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Research Article

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Synthesis and antitumor activity *in vitro* of glioperazine C and its derivatives

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ABSTRACT

Glioperazine C, a naturally occurring diketopiperazine, together with its thirteen derivatives, were synthesized in 35-47% overall yields. The first total synthesis of glioperazine C was achieved by intermolecular condensation and intramolecular cyclization. Their structures were characterized on the basis of ^{1}H, ^{13}C NMR, and those compounds were evaluated for their anticancer activities against K562, HT-29 and HepG2 cell lines. Results showed that glioperazine C containing D-Trp and D-Thr demonstrated potent anticancer activity against HepG2 cell line (IC_{50}=6.51μM).

Keywords: Glioperazine C, Dioxopiperazine, Cyclic dipeptides, Anticancer

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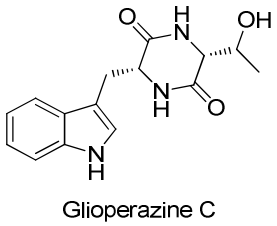
INTRODUCTION

2,5-Diketopiperazines are cyclic dipeptides from two amino acids with or without further structural modifications. These 2,5-diketopiperazines possessed attractive bioactivities including anti-tumor, neuroprotective, immune and metabolic regulatory, oxytocin inhibitory and anti-inflammatory effects, antibiotic activity, etc.[1] Glioperazine C (Fig.1), a natural 2,5-diketopiperazine containing an indole fragment, was first isolated from the mycelia of liquid fermentation culture of fungus (*Bionectra byssicola* F120) in 2007.[2] The development of convenient and efficient synthetic approaches for the preparation of large quantities of glioperazine C and their analogies would be highly desirable for their biological studies. Herein, we would like to report the synthesis and the antitumor evaluation *in vitro* of glioperazine C and its cyclic dipeptides derivatives.



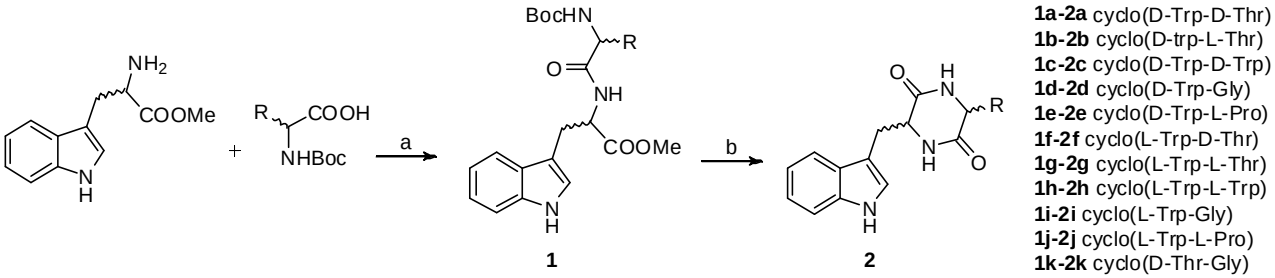
Glioperazine C

Fig. 1 The structure of glioperazine C

EXPERIMENTAL SECTION

All reagents and solvents were purchased from commercially suppliers and used without further purification. ^{1}H NMR spectra were recorded with a Bruker AM-400 NMR spectrometer with $CDCl_3$-d_6 or DMSO-d_6 as the solvent. ^{13}C NMR spectra were recorded at 100 MHz. All chemical shifts (δ_H and δ_C) were reported in parts per million (ppm) and the coupling constants were measured in hertz (Hz). Thin layer chromatography was performed using silica gel 60 F_{254} plates (Merck) with observation under UV when necessary. Chromatography was performed on 230-400 mesh silica gel.

2.2.1 Synthesis route of glioperazine C and its derivatives



1a-2a cyclo(D-Trp-D-Thr)
1b-2b cyclo(D-trp-L-Thr)
1c-2c cyclo(D-Trp-D-Trp)
1d-2d cyclo(D-Trp-Gly)
1e-2e cyclo(D-Trp-L-Pro)
1f-2f cyclo(L-Trp-D-Thr)
1g-2g cyclo(L-Trp-L-Thr)
1h-2h cyclo(L-Trp-L-Trp)
1i-2i cyclo(L-Trp-Gly)
1j-2j cyclo(L-Trp-L-Pro)
1k-2k cyclo(D-Thr-Gly)
1l-2l cyclo(D-Thr-D-Thr)

Condition and reagents. a) EDC, HOBt, Et_3N, DCM, r.t. 72%-90%; b) 1,4-dioxane/H_2O, 150 °C, 60%-73%.

Scheme 1. Synthesis route of glioperazine C and its derivatives

2.2.1.1 General procedure for the synthesis of N-Boc-dipeptide methyl esters (1a-1l) [3] [4]

To a solution of D/L-tryptophan methyl esters (5.0 mmol) in CH_2Cl_2, EDC (6.0 mmol), Et_3N (6 mmol), HOBT (6.0 mmol) and N-Boc-amino acids (6.0 mmol) was added at room temperature. The solution was stirred at room temperature for 3-5 h. After completion of the reaction, the solution was washed with brine (20 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The products (**1a-1l**) were obtained by purification with silica gel column chromatography (DCM:MeOH=100:1) in 72-90 % of yields.

2.2.1.2 General procedure for the synthesis of cyclic dipeptides (2a-2l) [5]

N-Boc-dipeptide methyl esters (**1a-1l**, 4.0 mmol) was dissolved in 20 mL of 1,4-dioxane/H_2O (1:3, v/v) in sealed tube. The solution was stirred at 150 °C for 10-16 h. After completion of the reaction, the crude products were obtained by evaporation under reduced pressure. The crude product was washed with water, ethanol and dichloromethane to give **2a-2l** in 63-82 % of yields.

Glioperazine C (**2a**). White solid, 63 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 0.2 Hz, 1H), 7.04 (t, *J* = 7.2Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 4.99 (d, *J* = 5.6 Hz, 1H), 3.92 (s, 1H), 3.87-3.63 (m, 1H), 3.49 (d, *J* = 28.4 Hz, 1H), 3.20 (t, *J* = 16.1 Hz, 2H), 0.94 (d, *J* = 6.5 Hz, 3H) ; ^{13}C NMR (100 MHz, DMSO-d_6) 20.1, 31.6, 56.2, 60.9, 67.7, 110.2, 111.7, 118.7, 119.0, 121.3, 124.5, 128.1, 136.6, 166.9, 168.4.

(3R,6S)-3-((1H-indol-3-yl)methyl)-6-((R)-1-hydroxyethyl)piperazine-2,5-dione (**2b**). White solid, 65 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 7.89 (s, 1H), 7.81 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.13 (s, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 4.96 (d, *J* = 4.8 Hz, 1H), 4.17 (d, *J* = 4.0 Hz, 1H), 3.95 (m, 1H), 3.26 (m, 4H), 1.03 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 20.2, 27.7, 54.6, 60.8, 68.4, 109.3, 111.6, 118.8, 119.0, 121.3, 124. 9, 128.2, 136.3, 168.5, 169.1.

(3S,6S)-3,6-bis((1H-indol-3-yl)methyl)piperazine-2,5-dione (**2c**). White solid, 60 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 2H), 7.69 (s, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 7.2 Hz, 2H), 6.95 (t, *J* = 7.2 Hz, 2H), 6.60 (d, *J* = 0.2 Hz, 2H), 3.87 (s, 2H), 2.71 (dd, 2H), 2.19 (dd, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 30.5, 30.5, 55.8, 55.8, 109.3, 109.3, 111.7, 111.7, 118.8, 118.8, 119.0, 119.0, 121.3, 121.3, 124.9, 124.9, 127.8, 127.8, 136.5, 136.5, 167.2, 167.2.

(S)-3-((1H-indol-3-yl)methyl)piperazine-2,5-dione (**2d**). White solid, 70%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91

(s, 1H), 8.08 (s, 1H), 7.75 (s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 6.6 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 4.01 (d, *J* = 2.6 Hz, 1H), 3.57 (s, 1H), 3.34 (m, 1H), 3.28 (d, *J* = 2.6 Hz, 1H), 3.25 (d, *J* = 4.6 Hz, 1H), 3.22 (d, *J* = 4.6 Hz, 1H), 3.03 (d, *J* = 4.5 Hz, 1H), 3.00 (d, *J* = 4.5 Hz, 1H), 2.82 (s, 1H), 2.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 29.6, 44.4, 55.7, 107.4, 113.6, 117.9, 120.2, 123.5, 126.1, 128.9, 135.4, 168.3, 169.3.

(3S,8aR)-3-((1H-indol-3-yl)methyl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (**2e**). White solid, 60 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.02 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 6.98 (s, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 4.60 (d, *J* = 4.7 Hz, 1H), 3.94-4.20 (m, 1H), 3.36 (m, 1H), 3.20 (m, 2H), 3.00 (dd, 1H), 1.9 (m, 1H), 1.52-1.74 (m, 2H), 1.23-1.45 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 22.3, 26.3, 28.2, 55.6, 58.8, 108.8, 112.3, 117.6, 118.6, 121.8, 123.9, 127.8, 135.4, 164.9, 168.4.

(3R,6S)-3-((1H-indol-3-yl)methyl)-6-((S)-1-hydroxyethyl)piperazine-2,5-dione (**2f**). White solid, 72 %. ^{1}H NMR (400 MHz, DMSO-d_6) 10.84 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.80 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 4.92 (d, *J* = 5.6 Hz, 1H), 4.18 (t, *J* = 4.4 Hz, 1H), 3.94 (dd, 1H), 3.21 (dt, 1H), 3.17 (s, 1H), 3.09 (dd, 1H), 1.03 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 20.2, 27.7, 54.6, 60.9, 68.4, 109.4, 111.6, 118.7, 119.4, 121.2, 124.9, 128.2, 136.3, 168.5, 169.0.

(3R,6R)-3-((1H-indol-3-yl)methyl)-6-((R)-1-hydroxyethyl)piperazine-2,5-dione (**2g**). White solid, 68 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.02 (s, 1H), 7.78 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.15 (s, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 4.98 (d, *J* = 5.8 Hz, 1H), 3.92 (s, 1H), 3.76 (s, 1H), 3.52 (s, 1H), 3.22 (d, *J* = 6.0 Hz, 2H), 0.94 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 20.1, 31.6, 56.2, 60.9, 67.7, 110.2, 111.7, 118.7, 119.0, 121.3, 124.5, 128.1, 136.6, 166.9, 168.4.

(3R,6R)-3,6-bis((1H-indol-3-yl)methyl)piperazine-2,5-dione (**2h**). White solid, 60 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 2H), 7.69 (s, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.04 (t, *J* =7.2, 2H), 6.95 (t, *J* =7.2, 2H), 6.60 (d, *J* = 0.2 Hz, 2H) , 3.87 (s, 2H), 2.71 (dd, 2H), 2.19 (dd, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 30.5, 30.5, 55.8, 55.8, 109.2, 109.2, 111.7, 111.7, 118.8, 118.8, 119.0, 119.0, 121.3, 121.3, 124.9, 124.9, 127.8, 127.8, 136.5, 136.5, 167.2, 167.2.

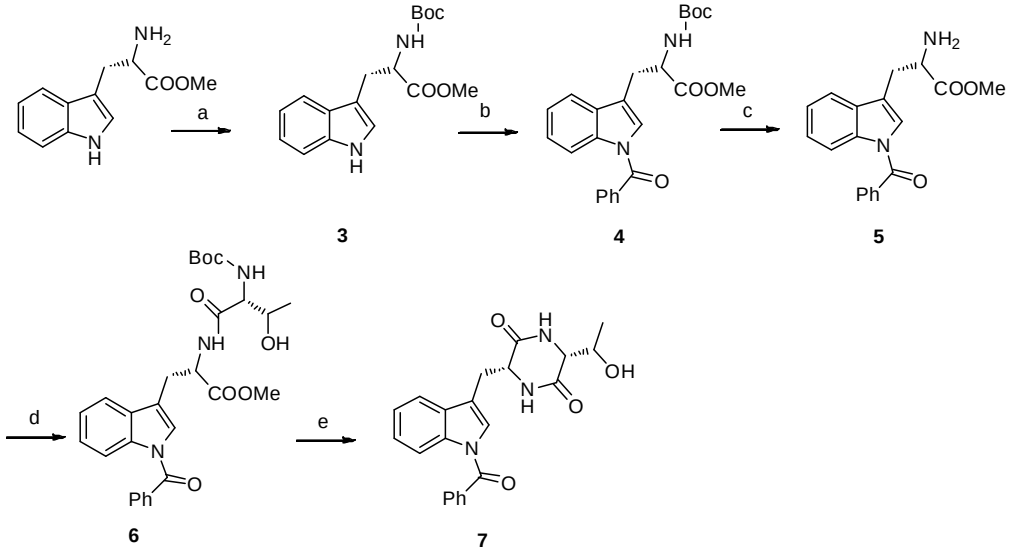
(R)-3-((1H-indol-3-yl)methyl)piperazine-2,5-dione (**2i**). White solid, 70 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.08 (s, 1H), 7.75 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 4.01 (d, *J* = 2.6 Hz, 1H), 3.57 (s, 1H), 3.33 (d, *J* = 2.6 Hz, 1H), 3.28 (d, *J* = 2.6 Hz, 1H), 3.24 (dd,1H), 3.02 (dd, 1H), 2.82 (s, 1H), 2.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 29.7, 44.3, 55.9, 108.9, 111.7, 118.9, 119.2, 121.4, 125.1, 127.9, 136.4, 166.2, 168.4.

(3R,8aR)-3-((1H-indol-3-yl)methyl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (**2j**). White solid, 65 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 7.73 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 4.30 (d, *J* = 4.7 Hz, 1H), 4.0 (m, 1H), 3.4 (m, 1H), 3.2 (m, 2H), 3.07 (dd, 1H), 1.9 (m, 1H), 1.6 (m, 2H), 1.3 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 22.3, 26.2, 28.1, 55.7, 58.9, 109.8, 111.7, 118.7, 119.1, 121.3, 124.9, 127.8, 136.4, 165.9, 169.5.

(S)-3-((S)-1-hydroxyethyl)piperazine-2,5-dione (**2k**). White solid, 68 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.95 (s, 1H), 5.06 (d, *J* = 6.0Hz, 1H), 4.02 (d, *J* = 6.0 Hz 1H), 3.83 (d, *J* = 16.8Hz 1H), 3.46 (d, *J* = 16.8Hz, 1H), 3.42 (s,1H), 1.08 (d, *J*=6.0,1H); ^{13}C NMR (100 MHz, DMSO-d_6) 20.4, 44.8, 61.2, 68.7, 167.4, 168.6.

(3S,6S)-3,6-bis((S)-1-hydroxyethyl)piperazine-2,5-dione (**2l**). White solid, 61 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 3H), 5.13 (d, *J* = 4.0Hz 2H), 3.99 (s, 2H), 3.33 (s, 2H), 1.10 (d, *J* = 4.0Hz 6H); ^{13}C NMR (100 MHz, DMSO-d_6) 20.8, 20.8, 60.8, 60.8, 67.8, 67.8, 166.9, 166.9.

2.2.2 Synthesis route of benzoyl substituted glioperazine C



Condition and reagents. a)Na_2CO_3, Et_3N $(Boc)_2O$, r.t.; b)Et_3N, DMAP, DCM, r.t; c)TFA, DCM, r.t.; d) EDC, HOBt, Et_3N, DCM, r.t.; e) 1,4-dioxane/H_2O, 150 °C

Scheme 2. Synthesis route of benzoyl substituted glioperazine C

2.2.2.1 (S)-methyl -2-((tert-butoxycarbonyl)amino)-3-(1H-indol-3-yl)propanoate (3)

To a stirred solution of D-tryptophan methyl ester (1.1 g, 5.0 mmol) and Et_3N (6.0 mmol, 0.88 mL) in 10 % Na_2CO_3 (15 mL) was slowly added $(Boc)_2O$ (6.0 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. After completion of the reaction, the solution was extracted with CH_2Cl_2 (15 mL×3) . The organic layers were combined and dried over anhydrous Na_2SO_4 and evaporated . The crude product was used in the next step without further purification.

2.2.2.2 (S)-methyl-3-(1-benzoyl-1H-indol-3-yl)-2-((tert-butoxycarbonyl) amino) propanoate (4)

To a stirred solution of compound **3** (844 mg, 2.0 mmol) in anhydrous CH_2Cl_2 was slowly added Et_3N (2.4 mmol, 0.35 mL), DMAP (0.2 mmol, 24 mg), benzoyl chloride (2.4 mmol, 0.28 mL) at 0 °C. The mixture was stirred at room temperature for 3 h under Ar. The reaction was quenched with water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated . The residue was purified by silica gel column chromatography (PE:EA=3:1) to give product **4** in 89 % yield.

2.2.2.3 (S)-methyl -2-amino-3-(1-benzoyl-1H-indol-3-yl)propanoate (5)

To a stirred solution of compound **4** (1.0 g, 0.24 mmol), in CH_2Cl_2 (5 mL) was dropwise added TFA (1.0 mL) at 0 °C. The solution was stirred at room temperature for 30 min. The reaction mixture was evaporated and the residue was used in the next step without further purification.

2.2.2.4(S)-methyl-3-(1-benzoyl-1H-indol-3-yl)-2-((2R,3R)-2-((tert-butoxycarbonyl)amino)-3-hydroxy butanamido) propanoate (6)

To a solution of (S)-methyl-2-amino-3-(1-benzoyl-1H-indol-3-yl)propanoate TFA salt (500 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) , EDC (230 mg, 1.3 mmol), Et_3N (0.18 mL, 2.4 mmol), HOBT (178 mg, 1.3 mmol) and N- Boc-D-Thr (289 mg, 1.3 mmol) was added at room temperature. The solution was stirred at room temperature for 4 h. After completion of the reaction, the solution was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated .The crude product was purified by silica gel column chromatography (DCM:MeOH=100:1) to gave compound **6** in 63 % yield.

2.2.2.5 (3R,6R)-3-((1-benzoyl-1H-indol-3-yl)methyl)-6-((R)-1-hydroxyethyl) piperazine-2,5-dione (7)

(S)-methyl-3-(1-benzoyl-1H-indol-3-yl)-2-((2R,3R)-2-((tert-butoxycarbonyl) amino)-3-hydroxy butanamido) propanoate (524 mg, 1 mmol) was dissolved in 5 mL of 1,4-dioxane/H_2O (1:3, v/v) in sealed tube. The solution was stirred at 150 °C for 12 h. After completion of the reaction, the crude products were obtained by evaporation under reduced pressure. The crude product was washed with water, ethanol and CH_2Cl_2 to give compound **7** in 40 % yield. White solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 7.9 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H), 8.05 (d, J = 2.4 Hz,

1H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.69 (dd, 2H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.36 (dt, 6.9 Hz, 2H), 7.28 (s, 1H), 5.08 (d, *J* = 5.7 Hz, 1H), 3.9 (m, 2H), 3.53 (s, 1H), 3.19 (dd, 2H), 1.02 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) 20.2, 31.1, 55.3, 60.9, 74.1, 116.3, 117.6, 119.7, 124.1, 125.1, 126.8, 129.2, 129.6, 131.5, 131.5, 132.5, 132. 6, 134.7, 136.2, 167.1, 168.1, 168.5.

2.3 Biological assay [6]

K562, Hep2 and HT-29 Cellswere cultured in 96-well plates at a density of 5×10^4 cells per well. Cells were treated with different concentrations of compounds in DMSO and incubated at 37 °C for 48 h. Cell viability was measured by a Cell Titer-Blue reagent-based assay. MTT assay was performed using Thermo microplate reader. The DMSO-treated controls were calculated as a cell viability value of 100%. The IC_{50} values were obtained by nonlinear regression using Graph Pad Prism 4.0. IC_{50} measurements for each compound were done three times.

RESULTS AND DISCUSSION

Thirteen synthesized cyclic dipeptides **2a-2l** and **7** were evaluated against K562, Hep2 and HT-29 Cells by MTT assay. The observed IC_{50} value is presented in Table 1.

Table 1 Cell growth inhibition of compounds 2a-2l and 7.

Compd		IC_{50} (μM)		
		K562	Hep2	HT-29
2a	cyclo(D-Trp-D-Thr)	>100	6.51	>100
2b	cyclo(D-Trp-L-Thr)	>100	>100	>100
2c	cyclo(D-Trp-D-Trp)	>100	>100	>100
2d	cyclo(D-Trp-Gly)	>100	>100	>100
2e	cyclo(D-Trp-L-Pro)	>100	>100	>100
2f	cyclo(L-Trp-D-Thr)	>100	>100	>100
2g	cyclo(L-Trp-L-Thr)	>100	>100	>100
2h	cyclo(L-Trp-L-Trp)	>100	>100	>100
2i	cyclo(L-Trp-Gly)	>100	>100	>100
2j	cyclo(L-Trp-L-Pro)	>100	>100	>100
2k	cyclo(D-Thr-Gly)	>100	>100	>100
2l	cyclo(D-Thr-D-Thr)	>100	>100	>100
7		>100	>100	>100

[a]Results are the average of three independent experiments, each done in duplicate. Standard deviations were below ±20%. [b] Acarbose is a reference compound.

As is shown in Table 1, compound **2a**, containing cyclo(D-Trp-D-Thr), exhibit potent inhibitory activities against Hep2 cell line with IC_{50} = 6.51 μM. However, the activity decreased after the cyclic dipeptide **2a** were modified from D-Trp-D-Thr into different sequences [D-Trp-D-Trp (**2c**), D-Trp-Gly (**2d**), D-Trp-L-Pro (**2e**), L-Trp-L-Trp (**2g**), L-Trp-L-Trp (**2h**), L-Trp-Gly (**2i**), L-Trp-L-Pro (**2j**), D-Thr-Gly (**2k**) and D-Thr-D-Thr (**2l**)] or various absolute configurations (D-Trp-L-Thr (**2b**), L-Trp-L-Thr (**2g**) and L-Trp-D-Thr (**2f**)]. Therefore, the sequence and configuration of **2a** were essential for the inhibitory activity. Moreover, replacement of the N-1-H in **2a** with the bulky benzoyl group as seen in compound **7** resulted in a decrease in activity.

CONCLUSION

In summary, we have synthesized glioperazine C and its derivatives and tested their antitumor activities against K562, Hep2 and HT-29 cell lines. The results show that glioperazine C has potent inhibitory activities against Hep2 cell line. The preliminary SAR study of these compounds led to the identification of a potent cytotoxic compound **2a**. Further modification of other position on glioperazine C and some other derivatives are ongoing.

Acknowledgment

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