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# SYNTHESIS OF COUMARIN DERIVATIVES VIA PECHMANN CONDENSATION AND NITRATION REACTION

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**Abstract :** Highly efficient method for the synthesis of 7-hydroxy-4-methyl coumarin has been developed using conc. Sulphuric acid at 5 °C to room temperature via optimized Pechmann condensation reaction. The product 7-hydroxy-4-methyl coumarin was successfully obtained in excellent yield. Further, the product 7-hydroxy-4-methyl coumarin was successfully utilized for the synthesis of 7-hydroxy-4-methyl-6-nitrocoumarin and 7-hydroxy-4-methyl-8-nitrocoumarin.

**Keywords –** Coumarins, Pechmann condensation, nitrocoumarin, Sulphuric acid.

## I. INTRODUCTION

Coumarins are obtained from natural and synthetic origin and constitute an important family of heterocyclic compounds with a benzo-α-pyrone moiety. Coumarins are widely distributed in various plants. For an, e.g., simple coumarin, which is the representative molecule, was found in the tonka bean (*Dipteryx odorata Wild*), and it has been extensively studied in pharmaceutical fields.[1] Coumarins are found in plants like the Rutaceae and Umbelliferae family. Essential oils like cinnamon bark oil, cassia leaf oil, and lavender oil are also rich sources of coumarins. Coumarins have important effects on plant physiology and biochemistry. Coumarins and their derivatives are involved in important plant physiological processes such as the actions of plant growth hormones and growth regulators, the control of photosynthesis, and respiration, as well as defense against infection.[2] Coumarins and their derivatives also show potent pharmacological activities, such as antimicrobial,[3] antidepressant,[4] anti-inflammatories,[5] antiasthmatic,[6] antitumor,[7] antiviral including anti-HIV.[8] Important coumarin derivatives such as Dicoumarol were found in moldy, wet, sweet-clover hay, and it shows anticoagulant activity.[9a] Osthole is another important compound that has a broad spectrum of pharmacological activities,[9b] was found in *Cnidium monnieri*. Whereas scoparone is an important bioactive compound with potential pharmacological properties including immunosuppression and vasorelaxation,[9c] was found in *Artemisia scoparia* (Fig. 1).

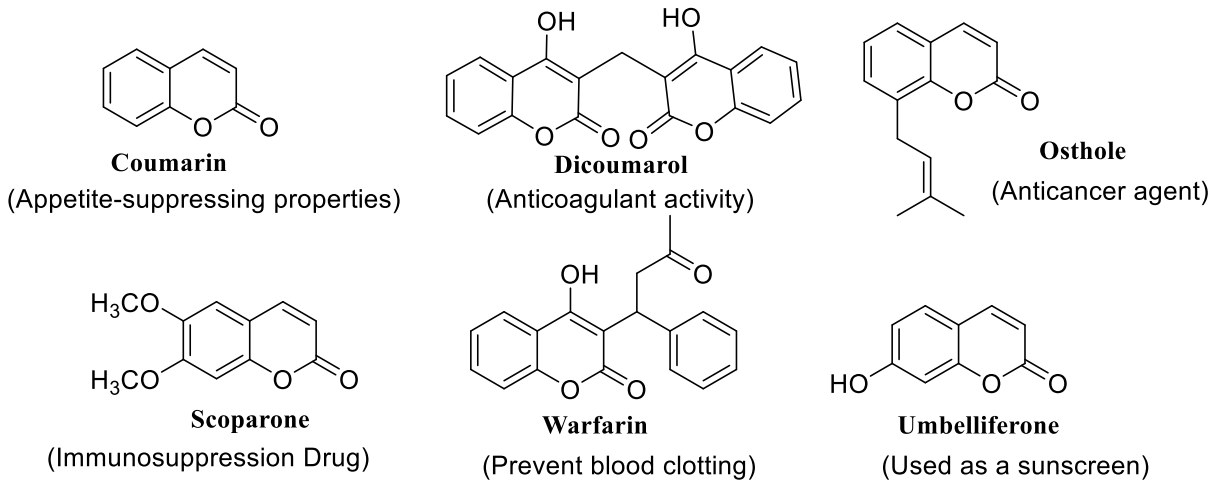



**Figure 1:** Bioactive compounds having coumarin motif.

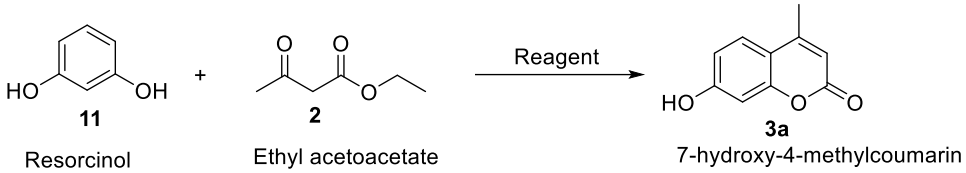
Warfarin is another naturally occurring bioactive compound containing the 4-hydroxy coumarin motif. It has been derived from woodruff as well as from lavender and utilized to prevent blood clotting in the veins, lungs, or heart.[9d] Another natural compound having the coumarin motif is 7-hydroxycoumarin, also known as umbelliferone,[9e] which is present in various plants, such as carrots, coriander, and garden angelica and used as a sunscreen, a fluorescence indicator, and a dye indicator.[10] Coumarins are important biologically active compounds; hence various methods have been developed to synthesize them.[11-14] Herein, we report the highly efficient method for the synthesis of 7-hydroxy-4-methyl coumarin has been developed using robust reagent conc. Sulphuric acid at 5 $^{o}$C to room temperature via optimized Pechmann condensation reaction.

## II. Results and discussions

### 1. Synthesis of coumarin *via* Pechmann condensation

To explore the feasibility of the reaction, we commenced our study using ethyl acetoacetate **2** and resorcinol **11** as model substrates in the presence of various acid catalysts at different temperatures (entries 1-6, Table 1.1). In our preliminary studies, we found that conc. $H_2SO_4$ is the optimum reagent to facilitate the Pechmann condensation reaction and afford the desired product 7-hydroxy-4-methyl coumarin **3a** in good yields. While in the presence of dil. $H_2SO_4$ and conc. HCl, the desired product **3a** was obtained in lower yields. After screening various conditions, we found that ethyl acetoacetate **2** and resorcinol **11** undergo smooth Pechmann condensation in the presence of conc. $H_2SO_4$ when the addition was carried out at 5 $^{o}$C (entries 5, Table 1.1). The reaction mixture was allowed to warm at room temperature and further stirred for 18 hours to afford the desired product 7-hydroxy-4-methyl coumarin **3a** after recrystallization in 88% yield (see; Table 1.1).

**Table 1.1** Optimization of reaction conditions for Pechmann condensation[a]




| Sr. No. | Resorcinol (in mmol) | Ethyl acetoacetate (in mmol) | Reagent | Temperature (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | 10 | 10 | 50% $H_2SO_4$ (10 mL) | 10 °C to r.t. | 36 | 30 |
| 2 | 10 | 20 | 50% $H_2SO_4$ (10 mL) | 10 °C to r.t. | 36 | 40 |
| 3 | 20 | 10 | 50% $H_2SO_4$ (10 mL) | 10 °C to r.t. | 36 | 35 |
| 4 | 10 | 10 | conc. $H_2SO_4$ (10 mL) | 10 °C to r.t. | 18 | 60 |
| **5** | **10** | **10** | **conc. $H_2SO_4$ (10 mL)** | **5 °C to r.t.** | **18** | **80** |
| 6 | 10 | 10 | conc.HCl (10 mL) | 10 °C to r.t. | 24 | 30 |

[a]Reaction conditions: Resorcinol (10-20 mmol), and ethyl acetoacetate (10-20 mmol) was added to the reagent under an open atmosphere at a specified temperature and stirred for 1 h, and the reaction mixture was allowed to warm at room temperature (r.t.) and stirred for a specified time; the progress of the reaction was monitored by TLC. [b]Isolated yield after recrystallization.

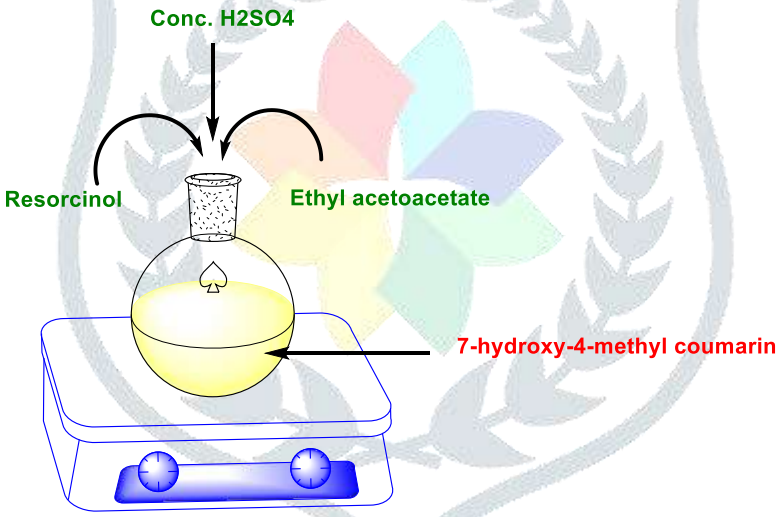
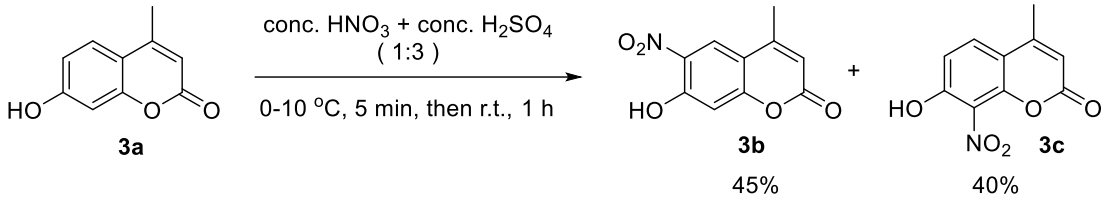



**Figure 2:** Synthesis of 7-hydroxy-4-methyl coumarin

## 2. Synthesis of nitrocoumarins

Nitro coumarins are important precursors in synthetic organic chemistry. They are used in the synthesis of aminocoumarins and dye synthesis. To obtain nitrocoumarins, we have successfully applied the following protocol for the synthesis of 7-hydroxy-4-methyl-6-nitrocoumarin **3b** and 7-hydroxy-4-methyl-8-nitrocoumarin **3c**. 7-Hydroxy-4-methylcoumarin **3a** upon nitration in the presence of conc. $HNO_3$ and conc. $H_2SO_4$ (1:3 ratio) at 0-10 °C gives a mixture of 7-hydroxy-4-methyl-6-nitrocoumarin and 7-hydroxy-4-methyl-8-nitrocoumarin. These two structural isomers were further purified by recrystallization to obtain each isomer in pure form (Scheme 1.1).




**Scheme 1.1** Synthesis of nitrocoumarins

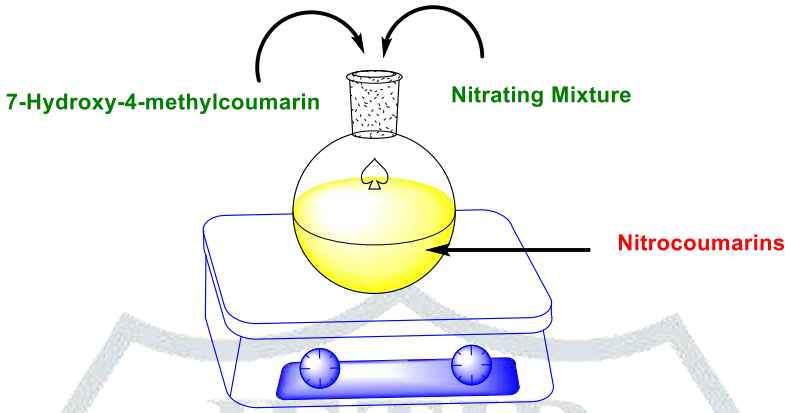



**Figure 3:** Synthesis of nitrocoumarins

## 5. Conclusions

In conclusion, we have successfully synthesized coumarins *via* an optimized Pechmann condensation reaction. 7-Hydroxy-4-methylcoumarin synthesized using Pechmann condensation reaction successfully utilized for the synthesis of nitrocoumarins. We have also successfully synthesized azocoumarin dye using coumarin which is stable under ordinary conditions.

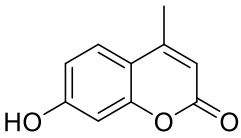
## II. Experimental Section

### 1. General

Unless otherwise noted, all reactions were carried out with distilled and dried solvents using oven-dried glassware. All reagents were purchased from commercial sources and used as received unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF254 pre-coated aluminum backed plates (2.5 mm) with detection by UV light. 1H NMR and 13C NMR spectra were recorded in DMSO-d6. Chemical shifts in 1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard or from the residual solvent peak as the internal standard and J values are given in Hz. 13C NMR spectra are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d6. 13C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry using HRMS ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as neat and reported in cm-1.

**2. Procedure A synthesis of coumarin *via* Pechmann condensation**

A mixture of resorcinol **11** (10 mmol) and ethyl acetoacetate **2** (10 mmol) was added in 10 ml of conc. $H_2SO_4$ at 5 $^oC$ and reaction mixture stirred for 1 h at 5 $^oC$. Then the reaction mixture was allowed to warm at room temperature and further stirred for 18 h in the open atmosphere. Then the reaction mixture was poured in ice-cold water with vigorous stirring. The precipitate was filtered and dried to obtain a crude product. The crude product was further purified by recrystallization by using aqueous ethanol to furnish pure desired product **3a** in 80% yield.




**7-Hydroxy-4-methylcoumarin (3a):**

Compound **3a** was synthesized following the procedure (A). The product was obtained as pale yellow crystals (1.41 g, 80% yield): Melting point: 187-189 $^oC$.

**IR (neat) $cm^{-1}$:** 3592, 3518, 3396, 1715, 1443, 1098, 938, 874, 676.

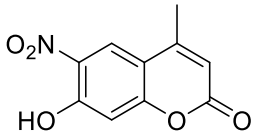
**$^1H$ NMR (400 MHz, DMSO-$d_6$):** δ 7.57 (d, *J* = 8.7 Hz, 1H), 6.79 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.69 (d, *J* = 2.4 Hz, 1H), 6.11 (d, *J* = 1.2 Hz, 1H), 2.35 (d, *J* = 1.2 Hz, 3H).

**$^{13}C$ NMR (100 MHz, DMSO-$d_6$):** δ 161.2, 160.4, 154.9, 153.6, 126.7, 112.9, 112.1, 110.3, 102.2, 18.2.

**HRMS (ESI TOF):** Calculated for $C_{10}H_9O_3$ $(M + H)^+$: 177.0551, Found: 171.0554.

**3. Procedure B for the synthesis of nitrocoumarins**

In a glass beaker, 7-hydroxy-4-methylcoumarin **3a** (1 g) was dissolved in 10 mL conc. $H_2SO_4$ and the beaker was kept in ice bath. When the temperature of the solution inside the beaker is around 0 $^oC$, 4 mL nitrating mixture (1 mL conc. $HNO_3$ and 3 mL conc. $H_2SO_4$) was slowly added in above solution maintaining the temperature below 10 $^oC$. After the addition of the nitrating mixture, the beaker was removed from the ice bath and kept at room temperature with stirring for about an hour. Then this whole solution was poured into another beaker having crushed ice with stirring. The crude product was filtered which is a mixture of nitrocoumarins. The crude product was added to ethanol and refluxed the solution for 5 minutes. The hot solution was filtered and the residue obtained was 7-hydroxy-4-methyl-6-nitrocoumarin **3b** in 45% yield. Filtrate was concentrated to reduce the volume and cooled in an ice bath, 7-hydroxy-4-methyl-8-nitrocoumarin **3c** crystallizes out from the filtrate. This 7-hydroxy-4-methyl-8-nitrocoumarin **3c** derivative was further purified by recrystallization from ethanol and obtained in 40 % yield.

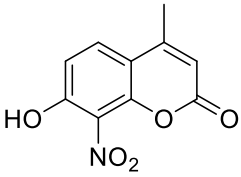


**7-Hydroxy-4-methyl-6-nitro-coumarin (3b):**

Compound **3b** was synthesized following the procedure (B). The product was obtained as a pale yellow crystals (0.56 g, 45% yield): Melting point: 201-203 $^{o}$C.

**IR (neat) cm$^{-1}$:** 3756, 2316, 2100, 1775, 1516, 1141, 1096, 922, 825, 687.

**HRMS (ESI TOF):** Calculated for $C_{10}H_8NO_5$ $(M + H)^+$: 222.0402, Found: 222.0402.



**7-hydroxy-4-methyl-8-nitro-coumarin (3c):**

Compound **3c** was synthesized following the general procedure (B). The product was obtained as pale yellow crystals 0.5 g, 40% yield): Melting point: 254-256 $^{o}$C.

**IR (neat) cm$^{-1}$:** 3769, 3454, 3356, 2123, 2007, 1777, 1595, 1479, 1159, 725, 654, 620.

**HRMS (ESI TOF):** Calculated for $C_{10}H_8NO_5$ $(M + H)^+$: 222.0402, Found: 222.0402.

**Appendix I:** Spectral data of synthesized compounds



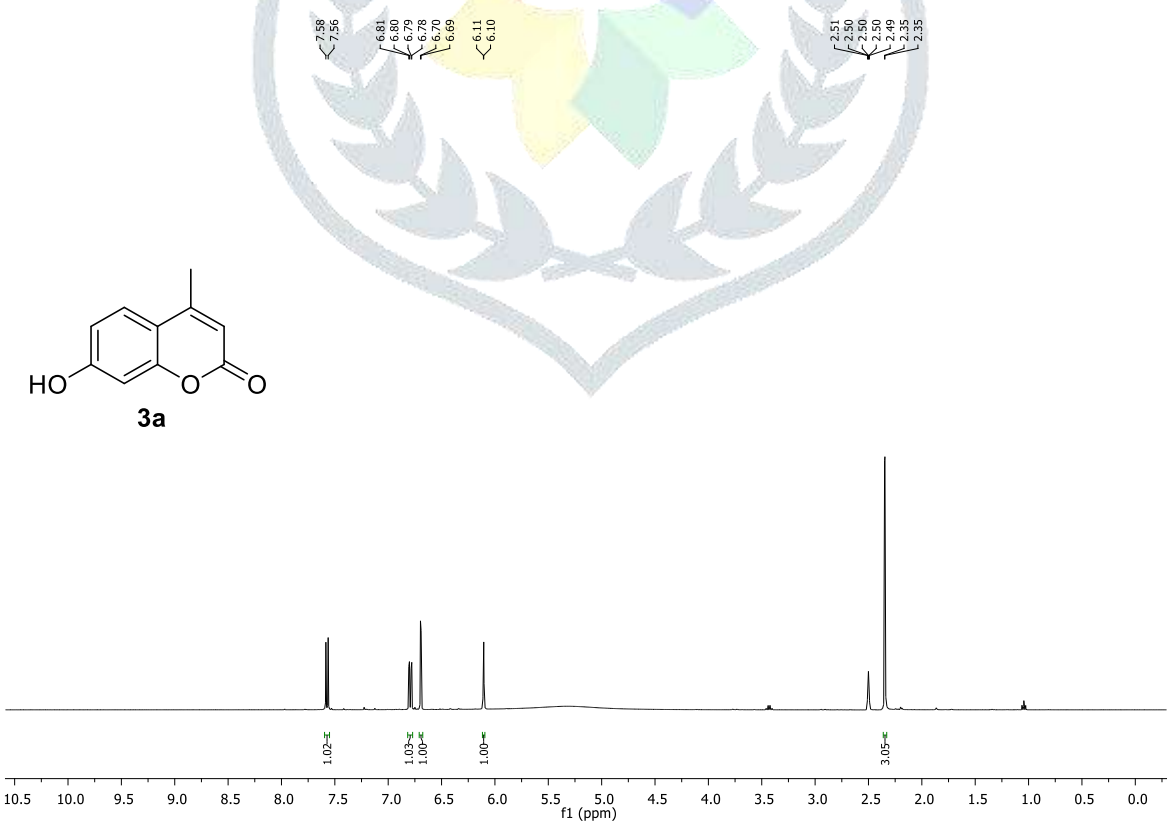



**Figure I.1:** $^{1}H$ NMR (400 MHz, DMSO-$d_6$) spectrum of compound **3a**

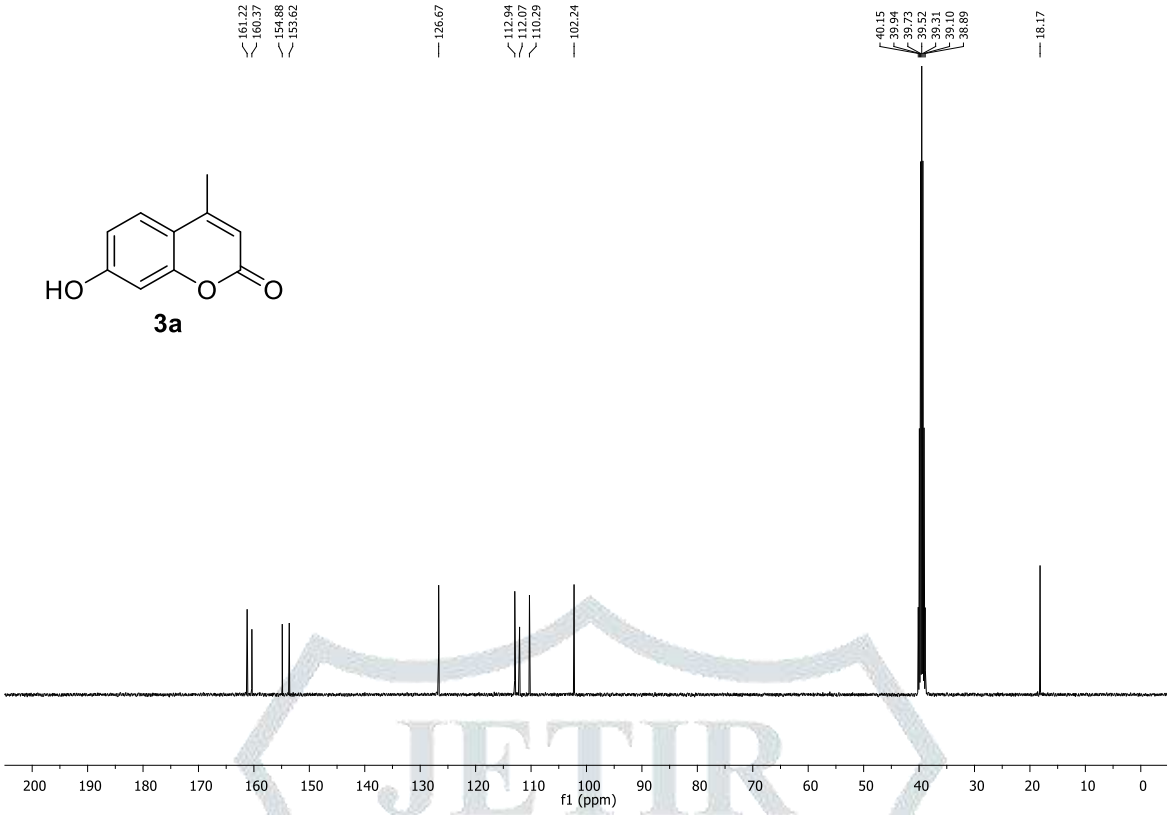



**Figure I.2:** $^{13}$C NMR (100 MHz, DMSO-$d_6$) spectrum of compound **3a**

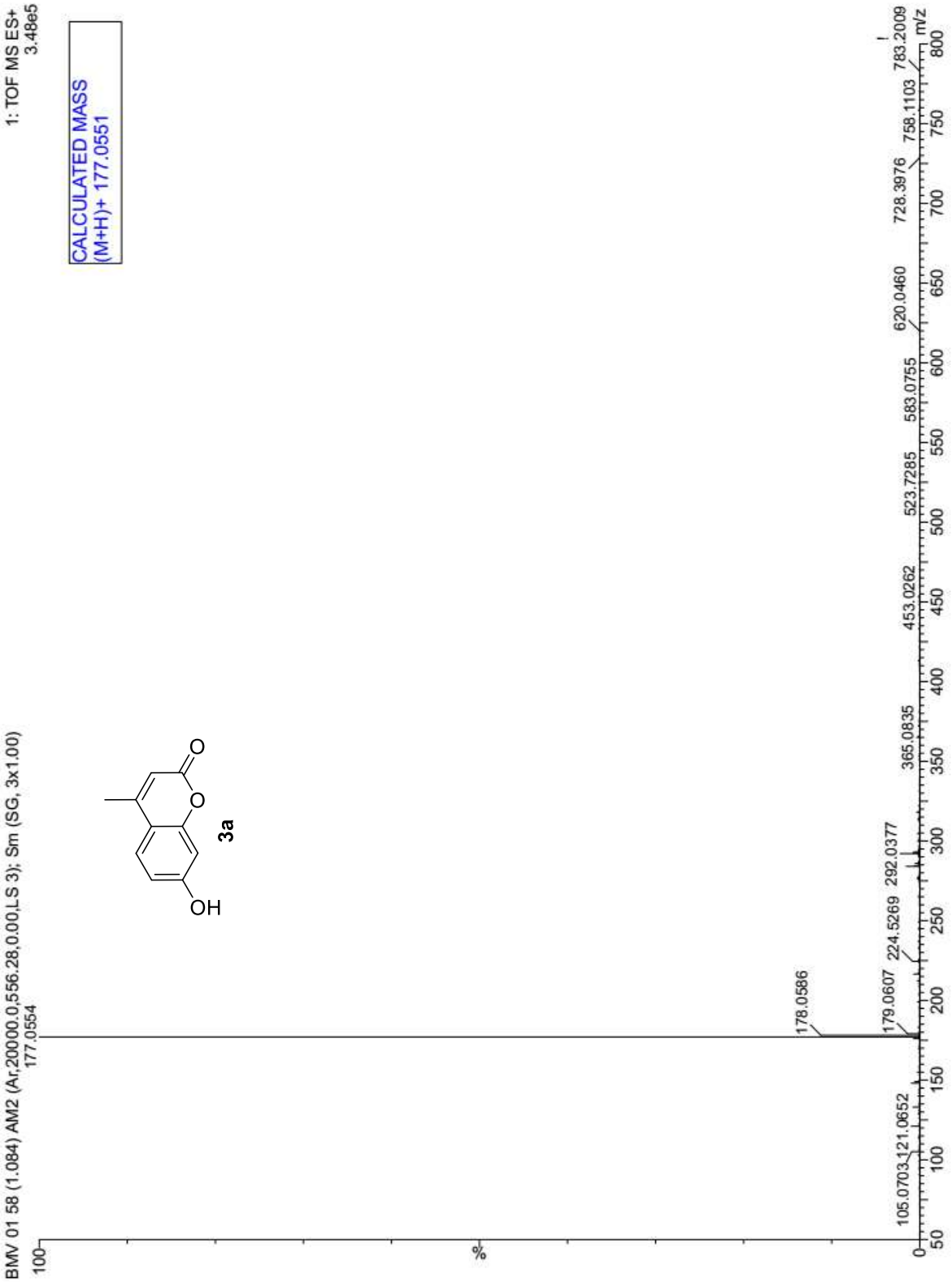



**Figure I.3:** H.R.M.S. spectra of compound **3a**

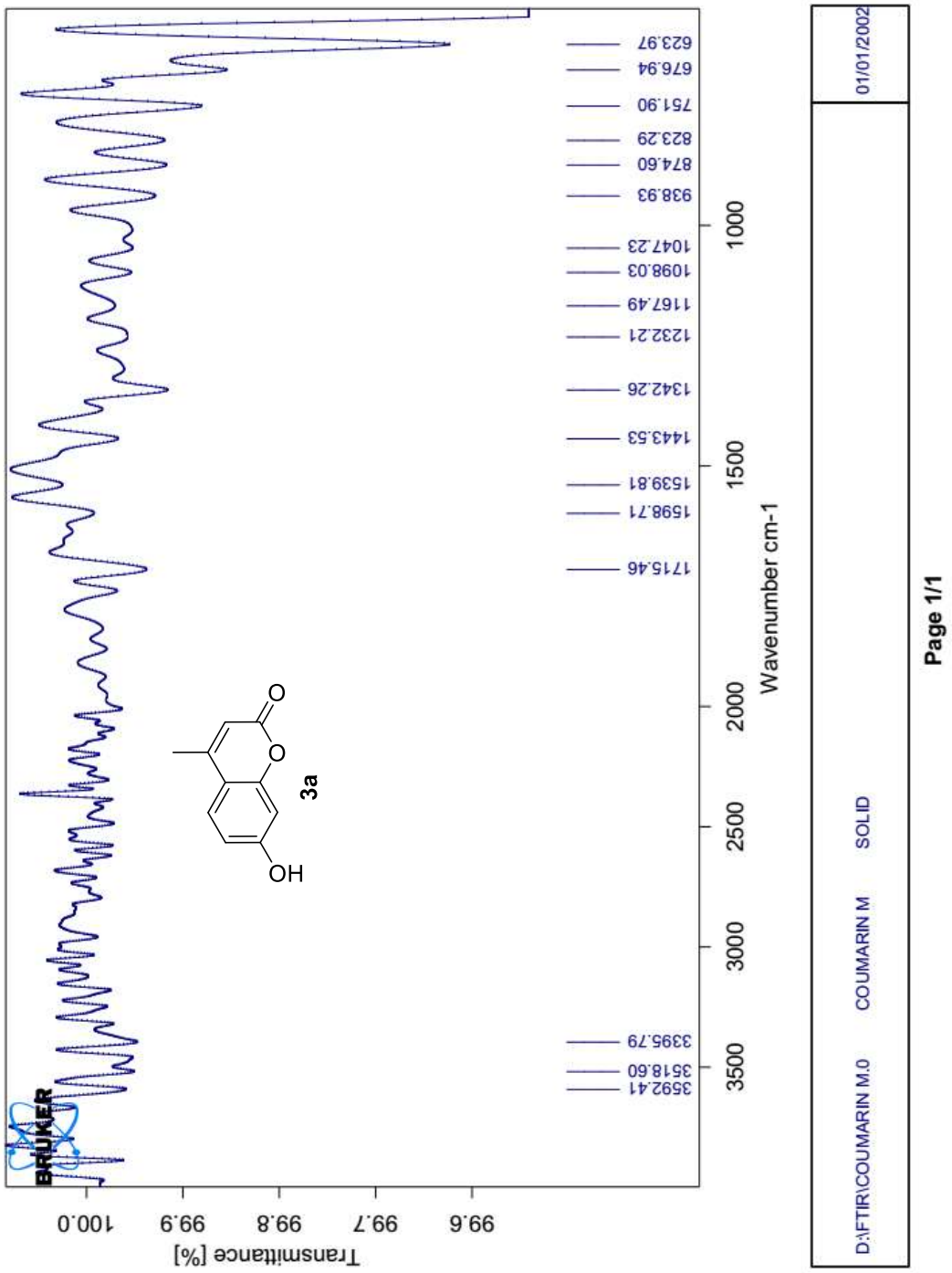



**Figure I.4:** I.R. spectra of compound **3a**

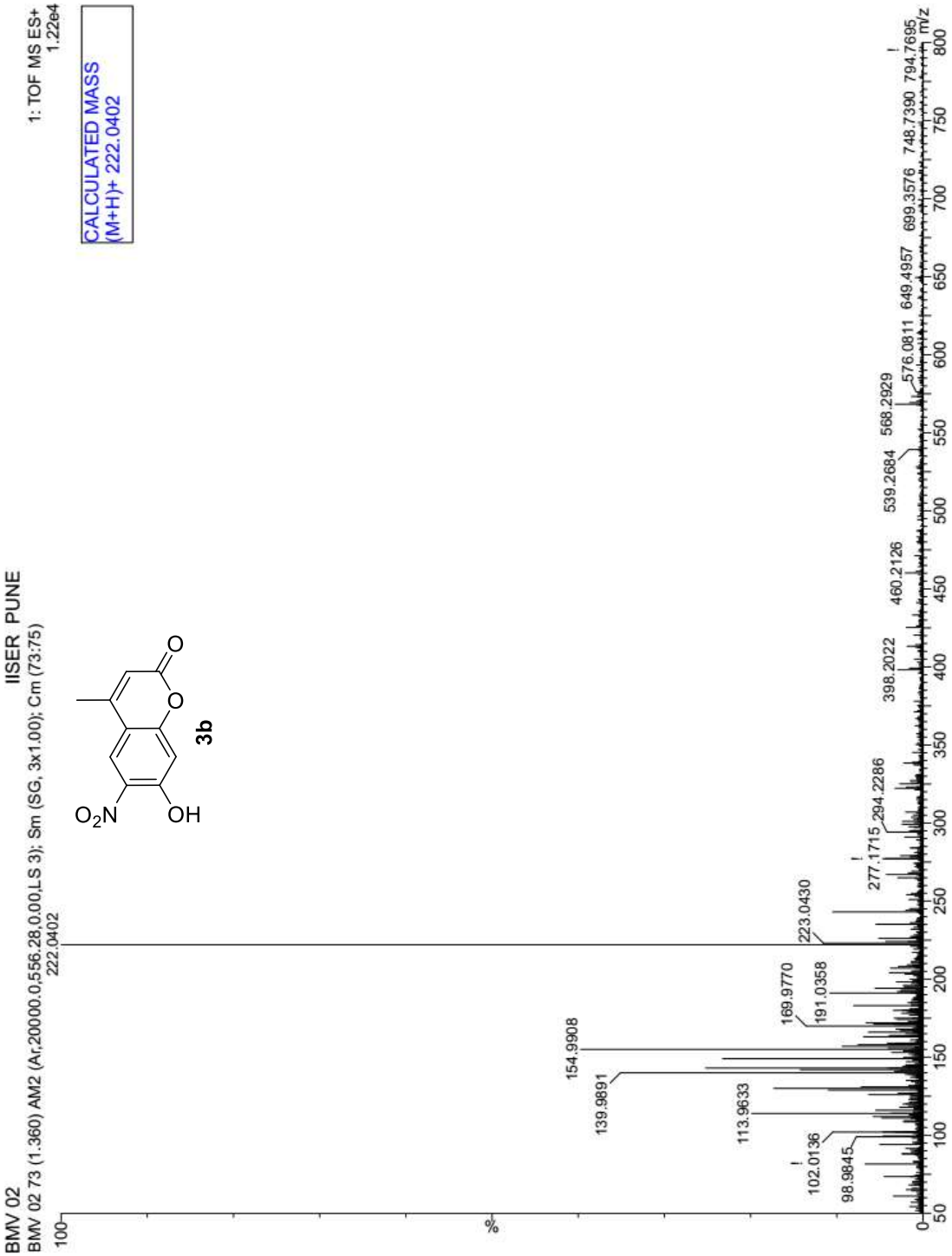



**Figure I.5:** H.R.M.S. spectra of compound **3b**

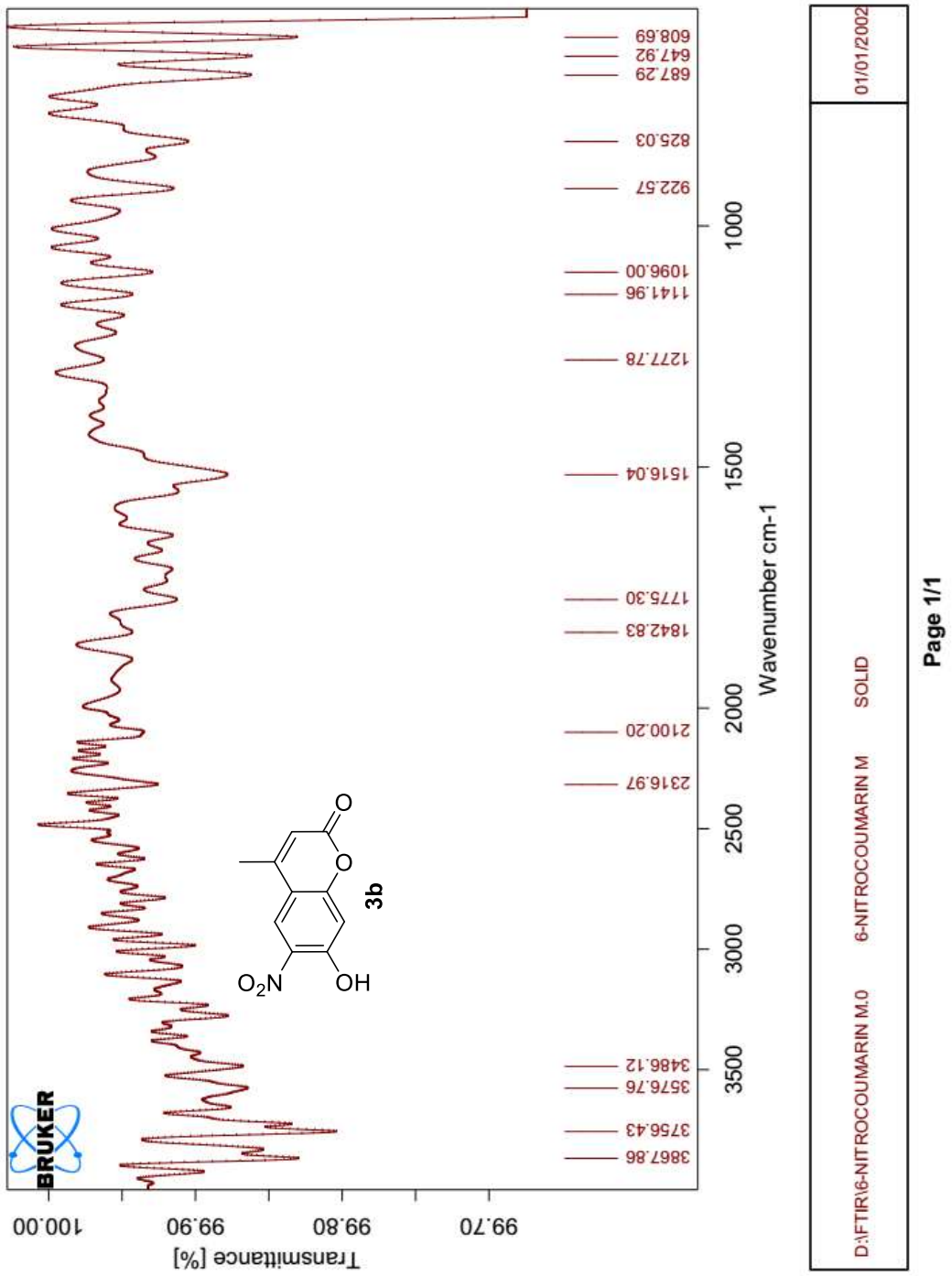



**Figure I.6:** I.R. spectra of compound **3b**

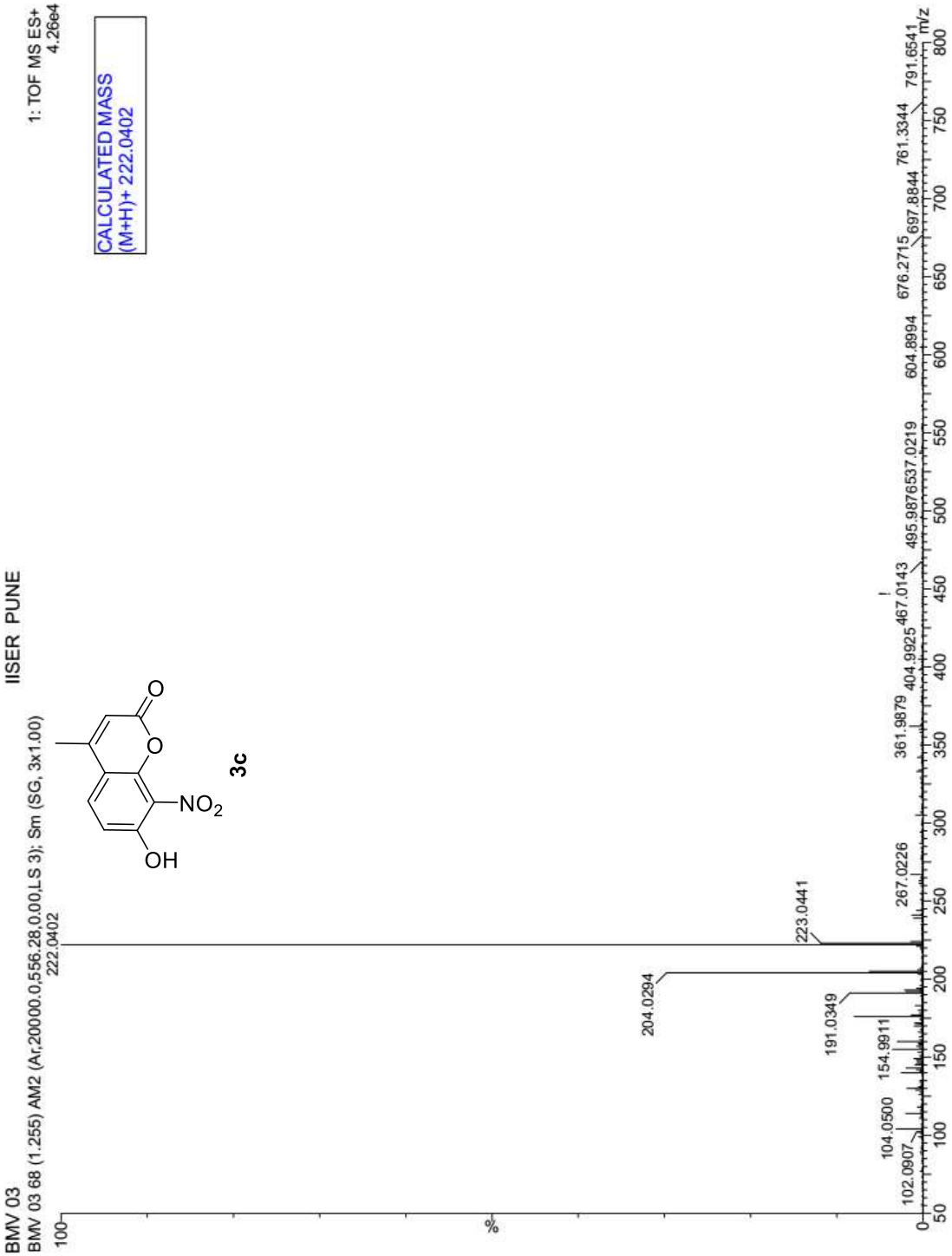



**Figure I.7:** H.R.M.S. spectra of compound **3c**

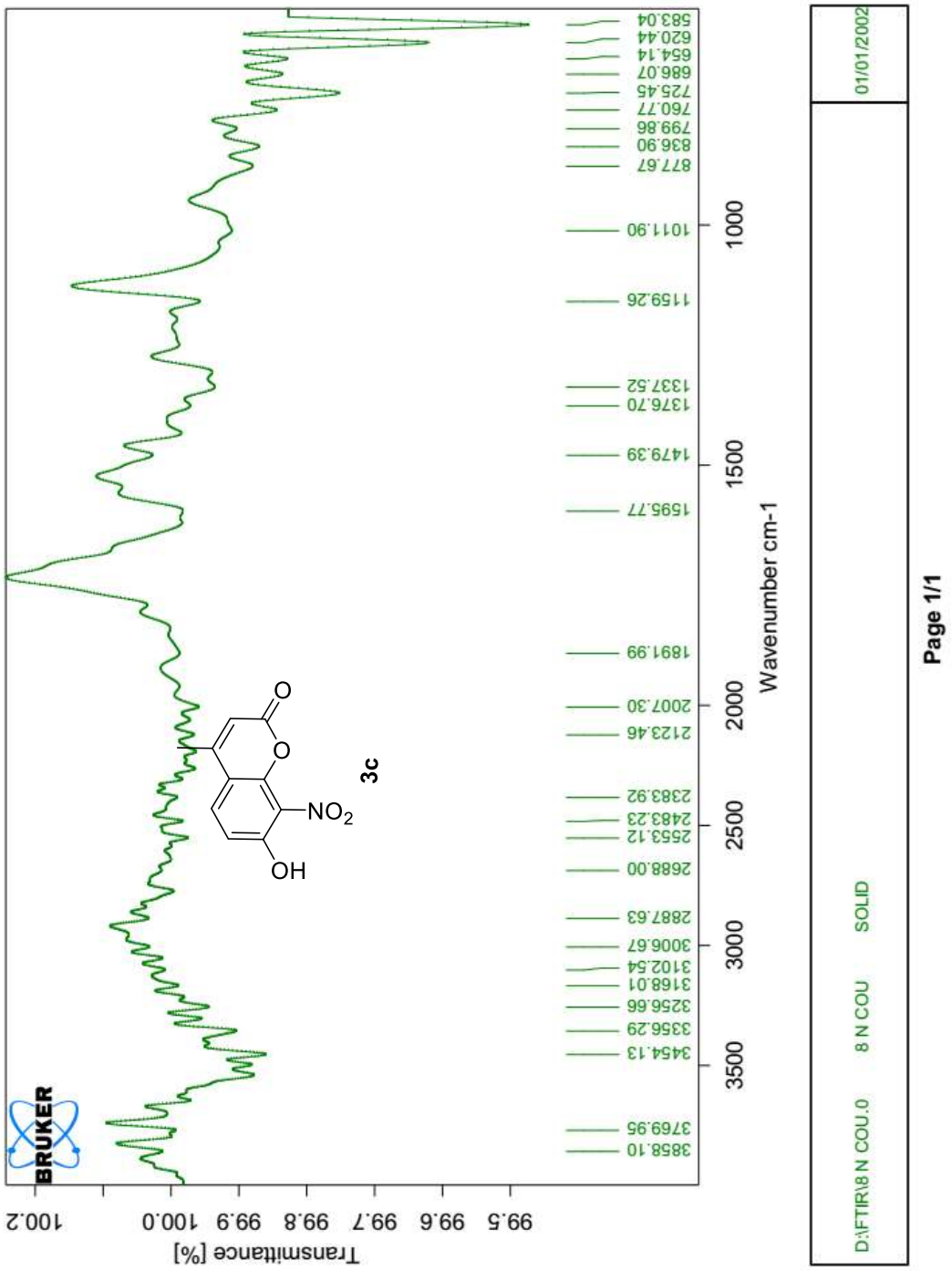



**Figure I.8:** I.R. spectra of compound **3c**

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