Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Towards dual photodynamic and antiangiogenic agents: a phthalocyanine-chalcone conjugate

Sinem Tuncel,[a] Jérémie Fournier-dit-Chabert,[b] Florian Albrieux,[c] Vefa Ahsen,[a] Sylvie Ducki,[b*] Fabienne Dumoulin[a*]

[a] *Gebze Institute of Technology, Department of Chemistry, P.O. Box 141, Gebze, 41400, Kocaeli, Turkey*

[b] *Clermont Université, ENSCCF, EA 987, LCHG, BP 10448, F-63000 Clermont-Ferrand, France*

[c] *Centre Commun de Spectrométrie de Masse UMR 5246, CNRS-Université Claude Bernard Lyon 1, Université de Lyon, Bâtiment Curien, 43, bd du 11 Novembre, 69622 Villeurbanne Cedex, France*

Supporting information

EXPERIMENTAL PROCEDURES

Synthesis

Materials and methods.

Solvents and chemicals were purchased from Aldrich or Alfa Aesar and used as received. Mass spectra were recorded on a MALDI (matrix assisted laser desorption ionization) BRUKER Microflex LT using 2,5-dihydroxybenzoic acid as the matrix and on a BRUKER MicroTOFQ-II with an ESI (electrospray ionization) ion source in positive mode. In this later case, the sample was infused at 150 µL/h in 50:50 water and acetonitrile with 0.1% of formic acid. The gas flow of the sprayer is 0.6 bar and the spray voltage is 3.5 kV. The capillary temperature is 200°C. The ions are transferred to the TOF by using mild conditions on ion optics (the two ion funnels, the hexapole, the quadrupole and the collision cell) to preserve the complex. The mass range of the TOF is 50-5000 *m/z*. IR spectrum was recorded between 4000 and 650 cm^{-1} using a Perkin Elmer Spectrum 100 FT-IR spectrometer with an attenuated total reflection (ATR) accessory featuring a zinc selenide (ZnSe) crystal. Electronic absorption spectra in the UV-visible region were recorded with a Shimadzu 2001 UV spectrophotometer using a 1 cm path length cuvette at room temperature. ^{1}H and ^{13}C NMR spectra were recorded in deuterated solvant solutions on a Bruker 400 MHz or on a Varian 500 MHz spectrometer. The HPLC system is an Agilent 1100 series HPLC system (ChemStation software) equipped with a G1311A pump and G1315B diode array detector monitoring the range 254–900 nm. A normal phase column Lichrosorb-SI-60 (250 × 4.6 mm) from Alltech. Associates, Inc. was used. The mobile phase was a 50/50 (v/v) mixture of chloroform-tetrahydrofuran. The flow-rate was set at 0.8 $mL.min^{-1}$. The column temperature was maintained at 28 ^{o}C.

Phthalocyanine **7** was prepared following a published procedure (S. Tuncel, F. Dumoulin, J. Gailer, M. Sooriyaarachchi, D. Atilla, M. Durmuş, D. Bouchu, H. Savoie, R. W. Boyle and V. Ahsen, *Dalton Trans*., 2011, **40**, 4067).

*Preparation of (2E)-3-(4-methoxy-3-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**4**).*[1]

A solution of 3,4,5-trimethoxyacetophenone **2** (2.10 g, 10 mmol), 3-nitro-4-methoxybenzaldehyde (**3)** (1.81 g, 10 mmol) and sodium hydroxide (4.00 g, 100 mmol) in methanol (15 mL) was stirred at room temperature for 15 hours. The brown precipitate was filtered and the solid was washed with small portions of ice-cold methanol (2 x 3 mL). The yellow solid was dried under vacuum

and afforded **4** as a yellow powder (3.11 g, 84 %). mp 142-144 °C. *m/z* (ES+) 374 (M+1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.94 (s, 3H), 3.97 (s, 6H), 4.03 (s, 3H), 7.15 (d, 1H, *J* 8.7 Hz), 7.28 (s, 2H), 7.44 (d, 1H, *J* 15.5 Hz), 7.76 (d, 1H, *J* 15.5 Hz) 7.79 (dd, 1H, *J* 2.2; 8.7 Hz), 8.18 (d, 1H, *J* 2.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.5 (2 CH_3), 56.8 (CH_3), 61.1 (CH_3), 106.4 (2 CH), 114.2 (CH), 122.3 (CH), 125.1 (CH), 128.1 (C), 133.6 (C), 135.1 (CH), 140.5 (C), 142.2 (CH), 143.3 (C), 153.8 (2 C), 154.8 (C), 189.3 (C=O).

*Preparation of (2E)-3-(3-amino-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**5**).*[1]

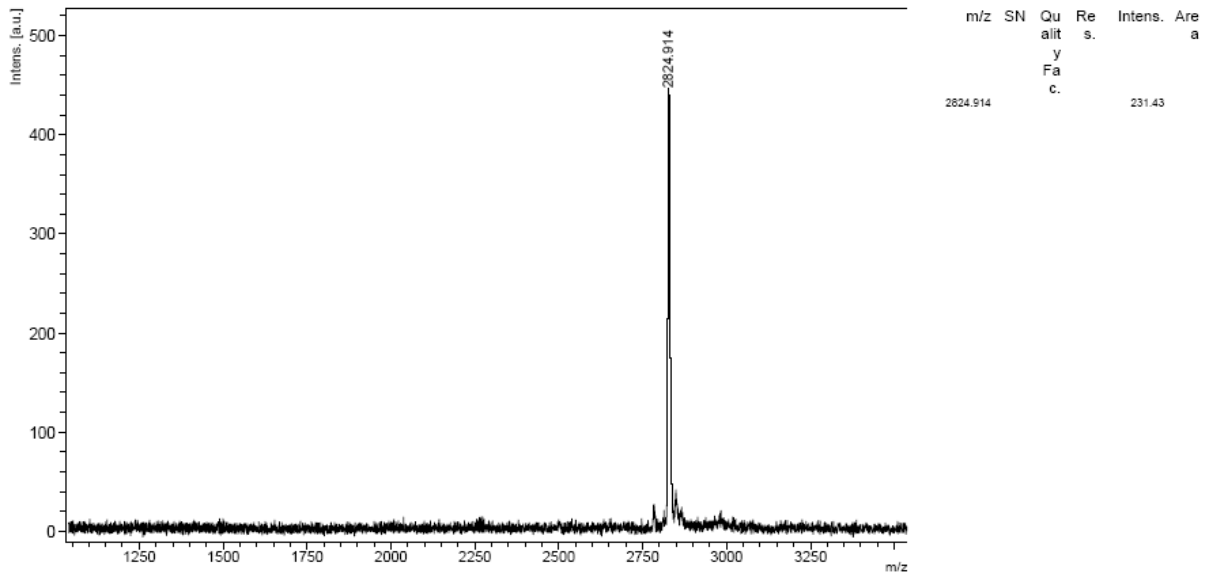
To a solution of the nitrochalcone **4** (746 mg, 2 mmol) were added iron powder (1.02 g, 20 mmol) in ethanol (20 mL) and a solution of hydrogen chloride (4 mL of a 0.2 M solution) and the mixture was heated under reflux at 80 ºC for 2 hours. The resulting solution was filtered over a short pad of silica, washed with DCM (50 mL) then concentrated. The solid was dissolved in DCM (20 mL) then washed with a concentrated $NaHCO_3$ solution (20 mL) then water (20 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to afford quantitatively a brown-orange sticky solid of **5** (686 mg). mp 90-92 °C. *m/z* (ES+) 345 (M+2, 20), 344 (M+1, 100). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.89 (s, 3H), 3.94 (s, 9H), 3.95 (m, 2 NH), 6.80 (d, 1H, *J* 8.2 Hz), 7.03 (d, 1H, *J* 8.2 Hz), 7.06 (bs, 1H), 7.28 (s, 2H), 7.32 (d, 1H, *J* 15.4 Hz), 7.73 (d, 1H, *J* 15.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4 (CH_3), 56.2 ($2CH_3$), 60.8 (CH_3), 106.1 (2CH), 110.4 (CH), 113.4 (CH), 119.4 (CH), 121.2 (CH), 128.2 (C), 134.3 (C), 137.0 (C), 142.4 (C), 145.8 (CH), 150.1 (C), 153.5 (2C), 190.0 (C=O).

*Preparation of (2E)-3-(3-isocyanato-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**6**).*

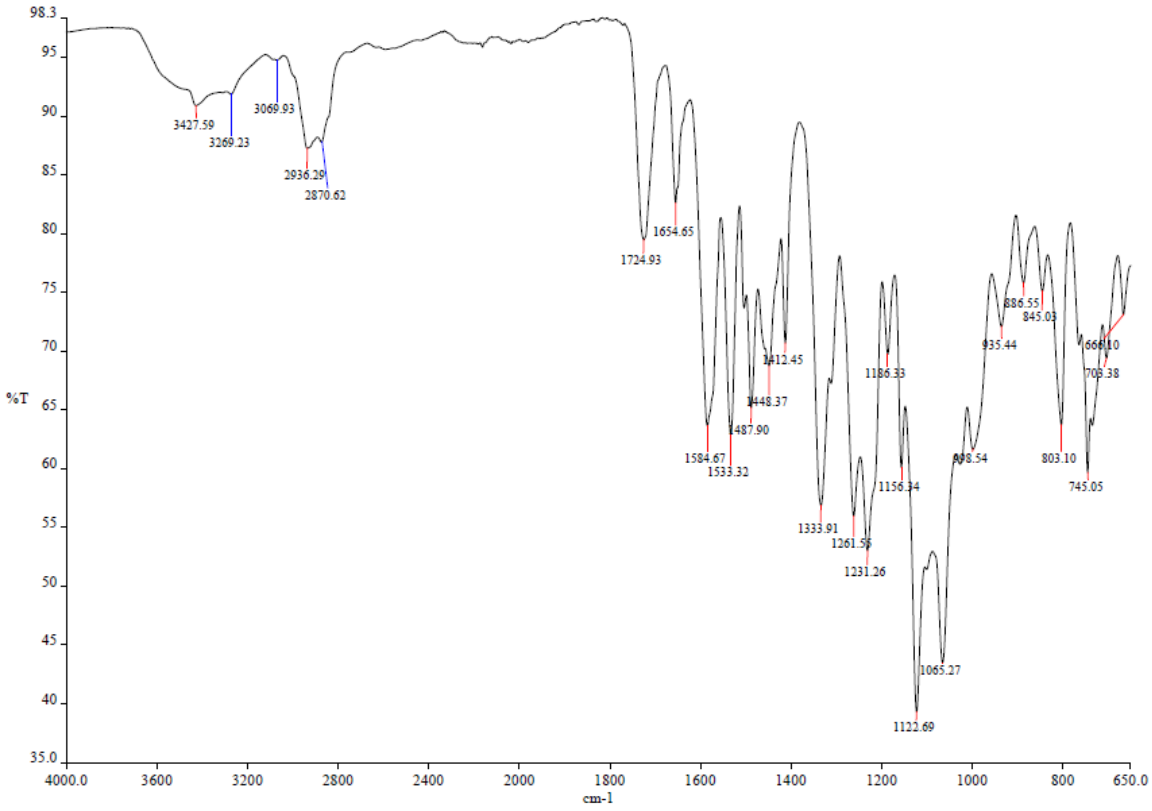
To a solution of the aminochalcone **5** (173 mg, 0.5 mmol) in dry toluene (10 mL) in a sealed tube was added triphosgene (50 mg, 0.17 mmol) portionwise then triethylamine (75 µL, 0.56 mmol). The solution was left to stir for 15 hours at 80 ºC, then the mixture was filtered and concentrated to afford quantitatively the corresponding isocyanate (**6**) as a yellow solid (185 mg). The compound was analyzed by NMR and used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.94 (s, 3H), 3.96 (s, 6H), 3.99 (s, 3H), 6.92 (d, 1H, *J* 8.0 Hz), 7.27 (s, 2H), 7.35 (bs, 1H), 7.35 (d, 1H, *J* 15.5 Hz), 7.42 (d, 1H, *J* 8.0 Hz), 7.72 (d, 1H, *J* 15.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.3 (CH_3), 56.4 ($2CH_3$), 61.0 (CH_3), 106.2 (2CH), 111.1 (CH), 120.7 (CH), 122.9 (CH), 124.9 (C), 128.3 (CH), 128.5 (C), 130.9 (C), 134.0 (C), 142.9 (C), 144.1 (CH), 153.7 (2C-O), 155.8 (C), 189.7 (C=O).

*Preparation of conjugate **1**.*

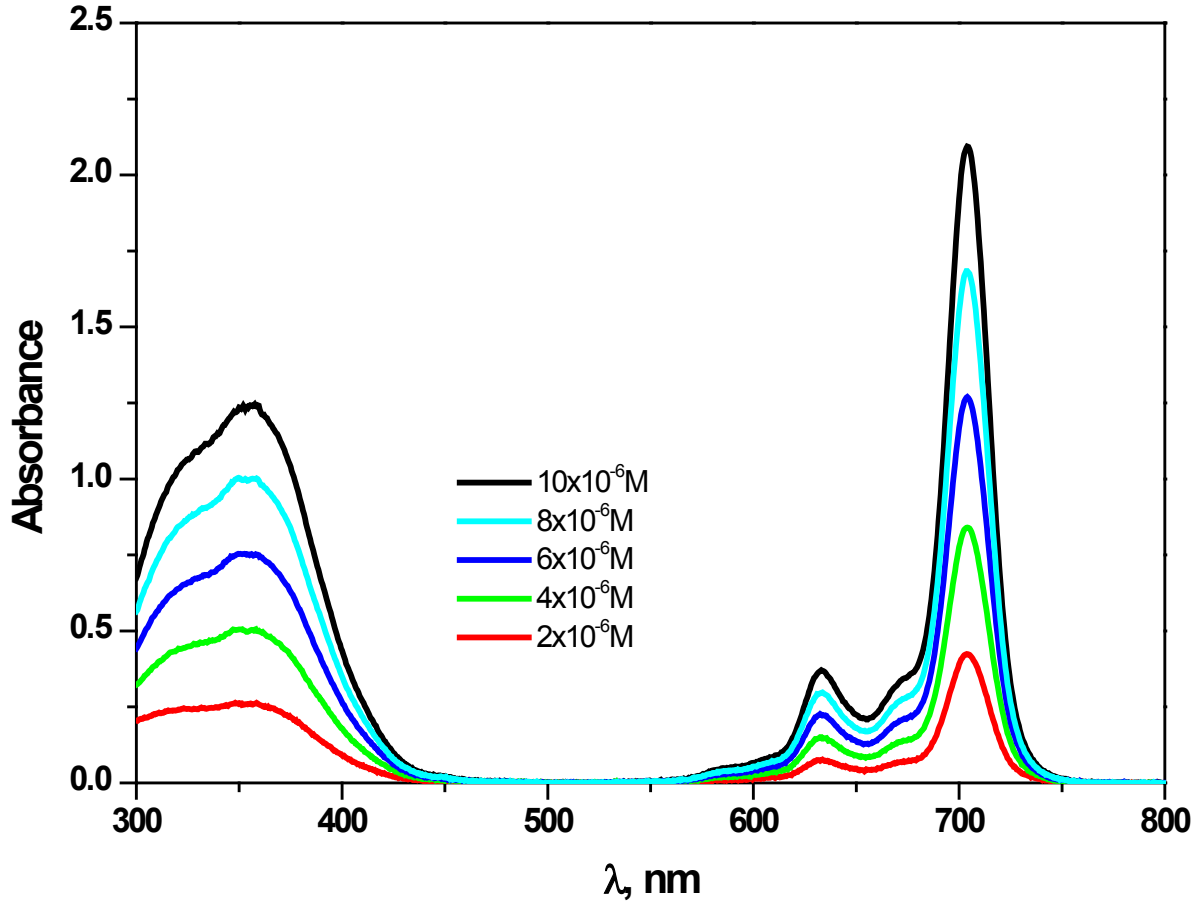
To a stirring solution of chalcone **6** (185 mg, 0.5 mmol) in a sealed tube with dry toluene (2 mL) were added, at room temperature, dry dichloromethane (2 mL) then the solid phthalocyanine **7** (13.5 mg, 0.01 mmol). The reaction was stirred under argon for 48 hours at 30 °C until three different phthalocyanine blue spots were visible on tlc. The crude mixture was concentrated then diluted in dichloromethane (10 mL) and successively washed with brine (10 mL), a saturated $NaHCO_3$ solution (10 mL) and water (10 mL). The resulting organic phase was dried over $MgSO_4$, filtered and concentrated then purified twice by flash chromography (SiO_2 25g; CH_2Cl_2/MeOH, 96:4) to afford 12.1 mg of the desired compound (74%). $C_{144}H_{156}N_{12}O_{44}Zn$, MW 2824.243. R_f 0.51 (25:1, CH_2Cl_2:EtOH). ATR-IR (ν, cm^{-1}): 3427.59 (N-H), 3269.23, 3069.93 (C-H_{ar}), 2936.29-2870.62 (C-H_{al}), 1724.93 (C=O), 1654.65 (C=C), 1584.67 (C=C_{ar}), 1533.32, 1487.90, 1448.37, 1412.45, 1333.91, 1261.56, 1231.26, 1186.33, 1156.34, 1122.69, 1065.27, 998.54, 935.44, 886.55, 845.03, 803.10, 745.05, 703.38, 666.10. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28-9.14 (m, 44 H, aromatics, CH=CH, NH), 3.46-5.05 (m, 112 H, CH_2, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.00, 149.17, 144.82, 144.75, 144.65, 142.19, 133.65, 132.00, 127.67, 124.13, 119.58, 109.78, 105.96, 71.21, 71.18, 71.17, 70.96, 70.95, 70.93, 70.70, 70.69, 70.64, 70.58, 70.57, 70.54, 70.52, 70.44, 70.42, 70.38, 69.80, 69.35, 69.33, 69.30, 64.27, 64.12, 60.92, 56.38, 55.67. MALDI-TOF-MS *m/z*: calcd 2824.243; found 2824.914 $[M]^+$. HRMS-ESI: *m/z* calcd for $C_{144}H_{157}N_{12}O_{44}Zn$, 2821.9703; found 2821.9590. *m/2z* calcd for $C_{144}H_{158}N_{12}O_{44}Zn$, 1411.4888; found 1411.4897. HPLC R_t : 8.54 min. UV-vis (DMSO): λ_{max} nm (log ε) 322 (5.03), 356 (5.10), 704 (5.32).

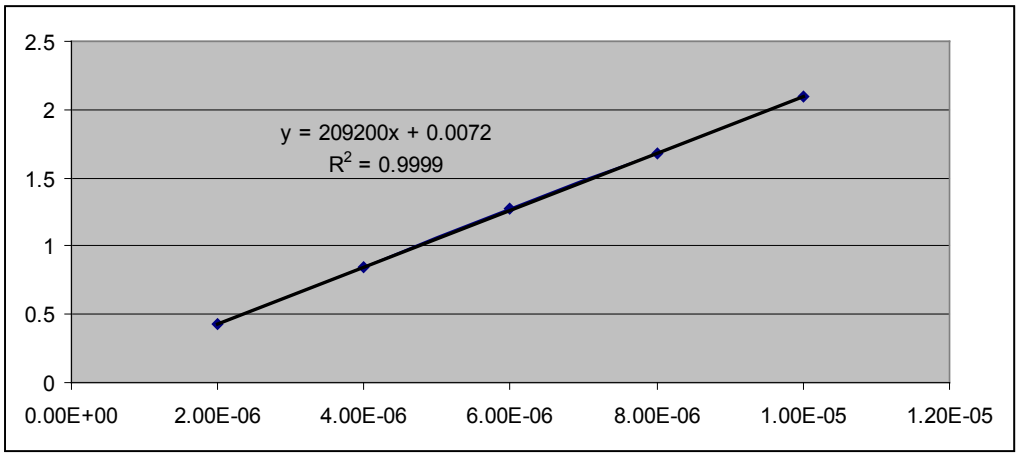


MALDI spectrum of **1** (matrix: dihydroxybenzoic acid)

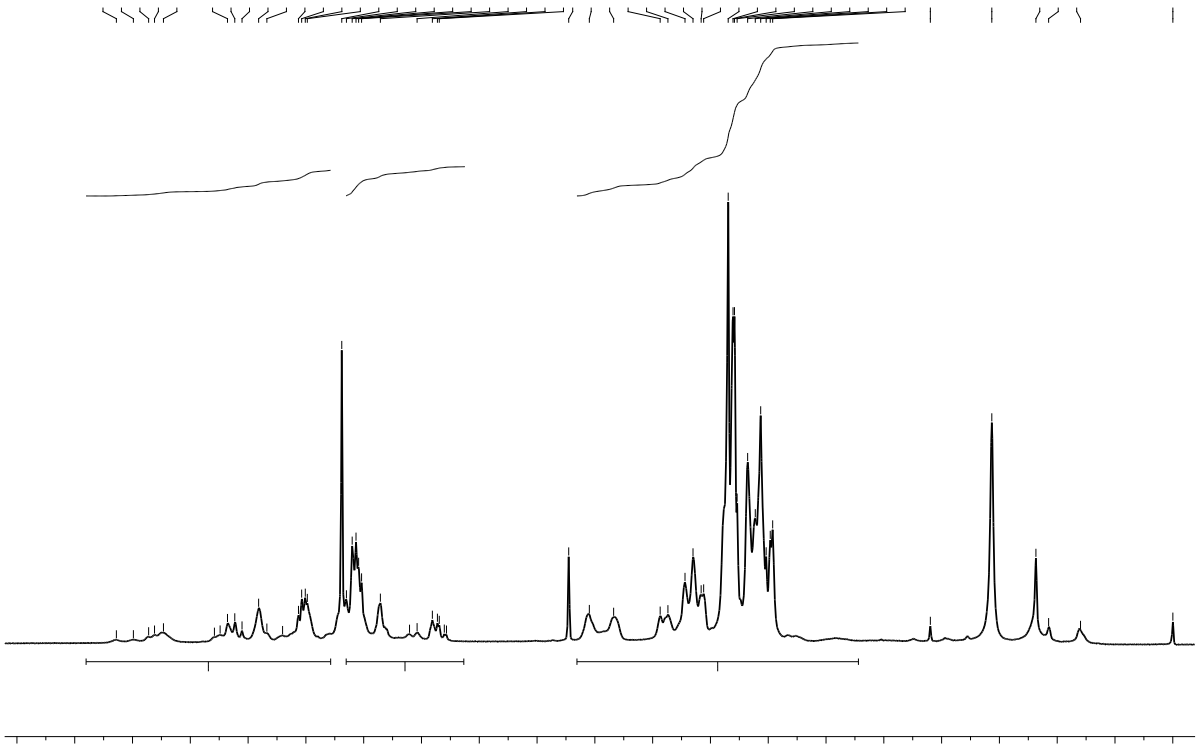


ATR-IR spectrum of **1**

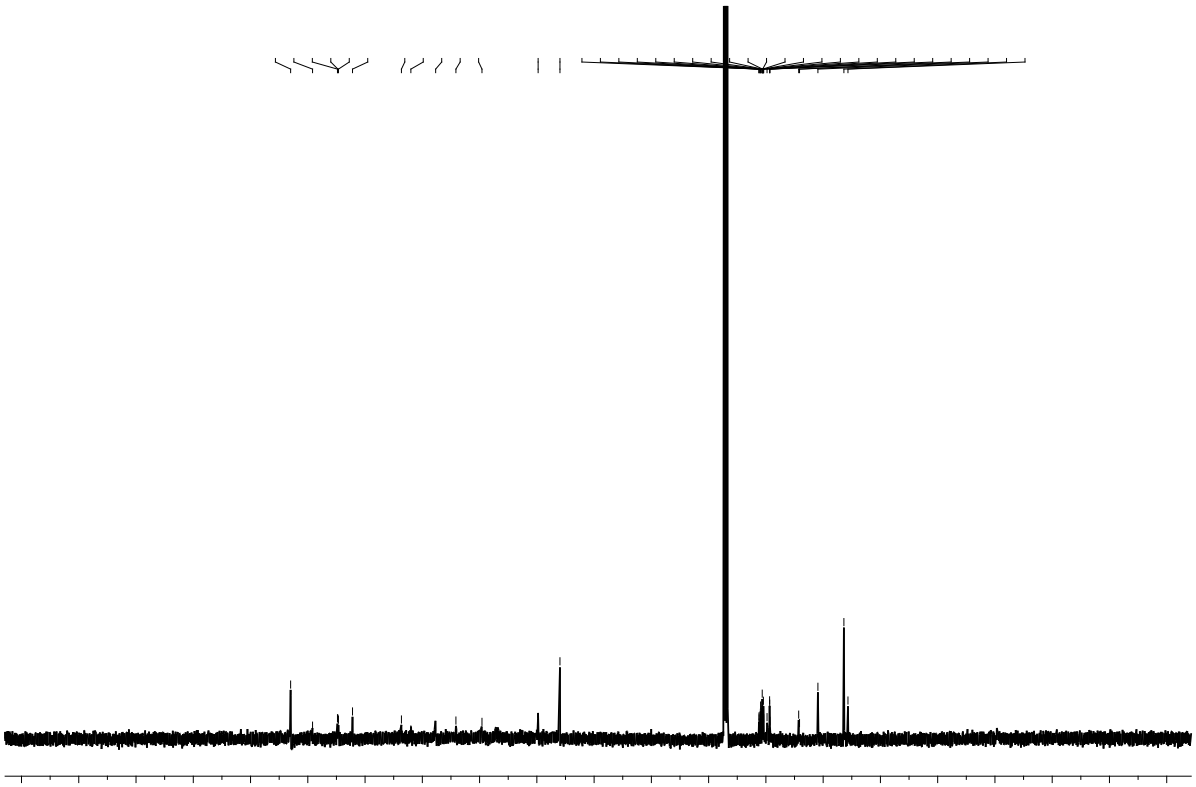




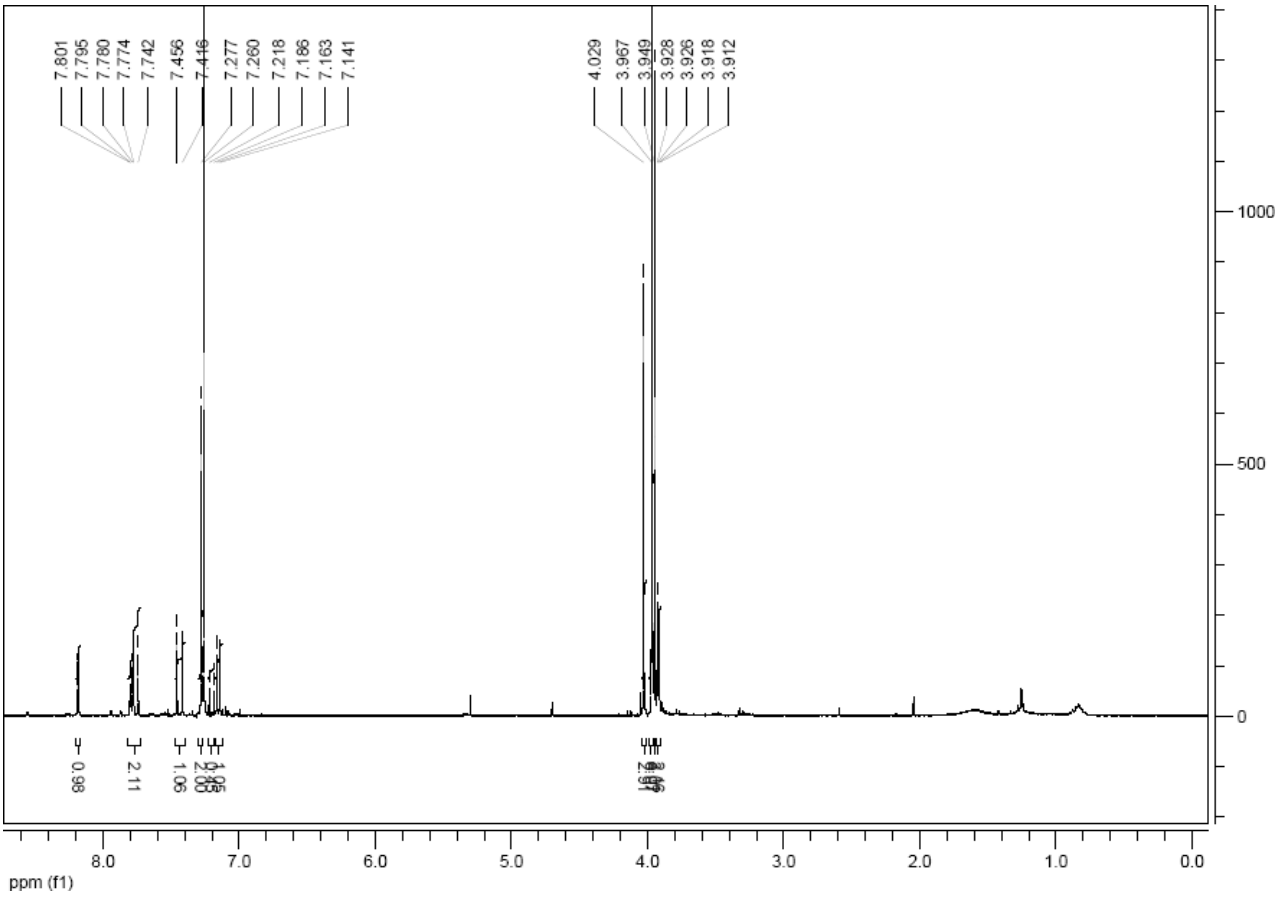
Electronic absorption data: spectrum in DMSO and absorbance-concentration linearity of **1** (log Ɛ = 5.32 at 704 nm)



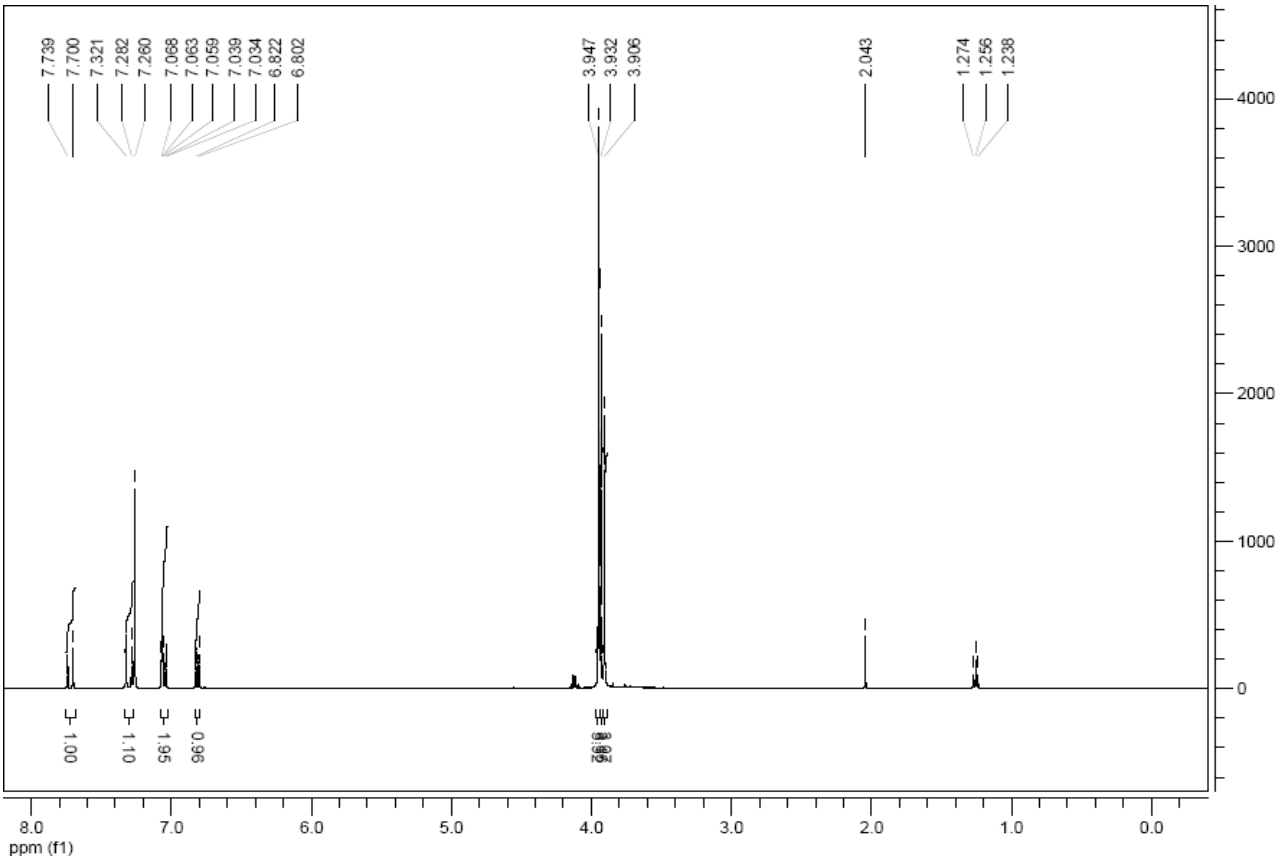
^{1}H NMR spectrum of **1** ($CDCl_3$)



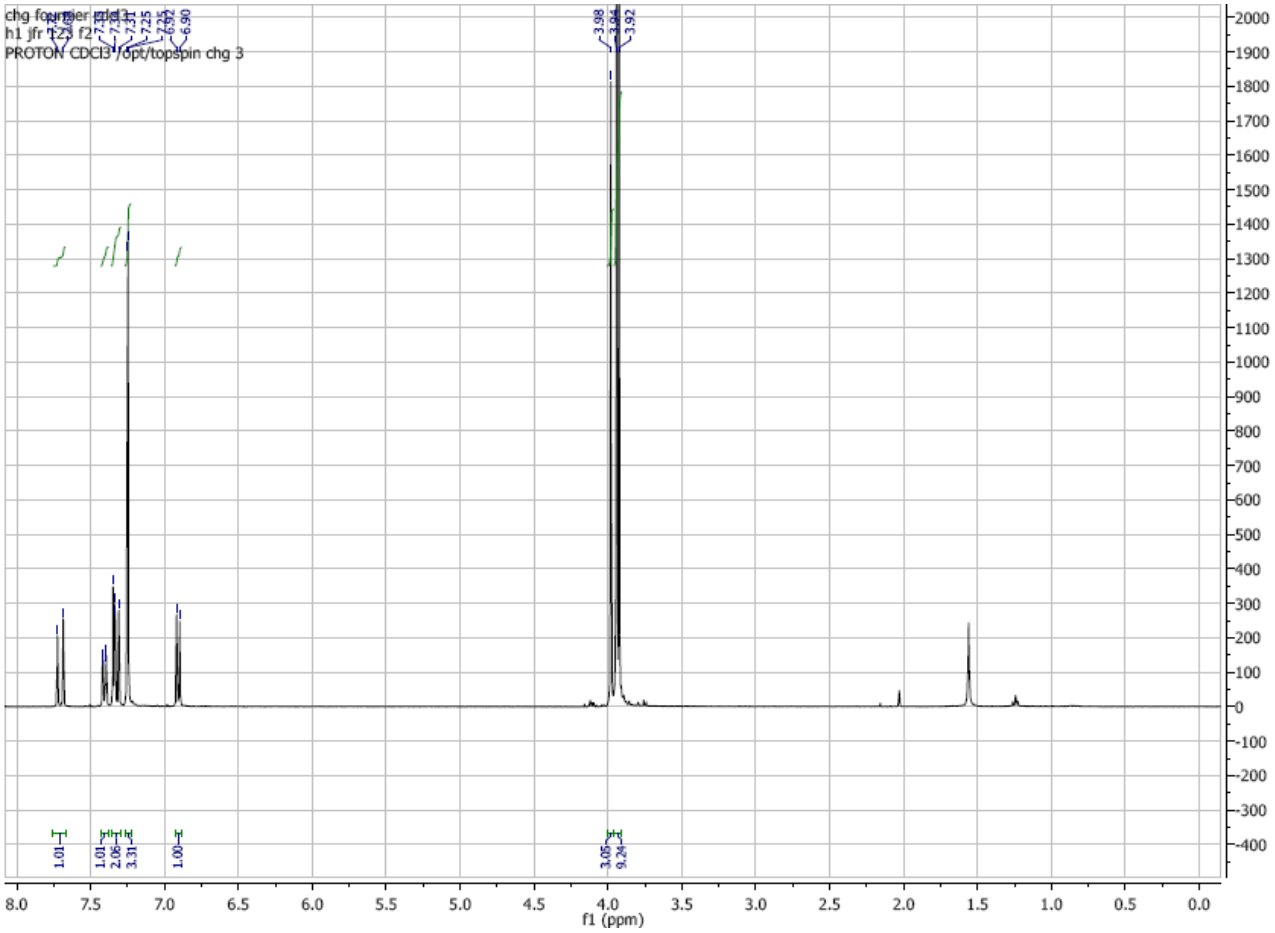
^{13}C NMR spectrum of **1** ($CDCl_3$)



^{1}H NMR spectra of compounds **4**



^{1}H NMR spectra of compounds **5**



[1]H NMR spectra of compounds **6**

REFERENCE

[1] M. Bonesi, M. R. Loizzo, G. A. Statti, S. Michel, F. Tillequin, F. Menichini, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1990.