Chinese Chemical Letters 26 (2015) 113–117

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Synthesis of new penicillin derivatives as drug-like molecules for biological screening

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ARTICLE INFO

Article history:
Received 22 May 2014
Received in revised form 8 July 2014
Accepted 22 August 2014
Available online 16 September 2014

Keywords:
Penicillin
Rearrangement
β-Lactam antibiotics
Nucleophilic ring opening

ABSTRACT

Chemical modification of penicillin β-lactam ring was made. Six thiazolidine amides were produced through N4-C7 β-lactam ring opening of penicillin V methyl ester with various aliphatic, aromatic, and heterocyclic primary amines. Five 8-hydroxypenillic acid derivatives with side chains of methyl, propyl, benzyl, and diethylaminoethyl groups were yielded *via* β-lactam ring rearrangement from 6-aminopenicillanic acid (6-APA). Parallel synthetic methods were used for the alkylation of 8-hydroxypenillic acid and β-lactam ring opening of penicillin V methyl ester. The biological activities of the compounds were evaluated.

1. Introduction

Penicillins are β-lactam antibiotics to kill many gram-positive, gram-negative and anaerobic organisms by blocking peptidoglycan biosynthesis [1–8]. β-Lactams are 4-memebered cyclic amides, depicted in 6-aminopenicillanic acid (6-APA) in Fig. 1 [9,10]. Various bonds in β-lactam can undergo cleavage to give acyclic systems or result into rearranged cyclic derivatives [11–15]. Cleavage of β-lactam bond (N_4-C_7) and conversion of β-lactam ring into other cyclic systems have been studied [16–18]. Nucleophilic opening of β-lactam bond using a primary amine forms thiazolidine amides [19,20].

In this paper, chemical modification of penicillin β-lactam ring was undertaken. β-Lactam ring rearrangement of 6-APA produced 8-hydroxypenillic acid derivatives with side chains of methyl, propyl, benzyl, diethylaminoethyl, and 2-(bromomethyl)benzo[d]thiazole groups. β-Lactam ring opening of penicillin V methyl ester yielded thiazolidine amides with *p*-methoxybenzylamine, anisidine, benzyl amine, thiophene methylamine, cyclopropane methyl amine, and nonyl amine. Parallel synthetic methods were developed for esterification of 8-hydroxypenillic acid and β-lactam ring opening of penicillin V methyl ester.

2. Experimental

Column chromatography was carried out by employing silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed on a silica gel w/uv254 uniplate™. Anhydrous organic solvents were purchased. Parallel synthesis was conducted on Mettler Toledo MiniBlock and MiniBlock XT. Melting points were determined using a Barnstead International MET-TEMP® capillary melting point apparatus model 1001D-120VAC. IR spectra were measured with a Perkin Elmer™ Spectrum One FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer (400 and 100 MHz, respectively), or a 500 MHz spectrometer (500 and 125.5 MHz, respectively). Abbreviations were as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectrometry (HRMS) spectra were obtained on a double-focusing mass spectrometer.

2.1. Procedure for synthesis of intermediate penicillin V

Potassium (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-(2-phenoxyacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (penicillin V). To a cooled and stirred solution of 2.76 g (12.5 mmol) of 6-APA in 60 mL of water containing 5.25 g (62.5 mmol) of sodium bicarbonate, a solution of 2.76 g (16.2 mmol) phenoxyacetyl chloride in 5 mL of acetone was added in one minute. The resulting mixture was stirred vigorously during 20 min while the temperature was kept at 10–15 °C. The clear solution was

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http://dx.doi.org/10.1016/j.cclet.2014.09.008

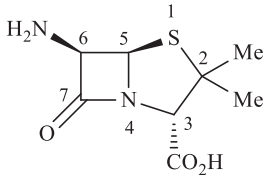

Fig. 1. Chemical structure of 6-aminopenicillanic acid (6-APA).

extracted twice with 15 mL portions of methyl isobutyl ketone (MIBK). The clear aqueous solution was cooled to 5–10 °C and acidified to pH 2 with a cold 5.0 mol/L sulfuric acid solution. The acidified aqueous solution was extracted with 50 mL MIBK twice. The MIBK extract was separated, washed with cold water, and dried for 10 min over anhydrous sodium sulfate. After filtration, 10 mL of a 25% solution of potassium 2-ethylhexanoate in butanol was added. The white crystalline material was collected by filtration, washed on the filter with dry acetone and dried *in vacuum*, yield 3.5 g (80%) penicillin V as a white solid. Mp: 210–211 °C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, 1H, J = 8.0 Hz), 7.27 (m, 2H), 6.92 (m, 3H), 5.42 (dd, 1H, J = 8.0 Hz, 4.0 Hz), 5.40 (d, 1H, J = 4.0 Hz), 4.62 (d, 2H, J = 2.2 Hz), 3.88 (s, 1H), 1.52 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.8, 169.0, 168.1, 158.1, 130.0, 121.7, 115.0, 74.6, 67.3, 66.7, 65.0, 57.8, 32.7, 27.8; HRMS (FAB) calcd. for $C_{16}H_{18}KN_2O_5S$ [M+H]$^+$: m/z 389.0584; found: 389.0995.

2.2. Procedure for synthesis of intermediate penicillin V methyl ester (*1*)

(2*S*,5*R*,6*R*)-Methyl 3,3-dimethyl-7-oxo-6-(2-phenoxyacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (**1**): Penicillin V (388 mg, 1.0 mmol) was suspended in 10 mL of dimethylformamide (DMF). Methyl iodide (1.4 g, 12.0 mmol) was added and stirred for 1 h at room temperature. After most of the solvent was removed under reduced pressure, the mixture was loaded on silica gel column for chromatography with EtOAc/hexane (1:9) as an eluent to yield product **1** (65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 2H), 7.04 (m, 1H), 6.93 (m, 2H), 5.75 (d, 1H, J = 4.0 Hz), 5.60 (d, 1H, J = 4.0 Hz), 4.57 (s, 2H), 4.49 (s, 1H), 3.80 (s, 3H), 1.61 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 168.1, 167.8, 156.9, 129.8, 122.4, 114.8, 70.5, 67.7, 67.1, 64.8, 58.0, 52.5, 31.8, 26.9; HRMS (FAB) calcd. for $C_{17}H_{21}N_2O_5S$ [M+H]$^+$: m/z 365.1170; found: 365.1194.

2.3. Procedure for synthesis of thiazolidine derivatives ***2a–2f***

(2*R*,4*S*)-Methyl 2-((*R*)-2-(4-methoxybenzylamino)-2-oxo-1-(2-phenoxyacetamido)ethyl)-5,5-dimethylthiazolidine-4-carboxylate (**2a**): Penicillin V methyl ester (**1**, 182.0 mg, 0.5 mmol) was taken in a round-bottomed flask and 15 mL of dry methylene chloride was added. Benzyl amine (108.0 mg, 1.0 mmol) was added at room temperature and the mixture was stirred overnight. Water was added into the mixture and the mixture was extracted with methylene chloride (2 × 20 mL). After washing with brine, the organic layer was dried over $NaSO_4$, concentrated and purified by column chromatography with EtOAc/hexane (1:1) as the eluent to yield product **2a** (55%) as a semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 1H, J = 7.36 Hz), 7.33–7.29 (m, 5H), 7.01 (m, 2H), 6.93 (m, 2H), 5.27 (s, 1H), 4.65 (m, 1H), 4.61 (m, 1H), 4.51 (s, 2H), 4.37 (dd, 1H, J = 5.9, 14.7 Hz), 3.75 (s, 3H), 3.55 (s, 2H), 1.48 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 168.9, 168.5, 157.1, 137.7, 129.7, 128.8, 127.9, 127.6, 122.1, 114.8, 72.6, 67.2, 65.4, 58.0, 56.8, 52.3, 43.8, 26.6, 26.4; HRMS (FAB) calcd. for $C_{24}H_{30}N_3O_5S$ [M+H]$^+$: m/z 472.1906; found: 472.1910.

(2*R*,4*S*)-Methyl 2-((*R*)-2-(4-methoxyphenylamino)-2-oxo-1-(2-phenoxyacetamido)ethyl)-5,5-dimethylthiazolidine-4-carboxylate (**2b**): Yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 7.67 (d, 1H, J = 6.4 Hz), 7.42 (m, 2H), 7.32 (m, 2H), 6.96 (m, 1H), 6.95 (m, 2H), 6.85 (m, 2H), 5.36 (m, 1H), 4.74 (m, 1H), 4.57 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.64 (s, 1H), 1.55 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 169.3, 166.6, 157.1, 156.7, 129.5, 129.8, 122.2, 121.8, 114.8, 114.2, 72.8, 67.3, 65.3, 58.0, 57.3, 55.5, 52.4, 26.8, 26.5; HRMS (FAB) calcd. for $C_{24}H_{30}N_3O_6S$ [M+H]$^+$: m/z 488.1855; found: 488.1849.

(2*R*,4*S*)-Methyl 5,5-dimethyl-2-((*R*)-2-oxo-1-(2-phenoxyacetamido)-2-(thiophen-3-ylmethylamino)ethyl)thiazolidine-4-carboxylate (**2c**): Yield: 63%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 1H, J = 7.56 Hz), 7.32 (m, 3H), 7.18 (s, 1H), 7.01 (m, 2H), 6.91 (m, 3H), 5.24 (d, 1H, J = 4.9 Hz), 4.72 (m, 1H), 4.62 (m, 1H), 4.52 (m, 1H), 4.50 (m, 2H), 3.73 (s, 3H), 3.56 (s, 2H), 1.47 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 168.9, 168.4, 157.1, 140.2, 129.7, 126.9, 126.2, 125.2, 122.1, 114.8, 72.5, 67.2, 65.5, 58.0, 56.7, 52.2, 38.2, 26.6, 26.5; HRMS (FAB) calcd. for $C_{22}H_{28}N_3O_5S_2$ [M+H]$^+$: m/z 478.1470; found: 478.1475.

(2*R*,4*S*)-Methyl 2-((*R*)-2-(benzylamino)-2-oxo-1-(2-phenoxyacetamido)ethyl)-5,5-dimethylthiazolidine-4-carboxylate (**2d**): Yield 54%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, 1H, J = 7.4 Hz), 7.46 (d, 1H, J = 8.0 Hz), 7.21 (m, 2H), 7.20 (m, 2H), 7.03 (m, 1H), 6.99 (m, 2H), 6.86 (m, 2H), 5.36 (m, 1H), 5.13 (m, 1H), 4.68 (m, 1H), 4.64 (m, 1H), 4.57 (m, 2H), 4.23 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 1.48 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 169.8, 168.3, 156.8, 137.8, 129.8, 128.6, 127.4, 122.0, 115.6, 74.9, 73.0, 72.4, 65.1, 58.0, 56.8, 52.3, 43.6, 26.5, 18.9; HRMS (FAB) calcd. for $C_{25}H_{32}N_3O_6S$ [M+H]$^+$: m/z 5 02.2011; found: 502.1992.

(2*R*,4*S*)-Methyl 2-((*R*)-2-(cyclopropylamino)-2-oxo-1-(2-phenoxyacetamido)ethyl)-5,5-dimethylthiazolidine-4-carboxylate (**2e**): Yield 64%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 1H, J = 7.7 Hz), 7.29 (m, 2H), 7.01 (m, 2H), 6.80 (m, 1H), 5.17 (d, 1H, J = 8.0 Hz), 4.51 (s, 1H), 4.50 (s, 2H), 3.75 (s, 3H), 3.66 (s, 1H), 2.70 (m, 1H), 1.53 (s, 3H), 1.19 (s, 3H), 0.73 (m, 2H), 0.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 169.8, 168.9, 157.2, 129.7, 122.1, 114.8, 72.7, 67.2, 65.8, 58.3, 56.8, 52.3, 27.0, 26.6, 22.7, 6.5, 6.4; HRMS (FAB) calcd. for $C_{20}H_{28}N_3O_5S$ [M+H]$^+$: m/z 422.1749; found: 422.1739.

(2*R*,4*S*)-Methyl 5,5-dimethyl-2-((*R*)-2-(nonylamino)-2-oxo-1-(2-phenoxyacetamido)ethyl)thiazolidine-4-carboxylate (**2f**): Yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 1H, J = 8 Hz), 7.24 (m, 2H), 6.98 (m, 1H), 6.90 (m, 2H), 6.84 (m, 1H), 5.15 (m, 1H), 4.57 (m, 1H), 4.48 (s, 1H), 3.71 (s, 3H), 3.68 (s, 1H), 3.51 (m, 1H), 3.17 (m, 2H), 1.51 (s, 3H), 1.45 (m, 2H), 1.21 (m, 14H), 1.17 (s, 3H), 0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 168.8, 168.7, 157.2, 129.6, 122.0, 114.8, 72.6, 67.3, 66.0, 58.3, 57.0, 52.1, 39.7, 31.8, 29.5, 29.4, 29.3, 29.2, 27.1, 26.9, 26.7, 22.6, 14.1; HRMS (FAB) calcd. for $C_{26}H_{42}N_3O_5S$ [M+H]$^+$: m/z 508.2845; found: 508.2828.

2.4. Procedure for synthesis of intermediate disodium salt of 8-hydroxypenillic acid (*3*)

Disodium 3,3-dimethyl-8-oxo-4-thia-1,7-diazabicyclo[3.3.0]-octane-2,6-dicarboxylic acid (**3**): Compound **3** was prepared in the method modified from Johnson and Hardcastle [17]. 4.5 g of 6-APA was dissolved in 100 mL of water containing 3.5 g (2.0 equiv.) of sodium bicarbonate. Carbon dioxide from dry ice was bubbled through the stirred mixture at room temperature for 24 h. The concentrated aqueous solution was then lyophilized overnight to yield 6.2 g (90%) of the product **3** as a pale yellow powder. Mp 228–230 °C (dec.). ^{1}H NMR (400 MHz, D_2O): δ 5.44 (d, 1H, J = 2.0 Hz), 4.15 (s, 1H), 4.13 (d, 1H, J = 2.0 Hz), 1.47 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, D_2O): δ 177.5, 175.9, 164.4, 73.6, 69.4, 59.5, 57.7,