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Synthesis and Biological Evaluation of Thiazolyl-Ethylidene Hydrazino-Thiazole Derivatives: A Novel Heterocyclic System

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Abstract: The reaction of 2-(1-(2-(2-(4-methoxybenzylidene)hydrazinyl)-4-methylthiazol-5-yl)ethylidene) hydrazinecarbothioamide with a range of hydrazonoyl chlorides and α-halo-compounds yielded three new series of thiazole derivatives. Chemical and physical techniques were used to analyze all newly prepared derivatives (^{1}H-NMR, ^{13}C-NMR, FT-IR and mass spectrometry). The potential antimicrobial and anticancer properties of the synthesized derivatives were investigated using various in vitro biological experiments. Most of the thiazole compounds tested were effective against Gram-positive and Gram-negative bacteria. In addition, a minimum inhibition concentration was determined for the antibiotic properties of the most active produced substances. The cytotoxic activities were tested on HepG-2 (liver carcinoma), HCT-116 (colorectal carcinoma) and MDA-MB-231 (breast carcinoma) cell lines in comparison with cisplatin reference drug and using colorimetric MTT assay. The results detected that compound **10c** was the most potent against the three tested cell lines. Interestingly, when the tested compounds were evaluated for their toxicity against normal (MRC-5) cells, they exhibited low toxic effects indicating the safe use of most of them that may require further in vivo and pharmacological studies.

Keywords: hydrazones; thiazoles; hydrazonoyl halides; cyclization; cytotoxicity; antimicrobial activity

1. Introduction

Cancer continues to be one of the world's major death causes. The current anticancer medication therapy is insufficient due to its lack of selectivity and target specificity, in addition to the presence of resistance and toxicity [1]. In order to combat the rapid development of medication resistance, antimicrobial drug researchers are currently concentrating on discovering new targets and chemical entities with antibacterial activity. Given the foregoing, there is a pressing need for ongoing advancement in the design and development of antimicrobial and anticancer medicines.

Several studies have been carried out with plenty of thiazoles towards different pathologies due to their numerous biological activities, including antimicrobial [2–5], cytotoxic [4–14], antiviral [15], anti-HIV [16], as antimicrobial [17] and analgesic [18]. Moreover, thiazole derivatives are among the most employed scaffolds in designing and identifying

new lead compounds, notably anticancer drugs [19–23]. In addition, thiazole-containing compounds have marked their appearance in several clinically available anticancer drugs, such as ixabepilone [24], dabrafenib [25] and dasatinib [26] (Figure 1).

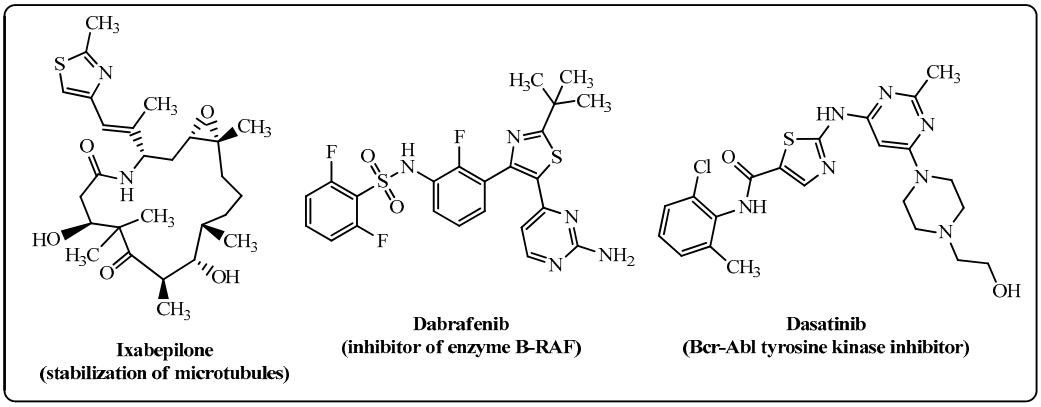


Figure 1. Examples of anticancer drugs bearing thiazole derivatives.

On the other hand, thiosemicarbazones are a wide group of compounds, representing great medical benefits against microbial diseases [27] and parasite diseases [28,29]. They have also been identified as one of the most interesting inhibitors of antitumor [30,31].

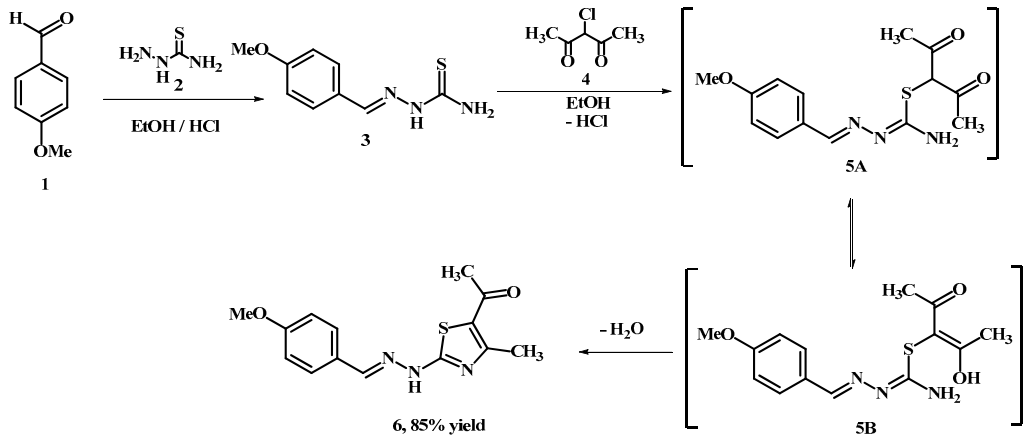
The use of current cancer therapy leads to decreasing immunity that makes the human body ready to fight any microbial infections. Thus, in this study, these heterocyclic systems could be applied to treat tumor and bacterial diseases.

The thiazoles mentioned above and bis-thiazoles biological activities, as well as our experience in the synthesis of new series of bioactive heterocyclic compounds [32–43] promoted us to synthesize some novel thiazolyl hydrazono thiazole derivatives from inexpensive laboratory available starting materials such as thiosemicarbazone derivative **3** to be examined as anticancer and antimicrobial agents.

2. Results and Discussion

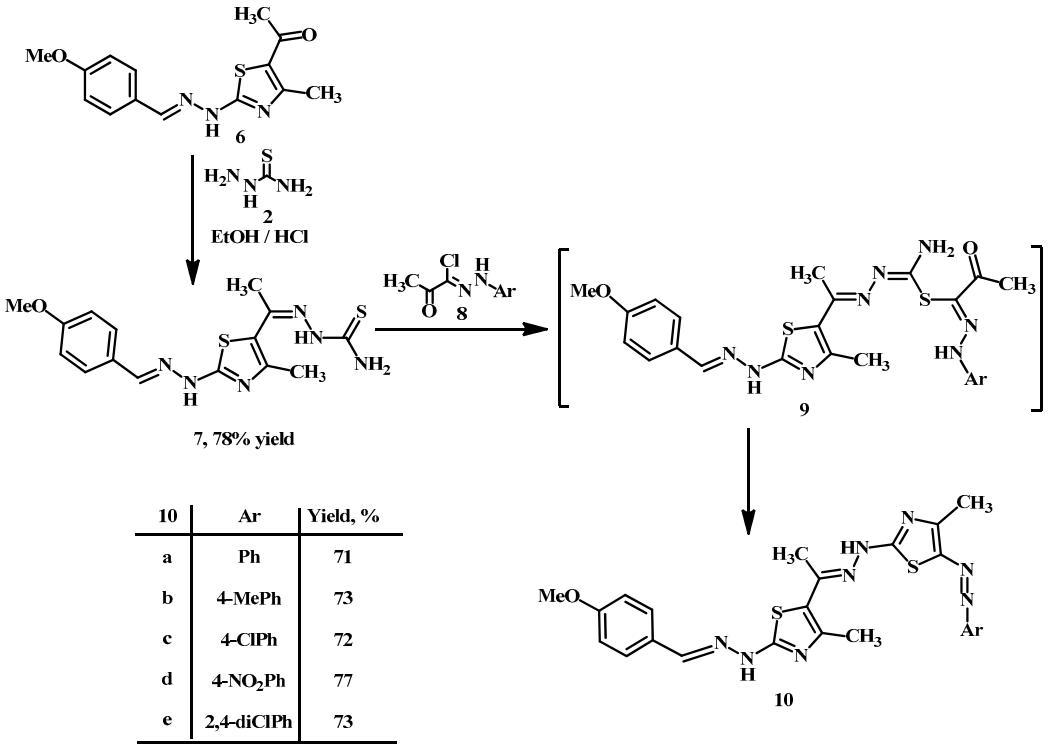
2.1. Chemistry

According to literature [44], the thiosemicarbazone derivative **3** (obtained from the reaction of *p*-anisaldehyde **1** with thiosemicarbazide **2**) reacts with α-chloro-acetylacetone **4** in refluxing ethanol to afford the acetylthiazole derivative **6**. The reaction presumably occurred via the elimination of HCl to afford the intermediate **5A** who tautomerisms into **5B**, which in role, undergoes cyclization via the elimination of water (Scheme 1).



Scheme 1. Synthesis of the thiosemicarbazone derivative **3** and the thiazole derivative **6**.

The acetylthiazole **6** was allowed to condense with **2** to afford the thiosemicarbazone derivative **7** Scheme 2). The IR spectrum of **7** revealed absorption band at υ_{max} = 3402, 3271 and 3201 cm^{-1} attributable to NH_2 and NH functions, 3055 and 2954 cm^{-1} due to aromatic and aliphatic C-H. The ^1H NMR spectrum of **7** demonstrated two methyl singlets at δ = 1.81 and 2.50 ppm, while the methoxy singlet appeared at δ = 3.80 ppm, the amino protons at δ = 7.75 ppm and two broad amino protons at δ = 11.30 and 11.95 ppm, beside the other olefinic and aromatic proton signals at their expected positions (cf. experimental).



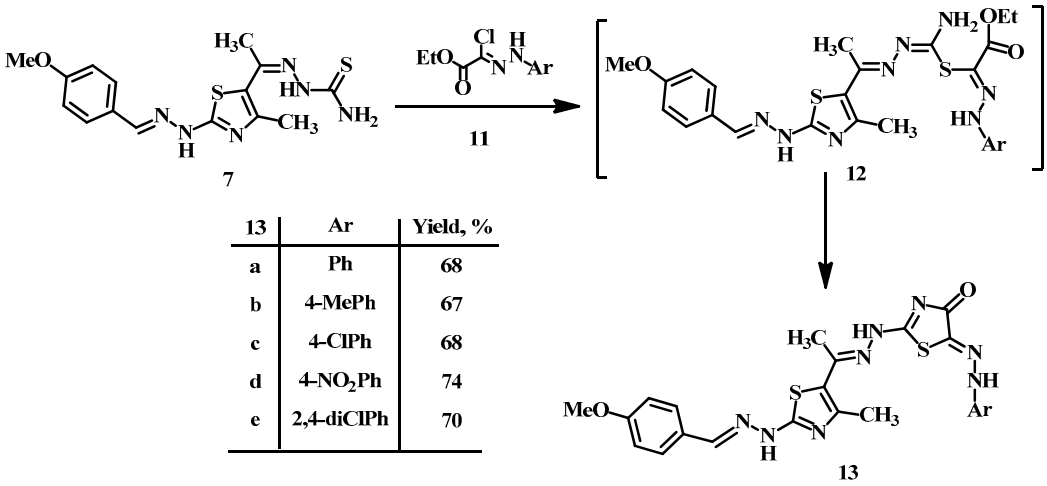
10	Ar	Yield, %
a	Ph	71
b	4-MePh	73
c	4-ClPh	72
d	4-NO_2Ph	77
e	2,4-diClPh	73

Scheme 2. Synthesis of thiazolylhydrazonothiazoles **10a**–**e**.

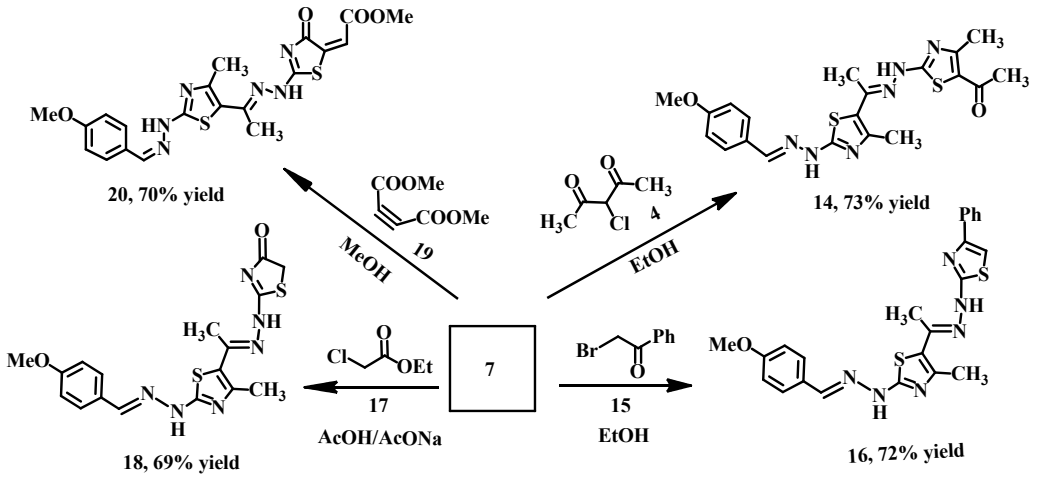
Compound **7** reacted with the hydrazonoyl chloride derivatives **8a**–**e** to yield the ethylidene hydrazine bis-thiazole derivatives **10a**–**e** (presumably via the intermediates **9a**–**e**), respectively.

To explore the synthetic potentialities of compound **7** and to synthesize another series of bis-thiazoles, it was allowed to react with ethyl hydrazonoyl chloride ester derivatives **11a**–**e** to afford the ethylidene hydrazine bis-thiazole derivatives **13a**–**e** [presumably via the intermediates **12a**–**e**], respectively (Scheme 3). Spectra of IR and ^1H NMR, as well as elemental analysis, are all in full and accord with the depicted structures **10a**–**e** and **13a**–**e** (cf. experimental).

Likewise, compound **7** reacted with α-chloro acetylacetone **4**, phenacyl bromide **15**, ethyl chloroacetate **17** and dimethyl acetylene dicarboxylate **19** to afford the ethylidene hydrazine bis-thiazole derivatives **14**, **16**, **18** and **20**, respectively (Scheme 4). Spectral and elemental content analyses are consistent with the proposed structures **14**, **16**, **18** and **20** (cf. experimental).



Scheme 3. Synthesis of thiazolylhydrazonothiazoles **13a**–**e**.



Scheme 4. Synthesis of the thiazolylhydrazonothiazole derivatives **14**, **16**, **18** and **20**.

The geometry of all synthesized compounds **3**, **6**, **7**, **10**, **13**, **14**, **16**, **18** and **20** are in E-configuration [45].

2.2. Biological Activities of the Selected Compounds

2.2.1. Antimicrobial Evaluation

Using the agar well diffusion method, the in vitro antimicrobial activity of the newly prepared derivatives was investigated against *Staphylococcus aureus* and *Bacillus subtilis* (Gram-positive bacteria), *Escherichia coli* and *Proteus vulgaris* (Gram-negative bacteria) as well as *Aspergillus fumigatus* and *Candida albicans* (fungal strains). The results of antimicrobial activity displayed variable in vitro antibacterial and antifungal activities (Table 1). However, compounds **10c**, **10d** and **13d** have no antimicrobial activities (Table 1).

In addition, to identify the minimum inhibitory concentration (MIC), the antimicrobial activities of the most active compounds were tested (Table 2).

Table 1. The in vitro antimicrobial results of the newly synthesized products at 10 mM expressed as inhibition zone diameter (mm) in the form of mean ± standard error.

Compound No.	Tested Microorganisms					
	Fungi		Gram +ve Bacteria		Gram −ve Bacteria	
	A. fumigatus RCMB 002568	*C. albicans* ATCC 10231	*B. subtilis* NRRL-B-543	*S. aureus* RCMB 010010	*E. coli* ATCC 25955	*P. vulgaris* ATCC 13315
6	13.4 ± 0.9	10.8 ± 0.7	9.3 ± 0.9	14.3 ± 1.1	8.2 ± 0.4	17.2 ± 1.2
7	18.5 ± 1.7	15.9 ± 1.3	15.8 ± 0.6	9.1 ± 0.7	9.7 ± 0.5	18.3 ± 1.1
10b	10.9 ± 0.8	16.2 ± 0.8	13.2 ± 0.8	8.5 ± 0.7	8.6 ± 0.6	10.1 ± 0.7
10e	0	0	8.2 ± 0.6	0	13.2 ± 0.9	8.4 ± 0.8
13a	9.1 ± 0.5	13.7 ± 0.9	10.9 ± 0.9	15.2 ± 0.8	8.3 ± 0.6	9.2 ± 0.8
13c	9.3 ± 0.6	14.1 ± 0.7	16.9 ± 1.3	15.8 ± 1.2	15.5 ± 1.1	12.4 ± 0.8
13e	0	0	8.3 ± 0.4	0	12.9 ± 0.9	7.5 ± 0.6
16	0	11.1 ± 0.8	9.3 ± 0.5	12.6 ± 0.9	10.1 ± 0.8	13.8 ± 1.4
20	10.2 ± 0.7	16.3 ± 1.2	12.4 ± 1.1	8.1 ± 0.5	8.9 ± 0.7	7.8 ± 0.5
*** Ketoconazole**	23.7 ± 1.1	27.6 ± 1.2	-	-	-	-
*** Ciprofloxacin**	-	-	29.4 ± 1.4	26.1 ± 1.7	25.7 ± 1.9	28.6 ± 1.8

* Ciprofloxacin and ketoconazole were used (at 1 mM conc.) as standard drugs against the tested bacteria and fungi, respectively.

Table 2. MIC of the newly synthesized products against the tested bacteria and fungi *.

Compound Code	*A. fumigatus* RCMB 002568	*C. albicans* ATCC 10231	*B. subtilis* NRRL-B-543	*S. aureus* RCMB 010010	*E. coli* ATCC 25955	*P. vulgaris* ATCC 13315
6	2500	5000	2500	1250	5000	625
7	312.5	625	625	5000	5000	312.5
10b	2500	625	1250	10,000	5000	5000
10e	>10,000	>10,000	10,000	>10,000	1250	10,000
13a	5000	1250	2500	1250	5000	5000
13c	2500	625	625	625	625	2500
16	>10,000	5000	5000	1250	5000	625
20	5000	625	2500	10,000	5000	10,000
Ketoconazole	3.9	1.9	-	-	-	-
Ciprofloxacin	-	-	0.24	0.98	0.49	0.24

* Antifungal and antibacterial activities were expressed as MIC values in μM.

The antifungal activity against the filamentous fungus Aspergillus fumigatus was in the following order: **7**, **6**, **10b**, **20**, **13c** and **13a**, respectively.

On the other hand, the activity order against Candida albicans "pathogenic yeast" was **10b**, **20**, **7**, **13c**, **13a**, **6** and **16**, respectively (Tables 1 and 2). Thus, compared to the ketoconazole reference antifungal drug, these compounds showed lower activity against Aspergillus fumigatus and Candida albicans.

Compound **13c** showed the highest activity against *Staphylococcus aureus* (but showing activity lower than the standard drug ciprofloxacin) followed by compounds **13a**, **6**, **16**, **7**, **10b** and **20**, respectively. Likewise, compound **13c** exhibited the highest activity against *Bacillus subtilis* followed by compounds **7**, **10b**, **21**, **13a**, **6**, **16**, **10e** and **10d**, respectively. Additionally, compound **7** showed the highest activity against *Proteus vulgaris* than the standard drug, followed by compounds **6**, **16**, **13c**, **10b**, **13a**, **10e** and **20**, respectively. The activity order against *Escherichia coli* was **13c**, **10e**, **7**, **16**, **20**, **6**, **10b** and **13a**, respectively, and showed lower sensitivity than the tested standard drugs (Tables 1 and 2).

2.2.2. Cytotoxic Activity

The in vitro growth inhibitory activity of the prepared products was examined versus the liver carcinoma cell line (HepG2), the colon carcinoma cell line (HCT-116) and the

breast carcinoma cell line (MDA-MB-231) using colorimetric MTT assay compared to the cisplatin anticancer reference drug. A dose–response curve was plotted from data generated, and IC_{50} was determined (the test compounds concentration needed to kill 1⁄2 of cell population) (Figure 2). The average IC_{50} of three independent studies was used to calculate cytotoxic activity. Generally, the results in Table 3 and Figure 2 revealed that all the tested compounds have different inhibitory activity in a concentration-dependent manner. However, compounds **6**, **13e**, **16**, **20** and **13c** were less active than counterparts with a lower tendency to inhibit the three carcinoma cell lines. Interestingly, the presented results revealed that compounds **10c**, **7** and **10e** were the most active against the HepG2 giving potent IC_{50} values of 20.95, 30.6 and 38.84 µM, respectively, but still less active than cisplatin reference drug (8.63 µM). On the other hand, compounds **10c**, **10e** and **7** were the most active against the MDA-MB-231 giving a good IC_{50} value of 44.69, 57.78 and 64.08 µM, compared with the standard drug (cisplatin) with an IC_{50} value of 11.83 µM. Moreover, the highest inhibitory activity value against the HCT-116 was reported for compound **10c** (IC_{50}:25.37 µM) followed by **7**, **10e**, **13d**, **10b**, **13a**, **10d**, **13c**, **20**, **16**, **13e** and **6**, respectively. Similarly, the order of activity against the HepG2 was **10c**, **7**, **10e**, **10b**, **13d**, **10d**, **13a**, **13c**, **20**, **16**, **13e** and **6**, respectively. However, the activity order against MDA-MB-231 was **10c**, **7**, **10e**, **10b**, **10d**, **13d**, **13a**, **13c**, **20**, **16**, **13e** and **6**, respectively (Table 3).

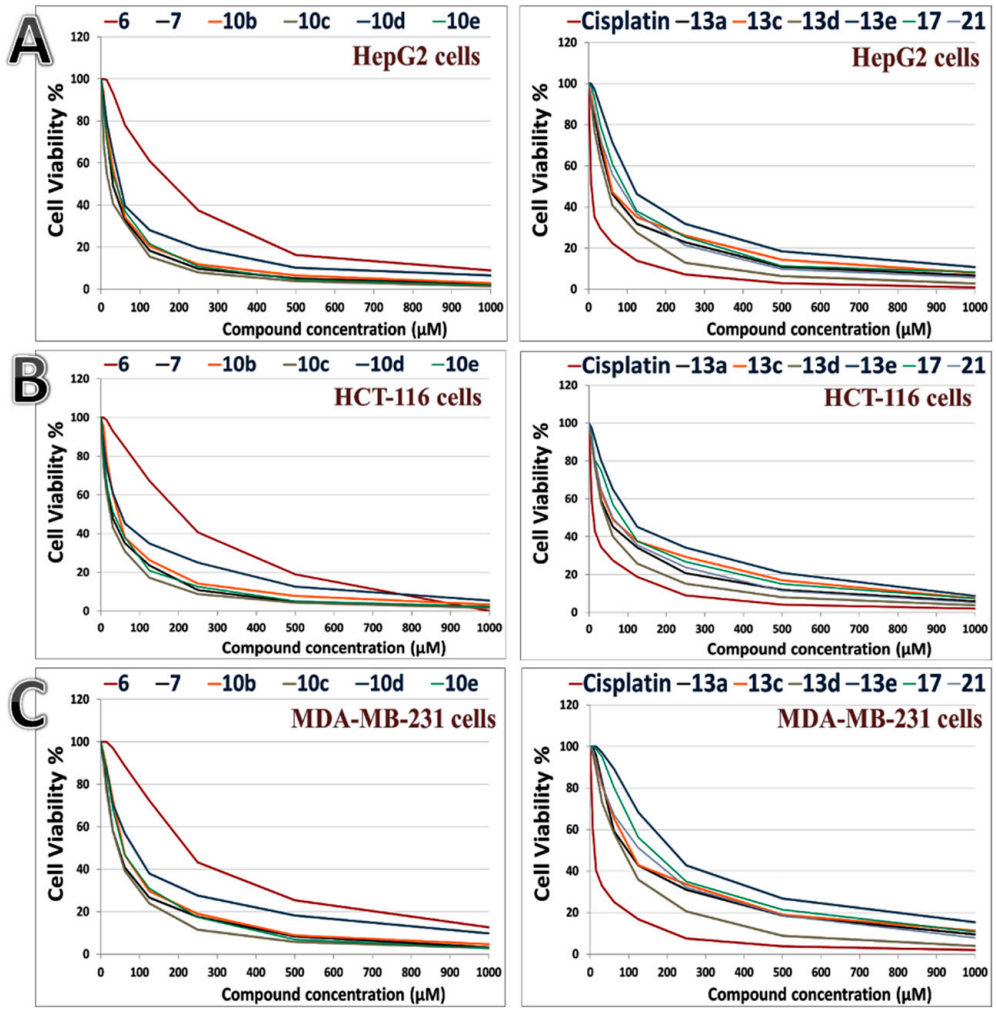


Figure 2. The in vitro inhibitory activity of the prepared compounds as a dose–response curve against (**A**) HepG2; (**B**) HCT-116; (**C**) MDA-MB-231.

Table 3. The inhibitory activities of the examined compounds against different carcinoma cell lines (as IC_{50} values).

Compound No.	IC_{50} Values * (μM)		
	HepG-2	HCT-116	MDA-MB-231
6	183.2 ± 10.46	206.34 ± 9.28	219.71 ± 8.57
7	30.67 ± 1.35	29.26 ± 1.12	64.08 ± 3.84
10b	40.73 ± 1.29	44.98 ± 1.36	58.63 ± 4.71
10c	20.95 ± 0.89	25.37 ± 0.91	44.69 ± 2.35
10d	49.57 ± 1.37	53.02 ± 1.26	85.4 ± 2.19
10e	38.84 ± 1.08	34.28 ± 0.92	57.78 ± 1.36
13a	57.26 ± 1.44	51.78 ± 1.39	97.42 ± 3.95
13c	59.01 ± 1.35	60.29 ± 1.57	105.21 ± 5.13
13d	49.15 ± 1.23	45.23 ± 1.19	85.64 ± 4.12
13e	115.79 ± 4.87	109.71 ± 3.45	214.57 ± 8.31
16	92.21 ± 2.85	84.89 ± 3.17	160.96 ± 6.42
20	81.68 ± 1.74	61.39 ± 2.25	133.45 ± 7.91
Cisplatin	8.63 ± 0.51	12.16 ± 0.68	11.83 ± 0.79

* The results are expressed as mean ± standard error.

The effects of the examined compounds and cisplatin standard drug were also measured on normal human lung fibroblast (MRC-5) cell line to produce a dose–response curve and to calculate the fifty percent cytotoxic concentration (CC_{50}) as indicated in Table 4.

Table 4. The efficiency and selectivity indices of the investigated derivatives.

Compound No.	CC_{50} Values (μM)	SI Values * (CC_{50}/IC_{50})		
		HepG-2	HCT-116	MDA-MB-231
6	734.13 ± 59.35	4.01	3.56	3.34
7	175.92 ± 18.24	5.74	6.01	2.75
10b	181.89 ± 15.07	4.47	4.04	3.10
10c	197.26 ± 13.48	9.42	7.78	4.41
10d	109.74 ± 5.92	2.21	2.07	1.29
10e	203.71 ± 11.83	5.24	5.94	3.53
13a	214.65 ± 14.21	3.75	4.15	2.20
13c	251.32 ± 30.94	4.26	4.17	2.39
13d	229.14 ± 17.29	4.66	5.07	2.68
13e	278.02 ± 28.64	2.40	2.53	1.30
16	211.96 ± 16.28	2.30	2.50	1.32
20	189.43 ± 11.91	2.32	3.09	1.42
Cisplatin	58.75 ± 3.87	6.81	4.83	4.97

* The CC_{50} values data that were measured as cytotoxic effects against normal human lung fibroblast (MRC-5) cell line (mean ± standard error).

By dividing the CC_{50} by the IC_{50} values, the selectivity index (SI) was calculated. Our results showed that most of the derivatives presented good selectivity index values more potent than cisplatin anticancer drug. When the tested compounds were evaluated for their toxicity against normal cells, they exhibited low toxic effects indicating the safe use of most of them that may require further in vivo and pharmacological studies.

3. Experimental Section

3.1. Synthesis

Synthesis of 1-{2-[N′-(4-methoxybenzylidene)-hydrazino]-4-methylthiazol-5-yl}-ethanone 6:

Compound **6** was prepared as described in the literature method: m.p. 214–216 °C (Lit. m.p. 214–215 °C) [44].

Synthesis of hydrazinecarbothioamide derivative 7:

A catalytic amounts of HCl (two drops, 37%) was added to a mixture of acetylthiazole derivative **6** (2.89 g, 10 mmol), thiosemicarbazide **2** (0.91 g, 10 mmol) in EtOH (20 mL). The mixture was refluxed for 2 h (followed with TLC). The formed product was isolated by filtration and recrystallized from dioxane to give pure product thiosemicarbazone product **7** as white microcrystals, 78% yield; m.p. 210–212 °C; δ_H: 1.81 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 7.05 (d, 2H, J = 12 Hz, Ar-H), 7.75 (s, 2H, NH_2), 7.83 (d, 2H, J = 12 Hz, Ar-H), 7.98 (s, 1H, N=CH), 11.30 (br s, 1H, NH), 11.95 (br s, 1H, NH) ppm; IR (KBr): v 3402, 3271, 3201, (NH_2 and 2NH), 3055 2954 (C-H), 1604, 11438, 1273, 1063, 1030 cm^{-1}; MS m/z (%): 362 (M^+), 281, 163, 106, 91 (100), 78, 63. Anal. Calcd for $C_{15}H_{18}N_6OS_2$ (362.47): C, 49.70; H, 5.01; N, 23.19. Found: C, 49.54; H, 5.00; N, 23.03%.

Synthesis of thiazole derivatives 10a–e and 13a–e:

A catalytic amount of TEA (0.07 mL, 1mmol) was added to a mixture of the appropriate hydrazonoyl chlorides **8a**–**e** or **11a**–**e** (1 mmol) and compound **7** (0.362 g, 1 mmol) in dioxane (20 mL). The formed mixture was refluxed for 2–5 h (followed by TLC). The formed product was isolated by filtration and recrystallized from ethanol to give pure **10a**–**e** and **13a**–**e**. The analytical data of the products **10a**–**e** and **13a**–**e** are depicted as shown below:

Compound 10a:

Orange solid, 71% yield; m.p. 181–183 °C; δ_H (DMSO-d_6): 1.89, 2.36, 2.49 (3s, 9H, $3CH_3$), 3.82 (s, 3H, OCH_3), 6.97–7.68 (m, 9H, Ar-H), 8.05 (s, 1H, N=CH), 10.55, 11.05 (2brs, 3H, 2NH) ppm; δ_C (DMSO-d_6): 9.0, 14.4, 26.8 (CH_3), 58.3 (OCH_3), 112.1, 114.5, 116.0, 122.8, 127.5, 130.0, 130.6, 131.4, 133.7, 138.2, 145.2, 147.3, 154.2, 159.5, 162.1, 165.7 (Ar-C or C=N) ppm; IR (KBr): v 3433, 3240 (2NH), 3046, 2924 (C-H) cm^{-1}; MS m/z (%): 504 (M^+), 412, 335, 250 (100), 173, 141, 91, 77, 63, 55. Anal. Calcd for $C_{24}H_{24}N_8OS_2$ (504.63): C, 57.12; H, 4.79; N, 22.21. Found: C, 57.01; H, 4.58; N, 22.05%.

Compound 10b:

Orange solid, 73% yield; m.p. 211–213 °C; δ_H (DMSO-d_6): 1.89, 2.25, 2.54, 2.57 (4s, 12H, $4CH_3$), 3.80 (s, 3H, OCH_3), 7.03–7.73 (m, 8H, Ar-H), 8.19 (s, 1H, N=CH), 10.63, 10.97 (2brs, 2H, 2NH) ppm; "a ^{13}C NMR spectrum could not be obtained due to insolubility; IR (KBr): v 3433, 3218 (2NH), 3037, 2931 (C-H), 1605, 1504, 1242, 1165, 1026 (C-H), 1496, 1242, 1172, 1026 cm^{-1}; MS m/z (%): 518 (M^+), 490, 343, 287, 204, 134, 106, 91 (100), 77, 65, 55. Anal. Calcd for $C_{25}H_{26}N_8OS_2$ (518.66): C, 57.89; H, 5.05; N, 21.60. Found: C, 57.98; H, 5.18; N, 21.48%.

Compound 10c:

Red solid, 72% yield; m.p. 198–200 °C; δ_H (DMSO-d_6): 1.89, 2.48, 2.55 (3s, 9H, $3CH_3$), 3.81 (s, 3H, OCH_3), 7.0–8.09 (m, 8H, Ar-H), 8.17 (s, 1H, N=CH), 10.63, 10.96 (2brs, 2H, 2NH) ppm; δ_C (DMSO-d_6): 9.0, 14.4, 26.4 (CH_3), 58.4 (OCH_3), 116.9, 117.0, 121.3, 122.6, 126.4, 126.5, 126.7, 133.9, 134.2, 137.3, 137.4, 138.5, 138.7, 145.2, 158.8, 161.2 (Ar-C or C=N) ppm; IR (KBr): v 3433, 3217 (2NH), 3070, 2924 (C-H), 1604, 1496, 1242, 1165, 1095 cm^{-1}; MS m/z (%): 539 (M^+), 363, 287, 153, 127, 111 (100), 91, 71, 55. Anal. Calcd for $C_{24}H_{23}ClN_8OS_2$ (539.08): C, 53.47; H, 4.30; N, 20.79. Found: C, 53.29; H, 4.17; N, 20.55%.

Compound 10d:

Brown solid, 77% yield; m.p. 236–238 °C; δ_H (DMSO-d_6): 1.88, 2.49, 2.61 (3s, 9H, $3CH_3$), 3.82 (s, 3H, OCH_3), 6.99–8.16 (m, 8H, Ar-H), 8.18 (s, 1H, N=CH), 10.99, 11.02 (2brs, 2H, 2NH) ppm; "a ^{13}C NMR spectrum could not be obtained due to insolubility; IR (KBr): v 3433, 3224 (2NH), 3029, 2939 (C-H), 1609 (C=N), 1496, 1319, 1249, 1103, 1026 cm^{-1}; MS m/z (%): 549 (M^+), 519, 374, 288, 207, 133, 108, 65 (100), 55. Anal. Calcd for $C_{24}H_{23}N_9O_3S_2$ (549.63): C, 52.45; H, 4.22; N, 22.94. Found: C, 52.61; H, 4.06; N, 22.72%.

Compound 10e:

Dark red solid, 73% yield; m.p. 209–211 °C; δ_H (DMSO-d_6): 1.91, 2.51, 2.63 (3s, 9H, $3CH_3$), 3.83 (s, 3H, OCH_3), 7.00–7.71 (m, 7H, Ar-H), 8.07 (s, 1H, N=CH), 9.64, 11.90 (2brs, 2H, 2NH) ppm; "a ^{13}C NMR spectrum could not be obtained due to insolubility; IR (KBr): v 3433, 3155 (2NH), 3043, 2916 (2NH),1608 (C=N), 1504, 1242, 1140, 1018 cm^{-1}; MS m/z

(%): 573 (M^+), 397, 287, 161 (100), 153, 134, 112, 90, 77, 63. Anal. Calcd for $C_{24}H_{22}Cl_2N_8OS_2$ (573.52): C, 50.26; H, 3.87; N, 19.54. Found: C, 50.14; H, 3.80; N, 19.33%.

Compound 13a:

Yellow solid, 68% yield; m.p. 205–207 °C; δ_H (DMSO-d_6): 2.34, 2.45 (2s, 6H, $2CH_3$), 3.82 (s, 3H, OCH_3), 7.03–7.99 (m, 9H, Ar-H), 8.07 (s, 1H, N=CH), 9.65, 10.55, 12.11(3brs, 3H, 3NH) ppm; δ_C (DMSO-d_6): 9.0, 14.5 (CH_3), 58.1 (OCH_3), 115.0, 117.5, 119.8, 123.1, 126.7, 129.8, 130.2, 131.9, 135.7, 137.2, 143.1, 149.1, 152.1, 156.6, 163.0 (Ar-C or C=N), 174.0 (C=O) ppm; IR (KBr): v 3419, 3326, 3155 (3NH), 3039, 2908 (C-H), 1712 (C=O), 1611 (C=N), 1558, 1435, 1303, 1249, 1095 cm^{-1}; MS m/z (%): 506 (M^+), 383, 241, 169 (100), 106, 91, 77, 54. Anal. Calcd for $C_{23}H_{22}N_8O_2S_2$ (506.60): C, 54.53; H, 4.38; N, 22.12. Found: C, 54.53; H, 4.38; N, 22.12%.

Compound 13b:

Yellow solid, 67% yield; m.p. 215–217 °C; δ_H (DMSO-d_6): 2.16, 2.38, 2.51 (3s, 9H, $3CH_3$), 3.81 (s, 3H, OCH_3), 7.0–7.85 (m, 8H, Ar-H), 8.05 (s, 1H, N=CH), 10.04, 10.40, 10.48 (3brs, 3H, 3NH) ppm; "a ^{13}C NMR spectrum could not be obtained due to insolubility; IR (KBr): v 3422, 3316, 3203 (3NH), 3044, 2927 (C-H), 1709 (C=O), 1606 (C=N), 1470, 1249, 1138, 1036 cm^{-1}; MS m/z (%): 520 (M^+), 466, 307, 216, 119, 91 (100), 77, 57. Anal. Calcd for $C_{24}H_{24}N_8O_2S_2$ (520.63): C, 55.37; H, 4.65; N, 21.52. Found: C, 55.16; H, 4.44; N, 21.37%.

Compound 13c:

Yellow solid, 68% yield; m.p. 155–157 °C; δ_H (DMSO-d_6): 2.35, 2.48 (2s, 6H, $2CH_3$), 3.81 (s, 3H, OCH_3), 7.0–7.65 (m, 8H, Ar-H), 8.10 (s, 1H, N=CH), 10.45 10.95 12.26 (3brs, 3H, 3NH) ppm; IR (KBr): v 3441, 3253, 3170 (3NH), 3041, 2939 (C-H), 1681 (C=O), 1608 (C=N), 1485, 1242, 1165, 1041 cm^{-1}; MS m/z (%): 541 (M^+), 407, 281, 153, 134, 111, 71, 55 (100). Anal. Calcd for $C_{23}H_{21}ClN_8O_2S_2$ (541.05): C, 51.06; H, 3.91; N, 20.71. Found: C, 51.18; H, 3.81; N, 20.53%.

Compound 13d:

Yellowish-brown solid, 74% yield; m.p. 225–227 °C; δ_H (DMSO-d_6): 2.36, 2.46 (2s, 6H, $2CH_3$), 3.80 (s, 3H, OCH_3), 7.0–8.12 (m, 9H, Ar-H + N=CH), 11.11 (br s, 1H, NH), 11.5 (br s, 1H, NH), 11.6 (br s, 1H, NH) ppm; "a ^{13}C NMR spectrum could not be obtained due to insolubility; IR (KBr): v 3427, 3310, 3194 (3NH), 3078, 2931 (C-H), 1705 (C=O), 1609 (C=N), 1512, 1327, 1249, 1165, 1018 cm^{-1}; MS m/z (%): 551 (M^+), 470, 398, 277, 205, 133, 90 (100), 76, 63, 55. Anal. Calcd for $C_{23}H_{21}N_9O_4S_2$ (551.60): C, 50.08; H, 3.84; N, 22.85. Found: C, 50.03; H, 3.72; N, 22.70%.

Compound 13e:

Yellow solid, 70% yield; m.p. 145–147 °C; δ_H (DMSO-d_6): 2.36, 2.46 (2s, 6H, $2CH_3$), 3.82 (s, 3H, OCH_3), 7.02–8.10 (m, 8H, Ar-H + N=CH), 9.95 (br s, 1H, NH), 11.05 (br s, 1H, NH), 11.9 (br s, 1H, NH) ppm; IR (KBr): v 3433, 3313, 3217 (3NH), 3041, 2924 (C-H), 1720 (C=O), 1612 (C=N), 1541, 1242, 1147, 1038 cm^{-1}; MS m/z (%): 575 (M^+), 473, 317, 204 (100), 106, 91, 57. Anal. Calcd for $C_{23}H_{20}Cl_2N_8O_2S_2$ (575.49): C, 48.00; H, 3.50; N, 19.47. Found: C, 47.92; H, 3.35; N, 19.29%.

Synthesis of thiazoles 14 and 16:

A mixture of hydrazinecarbothioamide **7** (0.362 g, 1 mmol) and 3-chloropentane-2,4-dione (**4**) or 2-bromo-1-phenylethanone (**15**) (1 mmol) in EtOH (20 mL) was refluxed for 3 h. The formed product was recrystallized from DMF to give the corresponding thiazole derivatives **14** or **16**.

Compound 14:

Yellow solid, 73% yield; m.p. 230–232 °C; δ_H(DMSO-d_6): 2.35, 2.40, 2.48, 2.57 (4s, 12H, $4CH_3$), 3.79 (s, 3H, OCH_3), 7.02–7.06 (d, 2H, J = 16 Hz, Ar-H), 7.65–7.69 (d, 2H, J = 16 Hz, Ar-H), 8.08 (s, 1H, N=CH), 8.19, 9.27 (2brs, 2H, 2NH) ppm; "a ^{13}C NMR spectrum could not be obtained due to insolubility; IR (KBr): v 3412, 3237 (2NH), 3036, 2939 (C-H), 1703 (C=O), 1605 (C=N), 1553, 1240, 1109, 1016 cm^{-1}; MS m/z (%): 442 (M^+), 362, 287, 120, 91 (100), 77, 65. Anal. Calcd for $C_{20}H_{22}N_6O_2S_2$ (442.56): C, 54.28; H, 5.01; N, 18.99. Found: C, 54.15; H, 4.88; N, 18.73%.

Compound 16:

Yellow solid, 72% yield; m.p. 228–230 °C; δ_H(DMSO-d_6): 2.51, 2.66 (2s, 6H, 2CH_3), 3.81 (s, 3H, OCH_3), 7.04 (s, 1H, thiazole- H5), 7.06-8.36 (m, 9H, Ar-H), 8.50 (s, 1H, N=CH), 9.65, 10.76 (2brs, 2H, 2NH) ppm; δ_C (DMSO-d_6): 14.4, 20.7 (CH_3), 56.8 (OCH_3), 102.9, 113.3, 115.0, 118.9, 123.9, 130.0, 131.8, 138.8, 140.8, 145.0, 152.0, 152.5, 159.8, 163.4, 168.7 (Ar-C or C=N) ppm; IR (KBr): v 3433, 3239 (2NH), 3001, 2938 (C-H), 1613 (C=N), 1512, 1257, 1172, 1026 cm^{-1}; MS m/z (%): 462 (M^+), 287, 246, 176, 134 (100), 120, 91, 77, 67. Anal. Calcd for $C_{23}H_{22}N_6OS_2$ (462.59): C, 59.72; H, 4.79; N, 18.17. Found: C, 59.79; H, 4.58; N, 18.03%.

Synthesis of thiazole derivative 18:

Anhydrous sodium acetate (0.33 g, 4 mmol) was added to a mixture of compound **7** (0.362 g, 1 mmol) and ethyl chloroacetate **17** (0.122 g, l mmol) in AcOH (20 mL). The mixture was refluxed for 4h, then the solid product was recrystallized from EtOH to afford the thiazolone derivative **18** as yellow solid, 69% yield; m.p. 235-237 °C δ_H(DMSO-d_6): 2.41 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.14 (s, 2H, CH_2), 6.97-7.00 (d, 2H, J = 12 Hz, Ar-H),7.65-7.68 (d, 2H, J =12 Hz, Ar-H), 8.16 (s, 1H, N=CH), 9.18, 10.38 (2brs, 2H, 2NH) ppm; δ_C (DMSO-d_6): 10.9, 14.5 (CH_3), 36.8 (CH_2), 56.9 (OCH_3), 103.3, 114.4, 116.4, 123.2, 130.5, 131.4, 136.8, 1459, 147.0, 159.5 (Ar-C or C=N), 176.7 (C=O) ppm; IR (KBr): v 3417, 3222 (2NH), 3026, 2918 (C-H), 1692 (C=O), 1606 (C=N), 1530, 1248, 1148, 1029 cm^{-1}; MS m/z (%): 402 (M^+), 312 (100), 215, 138, 78, 63. Anal. Calcd for $C_{17}H_{18}N_6O_2S_2$ (402.49): C, 50.73; H, 4.51; N, 20.88. Found: C, 50.62; H, 4.44; N, 20.63%.

Synthesis of thiazole derivative 20.

A mixture of dimethyl acetylene dicarboxylate **19** (0.142 g, 1 mmol) and compound **7** (0.362 g, 1 mmol) in dry methanol (20 mL) was refluxed for 2h the formed product was recrystallized from ethanol to give pure product **20** as yellow solid, 70% yield; m.p. 270–272 °C (DMF); δ_H(DMSO-d_6): 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.75 (s, 3H, $COOCH_3$), 3.80 (s, 3H, OCH_3), 6.63 (s, 1H, =CH-$COOCH_3$), 7.0–7.03 (d, 2H, J = 12 Hz, Ar-H), 7.61-7.64 (d, 2H, J =12 Hz, Ar-H), 8.12 (s, 1H, N=CH), 8.29, 9.98 (2brs, 2H, 2NH) ppm; δ_C (DMSO-d_6): 9.0, 25.2 (CH_3), 46.1, 56.8 (OCH_3), 115.5, 117.5, 118.7, 119.8, 124.6, 129.3, 129.8, 135.3, 138.1, 153.0, 154.0, 162.7 (Ar-C or C=N), 169.2, 173.1 (C=O) ppm; IR (KBr): v 3433, 3194 (2NH), 3055, 2900 (C-H), 1705, 1691 (2C=O), 1600 (C=N), 1504, 1311, 1242, 1165 cm^{-1}; MS m/z (%): 472 (M^+), 339, 256, 153, 133 (100), 103, 91, 77, 59. Anal. Calcd for $C_{20}H_{20}N_6O_4S_2$ (472.54): C, 50.83; H, 4.27; N, 17.78. Found: C, 50.64; H, 4.36; N, 17.61%.

3.2. Biological Evaluation

3.2.1. Antimicrobial Activity Assay

The antimicrobial activity was investigated for the newly synthesized compounds towards test pathogenic microorganisms using the well diffusion method. A detailed antimicrobial activity assay is attached in the supplementary data [46].

3.2.2. MIC Determination

The MIC was determined as the lowest concentration inhibiting microbial growth. A detailed MIC determination method is attached in the supplementary data [47].

3.2.3. Cytotoxicity Assay

For cytotoxicity and antitumor assays, the cell lines were suspended in medium at cell density of 5×10^4 cells/well in 96-well tissue culture plates, then incubated for 24 h. The tested compounds were then added into 96-well plates (six replicates) to achieve eight concentrations for each compound along with controls with media or 0.5% DMSO. After incubating for 24 h, the numbers of viable cells were determined by the MTT assay. Detailed cytotoxicity assay and IC50 values calculations are attached in the supplementary data [48,49].

3.2.4. Safety and Selectivity Index (SI)

The impacts of the tested compounds and cisplatin reference drug were measured on normal human lung fibroblast (MRC-5) cell line (obtained from the American Type Culture Collection, ATCC, Rockville, MD, USA) as mentioned previously to produce a dose–response curve and to calculate the 50% cytotoxic concentration (CC50) using GraphPad Prism software. By dividing the CC_{50} by the IC_{50} values, the SI was obtained. A SI of >10 indicates the safety of a compound [46].

4. Conclusions

We have efficiently synthesized a new series of bioactive thiazole derivatives, and their structures were elucidated using spectroscopic analyses (mass, IR, NMR and ^{13}C NMR). Moreover, their cytotoxic effectiveness against HCT-116, HepG-2 and MDA-MB-231cell lines was investigated. Our findings revealed that most compounds had good anticancer activity, and that the thiazole derivative **10c** had the most cytotoxic capability against the cell lines tested, with greater selectivity index values more powerful than the anticancer medication cisplatin. When the tested compounds were evaluated for their toxicity against normal cells, they exhibited low toxic effects indicating the safe use of most of them that may require further in vivo and pharmacological studies. Most of the new products exhibited satisfactory antibacterial activity, and compound **13c** showed the highest activity against Gram-(+ve) bacteria, *Staphylococcus aureus and Bacillus subtilis*. Compound **7**, on the other hand, had the best activity against the Gram-(-ve) bacteria, Proteus vulgaris.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/app11198908/s1, the spectra (Mass Spectra, IR Spectra, ^{1}HNMR Spectra, ^{13}CNMR Spectra) of the compounds (compound **6**, compound **10a**, compound **10b**, compound **10c**, compound **10d**, compound **10e**, compound **13a**, compound **13b**, compound **13c**, compound **13d**, compound **16**, compound **18**, compound **20**) are presented in Supplementary Materials (Figures S1–Figure S39).

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