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RESEARCH ARTICLE

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One-Pot Tandem Copper-Catalyzed Library Synthesis of 1-Thiazolyl-1,2,3-triazoles as Anticancer Agents

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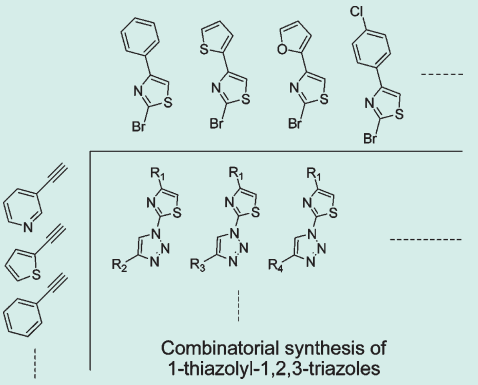
Supporting Information

ABSTRACT: One-pot multicomponent synthesis to assemble compounds has been an efficient method for constructing a compound library. We have developed one-pot tandem copper-catalyzed azidation and CuAAC reactions that afford 1-thiazolyl-1,2,3-triazoles with anticancer activity. By utilizing this one-pot synthetic strategy, we constructed a library of 1-thiazolyl-1,2,3-triazoles in search of the potent lead compound. Furthermore, 1-thiazolyl-1,2,3-triazoles were evaluated for anticancer activity against the multidrug-resistant cancer cells MES-SA/Dx5. Most of the 1-thiazolyl-1,2,3-triazoles revealed cytotoxic effect against cancer cells at micromolar to low micromolar range. Testing some of the most potent compounds (**5**{*4,2*−*4*} and **5**{*5,1*−*3*}) against the normal cell line Vero showed no significant toxicity (except **5**{*4,2*}) to normal cells. This result indicates that compounds **5**{*4,3*−*4*} and **5**{*5,1*−*3*} possessed good potency and selectivity to cancer cells over normal cells.



KEYWORDS: 1-thiazolyl-1,2,3-triazole, cytotoxic activity, CuAAC reaction, one-pot synthesis

INTRODUCTION

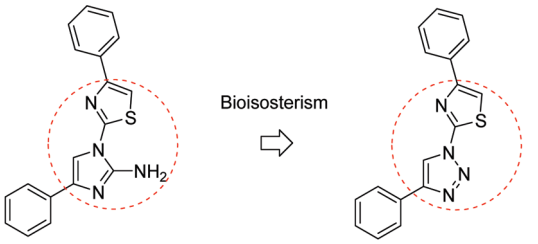
One-pot multicomponent synthesis provides a highly valuable synthetic tool to assemble compounds within a minimum number of synthetic steps.[1] The molecular complexity and diversity to be created by the facile formation in a one-pot transformation is quite suitable for combinatorial library synthesis.[2]

Cu(I)-promoted coupling reaction has been extensively used for the preparation of numerous synthetic molecules and biomolecules.[3] Cu(I)-promoted azidation reaction has been used as a facile method for the transformation of an aryl halide into an aryl azide.[4] Synthetic applications of aryl azide have become highly attractive alternatives to establish the nitrogen-linked aryl scaffolds.

Recently, the copper-catalyzed [3 + 2] azide and alkyne cycloaddition (CuAAC) reaction has drawn much attention.[5] This high yield and regioselective reaction has found numerous applications ranging from chemistry to biology. Furthermore, this highly reliable reaction allows rapid synthesis of combinatorial libraries for biological screening at low cost and with high efficiency. Copper-catalyzed azide−alkyne cycloaddition (CuAAC) reaction is widely utilized in the synthesis of biologically active compounds for the construction of 1,2,3-triazole. 1,2,3-Triazole is an important class of heterocycle as a chemical scaffold with interesting biological properties. Several therapeutically active compounds containing 1,2,3-triazoles have been reported, such as antimicrobials, anti-HIV agents, and kinase inhibitors.[6]

Tandem Cu(I)-catalyzed azidation and 1,3-dipolar [3 + 2] cycloaddition reactions between azides and terminal alkynes that can be carried out in one-pot combinatorial synthesis seems to be an attractive method. Recently, 2-aminothiazolyl imidazole has been found to exhibit promising anticancer activity.[7] In our continuous effort to search for new potent anticancer compounds with rapid and efficient synthetic strategies, and on the basis of the bioisosteric replacement of 2-aminothiazolyl imidazole, we have designed a new drug scaffold, that is, 1-thiazolyl-1,2,3-triazole, which could be efficiently prepared in one-pot combinatorially (Chart 1). To the best of our knowledge, 1-thiazolyl-1,2,3-triazoles have never been previously reported to possess anticancer activity.

Chart 1. Bioisosteric Replacement of 2-Aminothiazolyl Imidazole



Herein, we demonstrate an efficient combinatorial synthesis of 1-thiazolyl-1,2,3-triazoles by performing one-pot tandem

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copper-catalyzed azidation and CuAAC reactions. Additionally, we also evaluated the anticancer activity of these products, most of which exhibited significant inhibition of cancer cell growth.

RESULTS AND DISCUSSION

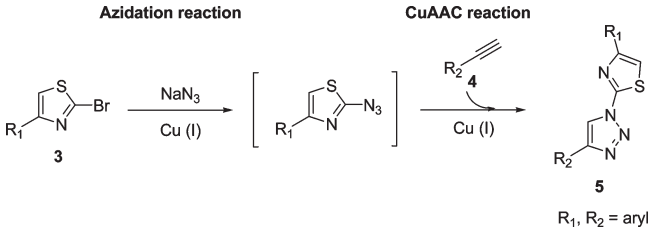
The synthetic strategy for the compound library is outlined in Chart 2. 1-Thiazolyl-1,2,3-triazole was used as the structural scaffold for the anticancer compound library synthesis, therefore enabling the exploration of the lead compound. A variety of 2-bromo-4-arylthiazoles and terminal alkynes were used as the building blocks to obtain a library of 1-thiazolyl-1,2,3-triazoles. This library of 1-thiazolyl-1,2,3-triazoles was efficiently assembled by employing the one-pot tandem copper-catalyzed reactions by means of azidation and CuAAC reactions.

We first synthesized 2-bromo-4-arylthiazoles **3**{*1*−*5*} for the further combinatorial assembling with terminal alkynes **4**{*1*−*5*} to give the desired 1-thiazolyl-1,2,3-triazoles **5**{*3*(*1*−*5*),*4*(*1*−*5*)}. Synthesis of 2-bromo-4-(2-furyl)thiazole **3**{*1*} is shown in Scheme 1. 2-Acetylfuran was used as a starting material for further reactions. Bromination of 2-acetylfuran was conducted by using bromine in diethyl ether-dioxane mixture.[8] Subsequently, substitution reaction of 2-bromoacetylfuran **1** with potassium thiocyanate provided (2-furoyl)methylthiocyanate **2** in 64% yield in two steps.[9] Cyclization of (2-furoyl)methylthiocyanate **2** was carried out by treatment with hydrogen bromide in glacial acetic acid to obtain 2-bromo-4-(2-furyl)thiazole **3**{*1*} in 83% yield.[10] Using the same strategy, 2-bromo-4-arylthiazoles **3**{*2*−*5*} were also prepared (Figure 1). Subsequently, we employed copper(I) iodide as catalyst with terminal alkynes **4**{*1*−*5*} in one pot through the azidation and CuAAC reactions to produce a library of diverse 1-thiazolyl-1,2,3-triazoles **5**{*3*(*1*−*5*),*4*(*1*−*5*)}. Optimized reaction conditions of the azidation and CuAAC reactions in one pot were conducted by using 2-bromo-4-(2-furyl)thiazole **3**{*1*}, sodium azide and phenylacetylene **4**{*1*} in the presence of copper(I) iodide and *N*,*N*′-dimethylethylenediamine (DMEDA) in *N*,*N*-dimethyl formamide (DMF) at 60 °C for 6 h to afford 1-thiazolyl-1,2,3-triazole **5**{*1*,*1*} in 71% yield.[11] By following the same procedure, a library of 1-thiazolyl-1,2,3-triazoles **5**{*3*(*1*−*5*),*4*(*1*−*5*)} was generated in one-pot tandem copper-catalyzed azidation and CuAAC reactions (Table 1).

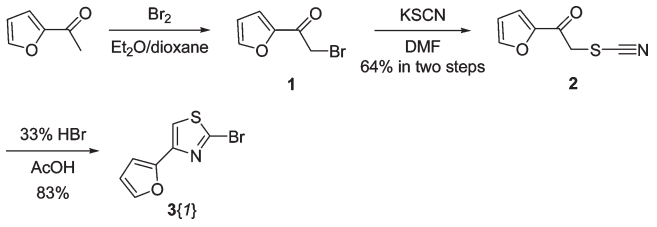
Since the drug resistance limits the effectiveness of many anticancer agents, development of a new class of anticancer agents for patients with drug-resistant cancer is potentially valuable. Thus, all the synthesized 1-thiazolyl-1,2,3-triazoles **5**{*3*(*1*−*5*),*4*(*1*−*5*)} were evaluated for cytotoxicity in the multiple drug resistant cancer cells MES-SA/Dx5. The cancer cell viability after treatments with the test compounds was measured using a colorimetric MTT assay system. The IC_{50} values of 1-thiazolyl-1,2,3-triazoles **5**{*3*(*1*−*5*),*4*(*1*−*5*)} against MES-SA/Dx5 cancer cells were determined and summarized in Table 2. Most of the 1-thiazolyl-1,2,3-triazoles (except compound **5**{*1*,*1*}) revealed cytotoxic effect against MES-SA/Dx5 cancer cells at micromolar range, while some of them were potent at low micromolar range.

We further examined the effect of R_1 and R_2 groups of 1-thiazolyl-1,2,3-triazoles on the anticancer activity. The anticancer activity of the phenyl group (**5**{*3*,*1*−*5*}) on the thiazole ring was superior to that of thiophenyl (**5**{*2*,*1*−*5*}) and furanyl (**5**{*1*,*1*−*5*}) groups, and the order of activity of R_1 group against MES-SA/Dx5 can be described as phenyl > thiophenyl > furanyl for most examples among these three substituents. Moreover, compounds with 4-halophenyl substituent on thiazole ring (**5**{*4*,*1*−*3*} and **5**{*5*,*1*−*3*}) were found to be more active than those with phenyl (**5**{*3*,*1*−*3*}) and heteroaryl (**5**{*1*,*1*−*3*} and **5**{*2*,*1*−*3*}) rings. However, compared with fluoro substituents **5**{*5*,*1*−*5*}, chloro substituents **5**{*4*,*1*−*5*} led to a slightly increased activity. Compounds **5**{*4*,*1*} and **5**{*4*,*2*} with their phenyl group bearing chloro

Chart 2. Tandem Copper-Catalyzed Synthesis



Scheme 1



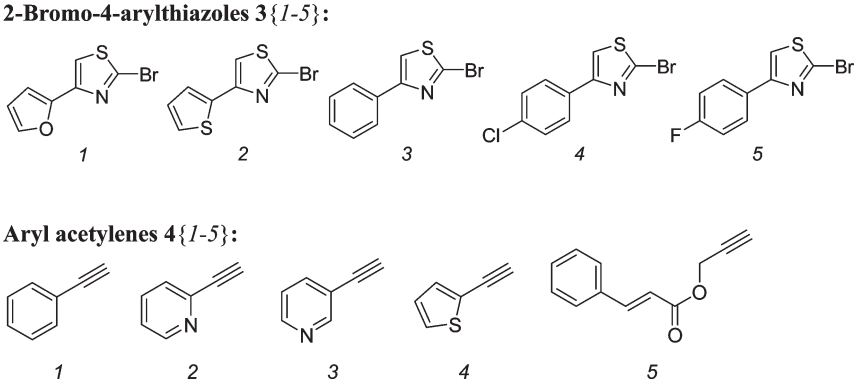


Figure 1. Building blocks for library synthesis.

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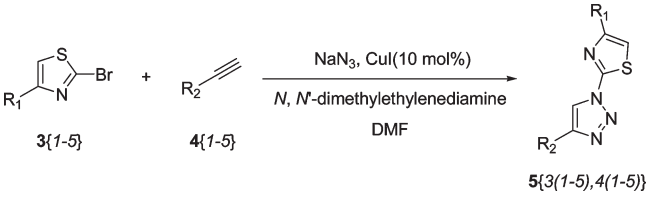
Table 1. Synthesis of 1-Thiazolyl-1,2,3-triazoles 5



3{1-5} 4{1-5} 5{3(1-5),4(1-5)}

entry	R_1	R_2	yield (%)[a]
5{1,1}	2-furanyl	phenyl	71
5{1,2}	2-furanyl	2-pyridinyl	69
5{1,3}	2-furanyl	3-pyridinyl	62
5{1,4}	2-furanyl	2-thiophenyl	66
5{1,5}	2-furanyl	(*E*)-$C_6H_5CH{=}CHCO_2CH_2$	58
5{2,1}	2-thiophenyl	phenyl	67
5{2,2}	2-thiophenyl	2-pyridinyl	61
5{2,3}	2-thiophenyl	3-pyridinyl	59
5{2,4}	2-thiophenyl	2-thiophenyl	60
5{2,5}	2-thiophenyl	(*E*)-$C_6H_5CH{=}CHCO_2CH_2$	58
5{3,1}	phenyl	phenyl	52
5{3,2}	phenyl	2-pyridinyl	60
5{3,3}	phenyl	3-pyridinyl	58
5{3,4}	phenyl	2-thiophenyl	48
5{3,5}	phenyl	(*E*)-$C_6H_5CH{=}CHCO_2CH_2$	52
5{4,1}	4-chlorophenyl	phenyl	61
5{4,2}	4-chlorophenyl	2-pyridinyl	55
5{4,3}	4-chlorophenyl	3-pyridinyl	57
5{4,4}	4-chlorophenyl	2-thiophenyl	58
5{4,5}	4-chlorophenyl	(*E*)-$C_6H_5CH{=}CHCO_2CH_2$	64
5{5,1}	4-fluorophenyl	phenyl	62
5{5,2}	4-fluorophenyl	2-pyridinyl	67
5{5,3}	4-fluorophenyl	3-pyridinyl	55
5{5,4}	4-fluorophenyl	2-thiophenyl	51
5{5,5}	4-fluorophenyl	(*E*)-$C_6H_5CH{=}CHCO_2CH_2$	63

[a] Isolated yields.

substituent at the para position enhanced the potency against the MES-SA/Dx5 cancer cell line dramatically. This indicates that an electron withdrawing group, especially chloro substituent, at the para position of the phenyl ring was important for the cytotoxic activity of 1-thiazolyl-1,2,3-triazoles.

We next turned our attention to the R_2 group on 1-thiazolyl-1,2,3-triazoles. As seen in Table 2, good activity was found among the phenyl, thiophenyl, and pyridinyl analogues. The aromatic ring seems to be an important requirement for the compound's cytotoxicity against MES-SA/Dx5 cells, especially 2- and 3-pyridinyl. Switching R_2 from aromatic ring to cinnamate ester (compounds 5{*1*−*5,5*}) resulted in partial loss of activity.

To test the selectivity of compounds, some of the potent compounds (5{*4,2*−*4*} and 5{*5,1*−*3*}) were further examined for their cytotoxicity against normal Vero cells (Table 3). Among them, except 5{*4,2*}, all compounds exhibited no significant toxicity to Vero cells up to the concentration of 250 μM, while the majority of these selected compounds demonstrated potent activity in MES-SA/Dx5 cancer cells. This suggested that these 1-thiazolyl-1,2,3-triazoles demonstrated the potency and selectivity to multidrug resistant cancer cells over normal cells.

Table 2. Anticancer Activity of 1-Thiazolyl-1,2,3-triazoles against Multiple Drug Resistant Cancer Cell Line MES-SA/Dx5[a]

compound	IC_{50} (μM)	compound	IC_{50} (μM)
5{*1,1*}	>250	5{*3,4*}	82.8 ± 10.0
5{*1,2*}	57.7 ± 3.7	5{*3,5*}	56.9 ± 4.1
5{*1,3*}	128.4 ± 5.3	5{*4,1*}	1.1 ± 0.1
5{*1,4*}	38.7 ± 7.2	5{*4,2*}	0.8 ± 0.1
5{*1,5*}	48.2 ± 5.2	5{*4,3*}	4.4 ± 0.7
5{*2,1*}	120.0 ± 27.5	5{*4,4*}	5.5 ± 0.3
5{*2,2*}	60.0 ± 4.3	5{*4,5*}	26.4 ± 2.4
5{*2,3*}	18.2 ± 1.6	5{*5,1*}	12.3 ± 2.3
5{*2,4*}	15.2 ± 2.4	5{*5,2*}	5.1 ± 1.6
5{*2,5*}	116.4 ± 10.6	5{*5,3*}	5.8 ± 1.1
5{*3,1*}	81.2 ± 8.2	5{*5,4*}	16.9 ± 2.1
5{*3,2*}	22.3 ± 2.5	5{*5,5*}	28.4 ± 2.7
5{*3,3*}	9.2 ± 0.3	colchicine	0.06 ± 0.01

[a] Experiment was performed in triplicate for three repeats, and IC_{50} values were expressed as mean ± SEM.

Table 3. Cytotoxicity of Selected 1-Thiazolyl-1,2,3-triazoles against Vero Cell Line[a]

compound	IC_{50} (μM)
5{*4,2*}	26.4 ± 1.4
5{*4,3*}	>250
5{*4,4*}	>250
5{*5,1*}	>250
5{*5,2*}	>250
5{*5,3*}	>250
Colchicine	0.5 ± 0.1

[a] Experiment was performed in triplicate for three repeats and IC_{50} values were expressed as mean ± SEM.

In conclusion, we have developed one-pot tandem copper-catalyzed azidation and CuAAC reactions for constructing a novel anticancer drug scaffold of 1-thiazolyl-1,2,3-triazole. Using this one-pot synthesis, a library of 1-thiazolyl-1,2,3-triazoles has been rapidly and efficiently synthesized. The synthesized compounds were evaluated for anticancer activity, and some of them demonstrated significant antiproliferative activity against drug-resistant cancer cells (MES-SA/Dx5) without obvious toxicity to normal cells (Vero). Further studies on the cellular and molecular mechanism of action of 1-thiazolyl-1,2,3-triazoles are in progress in our laboratory and will be reported in due course.

EXPERIMENTAL SECTION

Chemistry. All reactions were conducted in dried glassware under an oven at 120 °C overnight and cooled in a desiccator over anhydrous $CaSO_4$. All reagents were used as received from commercial suppliers unless otherwise stated. DMF was dried over calcium hydride for 72 h prior to vacuum distillation. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under a nitrogen atmosphere. Other solvents, including acetone, dichloromethane, and ethanol, were distilled over CaH_2 under nitrogen. The proton NMR spectra were obtained on a Bruker Avance 400 (400 MHz) spectrometer. Chloroform-*d* of spectrograde was used as solvent. All NMR chemical shifts were

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reported as δ values in parts per million (ppm), and coupling constants (J) were given in hertz (Hz). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, unresolved multiplet due to the field strength of the instrument; dd, doublet of doublet; dt, doublet of triplet; and ddd, doublet of doublet of doublet. High resolution mass spectra were carried out on a Bruker (Bio-TOF) mass spectrometer. Melting points were measured with a Büchi 510 melting point apparatus. Attenuated Total Reflectance (ATR) Fourier transform infrared spectra were collected with a Bruker Optics Tensor 27 spectrometer. Purification was performed by using preparative separations in flash column chromatography (Merck silica gel 60, particle size of 230−400 mesh). Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254). Compounds analyzed on the TLC plates were visualized by using UV light, I_2 vapor, or 2.5% phosphomolybdic acid in ethanol with heating.

General Procedure for the Synthesis of 1-Thiazolyl-1,2,3-triazoles 5

1-(4-(Furan-2-yl)thiazol-2-yl)-4-phenyl-1H-1,2,3-triazole 5{1,1}. To a solution of 2-bromo-4-(2-furyl)thiazole **3**{*1*} (253 mg, 1.1 mmol), phenylacetylene **4**{*1*} (111 mg, 1.1 mmol), CuI (21 mg, 0.11 mmol), DMEDA (14.5 mg, 0.16 mmol), sodium azide (215 mg, 3.3 mmol) were added in DMF (15 mL), and the reaction wrapped in aluminum foil to prevent further exposure to light. The resulting suspension was stirred under N_2 at 60 °C for 6 h. The mixture was cooled down to room temperature, and the catalyst was filtered off. The solvent was removed in vacuum. EtOAc (10 mL) and water (10 mL) were added. The separated aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with aqueous sat'd NH_4Cl and brine, dried over $MgSO_4$, and concentrated. The residual was purified by silica gel column chromatography (EtOAc/hexanes = 1/2) to give a white solid **5**{*1,1*} (230 mg, 71%). Mp = 135−137 °C. IR νmax (ATR): 3146, 1531, 1445, 1228 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.70 (s, 1H), 7.94 (d, J = 7.6 Hz, 2H), 7.50−7.47 (m, 3H), 7.42−7.39 (t, J=7.6 Hz, 1H), 7.34 (s, 1H), 6.85 (d, J=3.2 Hz, 1H), 6.54−6.52 (dd, J=3.2, 1.6 Hz, 1H). ^{13}C NMR (CDCl3): δ 157.1, 149.1, 148.4, 144.5, 142.7, 129.3, 128.9, 128.8, 126.0, 116.9, 111.5, 109.0, 107.8. HRMS calcd for $C_{15}H_{10}N_4OSH$ $(M+H)^+$ 295.0648, found 295.0664.

2-(1-(4-(Furan-2-yl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)pyridine 5{1,2}. Yield: 69%. Yellow solid. Mp = 154−157 °C. IR νmax (ATR): 2924, 2853, 1599, 1531, 1420, 1259 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.14 (s, 1H), 8.68 (d, J = 4.7 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 7.87 (dt, J=7.8, 1.6 Hz, 1H), 7.50 (d, J=1.6 Hz, 1H), 7.37 (s, 1H), 7.34 (dd, J = 7.8, 4.7 Hz, 1H), 6.86 (d, J = 3.4 Hz, 1H), 6.55 (dd, J=3.4, 1.6 Hz, 1H). ^{13}C NMR (CDCl3): δ 156.7, 149.6, 149.2, 149.1, 148.9, 144.6, 142.7, 136.8, 123.3, 120.6, 119.5, 111.6, 109.8, 107.9. HRMS calcd for $C_{14}H_9N_5SONa$ $(M+Na)^+$ 318.0420, found 318.0410.

3-(1-(4-(Furan-2-yl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)pyridine 5{1,3}. Yield: 62%. Brown solid. Mp = 144−146 °C. IR νmax (ATR): 3113, 1532, 1218 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.15 (s, 1H), 8.71 (s, 1H), 8.27 (d, J = 3.7 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.63−7.41 (m, 1H), 7.38−7.22 (m, 1H), 7.32 (s, 1H), 7.30 (s, 1H), 7.21−7.10 (m, 1H). ^{13}C NMR (CDCl3): δ 156.5, 149.7, 148.7, 148.2, 147.3, 138.9, 135.2, 133.8, 126.4, 125.3, 124.5, 123.3, 110.4, 108.6. HRMS calcd for $C_{14}H_9N_5OSH$ $(M+H)^+$ 296.0601, found 296.0646.

1-(4-(Furan-2-yl)thiazol-2-yl)-4-(thiophen-2-yl)-1H-1,2,3-triazole 5{1,4}. Yield: 66%. Brown solid. Mp = 146−149 °C. IR νmax (ATR): 3112, 1531, 1246, 1032 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.62 (s, 1H), 7.55 (dd, J = 3.6, 1.1 Hz, 1H), 7.51 (dd, J = 1.8, 0.6 Hz, 1H), 7.40 (dd, J=5.0, 1.1 Hz, 1H), 7.36 (s, 1H), 7.16 (dd, J=5.0, 3.6 Hz, 1H), 6.87 (d, J=3.4 Hz, 1H), 6.55 (dd, J=3.4, 1.8 Hz, 1H). ^{13}C NMR (CDCl3): δ 157.0, 149.2, 144.6, 143.7, 142.8, 131.5, 127.8, 126.0, 125.3, 116.3, 111.7, 110.0, 107.9. HRMS calcd for $C_{13}H_8N_4OS_2H$ $(M+H)^+$ 301.0212, found 301.0228.

(E)-(1-(4-(Furan-2-yl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)methyl cinnamate 5{1,5}. Yield: 58%. White solid. Mp = 137−140 °C. IR νmax (ATR): 2923, 1713, 1523, 1452, 1167 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.61 (s, 1H), 7.76 (d, J = 16.0 Hz, 1H), 7.54−7.52 (m, 2H), 7.49 (s, 1H), 7.42−7.38 (m, 3H), 7.32 (s, 1H), 6.84 (d, J = 2.9 Hz, 1H), 6.52−6.46 (m, 2H), 5.47 (s, 2H). ^{13}C NMR (CDCl3): δ 166.5, 156.8, 149.0, 145.8, 144.5, 143.9, 142.7, 134.0, 130.4, 128.8, 128.1, 121.5, 117.1, 111.6, 109.9, 107.9, 57.2. HRMS calcd for $C_{19}H_{14}N_4O_3SH$ $(M+H)^+$ 379.0859, found 379.0842. $C_{19}H_{14}N_4O_3SNa$ $(M+Na)^+$ 401.0679, found 401.0665.

4-Phenyl-1-(4-(thiophen-2-yl)thiazol-2-yl)-1H-1,2,3-triazole 5{2,1}. Yield: 67%. White solid. Mp = 139−141 °C. IR νmax (ATR): 3089, 2924, 1523, 1435, 1224 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.69 (s, 1H), 7.94 (d, J=8.6 Hz, 2H), 7.51−7.46 (m, 3H), 7.41 (d, J = 7.4 Hz, 1H), 7.34 (dd, J = 5.0, 0.9 Hz, 1H), 7.25 (s, 1H), 7.10 (dd, J=5.0, 3.7 Hz, 1H). ^{13}C NMR (CDCl3): δ 156.6, 148.4, 147.6, 137.0, 129.3, 128.9, 128.8, 127.8, 126.0, 125.9, 124.8, 116.9, 109.4. HRMS calcd for $C_{15}H_{10}N_4S_2H$ $(M+H)^+$ 311.0420, found 311.0405.

2-(1-(4-(Thiophen-2-yl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-pyridine 5{2,2}. Yield: 61%. Yellow solid. Mp = 186−189 °C. IR νmax (ATR): 2923, 2381, 1603, 1531, 1410 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.10 (s, 1H), 8.64 (d, J=4.7 Hz, 1H), 8.23 (d, J=7.9 Hz, 1H), 7.81 (dt, J=7.9, 1.7 Hz, 1H), 7.47 (dd, J=3.6, 0.9 Hz), 7.32 (dd, J=5.0, 0.9 Hz, 1H), 7.30−7.27 (m, 1H), 7.24 (s, 1H), 7.08 (dd, J=5.0, 3.6 Hz, 1H). ^{13}C NMR (CDCl3): δ 156.4, 149.6, 149.2, 148.9, 147.8, 137.1, 137.1, 127.8, 126.0, 124.9, 123.7, 120.8, 119.7, 109.5. HRMS calcd for $C_{14}H_9N_5S_2Na$ $(M+Na)^+$ 334.0192, found 334.0197.

3-(1-(4-(Thiophen-2-yl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-pyridine 5{2,3}. Yield: 59%. Brown solid. Mp = 169−170 °C. IR νmax (ATR): 2923, 1553, 1524, 1444, 1236 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.16 (s, 1H), 8.81 (s, 1H), 8.67 (d, J = 3.7 Hz, 1H), 8.30 (d, J=7.8 Hz, 1H), 7.53−7.52 (m, 1H), 7.46−7.42 (m, 1H), 7.37 (d, J = 4.7 Hz, 1H), 7.29 (s, 1H), 7.13−7.11 (m, 1H). ^{13}C NMR (CDCl3): δ 156.3, 149.8, 147.7, 147.2, 145.4, 136.8, 133.2, 127.8, 126.0, 125.6, 124.9, 123.7, 117.4, 109.6. HRMS calcd for $C_{14}H_9N_5S_2H$ $(M+H)^+$ 312.0372, found 312.0383.

4-(Thiophen-2-yl)-1-(4-(thiophen-2-yl)thiazol-2-yl)-1H-1,2,3-triazole 5{2,4}. Yield: 60%. Brown solid. Mp = 154−156 °C. IR νmax (ATR): 3079, 2923, 1527 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.61 (s, 1H), 7.55 (dd, J = 3.6, 1.1 Hz, 1H), 7.52 (dd, J = 3.7, 1.1 Hz, 1H), 7.40 (dd, J = 5.1, 1.1 Hz, 1H), 7.36 (dd, J = 5.1, 1.1 Hz, 1H), 7.27 (s, 1H), 7.15 (dd, J = 5.1, 3.6 Hz, 1H), 7.12 (dd, J = 5.1, 3.7 Hz, 1H). ^{13}C NMR (CDCl3): δ 156.3, 147.6, 143.6, 136.9, 131.4, 127.8, 127.7, 125.9, 125.9, 125.2, 124.8, 116.2, 109.5. HRMS calcd for $C_{13}H_8N_4S_3H$ $(M+H)^+$ 316.9984, found 316.9966.

(E)-(1-(4-(Thiophen-2-yl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-methyl Cinnamate 5{2,5}. Yield: 58%. White solid. Mp = 138−140 °C. IR νmax (ATR): 1700, 1625, 1525, 1158 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.63 (s, 1H), 7.78 (d, J=16.0 Hz, 1H), 7.56−7.51 (m, 3H), 7.42−7.40 (m, 3H), 7.36 (dd, J=5.0, 1.1 Hz, 1H), 7.27 (s, 1H), 7.12 (dd, J=5.0, 3.6 Hz, 1H), 6.50 (d, J=16.0 Hz, 1H), 5.49 (s, 2H). ^{13}C NMR (CDCl3): δ 166.6, 156.5, 147.8, 145.9, 144.0, 137.0, 134.2, 130.5, 128.9, 128.2, 127.9, 126.1, 125.0, 121.6,

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117.2, 109.6, 57.3. HRMS calcd for $C_{19}H_{14}N_4O_2S_2Na$ $(M+Na)^+$ 417.0450, found 417.0447.

4-Phenyl-1-(4-phenylthiazol-2-yl)-1H-1,2,3-triazole 5{3,1}. Yield: 52%. White solid. Mp = 136−138 °C. IR νmax (ATR): 1530, 1428, 1233 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.65 (s, 1H), 8.00−7.93 (m, 4H), 7.52−7.44 (m, 4H), 7.44−7.38 (m, 3H). ^{13}C NMR (CDCl3): δ 156.6, 153.0, 148.4, 133.3, 129.4, 128.9, 128.8, 128.7, 128.6, 126.1, 126.0, 116.8, 110.7. HRMS calcd for $C_{17}H_{12}N_4SH$ $(M+H)^+$ 305.0855, found 305.0884.

2-(1-(4-Phenylthiazol-2-yl)-1H-1,2,3-triazol-4-yl)pyridine 5{3,2}. Yield: 60%. Brown solid. Mp = 181−184 °C. IR νmax (ATR): 3111, 1530, 1420, 1232 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.10 (s, 1H), 8.66 (ddd, *J*=5.7, 1.7, 1.1 Hz, 1H), 8.24 (d, *J*=8.7, 0.9 Hz, 1H), 7.91 (dd, *J*=8.7, 1.1 Hz, 2H), 7.82 (dt, *J*=7.8, 1.7 Hz, 1H), 7.46 (dt, *J*=8.7, 2.4 Hz, 2H), 7.42 (s, 1H), 7.41−7.37 (m, 1H), 7.31−7.28 (m, 1H). ^{13}C NMR (CDCl3): δ 156.2, 153.0, 149.6, 149.2, 148.9, 136.8, 133.2, 128.8, 128.7, 126.0, 123.3, 120.6, 119.5, 110.8. HRMS calcd for $C_{16}H_{11}N_5SNa$ $(M+Na)^+$ 328.0627, found 328.0616.

3-(1-(4-Phenylthiazol-2-yl)-1H-1,2,3-triazol-4-yl)pyridine 5{3,3}. Yield: 58%. Yellow solid. Mp = 158−161 °C. IR νmax (ATR): 1526, 1477, 1408, 1230 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.14 (s, 1H), 8.81 (s, 1H), 8.65 (s, 1H), 8.29 (d, *J*=7.4 Hz, 1H), 7.92 (d, 2H, *J* = 7.4 Hz, 2H), 7.45−7.39 (m, 5H). ^{13}C NMR (CDCl3): δ 156.3, 153.1, 149.8, 147.2, 145.4, 133.2, 133.1, 128.8, 128.7, 126.1, 125.6, 123.7, 117.3, 111.0. HRMS calcd for $C_{16}H_{11}N_5SH$ $(M+H)^+$ 306.0808, found 306.0788.

1-(4-Phenylthiazol-2-yl)-4-(thiophen-2-yl)-1H-1,2,3-triazole 5{3,4}. Yield: 48%. Yellow solid. Mp = 154−156 °C. IR νmax (ATR): 1517, 1423, 1218 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.63 (s, 1H), 7.93 (d, *J*=8.7 Hz, 2H), 7.54 (dd, *J*=3.6, 0.9 Hz, 1H), 7.47 (t, *J*=8.7 Hz, 2H), 7.42−7.38 (m, 3H), 7.14 (dd, *J*=5.0, 3.6 Hz, 1H). ^{13}C NMR (CDCl3): δ 156.4, 153.0, 143.5, 133.2, 131.5, 128.8, 128.7, 127.7, 126.1, 125.9, 125.1, 116.2, 110.8. HRMS calcd for $C_{15}H_{10}N_4S_2H$ $(M+H)^+$ 311.0420, found 311.0402.

(E)-(1-(4-Phenylthiazol-2-yl)-1H-1,2,3-triazol-4-yl)methyl cinnamate 5{3,5}. Yield: 52%. White solid. Mp = 133−136 °C. IR νmax (ATR): 2924, 2853, 1709, 1636, 1531, 1443, 1165 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.65 (s, 1H), 7.93 (d, *J*=7.2 Hz, 2H), 7.78 (d, *J*=16.0 Hz, 1H), 7.56−7.54 (m, 2H), 7.49 (dd, *J*=8.5, 7.2 Hz, 2H), 7.43−7.40 (m, 5H), 6.50 (d, *J*=16.0 Hz, 1H), 5.49 (s, 2H). ^{13}C NMR (CDCl3): δ 166.6, 156.5, 153.2, 145.9, 144.0, 134.3, 134.2, 133.3, 130.5, 128.9, 128.8, 128.2, 126.2, 121.6, 117.6, 111.0, 57.4. HRMS calcd for $C_{21}H_{16}N_4O_2SNa$ $(M+Na)^+$ 411.0886, found 411.0874.

1-(4-(4-Chlorophenyl)thiazol-2-yl)-4-phenyl-1H-1,2,3-triazole 5{4,1}. Yield: 61%. White solid. Mp = 142−144 °C. IR νmax (ATR): 1613, 1531, 1466, 1212 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.73 (s, 1H), 7.97 (d, *J*=8.6 Hz, 2H), 7.88 (dd, *J*=6.7, 1.8 Hz, 2H), 7.53−7.43 (m, 5H), 7.42 (s, 1H). ^{13}C NMR (CDCl3): δ 156.8, 151.8, 148.5, 134.6, 131.8, 129.3, 129.0, 128.9, 128.8, 127.4, 126.0, 116.8, 111.0. HRMS calcd for $C_{17}H_{11}ClN_4SH$ $(M+H)^+$ 339.0471, found 339.0459.

2-(1-(4-(4-Chlorophenyl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-pyridine 5{4,2}. Yield: 55%. White solid. Mp = 186−188 °C. IR νmax (ATR): 1602, 1529, 1473, 1421 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.13 (s, 1H), 8.69 (br, 1H), 8.27 (d, *J*=7.9 Hz, 1H), 7.90−7.84 (m, 3H), 7.46 (d, *J*=9.1 Hz, 2H), 7.43 (s, 1H), 7.33 (dd, *J*=7.9, 5.3 Hz, 1H). ^{13}C NMR (CDCl3): δ 156.5, 151.9, 149.3, 148.9, 148.6, 137.2, 134.6, 131.7, 128.9, 127.3, 123.4, 120.7, 119.6, 111.1. HRMS calcd for $C_{16}H_{10}ClN_5SH$ $(M+H)^+$ 340.0418, found 340.0427.

3-(1-(4-(4-Chlorophenyl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-pyridine 5{4,3}. Yield: 57%. Yellow solid. Mp = 185−188 °C. IR νmax (ATR): 3096, 1602, 1529, 1473, 1421 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.16 (d, *J*=1.5 Hz, 1H), 8.82 (s, 1H), 8.67 (dd, *J*=4.7, 1.2 Hz, 1H), 8.31 (ddd, *J* = 7.9, 3.9, 1.8 Hz, 1H), 7.88 (d, *J* = 6.6 Hz, 2H), 7.48−7.44 (m, 4H). ^{13}C NMR (CDCl3): δ 156.5, 151.9, 149.8, 147.2, 145.4, 134.7, 133.2, 131.6, 129.0, 127.4, 125.6, 123.8, 117.2, 111.3. HRMS calcd for $C_{16}H_{10}ClN_5SH$ $(M+H)^+$ 340.0418, found 340.0423.

1-(4-(4-Chlorophenyl)thiazol-2-yl)-4-(thiophen-2-yl)-1H-1,2,3-triazole 5{4,4}. Yield: 58%. Yellow solid. Mp = 165−167 °C. IR νmax (ATR): 2924, 1527, 1472, 1243 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.63 (s, 1H), 7.88 (d, *J*=8.6 Hz, 2H), 7.56 (dd, *J*=3.6, 0.8 Hz, 1H), 7.47−7.40 (m, 4H), 7.16 (dd, *J*=4.9, 3.6 Hz, 1H). ^{13}C NMR (CDCl3): δ 156.6, 151.8, 143.6, 134.6, 131.7, 131.4, 129.0, 127.7, 127.4, 125.9, 125.2, 116.1, 111.1. HRMS calcd for $C_{15}H_9ClN_4S_2H$ $(M+H)^+$ 345.0030, found 345.0042.

(E)-(1-(4-(4-chlorophenyl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-methyl cinnamate 5{4,5}. Yield: 64%. White solid. Mp = 107−109 °C. IR νmax (ATR): 2924, 1713, 1636, 1526, 1162 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.63 (s, 1H), 7.86 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.77 (d, *J* = 16.0 Hz, 1H), 7.56−7.53 (m, 2H), 7.45 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.44−7.40 (m, 4H), 6.50 (d, *J* = 16.0 Hz, 1H), 5.49 (s, 2H). ^{13}C NMR (CDCl3): δ 166.5, 156.5, 151.8, 145.8, 143.9, 134.6, 134.0, 131.6, 130.4, 129.0, 128.8, 128.1, 127.3, 121.5, 117.1, 111.2, 57.2. HRMS calcd for $C_{21}H_{15}ClN_4O_2SH$ $(M+H)^+$ 423.0677, found 423.0692.

1-(4-(4-Fluorophenyl)thiazol-2-yl)-4-phenyl-1H-1,2,3-triazole 5{5,1}. Yield: 62%. Brown solid. Mp > 220 °C. IR νmax (ATR): 1603, 1528, 1482, 1232 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.73 (s, 1H), 7.97 (d, *J*=7.4 Hz, 2H), 7.93 (dd, *J*=8.6, 5.4 Hz, 2H), 7.51 (t, *J*=7.4 Hz, 2H), 7.45 (t, *J*=7.4 Hz, 1H), 7.36 (s, 1H), 7.18 (t, *J*=8.6 Hz, 2H). ^{13}C NMR (CDCl3): δ 162.9 (d, J_{C-F}=247.3 Hz), 156.8, 152.0, 148.4, 129.6, 129.4, 128.9, 128.8, 127.9 (d, J_{C-F} = 6.8 Hz), 126.0, 116.8, 115.7 (d, J_{C-F} = 21.6 Hz), 110.3. HRMS calcd for $C_{17}H_{11}FN_4SH$ $(M+H)^+$ 323.0761, found 323.0773.

2-(1-(4-(4-Fluorophenyl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-pyridine 5{5,2}. Yield: 67%. Yellow solid. Mp = 156−158 °C. IR νmax (ATR): 2923, 2854, 1601, 1530, 1481, 1421, 1216 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.10 (s, 1H), 8.67 (d, *J*=4.4 Hz, 1H), 8.25 (d, *J*=7.8 Hz, 1H), 7.90 (dd, *J*=8.6, 5.4 Hz, 2H), 7.84 (dt, *J*=7.8, 1.6 Hz, 1H), 7.36 (s, 1H), 7.33−7.29 (m, 1H), 7.16 (t, *J*=8.6 Hz, 2H). ^{13}C NMR (CDCl3): δ 163.0 (d, J_{C-F} = 247.1 Hz), 156.5, 152.1, 149.7, 149.2, 149.0, 136.4, 129.6, (d, J_{C-F}=2.7 Hz), 127.9 (d, J_{C-F}=8.1 Hz), 123.4, 120.7, 119.5, 115.8 (d, J_{C-F}=21.6 Hz), 110.4. HRMS calcd for $C_{16}H_{10}FN_5SH$ $(M+H)^+$ 324.0714, found 324.0698.

3-(1-(4-(4-Fluorophenyl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-pyridine 5{5,3}. Yield: 55%. Yellow solid. Mp > 220 °C. IR νmax (ATR): 3095, 1529, 1441, 1231 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.17 (s, 1H), 8.83 (s, 1H), 8.68 (d, *J*=4.7 Hz, 1H), 8.33 (d, *J*=7.8 Hz, 1H), 7.94 (dd, *J*=7.4, 5.7 Hz, 2H), 7.48−7.44 (m, 1H), 7.29 (s, 1H), 7.19 (t, *J*=8.3, 7.8 Hz, 2H). ^{13}C NMR (CDCl3): δ 163.0 (d, J_{C-F} = 247.1 Hz), 156.5, 152.1, 149.9, 147.2, 145.4, 133.2, 129.5, 127.9 (d, J_{C-F}=8.0 Hz), 125.6, 123.7, 117.2, 115.8 (d, J_{C-F} = 21.6 Hz), 110.6. HRMS calcd for $C_{16}H_{10}FN_5SH$ $(M+H)^+$ 324.0714, found 324.0720.

1-(4-(4-Fluorophenyl)thiazol-2-yl)-4-(thiophen-2-yl)-1H-1,2,3-triazole 5{5,4}. Yield: 51%. Gray solid. Mp = 210−212 °C. IR νmax (ATR): 3081, 1530, 1229 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.64 (s, 1H), 7.95−7.91 (m, 2H), 7.56 (dd, *J*=3.6, 0.9 Hz, 1H), 7.41 (dd, *J*=5.1, 0.9 Hz, 1H), 7.37 (s, 1H), 7.20−7.15 (m, 3H). ^{13}C

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NMR (CDCl3): δ 163.0 (d, J_{C-F} = 246.9 Hz), 156.5, 152.0, 143.6, 131.5, 129.5, 127.9 (d, J_{C-F} = 8.1 Hz), 127.7, 125.9, 125.2, 116.1, 115.8 (d, J_{C-F} = 21.7 Hz), 110.4. HRMS calcd for $C_{15}H_9FN_4S_2H$ $(M+H)^+$ 329.0325, found 329.0332.

(E)-(1-(4-(4-Fluorophenyl)thiazol-2-yl)-1H-1,2,3-triazol-4-yl)-methyl cinnamate 5{5,5}. Yield: 63%. White solid. Mp = 124−126 °C. IR νmax (ATR): 2924, 1706, 1634, 1527, 1167 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.61 (s, 1H), 7.88 (dd, J = 8.6, 5.2 Hz, 2H), 7.76 (d, J = 16.0 Hz, 1H), 7.54−7.51 (m, 2H), 7.41−7.37 (m, 3H), 7.33 (s, 1H), 7.14 (t, J = 8.6 Hz, 2H), 6.49 (d, J = 16.0 Hz, 1H), 5.48 (s, 2H). ^{13}C NMR (CDCl3): δ 166.6, 163.0 (d, J_{C-F} = 247.1 Hz), 161.7, 156.4, 152.0, 145.8, 143.9, 134.0, 130.4, 129.4 (d, J_{C-F} = 2.8 Hz), 128.8, 128.1, 127.9 (d, J_{C-F} = 8.1 Hz), 121.4, 117.1, 115.7 (d, J_{C-F} = 21.7 Hz), 110.5. HRMS calcd for $C_{21}H_{15}FN_4O_2SH$ $(M+H)^+$ 407.0973, found 407.0934. $C_{21}H_{15}FN_4O_2SNa$ $(M+Na)^+$ 429.0792, found 429.0771.

Cytotoxic Activity Assay. Human uterus sarcoma doxorubicin resistant cancer cells (MES-SA/Dx5) and african green monkey kidney epithelial cells (Vero) were seeded at 1×10^4 cells/100 μL/well and 1×10^3 cells/100 μL/well, respectively, in 96-well plates and incubated for 24 h at 37 °C in a 5% CO_2 incubator. Test compounds were dissolved in dimethylsulfoxide (DMSO) and diluted for cell treatment in culture medium containing DMSO at the final concentration of ≤0.5%. Cells were treated with test compounds of various concentrations in triplicates per concentration in the culture medium (200 μL/well) and incubated at 37 °C in a 5% CO_2 incubator for 72 h. A colorimetric assay using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) system was used to determine the cytotoxic activity of the testing compounds. Optical density (OD) values at 570 nm on a microtiter plate reader (MRX II, DYNEX) were measured. IC_{50}, the concentration that inhibited 50% of the cancer cell growth activity, was estimated. All experiments were repeated three times.

■ ASSOCIATED CONTENT

Supporting Information. Spectral data (^1H, ^{13}C NMR and HRMS) of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS

DMF, *N*,*N*-dimethyl formamide; EtOAc, ethyl acetate; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; HRMS, high resolution mass spectrometry; CuAAC, copper-(I)-catalyzed [3 + 2] azide and alkyne cycloaddition; DMEDA, *N*,*N*′-dimethylethylenediamine

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