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Schisanhenol derivatives and their biological evaluation against tobacco mosaic virus (TMV)

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ABSTRACT

Schisanhenol (**Sol**) was isolated from *Schisandra rubriflora*, and a series of derivatives (**1–16**, **15a-16a**, and **15b-16b**) were designed and prepared by chemical modification. The curative and protective effects of these dibenzocyclooctadiene lignan analogues against tobacco mosaic virus (TMV) were evaluated. Most analogues exhibited stronger protective effects than the positive control ningnanmycin. Dibromoschisanhenol (**6**) at 0.25 mM exhibited the strongest protective activity (83.5 ± 1.8% at 0.25 mM), and 14-(3, 5-dibenzyloxy)-benzoyloxyschisanhenol (**16**) showed a significant curative effect (78.0 ± 3.8% at 0.15 mM) that was much stronger than that of the commercial virucide ningnanmycin. This study is the first to demonstrate that natural dibenzocyclooctadiene lignans and analogues are active against plant viruses.

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1. Introduction

Pesticides are substances that attract and/or destroy pests [1]. They are defined by the Food and Agriculture Organization (FAO) as any substance or mixture of substances intended to prevent, destroy, or control any pest, including herbicides, algicides, avicides, virucides, rodenticides, insecticides, nematicides, plant regulators, defoliants, and desiccants [2]. Pesticides are one of the most important contributors to increase grain output. However, the growing research suggests that many pesticides are potentially toxic to humans and other desirable species and may leave environmental residues [3]. For the increased productivity and the enhanced quality of life, people increasingly seek pesticides with decreased environmental impact and demand less toxic pesticides to protect the environment [4–6]. Therefore, biogenic pesticides that developed from living organisms and that possess high efficiency, low toxicity, and high biocompatibility are increasingly a major research focus [7–10].

Viruses are an important class of crop pathogens and are known as "plant cancer" because of their great harmfulness and difficulty controlling their effects [11]. Tobacco mosaic virus (TMV) is a typical plant virus, and TMV research has made a significant contribution to the development of viral biology [11]. TMV is distributed globally. More than 500 species of plants from 36 families are known to be infected by TMV [12]. Many crops, including tobacco, tomatoes, potatoes, peppers, and cucumbers, are damaged by TMV, which causes more than $100 million in global losses annually [13]. No generally accepted anti-TMV compound has been found to date. Thus, TMV inhibitors are an important focus of current pesticide research and development.

Ningnanmycin, which is isolated from *Streptomyces noursei* var., is active against TMV and cucumber mosaic virus (CMV) [14]. However, its use is limited because of unsatisfactory cure rates and high control costs [15]. Many plant viruses

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have developed resistance as more pesticides are being used in agriculture. A novel biogenic TMV inhibitor with low toxicity, high selectivity and environmental compatibility is urgently needed.

The lignans are a group of natural products found in plants, which serve an antioxidant role in the plant's defenses against biotic and abiotic factors, and have shown anti-inflammatory and antioxidant activity in basic research models of human diseases [16]. Among these lignans, dibenzocyclooctadiene lignans interested us because of their important bioactivity and pharmacological activity against many pathogens and disorders, including peroxidation, hepatitis, tumours, and HIV-1 [17]. Dibenzocyclooctadiene lignans are natural products that are present in many species of the Schisandraceae family. Up to now, most studies on dibenzocyclooctadiene lignans were mainly focused on the hepatoprotective activity or other effects to human disease, and no investigation on these lignans or their derivatives against TMV has been reported [17].

Schisanhenol (**Sol**) is an important dibenzocyclooctadiene lignan from *Schisandra rubriflora* [18]. In the course of our research into derivatives of **Sol** and their bioactivities, we discovered novel compounds with strong activity against TMV. Here, we report a series of novel **Sol** derivatives (**1**–**16**, **15a**–**16a**, and **15b**–**16b**) obtained through the chemical modification of halogenation, oxidation, nitration, and acylation. Their anti-TMV activities and structure-activity relationships (SAR) are reported.

2. Experimental

2.1. General

Unless otherwise noted, all solvents and reagents were freshly distilled or purified using standard procedures. Nuclear magnetic resonance (NMR) spectra were obtained using an INOVA-400 MHz NMR spectrometer with $CDCl_3$ at room temperature; the chemical shifts are shown relative to tetramethylsilane (TMS). High resolution electron impact mass spectra (HR-EI-MS) were obtained using a Waters Autospec Premier P776 spectrometer. Analytical thin layer chromatography (TLC) was performed using precoated plates (silica gel GF254); spots were visualised with ultraviolet (UV) light and 5% H_2SO_4 in ethanol. The following abbreviations are used to designate multiplets: s = singlet, d = doublet, t = triplet, m = multiplet, and br.s = broad singlet. All first-order splitting patterns were assigned based on appearance. Schisanhenol (**Sol**) was isolated and purified from *S. rubriflora*. Compounds **1**, **3**, **5**–**8** and **12** were synthesised as previously described [17]. 1-Bromoethylbenzyl sulphide (**i**), 4-benzyloxylbenzoyl chloride (**ii**), and 3, 5-dibenzyloxylbenzoyl chloride (**iii**) were prepared according to a previously reported method [20–23].

2.2. Chemistry

2.2.1. Preparation of 4-chloro-11-bromoschisanhenol (*2*)

4-Chloro-11-bromoschisanhenol (**2**) was obtained from **1**. Bromine (10 μl) was added to a solution of 4-chloroschisanhenol (**1**, 197 mg, 0.45 mmol) in MeOH (6 ml). The solution was stirred in the dark at 20 °C for 24 h until the reaction was complete (based on TLC monitoring). A solution of 10% $Na_2S_2O_3$ was added dropwise until the solution lost its colour. The solution was extracted three times with ethyl acetate. The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated. The crude product was subjected to column chromatography on silica gel eluting with a gradient of petroleum ether and ethyl acetate (5:1 to 1:1) to afford **2** as a yellowish solid (144.5 mg, yield 56.3%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.73 (br.s, 1H, OH), 4.00 (s, 3H, 3 × $ArOCH_3$), 3.97 (s, 6H, 2 × $ArOCH_3$), 3.91 (s, 3H, $ArOCH_3$), 3.61 (s, 3H, $ArOCH_3$), 2.56 (d, 1H, J = 13.6 Hz, $ArCH_2$), 2.36 (m, 1H, $ArCH_2$), 2.25 (d, 1H, J = 14.0 Hz, $ArCH_2$), 2.00 (br.s, 1H, $ArCH_2$), 1.80 (br.s, 1H, CH), 1.65 (s, 1H, CH), 1.09 (d, 3H, J = 5.6 Hz, CH_3), 0.84 (d, 3H, J = 5.6 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 151.1 (s), 150.6 (s), 148.0 (s), 145.5 (s), 144.5 (s), 138.8 (s), 138.4 (s), 133.1 (s), 125.1 (s), 120.6 (s), 120.2 (s), 114.6 (s), 61.3 (q), 61.0 (q, 2 × C), 60.9 (q), 60.7 (q), 39.1 (d), 34.3 (t), 34.2 (t), 29.8 (d), 20.9 (q), 10.2 (q). HR-EI-MS (m/z): 514.0741 $[M]^+$ (calcd for $C_{23}H_{28}O_6ClBr$, 514.0758).

2.2.2. Preparation of 11-bromoschisanhenol (*4*)

Bromine (10 μl) was added to a solution of **Sol** (502 mg, 1.25 mmol) in carbon tetrachloride (20 ml). The solution was stirred in the dark at 20 °C until the reaction was complete (based on TLC), and a solution of 10% $Na_2S_2O_3$ was then added dropwise until the solution lost its colour. The solution was extracted three times with ethyl acetate. The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated, and the crude product was subjected to column chromatography on silica gel eluting with a gradient of petroleum ether and ethyl acetate (5:1) to afford **4** as a yellowish solid (104.0 mg, yield 17.3%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.40 (s, H. Ar-H), 5.81 (br.s, 1H, OH), 3.95 (s, 3H, $ArOCH_3$), 3.92 (s, 6H, 2 × $ArOCH_3$), 3.90 (s, 3H, $ArOCH_3$), 3.65 (s, 3H, $ArOCH_3$), 2.61 (m, 1H, $ArCH_2$), 2.50 (m, 2H, $ArCH_2$), 2.31 (m, 1H, $ArCH_2$), 1.91 (m, 1H, CH), 1.83 (m, 1H, CH), 1.09 (d, 3H, J = 6.8 Hz, CH_3), 0.81 (d, 3H, J = 6.8 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 150.7 (s), 150.6 (s), 146.5 (s), 144.4 (s), 138.9 (s, 2 × C), 134.3 (s), 133.6 (s), 125.7 (s), 116.6 (s), 114.6 (s), 107.3 (d), 61.1 (q), 61.0 (q), 60.9 (q, 2 × C), 55.7 (q), 38.9 (d), 38.5 (t), 34.2 (t), 33.3 (d), 21.0 (q), 12.9 (q). HR-EI-MS (m/z): 480.1153 $[M]^+$ (calcd for $C_{23}H_{29}O_6Br$, 480.1148).

2.2.3. Preparation of 12-demethylschisanhenol (*9*)

A solution of **Sol** (300 mg, 0.75 mmol) in acetic acid (50 ml) was added to a mixed acid solution (Ac_2O/95% HNO_3, 2:7 v:v; 8 ml) while cooled with ice. The solution was stirred at 0–5 °C for 5 h and then at room temperature for 24 h until the reaction was complete based on TLC. After being quenched with water and extracted three times with diethyl ether, the residue was purified with RP-18 silica gel column chromatography eluting with a gradient of MeOH and H_2O (7:3). After preparative TLC, **9** was obtained as a white solid (97.8 mg, yield 33.8%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.63 (s, 1H, Ar-H), 6.43 (s, 1H, Ar-H), 5.78 (br.s, 1H, OH), 5.64 (br.s, 1H, OH), 3.96 (s, 9H, 3 × OCH_3), 3.53 (s, 3H, OCH_3), 2.67 (m, 2H, $ArCH_2$), 2.35 (m, 1H, $ArCH_2$), 2.11 (d, 1H, J = 13.2 Hz, $ArCH_2$), 1.95 (br.s, 1H, CH), 1.82 (br.s, 1H, CH), 1.05 (d, 3H, J = 6.8 Hz, CH_3), 0.81 (d, 3H, J = 6.4 Hz, CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 150.6 (s), 147.3 (s), 146.7 (s), 144.5 (s), 135.8 (s), 135.4 (s), 134.4 (s), 133.8 (s), 120.3 (s), 116.5 (s), 107.4 (d), 107.1 (d), 61.0 (q), 60.5 (q), 56.0 (q), 55.7 (q), 40.8 (d), 39.2 (t), 35.3 (t), 33.6 (d),

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