

## Pyrohyperforin, A New Prenylated Phloroglucinol from *Hypericum perforatum*

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**Abstract:** Pyrohyperforin, a new prenylated phloroglucinol was isolated from *Hypericum perforatum*, its structure was established on the basis of spectral data.

**Keywords:** *Hypericum perforatum*, new prenylated phloroglucinol, pyrohyperforin.

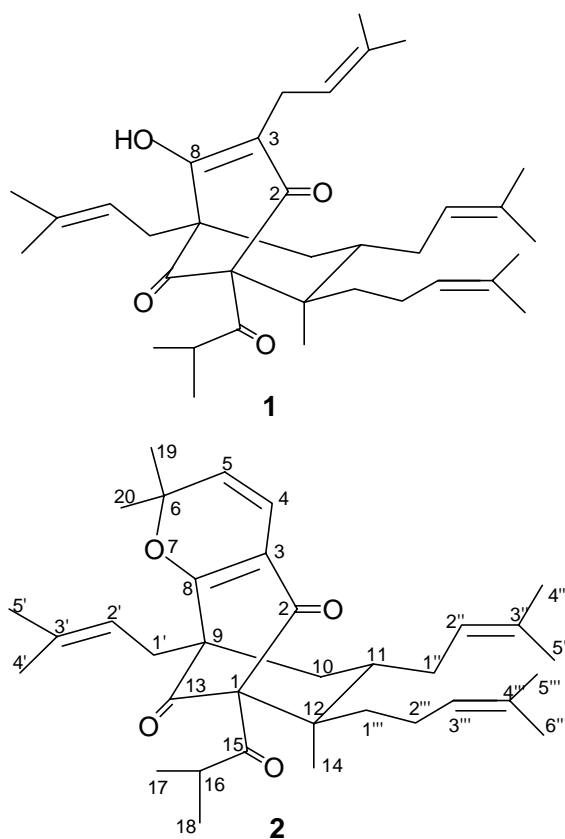
The antidepressant activity of *Hypericum perforatum* extracts has sparked great interest in the chemistry and biochemistry of its constituents, generating coverage also on the mainstream press<sup>1</sup>. The major limitation to a rational exploitation of the medicinal potential of this plant is our still incomplete knowledge of its active constituents. In the 1970s, Russian workers described the isolation and characterization of one active constituent named hyperforin (**1**) from *Hypericum perforatum*<sup>2,3</sup>. Then Norwegian workers confirmed the proposed structure and gave its absolute configuration<sup>4,5</sup>. From then on, the presence of its homologue, adhyperforin<sup>6</sup> and more polar analogues have also been described<sup>6,7,8</sup>. Here we report the isolation and structure characterization of pyrohyperforin (**2**), a new analogue of hyperforin.

Pyrohyperforin was obtained as an optically active colorless oil,  $[\alpha]_{\text{D}}^{25} +83.5$  (c, 0.0285, CHCl<sub>3</sub>), with the following spectral characteristics: IR (film),  $\nu$  1727.9, 1637.3, 1585.2, 1448.3, 1378.9, 1220.7, 1116.6, 1045.2 cm<sup>-1</sup>; UV (CHCl<sub>3</sub>),  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 254 (3.77), 315 nm (3.53); <sup>1</sup>H and <sup>13</sup>C NMR, **Table 1**.

The molecular formula was established by HREIMS ( $[\text{M}^+]$  534.3717, calcd. for C<sub>35</sub>H<sub>50</sub>O<sub>4</sub>, 534.3709) and evidence from the UV, IR, NMR data indicated that **2** was an analogue of hyperforin. A comparison of the formula of **2** with that of hyperforin revealed that **2** had two hydrogen atoms less than hyperforin. In the <sup>13</sup>C NMR spectrum, the three broad peaks of the  $\alpha$ -substituted enolized  $\beta$ -dicarbonyl system of hyperforin (C<sub>2</sub>, C<sub>3</sub>, C<sub>8</sub>) were replaced by three sharp singlets at  $\delta$  188.6 (C<sub>2</sub>), 114.7 (C<sub>3</sub>), 171.0 (C<sub>8</sub>), suggesting that the keto-enol equilibrium of the  $\beta$ -dicarbonyl system was covalently blocked by formation of an enol ether. IR also showed there was no free hydroxyl group. It was probable that the difference came from the formation of a pyrano-ring, which was composed of one of the four prenyl residues. **2** had a Z type of -CH=CH-, with  $\delta$  6.74 d (H<sub>4</sub>), 5.33 d (H<sub>5</sub>),  $J$  = 10.0 Hz and  $\delta$  115.5 (C<sub>4</sub>), 123.8 (C<sub>5</sub>). In the HMBC spectrum, the protons of C<sub>19</sub> ( $\delta$  28.5) correlated to C<sub>5</sub> ( $\delta$  123.8), C<sub>6</sub> ( $\delta$  82.0), C<sub>20</sub> ( $\delta$  28.7), the protons of

$C_{20}$  correlated to  $C_5$ ,  $C_6$ ,  $C_{19}$ . Protons of  $C_4$  and  $C_5$  also showed correlation with  $C_6$ . Therefore, the linkage of  $C_{19}-C_6-C_5-C_4$  and  $C_{20}-C_6-C_5-C_4$  was deduced. The chemical shift of  $C_6$  ( $\delta$  82.0) indicated it was an oxygen-bearing quaternary carbon. Since **2** had three carbonyls at  $\delta$  188.6 ( $C_2$ ), 206.3 ( $C_{13}$ ), 209.5 ( $C_{15}$ ), and the number of oxygen atoms in the formula was 4, the linkage of  $C_8-O-C_6$  was essential. The HMBC also showed correlation between  $H_4$  and  $C_2$ ,  $C_3$ ,  $C_8$ , between  $H_5$  and  $C_3$ . So the pyrano-ring was confirmed.

Figure 1



All other proton and carbon signals of **2** could be assigned using a combination of 1D, 2D techniques and comparison with hyperforin (only partially assigned NMR data are available)<sup>9</sup>, adhyperforin<sup>6</sup> and furohyperforin<sup>8</sup>. On the basis of these spectral data, the structure of pyrohyperforin **2** was established as that shown in **Figure 1**, and it was a new analogue of hyperforin **1**.

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**Table 1** NMR data for pyrohyperforin (2)

Position <sup>a</sup>	<sup>1</sup> H <sup>b</sup>	<sup>13</sup> C <sup>c</sup>	HMBC (H→C)
1		84.4	
2		188.6	
3		114.7	
4	6.47 d (10.0)	115.5	2, 3, 6, 8
5	5.33 d (10.0)	123.8	3, 6, 8, 19, 20
6		82.0	
8		171.0	
9		56.6	
10	1.42 m	38.9	1', 8, 9, 11, 12
	1.88 m		1', 1'', 8, 9, 11, 12, 13
11	1.63 m	43.5	1''', 9, 10, 12
12		49.1	
13		206.3	
14	1.01 s	13.6	1, 1''', 11, 12
15		209.5	
16	2.10 m	42.6	15, 17, 18
17	1.12 d (6.5)	20.6	15, 16, 18
18	1.07 d (6.5)	21.5	15, 16, 17
19	1.45 s	28.5	5, 6, 20
20	1.40 s	28.7	5, 6, 19
1'	2.40 dd (15, 8.4)	29.0	2', 3', 9, 10, 13
	2.48 dd (15, 6.7)		2', 3', 8, 9, 13
2'	4.99 m	119.4	1', 4', 5'
3'		133.9	
4'	1.66 s	26.0	2', 3', 5'
5'	1.67 s	18.2	2', 3', 4'
1''	1.86 m	25.0	2'', 3'', 11, 12
	2.08 m		2'', 3'', 10, 11
2''	5.05 m	124.8	4'', 5''
3''		131.2	
4''	1.63 s	25.7	2'', 3'', 5''
5''	1.58 s	18.0	2'', 3'', 4''
1'''	1.43 m	36.6	2''', 11, 12, 14
	1.89 m		1, 11, 12, 14
2'''	1.70 m	27.2	1''', 4'''
	2.10 m		3''', 4'''
3'''	4.95 m	122.8	5''', 6'''
4'''		133.4	
5'''	1.66 s	25.8	3''', 4''', 6'''
6'''	1.56 s	17.7	3''', 4''', 5'''

<sup>a</sup> Numbering according to reference 8. <sup>b</sup> Recorded in CDCl<sub>3</sub> at 400 MHz. <sup>c</sup> Recorded in CDCl<sub>3</sub> at 100 MHz.

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