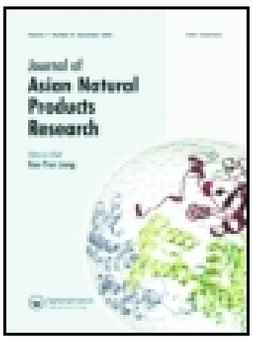

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Polycyclic polyprenylated acylphloroglucinol derivatives with neuroprotective effects from *Hypericum monogynum*

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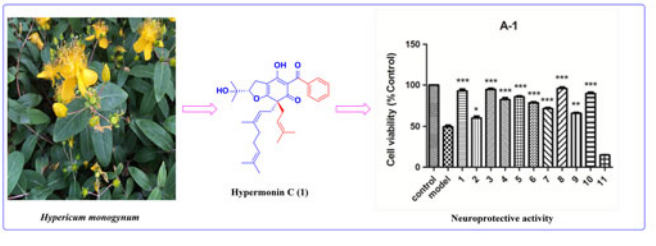
ABSTRACT

A new polycyclic polyprenylated acylphloroglucinol (PPAP), hypermonin C (**1**), along with nine known PPAPs (**2**–**10**) were obtained from the leaves and twigs of *Hypericum monogynum*. The structures of the isolates were determined on the basis of extensive spectroscopic analysis. The neuroprotective effects of the isolates against several chemical-induced injuries in SH-SY5Y and PC12 cells were assessed, and most of the compounds exhibited significant protective effects at 10 μg/ml. Especially, three compounds (**1**, **3**, and **7**) showed excellent neuroprotective activity with a cell viability of 92.4% $\sim$ 95.8% in KCl-induced SH-SY5Y cell injury. Their preliminary structure-activity relationship was also discussed and the configuration of substituent in furohyperforin may be critical for the neuroprotective activity of PPAP derivatives.



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Hypericum monogynum; polycyclic polyprenylated acylphloroglucinols (PPAPs); neuroprotective effects; structure-activity relationship

1. Introduction

Many neurological diseases are associated with neuronal damage, such as stroke, Alzheimer's disease, Huntington's disease, epilepsy, Parkinson's disease, and depression [1,2]. The protection of neurons played a key role in the prevention and

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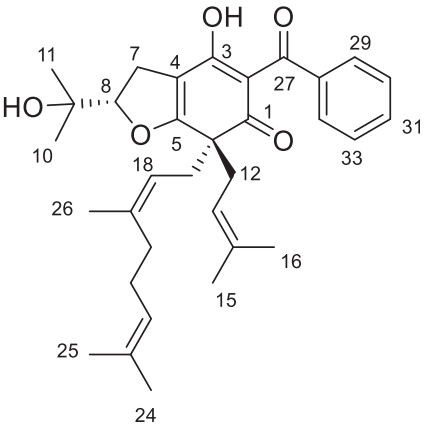

Figure 1. Structure of compound **1** isolated from *H. monogynum*.

treatment of neurological diseases. Nerve cell injury is characterized by multiple factors, multiple links and multiple pathways, and the therapeutic effect of intervention on a single link or pathway has been clinically proved to be very poor. Thus, it is of vital importance to find bioactive substances with multi-target intervention for neuronal injury. The PC12 (rat pheochromocytoma cells) and SH-SY5Y cell lines (human dopaminergic cells) are broadly used in studies due to their typical neuron characteristics [2–4].

Polycyclic polyprenylated acylphloroglupcinols (PPAPs) with highly oxygenated acylphloroglucinol-derived cores are usually decorated with prenyl and geranyl side chains, which were mainly isolated from the plants of *Hypericum* of Guttiferae family [5,6]. Most of them showed a broad range of biological activity such as antimicrobial, anti-inflammatory, antiviral, cytotoxic, antidepressant, and antioxidant activities [5–7]. Recently, a series of PPAPs with remarkable neuroprotective activity have been reported [8–11]. Especially, hyperforin, the first PPAP obtained from *Hypericum perforatum*, is famous for its clinical treatment of depression [12,13]. Moreover, some PPAPs with potential antidepressant-like activity were closely related to the protective effects on neural cells [2,14]. In order to further study PPAPs with neuroprotective activity from *Hypericum*, a new PPAP (**1**), along with nine known PPAPs (**2**–**10**) was obtained from *H. monogynum* (Figure 1). Herein, we reported the isolation and structural elucidation, as well as their neuroprotective effects on several chemical-induced injuries in SH-SY5Y and PC12 cells, including potassium chloride (KCl), nitroprusside (SNP), corticosterone (CORT), sodium glutamate (MSG), and sodium hyposulfate ($Na_2S_2O_4$).

2. Results and discussion

Compound **1** was isolated as light oil. Its molecular formula was assigned as $C_{33}H_{42}O_5$ based on the HRESIMS and ^{13}C NMR data with 13 degrees of unsaturation. The IR spectrum showed absorption broad bands of hydroxy (3440 cm^{-1}) and conjugated carbonyl (1632 cm^{-1}) groups. Its UV spectrum showed a strong absorption at 246 and 350 nm, indicating the presence of benzophenone. Analysis of the

Table 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR Data of 1 (in $CDCl_3$).

No.	δ_C, typle	δ_H, (J in Hz)
1	195.1, C	
2	107.8, C	
3	186.8, C	
4	110.0, C	
5	178.1, C	
6	55.2, C	
7	26.8, CH_2	3.02–3.07 (m), 2.94–3.00 (m)
8	92.6, CH	4.73 (dd, 10.2, 8.2)
9	71.6, C	
10	23.8, CH_3	1.21 (s)
11	26.3, CH_3	1.33 (s)
12	36.1, CH_2	2.70 (dd, 12.7, 4.2), 2.46–2.50 (m)
13	119.3, CH	4.87 (t, 6.4)
14	135.0, C	
15	25.7, CH_3	1.64 s
16	18.1, CH_3	1.62 s
17	37.3, CH_2	2.59–2.64 (m), 2.51–2.54 (m)
18	117.6, CH	4.98 (t, 7.6)
19	139.1, C	
20	39.8, CH_2	1.93–1.97 (m)
21	26.8, CH_2	1.98–2.02 (m)
22	123.8, CH	5.03 (t, 6.4)
23	131.8, C	
24	17.7, CH_3	1.56 (s)
25	25.7, CH_3	1.65 (s)
26	16.2, CH_3	1.60 (s)
27	194.5, C	
28	138.2, C	
29/33	127.7, CH	7.41–7.44 (m)
30/32	127.7, CH	7.35–7.39 (m)
31	130.8, CH	7.45–7.49 (m)

^{1}H NMR spectrum of **1** (Table 1) indicated the presence of seven singlet methyls, three olefinic protons at δ_H 5.03 (1H, t, $J = 6.4$ Hz), 4.98 (1H, t, $J = 7.6$ Hz), and 4.87 (1H, t, $J = 6.4$ Hz), and characteristic signals of five phenyl protons at δ_H 7.45–7.49 (1H, m), 7.41–7.44 (2H, m), and 7.35–7.39 (2H, m). The ^{13}C and DEPT NMR spectral data (Table 1) displayed 33 carbon resonances (Table 1), including seven methyl carbons, five methylenes, nine methines (eight olefinic carbons), and 12 quaternary carbons (eight olefinic and two carbonyl carbons). Further analysis of the ^{13}C NMR spectrum indicated that **1** possessed two carbonyl groups at C-1 (δ_C 195.1) and C-27 (δ_C 194.5), two enol quaternary carbons C-3 (δ_C 186.8) and C-5 (δ_C 178.1), and three quaternary carbons C-2 (δ_C 107.8), C-4 (δ_C 110.0), and C-6 (δ_C 55.2). The above mentioned data revealed that **1** was a PPAP. Further analysis of 1D NMR spectrum demonstrated that compound **1** had the same ring system as garcinenone F [7]. The difference was that the 2-methylpropanoyl group at C-2 in garcinenone F was replaced by an unsubstituted benzoyl moiety in compound **1** and the absence of resonance for the hydroxy group at C-16.

The planar structure of **1** was elucidated by 2D NMR spectroscopy. In the ^{1}H–^{1}H COSY spectrum, four isolated correlation signals were observed (H_2-7/H-8, H_2-12/H-13, H_2-17/H-18, and H_2-21/H-22), which constructed the four fragments highlighted by the bold bonds in Figure 2. In the HMBC spectrum, correlations from Me-10 and Me-11 to C-9 and C-8, and from H_2-7 to C-5, C-4, and C-3, together

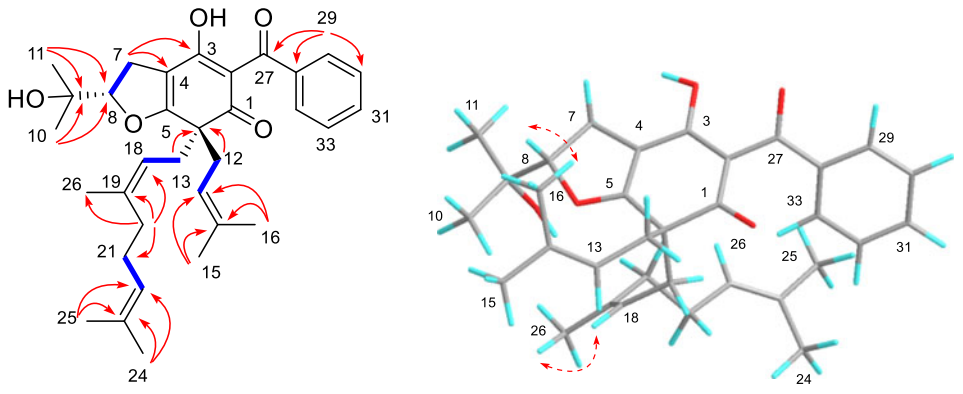

Figure 2. Key HMBC (⌒), $^{1}H–^{1}H$ COSY (—) and ROESY (⌒) correlations of **1**.

with a characteristic α,β-unsaturated carbonyl group [C-1 (δ_C 195.1), C-2 (δ_C 107.8), and C-3 (δ_C 186.8)] indicated the presence of a parent nucleus structure of the phloroglucinol and furan ring. In addition, the HMBC correlations between both Me-15 and Me-16 with C-14 (δ_C 135.0) and C-13 (δ_C 119.3), and between H-12 to C-6 (δ_C 55.2) confirmed the attachment of a prenyl side chain at C-6. Another geranyl group was assigned at C-6, which was determined by the HMBC correlations of Me-24 and Me-25 to C-23 (δ_C 131.8) and C-22 (δ_C 123.8), H-20 to C-26 (δ_C 16.2), C-21 (δ_C 26.8) , C-19 (δ_C 139.1) and C-18 (δ_C 117.6), and H-17 to C-6. From HMBC spectrum, the cross-peaks from phenyl protons H-30 and H-33 (δ_H 7.43, m) to carbonyl C-27 was observed. In addition, the characteristic olefinic quaternary carbon C-2 with small chemical shift (δ_C 107.8) indicated that the structural fragment of benzoyl group was linked to C-2 [15]. Hence, the structure of compound **1** was assigned.

The ROESY experiment assigned the relative configuration of **1** (Figure 2), in which cross-peaks from H-8 to Me-16 suggested that these groups were cofacial, and were randomly assigned as β-oriented. Thus, the isopentenyl side chain at C-6 was β-oriented. The Z configuration of the C-18/C-19 double bond was confirmed by the ROESY correlation of H-18/Me-26. Therefore, the relative configuration of **1** was established as shown in Figure 2. The absolute configuration of compound **1** was determined by comparison of the calculated electronic circular dichroism (ECD) with experimental ECD. An excellent fit was exhibited between the measured ECD spectra with the calculated ECD spectra (Figure 3). As a consequence, the absolute configuration of the two chiral centers for **1** was established as 4R and 8S respectively (Figure 1).

Nine known PPAPs, uralione E (**2**) [2], furoadhyperforin (**3**) [16], 1-(2-methyl-1-oxopropyl)-2,12-dioxo-3,10b-bis(3-methyl-2-butenyl)-6-hydroxy-11b-methyl-11a-(4-methyl-3-pentenyl)-5-oxatricyclo[6.3.1.04,8]-3-dodecene (**4**) [17], furohyperforin isomer (**5**) [18], uralodin B (**6**) [19], attenuatumione F (**7**) [20], oxepahyperforin (**8**) [21], hypercohin E (**9**) [22], and furohyperforin (**10**) [23] were identified by comparing their spectroscopic data with those reported in the literature.

The neuroprotective activity of all the compounds was assessed in SH-SY5Y and PC12 cells that underwent different damages induced by potassium chloride (KCl), nitroprusside (SNP), corticosterone (CORT), sodium glutamate (MSG), and sodium

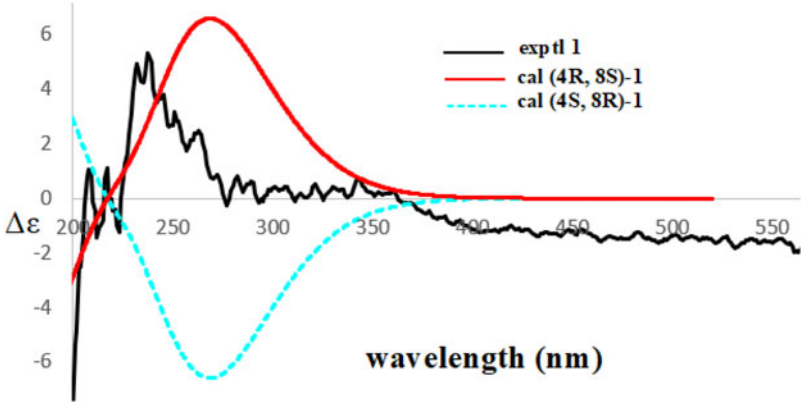

Figure 3. Experimental and calculated ECD spectra of **1**.

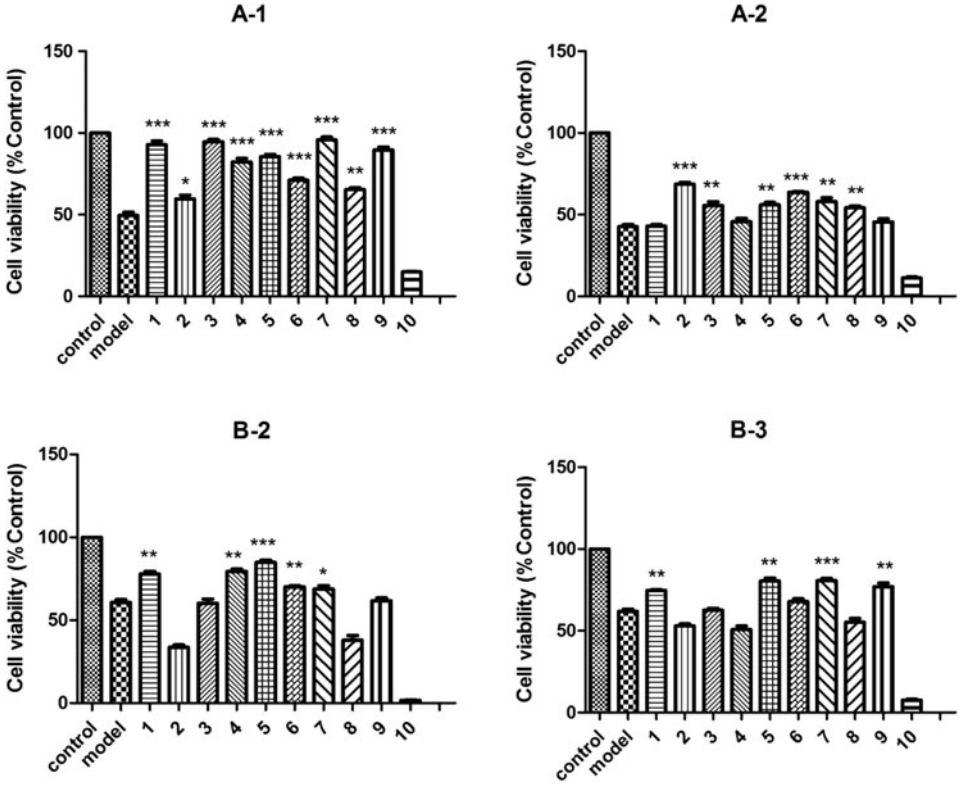

Figure 4. Neuroprotective activities of **1**–**10** against KCl, SNP, or CORT-induced injury in SH-SY5Y and PC12 cells (control: without the damage agents and compounds (**1**–**10**), model: A-1: KCl was added as the damage agent in SH-SY5Y, A-2: SNP was added as the damage agent in SH-SY5Y, B-2: SNP was added as the damage agent in PC12, B-3: CORT was added as the damage agent in PC12. $^{***}p < 0.001$ vs. model, $^{**}p < 0.01$ vs. model, $^{*}p < 0.05$ vs. model).

hyposulfate ($Na_2S_2O_4$). The viability of injured SH-SY5Y and PC12 cells was significantly affected by most of PPAPs at a concentration of 10 μg/ml in the four models as shown in Figure 4 (the data for other six models were shown in supporting

information). In Figure 4A-1, compounds **1**, **3**–**7**, and **9** showed outstanding protective effects with the cell viability of 71.12% ∼ 95.81% in KCl-induced SH-SY5Y cell injury, while compounds **2** and **6** showed good protective activities with improving cell viability of 68.51% and 63.66% in SNP-induced SH-SY5Y cell injury, respectively (Figure 4A-2). However, compound **5** showed excellent protective activity with a cell viability of 84.87% in SNP-induced PC12 cell injury comparing with other compounds (Figure 4B-1), while compound **7** revealed the strongest effect with a cell viability of 80.69% in CORT-induced PC12 cell injury (Figure 4B-2). Three compounds (**1**, **3**, and **7**) revealed excellent neuroprotective activity of 92.44% ∼ 95.81% in KCl-induced SH-SY5Y cell injury, and compounds **5** and **7** showed protective activity against cells damage in the four models (Figure 4).

The preliminary structure-activity relationship of neuroprotective activity of **1**–**10** could be analyzed. In the case of SH-SY5Y cell injury induced by KCl, compounds **1**–**9** showed good neuroprotective activity when the substituent on the furohyperforin or pyrohyperforin was α-oriented, while only compound **10** with a β-oriented substituent on the furohyperforin was inactive. Especially, **9** and **10** are a pair of epimers with opposite configuration only at the C-32 position in the furohyperforin, likewisely, **9** was active while **10** was inactive in the CORT-induced PC12 cell injury. It was also reported in the literatures [5,24] that the PPAPs with a pair of epimers showed different neuroprotective activity, compound with α-oriented substituent group on the furohyperforin was active, while compound with β-oriented substituent group on the furohyperforin was inactive. The above results implied that the configuration of substituent in furohyperforin may be responsible for the neuroprotective activity of PPAPs derivatives.

3. Experimental

3.1. General experimental procedures

Optical rotations were determined on a JASCOP-1020 polarimeter (Jasco, Easton Japan). UV spectra were detected on a Shimadzu UV-2401PC spectrometer (Shimadzu, Tokyo, Japan). IR spectra were determined on a Bruker FT-IR Tensor-27 infrared spectrophotometer (Bruker, Germany) with KBr disks. ^{1}H, ^{13}C NMR and 2D NMR spectra were recorded on Bruker Avance III 600 MHz spectrometers (Bruker-Biospin, Billerica, USA), using TMS as an internal standard. ESIMS and HR-ESIMS analysis were carried out on Waters Xevo TQS and Agilent 1290 UPLC/6540 Q-TOF mass spectrometers (Agilent Technologies, Waldbronn, Germany), respectively. Column chromatography was performed on silica gel (300–400 mesh; Qingdao Marine Chemical Co. Ltd., Qingdao, China), Sephadex LH-20 (40–70 μm, Amersham Pharmacia Biotech AB, Uppsala, Sweden), Lichroprep RP-C18 gel (40–63 μm, Merck, Darmstadt, Germany). HPLC separation was performed on an instrument consisting of a Hanbon NP7005c controller, a Hanbon NP7005 pump, and a Hanbon NU3000c dual λ absorbance detector, Jiangsu, China ., and an X-bridge (250 × 10 mm) preparative column packed with C18 (5 μm). All solvents used for general chromatography were analytical grade (Sinopharm Chemical Reagents Co. Ltd., China), and the solvents used for HPLC were HPLC grade (Cinc High Purily Solvents, Shanghai, China). Fractions were monitored by TLC (GF 254, Qingdao Marine Chemical Co.,

Ltd., Qingdao, China), and spots were visualized by heating silica gel plates immersed in 5% H_2SO_4 in ethanol.

3.2. Plant material

The leaves and twigs of *Hypericum monogynum* were collected in December 2014, in Leishan, Guizhou Province of China, which were identified by Dr. Wei Gu. A voucher specimen (H20141201) was deposited at the Key Laboratory of Chemistry for Natural Products of Guizhou Province and Chinese Academy of Sciences.

3.3. Extraction and isolation

The air-dried ground plant material (8.0 kg) was extracted with methanol (50 L, three times) under reflux. The combined MeOH extracts were concentrated under reduced pressure to give a crude residue (1.5 kg), which was subsequently suspended in water and extracted with EtOAc (10L × 4). The EtOAc portion (200 g) was chromatographed on a silica gel column eluted with PE/EtOAc and then $CHCl_3$/MeOH to yield eight fractions (A–H).

Fraction C (24.0 g) was applied to a RP-C18 column, eluted with a gradient of MeOH/H_2O (60:40 → 100:0) to get three fractions (C1–C3). Fraction C1 (5.7 g) was isolated over a Sephadex LH-20 column (MeOH) to afford four fractions (C1a–C1d), subsequently, fraction C1b (2.1 g) was fractionated on silica gel column eluted with PE-EtOAc (petroleum ether-ethyl acetate) (100:1 to 0:1) and further purified by preparative HPLC with MeOH-H_2O (85:15, 2.0 ml/min) to afford **1** (5 mg, retention time: 32.2 min). Fraction C2 (15.0 g) was subjected to repeated silica gel columns eluted with PE-EtOAc and PE-acetone and further purified by preparative HPLC with MeOH − H_2O (90:10, 2.0 ml/min) to afford **7** (13 mg, retention time: 25.5 min), **8** (14 mg, retention time: 28.7 min), and **9** (21 mg, retention time: 30.1 min).

Fraction B (12.0 g) was purified on a Sephadex LH-20 (MeOH) column to give five fractions (B1-B5), and fraction B1 (2.1 g) was further purified by repeated silica gel columns eluted with a gradient of PE-$CHCl_3$ (30:1 to 0:1) to get B1a (900 mg) and B1b (700 mg), then B1a was purified by semi-preparative HPLC with MeOH − H_2O (90:10, 2.0 ml/min) to yield **3** (19 mg, retention time: 35.2 min) and **4** (28 mg, retention time: 37.9 min). B1b was purified by TLC chromatography with PE-EtOAc (4:1) to aford impure products, which were purified by HPLC (MeOH − H_2O, 90:10, 2.0 ml/min) to give **5** (16 mg, retention time: 34.2 min) and **6** (12 mg, retention time: 36.2 min). Compounds **2** (60 mg, retention time: 33.9 min) and **10** (18 mg, retention time: 35.7 min) were obtained from fraction B2 (4.2 g) by repeated silica gel columns eluted with a gradient of PE-chloroform and PE-EtOA.

3.3.1. Hypermonin C (1)

Light red oil; $[\alpha]^{25}_{D}$ + 99.4 (*c* 0.17, MeOH); UV (MeOH) λ_{max}(log ε) 246 (5.32) and 250 (5.36) nm; IR (KBr) ν_{max} 3440, 2967, 2924, 2855, 1632, 1530, 1484, 1383, 1227, 1179, 687, 580 cm^{-1}; ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectral data in $CDCl_3$, see Table 1; HRESIMS: *m/z* 541.2924 $[M + Na]^+$ (calcd for $C_{33}H_{42}O_5Na$, 541.2924).

3.4. Neuroprotective assay

Adherent PC12 cells in logarithmic growth phase were selected and cultured in 96-well plates at a density of $8*10^3$ cells/well with RPMI1640 medium containing 5% fetal bovine serum (FBS) and 5% horse serum (HS). After incubated at 37 °C and 5% CO_2 for 24 hours, replacing the serum-free complete medium and adding the corresponding concentration of the drug. After two hours, the appropriate concentration of the damaging agent was added to the medium in the model group and the drug-administered group, and the control group was added to the serum-free complete medium supplement system, and the culture was continued for 24 hours in the incubator. And then the MTT solution was added. The absorbance was measured at 570 nm using a microplate reader.

SH-SY5Y adherent cells in logarithmic growth phase were trypsinized and incubated with RPMI1640 medium containing 10% fetal bovine serum in 96-well culture plates at a concentration of 5×10^3/well. After incubating for 24 h at 37 °C in a 5% CO_2 incubator, the serum-free complete medium was replaced and the corresponding concentration of the drug was added. After 2 hours, the appropriate concentration of the damaging agent was added to the medium in the model group and the drug-administered group, and the control group was added to the serum-free complete medium supplement system, then the culture was continued for 24 hours in the incubator. And then the MTT solution was added. The absorbance was measured at 570 nm using a microplate reader.

Disclosure statement

No potential conflict of interest was reported by the authors.

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