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Concise Synthesis of Pelanserine, Goshuyuamide II, and Wuchuyuamide II with Quinazolinedione Nuclei

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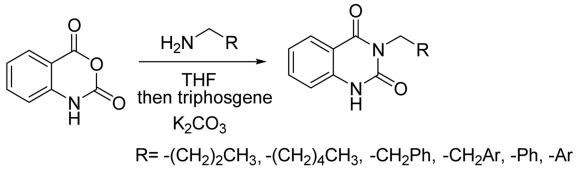
Quinazolinediones are important heterocycles[1] and have been shown to possess pharmacologically interesting properties, displaying, for example, anti-hypertensive,[2] anti-diabetic,[3] and immunosuppressive activities.[4] Among these, synthetic pelanserine (TR2515) (**1**)[5] is a well established potent anti-hypertensive agent, having activity comparable to the clinically used ketanserin[6] (Figure 1). Goshuyuamide II (**2**) is isolated from *Evodia officinalis*[7] and *E. rutaecarpa*.[8] Wuchuyuamide II (**3**) is isolated as a racemate from the fruit of *Evodia rutaecarpa*.[9] These plants have long been used as a traditional Chinese drugs (Chinese name "Wu-Zhu-Yu") in the treatment of headaches, abdominal pain, dysentery, postpartum haemorrhage, and amenorrhea.[10] This range of important biological activities and properties has stimulated research into the synthesis of pelanserine (**1**), goshuyuamide II (**2**), and wuchuyuamide II (**3**).

The synthesis of pelanserine (**1**) has already been reported by other group starting from isatoic anhydride in a 2-step reaction.[11] Before isolation of goshuyuamide II (**2**) as a natural product, the same compound was synthesized starting from isatoic anhydride in a 5-step reaction.[12] Although syntheses of pelanserine (**1**) and goshuyuamide II (**2**) have been reported, there is still demand for more concise and efficient synthetic routes. In particular, no synthesis of wuchuyuamide II (**3**) has been described thus far.

Recently, we developed a new and useful methodology for the one-step synthesis of a variety of quinazoline-2,4-diones starting from isatoic anhydride, primary amines, and triphosgene in the presence of a base (Scheme 1).[13] Using the developed methodology as a key step, we describe herein an efficient and concise synthesis of biologically active pelanserine (**1**) and naturally occurring two alkaloids, goshuyuamide II (**2**) and wuchuyuamide II (**3**).



Scheme 1

Results and Discussion

A one-step synthesis of perlanserine (**1**) was first attempted (Scheme 2). The reaction of isatoic anhydride (**4**) with readily available amine **5**[14] in THF at room temperature for 10 h was followed by further reaction by addition of triphosgene and K_2CO_3 at room temperature for 10 h to give pelanserine (**1**) in 40% yield. The structure of compound **1** was confirmed by ^{1}H NMR analysis and by direct comparison with reported data.[11]

Next, the total synthesis of goshuyuamide II (**2**) and wuchuyuamide II (**3**) were carried out as shown in Scheme 3. Treatment of **4** with tryptamine in THF at room temperature for 10 h followed by further reaction by the addition of triphosgene and K_2CO_3 at room temperature for 20 h provided **6** in 73% yield. Next, to convert **6** to goshuyuamide II (**2**), *N*-methylation of **6** was carried out. Reaction of **6** with one equivalent of methyl iodide in the presence of K_2CO_3 in THF provided the undesired product **7** (49%), which was *N*-methylated on the indole ring. In this reaction, no other products were produced. To protect the amine on the indole ring, *t*-butyl dicarbonate was used. Treatment of **6** with *t*-butyl dicarbonate in the presence of K_2CO_3 in refluxing THF

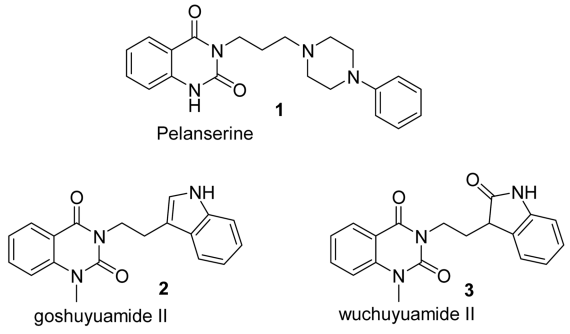
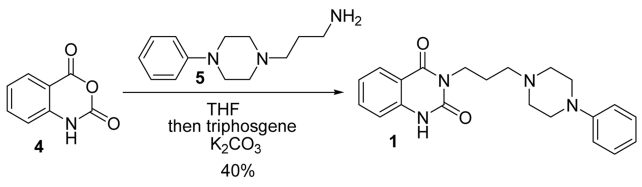
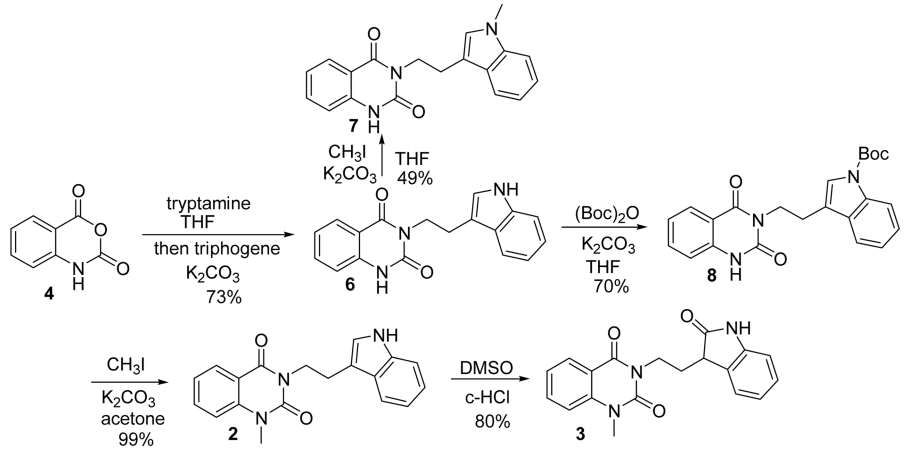


Figure 1



Scheme 2



Scheme 3

for 5 h gave **8** in 70% yield. *N*-Methylation of **8** with one equivalent of methyl iodide and K_2CO_3 in refluxing acetone for 4 h gave **2** in 99% yield. Importantly, in this step, deprotection of the Boc group was also accomplished to afford **2**. To complete the synthesis of wuchuyuamide II (**3**), the oxidation of the indole moiety of **2** was attempted according to a previously reported method.[15] Reaction of **2** with dimethyl sulfoxide and concentrated HCl provided **3** in 80% yield. The first total synthesis of wuchuyuamide II (**3**) was accomplished in a 4-step reaction. The spectroscopic data for synthetic materials **2** and **3** are in agreement with the reported data for the natural products.[8,9]

In conclusion, we have described the one-pot synthesis of biologically active pelanserine (**1**) starting from isatoic anhydride. Two naturally occurring alkaloids goshuyuamide II (**2**) and wuchuyuamide II (**3**) were also synthesized by a convergent sequence starting from isatoic anhydride. The overall yield of **2** was 51% in a 3-step reaction, and the yield of **3** was 40% in a 4-step reaction.

Experimental Section

All the experiments were carried out in a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model DPX (300 and 75 MHz, respectively) and a Varian VNS (600 and 150 MHz) spectrometer in $CDCl_3$, DMSO-d_6 or Pyridine-d_5. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer.

Pelanserine (1). To a solution of isatoic anhydride (163 mg, 1.0 mmol) in THF (15 mL) was added 3-(4-phenylpiperazin-1-yl)propan-1-amine (241 mg, 1.1 mmol). The mixture was stirred at room temperature for 10 h as CO_2 was evolved. Then triphosgene (296 mg, 1.0 mmol) and K_2CO_3 (690 mg, 5 mmol) was added and the resulting mixture was further stirred for 10 h to complete the reactions. The reaction mixture was quenched by the addition of aqueous saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic layer was washed with water (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give solid. The solid was recrystallized by ethanol to give pure product **1** (146 mg, 40%). mp 200-204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (1H, s), 8.12 (1H, d, J = 8.1 Hz), 7.56 (1H, t, J = 8.4 Hz), 7.25-7.18 (3H, m), 7.09 (1H, d, J = 8.1 Hz), 6.87-6.79 (3H, m), 4.19 (2H, t, J = 6.9 Hz), 3.12 (4H, m), 2.61-2.52 (6H, m), 2.01-1.92 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 152.3, 151.4, 138.7, 134.9, 129.0, 128.4, 123.3, 119.6, 116.0, 114.9, 114.7, 56.0, 53.1, 49.1, 39.6, 24.7; IR (KBr) 3428, 3055, 2929, 2829, 1712, 1660, 1600, 1499, 1452, 1411, 1378, 1283, 1239, 1150, 1059, 923, 814, 758 cm^{-1}.

3-[(2-(1*H*-indol-3-yl)ethyl]quinazoline-2,4(1*H*,3*H*)-dione (6). To a solution of isatoic anhydride (163 mg, 1.0 mmol) in THF (15 mL) was added tryptamine (176 mg, 1.1 mmol). The mixture was stirred at room temperature for 10 h as CO_2 was evolved. Then triphosgene (296 mg, 1.0 mmol) and K_2CO_3 (690 mg, 5 mmol) was added and the resulting mixture was further stirred for 20 h to complete the reaction. The reaction mixture was quenched by the addition of aqueous saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic layer was washed with water (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give solid. The solid was recrystallized by ethanol to give pure product **6** (223 mg, 73%). mp 306-307 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.3 (1H, s), 10.80 (1H, s), 7.98 (1H, d, J = 7.5 Hz), 7.69 (1H, d, J = 7.5 Hz), 7.65 (1H, dd, J = 7.8, 7.0 Hz), 7.35 (1H, d, J = 7.8 Hz), 7.23-7.18 (3H, m), 7.08 (1H, dd, J = 7.5, 7.0 Hz), 7.00 (1H, dd, J = 7.5, 7.0 Hz), 4.17 (2H, t, J = 8.1 Hz), 2.99 (2H, t, J = 8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.8, 150.0, 139.2, 136.2, 134.6, 127.0, 122.5, 122.1, 120.7, 118.1, 114.9, 113.7, 111.1, 111.0, 40.5, 23.3; IR (KBr) 3366, 3063, 1706, 1645, 1448, 1349, 1281, 1104, 1003, 740 cm^{-1}.

3-[(2-(1-Methyl-1*H*-indol-3-yl)ethyl]quinazoline-2,4(1*H*, 3*H*)-dione (7). To a solution of **6** (153 mg, 0.5 mmol) in acetone (10 mL) was added methyl iodide (70 mg, 0.5 mmol) and K_2CO_3 (345 mg, 2.5 mmol). The mixture was

stirred at reflux for 10 h. Then the reaction mixture was quenched with NH_4Cl solution (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic layer was washed with water (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the residue. Chromatography on silica gel using hexane/ethyl acetate (1:1) afforded **7** (78 mg, 49%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.63 (1H, d, J = 7.8 Hz), 7.34 (1H, d, J = 8.1 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.21 (1H, t, J = 7.8 Hz), 7.14 (2H, d, J = 7.8 Hz), 6.96 (1H, br s), 6.66 (1H, d, J = 8.1 Hz), 6.50 (1H, t, J = 7.8 Hz), 3.75-3.69 (2H, m), 3.07-3.03 (2H, m), 2.84 (3H, s); IR (KBr) 3408, 3051, 2925, 1915, 1721, 1632, 1586, 1515, 1453, 1426. 1331, 1276, 1171, 1094, 745 cm^{-1}.

***t*-Butyl-3-[(2-(2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)ethyl]-1*H*-indole-1-carboxylate (8).** To a solution of **6** (305 mg, 1.0 mmol) in THF (10 mL) was added *t*-butyl dicarbonate (262 mg, 1.2 mmol) and K_2CO_3 (690 mg, 5.0 mmol). The mixture was stirred at reflux for 5 h. Then the reaction mixture was quenched with NH_4Cl solution (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic layer was washed with water (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the residue. Chromatography on silica gel using hexane/ethyl acetate (4:1) afforded **8** (284 mg, 70%) as an oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (1H, d, J = 7.8 Hz), 8.00 (1H, s), 7.86 (1H, d, J = 7.8 Hz), 7.63 (1H, t, J = 7.8 Hz), 7.34 (1H, d, J = 7.8 Hz), 7.28 (1H, t, J = 7.5 Hz), 7.19-7.11 (3H, m), 7.06 (d, J = 8.1 Hz), 4.35-4.32 (2H, m), 3.17-3.14 (2H, m), 1.69 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4, 149.2, 148.6, 137.0, 136.2, 135.0, 129.0, 127.5, 123.9, 122.1, 119.5, 119.3, 114.6, 113.4, 112.7, 111.0, 87.1, 42.1, 27.6, 23.7; IR (KBr) 3382, 3055, 2976, 2920, 2852, 1768, 1709, 1663, 1611, 1479, 1400, 1364, 1285, 1242, 1144, 1013, 838, 742 cm^{-1}.

Goshuyuamide II (2). To a solution of **8** (200 mg, 0.49 mmol) in acetone (10 mL) was added methyl iodide (70 mg, 0.49 mmol) and K_2CO_3 (339 mg, 2.50 mmol). The mixture was stirred at reflux for 4 h. Then the reaction mixture was quenched with NH_4Cl solution (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic layer was washed with water (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the residue. Chromatography on silica gel using hexane/ethyl acetate (1:1) afforded **2** (155 mg, 99%) as a white solid. mp 205-209 °C; ^{1}H NMR (300 MHz, Pyridine-d_5) δ 11.67 (1H, s), 8.37 (1H, d, J = 7.8 Hz), 8.29-8.28 (1H, m), 7.62-7.55 (2H, m), 7.36 (1H, br s), 7.29-7.26 (2H, m), 7.24-7.19 (1H, m), 7.13 (1H, d, J = 7.8 Hz), 4.67-4.61 (2H, m), 3.48 (3H, s), 3.48-3.44 (2H, m); ^{13}C NMR (75MHz, Pyridine-d_5) δ 161.7, 151.0, 141.0, 137.7, 135.0, 128.6, 122.7, 121.8, 119.5, 119.3, 116.0, 114,1, 112.5, 111.9, 42.9, 30.4, 24.5; IR (KBr) 3341, 1693, 1648, 1485, 1429, 1398, 1350, 1098, 747 cm^{-1}.

Wuchuyuamide II (3). To a solution of **2** (100 mg, 0.31 mmol) in DMSO (22mL) was added concentrated HCl (51 mL) at 0 °C. The reaction mixture was stirred for 4.5 h at room temperature. Then reaction mixture was diluted with water (50 mL), neutralized with sodium hydrogen carbonate (50 mL), and extracted with ethyl acetate (100 mL × 3), dried ($MgSO_4$), and evaporated under reduced pressure to give the residue. Chromatography on silica gel using hexane/ethyl acetate (1:1) afforded **3** (83 mg, 80%) as a solid. mp 95-105 °C; ^{1}H NMR (300 MHz, Pyridine-d_5) δ 8.18 (1H, s), 8.14 (1H, d, J = 7.8 Hz), 7.62 (1H, t, J = 7.5 Hz), 7.32 (1H, d, J = 7.5 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.12 (1H, d, J = 7.8 Hz), 7.08 (1H, t, J = 7.8 Hz), 6.89 (1H, d, J = 7.8 Hz), 6.80 (1H, d, J = 7.8 Hz), 4.47-4.37 (1H, m), 4.23-4.14 (1H, m), 3.61-354 (1H, m), 3.51 (3H, s), 2.56-2.40 (1H, m), 2.31-2.22 (1H, m); ^{13}C NMR (75 MHz, Pyridine-d_5) δ 180.0, 162.3, 151.4, 144.4, 141.4, 135.5, 130.8, 129.1, 128.6, 125.2, 123.2, 122.2, 116.4, 114.7, 110.2, 45.1, 40.1, 30.9, 29.5; IR (KBr) 3448, 2960, 1704, 1654, 1615, 1485, 1433, 1401, 1357, 1261, 1197, 1107, 935, 754 cm^{-1}.

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