# Supporting Information

# Transformation of Santonin to a Naproxen Analogue with Anti-Inflammatory Activity

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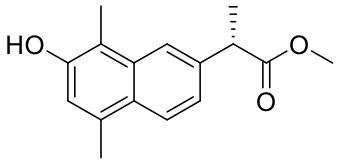



methyl (*S*)-2-(7-hydroxy-5,8-dimethylnaphthalen-2-yl)propanoate

Compound **2** was a light brown gummy solid; $^{1}$H NMR (400 MHz, methanol-$d_4$) δ 7.82 (d, $J$ = 8.8 Hz, 1H), 7.76 (d, $J$ = 1.6 Hz, 1H), 7.23 (dd, $J$ = 8.5, 1.6 Hz, 1H), 6.96 (s, 1H), 3.91 (q, $J$ = 14.2, 7.2 Hz, 1H), 3.64 (s, 3H), 2.55 (s, 3H), 2.45 (s, 3H), 1.54 (d, $J$ = 7.2 Hz, 3H).$^{13}$C NMR (100 MHz, methanol-$d_4$) δ 177.1, 152.9, 139.1, 135.8, 134.1, 128.3, 125.9, 122.9, 122.7, 119.6, 114.2, 52.5, 46.8, 19.2, 19.0, 10.5. ESI-MS: m/z 259.65 $[M+H]^+$; HRMS: m/z 259.1338 calculated for $C_{16}H_{19}O_3+H^+$ (259.1334).

**S1.** Mass Spectrum of **2**

## Qualitative Compound Report

| | | | |
|---|---|---|---|
| **Data File** | RJ-P-3.d | **Sample Name** | RJ-P-3 |
| **Sample Type** | Sample | **Position** | Vial 29 |
| **Instrument Name** | Instrument 1 | **User Name** | |
| **Acq Method** | vishal_12-01-13.m | **Acquired Time** | 19-04-2018 PM 5:03:41 |
| **IRM Calibration Status** | Success | **DA Method** | Default.m |
| **Comment** | | | |

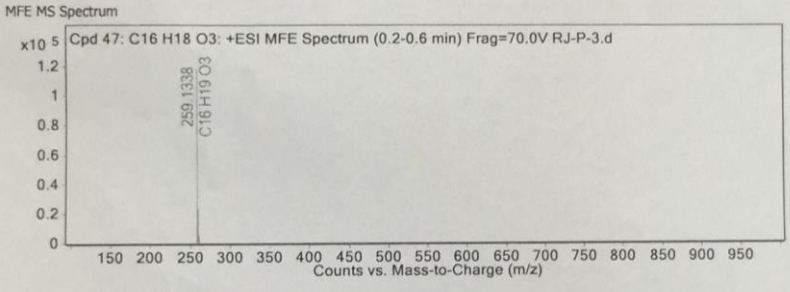
**Sample Group** **Info.**
**Acquisition SW Version** 6200 series TOF/6500 series Q-TOF B.05.01 (B5125)

**Compound Table**

| Compound Label | RT | Mass | Formula | MFG Formula | MFG Diff (ppm) | DB Formula |
|---|---|---|---|---|---|---|
| Cpd 47: C16 H18 O3 | 0.3 | 258.1265 | C16 H18 O3 | C16 H18 O3 | -3.45 | C16 H18 O3 |

| Compound Label | *m/z* | RT | Algorithm | Mass |
|---|---|---|---|---|
| Cpd 47: C16 H18 O3 | 259.1338 | 0.3 | Find by Molecular Feature | 258.1265 |

MFE MS Spectrum




**MS Spectrum Peak List**

| *m/z* | z | Abund | Formula | Ion |
|---|---|---|---|---|
| 259.1338 | 1 | 117846.28 | C16 H19 O3 | (M+H)+ |
| 260.1372 | 1 | 23532.27 | C16 H19 O3 | (M+H)+ |
| 261.1384 | 1 | 5484.25 | C16 H19 O3 | (M+H)+ |

**Predicted Isotope Match Table**

| Isotope | *m/z* | Calc m/z | Diff (ppm) | Abund % | Calc Abund % | Abund Sum % | Calc Abund Sum % |
|---|---|---|---|---|---|---|---|
| 1 | 259.1338 | 259.1329 | -3.66 | 100 | 100 | 80.24 | 83.53 |
| 2 | 260.1372 | 260.1363 | -3.48 | 19.97 | 17.64 | 16.02 | 14.73 |
| 3 | 261.1384 | 261.1389 | 1.79 | 4.65 | 2.08 | 3.73 | 1.74 |

--- End Of Report ---

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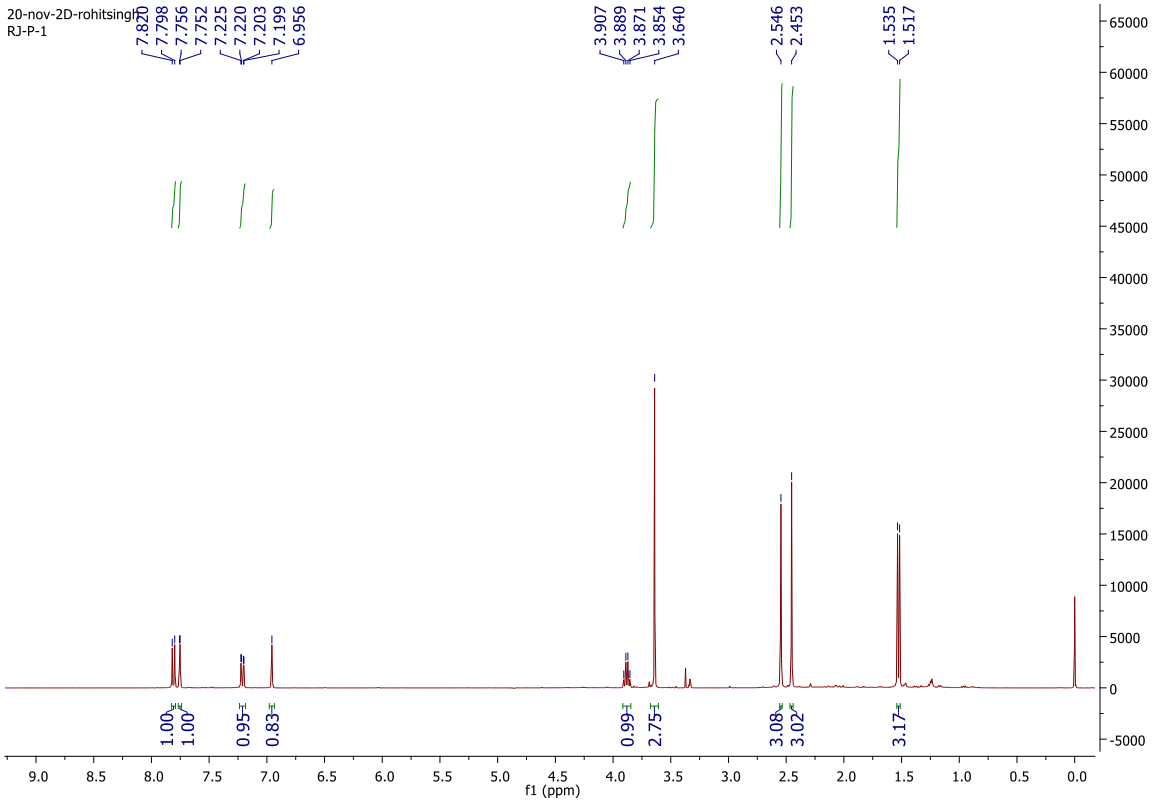
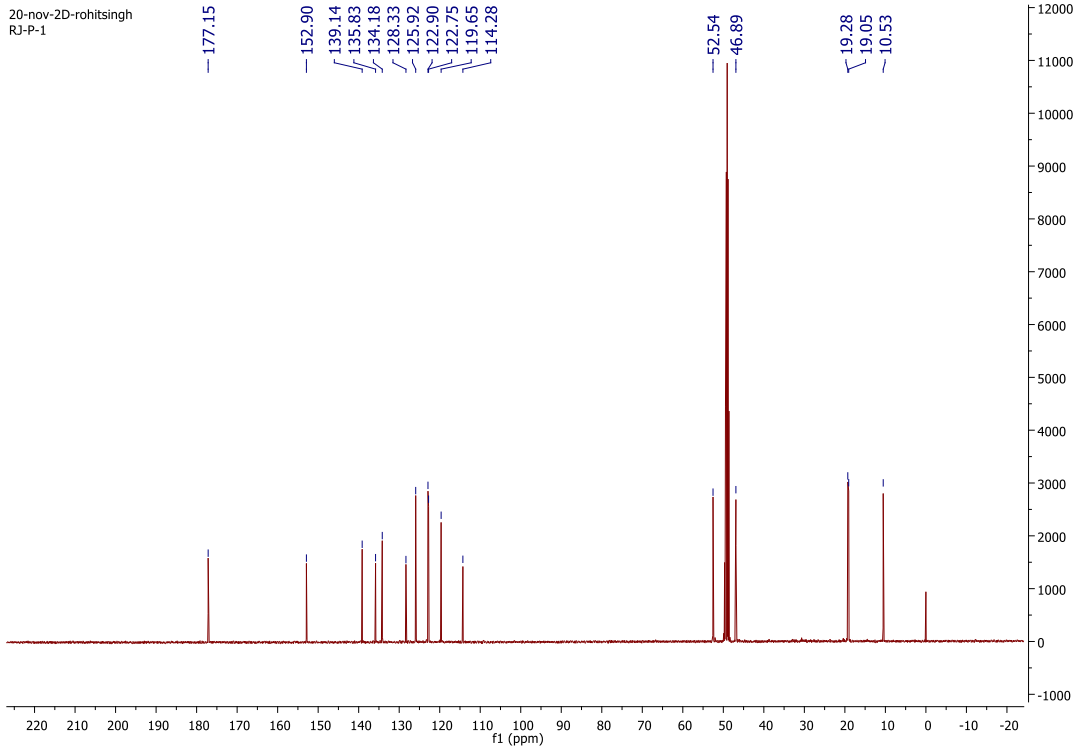
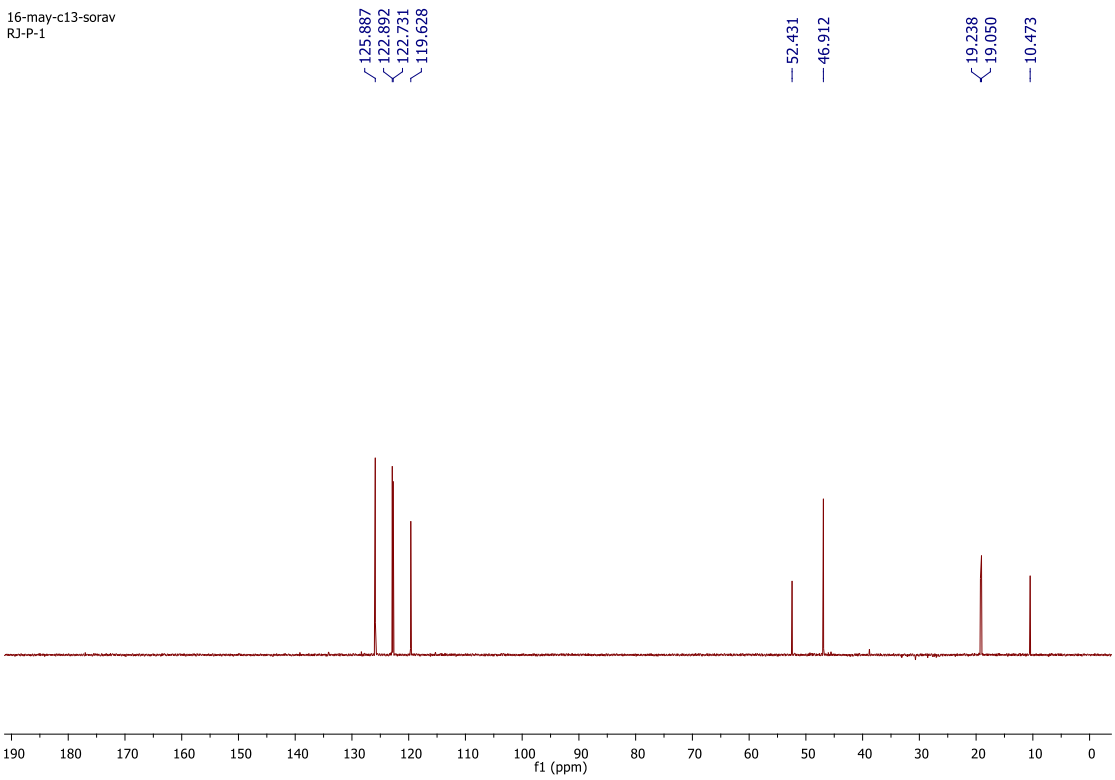
**S2.** $^{1}$H NMR Spectrum of **2** in $CD_3OD$



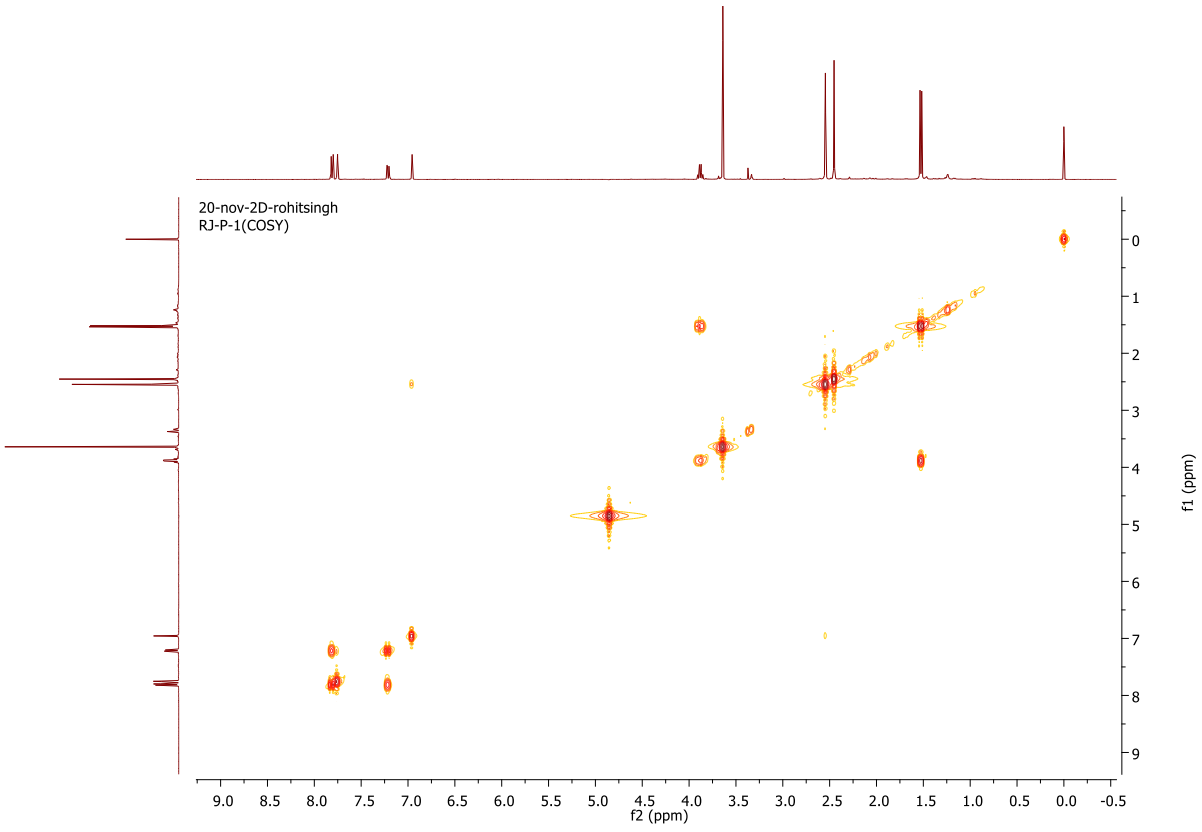

**S3.** $^{13}$C NMR Spectrum of **2** in $CD_3OD$



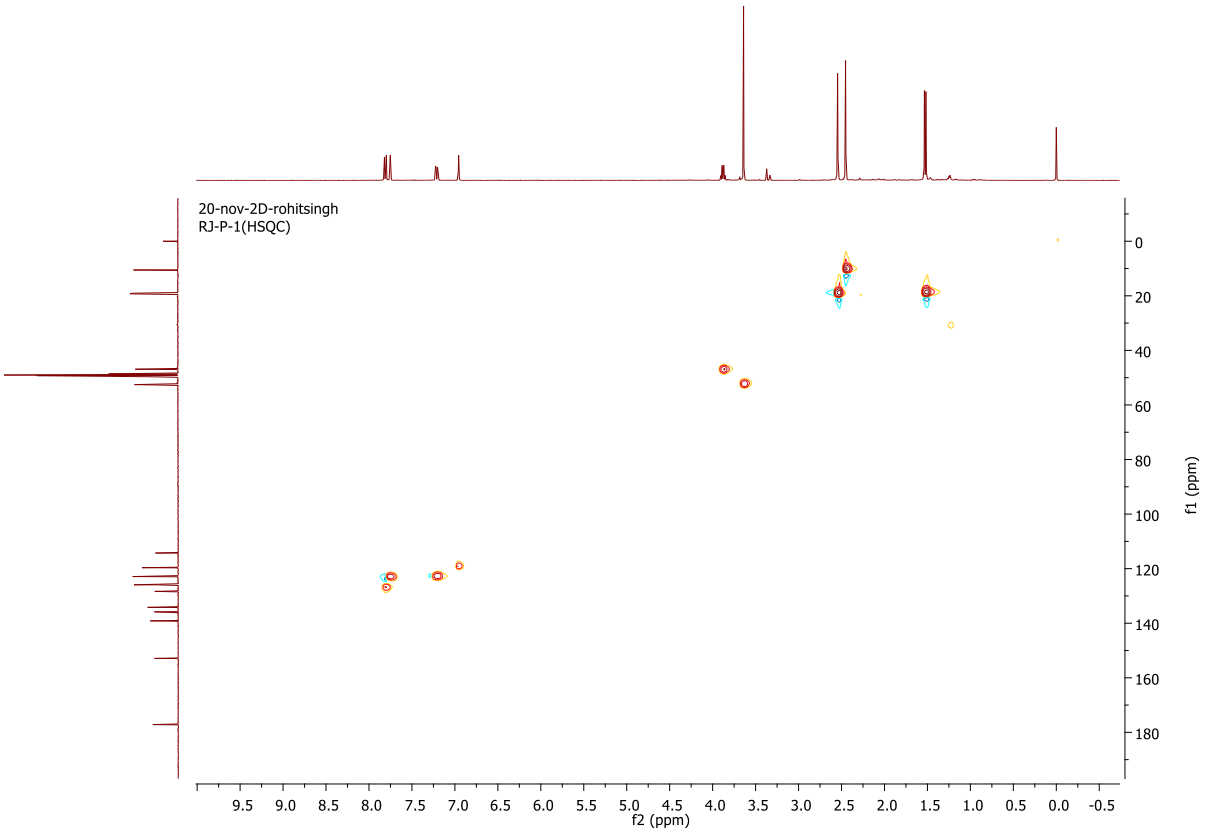

**S4.** DEPT-135 Spectrum of **2** in $CD_3OD$



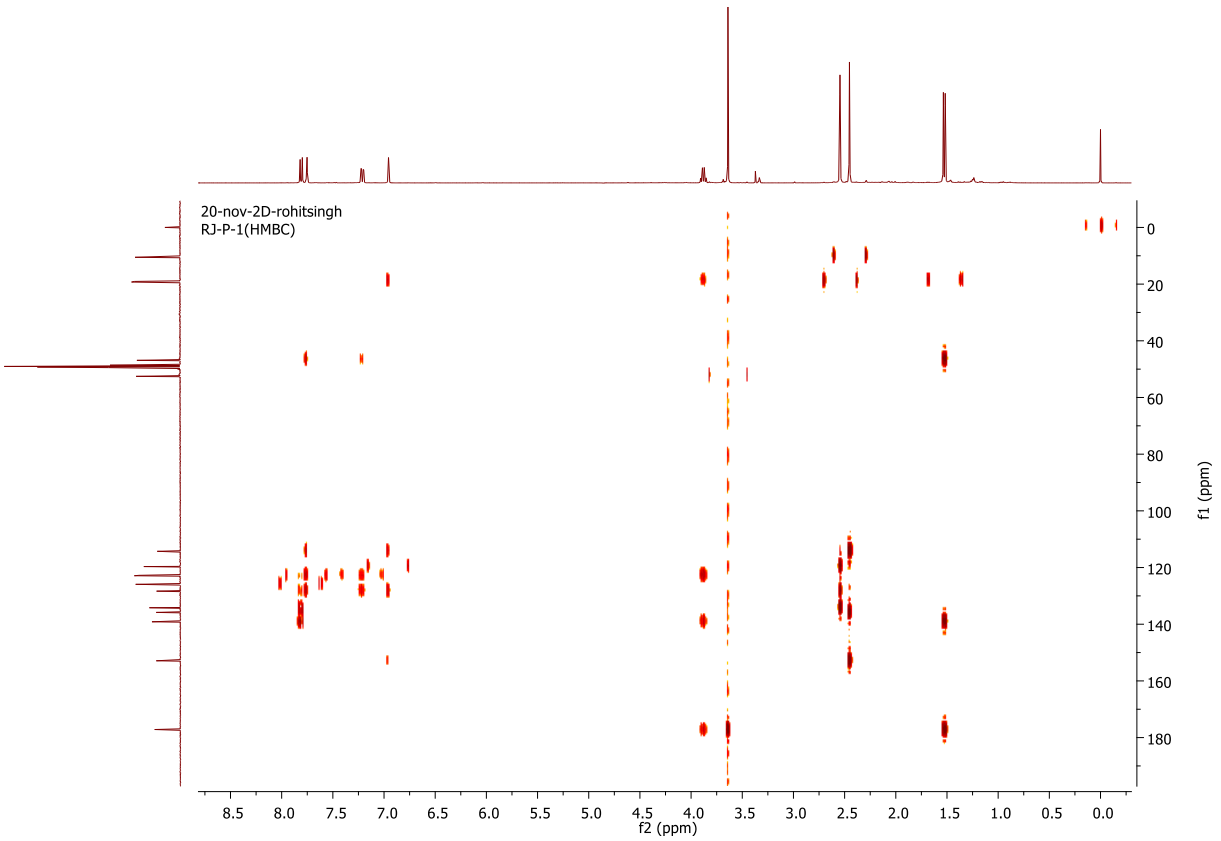

**S5.** COSY Spectrum of **2** in $CD_3OD$



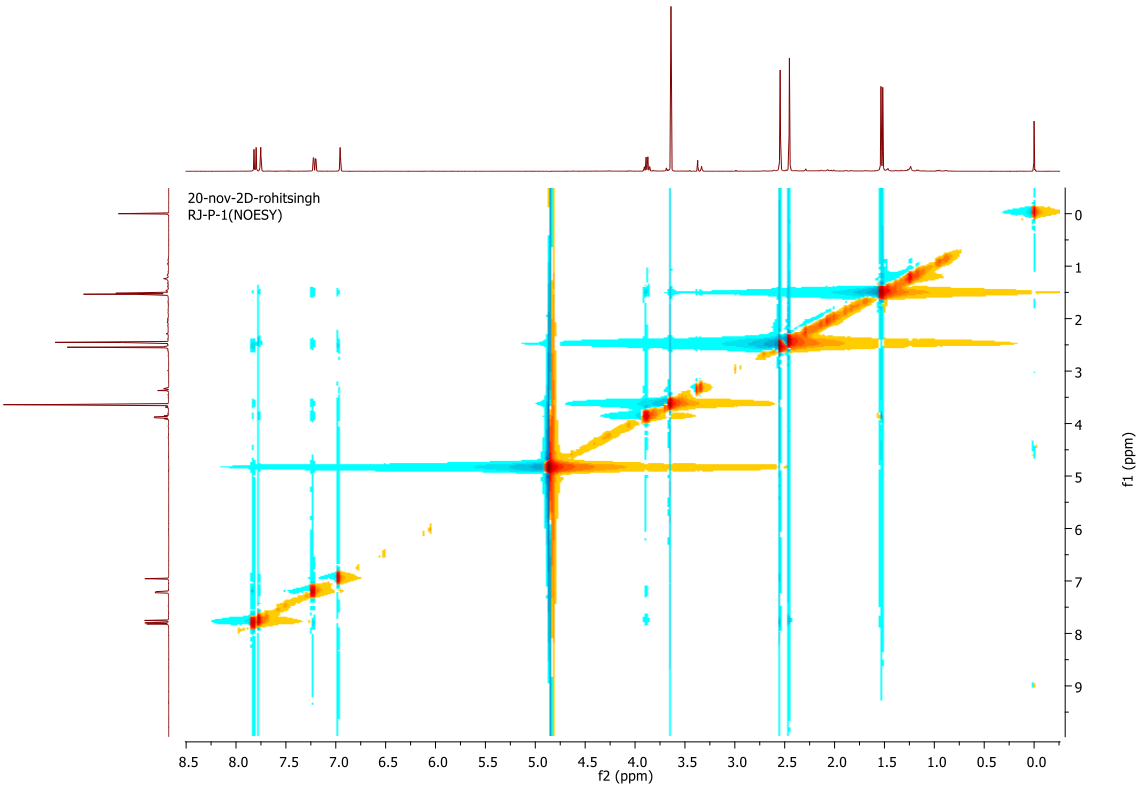

**S6.** HSQC Spectrum of **2** in $CD_3OD$




**S7.** HMBC spectrum of **2** in $CD_3OD$




**S8**. NOESY spectrum of **2** in $CD_3OD$

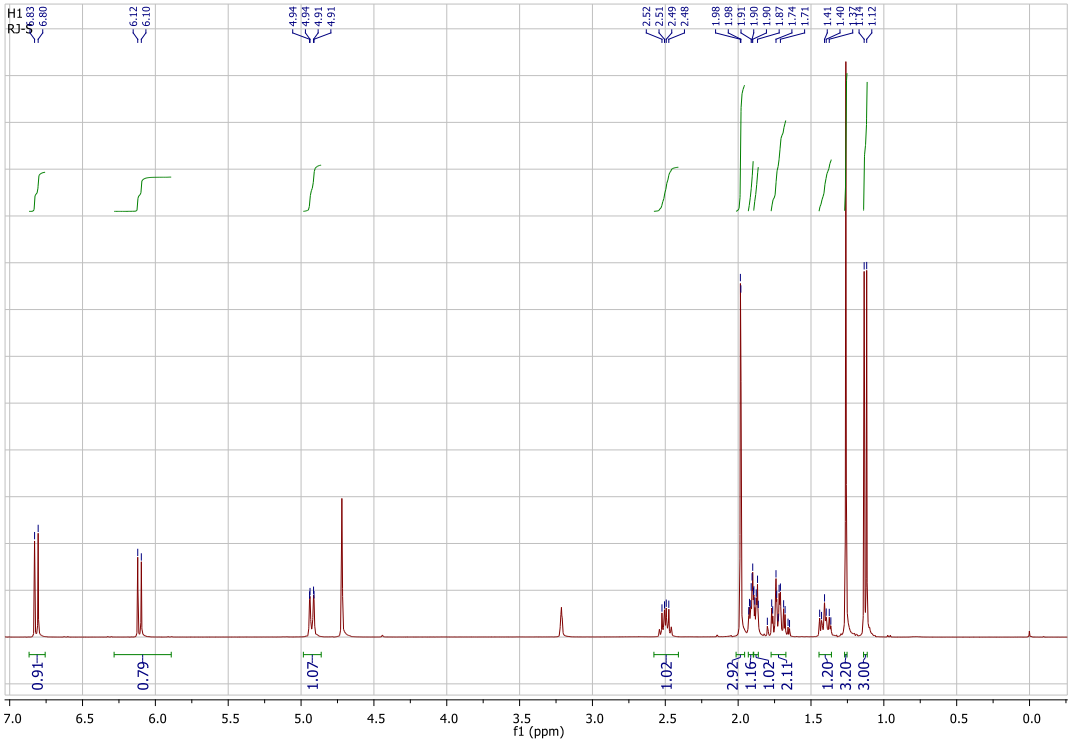



**S9.** *In vitro* COX-1 and COX-2 inhibition assay test result

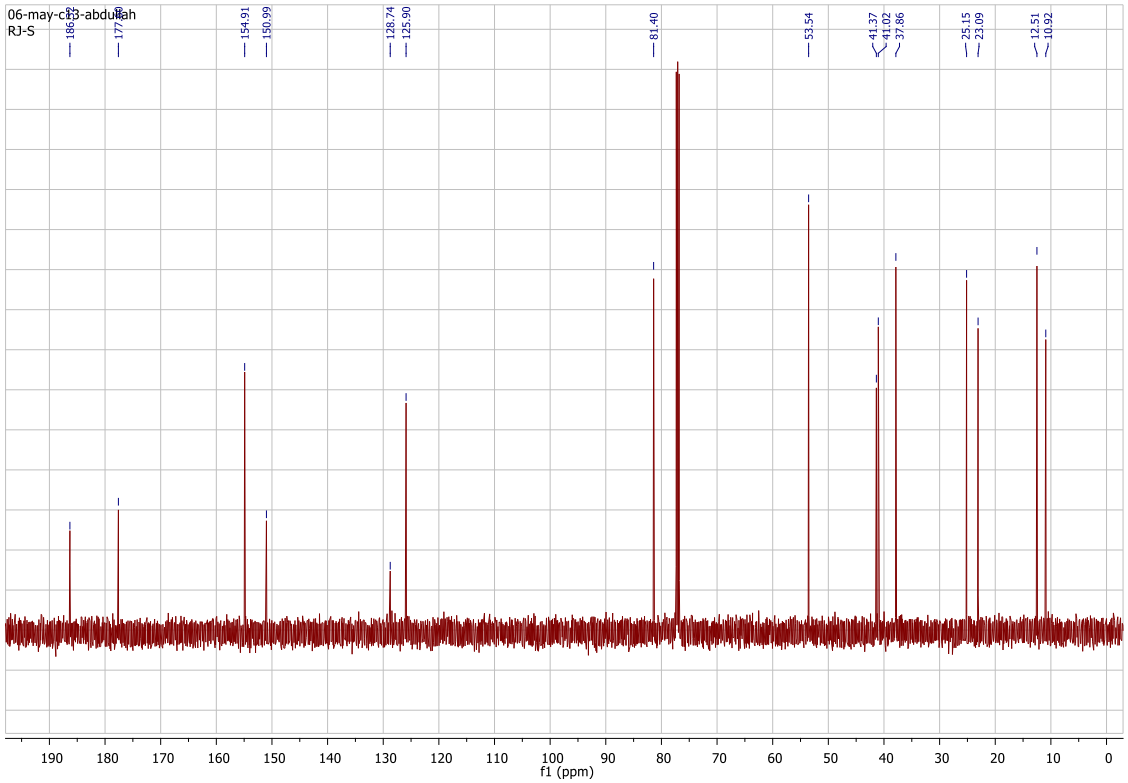
| Compound | % of COX inhibition at 30 µM | | COX inhibition ($IC_{50}$) | | Selectivity* |
|---|---|---|---|---|---|
| | COX-1 | COX-2 | COX-1 | COX-2 | COX-1 $IC_{50}$ / COX-2 $IC_{50}$ |
| **2** | 52.98±4.62 (8.73) | 21.85±1.37 (6.26) | 31.02 | 66.13 | 0.496 |
| Indomethacin | 44.38±7.44 (16.77) | - | | | |
| Etricoxib | - | 59.47±2.13 (3.59) | | | |
| Naproxen | 38.30±0.49 (1.29) | 24.16±1.06 (4.42) | | | |

*****The selectivity of compound may be determined based on the ratio of their $IC_{50}$ values as described for other study.[1]

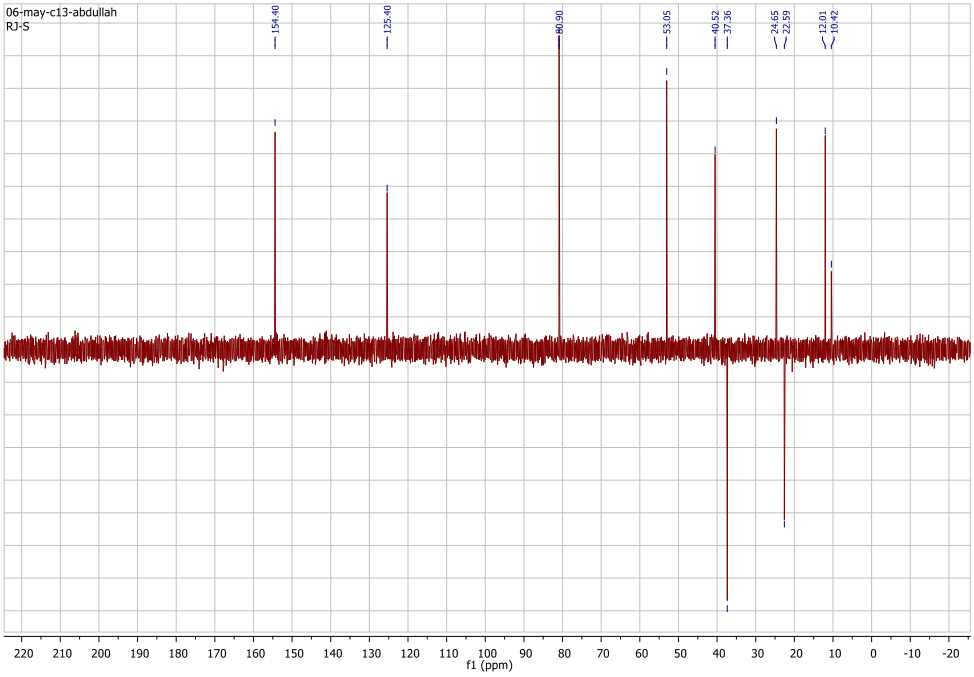
**S10.** $^{1}$H NMR Spectrum of **1** in $CDCl_3$



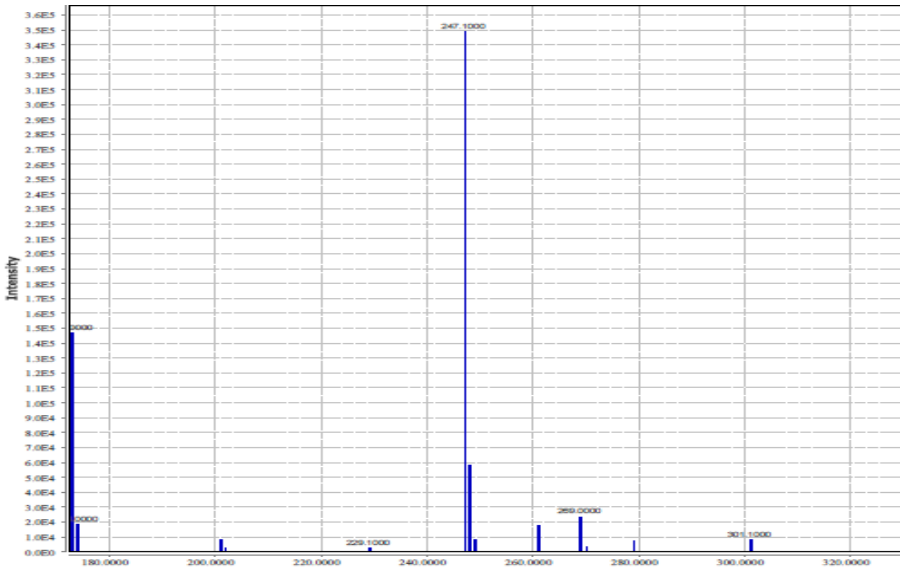

**S11.** $^{13}$C NMR Spectrum of **1** in $CDCl_3$



**S12.** DEPT 135 Spectrum of **1** in $CDCl_3$




**S13.** Mass spectrum of 1




**S14. Notes**

**Publication no:**

CSIR-IIIM Communication number: IIIM/2205/2018

CSIR-IITR Communication number: 3551

## S15. Authors contributions

S.K.J., R.A.V. and S.K.R. designed, executed, and coordinated this whole study; R.S. and S.K.J. designed and executed initial experiment and optimization of chemical modification. S.K.R. designed the biological experiments. K.M. excecuted anti-inflammatory experiments. A.A. and D.K.P. desined and developed method for LCMS. B.G. scaled up both santonin and analogue in grams quantity. Manuscript written by S.K.J. and S.K.R.

## S16. References

(1) Cao, H.; Yu, R.; Tao, Y.; Nikolic, D.; van Breemen, R. B. *J. Pharm. Biomed. Anal.* **2011**, *54*, 230-235.