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Synthesis of 4-(2-fluorophenyl)-7-methoxycoumarin: experimental and computational evidence for intramolecular and intermolecular C-F⋯H-C bond

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Abstract

4-(2-fluorophenyl)-7-methoxycoumarin (6) was synthesized by Pechmann reaction under mild conditions via a three step-reaction. The solution-state $^1$H NMR spectra of 6 showed a strong intramolecular interaction between F and H5 ($J_{FH} = 2.6$ Hz) and $^{13}$C NMR suggested that this C-F⋯H-C coupling is a through-space interaction. The 2-D HOESY spectrum and $^1$H-$^{19}$F 1-D spectrum were also done to confirm this F⋯H interaction. The single crystal X-ray structure and the DFT-optimized structure showed that the fluorinated phenyl ring favours the orientation with the fluorine atom is closer to H5 than H3. The X-ray structure also showed the existence of the intermolecular C-F⋯H-C interactions.

Keywords
Introduction

Coumarins constitute one of the big classes of naturally occurring compounds. The first coumarin was isolated from the tonka bean (*Dipteryx odorata*) in 1820 and, to date, more than 1300 coumarins have been identified from natural sources [1-2]. Coumarins have been reported to play a vital role as food and cosmetics constituents, cigarettes additives, and dye-sensitized solar cells [3-4]. In addition, coumarins possess some biological activities such as anti-inflammatory [5], anti-tumor [6], anti-oxidant [7], anti-bacterial [8], hepatoprotective, anti-coagulant, anti-viral and anti-thrombotic activities [9]. The variety of uses of these compounds resulted in an increase in demand for large quantities of coumarins. Due to an insufficient natural supply to meet this demand for these compounds, numerous methods for the synthesis of these compounds have been developed, examples are the Pechmann condensation, Stille coupling reaction, Knoevenagel condensation, Heck coupling reaction, Perkin reaction, Kostanecki reaction, Baylis-Hillman reaction, Michael reaction, Suzuki-Miyaura cross-coupling reaction, Negishi cross-coupling reaction and Wittig reaction [10-14].

The concept of the incorporation of fluorine into organic molecules has gained much interest since Fried and Sabo reported the improvement of the therapeutic index of cortisol by the incorporation of a fluorine atom in the 9α position of the structure [15]. Since then, the fluorine-containing drugs have come onto the market and they are amongst the best-selling pharmaceutical drugs, including Lipitor®, Prevacid®, Advair Discus® and Lexapro® [16-18]. The incorporation of fluorine may improve the activity
of biologically active compounds as it imparts a variety of properties such as enhanced binding interaction, metabolic stability, and reaction selectivity by changing physical and chemical properties [19-22].

Hydrogen bonds (HBs) are associated with highly electronegative atoms (oxygen, nitrogen, fluorine) and have been observed to govern the conformational structure of some molecules as well as the alignment of the molecules within a crystal structure [23-25]. Moreover, HBs have been reported to play a vital role in a ligand-receptor interaction that determines the biological activity of a molecule. Oxygen and nitrogen have been proven to be good hydrogen-bond acceptors which form strong intermolecular and intramolecular hydrogen bonds, however, fluorine is still denied hydrogen-bond acceptor status by some scientists.

There is evidence of the existence of C-F···H interaction in organic molecules [26-27]. Early reports by Glusker and co-workers in 1983 and 1994 showed C-F···H interactions in structures found in the Cambridge Crystallographic Data Centre database [28]. Similar evidence was reported by Howard, O’Hagan, Desiraju and their co-workers where the C-F···H interaction was observed, although the conclusions of the two groups were different – O’Hagan et al concluded that fluorine is not a good hydrogen-bond acceptor, whereas Desiraju et al concluded that the interaction has genuine hydrogen-bond character [20, 29-30].

The C-F···H-C interaction is amongst the weakest of hydrogen bonding phenomena because a carbon acid (C-H) is weak, therefore is a weak donor, and the acceptor is non-polarizable, therefore is a poor acceptor [29, 31-32]. Wang and co-workers reported the existence of the C-F···H-C intramolecular hydrogen bond in the structure of aromatic triazole foldmers [33]. In their study, using crystallographic and DFT data, they concluded that their folded conformers are held by C-F···H-C hydrogen bonds. To further these studies, we have synthesized a fluorine-containing phenylcoumarin.
in order to study the fluorine-hydrogen bond. The crystal structure and solution-state NMR data of the coumarin 6 were studied to examine any C-F⋯H-C hydrogen bond interactions. DFT calculations were performed to determine the preferred conformations of the structure that might exhibit a C-F⋯H-C hydrogen bond.

Results and Discussion

Synthesis of 2-fluorophenylcoumarin (6)

4-(2-fluorophenyl)-7-methoxycoumarin (6) was synthesized under mild conditions via a three step-reaction (Scheme 1) and the first step was the synthesis of a fluorinated β-keto ester (3). Methyl acetoacetate (2) was treated with MgCl₂, Et₃N and nBuLi in DCM and then with 2-fluorobenzoyl chloride (1) to yield methyl 2-fluorobenzoylacetic (3). These reactions are very rare in the literature, however, there are similar reactions for the synthesis of β-keto esters as reported by Sijbesma et al. [34] and Anwar [35]. The second step of the synthesis was the Pechmann reaction, commonly used for the synthesis coumarins [36-37]. Methyl 2-fluorobenzoylacetic (3) was reacted with resorcinol (4) in the presence of H₂SO₄ at 35 °C, and 7-hydroxy-4-(2-fluorophenyl)coumarin (5) was obtained as a light yellow solid. The last step of the synthesis was the methylation of the hydroxyl group of coumarin (5) with dimethyl sulfate, to form 4-(2-fluorophenyl)-7-methoxycoumarin (6).
Scheme 1: Synthesis of 4-(2-fluorophenyl)-7-methoxycoumarin (6)

Discussion

During the synthesis of coumarin 6, solution-state NMR spectroscopy was used to characterize compounds 3, 5, and 6 (¹H and ¹³C spectra are available in the Supporting Information). The ¹H spectrum of coumarin 6 showed H···F interactions for H₃', H₄', H₅' and H-6' which is typical though-bond (TB) coupling. However, the peaks that caught our particular attention were the singlet peak at 6.25 ppm and a doublet-of-doublets (dd) peak at 7.16 ppm assigned to H3 and H5, respectively (Figure 1). The H5 signal was expected to be a doublet (not a dd) due to ³J coupling to H6, since an H,H-COSY experiment does not show coupling between H5 and H8. It became clear that the splitting of the signal from H5 was due to coupling with the ¹⁹F atom by comparing the spectra from the ¹H and ¹H-¹⁹F experiments (Figure 1) which showed the H5 peak as a doublet with ¹⁹F decoupling. While the doublet-of-doublets signal for H5 collapses into a doublet with ¹⁹F decoupling, there are no significant changes in the line-shape for the signal of H3 with ¹⁹F decoupling (Figure 1).
The question posed at this point was “is this a through-bond (TB) or through-space (TS) effect”?

![Figure 1: 1H NMR spectra for the “aromatic” region of coumarin 6; comparison of 1H spectrum (lower trace, blue) and 1H-{19F} spectrum (upper trace, red).](image)

To answer this question, we analysed a 13C-{1H} spectrum of coumarin 6 and the signal corresponding to C5 was found to be a doublet \( (J = 1.4 \text{ Hz}) \) but the signals corresponding to C4 and C4a were singlets, and this indicates that this coupling is not a TB effect, because if it were a TB effect, the signals for C4 and C4a would also likely be split. To confirm our findings, we further ran a 19F-1H HOESY experiment and it showed clear H5-19F and H3-19F coupling (Figure 2). Evidence of a HOESY interaction between H5-19F and H3-19F indicates that neither the H3-19F nor the H5-19F interaction limits the C4-C1’ bond rotation.
Figure 2: $^{19}$F-$^1$H HOESY NMR spectrum for coumarin 6 illustrating three through-space interactions.

The geometry of coumarin 6 (single molecule, gas phase) was optimized using the B3LYP functional and the 6-311G basis set, as implemented in Gaussian-09W (Rev. C.01). The superposition of the single-crystal X-ray structure (red) and the optimized structure (green) is shown in Figure 3.
Figure 3: Superposition of single-crystal X-ray structure (red) and DFT-optimized structure (green); RMSD 0.3 Å (hydrogen atoms omitted for clarity).

The X-ray crystal structure (ORTEP) and DFT optimized geometric structure are shown in Figure 4. The optimized structure has a dihedral angle, $\phi$ (C2'-C1'-C4-C4a) of 65.3°. Following the optimization, the dihedral angle $\phi$ was varied through a 360° rotation to examine the effect of changing the relative position of the fluorinated ring and the energy profile for this variation is shown in Figure 5. When $\phi = 5^\circ$, the F···H5 distance is at its shortest ($d_{F \cdots H5} = 2.0$ Å) and the fluorinated ring is almost coplanar with the coumarin ring, and the molecule is at its least stable conformation due to the electron-electron (e-e) repulsion of H5 and fluorine. The second least stable conformation is found at $\phi = 185^\circ$, with the fluorine atom and H3 in close proximity ($d_{F \cdots H3} = 2.0$ Å).
**Figure 4:** X-ray crystal structure, ORTEP (A) and DFT optimised structure (B) for coumarin (6).

**Figure 5:** Plots of Relative Energy (black trace, no units), Interatomic Distance F-H5 (red trace, Å), Interatomic Distance F-H3 (blue trace, Å) as a function of Dihedral Angle $\phi$ C2'-C1'-C4-C4a (°).
The theoretical NMR data for twenty four conformations of coumarin 6 were obtained from Gaussian 09W (Rev C.01) at the B3LYP/6-311G level. Geometry optimization and calculation of NMR parameters for TMS and CCl\textsubscript{3}F at the same level provided reference chemical shifts for \textsuperscript{1}H, \textsuperscript{13}C, and \textsuperscript{19}F. The chemical shifts for the lowest energy structure (\(\phi = 65.3^\circ\)) and the most unstable conformer (\(\phi = 5^\circ\)) are used as examples (Table 1). The theoretical chemical shifts for the carbons appeared to be shifted downfield relative to the experimental carbon peaks (for both stable and unstable conformers) as shown by ‘change’ (\(\Delta = -ve, \text{experimental} – \text{theoretical}\)) in Table 1. Comparing the experimental and the calculated \textsuperscript{13}C-NMR chemical shifts for both the optimized and least-stable DFT-generated conformations, the RMSD values were found to be 8.84 ppm and 8.79 ppm, respectively. The RMSD value for the calculated \textsuperscript{1}H-NMR chemical shifts of the optimized conformer was found to be substantially smaller (RMSD = 0.14 ppm) than that for the least-stable conformer (RMSD = 0.57 ppm).

<table>
<thead>
<tr>
<th>Atom</th>
<th>Exp</th>
<th>(\phi = 65.3^\circ) \textsuperscript{a}</th>
<th>(\phi = 5^\circ) \textsuperscript{b}</th>
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<tr>
<td></td>
<td>(\delta) (ppm)</td>
<td>(\delta) (ppm)</td>
<td>(\Delta) (ppm)\textsuperscript{c}</td>
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<td>0.25</td>
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<tr>
<td>C-4a</td>
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<td>C-5</td>
<td>127.8</td>
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<tr>
<td>H-5</td>
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<td>C-6</td>
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<tr>
<td>C-1'</td>
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<td>135.2</td>
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<tr>
<td>C-3'</td>
<td>116.3</td>
<td>123.0</td>
<td>-6.7</td>
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Table 1: Experimental and theoretical (gas phase) \textsuperscript{1}H and \textsuperscript{13}C chemical shift (\(\delta\)) for atoms within six bonds from fluorine for coumarin 6 and RMSD values.
<table>
<thead>
<tr>
<th></th>
<th>7.29</th>
<th>7.20</th>
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<tr>
<td>H-3’</td>
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<tr>
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<td>H-4’</td>
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<tr>
<td>H-5’</td>
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<tr>
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<td>7.31</td>
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<td>8.06</td>
<td>-0.83</td>
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<tr>
<td>RMSD values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-2’</td>
<td>160.9</td>
<td>169.1</td>
<td>-8.2</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>13C NMR = 8.84 ppm</th>
<th>1H NMR = 0.138 ppm</th>
<th>13C NMR = 8.79 ppm</th>
<th>1H NMR = 0.569 ppm</th>
</tr>
</thead>
</table>

**a**Conformer with ϕ = 65 °
**b**Conformer with ϕ = 5 °
**c**Experimental – theoretical eg. C-2: 160.9 - 169.1 = -8.2 ppm

The single crystal X-ray analysis of coumarin 6 was carried out as it has not been reported previously [CCDC No.: 1868146]. The crystals of 6 were obtained by slow evaporation of methanol/dichloromethane and were found to be of the monoclinic crystal system with space group C2/c (Figure 4, A).

The crystal structure shows that the fluorinated phenyl ring is at a torsion angle (ϕ, C2'-C1'-C4-C4a angle) of 54.44° to the coumarin moiety. The F⋯H5 TS-distance of 2.547 Å is small enough to induce some rotational constraint on the C4 and C1’ bond, as the constraint was observed at an F⋯H distance of 2.9 Å [33]. The short contact interactions show that there are C-F⋯H-C intermolecular interactions to the neighboring molecules that play a crucial role in crystal packing (Figure 5).
As mentioned above, the structure of coumarin 6 was optimized and the dihedral angle, $\phi$ (C2'-C1'-C4-C4a) was found to be $65.3^\circ$ (Figure 4, B), which is comparable close to that found in the crystal structure ($\phi = 54.4^\circ$). The TS distance between F and H5 for the optimized structure is 2.807 Å which is relatively close to that of the crystal structure (2.547 Å, shown in Figure 4, A). Selected comparisons are shown in Table 2.

**Figure 5**: Short contacts within the single-crystal X-ray structure of coumarin 6.

<table>
<thead>
<tr>
<th>Run</th>
<th>TS distance (Å)</th>
<th>Dihedral angle (°)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>F·H5</td>
<td>F·C5</td>
</tr>
<tr>
<td>6 (exp)</td>
<td>2.547</td>
<td>2.934</td>
</tr>
<tr>
<td>6 (DFT)</td>
<td>2.807</td>
<td>3.174</td>
</tr>
<tr>
<td>Difference</td>
<td>0.260</td>
<td>0.24</td>
</tr>
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</table>
Conclusion

The synthesis of 4-(2-fluorophenyl)-7-methoxycoumarin (6) via the Pechmann reaction was successful. The solution-state $^1$H and $^{13}$C NMR spectra of 6 showed that there is a strong intramolecular interaction between F and H5 ($J_{FH} = 2.6$ Hz) and suggest that this interaction is through-space C-F···H-C coupling, since C5 is coupled to F ($J_{FC} = 1.4$ Hz) whereas C4 and C4a are not. The 2-D HOESY spectrum shows the F···H5 coupling and also F···H3 coupling, seemingly weaker than F···H5 since splitting of the H3 signal is not observed in the $^1$H and $^1$H-$^1$F 1-D spectra. The single crystal X-ray structure showed that the fluorinated phenyl ring is orientated in a manner that brings the fluorine atom closer to H5 than H3. The same orientation was observed in the DFT-optimized (B3LYP/6-311G) structure. The X-ray data also showed the intermolecular C-F···H-C interactions which, together with other interactions, are resposible for the crystal packing.

Experimental

General

All reagents (including solvents) were purchased from the chemical suppliers Aldrich, Fluka and Merck. For all moisture-sensitive reactions, the glassware was thoroughly dried in an oven at ca. 140 °C for 12 h prior to use, and anhydrous solvents were used under inert conditions. Qualitative thin-layer chromatography (TLC, silica gel 60, aluminum backed) was used to monitor reactions. Visualization of the TLC plates was achieved using an iodine tank and/or fluorescence on exposure to short wavelength ultraviolet light (254 nm). For purification, column chromatography (silica gel 60, 0.040-0.063 mm) or centrifugal chromatography conducted on a Harrison...
Research Chromatotron model 7924T (glass plates coated with silica gel 60 PF$_{254}$ containing gypsum, 2 and 4 mm thick layer) was used.

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 400 spectrometer equipped with a 5 mm BBOZ probe at frequencies of 400 MHz, 100 MHz, and 376 MHz for $^1$H, $^{13}$C, and $^{19}$F respectively. High-resolution mass spectrometry (HRMS) was performed on a Waters LCT Premier time-of-flight mass spectrometer.

**Synthesis of methyl 2-fluorobenzoylacetaate (3)**

To a stirred mixture of MgCl$_2$ (2.0 g, 21 mmol) and Et$_3$N (2.1 g, 21 mmol) in dry DCM (15 mL) at room temperature, methyl acetoacetate (2.0 g, 17 mmol) was added slowly. The mixture was stirred for 30 min before the temperature was reduced to 0 °C. n-BuLi (20 mL of a 1.6 M in hexane, 32 mmol) was added slowly into the mixture and the mixture was stirred for a further 30 min. 2-Fluorobenzoyl chloride (2.7 g, 17 mmol) was added dropwise into the mixture and the mixture was stirred for 15 min. The reaction mixture was allowed to reach room temperature and was stirred overnight. To the reaction, was added 5 M HCl (8 mL) and distilled water (10 mL) and the mixture was extracted with DCM (3 x 30 mL). The organic layer was dried over anhydrous MgSO$_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 10% EtOAc in hexane as eluent and 3 was obtained as a light orange viscous liquid (2.7 g, 81%), TLC $R_f$ 0.50 (Hexane-EtOAc, 9:1). $^1$H NMR (400 MHz, CDCl$_3$) 3.76 (3H, s, H-4), 4.01 (2H, d, $J = 3.4$, H-2), 7.15 (1H, ddd, $J = 12.1$, 8.5, 1.0, H-3'), 7.26 (1H, t, $J = 7.5$, H-5'), 7.57 (1H, m, H-4'), 7.95 (2H, td, $J = 7.6$, 1.9, H-6'). $^{13}$C NMR (100 MHz, CDCl$_3$) 49.6 (d, $J = 8.1$, C-2), 52.3 (C-4), 116.7 (d, $J = 24.1$, C-3'), 124.7 (d, $J = 2.9$, C-6'), 129.3 (d, $J = \ldots$)
21.7 (C-1'), 131.0 (d, J = 2.3, C-5'), 135.5 (d, J = 9.6, C-4'), 162.2 (d, J = 254.3, C-2'), 167.8 (d, J = 3.0, C-3), 190.1 (d, J = 3.7, C-1).

**Synthesis of 7-hydroxy-4-(2-fluorophenyl)coumarin (5)**

To a mixture of resorcinol (2.0 g, 18 mmol) and methyl 2-fluorobenzoylacetate (3.5 g, 18 mmol) was added H_2SO_4 (8 mL, 75%). The temperature of a stirred mixture was increased to 35 °C. After stirring for 5 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 60% EtOAc in hexane as eluent and 5 was obtained as a light yellow solid (4.2 g, 91%), mp 204-207 °C, TLC Rf 0.45 (Hexane-EtOAc, 2:3). ¹H NMR (400 MHz, DMSO-d₆) 6.24 (1H, s, H-3), 6.77 (1H, dd, J = 8.6, 2.4, H-6), 6.81 (1H, d, J = 2.4, H-8), 7.03 (1H, dd, J = 8.6, 2.6, H-5), 7.37-7.45 (2H, m, H-3',6'), 7.50 (1H, td, J = 7.5, 1.8, H-5'), 7.61 (1H, m, H-4'), 10.67 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆) 102.6 (C-8), 110.7 (C-4a), 112.1 (C-3), 113.4 (C-6), 116.1 (d, J = 21.3, C-3'), 122.7 (d, J = 15.3, C-1'), 125.2 (d, J = 3.6, C-6'), 127.9 (d, J = 1.6, C-5), 130.8 (d, J = 2.9, C-5'), 132.0 (d, J = 8.2, C-4'), 150.3 (C-4), 155.2 (C-8a), 158.6 (d, J = 248.6, C-2'), 160.0 (C-2), 161.6 (C-7). HRMS (ESI⁺): Found [M+Na]^+ 279.0437, Calc. for C₁₅H₉O₅FNa 279.0433.

**Synthesis of 4-(2-fluorophenyl)-7-methoxycoumarin (6)**

A mixture of 7-hydroxy-4-(2-fluorophenyl)coumarin (0.77 g, 3.0 mmol), dimethyl sulfate (0.76 g, 6.0 mmol) and K₂CO₃ (0.83 g, 6.0 mmol) was refluxed in acetone (20 ml) for 4h. The reaction mixture was cooled to room temperature and and brine (50 ml) was added then extracted with ethyl acetate (3 x 40 ml). The organic layer was dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The resulting
light yellow product was purified by silica gel column chromatography with 60% EtOAc in hexane as eluent and 6 was obtained as a yellow crystalline solid (0.78 g, 2.9 mmol, 97%), mp 167-170 °C, TLC Rf 0.54 (Hexanes-EtOAc, 3:2). \(^1\)H NMR (400 MHz, CDCl\(_3\)) 3.88 (3H, s, OMe), 6.25 (1H, s, H-3), 6.79 (1H, dd, \(J = 8.9, 2.5\), H-6), 6.89 (1H, d, \(J = 2.5\), H-8), 7.16 (1H, dd, \(J = 8.9, 2.5\), H-5), 7.23 (1H, t, \(J = 8.9\), H-6'), 7.29 (1H, td, \(J = 7.8, 1.0\), H-3'), 7.35 (1H, td, \(J = 7.8, 1.9\), H-5'), 7.50 (1H, m, H-4'). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 55.8 (OMe), 101.0 (C-8), 112.4 (C-4a), 112.5 (C-3), 113.5 (C-6), 116.3 (d, \(J = 21.9\), C-3'), 123.2 (d, \(J = 15.4\), C-1'), 124.7 (d, \(J = 3.7\), C-6'), 127.8 (d, \(J = 1.4\), C-5), 130.5 (d, \(J = 3.1\), C-5'), 131.5 (d, \(J = 7.9\), C-4'), 150.5 (C-4), 155.7 (C-8a), 159.1 (d, \(J = 250.0\), C-2'), 160.9 (C-2), 163.0 (C-7). HRMS (ESI\(^+\)):

Found [M+Na]\(^+\) 293.0587, Calc. for C\(_{16}\)H\(_{11}\)O\(_3\)FNa 293.0590.

**Supporting Information**

Supporting Information File 1

Copies of NMR spectra for compound 3, 5 and 6.

HRMS for compound 6.

Single crystal X-ray data for compound 6.

**Acknowledgements**

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References

18. Gether, U.; Andersen, P. H.; Larsson, O. M.; Schousboe, A. Trends in Pharmacological Sciences 2006, 27, 375-383. doi:http://dx.doi.org/10.1016/j.tips.2006.05.003