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Spectral assignments and structural studies of a warfarin derivative stereoselectively formed by tandem cyclization

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ABSTRACT

The structural elucidation of a Mannich condensation product of *rac*–Warfarin with benzaldehyde and methyl amine was carried out using IR, Mass, ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY, DEPT–135, HMBC, NOESY spectra and single crystal X-ray diffraction. Formation of a new pyran ring *via* a tandem cyclization in the presence of methyl amine was observed. The optimized geometry and HOMO–LUMO energy gap along with other important physical parameters were found by Gaussian 09 program using HF 6–31G (d, p) and B3YLP/DFT 6–31G (d, p) level of theory. The preferred conformation of the piperidine ring in solution state was found to be chair from the NMR spectra. Single crystal X-ray diffraction and optimized geometry (by theoretical study) also confirms the chair conformation in the solid state.

1. Introduction

2,6–Disubstituted–4–piperidines [1] are being constituents of a number of alkaloids which have broad spectrum of biological activities. Bicyclic systems with *N*–methyl piperidine and pyran units [2] together showed a distinct potential pattern of selectivity towards antitumor activity. Aza spirosystems [3] containing substituted piperidinyl rings exhibit antibacterial and antifungal activities. Antimycobacterial evaluation carried out to explore the biological efficacy of pyran derivatives [4,5] of *N*–methyl piperidone is also known. 4–Hydroxycoumarin derivatives such as Warfarin, Acenocoumarol [6–9] possess anticoagulant and rodenticidal properties. Warfarin is being studied extensively due to its pharmacological properties. Racemic sodium warfarin is the most widely used antithrombotic drug in USA and Canada.

Multicomponent reactions involving three or more different substrates reacting in a well–defined manner to form a single compound has emerged as a powerful tool for synthesizing biologically potent molecules [10]. Tandem reactions often afford stereoselectivity [11–17] of medicinally important structural moieties in a facile manner. It is noteworthy that hybrid molecules play an important role in biological activity. Prompted by these reports, we have tried to synthesize a molecular hybrid (**5**) containing both coumarin and substituted piperidine moiety through a one–step Mannich reaction. The reaction proceeded one step further to form a cyclized product (**4**) containing an additional pyran ring with the expected piperidine and coumarin rings. The structure and stereochemistry of the newly synthesized product is established through IR, Mass, ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY,^{1}H–^{13}C COSY, DEPT–135, HMBC, NOESY spectra and through single crystal X-ray diffraction analysis. Theoretical studies have also been carried out using HF/6–31G (d, p) and B3YLP/DFT 6–31G (d, p) methods to deduce optimized geometry, HOMO–LUMO energy gap, NLO properties and Mulliken charge distribution etc.

2. Experimental

2.1. Synthesis of compound 4

The parent compound *rac*–warfarin (**3**) was prepared from 4–hydroxycoumarin (**1**) and benzylidene acetone (**2**) by the Michael addition reaction as reported in the literature [6]. The title compound **4** was prepared from *rac*–warfarin as follows: A mixture of 1 mmol (0.31 g) of *rac*–warfarin, 2 equivalents (0.21 mL) of benzaldehyde and 2 equivalents (0.17 mL) of methyl amine solution (40% in water) in ethanol was heated to boiling on a hot plate. Colourless crystals thus precipitated on cooling were recrystallized from ethanol to get the product in pure form. Single crystal suitable

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for X-ray diffraction analysis was obtained by slow evaporation of a solution of compound **4** in ethanol.

2.2. Spectral measurements and X-ray diffraction

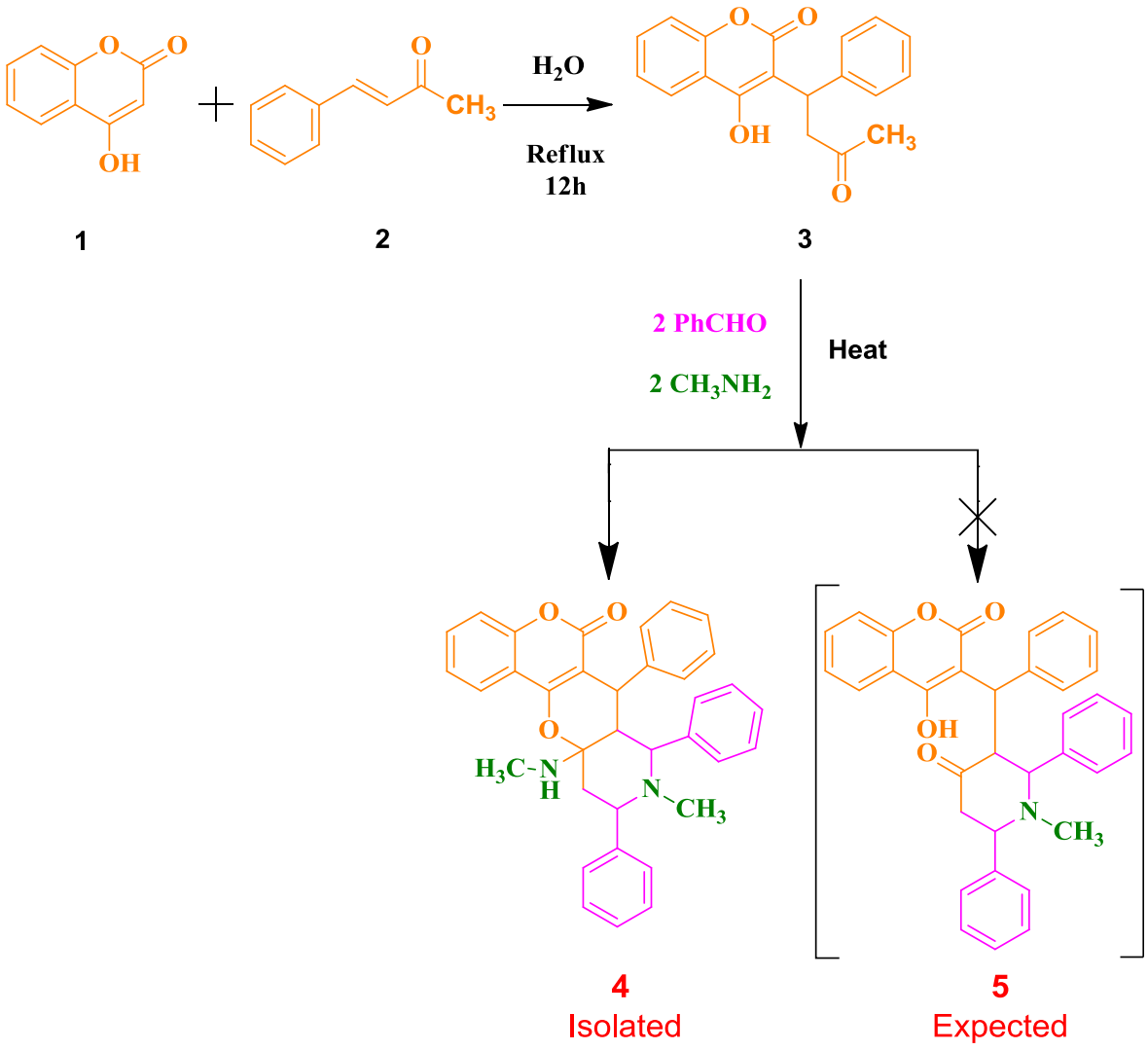
FT–IR spectrum was recorded on a NICOLET AVATAR 360 FT–IR spectrometer and the pellet technique (KBr) was adopted to record the spectrum. LC–Mass spectrum was recorded on a Shimadzu–LCMS 2010A mass spectrometer.

NMR spectra were recorded on a Bruker ULTRASHILED 400 PLUS spectrometer (Bruker Biospin gmBH, Rheinstetten, Germany) at around 294 K. Deuterated chloroform was used as a solvent to dissolve the compound **4**. The quantity of sample (compound **4**) taken for ^{1}H NMR and ^{1}H decoupled ^{13}C NMR were 10 mg and 50 mg respectively in 0.5 mL of $CDCl_3$. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the TMS, $\delta = 0$ ppm. Spin multiplicities are expressed as singlet (s), doublet (d), triplet (t), doublet of doublets (dd) and multiplet (m). Coupling constants (J) are given in Hz. The ^{1}H NMR data were acquired at 400 MHz frequency with number of scans = 16, acquisition time = 3.98 s, relaxation time = 1 s, 90° pulse width (P1) = 13.50 μs, spectral width = 8223.685 Hz, line broadening = 0.30 Hz, and FT size = 65,536. A frequency at 100 MHz was observable for ^{13}C NMR spectrum with number of scans = 2000, acquisition time = 1.36 s, relaxation time = 2 s, 90° pulse width (P1) = 8.25 μs, spectral width = 24,038.461 Hz, line broadening = 1.00 Hz, and FT size = 32,768. ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY, HMBC, DEPT–135 and NOESY spectra were measured with the pulse sequence gcosy, ghsqc, ghmbc, deptsp 135 and noesy respectively.

Single crystal X-ray diffraction analysis was carried out at 298 K using a three circle Bruker SMART–APEX CCD area detector system under Mo Kα (λ = 0.71073 Å) graphite monochromated X-ray beam with a crystal to detector distance of 60 mm and a collimator of 0.5 mm. The total number of reflections was equal to 5582. The structural refinement was done using *SHELXL 97* by full–matrix least–squares method with anisotropic temperature parameter for all non-hydrogen atoms.

2.3. Theoretical calculations

Theoretical calculations were done by considering the crystal structure of compound **4** as the initial structure using HF and B3YLP/DFT methods using 6–31G (d, p) as the basis set in Gaussian 09 package [18] to optimize the structure. The lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) energy differences for the molecule were calculated by



Scheme 1. Synthetic scheme of compound **4**.