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Synthesis and biological activities of petromurin C nitrile derivatives

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Abstract: A series of nitrile derivatives of Petromurin C were synthesized and assessed for their cytotoxic effects on tumor cell lines and inhibitory activity against *Mycobacterium tuberculosis* (M.tb H37Ra). Bromoalkyl nitriles ($Br(CH_2)nCN$; n=1-5) and (o-, m-, p-) bromomethyl benzonitriles were used as alkylating reagents. The majority of the syntheses consisted of O-alkylated derivatives in which the two NH group were not alkylated, as expected from the treatment of petromurin C with K_2CO_3 in DMF followed by treatment with alkylating reagents. Similarly, treatment of Petromurin C with NaH in DMF and the treatment with alkylating reagents yielded both OR and bis-NR alkylated structures. In the first method, 7 different O-alkyl Petromurin C derivatives were obtained. The second method yielded 7 different Petromurin-C derivatives containing both O-alkyl and bis-N-alkyl groups. Notably, compounds **1-4** and **7-10** demonstrated selective inhibitory activity against the acute myeloid leukemia cell line MV4-11, with IC_{50} values ranging from 12.96 to 20.00 µM. Compound **15** exhibited a minimum inhibitory concentration (MIC) of 6.25 µM against M.tb H37Ra. Importantly, all synthesized compounds showed negligible inhibition (below 50%) against human normal cell lines L-02 and 293T at a concentration of 100 µM. These findings suggest that the compounds possess high efficacy and low toxicity, indicating their potential as novel therapeutic agents for the treatment of leukemia and tuberculosis.

Keywords: Petromurin C; structural modification; nitrile groups; cytotoxic activity; anti-tubercular activity.

1. Introduction

Microorganisms, including actinomycetes and fungi, possess the capability to synthesize a wide variety of structurally diverse secondary metabolites[1-4], many of which have been successfully developed into clinical drugs, such as penicillin[5], erythromycin[6], and vancomycin[7]. Nonetheless,

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natural products often face challenges such as poor water solubility, low stability, and limited selectivity. Structural modification, involving the alteration of molecular frameworks or functional groups, can optimize the physicochemical properties of these compounds, enhance their biological activity, and reduce toxic side effects[8]. Our research group previously conducted a systematic isolation of *Aspergillus* sp. GZWMJZ-258, resulting in the high-yield acquisition of the bisindole biphenyl compound petromurin C[9]. The vitro activity assays demonstrated that petromurin C exhibits inhibitory effects on the human acute myeloid leukemia (AML) cell line MV4-11. Due to its poor solubility, structural modification was undertaken to introduce polar groups to improve its solubility.

In recent decades, the nitrile group has attained significant prominence in the field of medicinal chemistry[10]. Its distinctive properties—characterized by a highly polar carbon-nitrogen triple bond, substantial electron-withdrawing capability, and a compact size (approximately one-eighth that of a methyl group)—facilitate deep penetration into target proteins and the formation of hydrogen bond interactions with critical amino acid residues, such as serine and arginine, within active sites[11]. As a bioisostere for functional groups such as carbonyls and halogens[12], the incorporation of nitrile moieties into small-molecule drugs can modulate physicochemical properties, enhance target binding affinity, and improve therapeutic efficacy. Furthermore, nitriles serve as metabolic blocking groups, inhibiting oxidative metabolism and thereby enhancing in vivo metabolic stability. Clinically, a variety of nitrile-containing drugs have been developed for the treatment of conditions including lung cancer, breast cancer, and chronic myeloid leukemia. Notable examples include neratinib, pelitinib, and bosutinib, which are utilized in the treatment of breast cancer and non-small cell lung cancer[13], bosutinib for imatinib-resistant chronic myeloid leukemia[14], and glasdegib for AML treatment[15]. This research investigates the synthesis of novel petromurin C derivatives containing nitrile groups and assesses their antitumor properties as well as their activity against *Mycobacterium tuberculosis*.

2. Experimental

2.1. General

Detailed information on this section was given in supporting information of the article.

2.2. Synthesis

*Synthesis of Compound **1***: To a solution of petromurin C (50.0 mg, 0.11 mmol) in dry N,N-dimethylformamide (DMF)(5 mL) was added 1 *M* aqueous K_2CO_3 (165 μL, 0.165 mmol). The mixture was stirred at room temperature for 30 min, then bromoacetonitrile (26.7 mg, 0.22 mmol) was added. The mixture was stirred for 4 hours at room temperature. After adding ethyl acetate (20 mL), the mixture was washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10 × 250 mm, 5 μm) using 45% acetonitrile and 55% distilled water (containing 0.5‰ trifluoroacetic acid (TFA)) at a flow rate of 4 mL/min to obtain compound **1**; 13.0 mg (yield 24%) as a white solid; IR (KBr, cm^{-1}) ν: 3363, 2933, 2253, 1683, 1627, 1581, 1457, 1393, 1272, 1189, 1059, 955, 887, 743; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.31 (brs, 1H), 11.30 (brs, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.44 (d, J = 7.4 Hz, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 6.89 (dd, J = 8.8, 2.4 Hz, 1H), 5.09 (s, 2H), 3.47 (s, 6H), 3.44 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.4, 147.6×2, 147.6×2, 135.9, 132.1, 127.4, 127.0, 126.7, 125.3, 122.3, 121.9, 120.8, 120.3, 118.7 (CN), 117.2, 112.3, 111.4, 111.0, 107.1, 106.9, 104.8, 60.3×2, 60.3×2, 54.7; HRESIMS(M-H) *m/z*: calculated for $C_{28}H_{24}N_3O_5$ 482.1710, detected 482.1712.

*Synthesis of Compound **2***: To a solution of petromurin C (50.0 mg, 0.11 mmol) in dry DMF (5 mL) was added 1 *M* aqueous K_2CO_3 (165 μL, 0.165 mmol). The mixture was stirred at room temperature for 30 min, then 4-bromobutyronitrile (32.5 mg, 0.22 mmol) was added. The mixture was stirred for 4 hours at room temperature. After adding ethyl acetate (20 mL), the mixture was washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 μm) using 45% acetonitrile and 55% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **2**; 33.0 mg (yield 58%) as a brown solid; IR (KBr, cm^{-1}) ν: 3367, 2929, 2253, 1683, 1647, 1625, 1457, 1394, 1273, 1204, 1128, 1061, 749; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) *δ* 11.28 (brs, 1H), 11.16 (brs, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 7.1 Hz, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.42 (d, *J* = 7.1 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.11 (t, *J* = 7.1 Hz, 1H), 7.00 (t, *J* = 7.1 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 2H), 3.45 (s, 6H), 3.43 (s, 6H), 2.66 (t, *J* = 6.0 Hz, 2H), 2.01 (m, 2H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) *δ* 152.1, 147.6×4, 135.9, 131.3, 127.4, 127.0, 126.1, 125.2, 122.1, 120.8, 120.4, 118.7 (CN), 112.0 ,111.4, 106.9, 106.8, 66.3, 60.3×2, 60.3×2, 24.9, 13.4; HRESIMS(M+Na) *m/z*: calculated for $C_{30}H_{29}N_3O_5Na$ 534.1999, detected 534.1991.

*Synthesis of Compound **3***: To a solution of petromurin C (50.0 mg, 0.11 mmol) in dry DMF (5 mL) was added 1 *M* aqueous K_2CO_3 (165 µL, 0.165 mmol). The mixture was stirred at room temperature for 30 min, then 5-bromovaleronitrile (35.6 mg, 0.22 mmol) was added. The mixture was stirred for 4 hours at room temperature. After adding ethyl acetate (20 mL), the mixture was washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 µm) using 50% acetonitrile and 50% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **3**; 43.3 mg (yield 82%) as a brown solid; IR (KBr, cm^{-1}) *ν*: 3409, 2933, 2247, 1684, 1621, 1459, 1393, 1273, 1203, 1058, 998, 756; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) *δ* 11.28 (brs, 1H), 11.14 (brs, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.96 (t, *J* = 6.0 Hz, 2H), 3.46 (s, 6H), 3.43 (s, 6H), 2.56 (t, *J* = 6.0 Hz, 2H), 1.80 (m, 2H), 1.73 (m, 2H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) *δ* 152.3, 147.6×2, 147.6×2, 135.9, 131.2, 127.5, 127.0, 126.0, 125.2, 122.2, 122.1, 120.8, 120.7, 120.3, 118.7 (CN), 111.9, 111.4, 111.4, 107.0, 106.8, 103.2, 67.0, 60.3×2, 60.3×2, 28.0, 21.9, 16.1; HRESIMS(M+Na) *m/z*: calculated for $C_{31}H_{31}N_3O_5Na$ 548.2156, detected 548.2146.

*Synthesis of Compound **4***: To a solution of petromurin C (50.0 mg, 0.11 mmol) in dry DMF (5 mL) was added 1 *M* aqueous K_2CO_3 (165 µL, 0.165 mmol). The mixture was stirred at room temperature for 30 min, then 6-bromohexanenitrile (38.7 mg, 0.22 mmol) was added. The mixture was stirred for 4 hours at room temperature. After adding ethyl acetate (20 mL), the mixture was washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 µm) using 50% acetonitrile and 50% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **4**; 25.0 mg (yield 77%) as a brown solid; IR (KBr, cm^{-1}) ν: 3402, 2935, 2247, 1622, 1553, 1459, 1393, 1275, 1202, 1118, 1058, 999, 746; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) *δ* 11.28 (s, 1H), 11.13 (s, 1H), 7.46 (s, 1H), 7.43 (m, 3H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 3.93 (t, *J* = 6.1 Hz, 2H), 3.45 (s, 6H), 3.43 (s, 6H), 2.50 (m, 2H), 1.73 (m, 2H), 1.61 (m, 2H), 1.52 (m, 2H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) *δ* 152.4, 147.6×4, 135.89, 131.1, 127.5, 127.0, 126.0, 125.2, 122.2, 122.0, 120.8, 120.7, 120.3, 118.7 (CN), 111.9, 111.4, 111.4, 106.9, 106.7, 103.2, 67.6, 60.3×2, 60.3×2, 28.1, 24.9, 24.6, 16.1; HRESIMS(M+Na) *m/z*: calculated for $C_{32}H_{33}N_3O_5Na$ 562.2312, detected 562.2302.

*Synthesis of Compound **5***: To a solution of petromurin C (50.0 mg, 0.11 mmol) in dry DMF (5 mL) was added 1 *M* aqueous K_2CO_3 (165 µL, 0.165 mmol). The mixture was stirred at room temperature for 30 min, then alpha-bromo-p-tolunitrile (43.1 mg, 0.22 mmol) was added. The mixture was stirred for 4 hours at room temperature. After adding ethyl acetate (20 mL), the mixture was washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 µm) using 55% acetonitrile and 45% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **5**; 24.0 mg (yield 72%) as a white solid; IR (KBr, cm^{-1}) ν: 3385, 2931, 2229, 1717, 1684, 1653, 1559, 1508, 1457, 1394, 1273, 1059, 999, 957, 746; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) *δ* 11.29 (brs, 1H), 11.19 (brs, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 2.3 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 2.2 Hz, 1H), 6.89 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.19 (s, 2H), 3.42 (s, 6H), 3.41 (s, 6H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) *δ* 151.7, 147.6×2, 147.5×2, 143.8, 135.9, 132.2×2, 131.3, 127.9×2, 127.4, 127.0, 126.2, 125.2, 122.0×2, 120.8, 120.3, 118.8, 118.7 (CN), 112.1, 111.5, 111.4, 110.1, 106.9, 106.8, 103.9, 68.8, 60.2×2, 60.2×2; HRESIMS(M+Na) *m/z*: calculated for $C_{34}H_{29}N_3O_5Na$ 582.1999, detected 582.1985.

*Synthesis of Compound **6***: To a solution of petromurin C (50.0 mg, 0.11 mmol) in dry DMF (5 mL) was added 1 *M* aqueous K_2CO_3 (165 μL, 0.165 mmol). The mixture was stirred at room temperature for 30 min, then alpha-bromo-m-tolunitrile (43.1 mg, 0.22 mmol) was added. The mixture was stirred 4 hours at room temperature. After adding ethyl acetate (20 mL), the mixture was washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 μm) using 55% acetonitrile and 45% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **6**; 46.6 mg (yield 83%) as a brown solid; IR (KBr, cm^{-1}) ν: 3395, 2929, 2230, 1716, 1699, 1684, 1650, 1558, 1541, 1457, 1394, 1273, 1202, 1001, 957, 798; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.28 (brs, 1H), 11.19 (brs, 1H), 7.89 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.89 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.15 (s, 2H), 3.43 (s, 6H), 3.41 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.7, 147.6×2, 147.6×2, 139.7, 135.9, 132.2, 131.4, 131.3, 130.8, 129.7, 127.4, 127.0, 126.2, 125.2, 122.1, 120.8, 120.3, 118.8, 118.7 (CN), 112.1, 111.6, 111.4, 111.3×2, 106.9, 106.8, 103.9, 68.5, 60.3×2, 60.2×2; HRESIMS(M+Na) *m/z*: calculated for $C_{34}H_{29}N_3O_5Na$ 582.1999, detected 582.1989.

*Synthesis of Compound **7***: To a solution of petromurin C (50.0 mg, 0.11 mmol) in dry DMF (5 mL) was added 1 *M* aqueous K_2CO_3 (165 μL, 0.165 mmol). The mixture was stirred at room temperature for 30 min, then 2-cyanobenzyl bromide (43.1 mg, 0.22 mmol) was added. The mixture was stirred for 4 hours at room temperature. After adding ethyl acetate (20 mL), the mixture was washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 μm) using 55% acetonitrile and 45% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **7**; 43.3 mg (yield 77%) as a brown solid; IR (KBr, cm^{-1}) ν: 3396, 2929, 2229, 1868, 1845, 1828, 1716, 1700, 1650, 1558, 1541, 1508, 1457, 1394, 1340, 1059, 999, 765; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.28 (s, 1H), 11.21 (s, 1H), 7.87 (d, *J* = 7.3 Hz, 1H), 7.73 (d, *J* = 7.3 Hz,, 1H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.47 (s, 1H), 7.46 (s, 1H), 7.43 (m, 2H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.12 (m, 1H), 7.02 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 5.23 (s, 2H), 3.43 (s, 12H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.8, 147.6×2, 147.6×2, 140.9, 135.9, 133.3, 133.1, 131.5, 129.4, 128.7, 127.4, 127.1, 126.3, 125.2, 122.1, 122.0, 120.8, 120.3, 118.7 (CN), 117.3, 112.1, 111.6, 111.4, 111.1, 107.0, 106.9, 104.2, 68.3, 60.3×2, 60.3×2; HRESIMS(M+Na) *m/z*: calculated for $C_{34}H_{29}N_3O_5Na$ 582.1999, detected 582.1992.

*Synthesis of Compound **8***: To a mixture of NaH (60% dispersion in mineral oil) (15.4 mg, 0.385 mmol) in dry DMF (5 mL) was added petromurin C (50.0 mg, 0.11 mmol) under an argon atmosphere. The mixture was stirred at 0°C for 30 min, then bromoacetonitrile (52.8 mg, 0.44 mmol) was added slowly. The mixture was stirred for 4 hours at room temperature. After adding H_2O (2 mL), the mixture was extracted with ethyl acetate (20 mL), washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10 × 250 mm, 5 μm) using 45% acetonitrile and 55% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **8**; 10.5 mg (yield 17%) as a white solid; IR (KBr, cm^{-1}) ν: 2933, 2256, 1684, 1621, 1460, 1360, 1321, 1275, 1197, 1059, 1023, 955, 742; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.64 (s, 1H), 7.61 (s, 1H), 7.49 (d, *J* = 8.9 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.66 (s, 2H), 5.64 (s, 2H), 5.15 (s, 2H), 3.51 (s, 6H), 3.49 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.3, 147.6×4, 135.7, 131.8, 129.7, 128.4, 128.4, 127.9, 122.1, 121.6, 121.3, 121.0, 120.2, 117.0 (CN), 116.7 (CN)×2, 112.4, 110.9, 109.8, 108.6, 108.5, 105.5, 60.5×2, 60.5×2, 54.5, 34.15, 34.0; HRESIMS(M+Na) *m/z*: calculated for $C_{32}H_{27}N_5O_5Na$ 584.1904, detected 584.1894.

*Synthesis of Compound **9***: To a mixture of NaH (60% dispersion in mineral oil) (15.4 mg, 0.385 mmol) in dry DMF (5 mL) was added petromurin C (50.0 mg, 0.11 mmol) under an argon atmosphere. The mixture was stirred at 0°C for 30 min, then 3-bromopropionitrile (58.9 mg, 0.44 mmol) was added slowly. The mixture was stirred 4 hours at room temperature. After adding H_2O (2 mL), the mixture was extracted with ethyl acetate (20 mL), washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10 × 250 mm, 5 µm) using 55% acetonitrile and 45% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **9**; 20 mg (yield 33%) as a brown solid; IR (KBr, cm^{-1}) ν: 2931, 2852, 2253, 1683, 1628, 1558, 1461, 1394, 1358, 1275, 1203, 1131, 1059, 748; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.69 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.61 (t, *J* = 6.4 Hz, 2H), 4.52 (t, *J* = 6.4 Hz, 2H), 3.44 (s, 12H), 3.11 (t, *J* = 6.4 Hz, 2H), 3.07 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (150MHz, DMSO-d_6) δ 151.1, 147.6×4, 135.4, 129.9, 128.8, 128.6, 128.5, 127.7, 122.1, 121.4, 121.3, 120.8, 119.3, 118.9 (CN), 118.8 (CN), 111.4, 110.2, 109.9, 107.1, 106.1, 104.9, 60.4×2, 60.4×2, 41.5, 41.3, 18.7×2; HRESIMS(M+Na) *m/z*: calculated for $C_{32}H_{30}N_4O_5Na$ 573.2108, detected 573.2103.

*Synthesis of Compound **10***: To a mixture of NaH (60% dispersion in mineral oil) (15.4 mg, 0.385 mmol) in dry DMF (5 mL) was added petromurin C (50.0 mg, 0.11 mmol) under an argon atmosphere. The mixture was stirred at 0°C for 30 min, then 4-bromobutyronitrile (65.1 mg, 0.44 mmol) was added slowly. The mixture was stirred 4 hours at room temperature. After adding H_2O (2 mL), the mixture was extracted with ethyl acetate (20 mL), washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 µm) using 55% acetonitrile and 45% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **10**; 20 mg (yield 28%) as a brown solid; IR (KBr, cm^{-1}) ν: 2931, 2247, 1700, 1683, 1650, 1621, 1556, 1541, 1470, 1457, 1394, 1210, 1061, 957, 798; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.88 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.37 (t, *J* = 6.9 Hz, 2H), 4.33 (t, *J* = 6.8 Hz, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.47 (s, 6H), 3.45 (s, 6H), 2.66 (t, *J* = 7.1 Hz, 2H), 2.47 (t, *J* = 6.3 Hz, 2H), 2.45 (t, *J* = 6.2 Hz, 2H), 2.15 (m, 4H), 2.01 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.9, 148.0×2, 148.0×2, 136.0, 131.5, 129.7, 129.0, 128.4, 128.0, 122.2, 122.1, 121.6, 121.4, 120.8, 120.5, 119.6×3 (CN), 112.1, 110.9, 110.1, 107.2, 106.8, 104.5, 66.8, 60.8×2, 60.8×2, 44.9, 44.7, 26.2, 26.2, 25.3, 14.3, 14.2, 13.9; HRESIMS(M+Na) *m/z*: calculated for $C_{38}H_{39}N_5O_5Na$ 668.2843, detected 668.2823.

*Synthesis of Compound **11***: To a mixture of NaH (60% dispersion in mineral oil) (15.4 mg, 0.385 mmol) in dry DMF (5 mL) was added petromurin C (50.0 mg, 0.11 mmol) under an argon atmosphere. The mixture was stirred at 0°C for 30 min, then 5-bromovaleronitrile (71.2 mg, 0.44 mmol) was added slowly. The mixture was stirred 4 for hours at room temperature. After adding H_2O (2 mL), the mixture was extracted with ethyl acetate (20 mL), washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 µm) using 60% acetonitrile and 40% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **11**; 40 mg (yield 53%) as a brown solid; IR (KBr, cm^{-1}) ν: 2929, 2246, 1618, 1490, 1423, 1394, 1321, 1268, 1212, 1065, 1023, 923, 745; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.56 (s, 1H), 7.55 (s, 1H), 7.50 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.44 (s, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.34 (t, *J* = 6.6 Hz, 2H), 4.29 (t, *J* = 6.5 Hz, 2H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.45 (s, 6H), 3.43 (s, 6H), 2.55 (m, 6H), 1.90 (m, 4H), 1.80 (m, 2H), 1.73 (m, 2H), 1.53 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.6, 147.6×2, 147.6×2, 135.6, 130.9, 129.4, 128.8, 127.9 127.5, 121.9, 121.7, 121.0, 120.8, 120.7, 120.6, 118.9×3 (CN), 111.5, 110.5, 109.8, 106.8, 105.9, 103.7, 67.0, 60.31×2, 60.3×2, 44.8, 44.7, 28.9, 28.8, 28.0, 22.3, 22.2, 21.9, 16.1, 15.8, 15.8; HRESIMS(M+Na) *m/z*: calculated for $C_{41}H_{45}N_5O_5Na$ 710.3313, detected 710.3309.

*Synthesis of Compound **12***: To a mixture of NaH (60% dispersion in mineral oil) (15.4 mg, 0.385 mmol) in dry DMF (5 mL) was added petromurin C (50.0 mg, 0.11 mmol) under an argon atmosphere. The mixture was stirred at 0°C for 30 min, then 6-bromohexanenitrile (77.4 mg, 0.44 mmol) was added slowly. The mixture was stirred 4 hours at room temperature. After adding H_2O (2 mL), the mixture was extracted with ethyl acetate (20 mL), washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 μm) using 60% acetonitrile and 40% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **12**; 28.6 mg (yield 36%) as a brown solid; IR (KBr, cm^{-1}) ν: 2932, 2866, 2244, 1650, 1556, 1541, 1485, 1470, 1456, 1393, 1319, 1272, 1207, 1120, 959, 797; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.54 (s, 1H), 7.53 (d, *J* = 7.3 Hz, 1H), 7.49 (s, 1H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.30 (t, *J* = 6.8 Hz, 2H), 4.25 (t, *J* = 6.7 Hz, 2H), 3.94 (t, *J* = 6.3 Hz, 2H), 3.45 (s, 6H), 3.43 (s, 6H), 2.50 (m, 2H), 2.46 (m, 4H), 1.84 (m, 4H), 1.73 (m, 2H), 1.59 (m, 6H), 1.51 (m, 2H), 1.35 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.6, 147.6×4, 135.6, 130.9, 129.4, 128.8, 127.9, 127.4, 121.9, 121.7, 120.9, 120.8, 120.7, 120.6, 118.8×3 (CN), 111.4, 110.4, 109.8, 106.1, 105.7, 103.7, 67.6, 60.3×4, 45.4, 45.3, 29.0, 29.0, 28.1, 25.4, 25.4, 25.0, 24.6, 24.4×2, 16.2×2, 16.1; HRESIMS(M+Na) *m/z*: calculated for $C_{44}H_{51}N_5O_5Na$ 752.3782, detected 752.3795.

*Synthesis of Compound **13***: To a mixture of NaH (60% dispersion in mineral oil) (15.4 mg, 0.385 mmol) in dry DMF (5 mL) was added petromurin C (50.0 mg, 0.11 mmol) under an argon atmosphere. The mixture was stirred at 0°C for 30 min, then alpha-bromo-p-tolunitrile (86.2 mg, 0.44 mmol) was added slowly. The mixture was stirred 4 hours at room temperature. After adding H_2O (2 mL), the mixture was extracted with ethyl acetate (20 mL), washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10 × 250 mm, 5 μm) using 60% acetonitrile and 40% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **13**; 45 mg (yield 52%) as a brown solid; IR (KBr, cm^{-1}) ν: 3119, 2927, 2852, 2229, 1844, 1735, 1700, 1650, 1558, 1539, 1506, 1457, 1398, 1319, 1062, 818, 742; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.83 (m, 3H), 7.82 (m, 3H), 7.71 (s, 1H), 7.69 (s, 1H), 7.63 (d, *J* = 5.3 Hz, 2H), 7.47 (m, 2H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.38 (s, 1H), 7.36 (s, 2H), 7.35 (s, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.67 (s, 2H), 5.62 (s, 2H), 5.19 (s, 2H), 3.44 (s, 6H), 3.42 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.3, 147.6×2, 147.6×2, 144.3, 144.3, 143.7, 135.7, 132.6×2, 132.3×2, 131.2, 130.2, 129.3, 128.8, 128.1, 127.9, 127.7×2, 127.6×2, 127.6×2, 121.8, 121.8, 121.4, 120.8, 119.4, 118.9, 118.7 (CN)×3, 113.9, 112.0, 110.9, 110.2×2, 110.1, 107.2, 106.9, 104.3, 68.8, 60.4×2, 60.3×2, 48.8, 48.7; HRESIMS(M+Na) *m/z*: calculated for $C_{50}H_{39}N_5O_5Na$ 812.2854, detected 812.2825.

*Synthesis of Compound **14***: To a mixture of NaH (60% dispersion in mineral oil) (15.4 mg, 0.385 mmol) in dry DMF (5 mL) was added petromurin C (50.0 mg, 0.11 mmol) under an argon atmosphere. The mixture was stirred at 0°C for 30 min, then 2-cyanobenzyl bromide (86.2 mg, 0.44 mmol) was added slowly. The mixture was stirred 4 hours at room temperature. After adding H_2O (2 mL), the mixture was extracted with ethyl acetate (20 mL), washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10 × 250 mm, 5 μm) using 60% acetonitrile and 40% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **14**; 50 mg (yield 57%) as a brown solid; IR (KBr, cm^{-1}) ν: 2933, 2224, 1713, 1605, 1555, 1463, 1390, 1282, 1199, 1055, 949, 759; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.93 (d, *J* = 7.7 Hz, 2H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.72 (m, 2H), 7.67 (s, 1H), 7.66 (s, 1H), 7.63 (m, 2H), 7.53 (m, 1H), 7.49 (m, 3H), 7.44 (d, *J* = 8.9 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.09 (m, 2H), 7.00 (t, *J* = 8.0 Hz,, 1H), 6.95 (d, *J* = 8.9 Hz, 3H), 5.79 (s, 2H), 5.76 (s, 2H), 5.24 (s, 2H), 3.47 (s, 6H), 3.47 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.4, 147.7×2, 147.6×2, 141.8, 141.8, 140.7, 135.9, 133.7, 133.7, 133.3, 133.3, 133.3, 133.2, 131.5, 130.2, 129.4, 129.2, 128.8×2, 128.4, 128.1, 127.7, 127.4, 127.3, 121.7, 121.5, 120.9, 119.5, 117.4 (CN), 117.3×2 (CN), 115.6, 113.9, 112.1, 111.1, 110.8, 110.2, 109.9, 107.4, 107.2, 104.6, 68.2, 60.4×2, 60.4×2, 47.7, 47.5; HRESIMS(M+Na) *m/z*: calculated for $C_{50}H_{39}N_5O_5Na$ 812.2843, detected 812.2824.

*Synthesis of Compound **15***: To a mixture of NaH (60% dispersion in mineral oil) (15.4 mg, 0.385 mmol) in dry DMF (5 mL) was added petromurin C (50.0 mg, 0.11 mmol) under an argon atmosphere. The mixture was stirred at 0°C for 30 min, then alpha-bromo-m-tolunitrile (86.2 mg, 0.44 mmol) was added slowly. The mixture was stirred 4 hours at room temperature. After adding H_2O (2 mL), the mixture was extracted with ethyl acetate (20 mL), washed with brine (30 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC on a *YMC-Pack ODS-A* column (10×250 mm, 5 µm) using 60% MeCN and 40% distilled water (containing 0.5‰ TFA) at a flow rate of 4 mL/min to obtain compound **15**; 24.9 mg (yield 29%) as a brown solid; IR (KBr, cm^{-1}) ν: 3366, 2975, 2230, 1845, 1700, 1684, 1671, 1650, 1558, 1541, 1457, 1398, 1202, 1051, 957, 880; ^1H NMR (600 MHz, DMSO-d_6) δ 7.89 (brs, 1H), 7.78 (m, 2H), 7.75 (m, 2H), 7.73 (m, 2H), 7.65 (m, 2H), 7.57 (m, 3H), 7.56 (m, 2H), 7.53 (d, J = 8.9 Hz, 1H), 7.46 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.9, 2.4 Hz, 1H), 5.62 (s, 2H), 5.58 (s, 2H), 5.15 (s, 2H), 3.46 (s, 6H), 3.45 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.3, 147.6×2, 147.5×2, 140.3, 140.2, 139.5, 135.6, 132.3, 131.8, 131.8, 131.4, 131.2, 131.1, 130.8, 130.3, 130.3, 130.0, 129.9, 129.9, 129.6, 129.2, 128.2, 127.8, 121.8, 121.8, 121.4, 120.8, 119.4, 118.8 (CN), 118.7×2 (CN), 112.0, 111.5, 111.5, 111.3×2, 111.0, 110.1, 107.2, 106.9, 104.3, 68.5, 60.4×2, 60.3×2, 48.4, 48.2; HRESIMS(M+Na) *m/z*: calculated for $C_{50}H_{39}N_5O_5Na$ 812.2843, detected 812.2830.

2.3. Biological Activity Assays

2.3.1. Cytotoxic Activity

In this study, the CCK-8 assay (Cell Counting Kit-8)[16] was employed to evaluate the growth inhibitory effects of various compounds on MV4-11 (human myeloid monocytic leukemia cells), HL-60 (human leukemia cells), K-562 (human chronic myeloid leukemia cells), L-02 (human normal liver cells), and 293T (human embryonic kidney cells).

2.3.2. Anti Mycobacterium tuberculosis Activity

The MIC values were determined using a modified microdilution method in 96-well U-bottom plates[17]. Indicator bacteria: *Mycobacterium tuberculosis* (M.tb H37Ra) .

3. Results and Discussion

3.1. Chemistry

The present study aimed to perform structural modifications at the phenolic hydroxyl group and the nitrogen atom of petromurin C (Figure 1). In our previous work[9], a series of derivatives were synthesized by grafting various functional moieties onto the phenolic hydroxyl group. This earlier approach employed solid potassium carbonate or potassium hydroxide as base in N,N-dimethylformamide (DMF) as the solvent. However, the method was hampered by several limitations, such as extended reaction times and low yields of the target products. Considering that the poor solubility of inorganic bases in DMF was likely a major factor limiting the reaction efficiency, the present study introduced a pre-dissolution step for the base prior to the reaction. When this improved method was applied to the modification of petromurin C with bromoacetonitrile, a significant increase in reaction efficiency was observed, yielding the target compound **1**. Further experiments revealed that this approach selectively promoted substitution at the phenolic hydroxyl group of petromurin C, while modifications at the nitrogen atom remained unsuccessful. To explore this observation, reaction conditions were optimized by increasing the equivalents of the inorganic base solution and bromo-substituted nitrile reagents, as well as prolonging the reaction time. Subsequent analysis confirmed that no nitrogen-modified products were formed. Additionally, the same method was successfully applied to react petromurin C with various other bromo-substituted nitrile reagents, leading to the synthesis of compounds **2-7** (Figure 2). However, when bromopropionitrile was used as the modifying agent, the expected compound **16** was not obtained.

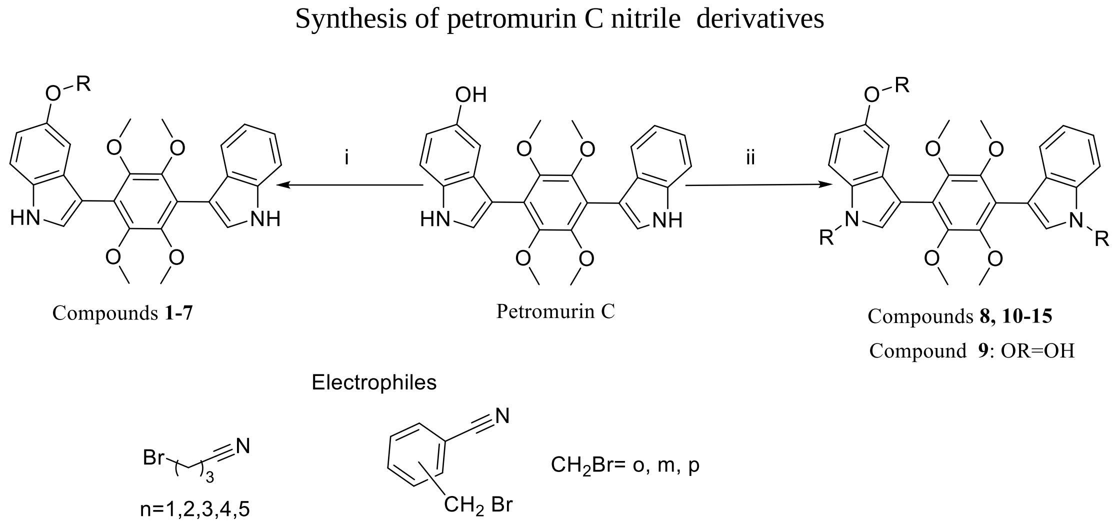

Figure 1. The synthetic route of petromurin C derivatives. Reagents and condutions. (i) 1 M aqueous K_2CO_3, dry N,N-Dimethylformamide, r.t., 4 h. (ii) NaH (60% dispersion in mineral oil), dry N,N-Dimethylformamide, 0°C to r.t., 4 h.

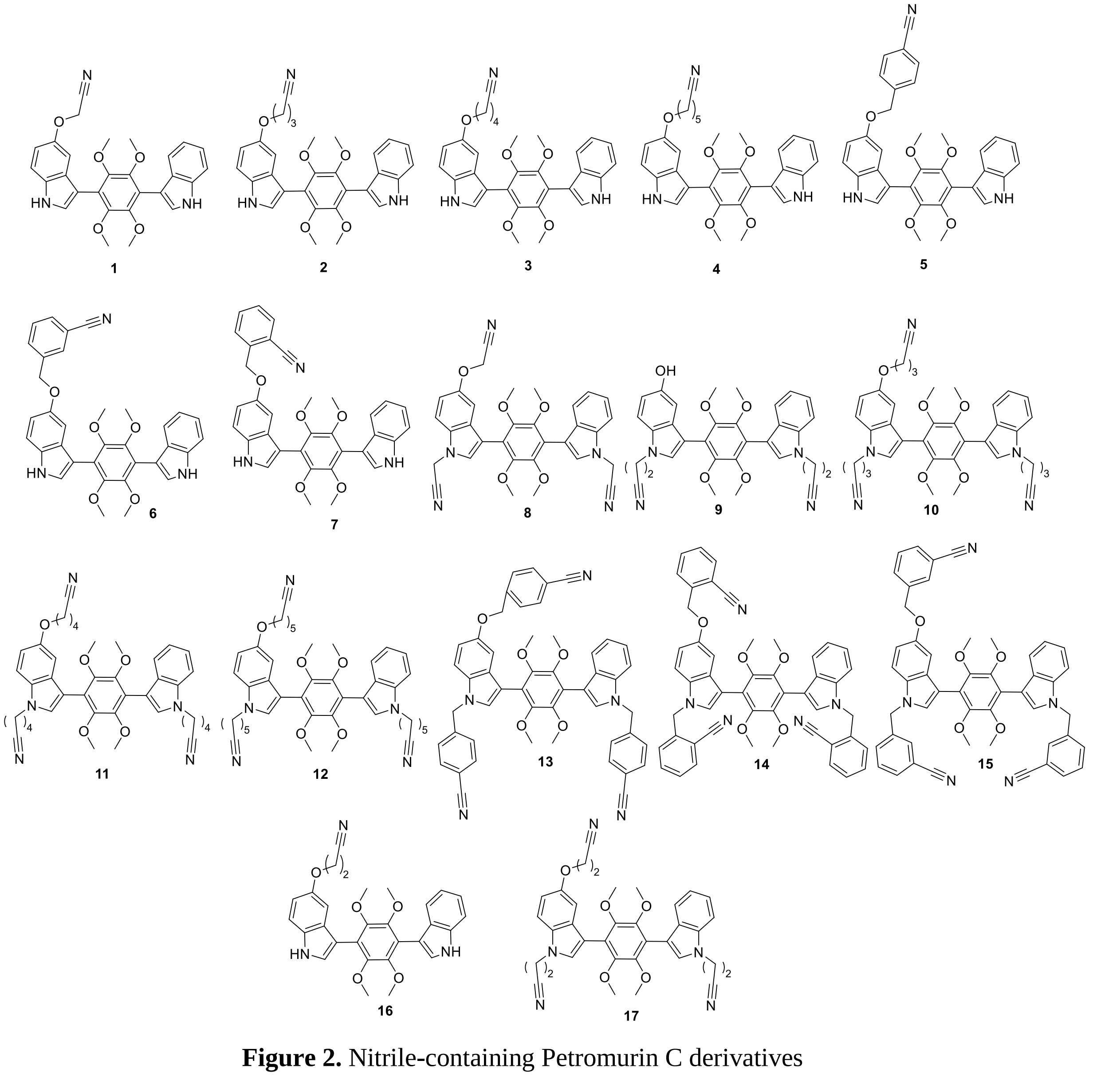

Figure 2. Nitrile-containing Petromurin C derivatives

Since the aforementioned method failed to achieve modification at the nitrogen atom, we hypothesized that the weak basicity of the inorganic base (e.g., potassium carbonate) might be the primary limiting factor. Compared to the phenolic hydroxyl group, the nitrogen atom in petromurin C is surrounded by considerably greater steric hindrance, which necessitates a stronger base to enhance its nucleophilic reactivity. Therefore, we replaced the base with sodium hydride (NaH) and repeated the modification reaction using bromoacetonitrile. The results indicated that this new reaction system not only efficiently afforded the desired compound **8**. Using this strongly basic system, we further synthesized compounds **10-15** by reacting petromurin C with various bromo-substituted nitrile reagents. However, when bromopropionitrile was employed, the expected compound **17** was not obtained; instead, only compound **9** was detected. This result confirms that substitution at the phenolic hydroxyl group does not occur during the modification of petromurin C with bromopropionitrile.

In this study, structural modifications were conducted using petromurin C as the initial substrate. Alkylation substitution reactions were employed to introduce nitrile groups onto phenolic hydroxyl groups and nitrogen atoms, resulting in the synthesis of 15 derivatives.

3.2. Biological Assay

3.2.1. Cytotoxic Activity

Table1. The cytotoxicity data of nitrile-containing petromurin C derivatives [IC_{50} (μM) ±SD]

Compounds	**MV4-11**	**K562**	**HL-60**	**L-02**	**293T**
1	14.86±0.63	>20	>20	>100	>100
2	12.96±0.22	>20	>20	>100	>100
3	15.60±0.53	>20	>20	>100	>100
4	16.35±1.19	>20	>20	>100	>100
5	>20	>20	>20	>100	>100
6	>20	>20	>20	>100	>100
7	19.65±0.36	>20	>20	>100	>100
8	20.00±0.65	>20	>20	>100	>100
9	14.81±0.70	>20	>20	>100	>100
10	18.42±0.92	>20	>20	>100	>100
11	>20	>20	>20	>100	>100
12	>20	>20	>20	>100	>100
13	>20	>20	>20	>100	>100
14	>20	>20	>20	>100	>100
15	>20	>20	>20	>100	>100
Cisplatin	0.13±0.01	-	-	-	-

The in vitro cytotoxic activities of all Petromurin C derivatives were assessed using the CCK-8 cytotoxicity assay, with the results presented in (Table 1). The study employed multiple cell lines, including MV4-11, HL-60, K-562, L-02, and 293T. The findings indicated that the derivatives exhibited significant inhibitory activity against human acute myeloid leukemia MV4-11 cells, with those substituted with aliphatic cyano groups demonstrating superior activity compared to derivatives with aromatic cyano substitutions. Notably, at a concentration of 100 μM, the synthesized derivatives exhibited low toxicity towards normal human cell lines L-02 and 293T. Although their potency against MV4-11 was lower than that of the positive control drug cisplatin, the derivatives demonstrated improved safety profiles.

3.2.2. Anti-Mycobacterium Tuberculosis Activity

Additionally, all derivatives were tested against *Mycobacterium tuberculosis*, with compound **15** exhibiting strong inhibitory activity, as evidenced by a minimum inhibitory concentration (MIC) value of 6.25 μM (Table 2).

Table2. The anti-*Mycobacterium tuberculosis* data (MIC, μM)

Compounds	**Indicator bacteria**
	M.tb H37Ra
1-14	>50
15	6.25
Isoniazid	0.03

4. Conclusion

In summary, we have successfully synthesized a series of nitrile-containing Petromurin C derivatives and conducted an in vitro evaluation of their anti-tumor and anti-*Mycobacterium tuberculosis* activities. The majority of the derivatives containing cyano groups demonstrated moderate efficacy against MV4-11 cells. Notably, compound **15** exhibited significant inhibitory activity against *Mycobacterium tuberculosis*. Furthermore, these derivatives were characterized by low toxicity towards normal cells. It is our aspiration that this research will contribute valuable insights to the field of drug discovery, particularly concerning chemical entities incorporating cyano groups.

Acknowledgements

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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