# Lignanamides and Nonalkaloidal Components of *Hyoscyamus niger* Seeds

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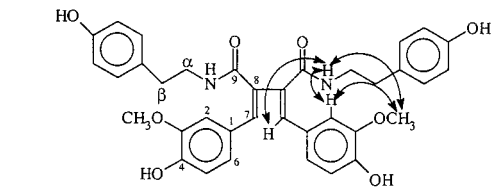
Four lignanamides, a tyramine derivative, and 10 other nonalkaloidal components were isolated from the seeds of *Hyoscyamus niger*. Among them, hyoscyamide (**1**), 1,24-tetracosanediol diferulate (**6**), and 1-*O*-(9*Z*,12*Z*-octadecadienoyl)-3-*O*-nonadecanoyl glycerol (**7**) are new structures. The other compounds were identified as grossamide, cannabisin D, cannabisin G, *N*-*trans*-feruloyl tyramine, 1-*O*-octadecanoyl glycerol, 1-*O*-(9*Z*,12*Z*-octadecadienoyl) glycerol, 1-*O*-(9*Z*,12*Z*-octadecadienoyl)-2-*O*-(9*Z*,12*Z*-octadecadienoyl) glycerol, 1-*O*-(9*Z*,12*Z*-octadecadienoyl)-3-*O*-(9*Z*-octadecenoyl) glycerol, rutin, vanillic acid, *β*-sitosterol, and daucosterol. Grossamide, and cannabisins D and G exhibited moderate cytotoxicity in cultured LNCaP human prostate cancer cells.

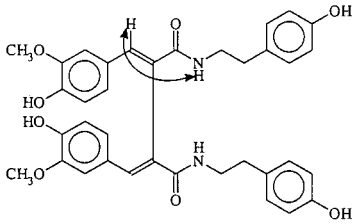
The genus *Hyoscyamus* (Solanaceae) is well known for the production of anticholinergic tropane alkaloids.[1] Crude drugs derived from this genus of plants, such as henbane (the leaves of *H. niger* L.), were used to relieve spasms of the gastrointestinal tract and to induce a sedative effect.[2] On the other hand, the seeds of *H. niger* L. are known as Tian-Xian-Zi (literally meaning Fairy Lady Seeds) in Chinese medicine and used as an antispasmodic, sedative, and analgesic agent, occasionally prescribed for the treatment of stomach cramps, heavy coughs, neuralgia, and manic psychosis.[3] This crude drug is classified as a "toxic drug" in Chinese medicine due to its narrow therapeutic window and potential toxicity.[4]

Previous chemical investigations have resulted in the isolation of a number of alkaloids from various part of *H. niger*. For example, hyoscyamine, its racemic form atropine, and scopolamine are often found in the leaves,[5] while the root part was reported to contain apoatropine (atropamine) and cuscohygrine.[6] Besides tropane alkaloids, seven nortropane alkaloids known as the calystegins have been found in *H. niger*.[7] While the alkaloidal contents of *H. niger* are well documented, its nonalkaloidal composition is poorly understood. As part of our studies on the chemical composition of potentially toxic Chinese herbal drugs,[8−13] we have reported on the isolation of withanolides from Tian-Xian-Zi.[10] Further studies have now led to the isolation of additional constituents. This paper reports the lignanamides and other nonalkaloidal compounds obtained from an extract of *H. niger* seeds, including four lignanamides (**1**−**4**), a tyramine derivative (**5**), a new ferulic acid ester derivative (**6**), and a new glycerol fatty acid ester (**7**), together with four glycerol fatty acid esters (**8**−**11**), rutin, vanillic acid, *β*-sitosterol, and daucosterol.

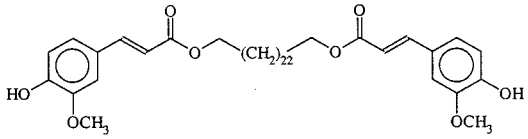
Hyoscyamide (**1**) was obtained as a yellow amorphous powder; several attempts to crystallize the compound in various solvents were unsuccessful. Its molecular formula, $C_{36}H_{36}N_2O_8$, was determined by HRFABMS. The $^1$H NMR spectrum and COSY data (Table 1) suggested the presence of three aromatic protons, an olefinic proton, a methoxyl group, and a tyramine moiety. These data were similar to those of *N*-*trans*-feruloyl tyramine (**5**), except for the



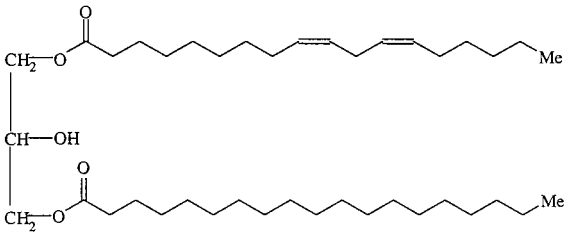
**1**



**4**



**6**



**7**

indicates NOE

presence of a singlet olefinic proton signal (*δ* 7.83) in the spectrum of **1** as compared to a pair of *trans* olefinic proton signals in the spectrum of **5**. The molecular formula of **1** was consistent with a dimer of feruloyl tyramine; thus the molecule appeared to be a symmetrical structure. In the HMBC spectrum of **1**, the proton signal at *δ* 7.83 exhibited long-range correlation with two aromatic methine carbon signals at *δ* 113.8 (C-2) and 128.5 (C-6), as well as with a carbonyl carbon signal at *δ* 169.3 (C-9). This information led to the assignment of the proton signal at *δ* 7.83 to H-7. Thus, it followed that the two units of feruloyl tyramine were connected between the C-8 and C-8′ positions. Ex-

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**Table 1.** NMR Data of Hyoscyamide (**1**)

| position | carbon shift | proton shift[a] | long-range $^1H-^{13}C$ correlation[b] |
|---|---|---|---|
| 1,1′ | 125.6 | | |
| 2,2′ | 113.8 | 7.15, 2H, d (2.0) | C-6, 6′ |
| 3,3′ | 151.5 | | |
| 4,4′ | 156.9 | | |
| 5,5′ | 118.6 | 6.66, 2H, d (8.3) | |
| 6,6′ | 128.5 | 6.98, 2H, dd (2.0, 8.3) | |
| 7,7′ | 143.0 | 7.83, 2H, s | C-2, 2′, 6, 6′, 9, 9′ |
| 8,8′ | 125.2 | | |
| 9,9′ | 169.3 | | |
| α,α′ | 43.6 | 3.43, 2H, p (6.8) | |
| | | 3.17, 2H, p (6.8) | |
| *β*,*β*′ | 36.4 | 2.47, 2H, p (6.8) | |
| | | 2.37, 2H, p (6.8) | |
| 1″,1‴ | 131.7 | | |
| 2″,6″ | 131.4 | 6.77, 2H, d (8.3) | C-4″, *β* |
| 3″,5″ | 117.1 | 6.57, 2H, d (8.3) | C-1″, 2″, 6″ |
| 2‴,6‴ | 131.4 | 6.77, 2H, d (8.3) | C-4‴, *β*′ |
| 3‴,5‴ | 117.1 | 6.57, 2H, d (8.3) | C-1‴, 2‴, 6‴ |
| 4″,4‴ | 157.7 | | |
| -$OCH_3$ | 56.7 | 3.66, 3H, s | C-3 |
| -$OCH_3$′ | 56.7 | 3.66, 3H, s | C-3′ |
| NH, NH′ | | 6.97, 2H, t (8.3)[c] | |

[a] Coupling constants (in Hz) are given in parentheses. [b] Results based on a standard HMBC spectrum. Listed are the carbon signals showing correlation with the indicated proton resonance. [c] Data obtained in DMSO. All other data were obtained in MeOH-$d_4$.

amination of the NMR spectral data of **1** further revealed similarity with those of cannabisin G (**4**), which is a dimer of (*E*)-*N*-feruloyl tyramine. However, a comparison of the DIFNOE (in DMSO) results of the two compounds revealed a significant difference. Specifically, the NH proton in **1** displayed an NOE with several proton signals [H-2 (*δ* 7.15), the methoxyl group (*δ* 3.66), and H-7 (*δ* 7.83)], whereas the NH proton of cannabisin G (**4**) only showed an NOE with H-7 (*δ* 7.83). Such a difference led to the assignment of a *Z* relation at the $C_7-C_8$ double bond in compound **1**, as compared with the *E* relationship in **4**. Therefore, compound **1** was established as a dimer of (*Z*)-*N*-feruloyl tyramine and given the trivial name of hyoscyamide.

Compounds **2**−**5** were identified as grossamide (**2**),[14−16] cannabisin D (**3**),[17] cannabisin G (**4**),[18] and *N*-*trans*-feruloyl tyramine (**5**),[15,19] respectively, by comparing their spectral properties with those reported in the literature. The lignanamides are a small group of natural products presumably biosynthesized by oxidative coupling during the process of lignan biosynthesis.[20,21]

Compound **6** was obtained as white amorphous powder; several attempts to crystallize the compound were unsuccessful. Its molecular formula, $C_{44}H_{66}O_8$, was established by HRFABMS. The COSY spectra displayed signals for three aromatic protons (*δ* 7.04, d, *J* = 2.0 Hz; *δ* 7.07, dd, *J* = 2.0, 8.4 Hz; *δ* 6.92, d, *J* = 8.4 Hz) and a pair of *trans* olefinic protons (*δ* 7.61, d, *J* = 15.6 Hz; *δ* 6.29, d, *J* = 15.6 Hz), attributed to a *trans*-feruloyl substructure. The NMR data further revealed an aliphatic structure that did not contain any terminal methyl group. Except for the signal at *δ* 64.6 (C-10, 10′), all aliphatic methylene carbons appeared as overlapping signals between *δ* 26.1 and 28.8. The HMBC spectrum displayed long-range coupling between $\delta_H$ 4.19 (H-10, 10′) and $\delta_C$ 167.3 (carbonyl carbon, C-9, 9′), suggesting an aliphatic alcohol ferulate structure. Finally, a symmetrical structure was implied by the molecular weight of the molecule. Indeed, the FABMS exhibited a fragment ion at *m*/*z* 369, corresponding to [$M^+$ − (2 × feruloyl) + 1]. The length of the aliphatic chain was estimated to contain 24 carbons based on the molecular mass. Compound **6** was thus determined to be 1,24-tetracosandiol diferulate.

Compound **7** was obtained as an oil. The HREIMS suggested a molecular formula $C_{40}H_{74}O_5$ for this compound. A comparison of the NMR data between compounds **7** and **9** indicated that the proton signals of the fatty acid portion were similar in these two structures, with the exception that the integration values for the signals at *δ* 2.34 (4H, t, *J* = 7.3 Hz, H-2′, 2″), *δ* 1.63 (4H, m, H-3′, 3″), and *δ* 0.89 (6H, t, *J* = 6.4 Hz, H-18′, 19′) in **7** doubled those in **9**. These data suggested the presence of two fatty acid chains in **7**. Two *cis* double bonds were implied by proton signals at *δ* 5.34 (4H, m, *J* < 7) and carbon signals at *δ* 130.2, 130.0, 128.0, and 127.9. In the CIMS spectrum, the ion fragments at *m*/*z* 263 $[C_{17}H_{31}CO]^+$ and 279 $[C_{17}H_{31}CO_2]^+$ were consistent with an octadecadienoyl structure, and signals at *m*/*z* 337 [$M^+ - C_{18}H_{37}CO_2$] and 353 [$M^+ - C_{18}H_{37}CO$] implied a glycerol octadecadienoate structure. It followed that the rest of the molecule could be a nonadecanoyl group. Finally, ion fragments at *m*/*z* 111, 137, 151, 165, and 179 were consistent with a 9,12-octadecadienoyl structure. Indeed, linoleic acid was detected on ODS TLC [MeOH−$H_2O$−acetic acid (4.2:0.4:0.4)] following hydrolysis. The $^1H$ NMR spectrum of **7** also displayed signals for a 1,3-disubstituted glycerol. The foregoing evidence led to the determination of compound **7** as 1-*O*-(9*Z*,12*Z*-octadecadienoyl)-3-*O*-nonadecanoyl glycerol. Naturally occurring glycerides containing nonadecanoyl ester are rare, an example being found in the fish oils.[22]

Four other glycerides were identified as 1-*O*-octadecanoyl glycerol (**8**),[23] 1-*O*-(9*Z*,12*Z*-octadecadienoyl) glycerol (**9**),[24] 1-*O*-(9*Z*,12*Z*-octadecadienoyl)-2-*O*-(9*Z*,12*Z*-octadecadienoyl) glycerol (**10**),[25] and 1-*O*-(9*Z*,12*Z*-octadecadienoyl)-3-*O*-(9*Z*-octadecenoyl) glycerol (**11**),[26] respectively, by interpretation of their physical and spectral data. Compound **11** was previously obtained by hydrolysis of vegetable oils,[26] and it is now reported for the first time as a naturally occurring compound. Rutin,[27] vanillic acid,[28] *β*-sitosterol,[29,30] and daucosterol[31] were also obtained during the course of isolation.

Compounds **1**−**11** were subjected to a screening test for cytotoxicity using human prostate cancer LNCaP cells. Grossamide ($IC_{50}$ = 33 *μ*M), cannabisin G ($IC_{50}$ = 76 *μ*M), and cannabisin D ($IC_{50}$ = 81 *μ*M) displayed low levels of inhibitory activity; other compounds were inactive ($IC_{50}$ > 100 *μ*M). Grossamide and cannabisin D have been shown previously to possess feeding deterrent properties.[32]

## Experimental Section

**General Experimental Procedures.** Melting points were measured on a Leica Galen III apparatus and uncorrected. IR spectra were recorded on a Perkin-Elmer 16PC FTIR spectrometer. $^1H$ and $^{13}C$ NMR data were obtained from a JEOL JNM-EX-400 FT-NMR spectrometer at 400 and 100 MHz, respectively, with TMS as internal standard. EIMS, CIMS, and FABMS were determined on a Finnigan TSQ7000 mass spectrometer; HRFABMS data were obtained from a Bruker APEX FT-MS instrument. For the bioassay, human prostate cancer LNCaP cell line was obtained from the American Type Culture Collection (ATCC CRL1740) and maintained in RPMI supplemented with 10% fetal bovine serum (FBS), 100 *μ*g/mL streptomycin, and 100 IU/mL penicillin at 37 °C in a humidified atmosphere of 5% $CO_2$.

**Plant Material.** The seeds of *Hyoscyamus niger* were obtained from a herbal drug supplier in Beijing in 1994 and authenticated at the National Institute for the Control of Pharmaceutical and Biological Products, Beijing. A voucher specimen (Ma-94-015) has been deposited in the herbarium of the same institution.

**Extraction and Isolation.** Air-dried seeds of *H. niger* (5 kg) were ground and defatted with hexane before being extracted with 95% EtOH at room temperature. The EtOH extract was concentrated and partitioned between $CHCl_3$ and $H_2O$. A precipitate (50 g) obtained from the interface between the $CHCl_3$ and $H_2O$ layers was dissolved in MeOH and chromatographed over Si gel eluted with mixtures of $CHCl_3$−MeOH of increasing polarity. The effluents were combined into 11 fractions based on their TLC patterns. Fraction 2 was purified by Si gel chromatography washed with $CHCl_3$-(saturated with $NH_3$)−MeOH mixtures to afford grossamide (**2,** 300 mg). Fraction 4 was purified on Sephadex LH-20 eluted with MeOH, followed by Si gel chromatography using $CHCl_3$−MeOH−$N(CH_2CH_3)_3$ mixtures as the mobile phase, and finally by ODS chromatography eluted with a mixture of MeOH−$H_2O$ (1:1) to afford cannabisin D (**3**, 85 mg). Fraction 6 was further separated by Si gel chromatography eluted with $CHCl_3$−MeOH−$NH_3$ mixtures. The major fractions were further purified by Si gel chromatography using a mixture of $CHCl_3$−EtOAc as solvent and followed by Si gel preparative TLC developed in a mixture of $CHCl_3$−EtOAc−MeOH (3:5:0.3), from which hyoscyamide (**1,** 7 mg) was obtained. Fraction 7 was separated by Si gel chromatography using a mixture of $CHCl_3$−MeOH as the mobile phase and purified on Si gel preparative TLC developed by a mixture of $CHCl_3$−MeOH (4.1: 0.9) to afford cannabisin G (**4**, 35 mg) and *N-trans*-feruloyl tyramine (**5**, 30 mg).

The aqueous portion of the original EtOH extract was washed with $CHCl_3$ and n-BuOH successively. The $CHCl_3$-soluble part (2.5 g) was chromatographed over Si gel using mixtures of $CHCl_3$−MeOH as the mobile phase. The effluents were combined into 10 fractions based on TLC patterns. Fraction 2 was purified by Si gel chromatography eluted with a hexane−acetone mixture to afford $\beta$-sitosterol (12 mg). Fraction 5 was further purified by Si gel chromatography using a $CHCl_3$−acetone mixture to afford **6** (10 mg). Fraction 8 was purified by Si gel chromatography using a $CHCl_3$−MeOH mixture to afford daucosterol (20 mg).

The BuOH-soluble part (28 g) was chromatographed over ODS gel using mixtures of MeOH−$H_2O$ as the mobile phase. The effluents were combined into 10 fractions based on TLC patterns. Fraction 3 was purified by ODS chromatography eluted with MeOH−$H_2O$ mixture to afford vanillic acid (4 mg). Fraction 7 was purified by ODS chromatography eluted with a MeOH−$H_2O$ mixture to afford rutin (50 mg).

The hexane-soluble part (200 mL of oil) was separated on a Si gel column using hexane and mixtures of hexane−acetone of increasing polarities as the solvent system. The effluents were combined into four fractions based on their TLC patterns. Fraction 1 was purified by ODS chromatography using a mixture of MeOH−$H_2O$ (9:1) to afford **10** (900 mg), **7** (20 mg), and **11** (60 mg). Fractions 3 and 4 were further purified by Si gel chromatography eluted with a hexane−acetone mixture to afford **8** (85 mg) and **9** (200 mg).

Known compounds were identified by interpretation of their NMR and other physical data and by comparison with literature values.

**Hyoscyamide (1):** yellow amorphous powder; $C_{36}H_{36}N_2O_8$; HRFABMS *m/z* 625.2532 [M$^+$+1] (calcd 625.2549); $^1$H and $^{13}$C NMR, see Table 1.

**1,24-Tetracosandiol diferulate (6):** white amorphous powder; $C_{44}H_{66}O_8$; HRFABMS *m/z* 723.4818 [M$^+$+1] (calcd 723.4836); FABMS *m/z* 723 [M$^+$ + 1], 369 [M$^+$ − 2×feruloyl +1], 323 [$C_{23}H_{46}$ + H]$^+$, 194 [ferulic acid]$^+$, 177 [feruloyl group]$^+$; IR $\nu_{max}$ (KBr) 3422, 2918, 2850, 1712, 1630, 1596, 1518, 1466, 1272, 1174, 816, 720 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61 (2H, d, $J$ = 15.6 Hz, H-7,7′), 7.07 (2H, dd, $J$ = 2.0, 8.4 Hz, H-6,6′), 7.04 (2H, d, $J$ = 2.0 Hz, H-2,2′), 6.92 (2H, d, $J$ = 8.4 Hz, H-5,5′), 6.29 (2H, d, $J$ = 15.6 Hz, H-8,8′), 5.88 (bs, −OH), 4.19 (4H, t, $J$ = 6.6 Hz, H-10,10′), 3.93 (6H, s, H-$OCH_3$, $OCH_3$′), 1.68 (4H, p, $J$ = 7.2 Hz, H-11,11′), 1.40−1.25 (44H, overlapped, H-11−21, 11′−21′); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.3 (C-9,9′), 147.8 (C-3,3′), 146.6 (C-4,4′), 144.5 (C-7,7′), 126.9 (C-1,1′), 122.9 (C-6,6′), 115.6 (C-8,8′), 114.6 (C-5,5′), 109.2 (C-2,2′), 64.6 (C-10,10′), 56.0 (C-$OCH_3$, $OCH_3$′), 28.8 (C-11,11′), 29.7−26.1 (C-11−21, 11′−21′).

**1-*O*-(9*Z*,12*Z*-Octadecadienoyl)-3-nonadecanoyl glycerol (7):** oil, $C_{40}H_{74}O_5$; HREIMS *m/z* 634.5516 M$^+$ (calcd 634.5536); EIMS *m/z* 634 [M$^+$], 149, 135, 111, 109; CIMS ($CH_4$) *m/z* 635 [M$^+$ + 1], 353 [M$^+$ − 281], 337 [M$^+$ − 297], 279 [$C_{17}H_{31}$-$CO_2$]$^+$, 263 [$C_{17}H_{31}CO$]$^+$, 179, 165, 154, 151, 137, 123, 111, 109; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.34 (4H, m, H-9′, 10′, 12′, 13′), 4.14 (4H, m, H-1a, 1b, 3a, 3b), 3.73 (1H, m, H-2), 2.77 (2H, t, $J$ = 7.3 Hz, H-11′), 2.34 (4H, t, $J$ = 7.3 Hz, H-2′, 2″), 2.05 (4H, q, $J$ = 6.8 Hz, H-8′, 14′), 1.63 (4H, m, H-3′, 3″), 1.31 (44H, m), 0.89 (6H, t, $J$ = 6.40, H-18′, 19″); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.9 (C-1′, C-1″), 130.2, 130.0, 128.1, 127.9 (C-9′, 10′, 12′, 13′), 68.4 (C-2), 65.1 (C-1, C-3), 34.1 (C-2′, C-2″), 31.7, 31.5 (C-16′, 16″), 29.7−29.0 (18 × C), 27.7, 27.2 (C-8′, 14′), 25.6 (C-11′), 24.9 (C-3′, 3″), 22.6 (C-17′, 17″), 14.1,14.0 (C-18′, 19″).

**1-*O*-(*cis*,*cis*-9,12-Octadecadienoyl)-3-*O*-(*cis*-9-octadecenoyl) glycerol (11):** oil, $C_{39}H_{70}O_5$; CIMS ($CH_4$) *m/z* 619 [M$^+$ + 1], 339 [M$^+$ − 279], 337 [M$^+$ − 281], 263 [$C_{17}H_{31}CO$]$^+$, 193, 181, 179, 167, 165, 153, 151, 139, 137, 111; EIMS *m/z* 619 [M$^+$ + 1], 353 [M$^+$ − 265], 339, 262, 178, 164, 149, 135, 109; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.30 (6H, m, H-9′, 10′, 12′, 13′, 9″, 10″), 4.14 (4H, m, H-1a, 1b, 3a, 3b), 3.73 (1H, m, H-2), 2.77 (2H, t, $J$ = 6.8 Hz, H-11′), 2.32 (4H, t, $J$ = 7.8 Hz, H-2′, 2″), 2.04 (8H, m, H-8′, 14′, 8″, 11″), 1.63 (4H, m, H-3′, 3″), 1.30 (34H, m), 0.88 (6H, m, H-18′, 18″); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.8 (C-1′, C-1″), 130.1, 129.9, 129.6, 128.0, 127.8 (C-9′, 10′, 12′, 13′, 9″, 10″), 68.2 (C-2), 65.0 (C-1, C-3), 34.2, 34.0 (C-2′, C-2″), 31.8, 31.5 (C-16′, 16″), 29.7−29.0 (13 × C), 27.1 (C-8′, 14′, 8″, 11″), 25.6 (C-11′), 24.8 (C-3′, 3″), 22.6, 22.5 (C-17′, 17″), 14.0 (C-18′, 18″).

**Hydrolysis of 7.** Compound **7** (10 mg) was dissolved in MeOH (2 mL), to which a solution of MeOH−$H_2O$ (1:1) (containing 0.5 N NaOH, 3 mL) was added. The mixture was refluxed for 1 h. After cooling, the solution was neutralized with acetic acid and evaporated to dryness. The residue was dissolved in $CHCl_3$ and chromatographed on a ODS TLC using MeOH−$H_2O$−acetic acid (4.2:0.4:0.4). Linoleic acid was detected by comparing with an authentic sample.

**Cytotoxicity Assay.** LNCaP cells (2 × 10$^5$ cells/well/0.1 mL) were cultured in 96-well culture plates (Nunc, Denmark) in the presence of different concentrations of test compounds for 48 h at 37 °C in a 5% $CO_2$ incubator. Cells were then treated with MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) at 37 °C for 4 h. The reaction product, formazan, was extracted with anhydrous dimethyl sulfoxide (DMSO), and the absorbance was read at 540 nm. All experiments were performed in triplicate.

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