ABSTRACT: Three isoindolinone alkaloids (1–3), including one new isoindolinone-type alkaloid, meyeroguilline E (1), and six other known compounds (4–9) were isolated from the poisonous mushroom Chlorophyllum molybdites (Agaricaceae). The structure of the new compound was determined using extensive spectroscopic analyses via one-dimensional (1D) and two-dimensional (2D) NMR data interpretation and high-resolution electrospray ionization mass spectrometry (HR-ESI-MS). To the best of our knowledge, compound 1 is the first example of a natural isoindolinone with a butanoic acid moiety, and this study is the first to detect the other known compounds (2–9) in C. molybdites. The isolated compounds (1–9) were examined for their multidrug resistance (MDR) reversal activity against MES-SA, MES-SA/DX5, HCT15, and HCT15/CL02 human cancer cells. Based on the results, 20 μM of compounds 3 and 6 slightly potentiated paclitaxel (TAX)-induced cytotoxicity in MES-SA/DX5, HCT15, and HCT15/CL02 cells; however, the compounds had no effect on the cytotoxicity against MES-SA and nonMDR cells.

1. INTRODUCTION

Chlorophyllum molybdites (Meyer ex Fr.) Mass. (Agaricaceae), a false parasol or green-spored parasol, is a widespread poisonous mushroom that usually grows on lawns and parks in tropical and subtropical regions. This poisonous mushroom is also distributed in a restricted area throughout Korea and Japan. Owing to a mushroom poisoning accident, C. molybdites has been reported to be a gastrointestinal irritant for over a century in many countries, including North America. Further, there are increasing reports of C. molybdites poisoning worldwide each year. The representative toxin of C. molybdites, which causes serious gastrointestinal discomfort that can last 1–6 h after ingestion, is a toxic protein called molybdrophtylin. Previous chemical investigation of this mushroom revealed the presence of two pyrrolidine alkaloids, lepiothins A and B, α-methylglyceric acid, fatty acid derivatives, simple alkaloids, and steroid derivatives. In particular, some steroids isolated from C. molybdites were reported to exert cytotoxicity against human gastric carcinoma Kato III cells, with IC₅₀ values ranging from 2.69 to 14.27 μg/mL.

As part of the continuing research to isolate bioactive novel natural products and elucidate their structures from diverse natural resources, we investigated potentially bioactive metabolites from poisonous mushrooms. In the present study, the bioactive compounds from a methanol (MeOH) extract of the fruiting bodies of C. molybdites were assessed using liquid chromatography–mass spectrometry (LC/MS)-guided analysis. The MeOH extract of C. molybdites fruiting bodies was subjected to solvent partitioning and intensive chemical analysis using repeated column chromatography and semipreparative HPLC. This separation process led to the isolation of three isoindolinone alkaloids (1–3) and six other known compounds (4–9). The structure of the new compound (1) was established via detailed one-dimensional (1D) and two-dimensional (2D) NMR and high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) analyses. Herein, the isolation and structural determination of compounds 1–9 have been described, and their multidrug resistance (MDR) reversal activity has been determined.

2. RESULTS AND DISCUSSION

2.1. Isolation and Structural Elucidation of Compounds 1–9. The MeOH extract of the fruiting bodies of C. molybdites was subjected to solvent partitioning using four organic solvents, namely, hexane, CH₂Cl₂, EtOAc, and BuOH. The four main fractions derived from solvent partitioning, i.e., hexane-, CH₂Cl₂-, EtOAc-, and BuOH-soluble fractions, were...
subjected to LC/MS analysis, which revealed that the CH$_2$Cl$_2$- and EtOAc-soluble fractions contained metabolites of interest, including N-containing compounds. Accordingly, the CH$_2$Cl$_2$- and EtOAc-soluble fractions were subjected to intensive chemical analysis by repeated column chromatography and semipreparative HPLC under the guidance of LC/MS analysis (Figure 1). This analysis led to the isolation of three isoindolinone alkaloids (1–3) (Figure 2), including one new isoindolinone-type alkaloid, meyeroguilline E (1), and six other known compounds (4–9).

Meyeroguilline E (1) was isolated as a white powder. Further, the HR-ESI-MS data of 1 revealed quasi-molecular ion peaks of [M + Na]$^+$ at m/z 288.0845 (calculated for C$_{13}$H$_{15}$NO$_5$Na, 288.0848) and [2M + Na]$^+$ at m/z 553.1794 (calculated for C$_{26}$H$_{30}$N$_2$O$_{10}$Na, 553.1798) in the positive-ion mode (Figure S1), which aligns with the molecular formula C$_{13}$H$_{15}$NO$_5$. Of note, this molecular formula was corroborated by the NMR spectroscopic data (Table 1). The IR spectrum of 1 exhibited absorption bands for the hydroxyl (3440 cm$^{-1}$) and carbonyl (1712 and 1620 cm$^{-1}$) groups, and its $^1$H NMR spectrum (Table 1 and Figure S2) revealed the presence of resonances for two meta-coupled aromatic protons at $\delta$H 6.67 (1H, d, $J = 2.0$ Hz) and 6.47 (1H, d, $J = 2.0$ Hz); four methylenes at $\delta$H 4.30 (2H, s), 3.63 (2H, t, $J = 7.0$ Hz), 2.38 (2H, t, $J = 7.0$ Hz), and 1.99 (2H, m); and one methoxy group OCH$_3$ at $\delta$H 3.58, s 47.8 CH$_2$

| position | $\delta$H | $\delta$C |
|----------|-----------|-----------|
| 1        | 169.6 C   |           |
| 3        | 4.30, s   | 47.2 CH$_2$|
| 3a       |           | 118.9 C   |
| 4        |           | 153.1 C   |
| 5        | 6.47, d (2.0) | 105.4 CH |
| 6        |           | 159.1 C   |
| 7        | 6.67, d (2.0) | 99.9 CH  |
| 7a       |           | 133.0 C   |
| 8        | 3.63, t (7.0) | 41.3 CH$_2$|
| 9        | 1.99, m   | 23.1 CH$_2$|
| 10       | 2.38, t (7.0) | 30.4 CH$_2$|
| 11       |           | 173.7 C   |
| OCH$_3$  | 3.58, s   | 47.8 CH$_2$|

Coupling constants (Hz) are presented in parentheses, and the $^{13}$C NMR data were assigned based on the HSQC and HMBC experiments.
at $\delta_{\text{H}}$ 3.58 (3H, s). The $^{13}$C NMR data (Table 1) revealed 13 carbon resonances comprising six nonprotonated carbons [$\delta_{\text{C}}$ 173.7, 169.6, 159.1, 153.1, 133.0, and 118.9], two protonated aromatic carbons [$\delta_{\text{C}}$ 105.4 and 99.9], four methylene carbons [$\delta_{\text{C}}$ 47.2, 41.3, 30.4, and 23.1], and one methyl carbon [$\delta_{\text{C}}$ 47.8]. The above NMR data suggest that compound 1 was similar to meyeroguilline D ($\Delta$3), except for the presence of an additional methylene group and one methoxy group in 1. Accordingly, compound 1 could be an analogue belonging to the isoidolinone class. Detailed analysis of the $^1$H→$^1$H COSY and heteronuclear single quantum coherence (HSQC) data (Figures S3 and S4) indicated the presence of one spin fragment of H$_2$-8/H$_2$-9/H$_2$-10 (Figure 3). The heteronuclear multiple bond correlation (HMBC) correlations from H$_2$-9 to C-11 and OCH$_3$ to C-11 confirmed the methoxyl group at C-11, indicating the presence of butanoic acid methyl ester as a side chain (Figure S5). The HMBC correlations from H-5 to C-3a and C-7; from H-7 to C-1, C-3a, and C-5; and from H$_2$-3 to C-3a and C-7a constructed an isoidolinone moiety, and the linkage of the butanoic acid methyl ester to N-2 of the isoidolinone core was established by the HMBC correlation from H$_2$-8 to C-3 and C-1 (Figure 3). Hence, the chemical structure of 1 was elucidated, as shown in Figure 2, and named meyeroguilline E. To the best of our knowledge, compound 1 is the first example of a natural isoidolinone with a butanoic acid moiety.

The known compounds were identified as 4,6-dihydroxy-2,3-dihydro-1H-isoindol-1-one (2),$^{20}$ meyeroguillines D (3),$^{19}$ S'-methylthioadenosine (4),$^{21}$ (E)-2-decenedioic acid (5),$^{22}$ pantheric acid C (6),$^{23}$ S'-phenylisoxazole (7),$^{24}$ benzoic acid (8),$^{25}$ and 5,10-dihydrobenzo[g]pteridine-2,4-(1H,3H)-dione (9) $^{26}$ (Figure 4) based on a comparison of their NMR spectroscopic data with reported values and the results of LC/MS analysis. To the best of our knowledge, all known compounds (2–9) were isolated for the first time from C. molybdites. Among the substances isolated from C. molybdites, S'-methylthioadenosine (4) is called S'-methylthioadenosine (MTA) and is the S-methyl derivative of adenosine. MTA is an intermediate in the methionine salvage pathway, also called the S'-methylthioadenosine (MTA) cycle, which recycles the sulfur of MTA, a byproduct of the biosynthesis of polyamine and the plant hormone, ethylene.$^{27}$ As the source of the sulfur atom in MTA, methionine (MET) was first identified in 1923, and the methyl group of MTA is derived from S'-adenosylmethionine, which is synthesized from MET and adenosine triphosphate (ATP) through the catalysis of MET adenosyltransferases.$^{28}$

![Figure 3. Key $^1$H→$^1$H COSY (bold blue line) and HMBC (red arrows) correlations of compound 1.](image)

2.2. Evaluation of the Multidrug Resistance (MDR) Reversal Activity of the Isolated Compounds. According to our previous study,$^{29}$ isoidolinone alkaloids isolated from the mushroom Hericium erinaceum showed cytotoxic activity against the human cancer cell lines, A549, SK-OV-3, SK-MEL-2, and HCT-15. Based on these results, the cytotoxic activity of the isoidolinone alkaloids and the other known compounds identified in C. molybdites was investigated. All compounds tested in this study had little effect on the growth of A549, SK-OV-3, SK-MEL-2, and HCT-15 human cancer cells up to 30 $\mu$M (data not shown).

The MDR reversal activities of these compounds were tested in the human colorectal cancer cell line (HCT15), doxorubicin-resistant HCT15/CL02 cells, uterine carcinoma cell line (MES-SA), and doxorubicin-resistant MES-SA/DX5 cells. The cytotoxicity of paclitaxel (TAX) against the MES-SA, MES-SA/DX5, HCT15, and HCT15/CL02 human cancer cells increased in a concentration-dependent manner. The effects of the compounds tested in this study and verapamil (VER) on the cytotoxicity of TAX in these cells are summarized in Table 2. The EC$_{50}$ of TAX was 0.81, 1251.14, 25.64, and 91.73 nM against MES-SA, MES-SA/DX5, HCT15, and HCT15/CL02 cells, respectively (Table 2). These data indicate that the MES-SA/DX5 and HCT15/CL02 cells were more resistant to TAX than parental MES-SA and HCT15 cells by approximately 1544.6- and 3.6-fold, respectively. The isolated compounds did not inhibit cell growth at the experimental concentration of 20 $\mu$M (data not shown). However, 20 $\mu$M of compounds 3 and 6 slightly potentiated TAX-induced cytotoxicity in MES-SA/DX5, HCT15, and HCT15/CL02 cells (Figure 5). When 100 nM

![Figure 4. Structures of the known compounds (4–9).](image)

| compounds co-treated | cytotoxicity of paclitaxel (EC$_{50}$μM) |
|---------------------|------------------|
|                      | MES-SA | MES-SA/DX5 | HCT15 | HCT15/CL02 |
| none                | 0.81   | 1251.14     | 25.64  | 91.73      |
| 1                   | 0.93   | 1009.24     | 27.18  | 84.52      |
| 2                   | 0.86   | 1204.27     | 24.73  | 93.44      |
| 3                   | 1.07   | 643.92      | 13.49  | 22.71      |
| 4                   | 0.79   | 1012.80     | 23.18  | 94.75      |
| 5                   | 0.76   | 1013.39     | 30.27  | 108.76     |
| 6                   | 0.92   | 834.65      | 21.07  | 24.78      |
| 7                   | 0.90   | 988.46      | 26.14  | 81.45      |
| 8                   | 1.04   | 1067.45     | 20.84  | 62.91      |
| 9                   | 0.95   | 1087.96     | 23.48  | 64.35      |
| VER                 | 0.81   | 96.43       | 0.28   | 0.75       |

*EC$_{50}$: effective concentration that induces 50% cell growth inhibition.

$^{a}$EC$_{50}$ values are reported for the cytotoxicity of paclitaxel against human cancer cell lines.
of TAX was employed, the survival fraction against HCT15 cells was shifted by compounds 3 and 6 from 0.43 to −14.59 and −25.01, respectively. For HCT15/CL02 cells, compounds 3 and 6 enhanced the survival fraction from 46.94 to 28.40 and 19.65 at 100 nM TAX, and −11.66 to −33.93 and −41.46 at 1000 nM TAX, respectively. The two active compounds, 3 and 6, also shifted the survival fraction of TAX against MES-SA/CX5 cells from 57.78 to 25.76 and 35.01, respectively, at 1000 nM TAX. In the presence of 10 μM VER, the survival fraction of TAX was potentiated in MES-SA/DX5, HCT15, and HCT15/CL02 cells (Figure 5). However, all compounds (20 μM) or VER (10 μM) had no effect on the cytotoxicity against MES-SA and nonMDR cells.

3. CONCLUSIONS

In this study, a chemical investigation of the MeOH extract from the fruiting bodies of the poisonous mushroom C. molybdites resulted in the isolation and identification of a new isoindolinone-type alkaloid, meyeroguilline E (1), and eight known compounds (2−9). In the present study, the new compound (1) was reported to be the first example of a natural isoindolinone with a butanoic acid moiety, and the other known compounds 2−9 were isolated from C. molybdites for the first time. Among the isolated compounds, 20 μM of compounds 3 and 6 slightly potentiated the paclitaxel (TAX)-induced cytotoxicity to MES-SA/DX5, HCT15, and HCT15/CL02 cells. Further, compounds 3 and 6 enhanced the survival fraction at 1000 nM of TAX from −11.66 to −33.93 and −41.46, respectively, in HCT15/CL02 cells.

4. EXPERIMENTAL SECTION

4.1. General Experimental Procedure. Optical rotation was measured using a Jasco P-2000 polarimeter (Jasco, Easton, MD). The infrared (IR) spectra were recorded on a Bruker IFS-66/S FT-IR spectrometer (Bruker, Karlsruhe, Germany), while the ultraviolet (UV) spectra were acquired on an Agilent 8453 UV−visible spectrophotometer (Agilent Technologies, Santa Clara, CA). The nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AVANCE III HD 850 NMR spectrometer with a 5 mm TCI CryoProbe operating at 850 MHz (proton, 1H) and 212.5 MHz (13C, Bruker, Karlsruhe, Germany), with chemical shifts given in ppm (δ) for the 1H and 13C NMR analyses. Semipreparative HPLC was performed using a Shimadzu Prominance HPLC System, with SPD-20A/20AV Series Prominence HPLC UV−vis detectors (Shimadzu, Tokyo, Japan) and a Phenomenex Luna C18 column (250 × 10 mm, 5 μm; flow rate: 2 mL/min; Phenomenex, Torrance, CA). Liquid chromatography−mass spectrometry (LC/MS) analysis was performed using an Agilent 1200 Series HPLC system equipped with a diode array detector and 6130 Series ESI mass spectrometer using an analytical Kinetex C18 100 A column (100 × 2.1 mm, 5 μm; flow rate: 0.3 mL/min; Phenomenex, Torrance, CA). All high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) data were obtained using an Agilent 6545 Q-TOF LC/MS spectrometer (Agilent Technologies, Santa Clara, CA). Silica gel 60 (230−400 mesh; Merck, Darmstadt, Germany) and RP-C18 silica gel (230−400 mesh; Merck) were used for column chromatography. Sephadex LH-20 (Pharmacia, Uppsala, Sweden) was employed as the packing material for molecular sieve column chromatography. Merck precoated silica gel F254s plates and RP-C18 F254s plates were used for thin-layer chromatography. After thin-layer chromatography, spots were detected under UV light or by heating after spraying with anisaldehyde-sulfuric acid.

4.2. Fungal Material. Fruiting bodies of Chlorophyllum neomastoideum were collected from a mixed forest in Pocheon, GyeongGii-do, Korea, in August 2020. The samples were identified by one of the authors (R. Ryoo) via DNA analysis; fungal-specific PCR primers, ITS1 and ITS4, were used to...
amplify the internal transcribed spacer (ITS) region. The DNA sequence of this material was analyzed according to a modified method.30 The homology of the ITS sequence was matched with that of C. neomastoideum (syn. Macrolepiota neomastoidea) with the highest score in the NCBI GenBank database. A voucher specimen (SKKU 2020-08-CN) was deposited at the herbarium of the School of Pharmacy, Sungkyunkwan University, Suwon, Korea.

4.3. Extraction and Isolation. Dried C. molybdite fruiting bodies (1.7 kg) were extracted with 100% methanol (MeOH, 3.0 L × 3) and filtered. The resulting extract was vacuum-concentrated using a rotary evaporator to obtain the MeOH extract (449.3 g). The concentrated MeOH extract was suspended in distilled water (700 mL) and solvent-partitioned three times each with hexane, dichloromethane (CHCl, 3), ethyl acetate (EtOAc), and n-butanol (n-BuOH) to obtain four fractions: hexane-soluble (24.2 g), CHCl-soluble (3.7 g), EtOAc-soluble (1.0 g), and n-BuOH-soluble (15.4 g). Based on LC-MS analysis of each fraction derived from solvent partitioning, the CHCl- and EtOAc-soluble fractions were identified to harbor compounds of interest, including N-containing compounds since we found that HRESIMS of peak in the CHCl fraction showed an m/z 146.0610 ([M + H]+) (calculated for C۷H۱۴NO, 146.0606) in the positive-ion mode, and HRESIMS of peaks in the EtOAc fraction revealed m/z 288.0845 ([M + Na]+) (calculated for C۹H۱۳NO۳Na, 288.0848), m/z 188.0328 ([M + Na]+) (calculated for C۶H۱۲NO۳ Na, 188.0324), and m/z 232.0583 ([M + Na]+) (calculated for C۶H۱۱NO۳Na, 232.0586) in the positive-ion mode. The CHCl-soluble fraction (3.7 g) was separated using silica gel open column chromatography using a gradient solvent system of CHCl/MeOH (80:1, CHCl/MeOH to 100% MeOH) to yield seven fractions (A–G). Fraction C (37.1 mg) was purified using semipreparative HPLC (20% MeOH) on a Phenomenex Luna phenyl-hexyl column to obtain compound 7 (tR = 32.0 min, 0.6 mg). The EtOAc-soluble fraction (1.0 g) was separated using silica gel open column chromatography using a gradient solvent system of CHCl/MeOH (30:1, CHCl/MeOH to 100% MeOH) to yield five fractions (1–V). Fraction I (190.0 mg) was separated by reversed phase silica gel open column chromatography using 100% MeOH to yield six subfractions (11–16). Subfraction I2 (98.1 mg) was purified by semipreparative HPLC (55% MeOH) on a Phenomenex Luna phenyl-hexyl column to obtain compounds 5 (tR = 17.0 min, 4.0 mg) and 6 (tR = 23.5 min, 0.5 mg). Subfraction I3 (30.0 mg) was purified by semipreparative HPLC (45% MeOH) on a Phenomenex Luna C18 column to obtain compounds 1 (tR = 26.5 min, 1.0 mg) and 8 (tR = 38.0 min, 1.0 mg). Fraction II (124.3 mg) was separated by Sephadex LH-20 open column chromatography using 100% MeOH to yield five subfractions (II1–II5). Subfraction II4 (45.9 mg) was purified by semipreparative HPLC (20% MeOH) on a Phenomenex Luna C18 column to obtain compounds 3 (tR = 15.0 min, 1.0 mg) and 9 (tR = 19.0 min, 0.8 mg). Subfraction II5 (19.6 mg) was purified by semipreparative HPLC (18% MeOH) on a Phenomenex Luna C18 column to obtain compounds 2 (tR = 17.0 min, 1.0 mg) and 4 (tR = 25.5 min, 1.0 mg).

4.3.1. Meyeroguilline E (1). White powder; UV (MeOH) λmax (log ε) 215 (4.18), 252 (2.00), 305 (1.76) nm; IR (KBr): νmax = 3440, 2928, 1712, 1620, 1353, 1155 cm−1; 1H (850 MHz) and 13C (212.5 MHz) NMR data, Table 1; HRESIMS (positive-ion mode) m/z 288.0848 [M + Na]+ (calculated for C۷H۱۴NO۳Na, 288.0845), and m/z 553.1798 [2M + Na]+ (calculated for 2C۷H۱۴NO۳Na, 553.1794).

4.4. Cancer Cells. The human colorectal cancer cell line HCT15, uterine carcinoma cell line MES-SA, and its doxorubicin-resistant subline MES-SA/DX5 were purchased from American Type Culture Collection (Rockville, Maryland). HCT15/CL02 cells were established from HCT15 cells at the Korea Research Institute of Chemical Technology.31 Cell cultures were conducted in Falcon T-25 (Becton Dickinson, Lincoln Park, NJ) flasks containing 10 mL of RPMI-1640 medium with glutamine, sodium bicarbonate, gentamycin, amphotericin, and 5% fetal bovine serum (FBS). The cells were dissociated using 0.25% trypsin and 3 mM EDTA solution for passaging. The cells were maintained in an incubator at 37 °C in a humidified atmosphere of 5% CO2.

4.5. MDR Reversal Assay. The ability of the samples to potentiate the cytotoxicity of paclitaxel (TAX) was evaluated in the MES-SA, MES-SA/DX5, HCT15, and HCT15/CL02 cell lines as previously described.32 The cells were then inoculated over a series of standard 96-well flat-bottom microplates and preincubated for 24 h to allow attachment to the microtiter plate. The attached cells were incubated with serial dilutions of TAX in the absence or presence of each sample or verapamil. After continuous exposure to the compounds for 72 h, the culture medium was removed from each well and the cells were fixed with 10% cold TCA at 4 °C for 1 h. After washing with distilled water, the cells were stained with 0.4% SRB solution and incubated for 30 min at room temperature. The cells were then washed again and solubilized with 10 mM unbuffered Tris base solution (pH 10.5). The absorbance was measured spectrophotometrically at 520 and 690 nm using a microtiter plate reader (Molecular Devices, Sunnyvale, CA). To eliminate the effects of nonspecific absorbance, the absorbance at 690 nm was subtracted from that at 520 nm. The cell survival fractions were calculated via three basic measurements: time zero (Tz) at the beginning of drug incubation, cell control (CC) at the end of incubation without drug, and drug treatment (DT) at the end of the drug incubation period. CC is the fraction of cells incubated with the MDR reversal sample alone. If DT ≥ Tz, the net perfect cell growth inhibition was calculated as (DT − Tz)/(CC − Tz) × 100. If DT < Tz, the net percentage of cell-killing activity was calculated as (DT − Tz)/Tz × 100. All data represent the average values of three wells in each experiment.

Associated Content

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06155.

HRESIMS, 1D and 2D NMR spectra of compound 1 (PDF)

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(30) Lee, S. B.; Taylor, J. W. Isolation of DNA from Fungal Mycelia and Single Spores. In PCR Protocols, A Guide to Methods and Applications; Academic Press, 1990; pp 282−287.

(31) Choi, S. U.; Kim, N. Y.; Choi, E. J.; Kim, K. H.; Lee, C. O. Establishment of doxorubicin-resistant subline derived from HCT15 human colorectal cancer cells. Arch. Pharm. Res. 1996, 19, 342−347.

(32) Choi, S. U.; Lee, C. O.; Kim, K. H.; Choi, E. J.; Park, S. H.; Shin, H. S.; Yoo, S. E.; Jung, N. P.; Lee, B. H. Reversal of multidrug resistance by novel verapamil analogs in cancer cells. Anticancer Drugs 1998, 9, 157−165.