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Tổng hợp và đánh giá độc tính tế bào của các dẫn xuất benzimidazole kết hợp amino acid

TÓM TẮT

Benzimidazole và các dẫn xuất của nó thể hiện hoạt tính sinh học đa dạng như kháng khuẩn, kháng virus, kháng viêm và đặc biệt là kháng ung thư. Hơn nữa, các báo cáo cũng cho thấy tiềm năng của các cấu trúc kết hợp giữa benzimidazole và amino acid/peptide trong nghiên cứu thiết kế các tác nhân kháng khuẩn và kháng ung thư mới. Trong báo cáo này, một qui trình tổng hợp hiệu quả gồm ba bước đã được phát triển thành công hướng đến các cấu trúc lai hóa bằng cách kết hợp các amino acid vào khung benzimidazole. Dựa trên qui trình này, sáu dẫn xuất benzimidazole kết hợp amino acid mới đã được tổng hợp thành công với hiệu suất từ khá đến tốt (45-80%). Cấu trúc của các dẫn xuất này đã được xác định đầy đủ dựa trên các dữ liệu phổ nghiệm bao gồm HR-ESI-MS, 1D và 2D NMR. Thử nghiệm độc tính tế bào cho thấy các hợp chất **7a** và **7c** có độc tính tế bào từ trung bình đến khá tốt đối với ba dòng tế bào ung thư ở người bao gồm A549, HeLa và MCF-7. Đáng chú ý, hợp chất **7c** (IC_{50} = 18,88 µM) mang nhóm L-phenylalanine ethyl ester thể hiện độc tính tốt trên dòng tế bào MCF-7 so với đối chứng dương 5-fluorouracil (IC_{50} = 8,59 µM).

Từ khóa: *Amino acid, benzimidazole, độc tính tế bào, hợp chất dị vòng, lai hóa phân tử.*

Synthesis and cytotoxicity evaluation of benzimidazole conjugated amino acid derivatives

ABSTRACT

Benzimidazole and its derivatives displayed diverse biological activities such as antimicrobial, antiviral, anti-inflammatory, and especially anticancer. Furthermore, it was also reported that the benzimidazole and amino acid/peptide conjugates displayed potential in designing novel antimicrobial and anticancer agents. In this report, an efficient three-step synthetic method has been successfully developed towards hydrid structures by incorporating amino acids into the benzimidazole scaffold. Based on this procedure, six novel benzimidazole-conjugated amino acid derivatives have been successfully synthesized in reasonable to good yields (45–80%). The structures of these derivatives were fully determined based on spectroscopic data including HR-ESI-MS, 1D and 2D NMR. Cytotoxicity assays indicated that compounds **7a** and **7c** possessed moderate to rather good cytotoxicities against the three human cancer cell lines including A549, HeLa and MCF-7. Notedly, compound **7c** (IC_{50} = 18.88 μM) with the L-phenylalanine ethyl ester moiety displayed good cytotoxicity on the MCF-7 cell line as compared to the positive control 5-fluorouracil (IC_{50} = 8.59 μM).

Keywords: *Amino acids, benzimidazole, cytotoxicity, heterocyclic compounds, molecular hybridization.*

1. INTRODUCTION

Nitrogen-containing heterocyclic compounds have exhibited diverse pharmacological activities, due to the ability of the nitrogen atom to easily form hydrogen bonding with biological receptors.[1] Among those, benzimidazole, an integral part of the structure of vitamin B_{12}, has exhibited a broad spectrum of biological activities including antimicrobial,[2] antiviral,[3] anti-inflammatory,[4] antiulcer,[5] and especially anticancer.[6-9] Several anticancer drugs bearing the benzimidazole moiety's core structure have been approved by the FDA such as bendamustine for treating chronic lymphocytic leukemia, selumetinib for treating neurofibromatosis type 1, binimetinib for treating certain types of melanoma.

Besides, α-amino acids played a crucial role in the human body, from building proteins to participating in critical metabolic functions. These structural features have been commonly employed in drug synthesis and structural modification. Conjugation of pharmacophores and amino acids was reported to produce new hybrid molecules with enhanced pharmacological activity,[10] improved water solubility,[11] and reduced cytotoxicity.[12]

Several benzimidazole-conjugated amino acid derivatives have been known to demonstrate as lead anticancer agents. As shown in Figure 1, the poly (ADP-ribose) polymerase (PARP) inhibitor, veliparib[13] (an anticancer drug) and the strong cytotoxic agent, compound **1**[14] share the common structural features of a benzimidazole core conjugated to an amino acid moiety at the C-2 position. Additionally, compound **2**[15] bearing the tryptophan moiety at the C-5 position of the heterocycle ring, acted as a potent sirtuin (Sirt) inhibitor. In light of these facts and in the hope to obtain novel compounds with significant anticancer activity, this paper reports the synthesis of benzimidazole-conjugated amino acid derivatives *via* *N*-1 position of the benzimidazole core and their *in vitro* cytotoxicity against the three human cancer cell lines including cervical cancer (HeLa), breast cancer (MCF-7), and lung cancer (A549) cell lines.

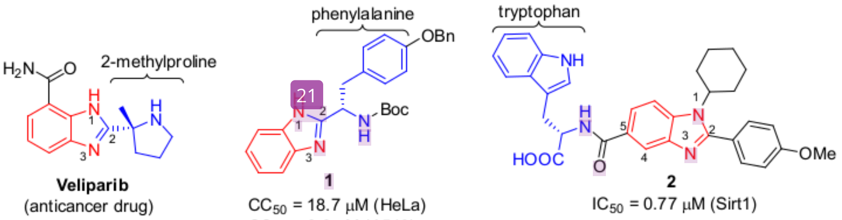


Figure 1. Several benzimidazole-conjugated amino acid derivatives as potent cytotoxic agents

2. MATERIALS AND METHODS

2.1. Chemistry

2.1.1. General information

Reactions were monitored by thin layer chromatography (TLC) on 0.2 mm pre-coated silica gel 60 F254 plates (Merck). 1D and 2D NMR spectra were measured with a JEOL 400 MHz spectrometer using DMSO-d_6 as solvent.

High resolution electrospray ionization (HRESI)-MS data were performed on a X500R QTOF spectrometer. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane (Me_4Si, $\delta = 0$); J values are given in Hertz. Silica gel 60 (0.063–0.200 mm, Prolabo) was used for column chromatography. Melting points (Mp, °C) were recorded on an INE-X-4 melting point apparatus with microscope and were uncorrected. All chemicals used in this study were of analytical grade.

2.1.2. General procedure for the synthesis of benzimidazole-conjugated amino acid derivatives

Synthesis of compounds 5a-c

A mixture of compound **3a-b** (1 mmol), L-amino acid ethyl/methyl ester hydrochlorides **4a-c** (1.5 mmol), $NaHCO_3$ (1.5 mmol), and NaOAc (10 mmol) in water (4 mL) was stirred at 100 °C for 8 hours. After completion, the reaction mixture was cooled down to room temperature. The pH of the mixture was adjusted to 7 by using the saturated aqueous solution of NH_4Cl. The mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and solvent was then evaporated under reduced pressure to give compounds **5a-c**, which were used for the next step without any further purification.

Synthesis of derivatives 7a-c

A mixture of compound **5a-c** (1 mmol), aldehyde **6** (1.1 mmol), $Na_2S_2O_4$ (4 mmol) in dimethylsulfoxide (DMSO, 4 mL) was stirred at 90 °C for 2-4 hours. After completion, the reaction mixture was cooled down to room temperature. The pH of the mixture was adjusted to 7 by using the saturated aqueous solution of $NaHCO_3$. The mixture was extracted with ethyl acetate (3×20 mL). The combined ethyl acetate layers were washed with brine, and dried over anhydrous Na_2SO_4, and solvent was evaporated. Purification of the crude products by silica gel column chromatography afforded derivatives **7a-c**.

Ethyl (*S*)-2-(5-chloro-2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-1-yl)-3-methylbutanoate (7a): Orange-yellow gel-like. Yield 48%. ^1H-NMR (400 MHz, DMSO-d_6, δ ppm): 7.77 – 7.74 (m, 2H), 7.68 – 7.64 (m, 2H), 7.32 (dd, J = 2.2, 8.7 Hz, 1H), 7.19 – 7.15 (m, 2H), 4.66 (d, J = 11.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 2.84 – 2.75 (m, 1H), 1.2 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H), 0.29 (d, J = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 168.5, 160.6, 155.9, 143.8, 132.5, 131.1, 126.8, 122.6, 121.3, 118.7, 114.3, 114.1, 65.1, 61.7, 55.3, 28.0, 19.5, 18.0, 13.8. HR-ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{24}ClN_2O_3^+$, 387.1470; found, 387.1474.

Methyl (*S*)-2-(2-(4-methoxyphenyl)-5-methyl-1*H*-benzo[*d*]imidazol-1-yl)-3,3-dimethylbutanoate (7b): White solid. Mp 127–129 °C. Yield 45%. ^1H-NMR (400 MHz, DMSO-d_6, δ ppm): 7.58 (d, J = 8.7 Hz, 2H), 7.45 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.7 Hz, 2H), 7.06 (dd, J = 1.2, 8.5 Hz, 1H), 5.13 (s, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 2.41 (s, 3H), 0.82 (s, 9H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 168.5, 160.1, 154.6, 143.0, 132.3, 131.0, 123.6, 122.7, 118.9, 114.3, 113.2, 65.4, 55.2, 52.5, 37.2, 27.6, 20.9. HR-ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{27}N_2O_3^+$, 367.2016; found, 367.2017.

Ethyl (*S*)-2-(5-chloro-2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-1-yl)-3-phenylpropanoate (7c): Orange-yellow gel-like. Yield 53%. ^1H-NMR (400 MHz, DMSO-d_6, δ ppm): 7.71 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.35 (dd, J = 2.1, 8.7 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.03 – 6.96 (m, 6H), 6.54 (d, J = 7.1 Hz, 2H), 5.43 (t, J = 8.0 Hz, 1H), 4.26 – 4.20 (m, 2H), 3.82 (s, 3H), 3.44 (d, J = 8.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 168.6, 160.3, 155.6, 143.7, 135.8, 132.4, 130.5, 128.4, 128.1, 126.7, 126.6, 122.6, 121.1, 118.8, 113.8, 113.2, 61.8, 59.6, 55.2, 34.3, 13.8. HR-ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{25}H_{24}ClN_2O_3^+$, 435.1470; found, 435.1473.

Synthesis of derivatives 8a-c

To a 25 mL round-bottom flask containing 0.5 mmol of ester **7a-c** and $LiOH{\cdot}H_2O$ (1.5 mmol) was added 4 mL of the solvent system ($MeOH:H_2O=8:1$). The resulting mixture was stirred at room temperature for 24 hours. At the end of the reaction, the pH of the mixture was adjusted to 3 using 1N HCl solution. The resulting mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and solvent was evaporated. Purification of the crude products by silica gel column chromatography afforded the desired derivatives **8a-c**.

(*S*)-2-(5-Chloro-2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-1-yl)-3-methylbutanoic acid (8a): White solid. Mp 201–204 °C. Yield 80%. ^1H-NMR (400 MHz, DMSO-d_6, δ ppm):

7.76 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.70 – 7.67 (m, 2H), 7.31 (dd, J = 2.1, 8.7 Hz, 1H), 7.19 – 7.16 (m, 2H), 4.61 (d, J = 11.0 Hz, 1H), 3.87 (s, 3H), 2.80 – 2.70 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.26 (d, J = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 170.1, 160.5, 155.9, 143.8, 132.5, 131.0, 126.7, 122.5, 121.5, 118.7, 114.3, 114.1, 65.2, 55.3, 27.7, 19.7, 17.9. HR-ESI-MS (m/z): [M+H]$^+$ calcd. for $C_{19}H_{20}ClN_2O_3^+$, 359.1157; found, 359.1159.

(*S*)-2-(2-(4-Methoxyphenyl)-5-methyl-1*H*-benzo[*d*]imidazol-1-yl)-3,3-dimethylbutanoic acid (8b): White solid. Mp 265–268 °C. Yield 66%. ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 7.56 (d, J = 8.7 Hz, 2H), 7.47 – 7.44 (m, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.05 (dd, J = 1.4, 8.5 Hz, 1H), 5.00 (s, 1H), 3.85 (s, 3H), 2.41 (s, 3H), 0.83 (s, 9H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 169.6, 160.0, 154.7, 143.0, 132.3, 130.9, 130.8, 123.3, 122.9, 118.8, 114.2, 113.5, 65.6, 55.2, 36.8, 27.7, 20.9. HR-ESI-MS (m/z): [M+H]$^+$ calcd. for $C_{21}H_{25}N_2O_3^+$, 353.1860; found, 353.1860.

(*S*)-2-(5-Chloro-2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazol-1-yl)-3-phenylpropanoic acid (8c): White solid. Mp 122–124 °C. Yield 68%. ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 7.70 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.35 (dd, J = 2.0, 8.6 Hz, 1H), 7.09 (t, J = 7.3 Hz, 1H), 7.03 – 6.96 (m, 6H), 6.53 (d, J = 7.2 Hz, 2H), 5.36 – 5.32 (m, 1H), 3.81 (s, 3H), 3.43 – 3.41 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 170.2, 160.2, 155.6, 143.7, 136.2, 132.5, 130.4, 128.3, 128.0, 126.6, 126.4, 122.5, 121.3, 118.7, 113.8, 113.3, 59.8, 55.2, 34.4. HR-ESI-MS (m/z): [M+H]$^+$ calcd. for $C_{23}H_{20}ClN_2O_3^+$, 407.1157; found, 407.1164.

2.2. Cytotoxicity evaluation

The cytotoxic activities of the synthesized compounds were evaluated against three human cancer cell lines (HeLa, MCF-7, and A549) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay with specific modifications as described.[16] The synthesized compounds were dissolved in DMSO to make 10 mM stock solutions. Serial dilutions were prepared in the culture medium. The positive control, 5-fluorouracil (5-FU), was dissolved in DMSO to make a 10 mM stock solution and then stored at −20 °C until use.

The human cancer cell lines were cultured in α-minimum essential medium (α-MEM), supplemented with 1% antibiotic antimycotic solution and 10% fetal bovine serum, at 37 °C and in 5% CO_2 atmosphere. Cells at 80–90% confluency were harvested and centrifuged at 3,000 rpm for 3 min. The supernatant was discarded and the cell pellet was resuspended in fresh medium. Aliquots (100 μL) of the cells were seeded in 96-well plates (1×10^4 cells/well) and incubated for 24 hours. The cells were then washed with phosphate-buffered saline (PBS), and five concentrations of tested compounds (6.25, 12.5 25, 50, 100 μM), including the positive control, 5-FU, were added to the wells. After 72 hours incubation, the cells were washed with PBS, and 100 μL aliquots of medium containing MTT solution (5 mg/mL) were added to each well and incubated for 3 hours. The absorbance was recorded using a microplate reader at 570 nm. Percent proliferation inhibition was calculated using the following formula:

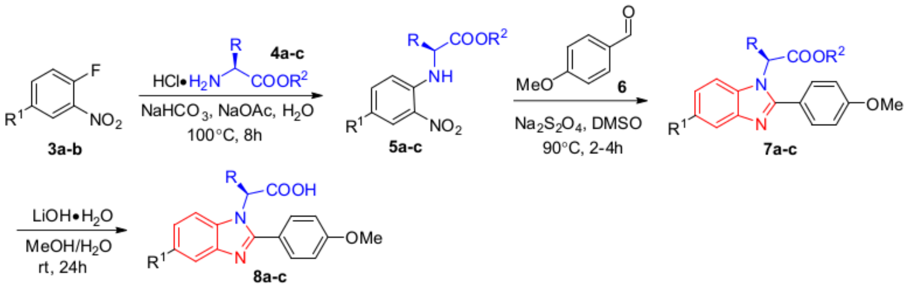
$$\% \text{ Proliferation cell inhibition} = [(A_t - A_b)/(A_c - A_b)] \times 100$$

A_t: Absorbance of test compound, A_b: Absorbance of blank, A_c: Absorbance of control.

The concentrations (IC_{50} values) of the compounds required to inhibit 50% of the growth of the human cancer cell lines were calculated based on the relationship between the concentrations and the percentage of inhibition, using the GraphPad Prism 5.0 software. Each experiment was performed three times, and all data are presented as mean ± standard deviation (S.D.).

3. RESULTS AND DISCUSSION

The three-step synthetic procedure towards the desired benzimidazole-conjugated amino acid derivatives was depicted in Scheme 1. The precursors *N*-substituted *o*-nitroanilines **5a-c**, were prepared *via* the nucleophilic aromatic substitution reaction of *o*-fluoro-nitrobenzenes **3a-b** and the free amino moiety of **4a-c**.[9] Next, the condensation reaction between **5a-c** and aldehyde **6** using sodium dithionite ($Na_2S_2O_4$) in DMSO through a one-pot nitro-reductive cyclization route[17] afforded derivatives **7a-c** in moderate yields (Table 1)**.** Finally, the saponification reaction of **7a-c** took place readily using lithium hydroxide under mild conditions to afford the corresponding derivatives **8a-c** in reasonable to good yields (Table 1).



Scheme 1. Synthetic procedure towards the benzimidazole-conjugated amino acid derivatives

Table 1. Synthetic yields and cytotoxicities of the synthesized compounds

Code	Structure	Yield^a (%)	IC$_{50}$^{b} (μM)		
			HeLa	MCF-7	A549
7a		48	25.54 ± 0.84	25.86 ± 1.25	35.85 ± 0.69
7b		45	>100	>100	>100
7c		53	21.57 ± 0.45	18.88 ± 0.13	25.97 ± 0.20
8a		80	>100	>100	>100
8b		66	>100	>100	>100
8c		68	>100	>100	>100
5-FU			6.36 ± 0.39	8.59 ± 0.72	3.92 ± 0.22

^{a}Isolated yields; ^{b}IC$_{50}$: 50% inhibitory concentration. Data are presented as mean ± standard deviation (S.D.) (n = 3).

The synthesized compounds **7a**–**c** and **8a**–**c** were tested for their cytotoxicities against the three human cancer cell lines, including cervical cancer (HeLa), breast cancer (MCF-7), and lung cancer (A549) cell lines using MTT assay (Table 1). The results indicated that compound **7b** and three compounds **8a**–**c** with the free carboxylic moiety showed no cytotoxicity towards the tested cancer cell lines at the tested concentration. In contrast, two compounds **7a** and **7c** (IC$_{50}$ = 18.88–35.85 μM) with the ester moiety being maintained exhibited rather good cytotoxicities compared to the positive control 5-FU (IC$_{50}$ = 3.92–8.59 μM). These results likely emphasized the role of the ester moiety compared to the corresponding free carboxylic moiety (compared the activity of **7a** and **7c** against **8a** and **8c**). The higher activity was probably due to the better penetration ability through the plasma membrane of the ester moiety than the carboxylic acid functionality as indicated in previous reports.[18-19] Notedly, compound **7c** (IC$_{50}$ = 18.88 μM) with the L-phenylalanine ethyl ester moiety displayed the best cytotoxicity towards the MCF-7 cancer cell line as compared to 5-FU (IC_{50} = 8.59 µM). The two structures **7a** and **7c** could be served as the starting point for further optimization towards the potent cytotoxicity agents.

4. CONCLUSION

Six novel benzimidazole-conjugated amino acid derivatives were successfully designed and synthesized in reasonable to good yields based on a three-step synthetic procedure starting from commercially available *o*-fluoro-nitrobenzenes. Among those, compound **7c** displayed rather good cytotoxicity against the breast cancer cell line (MCF-7). This structure could be considered as a lead compound that merit further optimization and development of novel anticancer agents.

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