Synthesis and evaluation of biological properties of ferrocenyl-podophyllotoxin conjugates

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Contents

Figure S1 S2
X-ray experimental S3
NMR spectra S5
References S35
Figure S1. HPLC chromatograms:  
a) Oregon Green diacetate – reference  
b) Oregon Green diacetate – after 1h – complete hydrolysis  
c) Podophyllotoxin (PPT) – reference  
d) Compound 17 – control sample  
e) Compound 17 after 2h
X-ray experimental

A specimen of 33, approximate dimensions 0.050 mm x 0.100 mm x 0.300 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on BRUKER KAPPA APEX-II Ultra diffractometer, with molybdenum rotating anode as X-ray source and multilayer focusing mirrors. The total exposure time was 6.59 hours. The data were collected with Bruker APEX-II software, integrated using, and were corrected for absorption effects using the multi-scan method (SADABS).

The integration of the data with the Bruker SAINT software package, using a triclinic unit cell and a narrow-frame algorithm, yielded a total of 103731 reflections to a maximum θ angle of 33.62° (0.64 Å resolution), of which 18596 were independent (average redundancy 5.578, completeness = 99.7%, Rint = 3.60%) and 17703 (95.20%) were greater than 2σ(F²). The final cell constants of \( a = 10.0851(5) \) Å, \( b = 10.8685(5) \) Å, \( c = 15.5678(8) \) Å, \( \alpha = 91.650(2)^\circ \), \( \beta = 92.190(2)^\circ \), \( \gamma = 111.5072(19)^\circ \), volume = 1584.73(16) Å³, are based upon the refinement of the XYZ-centroids of 9893 reflections above 20 σ(I) with 4.347° < 2θ < 64.32°. Data were corrected for absorption effects using the multi-scan method (SADABS³). The ratio of minimum to maximum apparent transmission was 0.928. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9424 and 1.0000.

The structure was solved by direct methods using SXELXS⁴ and refined by full-matrix least squares procedure with SHELXL⁵ within OLEX2⁶ graphical interface. Figures were produced with Ortep3v2⁶ and Mercury_3.5⁷ software. Flack parameter was estimated using \( [(I+)-(I^-)]/[\langle I+\rangle+\langle I^-\rangle] \) quotients⁸.

All H atoms were visible in the residual density map, but were added geometrically and refined in riding approximation. No strong H-bonds, requiring more specific H atom treatment, were present in the analyzed crystal structure.

Detailed information about the data processing, structure solution and refinement is presented in Table S1.

Table S1.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C₃₄H₃₁FeN₅O₇, CH₂Cl₂</td>
</tr>
<tr>
<td>Formula weight</td>
<td>734.39</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.050 x 0.100 x 0.300 mm</td>
</tr>
<tr>
<td>Crystal system</td>
<td>triclinic</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>( a = 10.0851(5) ) Å, ( \alpha = 91.650(2)^\circ )</td>
</tr>
<tr>
<td></td>
<td>( b = 10.8685(5) ) Å, ( \beta = 92.190(2)^\circ )</td>
</tr>
<tr>
<td></td>
<td>( c = 15.5678(8) ) Å, ( \gamma = 111.5072(19)^\circ )</td>
</tr>
<tr>
<td>Volume</td>
<td>1584.73(16) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.539 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.701 mm⁻¹</td>
</tr>
<tr>
<td>Description</td>
<td>Value</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td><strong>Theta range for data collection</strong></td>
<td>1.31 to 33.62°</td>
</tr>
<tr>
<td><strong>Index ranges</strong></td>
<td>-14≤h≤14, -15≤k≤15, -21≤l≤21</td>
</tr>
<tr>
<td><strong>Reflections collected</strong></td>
<td>103731</td>
</tr>
<tr>
<td><strong>Independent reflections</strong></td>
<td>18596 [R(int) = 0.0360]</td>
</tr>
<tr>
<td><strong>Coverage of independent reflections</strong></td>
<td>99.6%</td>
</tr>
<tr>
<td><strong>Absorption correction</strong></td>
<td>multi-scan</td>
</tr>
<tr>
<td><strong>Max. and min. transmission</strong></td>
<td>1.0000 and 0.9424</td>
</tr>
<tr>
<td><strong>Structure solution technique</strong></td>
<td>direct methods</td>
</tr>
<tr>
<td><strong>Refinement method</strong></td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td><strong>Function minimized</strong></td>
<td>Σ w(Fo² - Fc²)²</td>
</tr>
<tr>
<td><strong>Data / restraints / parameters</strong></td>
<td>18596 / 3 / 871</td>
</tr>
<tr>
<td><strong>Goodness-of-fit on F²</strong></td>
<td>1.036</td>
</tr>
<tr>
<td>Δ/σ_max</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Final R indices</strong></td>
<td>17703 data; l&gt;2σ(I) R₁ = 0.0249, wR₂ = 0.0614</td>
</tr>
<tr>
<td></td>
<td>all data R₁ = 0.0272, wR₂ = 0.0624</td>
</tr>
<tr>
<td><strong>Weighting scheme</strong></td>
<td>w=1/[σ²(Fo²)+(0.0369P)²+(0.0198P)]</td>
</tr>
<tr>
<td></td>
<td>where P=(Fo²+2Fc²)/3</td>
</tr>
<tr>
<td><strong>Absolute structure parameter</strong></td>
<td>0.006(0)</td>
</tr>
<tr>
<td><strong>Largest diff. peak and hole</strong></td>
<td>0.447 and -0.220 eÅ⁻³</td>
</tr>
<tr>
<td><strong>R.M.S. deviation from mean</strong></td>
<td>0.048 eÅ⁻³</td>
</tr>
</tbody>
</table>
NMR spectra

$^1$H NMR spectra of 17

$^{13}$C($^1$H) NMR spectra of 17
$^1$H-$^1$H COSY spectra of 17

$^1$H-$^{13}$C HMQC spectra of 17
$^{1}H-^{13}C$ HMBC spectra of 17

$^{1}H$ NMR spectra of 18
$^{13}$C-$^{1}$H NMR spectra of 18

$^{1}$H-$^{1}$H COSY spectra of 18
$^1$H-$^{13}$C HMQC spectra of 18

$^1$H-$^{13}$C HMBC spectra of 18
\(^1\)H NMR spectra of 19

\(^{13}\)C\(^{1}\)H NMR spectra of 19
$^1$H-$^1$H COSY spectra of 19

$^1$H-$^{13}$C HMQC spectra of 19
$^{1}$H-$^{13}$C HMBC spectra of 19

$^{1}$H NMR spectra of 20
$^{13}$C-$^1$H NMR spectra of 20

$^1$H-$^1$H COSY spectra of 20
$^1$H-$^{13}$C HMQC spectra of 20

$^1$H-$^{13}$C HMBC spectra of 20
$^1$H NMR spectra of 21

$^{13}$C{$^1$H} NMR spectra of 21
$^1$H-$^1$H COSY spectra of 21

$^1$H-$^{13}$C HMQC spectra of 21
$^1$H-$^13$C HMBC spectra of 21

$^1$H NMR spectra of 22
$^{13}$C-$^1$H NMR spectra of 22

$^1$H-$^1$H COSY spectra of 22
$^1$H-$^{13}$C HSQC spectra of 22

$^1$H-$^{13}$C HMBC spectra of 22
$^1$H NMR spectra of 23

$^{13}$C{$^1$H} NMR spectra of 23
$^1$H-$^1$H COSY spectra of 23

$^1$H-$^{13}$C HSQC spectra of 23
$^1$H-$^1$C HMBC spectra of 23

$^1$H NMR spectra of 24
$^{13}\text{C}^{1\text{H}}$ NMR spectra of 24

$^1\text{H}-^1\text{H}$ COSY spectra of 19
$^1$H-$^{13}$C HSQC spectra of 24

$^1$H-$^{13}$C HMBC spectra of 24
$^1$H NMR spectra of 33

$^{13}$C\{$^1$H} NMR spectra of 33
$^{1}H$-$^{1}H$ COSY spectra of 33

$^{1}H$-$^{13}C$ HSQC spectra of 33
$\text{H-}$C HMBC spectra of 33

$\text{H NMR spectra of 34}$
$^{13}$C-$^1$H NMR spectra of 34

$^1$H-$^1$H COSY spectra of 34
$^{1}H^{13}C$ HSQC spectra of 34

$^{1}H^{13}C$ HMBC spectra of 34
$^1$H NMR spectra of 35

$^{13}$C$\{^1$H$\}$ NMR spectra of 35
$^1$H-$^1$H COSY spectra of 35

$^1$H-$^{13}$C HSQC spectra of 35
$^1$H-$^1$C HMBC spectra of 35

$^1$H NMR spectra of 36
$^{13}$C{$^1$H} NMR spectra of 36

$^1$H-$^1$H COSY spectra of 36
$^1$H-$^{13}$C HSQC spectra of 36

$^1$H-$^{13}$C HMBC spectra of 36
References

1. APEX2 v2012.4-3 (Bruker AXS)
2. SAINT V8.18C (Bruker AXS Inc. 2011)
3. SADABS-2008/1 (Bruker, 2008)