Journal of Molecular Structure 1122 (2016) 318–323

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

# Experimental, DFT and molecular docking studies on 2-(2-mercaptophenylimino)-4-methyl-2H-chromen-7-ol

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ARTICLE INFO

*Article history:*
Received 21 February 2016
Received in revised form
7 May 2016
Accepted 1 June 2016
Available online 2 June 2016

*Keywords:*
Coumarin derivative
TD-DFT
Vibrational spectra
NLO response
AChE inhibitor

ABSTRACT

A new coumarin derivative 2-(2-mercaptophenylimino)-4-methyl-2H-chromen-7-ol **(COMSB)** was synthesized and characterized with the help of $^{1}H$,$^{13}C$ NMR, FT-IR, FT-Raman and mass spectrometry. All quantum calculations were performed at DFT level of theory using B3LYP functional and 6-31G (d,p) as basis set. The UV–Vis spectrum studied by TD-DFT theory, with a hybrid exchange-correlation functional using Coulomb-attenuating method (CAM-B3LYP) in solvent phase gives similar pattern of bands, at energies and is consistent with that of experimental findings. The detailed analysis of vibrational (IR and Raman) spectra and their assignments has been done by computing Potential Energy Distribution (PED) using Gar2ped. Intra-molecular interactions were analyzed by 'Atoms in molecule' (AIM) approach. Computed first static hyperpolarizability ($\beta_0 = 8.583 \times 10^{-30}$ esu) indicates non-linear optical (NLO) response of the molecule. Molecular docking studies show that the title molecule may act as potential acetylcholine esterase (AChE) inhibitor.



## 1. Introduction

Benzopyrone nucleus is one of important heterocyclic pharmacophore that occurs in several bioactive compounds. Coumarins are plant flavanoids containing benzopyrone framework and are widely distributed in nature. Coumarin and their derivatives have been found to show broad spectrum of pharmacological activities such as antitumor [1], anti-inflammatory [2], antibacterial [3,4], anti-coagulant [5], anti-HIV [6,7], anticancer [8] and CNS stimulant activities [9]. Some coumarins are known to have lipid lowering activity [10] and free radical scavenging properties [11]. They also find application in dyes [12] and photo-chemotherapy [13]. Pharmacological and therapeutic properties of coumarins can be changed by the type and pattern of substitutions on the basic chemical structure of the molecule [14–16]. Due to versatile biological activities, coumarins are subject of detailed investigations. Literature survey reveals that detailed quantum chemical study on structural and spectroscopic properties of title compound is not yet available. Quantum chemical calculations with density functional theory (DFT) method have been extensively used for study of different aspects of compounds [17–19]. In the view of various significance of coumarins, title compound 2-(2-mercaptophenylimino)-4-methyl-2H-chromen-7-ol (COMSB) has been synthesized and well characterized. DFT calculations on the molecular structure, spectroscopic properties and reactivity of the title compound have been reported. Non-linear response of the molecule is also computed. Using 'Quantum theory of atoms in molecule (QTAIM)', topological parameters calculated at bond critical points (BPC) has been used to understand various interactions in the synthesized molecule. To access the biological activity of the title compound, molecular docking studies have been performed against human acetylcholine esterase and reported.

## 2. Experimental details

Starting materials were purchased from Aldrich (USA) and used as supplied. All the solvents used were purified and dried according to standard procedures [20]. Melting points (°C) was determined in an open capillary by electro-thermal melting point apparatus. Elemental analysis (C, H, N and S) was performed on Varian Elementar – III analyzer. FT-IR spectrum was recorded in KBr pellets on Bruker model FTIR spectrometer from 4000 to 400 $cm^{-1}$ range. $^{1}H$ and $^{13}C$ NMR spectrum of synthesized compound was recorded on Bruker DRX-300 instrument (in DMSO-$d_6$) using TMS as an

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http://dx.doi.org/10.1016/j.molstruc.2016.06.001
0022-2860/

internal reference. The DART-mass spectrum was recorded on JEOL-Acc TOF JMS-T100LC mass spectrometer in $ESI^+$ mode. UV–Vis spectrum was obtained (in range of 200–500 nm) on LABTRONICS LT 2900 spectrophotometer equipped with a 10 mm quartz cell in solvent dichloromethane. The FT-Raman spectrum was recorded on a Bruker MultiRAM-RFS27 spectrometer in the region 4000–50 $cm^{-1}$ which uses 1064 nm Nd-YAG laser line for the excitation.

### 2.1. Synthesis of 2-(2-mercaptophenylimino)-4-methyl-2H-chromen-7-ol (COMSB: 3)

7-hydroxy-4-methyl coumarin (0.176 mg, 1 mmol) was dissolved in 15 mL hot ethanol followed by addition of 2-aminothiophenol (0.107 mL, 1 mmol). Trace amount (2–3 drops) of hydrochloric acid was added as catalyst and the reaction mixture was refluxed at room temperature until the reaction was complete. Progress of reaction was monitored with the help of thin layer chromatography (TLC). After the reaction was complete, the solvent was reduced and kept overnight in refrigerator. The obtained precipitate was filtered off, washed methanol followed by diethyl ether and then dried in air. The compound was recrystallized with ethanol to get pure product. The synthetic route showing formation of title compound **(COMSB)** is shown as Scheme 1. Yield: 69%, Colour: creamy white, M.p. 163–165 °C. DART MASS ($ESI^+$ mode) (*m*/*z*): obs. 249.1 a.m.u. (100%) [$M^+$-$H_2S$]. Elemental analysis calculated for $C_{16}H_{13}NO_2S$ (283.345): C 67.82, H 4.62, N 4.94, S 11.32% Found: C 68.09%, H 4.83%, N 4.86% and S 11.23%. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ (ppm): 6.73–6.74 (1H, d, H-7, $J$ = 2.4 Hz), 6.83–6.86 (1H, d, H-9, $J$ = 9.0 Hz), 6.80–6.83 (1H, d, H-10, $J$ = 9.0 Hz), 6.11 (1H, s, H-13, =C–H), 5.45 (1H, s, b, H-20, –O–H), 7.09–7.12 (1H, H-27, d, $J$ = 8.2 Hz), 7.56–7.59 (1H, H-29, d, $J$ = 8.7 Hz), 7.23–7.29 (2H, m, H-30, H-31), 2.35 (3H, s, H-16, H-17, H-18, $-CH_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ (ppm): 18.13 (-$CH_3$, C-15), 102.22 (C-2), 110.20 (H–C=, C-11), 111.97 (C-6), 112.94 (C-4), 119.81 (C-24), 122.49 (C-28), 123.13 (C-26), 126.55 (C-5), 130.88 (C-25), 134.32 (C-23), 141.22 (C-22), 153.57 (=C–$CH_3$, C-8), 154.83 (C=N, C-12), 160.34 (C-3), 161.30 (–C–OH, C-1). Dart-Mass spectrum of title compound is given as Supplementary Fig. 1. The $^1H$ and $^{13}C$ NMR spectrum is shown as Supplementary Figs. 2 and 3.

## 3. Computational details

All molecular calculations and geometry optimization of the title compound have been performed with Gaussian 09 program package [21] using Density Functional Theory (DFT) and B3LYP functional with 6-31G (d, p) as basis set. The energies and intensities of 25 spin allowed electronic transitions were calculated using TD-DFT theory with CAM-B3LYP method in vacuum and also in solvent using IEF-PCM model [22]. The first static hyperpolarizability ($\beta_0$) was calculated by the finite field perturbation method in vacuum [23]. Using the x, y and z components of $\beta$ obtained from Gaussian output, the magnitude of the mean first hyperpolarizability tensor was calculated. The normal mode analysis was performed and the potential energy distribution (PED) was done using Gar2ped program [24]. The calculated wavenumbers are scaled down using single scaling factor 0.9608 to discard of any harmonicity present in real system [25]. Presentation graphics and visualizations were done with the help of Gauss view 5.0 [26]. AIMALL software [27] was used to prepare molecular graph and compute topological parameters at bond critical point. All calculations were performed on Auto Dock 4.2 software [28] which uses Lamarckian Genetic Algorithm (LGA) [29,30]. The crystal structure of human acetylcholinase was obtained from RSCB Protein Data Bank. As required in the LGA, all water molecules were removed and polar hydrogen atoms were added followed by calculation of Gasteiger charges. All the docked ligands were optimized at same level of theory. The grid box Auto grid was used for preparation of the grid map. The ligand rigid roots were automatically set, and all torsions were defined as active. All other parameters were as set by default. The docked conformations were viewed using Python Molecular Viewer package [31].

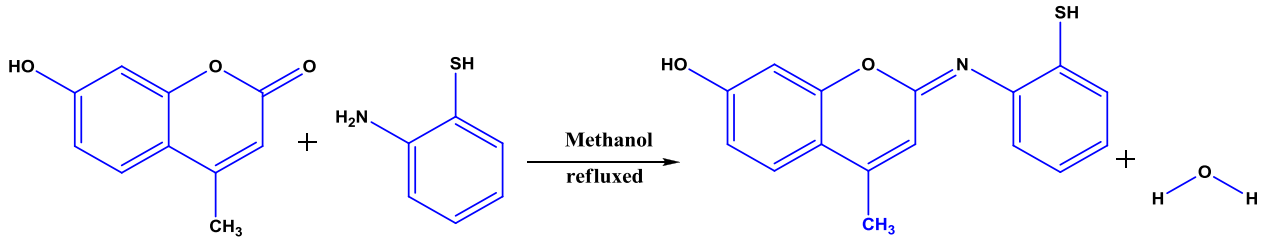
## 4. Results and discussion

### 4.1. Thermodynamic parameters and reaction feasibility

Thermodynamic quantities enthalpy (au.), Gibbs free energy (au.), entropy (cal/mol-K) for reactants, products and reaction, calculated at room temperature is given in Table 1. For overall reaction, the enthalpy change ($\Delta H_{Reaction}$), Gibbs free energy change ($\Delta G_{Reaction}$) and entropy change ($\Delta S_{Reaction}$) was calculated to be 15.688 kcal/mol, 18.198 kcal/mol and −5.563 cal/mol-K respectively. The positive values for $\Delta H$ and $\Delta G$ indicates that the reaction is highly endothermic and non-spontaneous at room temperature. The calculated equilibrium constant as Keq = $4.60 \times 10^{-14}$ (Keq ≪ 1) at room temperature, favours the formation of product at elevated temperature and therefore refluxing condition in presence of acid catalyst was required to synthesize the title compound.

### 4.2. Optimized structure, molecular electrostatic surface (MESP) potential and AIM calculations

The structure of title molecule was established with the help of spectral characterization and was then optimized. A relaxed PES scan along dihedral angle C12–N21–C22–C24 was performed to trace conformational flexibility of the molecule. After rotation around this dihedral angle, the minimum energy conformer was obtained on PES curve. The minimum energy conformer with (C12–N21–C22–C24) dihedral angle = −53.64°, was further




**Scheme 1.** The synthetic route for the formation of title compound (COMSB: 3).