3), 61.08 (OCH_3). MS (+API-ES): *m/z* 571.0 $[M+H]^+$.

RESULTS and DISCUSSION

In the present work, khellin **(1)** was isolated from the ripe fruits of *A. visnaga* L. and it was then hydrolyzed by using 10% KOH to form khellinone **(2)** which is a benzofuran derivative containing acetophenone group. The structure of khellin and khellinone was confirmed by comparing

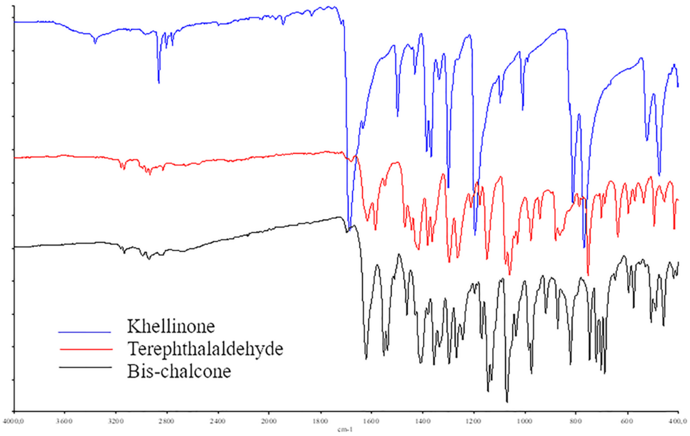


Figure 2. FT-IR spectra of khellinone, terephthalaldehyde and bis-chalcone (**3**).

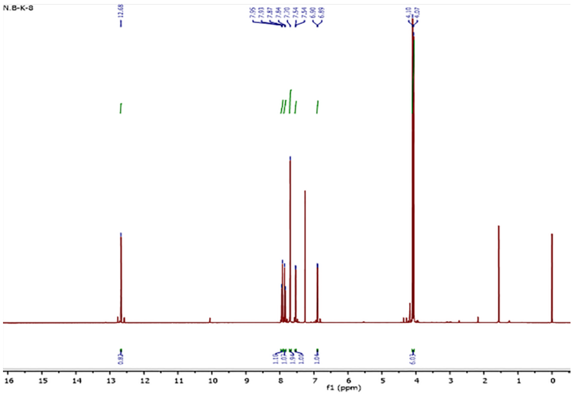


Figure 3. ^{1}H NMR spectrum of **3** in CDCl$_3$.

their melting points obtained experimentally with those found in the literatüre [13-15]. From the reaction of khellinone with terephthalaldehyde in the presence of NaOH, a new bis-chalcone **(3)** was obtained and the synthetic route to the compounds is outlined in Scheme 1 and Scheme 2.

The purification of bis-chalcone (**3**) was carried out by column chromatography. The crude product loaded on the chromatography column was first eluted with CH$_2$Cl$_2$ in order to remove the possible side products and unreacted starting materials, and then eluted with CH$_2$Cl$_2$/acetone (1:1) to collect bis-chalcone. The chemical structure of purified product was characterized by spectroscopic data (FT-IR, ^{1}H-NMR, ^{13}C-NMR, UV-Vis and mass) and elemental analyses. The elemental analyses and the physical measurement results confirmed the proposed structure of title molecule. The mass spectrum of **3** was recorded in CHCl$_3$ solution (Figure S1, in the supplementary file). In the spectrum, the molecular ion peak observed at m/z 571.0 which is attributed to [M+H]$^+$, provided the evidence for the formation of the suggested structure.

The ATR-FTIR spectrum (Figure 2) of **3** revealed a band at 1621 cm^{-1} indicating the presence of carbonyl (C=O) group. The band at 1551 cm^{-1} was assigned to the C=C group that is characteristic of the α,β-unsaturated carbonyl compounds. The IR frequency values of carbonyl and olefinic groups are lower than typical values (ca. 1700 cm^{-1} and 1650 cm^{-1}, respectively) because of the conjugation effect of C=C-C=O moiety. Also the presence of electron donor groups at *ortho*- positions of benzofuran rings shifted the IR frequencies of C=O and C=C bands to a lower values [16]. Moreover, the spectrum shows several weak bands in the region of 2835-3137 cm^{-1} corresponding to aliphatic and aromatic C-H stretching vibration frequencies.

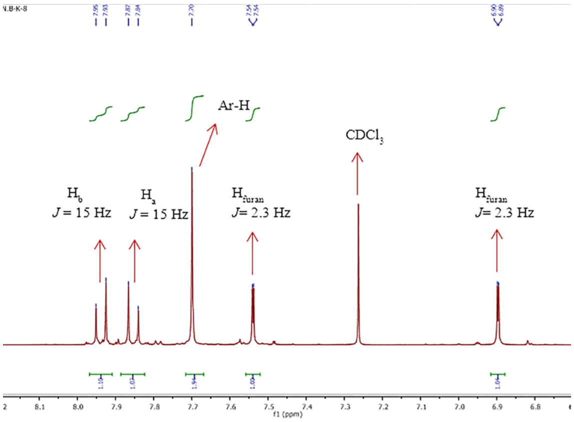
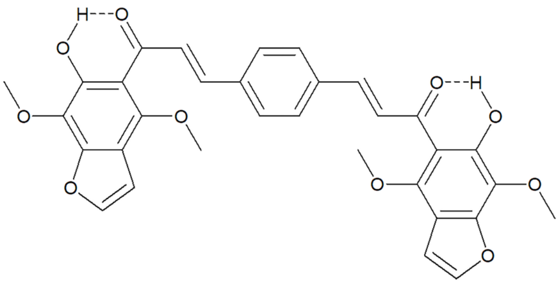


Figure 4. ^{1}H NMR spectrum of **3** (zoom in to 6.7-8.2 ppm range).



Scheme 3. Intramolecular hydrogen bonding at bis-chalcone.

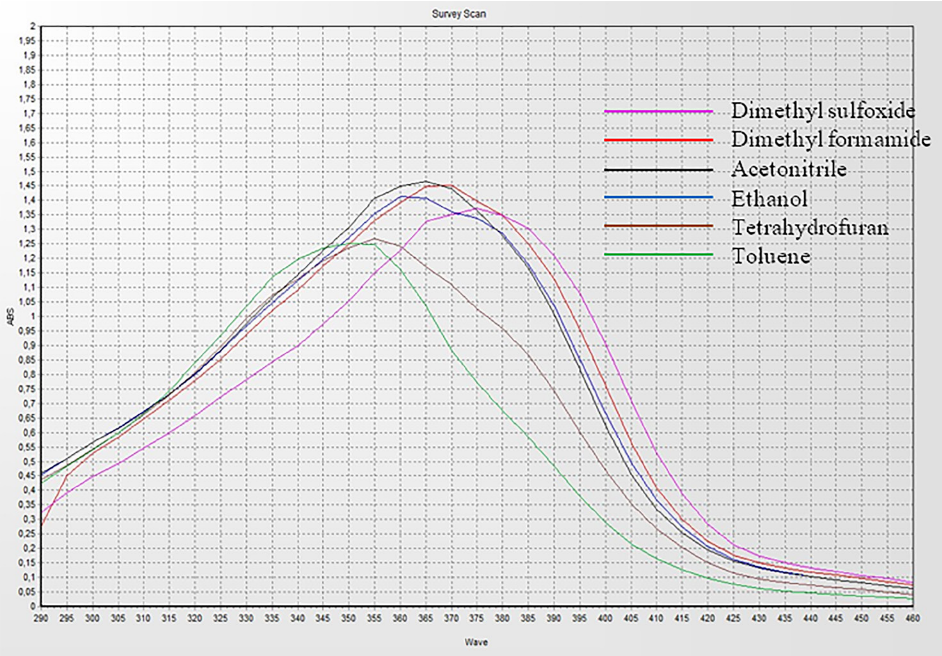


Figure 5. Electronic absorption spectra of **3** in six different solvents.

^{1}H NMR spectrum of **3** measured in $CDCl_3$ (Figure 3) exhibits two doublets at 7.94 ppm (*J*=15.6) and 7.85 ppm (*J*= 15.6), indicating the trans configuration of vinylic system due to the large coupling constant (*J*) values (Figure 4) [17]. The ethylenic protons adjacent to the carbonyl group (H_α) showed chemical shift at higher field (7.85 ppm) than those of H_β (7.94 ppm) which are more deshielded by carbonyl group due to the conjugation of the carbonyl group and double band [18]. The singlet signal observed at 12.68 ppm was attributed to phenolic protons of benzofuran moieties. The two vicinal protons in the furan ring were appeared as two doublets at 7.54 ppm (*J* = 2.3 Hz), and 6.90 ppm (*J* = 2.3 Hz) (Figure 4).

The structure of 3 was also supported by 13C APT NMR spectrum (Figure S2, in the supplementary file). The number of signals in the spectrum was consistent with the non-equivalent carbon atoms in the molecule. The carbonyl carbon atoms of the α,β-unsaturated ketone groups gave rise to a characteristic signal at 194.52 ppm. The negative signals at 61.08 and 62.03 ppm confirmed the presence of methoxy carbons in the benzofuran rings. The positive signals appeared between 150.77 and 153.27 ppm in the APT spectrum of 3, are likely to be ascribed to the quaternary carbons adjacent to the oxygen atoms. Signals due to aromatic ring, α, and β-carbon atoms were appeared in the range of 128.09-144.30 ppm. Relatively high chemical shift values for phenolic protons and carbonyl carbons (12.68 and 194.52 ppm, respectively) might be due to the formation of intramolecular hydrogen bonding between the carbonyl oxygens with phenolic hydroxyl protons (Scheme 3) [16].

The electronic spectra of chalcones have been extensively studied by a large number of researh groups. It was reported that UV spectrum of chalcones generally consists of two essential absorption bands: one usually appears at 340-390 nm referred to as band I and relatively a minor absorption band at 220-270 nm known as band II [19]. The characteristic band I of chalcones may be attributed to n-π* transitions of the whole molecule.

The electronic absorption spectra of bis-chalcone (3) were recorded in the region 300-500 nm (Figure 5), using freshly prepared 10-6 M solutions in six different solvents (toluene, tetrahydrofuran, ethanol, acetonitrile, dimethyl formamide and dimethyl sulfoxide) with increasing polarities from apolar to polar. The maximum absorption values of 3 were found to be in the range of 350-375 nm and upon increasing the polarity of solvents, noticeable batochromic shifts were observed in the UV spectra. The results obtained in the present study were consistent with the literature. Kumari et al. reported that the solvatochromic effect on absorption spectra of chalcone derivatives showed appreciable red shifts from apolar to polar solvents because of the intramolecular charge transfer (ICT) interactions. They suggested that the strong interaction between singlet excited state of chalcone molecules with polar solvents caused batochromic shifts in the electronic spectra due to large charge distribution between ground and singlet excited state of title molecules (20).

CONCLUSION

In the present study, it was reported the synthesis and spectral characterization of a new benzofuran derivative bis-chalcone obtained from the condensation reaction of terephthalaldehyde with khellinone which is the hydrolysis product of khellin. The spectral analyses revealed that the resonance-stabilized intramolecular hydrogen bonding in the bis-chalcone noticeably affects the spectroscopic properties of the compound, causes a considerable downfield shift of hydroxyl proton and carbonyl carbon signals in the NMR spectrum and also a shift to lower frequencies for carbonyl and vinyl group in the FT-IR spectrum. The effect of various solvents over electronic spectra of the title molecule was also studied and it was observed the long-wavelength absorption band undergoes a red (batochromic) shift with increasing solvent polarity which means excited state molecule is better stabilized by solvation than the molecule in the ground-state.

REFERENCES

1. Xue Y, LiuY, An L, Zhang, L, Yuan Y, Mou, J, Liu L, Zheng Y. Electronic structures and spectra of quinoline chalcones: DFT and TDDFT–PCM investigation. Computational and Theoretical Chemistry 965 (2011) 146-153. https://doi.org/10.1016/j.comptc.2011.01.042.
2. Gammill RB. The Synthesis and Chemistry of Functionalized Furochromones. 2. The Synthesis, Sommelet–Hauser Rearrangement, and Conversion of 4,9–Dimethoxy–7–[(methylthio)methyl]–5H–furo[3,2–g][1]benzopyran–5–one to Ammiol. Journal of Organic Chemistry 49 (1984) 5035–5041. DOI: 10.1021/jo00200a002.
3. Osman SA, Yosef HAA, Hafez TS, El–Sawy AA, Mousa HA, Hassan AS. Synthesis and Antibacterial Activity of Some Novel Chalcones, Pyrazoline and 3– Cyanopyridine Derivatives Based on Khellinone as well as Ni(II), Co(II) and Zn(II) Complexes. Australian Journal of Basic and Applied Sciences. 6 (2012) 852–863.
4. Baell JB, Gable RW, Harvey AJ, Toovey N, Herzog T, Hansel W, Wulff H. Khellinone Derivatives as Blockers of the Voltage–Gated Potassium Channel Kv1.3: Synthesis and Immunosuppressive Activity. Journal of Medicinal Chemistry 47 (2004) 2326–2336. DOI: 10.1021/jm030523s.
5. Ahmed Farag IS, Abd El–Hafez OM, Rybakov VB. Crystal Structure of a New Chalcone Compound Prepared from Khellinone. Crystal Research and Technology 25 (1990) 1399–1404. DOI: 10.1002/crat.2170251209.
6. Singh P, Anand A, Kumar V. Recent developments in biological activities of chalcones: A mini review. European Journal of Medicinal Chemistry 85 (2014) 758–777. https://doi.org/10.1016/j.ejmech.2014.08.033.
7. Shettigar S, Chandrasekharan K, Umesh G, Sarojini BK. Studies on nonlinear optical parameters of bis–chalcone derivatives doped polymer. Polymer 47 (2006) 3565–3567. https://doi.org/10.1016/j.polymer.2006.03.062.
8. Prabhu SR, Jayarama A, Chandrasekharan K, Upadhyaya V, Ng SW. Synthesis, growth, structural characterization, Hirshfeld analysis and nonlinear optical studies of a methyl substituted chalcone. Journal of Molecular Structure Volume 1136 (2017) 244-252. https://doi.org/10.1016/j.molstruc.2017.01.069
9. Arshad MN , Al–Dies AM, Asiri AM, Khalid M, Birinji AS, Al–Amry KA, Braga AAC. Synthesis, crystal structures, spectroscopic and nonlinear optical properties of chalcone derivatives: A combined experimental and theoretical study. Journal of Molecular Structure Volume 1141 (2017) 142-156. https://doi.org/10.1016/j.molstruc.2017.03.090.
10. Muhammad S, Al–Sehemi AG, Su Z, Xu H, Irfan A, Chaudhry AR. First principles study for the key electronic, optical and nonlinear optical properties of novel donor–acceptor chalcones. Journal of Molecular Graphics and Modelling. 72 (2017) 58–69. https://doi.org/10.1016/j.jmgm.2016.12.009.
11. Thabti S, Djedouani A, Rahmouni S, Touzani R, Bendaas A, Mousser H, Mousser A. Synthesis, X–ray crystal structures and catecholase activity investigation of new chalcone ligands. Journal of Molecular Structure 1102 (2015) 295–301. DOI: 10.1016/j.molstruc.2015.08.071.
12. Beltagy AM, Beltagy DM. Chemical composition of Ammi visnaga L. and New Cytotoxic Activity of its Constituents Khellin and Visnagin. Journal of Pharmaceutical Sciences and Research 7 (2015) 285–291.
13. Günaydın K, Beyazit N. The Chemical Investigations on the Ripe Fruits of Ammi visnaga (Lam.) Lamarck Growing in Turkey. Natural Product Research 18 (2004) 169–175. http://dx.doi.org/10.1080/14786410310001608091.
14. Anrep GV, Barsoum GS, Kenawy MR. The Pharmacological Actions of the Crystalline Principles of Ammi visnaga Linn. Journal of Pharmacy and Pharmacology 1 (1949) 164–176. DOI: 10.1111/j.2042–7158.1949.tb12395.x.
15. Schöberg A, Sina A. Khellin and Allied Compounds. Journal of American Chemical Society 72 (1950) 1611–1616. DOI: 10.1021/ja01160a051.
16. Tay MG, Tiong MH, Chia YY, Kuan SHC, Liu ZQ. A Way to Improve Luminescent Efficiency of Bis–Chalcone Derivatives. Journal of Chemistry 2016 (2016) 1–8. http://dx.doi.org/10.1155/2016/3608137.
17. Aksöz BE, Ertan R. Spectral Properties of Chalcones II. FABAD Journal of Pharmaceutical Sciences 37 (2012) 205–216.
18. Thirunarayanan G, Gopalakrishnan M, Vanangamudi G. IR and NMR spectral studies of 4–bromo–1–naphthyl chalcones–assessment of substituent effects. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 67 (2007) 1106–1112. DOI: 10.1016/j.saa.2006.09.034.
19. Mabry TJ, Markham KR, Thomas MB. The Ultraviolet Spectra of Chalcones and Aurones, in: The Systematic Identification of Flavonoids, Springer–Verlag, Berlin–Heidelberg–New York, pp. 227–250, 1970.
20. Kumari R, Varghese A, George L, Sudhakar YN. Effect of solvent polarity on the photophysical properties of chalcone derivatives. RSC Advances 7 (2017) 24204–24214. DOI: 10.1039/c7ra01705g.