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Synthesis and cytotoxicity evaluation of thiazole conjugated amino acid derivatives

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ABSTRACT

*This paper presents the three-step synthesis and cytotoxicity evaluation of the thiazole-conjugated amino acid derivatives. Starting from the commercially available benzophenone and thiourea, the thiazole structure was successfully constructed bearing the free amino groups at the C-2 position, which was then coupled with the carboxyl functionality of N-Boc L-phenylalanine, N-Boc L-proline and N-Boc L-tryptophane using CDI as the coupling reagent under mild basic conditions to provide the hybrid thiazole/N-Boc amino acid derivatives **5a-c**. Finally, the acidic promoted deprotection of the Boc groups afforded the desired hybrid thiazole/amino acid derivatives **6a-c** in reasonable total yields. Cytotoxicity assays indicated that the hybrids thiazole/L-proline (**6a**) and thiazole/L-tryptophan (**6c**) exhibited rather good cytotoxicity on the cervical cancer cell line (IC_{50} =18.86 and 18.25 µM, respectively). Notably, compound **5a** having the thiazole conjugated with unprotected N-Boc L-phenylalanine showed very good activity towards the lung cancer (IC_{50} = 15.72 µM), the cervical cancer (IC_{50} = 8.98 µM) and the breast cancer cell lines (IC_{50} = 8.07 µM), which were 1.3-, 1.2- and 2.5-fold, respectively, stronger activity than 5-FU (IC_{50} = 20.73, 10.67 and 20.43 µM, respectively).*

1. INTRODUCTION

Nowadays, cancer becomes one of the most life-threatening diseases. The GLOBOCAN 2020 estimates 19.3 million new cancer cases worldwide occurred in 2020 and almost 10.0 million cancer deaths (Deo et al., 2022). It is expected that the number would be 28.4 million cases in 2040, increasing by 47% from 2020. There are several ways for treating cancer, such as surgery, radiation therapy, biomarker testing, stem cell transplant, hyperthermia, photodynamic therapy, hormone therapy, targeted therapy, immunotherapy, or chemotherapy (Sawyers, 2004; Willett et al., 2007; Kirkwood et al., 2012; Baronzio et al., 2014; Abraham & Staffurth, 2016; Zugazagoitia et al., 2016; Waks & Winer, 2019; Kerr et al., 2021). Chemotherapy, also known as chemo, is a type of cancer treating method in which cancer cells are killed by drugs. However, besides killing fast-growing cancer cells, chemotherapy also affects normal cells that might lead to serious effects such as loss of hair, sores on mouth, or nausea (Love et al., 1989). Therefore, studies for developing new anticancer agents with enhanced activity but low side effects are increasingly in high demand around the world.

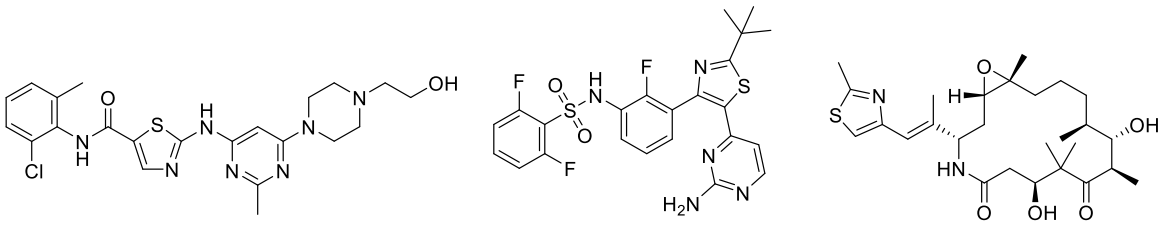


Figure 1. Some commercialized anticancer drugs containing thiazole structure

In the field of design and development of anticancer agents, nitrogen-based heterocycles have been more attractive due to their diverse bioactivities, especially anticancer activity. Among those, thiazole and its derivatives possess a broad spectrum of bioactivities, notably the anticancer activity (Mak et al., 2017; Ayati et al., 2019; Alizadeh & Hashemi, 2021). Several commercialized anticancer drugs bearing the thiazole moiety's core structure, such as Spyrcel for treating chronic myeloid leukemia, Tafinlar for treating skin cancer, or Ixempra for treating breast cancer (Figure 1). Besides, α-amino acids are essential biomolecules that function not only as structural components of living organisms but also play critical roles in various metabolic processes (Barrett & Lubec, 1991; Wu, 2009). Many commercially available anticancer drugs containing α-amino acids in the structures have been used in targeted cancer therapy (Conti et al., 2011).

Nowadays, molecular hybridization has become an increasingly interested method in drug design and development. This method allows the combination of two or more known biologically active structures to create a new hybrid molecule with enhanced biological activity as well as greater interaction with more biological targets (Kerru et al., 2017). Based on the known inherent anticancer activity of the thiazole scaffold and *α*-amino acids, the combination of these two structural features therefore is expected to produce novel structures with enhanced anticancer activity and lower undesirable side effects. In view of the above findings and also in continuing of our research in the design and development of anticancer agents (Bui et al., 2016, 2021, 2024; Hue et al., 2019; Quy et al., 2022; Le et al., 2024), this paper describes our initial research results on the synthesis of hybrid thiazole/amino acid derivatives. Cytotoxicity evaluation of the synthesized compounds was conducted on A549 (lung cancer), HeLa (cervical cancer), and MCF-7 (breast cancer) cell lines.

2. MATERIALS AND METHOD

2.1. Chemistry

2.1.1. General information

TLC method was applied to monitor the reactions and was performed on silica-gel 60 F_{254} plates (Merck). Purity of all used chemicals and solvents was of analytical grade. ^{1}H- and ^{13}C-NMR spectra were measured on Bruker Avance 600 MHz, JEOL 400 MHz and 100 MHz spectrometers. HRESI-MS (High-resolution electrospray ionization) data were conducted on Agilent 6530 qTOF and X500R QTOF spectrometer. Chemical shifts are displayed in ppm (parts per million) compared to $(CH_3)_4Si$ (δ=0); *J* values are given in Hertz. Abbreviation: TLC: thin layer chromatography; Hex: hexane; EtOAc: ethyl acetate; DMSO: dimethylsulfoxide; Boc: *tert*-butyloxycarbonyl; Et_3N: triethylamine; *i*-PrOH: isopropanol; CDI: 1,1'-carbonyldiimidazole; DBU: 1,8-diazabicyclo[5.4.0]undec-7-en;

THF: tetrahydrofuran; Mp: melting point.

2.1.2. General synthetic procedure of thiazole/amino acid hybrid derivatives

Synthesis of 2-aminothiazole (3)

To a solution of acetophenone (**1**) (0.600 g, 5 mmol), thiourea (**2**) (0.761 g, 10 mmol), and iodine (2.538 g, 10 mmol) in isopropanol (10 mL) was added triethylamine (0.5 mL) and the reaction was mixed at 100°C for 6 hours. The progress of the reaction was followed by using TLC. At the end, the reaction temperature was cooled down then saturated aqueous solution of $Na_2S_2O_3$ was added to destroy the excess iodine. An aqueous NH_3 solution was added to adjust the pH of the mixture to 7-8. Ethyl acetate was used to extract the resulting mixture (3 × 50 mL) and subsequent washed with 50 mL of brine solution, dried on Na_2SO_4 and removed under low pressure. Purification by column chromatography (Hex:EtOAc=4:1) afforded compound 2-aminothiazole (**3**) as a white solid. Yield 73.1%. Mp 138-140ºC. HRMS found

m/z 177.0553 $[M+H]^+$ (calcd. 177.0486, $C_9H_9N_2S$), *m/z* 176.0418 $[M]^+$ (calcd. 176.0408, $C_9H_8N_2S$). ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 7.80-7.78 (*m*, 2H), 7.38-7.33 (*m*, 2H), 7.25 (*tt*, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.06 (*s*, 2H), 7.00 (*s*, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 168.1, 149.7, 134.8, 128.4, 127.1, 125.4, 101.4.

Synthesis of the hybrid thiazole/N-Boc amino acids (5a-c)

A solution of 2-aminothiazole (**3**) (176.24 mg, 1 mmol), *N*-Boc amino acids (**4a-c**) (1.2 mmol), CDI (162.15 mg, 1.2 mmol), and DBU (76.12 mg, 0.5 mmol) in the THF:DMSO (1:1) solvent system (1 mL) was stirred at room temperature for 10 minutes and then at 100ºC for 10 hours. At the reaction equilibrium, extraction was done by using ethyl acetate (3 × 20 mL). The organic layers were then combined, sequentially washed with concentrated aqueous solutions of NH_4Cl (20 mL); Na_2CO_3 (20 mL), water (20 mL) and NaCl (2 × 20 mL); dried over anhydrous Na_2SO_4 and evaporated at low pressure, yielding the crude product. Purification was done by column chromatography (Hex:EtOAc=6:1) to provide the corresponding hybrid thiazole/*N*-Boc amino acids (**5a-c**).

***tert*-Butyl (*S*)-(1-oxo-3-phenyl-1-((4-phenylthiazol-2-yl)amino)propan-2-yl)carbamate (5a)**: White solid. Yield 21.7%. Mp 148-152ºC. HRMS found *m/z* 423.1726 $[M]^+$ (calcd. 423.1617, $C_{23}H_{25}N_3O_3S$), *m/z* 424.1412 $[M+H]^+$ (calcd. 424.1695, $C_{23}H_{26}N_3O_3S$). ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 12.52 (*s*, 1H), 7.91 (*d*, *J* = 7.2 Hz, 2H), 7.65 (*s*, 1H), 7.44 (*t*, *J* = 7.6 Hz, 2H), 7.38-7.27 (*m*, 6H), 7.21 (*t*, *J* = 7.2 Hz, 1H), 4.50-4.44 (*m*, 1H), 3.04 (*dd*, J_1 = 13.6 Hz, J_2 = 4.0 Hz, 1H), 2.83 (*dd*, J_1 = 13.2 Hz, J_2 = 10.6 Hz, 1H), 1.32 (*s*, 9H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 171.3, 157.7, 155.4, 148.8, 137.6, 134.2, 129.3, 128.7, 128.0, 127.8, 126.3, 125.6, 108.1, 78.2, 55.9, 36.9, 28.1.

***tert*-Butyl (*S*)-2-((4-phenylthiazol-2-yl)carbamoyl)pyrrolidine-1-carboxylate (5b):** White solid. Yield 43.3%. Mp 222-225ºC. HRMS found *m/z* 373.1469 $[M]^+$ (calcd. 373.1460, $C_{19}H_{23}N_3O_3S$), *m/z* 374.1594 $[M+H]^+$ (calcd. 374.1538, $C_{19}H_{24}N_3O_3S$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ ppm): 12.40 (*s*, 1H), 7.90 (*dd*, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.63 (*s*, 1H), 7.43 (*t*, *J* = 7.8 Hz, 2H), 7.37-7.31 (*m*, 1H), 4.44-4.37 (*m*, 1H), 3.46-3.44 (*m*, 1H), 3.37-3.34 (*m*, 1H), 2.25-2.20 (*m*, 1H), 1.93-1.86 (*m*, 2H), 1.84-1.80 (*m*, 1H), 1.40 (*s*, 3H), 1.25 (*s*, 6H). ^{13}C-NMR (150 MHz, DMSO-d_6, δ ppm): 171.9, 157.8, 152.8, 148.9, 134.2, 128.7, 127.7, 125.6, 108.2, 78.7, 59.3, 46.5, 30.8, 27.8, 23.4.

***tert*-Butyl (*S*)-(3-(1*H*-indol-3-yl)-1-oxo-1-((4-phenylthiazol-2-yl)amino)propan-2-yl)carbamate (5c):** White solid. Yield 49.7%. Mp 106-111ºC. HRMS found *m/z* 462.1721 [M]+ (calcd. 462.1726, $C_{25}H_{26}N_4O_3S$), *m/z* 463.1489 $[M+H]^+$ (calcd. 463.1804, $C_{25}H_{27}N_4O_3S$). ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 10.85 (*s*, 1H), 7.91 (*d*, *J* = 7.2 Hz, 2H), 7.75 (*d*, *J* = 8.0 Hz, 1H), 7.64 (*s*, 1H), 7.44 (*t*, *J* = 7.8 Hz, 2H), 7.35-7.31 (*m*, 2H), 7.21 (*d*, *J* = 2.0 Hz, 2H), 7.15 (*d*, *J* = 7.6 Hz, 1H), 7.06 (*t*, *J* = 7.3 Hz, 1H), 6.98 (*t*, *J* = 7.2 Hz, 1H), 4.54-4.49 (*m*, 1H), 3.16 (*dd*, J_1 = 14.4 Hz, J_2 = 5.2 Hz, 1H), 3.00 (*dd*, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1H), 1.32 (*s*, 7H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 171.7, 157.8, 155.2, 148.8, 135.9, 134.2, 128.7, 127.7, 127.1, 125.6, 124.1, 120.8, 118.7, 118.1, 111.2, 109.4, 108.1, 78.2, 55.0, 28.1, 27.4.

Synthesis of hybrid thiazole/amino acids (6a-c)

The 4N HCl/1,4-dioxane solution (1 mL) was slowly added to the a round-bottom flask containing 100 mg of compound (**5a-c**) and the resulting mixture was stirred for 15-30 minutes at room temperature. At the reaction end, the resulting mixture was neutralized using saturated $NaHCO_3$ solution and the pH of the mixture was adjusted to approximately 7-8 by saturated Na_2CO_3 solution. A white precipitate appeared. The solid was filtered, washed several times using water, and dried under vacuum to obtain the desired product. For compound (**6b**), the reaction mixture was extracted with ethyl acetate (3×20 mL) and the solvent was evaporated at low pressure to yield the crude product which was further purified by column chromatography on silica gel (Hex:EtOAc=6:1) gave the desired products (**6b**).

(*S*)-2-Methyl-3-phenyl-*N*-(4-phenylthiazol-2-yl)propanamide (6a): White solid. Yield 90.4%. Mp 197-199 ºC. HRMS found *m/z* 324.11671 $[M+H]^+$ (calcd. 324.11706, $C_{18}H_{18}N_3OS$) and *m/z* 322.10936 $[M-H]^-$ (calcd. 322.10141, $C_{18}H_{16}N_3OS$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ ppm): 7.89 (*dd*, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.61 (*s,* 1H), 7.43 (*t*, *J* = 7.5 Hz, 2H), 7.32 (*t*, *J* = 7.5 Hz, 1H), 7.28-7.24 (*m*, 4H), 7.20-7.19 (*m*, 1H), 5.33 (*s,* 2H), 3.75 (*dd*, J_1 = 7.8 Hz, J_2 = 6.0 Hz, 1H), 3.01 (*dd*, J_1 = 13.2 Hz, J_2 = 6.0 Hz, 1H), 2.75 (*dd,* J_1 = 13.2 Hz, J_2 = 7.8 Hz, 1H). ^{13}C-NMR (600 MHz, DMSO-d_6, δ -ppm): 174.0, 157.8, 148.8, 138.2, 134.2, 129.2, 128.7, 128.0, 127.7, 126.1, 125.6, 108.0, 56.3, 40.6.

(*S*)-*N*-(4-Phenylthiazol-2-yl)pyrrolidine-2-carboxamide (6b): White solid. Yield 22.5%. Mp 138-141ºC. HRMS found *m/z* 273.0945 $[M]^+$ (calcd. 273.0936, $C_{14}H_{15}N_3OS$), *m/z* 274.1053 $[M+H]^+$ (calcd. 274.1014, $C_{14}H_{16}N_3OS$). ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 7.90 (*dd*, J_1 = 8.6 Hz, J_2 = 1.2 Hz, 2H), 7.63 (*s*, 1H), 7.42 (*t*, *J* = 7.2 Hz, 2H), 7.32 (*t*, *J* = 7.4 Hz, 1H), 3.87 (*dd*, J_1 = 8.4 Hz, J_2 = 5.6 Hz, 1H), 2.97-2.86 (*m*, 2H), 2.12-2.03 (*m*, 1H), 1.85-1.77 (*m*, 1H), 1.68 (*q*, *J* = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 174.2, 158.4, 149.3, 134.8, 129.3, 128.3, 126.2, 108.6, 60.4, 47.2, 30.6, 26.3.

(*S*)-2-Amino-3-(1*H*-indol-3-yl)-*N*-(4-phenylthiazol-2-yl)propanamide (6c): White solid. Yield 30.6%. Mp 228-231ºC. HRMS found *m/z* 363.12739 $[M+H]^+$ (calcd. 363.12796, $C_{20}H_{19}N_4OS$) and *m/z* 361.11475 $[M–H]^-$ (calcd. 361.11231, $C_{20}H_{17}N_4OS$). ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 10.85 (*s*, 1H), 7.89 (*dd*, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 2H), 7.62-7.59 (*m*, 2H), 7.42 (*t*, *J* = 7.6 Hz, 2H), 7.34-7.30 (*m*, 2H), 7.14 (*d*, *J* = 2.0 Hz, 1H), 7.05 (*td*, J_1 = 7.0 Hz, J_2 = 1.2 Hz, 1H), 6.95 (*td*, J_1 = 8.0 Hz, J_2 = 0.9 Hz, 1H), 3.83 (*t*, *J* = 6.8 Hz, 1H), 3.15 (*dd*, J_1 = 14.2 Hz, J_2 = 6.2 Hz, 1H), 2.93 (*dd*, J_1 = 14.2 Hz, J_2 = 7.2 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 174.2, 157.8, 148.7, 136.0, 134.2, 128.6, 127.7, 127.3, 125.6, 123.7, 120.8, 118.5, 118.1, 111.2, 110.0, 108.0, 55.4, 30.6.

2.2. Cytotoxicity evaluation

Cytotoxicity of the prepared thiazole conjugated amino acids on the cancer cell lines A549, HeLa and MCF-7 was evaluated based on the MTT assay (Mosmann, 1983). The stock solution (10 mM) of the thiazoles was prepared in DMSO and dilutions were made using the culture medium. 5-FU (the positive control) was also dissolved in DMSO to make the stock solution and kept at −20 °C.

Cancer cells were cultured in α-MEM (α-minimum essential medium), containing 10% fetal bovine serum and 1% antibiotic antimycotic solution under a 5% CO_2 atmosphere and at 37°C. Cells with confluency of 80-90% were collected, centrifuged for 3 minutes at 3,000 rpm. After discarding the supernatant, cell pellet was suspended in fresh medium. 100 µL of cell aliquots were placed into 96-well plates (1×10^4 cells/well), incubated for 24 hours, washed by using phosphate-buffered saline (PBS), and five different concentrations of the prepared thiazoles (6.25, 12.5 25, 50, and 100 µM), and 5-FU, were then added to the wells. The cells (after 72 hours of incubation) were washed again with PBS and the medium containing MTT solution (5 mg/mL, 100 µL) was added to each well. Incubation was continued for an additional 3 hours. The absorbance was measured at 570 nm using a microplate reader. Inhibition percentage was evaluated based on the following formula:

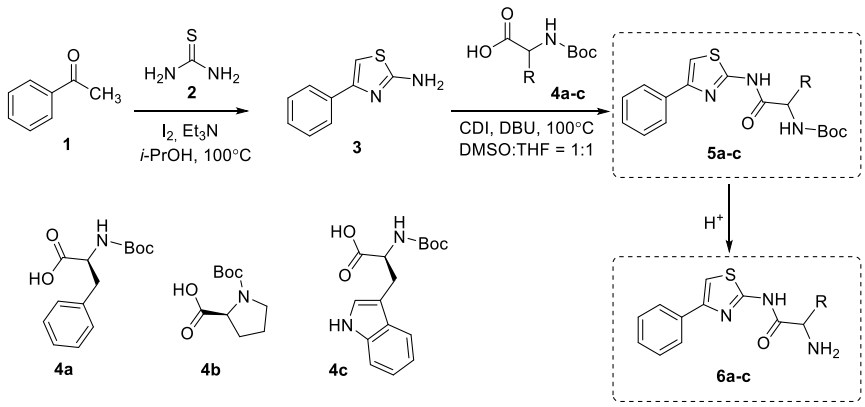
$$\% \text{ Proliferation cell inhibition} = [(A_t - A_b)/(A_c - A_b)] \times 100$$

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

The IC_{50} (half-maximal inhibitory concentrations) values of the tested compounds were determined by employing the software of GraphPad Prism 5.0, based on the relationship between percentage inhibition of cancer cell growth and the tested compound concentrations. All experiments were performed in triplicate, and data are presented as mean ± standard deviation (S.D.).

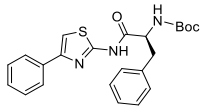
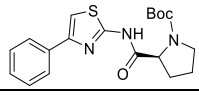
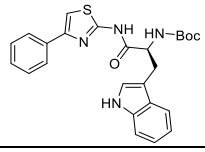
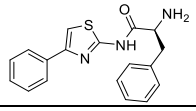
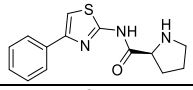
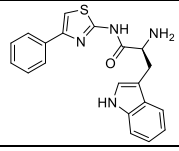
3. RESULTS AND DISCUSSION

The three-step synthetic procedure toward the desired thiazole-conjugated amino acid derivatives is depicted in Scheme 1. The first step was the condensation reaction between the commercially available acetophenone **1** and thiourea **2** using triethylamine as the base and iodine (I_2) as the oxidant (Abedi-Jazini et al., 2018). Under these conditions, the 2-aminothiazole core structure **3** was successfully constructed with the free amino substituent being served as the unit to facilitate binding to the amino acid group. The next step was the coupling reaction between the free amino group of **3** with the carboxyl functionality of amino acid **4a-c** using CDI as the coupling reagent under mild basic conditions to provide the thiazole conjugated *N*-Boc protected amino acids **5a-c** (Ivkovic et al., 2015; Métro et al., 2017). Finally, the Boc groups were then deprotected to afford the hybrid thiazole/amino acid derivatives **6a-c** in reasonable total yields (7.1-14.3%, Table 1).



Scheme 1. Synthetic procedure towards the hybrid thiazole/amino acid derivatives

Table 1. Synthesis and cytotoxicity evaluation of the hybrid thiazole/amino acid derivatives

Compound	Structure	Yield[a] (%)	IC_{50} (μM)		
			A549	HeLa	MCF-7
5a		15.9	**15.72 ± 0.11**	**8.98 ± 0.52**	**8.07 ± 1.88**
5b		31.7	> 100	> 100	88.08 ± 4.12
5c		36.3	ND	ND	ND
6a		14.3	> 100	**18.86 ± 2.53**	> 100
6b		7.1	> 100	> 100	> 100
6c		11.1	> 100	**18.25 ± 0.92**	> 100
5-FU[b]			20.73 ± 0.71	10.67 ± 0.42	20.43 ± 0.49

[a] *Isolated total yields.*

[b] *5-Fluorouracil was used as a positive control. Data are presented as mean ± SD (n=3). ND: not determined.*

Due to the lack of the required amount of compound **5c**, cytotoxicities were then initially evaluated for compounds **5a-b** and **6a-c** against the cancer cell lines A549, HeLa and MCF-7 using the MTT method. The results presented in Table 1 indicated that compounds **5b** and **6b** bearing the thiazole ring conjugated with the amino acid proline showed insignificant activity at the studied concentrations on the three tested cell lines. The hybrids thiazole/*L*-tryptophan (**6a**) and thiazole/*L*-tryptophan (**6c**) showed no activity on the MCF-7 and A549 cell lines at the tested concentration but exhibited better cytotoxicity on the HeLa (IC_{50} = 18.86 μM and 18.25 μM, respectively. Notably, compound **5a,**

having the thiazole conjugated with unprotected *N*-Boc *L*-phenylalanine, displayed strong cytotoxicity against all three cell lines (IC_{50} = 15.72 (A549), 8.98 (HeLa) and 8.07 μM (MCF-7), corresponding to 1.3-, 1.2- and 2.5-fold stronger activity than 5-FU (IC_{50} = 20.73, 10.67 and 20.43 μM, respectively). Interestingly, deprotection of the Boc group **5a** just led to a half decrease in activity of the resulting compound **6a** (IC_{50} = 18.86 μM). The same activity decrease was observed in the case of protected compound **6b** compared to unprotected compound **5b** against the breast cancer (MCF-7). The results suggest the role of the stereochemistry of the synthesized compounds for effective interaction at the active sites of the target. Further studies have been continuing to carry out in our lab in order to determine the cytotoxicity of compound **5c** and reason the relationship between structure and activity of the thiazole/amino acid derivatives for discovery of new cytotoxic agents.

4. CONCLUSION

Six hybrid thiazole/amino acid derivatives were successfully synthesized in reasonable total yields (11.1-36.3%) based on a three-step synthetic procedure, starting from commercially available benzophenone and thiourea. Cytotoxicity determination indicated that compound **5a**, having the thiazole conjugated with unprotected *N*-Boc *L*-phenylalanine, displayed 1.3- and 1.2-fold increase in activity against the A549 and HeLa cell lines, respectively, and 2.5-fold on the MCF-7 cell line as compared to 5-FU (the positive control). These results proved the potential of the thiazole-conjugated amino acid structures as candidates for further studies for developing anticancer drugs in the future.

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