Polycyclic Polyprenylated Acylphloroglucinols: Natural Phosphodiesterase - 4 inhibitors from Hypericum sampsonii

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**S50.** HSQC Spectrum of 7 in CDCl₃

**S51.** HMBC Spectrum of 7 in CDCl₃

**S52.** NOESY Spectrum of 7 in CDCl₃

**S53.** HRESIMS spectrum of 7

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**S1. Experimental Section.**

1.1. **Expression and purification of PDE4D2 protein.**

The cDNAs for expression of human PDE4D2 (catalytic domain, residues 86–413) were subcloned into the expression vector pET15b. All these resultant plasmids were transformed into *E. coli* strain BL21 (Codonplus) for over expression. The *E. coli* cells carrying these plasmids were grown in LB medium at 37 °C to OD₆₀₀ = 0.7, and then 0.1 mM isopropyl β-D-thiogalactopyranoside was added for further growth at 16 °C for 20–40 h. The recombinant protein was purified by Ni-NTA column (Qiagen). The purity of PDE4D2 protein was greater than 95% as shown by SDS–PAGE. A typical batch of purification yielded over 50 mg of PDE4D2 (catalytic domain) from 1 L cell culture.

1.2. **Enzymatic assay.**

The enzymatic activities of PDE4D catalytic domain and the inhibition of PDE4D by extracted compounds were assayed by using ³H-cAMP as substrates (20000–30000 cpm/assay) and the reactions were occured in mixture containing 50 mM Tris/HCl (pH 7.5), 10 mM MgCl₂, 0.5 mM DTT at room temperature (25 °C) for 15 min. The reactions were terminated by addition of 0.2 M ZnSO₄ and Ba(OH)₂. The reaction product ³H-cAMP was precipitated out, while unreacted ³H-cAMP remained in the supernatant. Radioactivity in the supernatant was measured in 2.5 mL Ultima Gold liquid scintillation cocktails
(PerkinElmer) by a PerkinElmer 2910 liquid scintillation counter. Each measurement was repeated at least three times. The IC\textsubscript{50} values were calculated by nonlinear regression. As a reference compound, rolipram purchased from Sigma was measured its IC\textsubscript{50} value before other assays.

**S2. Detailed information for ECD calculations of 1**

The absolute configuration of 1 was determined by quantum chemical TDDFT calculations of its theoretical ECD spectrum. Firstly, conformational analysis of the 1S, 5R, 7S, 23R, 24R, 28R stereoisomer was carried out via Monte Carlo searching using molecular mechanism with MMFF94 force field in the Spartan 08 program, resulting 14 conformers with relative energy within 2.0 kcal/mol. These conformers included conformational possibilities on the directions of the O-H bond at C-28 (three directions), and isopentenyl side chains on C-7 (two directions), and C-3 (three directions). The conformers with different directions of the O-H bond were ignored because of the far distance between the O-H bond and the chromophore, which will has little influence on the carbon skeleton and ECD spectrum. Then six conformers with different directions of the two isopentenyl side chains (1a-1f, Figure S1) were selected for further calculation. In addition, a simplified model with the absence of the two isopentenyl side chains (1g, Figure S1) was also designed and calculated. The conformers were reoptimized using DFT at the B3LYP/6-31G(d) level in vacuum by the Gaussian 09 program.\textsuperscript{1} The B3LYP/6-31G(d) harmonic vibrational frequencies were further calculated to confirm their stability. The energies, oscillator strengths, and rotational strengths of the first 60 electronic excitations were calculated using the TDDFT methodology at the B3LYP/6-311++G(2d,2p) level in vacuum. The ECD spectra were simulated by the overlapping Gaussian function (\(\delta = 0.4\) eV),\textsuperscript{2} in which velocity rotatory strengths of the first 50 exited states were adopted. To get the overall ECD spectra, the simulated spectra of the lowest energy conformers were averaged according to the Boltzmann distribution theory and their relative Gibbs free energy (\(\Delta G\)).


**Figure S1.** B3LYP/6-31G(d) optimized lowest energy 3D conformers (1a–1f) of 1 and model conformer (1g).
**ECD simulation:**

ECD spectrum of each conformation is simulated according to the overlapping Gaussian functions expressed as:

$$
\Delta \epsilon(E) = \frac{1}{2.296 \times 10^{-39} \sqrt{\pi \sigma}} \sum_{i} \Delta E_i R_i e^{-(E-E_i)^2/\sigma^2}
$$

Where $\sigma$ is half the bandwidth at 1/e peak height and expressed in energy units. The parameters $\Delta E_i$ and $R_i$ are the excitation energies and rotational strengths for the transition $i$, respectively.

The above function is converted to $\Delta \epsilon, \lambda$ (wavelength) correlations as:

$$
\Delta \epsilon(\lambda) = \frac{1}{2.296 \times 10^{-39} \sqrt{\pi \sigma}} \sum_{i} \Delta E_i R_i e^{-(1240\lambda-\Delta E_i)^2/\sigma^2}
$$

and then simulation were accomplished by using the Excel 2003 and the Origin 7.0 software.

To get the final spectra, all the simulated spectra of conformations of each compound were averaged according to their energy and the Boltzmann distribution theory expressed as:

$$
\frac{N_i^*}{N} = g_i e^{-\epsilon_i/k_B T} \sum g e^{-\epsilon_i/k_B T}
$$

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* R(velocity) 10**-40 erg-esu-cm
S3. CD spectra of compounds 2–7.

**Figure S2A.** CD spectra of homoadamantyl type PPAPs (compounds 2–5).

**Figure S2B.** CD spectra of adamantane type PPAPs (compounds 6 and 7).
S4. $^1$H NMR Spectrum of 1 in CDCl$_3$
S5. $^{13}$C NMR Spectra of 1 in CDCl$_3$
S6. $^1\text{H}-^1\text{H}$ COSY Spectrum of 1 in CDCl$_3$
S7. HSQC Spectrum of 1 in CDCl₃
S8. HMBC Spectrum of 1 in CDCl$_3$
S9. NOESY Spectrum of 1 in CDCl₃
S10. HRESIMS spectrum of 1
S11. $^1$H NMR Spectrum of 2 in CDCl$_3$
S12. $^{13}$C NMR Spectra of 2 in CDCl$_3$
S13. $^1$H-$^1$H COSY Spectrum of 2 in CDCl$_3$
S14. HSQC Spectrum of 2 in CDCl₃
S15. HMBC Spectrum of 2 in CDCl$_3$
S16. NOESY Spectrum of 2 in CDCl$_3$
S17. HRESIMS spectrum of 2
S18. $^1$H NMR Spectrum of 3 in CDCl$_3$
S19. $^{13}$C NMR Spectra of 3 in CDCl$_3$
$S20$. $^{1}H$-$^{1}H$ COSY Spectrum of 3 in CDCl$_3$
S21. HSQC Spectrum of 3 in CDCl₃
S22. HMBC Spectrum of 3 in CDCl₃
S23. NOESY Spectrum of 3 in CDCl$_3$
S24. HRESIMS spectrum of 3

**Y: 75**
**n: 801**
**RT: 4.95**
**AV: 1**
**NL: 3.55E5**
**T: FTMS + p ESI Full ms [250.00-1000.00]**

![HRESIMS Spectrum](image-url)
S25. Selected $^1\text{H}$$-^1\text{H}$ COSY and HMBC correlations of 3

**Figure S3.** Selected $^1\text{H}$$-^1\text{H}$ COSY (—) and HMBC (→) correlations of 3
S26. $^1$H NMR Spectrum of 4 in CDCl$_3$
**S27.** $^{13}$C NMR Spectra of 4 in CDCl$_3$
S28. $^1$H-$^1$H COSY Spectrum of 4 in CDCl$_3$
S29. HSQC Spectrum of 4 in CDCl₃
S30. HMBC Spectrum of 4 in CDCl₃
S31. NOESY Spectrum of 4 in CDCl₃
S32. HRESIMS spectrum of 4

YS-77d #576  RT: 4.75  AV: 1  NL: 8.74E4
T: FTMS + p ESI Full ms [250.00-1000.00]
S33. $^1$H NMR Spectrum of 5 in CDCl$_3$
S34. $^{13}$C NMR Spectra of 5 in CDCl₃
S35. $^1$H-$^1$H COSY Spectrum of 5 in CDCl$_3$
S36. HSQC Spectrum of 5 in CDCl₃
S37. HMBC Spectrum of 5 in CDCl₃
S38. NOESY Spectrum of 5 in CDCl₃
S39. HRESIMS spectrum of 5
S40. \(^1\)H NMR Spectrum of 6 in CDCl\(_3\)
S41. $^{13}$C NMR Spectra of 6 in CDCl₃
S42. $^1$H-$^1$H COSY Spectrum of 6 in CDCl$_3$
S43. HSQC Spectrum of 6 in CDCl₃
S44. HMBC Spectrum of 6 in CDCl₃
S45. NOESY Spectrum of 6 in CDCl₃
S46. HRESIMS spectrum of 6

[Graph showing mass/charge (m/z) values for yhsz-37a #318 with RT: 3.01, AV: 1, NL: 1.50E5. T: FTMS - p ESI Full ms [200.00-800.00].]
S47. $^1$H NMR Spectrum of 7 in CDCl₃
S48. $^{13}$C NMR Spectra of 7 in CDCl$_3$
S49. $^1$H-$^1$H COSY Spectrum of 7 in CDCl$_3$
S50. HSQC Spectrum of 7 in CDCl₃
S51. HMBC Spectrum of 7 in CDCl₃
S52. NOESY Spectrum of 7 in CDCl$_3$
S53. HRESIMS spectrum of 7

41A #309 RT: 2.59 AV: 1 NL: 7.86E5
F: FTMS + p ESI Full ms [150.00-800.00]

[Graph showing a mass spectrum with peaks at m/z values and intensities marked]