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Hyphenone A, the first 3,3-diisoprenylated bicyclic polyprenylated acylphloroglucinols as $Ca_v3.1$ T-type calcium channel inhibitor from *Hypericum henryi*

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ABSTRACT

Hyphenone A (**1**), a new type of bicyclic polyprenylated acylphloroglucinols (BPAPs) featured with an unprecedented 3,3-diisoprenylated 1,3,5-trione core, were characterized from the roots of *Hypericum henryi* together with two new congeners (hyphenones B–C, **2**–**3**) and five known biosynthetic related PPAPs. Biogenetically, **1** should be derived from a novel 3,3,5,5-tetraisoprenylated MPAPs precursor. Their structures were elucidated by comprehensive spectroscopic data and X-ray diffraction. Moreover, **1**–**3** were identified as the first PPAPs type $Ca_v3.1$ T-type calcium channel (TTCC) inhibitors, with IC_{50} values of 7.07, 6.19, and 5.47 μM, respectively.

Polycyclic polyprenylated acylphloroglucinols (PPAPs), a special class of hybrid natural products exclusively characterized from the family of Guttiferae, are originated from a mixed biosynthetic pathway of polyketide and isoprenylation [1,2]. This kind of metabolites possess intriguing structures and a broad range of biological activities such as cytotoxicities, anti-inflammatory, antidepressant, antioxidant, anti-HIV, and antibacterial activity. Therefore, PPAPs have received considerable attentions from both chemical and pharmaceutical communities [1,2]. Up to now, more than 750 PPAPs with diverse bridged-cyclic, adamantane, *homo*-adamantane, spirocyclic, and some other complicated architectures have been characterized [1]. It is noteworthy that all of these reported PPAPs are biosynthetically derived by the further cyclization from a common precursor, monocyclic polyprenylated acylphloroglucinols (MPAPs) [1,3–6].

Our group has focused on the systematic studies on PPAPs for more than 10 years and have discovered more than 400 PPAPs with intriguing structures and potential bioactivities [1,7,8]. However, to date, most of the phytochemical investigations were carried out on the aerial parts of different Guttifarae plants, while only a little few studies of the roots have been conducted [9–17]. *Hypericum henryi* is one of the most widely distributed and abundant species of the genus *Hypericum* in China [18]. Its aerial parts and fruits have been extensively investigated and a series of isoprenylated acylphloroglucinols derivatives have been characterized [19–23]. However, the chemical profiles of the roots of this plant have never been revealed. Therefore, the roots of this plant were phytochemically studied and hyphenone A (**1**) (Fig. 1), the first 3,3-diisoprenylated bicyclic polyprenylated acylphloroglucinols (BPAPs), was obtained together with two new homologues (hyphenones B–C, **2**–**3**) (Fig. 1) and five known PPAPs [4–8,24–27]. Their structures were identified by comprehensive spectroscopic analysis, and the absolute configuration of **1** was defined by X-ray diffraction data. Structurally, compound **1** is the first 3,3-diisoprenylated BPAPs. Differing from all of the reported PPAPs that biogenetically derived from a common 3,5,5-triisoprenylated MPAPs precursor, hyphenone A (**1**) should originated from a distinct MPAPs precursor with an unreported 3,3,5,5-tetraisoprenylated acylphloroglucinols core, which implied that **1** could be seen as a new type of PPAPs. Furthermore, we initially revealed that compounds **1**–**3** potently and dose-dependently inhibited

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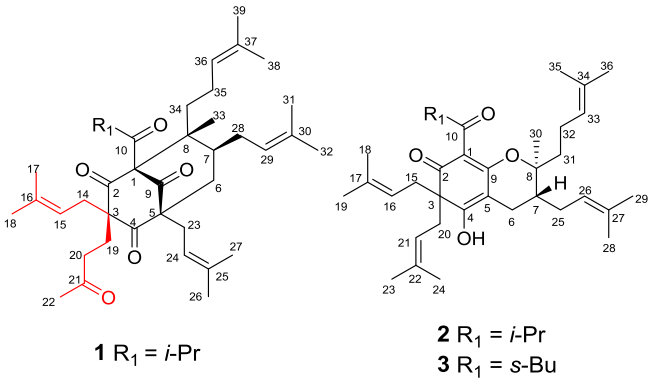


Fig. 1. Structures of hyphenones A–C (**1**–**3**).

the peak currents of $Ca_v3.1$ TTCC, an attractive therapeutic target for neuropathic pain, absence epilepsy, insomnia, and Parkinson's disease [28–30], having IC_{50} values of 7.07, 6.19, and 5.47 μM, respectively. In this paper, the isolation, structural elucidation, plausible biosynthetic pathway, and bioactivity evaluations of these compounds are presented.

Hyphenone A (**1**) [31] was purified as colorless crystals. Its molecular formula was determined to be $C_{39}H_{58}O_5$ based on the $[M+Na]^+$ ion peak at *m/z* 629.4183 (calc. 629.4176) in its HRESIMS spectrum and ^{13}C NMR data, suggesting 11 degrees of unsaturation. The IR spectrum displayed characteristic absorption bands of carbonyl groups at 1723 and 1700 cm^{-1}. The ^1H NMR spectrum (Table 1) signals showed one isopropyl group (δ_H 1.17, d, J = 7.3 Hz; 0.98, d, J = 7.3 Hz; 2.18, sept.; J = 7.3 Hz), four olefinic protons (δ_H 5.08, 5.03, 4.99, 4.84), and two singlet methyl groups (δ_H 0.99, 2.09). The ^{13}C and DEPT NMR (Table 1) data revealed the existence of 39 carbons, corresponding to four ketones at δ_C 209.0 (C-2), 208.9 (C-4), 208.0 (C-9), 209.2 (C-10), four quaternary carbons at δ_C 87.9 (C-1), 69.4 (C-3), 66.9 (C-5), 56.8 (C-8), one methine at δ_C 45.8 (C-7), two methylenes, one methyl, and 23 other signals ascribable to an isopropyl, four isoprenyls, and another four carbon signals (δ_C 31.2, C-19; 37.2, C-20; 208.1, C-21; 29.9, C-22). The key ^1H–^1H COSY correlation of H_2-19/H_2-20 and HMBC correlations from Me-22 to C-20 and C-21 assembled these four carbons to be a 2-butanone. Moreover, the carbonyls and isoprenyls account for nine degrees of unsaturation, then the remaining degrees required **1** to be a bicyclic system. Based on the observations mentioned above, conjugated with the fact that a number of PPAPs have been reported from this plant, **1** should be ascribed to be a PPAPs-type metabolite.

In the ^{13}C NMR spectrum, obvious signals for a typical bicyclo [3.3.1]nonane-2,4,9-trione core of PPAPs type metabolites can be easily distinguished at δ_C 87.9, C-1; 209.0, C-2; 69.4, C-3; 208.9, C-4; 66.9, C-5; 47.3, C-6; 45.8, C-7; 56.8, C-8; and 208.0, C-9. Detailed analysis of these spectral data displayed that the difference for the core of **1** from the normal type A BPAPs lies in that the quaternary sp^2 carbon at C-3 for the normal BPAPs was

Table 1
^1H (600 MHz) and ^{13}C (150 MHz) NMR Data of **1**–**3** in MeOD.

No.	**1**		**2**		**3**	
	δ_c	δ_H (J in Hz)	δ_c	δ_H (J in Hz)	δ_c	δ_H (J in Hz)
1	88.0		107.5		108.6	
2	206.2		199.4		200.2	
3	69.4		60.8		60.9	
4	208.9		198.0	198.2		
5	66.9		107.5	107.6		
6	47.3	2.18, overlap 1.70, overlap	22.5	2.47, dd (5.2, 17.3) 1.94, dd (8.9, 17.3)	22.3	2.43,dd (4.4, 17.3) 1.99, dd (7.4, 17.3)
7	45.9	1.60, overlap	37.6	1.84, overlap	37.5	1.84, overlap
8	56.8		85.6	85.6		
9	209.0		166.6	166.6		
10	209.2		202.8	201.5		
11	42.9	2.18, sept (7.3)	37.5	3.75, sept (6.5)	43.8	3.66, sept (6.5)
12	22.2	1.17, d (7.3)	20.4	1.16, d (6.5)	17.6	1.16, d (6.5)
13	20.9	0.98, d (7.3)	19.6	1.16, d (6.5)	28.6	1.78, m 1.46, m
14	29.4	2.63, overlap 2.57, overlap			12.2	0.88, t (8.2)
15	120.6	5.03, t (8.0)	40.0	2.60	39.9	2.61
16	136.8		119.2	4.74, t (7.4)	119.2	4.73, t (5.4)
17	26.5	1.59, s	136.1		136.0	
18	18.4	1.56, s	18.1	1.63, s	26.1	1.73, s
19	31.2	1.73, overlap	26.0	1.53, s	18.1	1.61, s
20	37.2	2.48, m 2.31, m	39.8	2.60	39.7	2.61
21	208.1		119.1	4.74, t (7.4)	119.2	4.73 t (5.4)
22	29.9	2.09, s	136.1		136.0	
23	32.4	2.57, m 2.41, m	18.0	1.73, s	18.0	1.55, s
24	120.2	5.08, t (8.0)	26.0	1.62, s	26.0	1.61, s
25	136.3		29.7	2.21, overlap 1.84, overlap	29.5	2.21 m 1.84, overlap
26	26.2	1.56, s	123.1	5.18, t (5.8)	123.2	5.18, t (7.6)
27	18.1	1.67, s	134.5		134.5	
28	29.0	2.04, m 1.73, overlap	18.0	1.53, s	18.0	1.50, s
29	123.1	4.84, t (8.0)	26.0	1.53, s	26.0	1.53, s
30	134.6		20.6	1.26, s	21.0	1.29, s
31	26.0	1.73, s	39.3	1.78, overlap	39.6	2.61
32	18.1	1.67, s	23.0	2.10, m	23.0	2.09, m
33	13.8	0.99, s	124.7	5.11, t (7.4)	124.6	5.09, t (6.7)
34	38.1	1.99, dd (5.2, 15.0) 1.01, d (5.2)	133.0		133.0	
35	26.4	2.18, overlap 1.91, m	25.9	1.67, s	17.9	1.50, s
36	125.5	4.99, s	17.8	1.53, s	25.9	1.67, s
37	132.4					
38	17.8	1.56, s				
39	25.9	1.67, s				

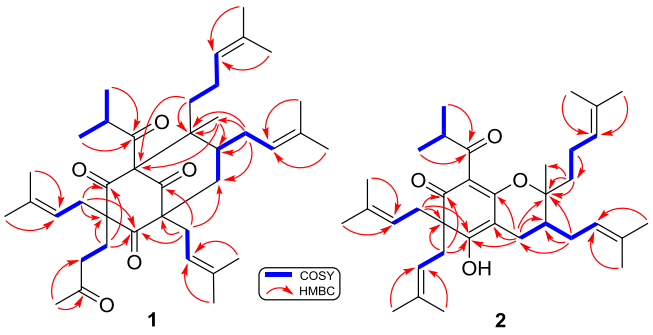


Fig. 2. Key HMBC and $^{1}H–^{1}H$ COSY correlations of **1** and **2**.

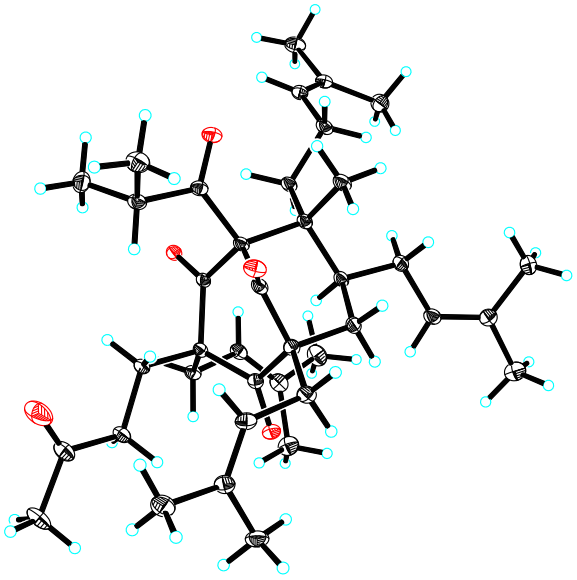


Fig. 3. X-ray crystallographic of compound **1**.

replaced by a quaternary sp^3 at δ_C 69.4 ppm in **1**, which indicated **1** should be a 3,3-disubstituted BPAPs derivative. This deduction, as well as the locations of four isoprenyls and the mentioned 2-butanone, can be further confirmed by the HMBC correlations from H_2-14 and H_2-19 to C-2, C-3, C-4; from H_2-23 to C-4, C-5, C-6, and C-9; from H_2-28 to C-6, C-7 and C-8; from H_2-34 and Me-33 to C-1, C-7, and C-8 (Fig. 2). Therefore, the planar structure of **1** was defined as shown.

The relative configuration of **1** was assigned by analysis of the ROESY spectrum. The NOE correlations of H-6(δ_H 2.18)/H-23, H-6 (δ_H 2.18)/Me-33, Me-33/Me-13, and Me-22/Me-26/Me-12 demonstrated that Me-33, C-28, C-23, and C-19 were all β-oriented, while C-34, C-14, H-7 were all α-oriented. Finally, the absolute configuration of **1** was determined as 1*R*,3*S*,5*R*,7*S*,8*R* by the X-ray diffraction data unequivocally (Fig. 3) [32].

Hyphenone B (**2**) [33] was obtained as yellow oil. Its molecular formula, $C_{35}H_{52}O_4$, was determined by its ^{13}C NMR and positive HRESIMS (*m*/*z* 537.3956, $[M+H]^+$, calc. 537.3938), indicating 10 degrees of unsaturation. The ^{1}H NMR data (Table 1) gave signals of four olefinic protons (δ_H 5.18, 5.11, 4.74, 4.74), nine methyl singlets (δ_H 1.26–1.73), and one isopropyl group (δ_H 1.16, d, *J* = 6.5 Hz; 1.16, d, *J* = 6.5 Hz; 3.75, sept., *J* = 6.5 Hz). The ^{13}C and DEPT NMR (Table 1) spectra displayed 35 carbon resonances incorporating the diagnostic signals at δ_C 107.6 (C-1), 199.4 (C-2), 60.8 (C-3), 198.0 (C-4), 107.5 (C-5), and 166.6 (C-9) for a phloroglucinol core, a isobutyryl (δ_C 202.8, C-10; 37.5, C-11; 20.4, C-12; 19.6, C-13), four isoprenyls, as well as other 5 signals assignable to a functionalized isoprenyl unit (including a oxygenated quaternary carbon at δ_C 85.6, one methine, two methylenes, and one methyl). Aforementioned data indicated that **2** should be a polyprenylated acylphloroglucinols derivative [1,2]. The structure of the functionalized isoprenyl unit was deduced by the $^{1}H–^{1}H$ COSY correlations of H-7/H_2-6 together with HMBC correlations from Me-30 and H_2-31 to C-7 and C-8. Subsequently, the HMBC correlations of H_2-6 with C-4, C-9, and C-5 deduced that the C-6 was linked to C-5 of the phloroglucinol core. Moreover, the attachment of two isoprenyls to C-7 and C-31 can be evidenced by the $^{1}H–^{1}H$ COSY correlations of H_2-31/H_2-32 and H-7/H_2-25 as well as the HMBC correlations from H_2-25 to C-8, C-7, and C-6 and from H_2-32 to C-8 and C-31. In addition, the remaining two isoprenyls were both attached to C-3, as supported by the HMBC correlations from H_2-15 and H_2-20 to C-2, C-3, and C-4. Then, the six membered ether ring was proposed by the downfield chemical shifts of C-8 (δ_C 85.6) and C-9 (δ_C 166.6) as well as the degrees of the unsaturation. Hence, the structure of **2** was elucidated. The relative configurations of C-8 and C-7 were elucidated based on the NOE interactions of Me-30/H-6(δ_H 2.47) and H-6(δ_H 1.94)/H-7 (Fig. 4).

Hyphenone C (**3**) [34] was obtained as yellow oil and gave the molecular formula $C_{36}H_{54}O_4$, according to ^{13}C NMR (Table 1) and positive HRESIMS (*m*/*z* 551.4115, $[M+H]^+$, calc. 551.4095). The 1D and 2D NMR data indicated that the structures of **2** and **3** are similar to each other. The only difference lied in that the signals for the isopropyl in **2** were replaced by signals for *sec*-butyl in **3** as confirmed by HMBC correlations from Me-12 (δ_H 1.16) to C-10 (δ_C 201.5), C-11 (δ_C 43.8), and C-13 (δ_C 28.6); and from Me-14 (δ_H 0.88) to C-11 (δ_C 43.8) and C-13 (δ_C 28.6). The relative configuration of **3** was also determined to be the same as that of **2** by detailed analysis of 2D NMR spectroscopic data.

As shown in Scheme 1, the putative biosynthetic pathway of the isolates can be summarized as follows: simple acylphloroglucinol yielded two essentially different precursors MPAPs (i) and MPAPs (ii) by isoprenylation; MPAPs (ii) undergoes further cyclization to afford **2**–**3**. Compounds **4**–**8** were derived from MPAPs (i) through the further cyclization of phloroglucinol core and isoprenyl chains as described in the literatures [1,3–6]. In another pathway, MPAPs (ii) could further isoprenylate to generate an unprecedented precursor, 3,3,5,5-tetraisoprenylated MPAPs, which may undergo further acid catalysis and oxidization reactions to afford **1**. Although the new MPAPs may be derived from MPAPs (i) or MPAPs (ii), the formation of compounds **2**–**3** indicated the new MPAPs was more likely originated from MPAPs (ii). So, it's obviously that **1** could be seen as a new class of PPAPs compared to the normal PPAPs as exemplified by compounds **4**–**8**.

Biogenetically, the previous reported PPAPs were all originated from 3-monoisoprenylated MPAPs, and 3,3-diisoprenylated MPAPs have never been reported as precursor of PPAPs type metabolites [3,4,6,35]. In fact, natural 3,3,5,5-tetraisoprenylated MPAPs have also never been reported up to now. As the name suggested, PPAPs represented a special class of hybrid natural products with polyiso-

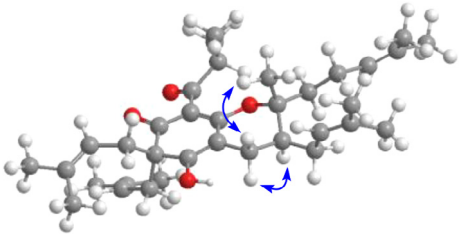
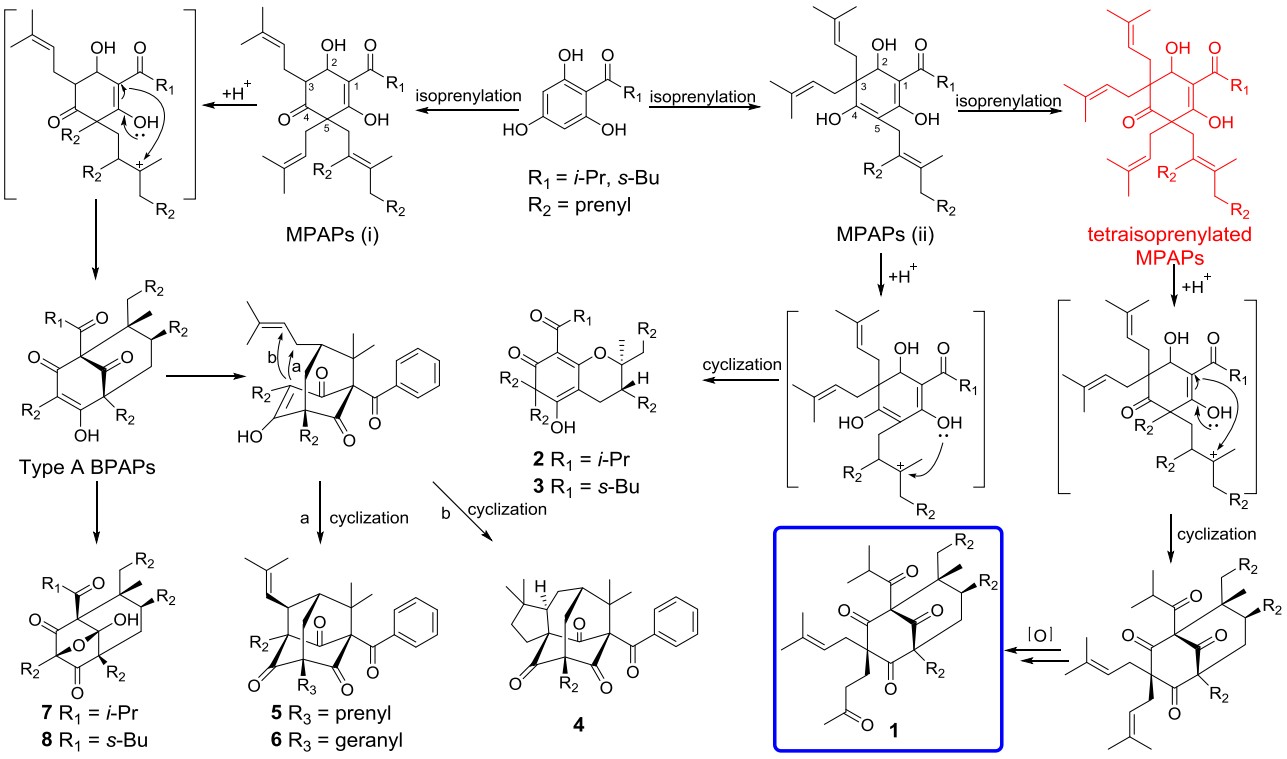


Fig. 4. Key NOE correlations of compound **2**.



Scheme 1. Putative biosynthetic pathway for compounds **1**–**8**.

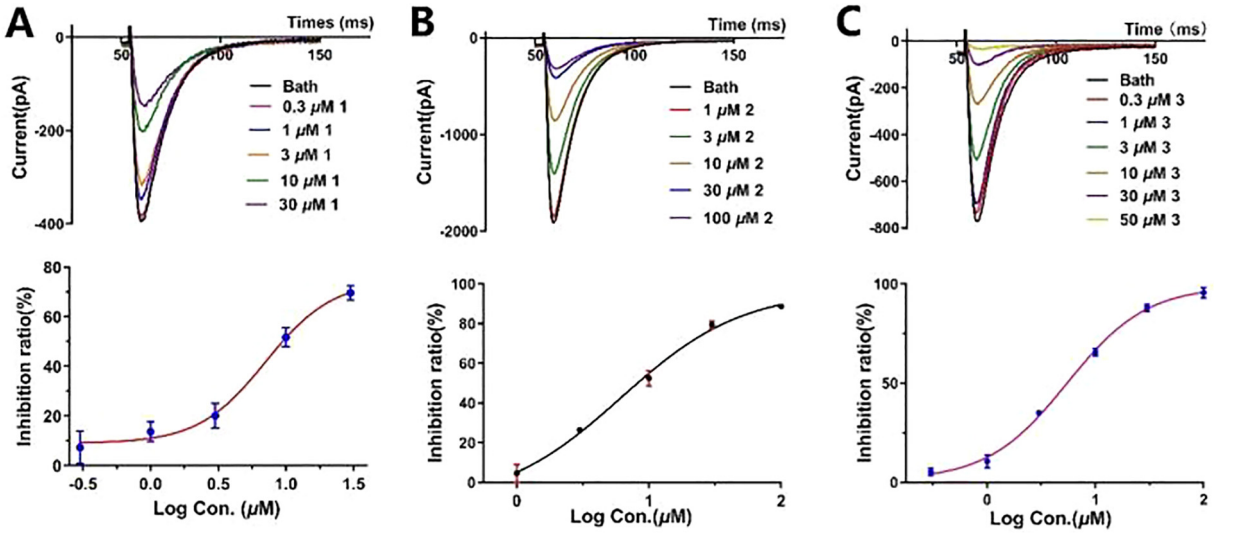


Fig. 5. Inhibitory effects of Compounds **1**–**3** (A–C) on $Ca_v3.1$. Up panel: Representative $Ca_v3.1$ peak current traces elicited by 150 ms depolarization to −40 mV at 3 s intervals from a holding potential (HP) of −100 mV in the absence (control) and presence of different concentrations of **1**–**3**, respectively. Down panel: Dose-response relationships of **1**–**3** for $Ca_v3.1$ at HP of − 100 mV, respectively. Data points represent mean ± SD of three or five measurements. The solid curve represents a fit to the Hill equation. The IC_{50} values of **1**–**3** are 7.07 μM, 6.19 μM, and 5.47 μM, respectively. While, the Hill coefficient of these compounds are 1.75, 0.95, and 1.18 μM, respectively.

prenylation, therefore the number, the position, as well as the substituted patterns of the isoprenylation were all crucial factors for the structural diversity and complexity of PPAPs. For example, PPAPs with a bicyclo[3.3.1]nonane-2,4,9-trione core account for the majority of the natural PPAPs, and their classification (types A and B) was based on the connection of C-1 to the isoprenyl at C-5 or C-3 separately. Similarly, the structural difference between adamantane and *homo*-adamantane type PPAPs was also originated from the different cyclized position of the isoprenyl group at C-8 to C-3 [1,2]. So, the characterization of hyphenone A (**1**) as the first 3,3-diisoprenylated PPAPs implied that more PPAPs derived from this unique 3,3,5,5-tetraisoprenylated MPAPs precursor are desirable. In addition, although many studies about the biosynthesis of PPAPs have been reported, more in-depth research works are still needed to uncover the interesting pathway of this special group of metabolites [1–4,6,36].

As noted in the introduction, $Ca_v3.1$ TTCC inhibitors hold great potential for the treatment of a variety of neurological disorders

[28–30]. In the present study, we firstly demonstrate that compounds **1**–**3** inhibit $Ca_v3.1$ TTCC peak currents with a dose-dependent ways among their testing concentration range (Fig. 5 and Table S1). The IC_{50} values of **1**–**3** on $Ca_v3.1$ TTCC are 7.07, 6.19, and 5.47 μM, respectively. While, the Hill coefficient of these compounds are 1.75, 0.95, and 1.18, respectively (Fig. 5). Mibefradil, the positive control, indicates more potent activities than **1**–**3**, with an IC_{50} value of 1.12 μM (Fig. 5). Interestingly, the maximal inhibition of **1** is around 70% under the saturated concentration of 30 μM (Fig. 5; Table S1), indicating **1** act allosterically on $Ca_v3.1$ gating rather than blocks channel conduction. Besides, the inhibitory effects of **1**–**3** are hard to wash out. These phenomenon suggest that the binding sites of **1**–**3** may be buried deeply inside the channel. Aforementioned action characteristics of the isolated compounds deserve to be elucidated in future.

In summary, hyphenone A (**1**), a novel PPAPs originated from an unprecedented 3,3-diisoprenyated MPAPs precursor, was isolated from the roots of *H. henryi* together with two new congeners (hyphenones B–C, **2**–**3**) and five known PPAPs. Structurally, compound **1** represents the first example of PPAP featured with diisorenylation at C-3. In addition, compound **1** was a rarely reported BPAPs with 1,3,5-trione phloroglucinol core, which differed from the normal BPAPs featured with enolized 1,3-diketo phloroglucinol core. Biosynthetically, compound **1** could be derived from a new type of 3,3,5,5-tetraisoprenylated MPAPs. Moreover, compounds **1**–**3** are the first PPAPs type $Ca_v3.1$ TTCC inhibitors deserve for in-depth research in future. Altogether, the discovery of this new kind of BPAP further enriches structural type and biological activity of PPAPs.

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Appendix A. Supplementary data

Supplementary data (the details of isolation and biological experimental procedures, original 1D and 2D NMR; MS and HR-ESIMS spectroscopic data for compounds **1**–**3**) to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151220.

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[31] Hyphenone A (**1**): colorless crystal; mp 89–91 ; [α]+13 (*c* 0.22, MeOH); UV (MeOH) λ_{max} (log ε) 287(1.05), 197(2.90), 280(1.04) nm; IR (KBr) ν_{max} 2971, 2929, 2914, 2876, 2862, 1723, 1700, 1682, 1443, 1377 cm^{-1}; ^1H and ^{13}C NMR data, see table 1; ESIMS *m*/*z* 607 $[M + H]^+$; HRESIMS *m*/*z* 629.4183 $[M + Na]^+$ (calcd for $C_{39}H_{58}O_5$, 629.4176).
[32] Crystal data for compound **1**: $C_{39}H_{58}O_5$, M = 606.85, a = 10.9335(3) Å, b = 11.6132(3) Å, c = 14.4251(4) Å, α = 96.4500(10)°, β = 98.2370(10)°, γ = 90.1280(10)°, V = 1800.92(8) $Å^3$, T = 100.(2) K, space group *P*1, Z = 2, μ (Cu Kα) = 0.562 mm^{-1}, 66,083 reflections measured, 13,812 independent reflections (R_{int} = 0.0307). The final R_1 values were 0.0324 ($I > 2\sigma(I)$). The final wR (F^2) values were 0.1046 ($I > 2\sigma(I)$). The final R_1 values were 0.0329 (all data). The final wR (F^2) values were 0.1059 (all data). The goodness of fit on F^2 was 0.969. Flack parameter = 0.04(3).
[33] Hyphenone B (**2**): yellow oil; [α]+35 (*c* 0.21, MeOH); UV (MeOH) λ_{max} (log ε) 313(2.48), 198(2.92), 270(2.12) nm; IR (KBr) ν_{max} 3426, 2972, 2928, 2876, 2859, 1730, 1644, 1595 cm^{-1}; ^1H and ^{13}C NMR data, see table 1; ESIMS *m*/*z* 537 $[M + H]^+$; HRESIMS *m*/*z* 537.3956 $[M + H]^+$ (calcd for $C_{35}H_{52}O_4$, 537.3938).
[34] Hyphenone C (**3**): yellow oil; [α] +19 (*c* 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 314(2.56), 197(2.99), 269(2.04) nm; IR (KBr) ν_{max} 3433, 2968, 2927, 2876, 2859, 1637, 1594, 1449 cm^{-1}; ^1H and ^{13}C NMR data, see table 1; ESIMS *m*/*z* 551 $[M + H]^+$; HRESIMS *m*/*z* 551.4115 $[M + H]^+$ (calcd for $C_{36}H_{54}O_4$, 551.4095).
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