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Synthesis and Biological Evaluation of Some New Thieno[2,3-*b*]pyridine-based Compounds As Antimicrobial and Anticancer Agents

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Abstract

The risk elicited by the evolution of antimicrobial resistance, in addition to the annual increase in cancer rates, constitute the greatest threat to global health, which led to an urgent need to discover new molecules having potent antimicrobial and anticancer properties. Therefore, the present study involved with the synthesis of some new thieno[2,3-*b*]pyridine-based compounds **3a-c–6a,b** via treatment of the starting 3-aminothienopyridine derivatives **2a,b** with aryl isothiocyanates, maleic anhydride and cyclopentanone to afford the target 3-substituted-thienopyridine compounds **3a-c–5a,b**. Also, the synthetic target cyclopentapyrido-thienopyridine-9-amines **6a,b** were obtained upon treatment of the new 3-cyclopentylideneamino derivatives with phosphorous oxychloride. All the target compounds were evaluated for their in vitro antimicrobial activity against a panel of five bacterial and five fungal strains. Also, the cytotoxic potency of the target compounds was evaluated against two human cancer cell lines; hepatocellular carcinoma (HepG-2) and breast cancer cells (MCF-7). The new compounds showed promising antimicrobial and anticancer activities compared with the reference drugs. The most potent antimicrobial activity was revealed by **3c** with MIC values range 4-16 µg/mL. While, the most potent cytotoxicity against both HepG-2 and MCF-7 cells was showed by **4b** with IC_{50} values 3.12 µM and 20.55 µM, respectively.

***Keywords*:** Thieno[2,3-*b*]pyridines; Antibacterial activity; Antifungal activity; HepG-2 cells; MCF-7 cells.

1. Introduction

In the present century, the risk of infectious diseases related to microbial resistance has increased at frightening levels, which representing a threat to global health [1, 2]. Many bacterial and fungal strains change over time and develop resistance to the current antibiotics making infections harder to cure and no longer respond with the antibiotics used to treat them [3, 4]. Antimicrobial resistance is predicted to be in the coming decades the direct cause of millions of deaths, unless urgent actions are taken for mitigating this risk [5, 6]. Accordingly, the discovery of new antimicrobial agents having different modes of action represents an important approach to counter the resistance mechanisms [7]. In addition, cancer represents a global health issue and ranks as a leading cause of death [8]. Liver and breast cancers are among the most common cancer types due to their high incidence and morbidity [9, 10]. Moreover, the extensive side effects of anticancer drugs alongside the growing resistance of cancer cells against the common chemotherapy agents, are causing elevation of the mortality rate of cancer patients. Therefore, there is an urgent need to find new potent anticancer candidates having more selectivity and less toxicity than the present drugs [11, 12]. In addition, cancer patients due to their weakness and immunosuppression are subjected to great risk of the drug-resistant infections [13], which necessitates the discovery of new anticancer agents having dual activity against pathogenic microbes besides their cytotoxicity against cancer cells [14,15]. On the other hand, thieno[2,3-*b*]pyridine compounds attracted great interest due to their various pharmacological activities such as, anticancer [16,17], antimicrobial [18,19], anti-inflammatory [20], antiviral [21] and antiangiogenic [22] activities. Furthermore, many recent studies interested with the discovery of thieno[2,3-*b*]pyridine-based compounds as significant anticancer and antimicrobial candidates [23-25] (Fig. 1). Based on the foregoing, the present

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study includes synthesis of new thieno[2,3-*b*]pyridine compounds **3a-c–5a,b** carrying different structural motifs as, arylthioureido, 4-amino-4-oxobut-2-enoic acid and cyclopentylideneamino moieties, which renewed with their biological importance [26-28]. Moreover, the significant antimicrobial and anticancer activities of the reported tetracyclic cyclohexapyrido-thienopyridine derivatives [18, 29] gave the motive to synthesize and study the biological activity of the new tetracyclic cyclopentapyrido-thienopyridine compounds **6a,b**. Next, all the compounds were evaluated as antimicrobial agents against five strains of gram-positive and gram-negative bacteria along with five strains of yeast and fungi. Also, all the new compounds were screened as anticancer agents against hepatocellular carcinoma (HepG2) and breast cancer (MCF-7) cell lines.

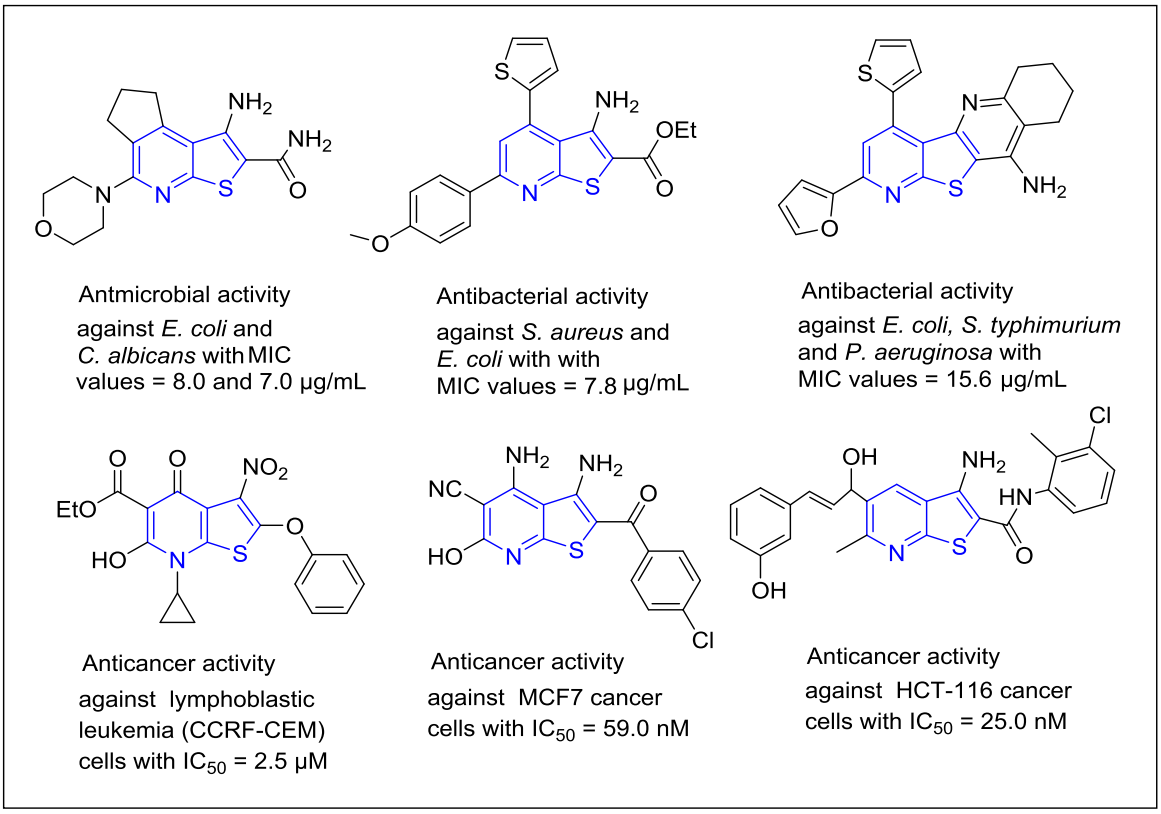


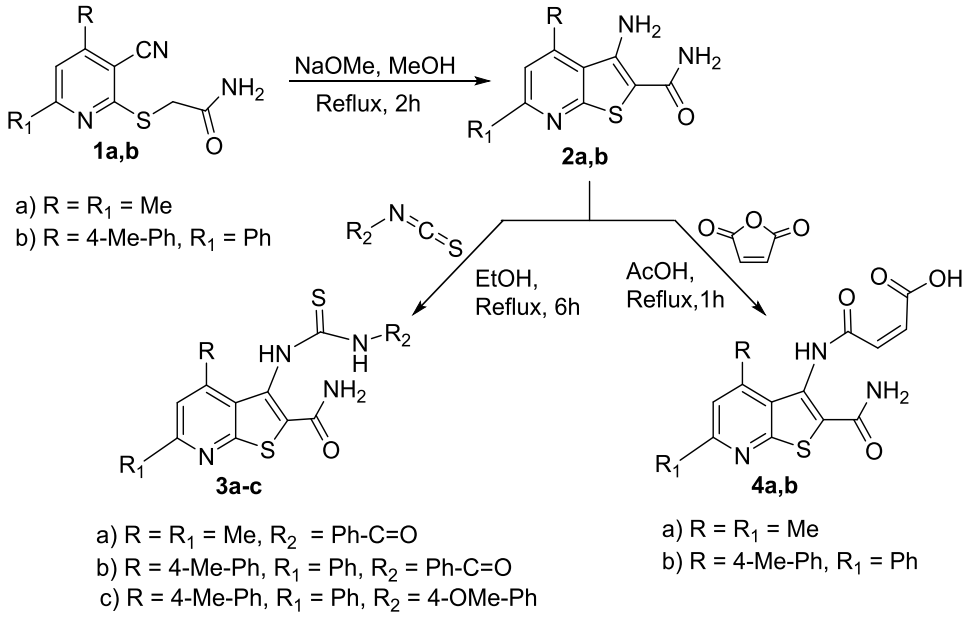
Fig. 1. Some reported thieno[2,3-*b*]pyridine-based compounds as potential antimicrobial or anticancer agents.

2. Result and discussion

2.1. Chemistry

This work includes synthesis of new thieno[2,3-*b*]pyridine derivatives **3a-c–6a,b** according to the synthetic routs illustrated in Scheme 1, 2. The molecular structures of all the target compounds were established by their correct elemental microanalyses and their IR, Mass and NMR spectral data. The starting compounds 3-aminothieno[2,3-*b*]pyridine-2-carboxamides **2a,b** were synthesized via a base catalyzed cyclization of 2-((3-cyano-pyridin-2-yl)thio)acetamide derivatives **1a,b** in refluxing NaOMe/MeOH solution [30]. Then, the 3-amino derivatives **2a,b** were refluxed with benzoyl isothiocyanate and/or 4-methoxyphenyl isothiocyanate in ethanol to afford 3-arylthioureido-thieno[2,3-*b*]pyridine-2-carboxamides **3a-c** via nucleophilic addition of the amine NH_2 on the N=C of the isothiocyanates, whereas the NH^- added on the C which has δ+ charge and the H^+ added on the N which has δ- charge to give the thiourea derivatives. ^{1}H NMR spectra of **3a-c** showed two D_2O exchangeable signals at the range δ11.12-12.86 ppm assignable to the two NH groups of the new arylthioureido moieties alongside the signals of the aromatic protons at their expected regions. Also, the signal at δ 3.71 ppm in the ^{1}H NMR spectrum of 3-(4-methoxyphenyl)thioureido) derivative **3c** assisted the presence of OCH_3 group of the 4-methoxyphenyl moiety. Moreover, the ^{13}C NMR spectra of **3a-c** showed the signals of the parent carbons, the signals corresponding to the carbons of the new aryl moieties, and gave additional support to their structures with the signal of the C=S carbon at the range δ 180.5-1181.64 ppm. Additionally, the

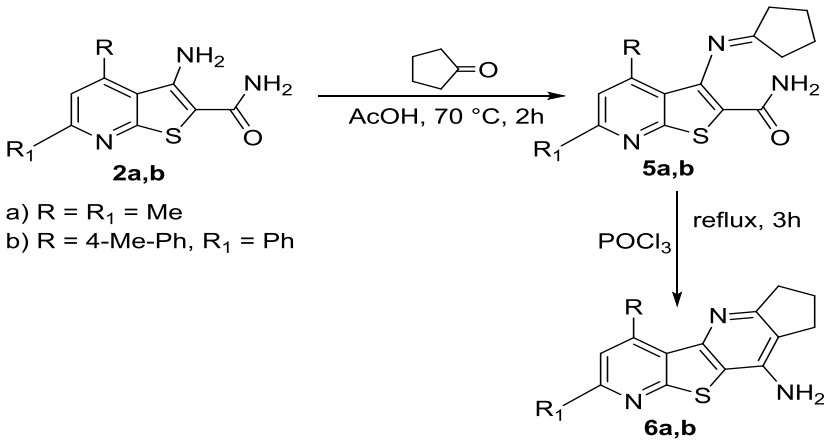
synthetic target **4a,b** were obtained by reaction of **2a,b** with maleic anhydride in glacial acetic acid. The reaction occurred via attacking of the NH_2 nitrogen of **2a,b** on the lactone carbonyl of maleic anhydride, which causes ring opening and the formation of the 4-((2-carbamoyl-thieno[2,3-*b*]pyridin-3-yl)amino)-4-oxobut-2-enoic acids **4a,b** (Scheme 1). IR spectra of the acid derivatives **4a** and **4b** exhibited broad absorption bands at 3431 cm^{-1} and 3405 cm^{-1} due to the acid OH group, respectively, besides two strong absorption bands corresponding to the parent amide C=O and the carboxylic acid C=O groups at the region 1682-1642 cm^{-1}. Also, ^{1}H NMR spectra of **4a,b** showed two D_2O exchangeable signals at the range δ 12.32-13.36 ppm representing NH and OH protons of the acid side chain alongside the signals related to CH=CH protons as doublet signals at the range δ 6.44-6.64 ppm. Moreover, the ^{13}C NMR spectra of **4a,b** revealed two signals at the range δ 166.52-167.17 ppm of the new 2C=O carbons, which confirming the existence of the 4-oxobut-2-enoic acid moiety.



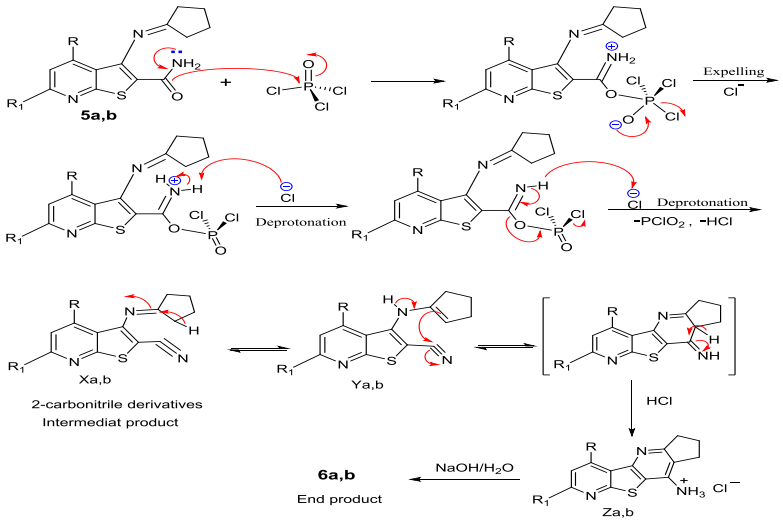
Scheme 1. Synthesis of thieno[2,3-*b*]pyridine derivatives **3a-c;4a,b**.

Furthermore, the starting amines **2a,b** underwent condensation reaction with cyclopentanone to yield, the Schiff bases, 3-(cyclopentylideneamino)-thieno[2,3-*b*]pyridine2-carboxamide derivatives **5a,b**. Whereas, subsequent treatment of **5a,b** with refluxing $POC1_3$ afforded, through intramolecular cyclization, the tetracyclic cyclopenta[e]pyrido[3',2':4,5]thieno[3,2-*b*]pyridin-9-amines **6a,b** (Scheme 2). The proposed mechanism of the cyclization includes amide dehydration of the 2-carboxamide derivatives **5a,b** with $POC1_3$ to form the 2-carbonitrile derivatives Xa,b as an intermediate products, which tautomerize to the enamines Ya,b. The enamines react intramolecular with the nitrile group in the acidic medium forming the hydrochloride salts Za,b, which afforded, during the work up with sodium hydroxide solution, the free tetracyclic amines **6a,b** (Scheme 3).

The presence of the cyclopentylidene moiety of **5a,b** was confirmed by ^{1}H NMR spectra, which revealed multiplet signals at the range δ 1.34-2.06 ppm assignable for the $4CH_2$ protons. Also, ^{13}C NMR spectra of **5a,b** showed three signals at the range δ 25.87-36.01 ppm related to the $4CH_2$ carbons of cyclopentylidene moiety. While, the absence of C=O band of the parent $CONH_2$ at position-3 in IR spectra of the tetracyclic derivatives **6a,b** supported the cyclization of **5a,b**. In addition, ^{1}H NMR spectra of **6a,b** showed three signals corresponding to the protons of $3CH_2$ at δ 1.68-2.79 ppm, besides a singlet D_2O exchangeable signal related to the newly formed amine NH_2 at δ 6.51 and 6.34 ppm, respectively. Further support to the structures of the new compounds **3a-c–6a,b** was gained by their mass spectra, which representing the correct molecular ion peaks.



Scheme 2. Synthesis of thieno[2,3-*b*]pyridine-based compounds **5a,b;6a,b**



Scheme 3. A proposed mechanism of the cyclization of **5a,b** to the tetracyclic amines **6a,b**.

2.2. In vitro Antimicrobial Evaluation

The new theino[2,3-*b*]pyridine compounds (**3a-c–6a,b**) were evaluated as antibacterial agents against three gram-positive bacteria *(Staphylococcus aureus 25923, Bacillus subtilis 6633, Bacillus cereus 33018)* and two gram-negative bacteria *(Escherichia coli 8739, Salmonella typhimurium 14028)* compared with the reference drug Amoxicillin trihydrate. Additionally, the antifungal activities of the new compounds were evaluated against three yeasts (*Candida tropical 750, Candida albicans 10231, Saccharomycese cerevisiae)* and two fungi *(Aspergillus niger EM77, Aspergillus flavus)* compared with clotrimazole as a reference drug. The determined values of diameter of inhibition zone (DIZ) in (mm) and the Minimum Inhibitory Concentration (MIC) values in (µg/mL) for the target compounds and the reference drugs against the tested bacterial and fungal strains were listed in Table 1 and Table 2, respectively.

Structure activity relationship (SAR)

Based on the MIC values listed in Table 1, the target theino[2,3-*b*]pyridine derivatives showed a wide variety of antibacterial activities against the tested bacterial strains. The 3-arylthioureido derivatives **3a-c** revealed antibacterial activities varied from potent to weak with MIC values range

(8-128) µg/mL. The most potent activity was showed by 3-(4-methoxyphenyl)thioureido) derivative **3c** with MIC values range (4-8) µg/mL, which equal to that of Amoxicillin against (*S. aureus, B. subtilis and E. coli*) and more potent than Amoxicillin against (*B. cereus and S. typhimurium*) with MIC value = 8 µg/mL. While, the 3-(3-benzoylthioureido)-6-phenyl-4-(p-tolyl) derivative **3b** exhibited potent to moderate activity with MIC values range (8-32) µg/mL and the 3-(3-benzoylthioureido)-4,6-dimethyl derivative **3a** gave lower activity varied from moderate to weak against the five tested bacteria with MIC values range (32-128) µg/mL. In addition, the 4-((2-carbamoyl-6-phenyl-4-(p-tolyl)thieno[2,3-*b*]pyridin-3-yl)amino)-4-oxobut-2-enoic acid (**4b**) showed significant activity against the three tested gram-positive bacteria with MIC values range (8-16) µg/mL and exhibited the most potent activity against *E. coli* and *S. typhimurium* with MIC values 4 and 8 µg/mL, respectively. However, the 4,6-dimethyl analogue **4a** revealed weak activity against the five tested bacterial strains with MIC values range (64-128) µg/mL. Also, It has been found that the 3-(cyclopentylideneamino)-4-(p-tolyl)-6-phenyl derivative **5b** is more potent than 4,6-dimethyl derivative **5a** against the five bacterial strains, it showed antibacterial activity varied from moderate against the gram-positive bacteria to weak against the gram-negative bacteria with MIC values range (16-64) µg/mL, while **5a** was weak or inactive against the tested strains. The cyclization of **5a,b** to afford the tetracyclic derivatives **6a,b** led to limited increase in the activity against some of the tested bacterial strains.

On the other hand, according to the MIC values listed in Table 2, the antifungal activity of the target thieno[2,3-*b*]pyridines against the tested yeasts and fungal strains is less potent than their activity against the tested bacterial strains. Whereas, the most potent activity was exhibited by 3-(4-methoxyphenyl)thioureido) derivative **3c**, the one of the most potent antibacterial activity, with MIC values range (8-16) µg/mL. The activity of **3c** equalized with that of Clotrimazole against four of the tested strains but it showed less activity against *C. tropical* with MIC value = 16 µg/mL compared with the MIC value = 8 µg/mL of Clotrimazole. Also, 4-oxobut-2-enoic acid derivative **4b** showed antifungal activity against *A. flavus and A. niger* equal in potency to Clotrimazole with MIC values = 8 µg/mL, while its activity against yeasts strains ranging from potent against *S. cerevisiase* to moderate against *C. albicans and C. tropical* with MIC values range (16-32) µg/mL.

The target compounds **3a,b** and **6a,b** showed antifungal activities varied from moderate to weak with MIC values range (32-128) µg/mL. While, the other compounds **4a**, **5a** and **5b** showed weak or no activity against the tested fungal strains.

Table 1: Antibacterial activities of the new compounds represented as DIZ values in mm and (MIC values in µg/mL).

Compd.	Gram-positive Bacteria			Gram-negative Bacteria	
	S. aureus	*B. subtilis*	*B. cereus*	*E. coli*	*S. typhimurium*
3a	24 (32)	22 (64)	18 (128)	22 (64)	16 (128)
3b	28 (16)	30 (8)	24 (32)	30 (8)	30 (8)
3c	30 (4)	32 (8)	31 (8)	29 (8)	29 (8)
4a	18 (64)	17 (128)	15 (128)	19 (64)	19 (64)
4b	26 (8)	23 (16)	24 (16)	30 (4)	30 (4)
5a	16 (128)	18 (128)	–	–	–
5b	28 (16)	26 (32)	25(32)	19 (64)	19 (64)
6a	20 (64)	21 (64)	18 (128)	-	-
6b	28 (16)	25 (32)	27 (16)	24 (32)	24 (32)
Amoxicillin	30 (4)	29(8)	28 (16)	27 (8)	28 (16)

Table 1: Antifungal activities of the new compounds represented as DIZ values in mm and (MIC values in µg/mL).

Compd.	Yeasts			Fungi	
	C. albicans	*C. tropicals*	*S. cerevisiase*	*A. flavus*	*A. niger*
3a	23 (32)	18 (64)	17 (128)	15 (128)	16 (128)
3b	18 (64)	19 (64)	25 (32)	18 (64)	15 (128)
3c	29 (16)	28 (16)	33 (8)	29 (8)	32 (8)
4a	18 (128)	17 (128)	18 (128)	–	–
4b	14 (32)	25 (32)	29 (16)	30 (8)	29 (8)
5a	18 (128)	20 (64)	–	15 (128)	–
5b	–	19 (64)	20 (64)	–	20 (64)
6a	20 (64)	23(32)	17 (64)	21 (64)	22 (64).
6b	24 (32)	25 (32)	26 (32)	20 (64)	25 (32)
Clotrimazole	28 (16)	30 (8)	35 (8)	30 (8)	31 (8)

2.3. In vitro Cytotoxic Activity Evaluation

The *in vitro* cytotoxicity of the target thieno[2,3-*b*]pyridine compounds **3a-c**–**6a,b** was evaluated against two cancer cell lines (HepG-2 and MCF-7) compared with doxorubicin and cisplatin as positive controls by using MTT method. The IC_{50} values in µM (concentrations of the compounds that caused 50% inhibition of cell viability) were determined for the tested compounds and the reference drugs and listed in (Table 3, Fig. 2).

Structure activity relationship (SAR)

The resultant data showed that, the tested compounds have cytotoxicity against HepG-2 cancer cells more potent than their cytotoxicity against MCF-7 cells. The most potent cytotoxicity against HepG-2 cell line revealed by the 4-oxobut-2-enoic acid derivative **4b** of IC_{50} = 3.12 µM, which exceed the activity of doxorubicin of IC_{50} = 3.89 µM. Also, **4b** exhibited the most potent cytotoxic activity against MCF-7 cells of IC_{50} = 20.55 µM, which slightly more potent than cisplatin of IC_{50} = 20.70 µM. Moreover, 3-(4-methoxyphenyl)thioureido) derivative **3c** showed significant cytotoxicity, compared with the reference drugs, against HepG-2 and MCF-7 cells with IC_{50}s; 3.45, 20.61µM, respectively. The tetracyclic derivative **6b** came after **4b** and **3c** in the potency against HepG-2 and MCF-7 cells with IC_{50}s; 4.80, 25.20 µM, respectively. The other target compounds showed dramatic lowering in the cytotoxicity than the reference drugs against HepG-2 and MCF-7 cell lines with IC_{50} values range 13.57-93.02 µM and 33.49-105.41µM, respectively.

Table 1: *In vitro* cytotoxic activity of the target compounds represented as IC_{50} values (µM).

Compd.	IC_{50} (µM)	
	HepG-2	MCF-7
3a	93.02 ± 2.71	103.02 ± 2.76
3b	35.71 ± 1.34	105.41 ± 3.85
3c	3.45 ± 0.21	20.61 ± 0.56
4a	46.22 ± 1.14	87.33 ±2.42
4b	3.12 ± 0.16	20.55 ± 0.98
5a	56.43 ±1.93	61.58 ±1.61

5b	13.57 ± 0.89	33.49 ± 1.77
6a	30.71 ± 1.63	46.72 ± 1.45
6b	4.80 ± 0.36	25.20 ± 1.02
Doxorubicin	3.89 ± 0.32	3.58 ± 0.41
Cisplatin	---	20.70 ± 0.83

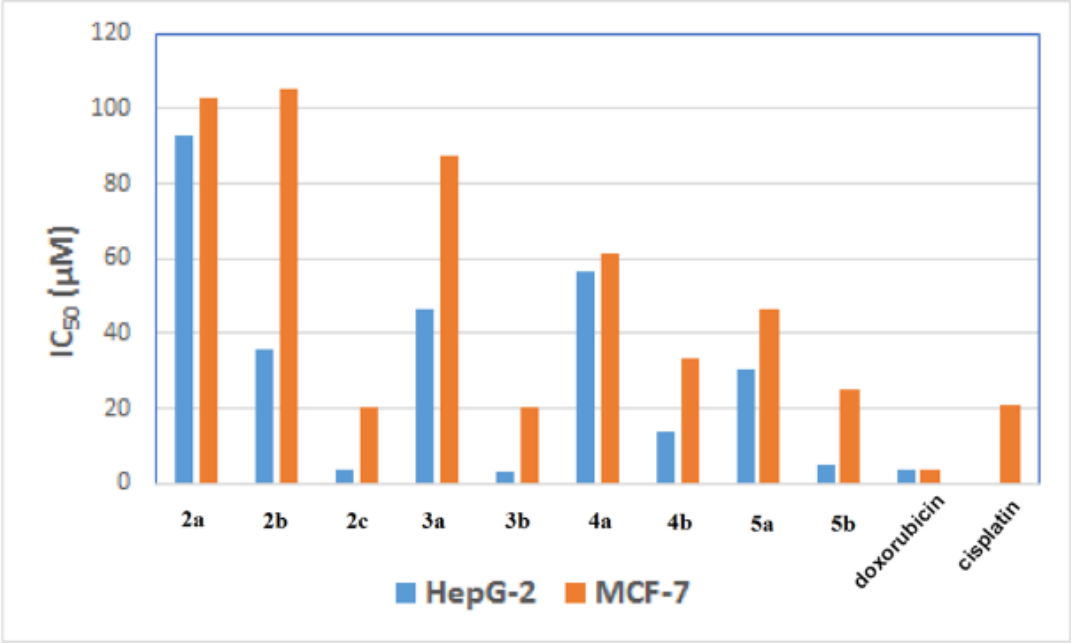


Fig. 2. The cytotoxicity of the new thieno[2,3-*b*]pyridines against HepG-2 and MCF-7 cell lines.

3. Experimental

3.1. Chemistry

All melting points are uncorrected and were taken in open capillary tubes using an Electro thermal IA9100 digital melting point apparatus. Elemental microanalyses were carried out at the the Micro Analytical Unit at Cairo University. Mass spectra (MS) were performed at 70 e.v by GCMS-QP1000 EX spectrometer using the Electron Ionization Technique (EI) at Al-Azhar University, Cairo, Egypt. Infrared spectra were recorded in National Research Centre, by using the KBr disc technique on a Jasco FT/IR-360 plus Infrared spectrometer at the range (400- 4000 cm-1), made in Japan. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker High Performance Digital FT-NMR Spectrometer Advance III (400/100 MHz) and in the presence of TMS as the internal standard, Ain Shams University, Cairo, Egypt. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60, F 254, Merck, Darmstadt, Germany) using chloroform/methanol (3:1, v/v) and the spots were detected by exposure to UV lamp at δ 254 nanometer for few seconds and by iodine vapor. The chemical names given for the prepared compounds are according to the IUPAC system. The starting compounds 3-amino-thieno[2,3-*b*]pyridine-2-carboxamides (**2a,b**) were prepared as the reported method [30].

Synthesis of 3-arylthioureido-thieno[2,3-*b*]pyridine-2-carboxamides 3a-c

A mixture of compounds **2a,b** (1 mmol) and benzoyl or p-methoxyphenyl isothiocyanate (1 mmol) in absolute ethanol (20 mL) was refluxed for 6h. The reaction mixture was then evaporated till dryness under reduced pressure and the residue was treated with cold water. The formed solid was collected by filtration and recrystallized from ethanol to give compounds **3a-c**

3-(3-Benzoylthioureido)-4,6-dimethylthieno[2,3-b]pyridine-2-carboxamide (3a)

Yield 72%, brown powder, m.p. 261 °C; IR (KBr, υ_{max}/cm^{-1}): 3317, 3194 (NH), 3041 (CH-aromatic), 2922 (CH-aliphatic), 1672, 1643 (C=O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 2.61 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 6.80 (s, 2H, NH_2, D_2O exchangeable), 7.02 (s, 1H, Ar-H), 7.29 (d, 2H, *J* = 13.2 Hz, Ar-H), 7.50-7.88 (m, 3H, Ar-H), 11.24, 11.79 (2s, 2H, 2NH, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d6, δ ppm):19.24, 24.27 ($2CH_3$), 122.51, 123.04, 127.56, 127.98, 128.82, 133.15, 136.02, 145.01, 156.94, 158.02 (Ar-C), 162.69, 167.88 (2 C=O), 180.78 (C=S). MS, m/z (%): 384 ($M^{+\cdot}$, 48). Anal. Calcd. for $C_{18}H_{16}N_4O_2S_2$ (384.47): C, 56.23; H, 4.19; N, 14.57; S, 16.68%; Found: C, 55.95; H, 3.90; N, 14.32; S, 16.38%.

3-(3-Benzoylthioureido)-6-phenyl-4-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamide (3b)

Yield 78%, yellow powder, m.p. 235-236 °C; IR (KBr, υ_{max}/cm^{-1}): 3392, 3171 (2NH), 3041 (CH-aromatic), 2919 (CH-aliphatic), 1668, 1643(C=O), ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 2.43 (s, 3H, CH_3), 7.09 (s, 2H, NH_2, D_2O exchangeable), 7.13-8.27 (m, 15H, Ar-H), 11.19, 11.86 (2s, 2H, 2NH, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d6, δ ppm): 21.38 (CH_3), 119.61, 126.21, 127.54, 127.63, 127.90, 128.60, 128.97, 129.36, 129.78, 130.19, 132.30, 133.33, 133.52, 134.21, 137.72, 138.08, 148.31, 155.36, 159.40 (Ar-C) 162.69, 167.88 (2 C=O) 181.64 (C=S). MS, m/z (%): 522 ($M^{+\cdot}$, 25). Anal. Calcd. for $C_{29}H_{22}N_4O_2S_2$ (522.64): C, 66.65; H, 4.24; N, 10.72; S, 12.27%; Found: C, 66.87; H, 4.52; N, 10.34; S, 12.51%.

3-(3-(4-Methoxyphenyl)thioureido)-6-phenyl-4-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamide (3c)

Yield 76%, yellow powder, m.p. 220-221 °C; IR (KBr, υ_{max}/cm^{-1}): 3440, 3340, 3174, (NH), 3054 (CH-aromatic), 2919, 2852 (CH-aliphatic), 1644 (C=O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 2.43 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 6.84 (s, 2H, NH_2, D2O exchangeable), 7.24-8.36 (m, 14H, Ar-H), 11.12, 11.71 (2s, 2H, NH, D2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d6, δ ppm): 21.36 (CH_3), 55.94 (OCH_3), 114.32, 119.63, 125.98, 127.22, 127.61, 127.95, 128.45, 129.37, 129.74, 129.98, 130.86, 132.31, 133.22, 137.58, 138.04, 148.31, 155.36, 159.40, 159.97 (Ar-C) 162.64 (C=O) 180.51 (C=S). MS, m/z (%): 524 ($M^{+\cdot}$, 62). Anal. Calcd. for $C_{29}H_{24}N_4O_2S_2$ (524.66): C, 66.39; H, 4.61; N, 10.68; S, 12.22%; Found: C, 66.68; H, 4.79; N, 10.32; S, 12.51%.

Synthesis of 4-((2-carbamoyl-thieno[2,3-*b*]pyridin-3-yl)amino)-4-oxobut-2-enoic acid 4a,b

A mixure of **2a,b** (5 mmol) and maleic anhydride (0.49 g, 5 mmol) in glacial acetic acid (20 mL) was refluxed for1h, then the solvent was evaporated under vacuum. The oily residue was treated with $CHCl_3$. The formed solid was collected by filtration and recrystallized from acetone to give **4a,b**.

(Z)-4-((2-Carbamoyl-4,6-dimethylthieno[2,3-b]pyridin-3-yl)amino)-4-oxobut-2-enoic acid (4a)

Yield 71 %, brown powder, m.p. 360-361 °C; IR (KBr, υ_{max}/cm^{-1}): 3405 (OH, broad), 3351, 3232, 3179 (NH), 2920, 2854 (CH-aliphatic), 1670, 1642 (C=O), ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 2.59 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 6.52, 6.64 (2d, 2H, *J* = 12.4 Hz, 2CH=), 7.09 (s, 1H, Ar-H), 7.19 (s, 2H, NH_2, D_2O exchangeable), 12.56 (s, 1H, NH, D_2O exchangeable), 13.36 (broad s, 1H, OH, D_2O exchangeable).^{13}C NMR (100 MHz, DMSO-d6, δ ppm):19.21, 24.33 ($2CH_3$), 113.11, 122.47, 122.99, 137.12, 138.55, 144.98, 145.16, 156.97, 157.89 (Ar-C, CH=CH), 162.51, 166.74, 167.09 (3C=O). MS, m/z (%): 319 ($M^{+\cdot}$, 25). Anal. Calcd. for $C_{14}H_{13}N_3O_4S$ (319.34): C, 52.66; H, 4.10; N, 13.16; S, 10.04%; Found: C, 52.95; H, 4.41; N, 12.80; S, 10.25%.

(Z)-4-((2-Carbamoyl-6-phenyl-4-(p-tolyl)thieno[2,3-b]pyridin-3-yl)amino)-4-oxobut-2-enoic acid (4b)

Yield 72%, yellow powder, m.p. 345 °C; IR (KBr, υ_{max}/cm^{-1}): 3431(OH, broad), 3336, 3240, 3183 (NH), 3065 (CH-aromatic), 2919 (CH-aliphatic), 1682, 1647 (C=O), ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 2.45 (s, 3H, CH_3), 6.44 (d, 2H, *J* = 10.8 Hz, CH=CH), 7.21 (s, 2H, NH_2, D_2O exchangeable), 7.32 (d, 2H, *J* = 6.0 Hz, Ar-H), 7.52-7.66 (m, 5H, Ar-H), 8.02 (s, 1H, Ar-H), 8.27 (d, 2H, *J* = 4.4 Hz, Ar-H), 12.32 (s, 1H, NH, D_2O exchangeable), 13.08 (broad s, 1H, OH, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d6, δ ppm): 21.34 (CH_3), 113.15, 118.09, 119.43, 127.66, 128.01, 128.60, 129.31, 129.82, 132.28, 133.37, 137.92, 138.17, 140.25, 144.92, 149.97, 155.41, 159.37 (Ar-C, CH=CH), 162.47, 166.52, 167.17 (3C=O). MS, m/z (%): 457 ($M^{+\cdot}$, 25). Anal. Calcd. for $C_{25}H_{19}N_3O_4S$ (457.50): C, 65.63; H, 4.19; N, 9.18; S, 7.01%; Found: C, 65.39; H, 3.95; N, 9.44; S, 6.75%.

Synthesis of 3-(cyclopentylideneamino)thieno[2,3-*b*]pyridine-2-carboxamide 5a,b

A mixture of compounds **1a,b** (5 mmol) and cyclopentanone (0.42 g, 5 mmol) in glacial acetic acid (20 mL) was heated at 70 °C for 2 h. The reaction mixture was concentrated and poured onto cold water. The obtained solid was collected by filtration, washed with water, and recrystallized from dioxane to give compounds **5a,b**.

3-(Cyclopentylideneamino)-4,6-dimethylthieno[2,3-b]pyridine-2-carboxamide (5a)

Yield 75%, grey solid, m.p. 252 °C; IR (KBr, υ_{max}/cm^{-1}): 3345, 3226 (NH), 3033 (CH-aromatic), 2924 (CH-aliphatic), 1646 (C=O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 1.71- 2.06 (m, 8H, $4CH_2$), 2.50 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.07 (s, 1H, Ar-H), 8.02 (s, 2H, NH_2, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d6, δ ppm):19.25, 24.36 ($2CH_3$), 25.89 ($2CH_2$), 31.92, 35.98 ($2CH_2$), 122.41, 123.02, 142.33, 144.95, 150.01, 156.98, 157.90, 161.45 (Ar-C, C=N), 162.48 (C=O). MS, m/z (%): 287 ($M^{+\cdot}$, 77). Anal. Calcd. for $C_{15}H_{17}N_3OS$ (287.38): C, 62.69; H, 5.96; N, 14.62; S, 11.16%; Found: C, 62.42; H, 5.71; N, 14.99; S, 11.38%.

3-(Cyclopentylideneamino)-6-phenyl-4-(p-tolyl)thieno[2,3-b]pyridine-2-carboxamide (5b)

Yield 80%, yellow solid, m.p. 258-259 °C; IR (KBr, υ_{max}/cm^{-1}): 3409, 3180 (NH), 3043 (CH-aromatic), 2920 (CH-aliphatic), 1644 (C=O), ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 1.34-1.87 (m, 8H, $4CH_2$), 2.42 (s, 3H, CH_3), 7.38 (d, 2H, *J* = 6.8 Hz, Ar-H), 7.49-7.54 (m, 5H, Ar-H), 7.83 (s, 2H, NH_2, D_2O exchangeable), 8.06 (s, 1H, Ar-H), 8.21 (d, 2H, *J* = 6.0 Hz, Ar-H). ^{13}C NMR (100 MHz, DMSO-d6, δ ppm): 21.39 (CH_3), 25.87($2CH_2$), 32.11, 36.01 ($2CH_2$), 119.43, 127.12, 127.69, 127.99, 128.57, 129.27, 129.79, 132.31, 140.21, 145.01, 149.12, 150.03, 155.47, 159.44, 161.07 (Ar-C, C=N), 162.33 (C=O).MS, m/z (%): 425 ($M^{+\cdot}$, 25). Anal. Calcd. for $C_{26}H_{23}N_3OS$ (425.55): C, 73.38; H, 5.45; N, 9.87; S, 7.53%; Found: C, 73.62; H, 5.69; N, 9.61; S, 7.89%.

Synthesis of 7,8-dihydro-6*H*-cyclopenta[e]pyrido[3',2':4,5]thieno[3,2-*b*]pyridin-9-amine 6a,b

A solution of compounds **4a,b** (2 mmol) in phosphorous oxychloride (10 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured with stirring onto an ice–water mixture. The acidic medium was neutralized by adding aqueous NaOH solution (10%) to pH 7. The formed solid was isolated by filtration, washed with water, and recrystallized from ethanol to give the free amines **6a,b.**

2,4-Dimethyl-7,8-dihydro-6H-cyclopenta[e]pyrido[3',2':4,5]thieno[3,2-b]pyridin-9-amine (6a)

Yield 68%, pale yellow solid, m.p. 185-186 °C; IR (KBr, υ_{max}/cm^{-1}): 3422, 3344 (NH), 2920 (CH-aliphatic). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 1.68 (t, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.62-2.78 (m, 4H, $2CH_2$), 2.89 (s, 3H, CH_3), 6.51 (s, 2H, NH_2, D_2O exchangeable), 7.16 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d6, δ ppm):19.33, 24.28 ($2CH_3$), 26.02 ($2CH_2$), 32.15, 36.01($2CH_2$), 122.51, 123.09, 142.27, 145.04, 149.89, 157.12, 157.87, 161.66, 162.18 (Ar-C), MS, m/z (%): 269 ($M^{+\cdot}$, 77). Anal. Calcd. for $C_{15}H_{15}N_3S$ (269.37): C, 66.88; H, 5.61; N, 15.60; S, 11.90%; Found: C, 67.13; H, 5.23; N, 15.95; S, 11.62%.

2-Phenyl-4-(p-tolyl)-7,8-dihydro-6H-cyclopenta[e]pyrido[3',2':4,5]thieno[3,2-b]pyridin-9-amine (6b)

Yield 68%, pale yellow solid, m.p. 175 °C; IR (KBr, υ_{max}/cm^{-1}): 3425, 3336 (NH), 3027 (CH-aromatic), 2921 (CH-aliphatic), ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 2.01(t, 2H, CH_2), 2.43 (s, 3H, CH_3), 2,69 (t, 2H, CH_2), 2.79 (t, 2H, CH_2), 6.34 (s, 2H, NH_2, D_2O exchangeable) 7.26 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.47-7.55 (m, 3H, Ar-H), 7.64 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.81(s, 1H, Ar-H), 8.23 (d, 2H , *J* = 7.2 Hz, Ar-H). ^{13}C NMR (100 MHz, DMSO-d6, δ ppm): 21.51 (CH_3), 22.67, 28.18, 33.77 ($3CH_2$), 119.47, 119.61, 127.55, 127.67, 129.11, 129.30, 129.92, 130.04, 130.58, 133.40, 138.99, 139.61, 148.30, 150.43, 155.99, 157.00, 161.40, 162.30 (Ar-C). MS, m/z (%): 407 ($M^{+\cdot}$, 48). Anal. Calcd. for $C_{26}H_{21}N_3S$ (407.54): C, 76.63; H, 5.19; N, 10.31; S, 7.87%; Found: C, 76.23; H, 4.95; N, 10.53; S, 7.58%.

3.2. Antimicrobial Assay

All the new synthesized compounds (**3a-b–6a,b**) and the reference drugs were screened for their *in vitro* antibacterial and antifungal activity. The diameter of inhibition zone (DIZ) assay was performed by agar disk diffusion method [31] and the Minimum Inhibitory Concentration (MIC) of the compounds was then evaluated using broth dilution method [32]. Whereas, two-fold serial dilution at the concentrations (128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25 µg/ml) was used to investigate the MIC values. The determined values of DIZ in (mm) and the MIC values in (µg/mL) for the target compounds and the reference drugs against the tested bacterial and fungal

strains were listed in Table 1 and Table 2, respectively.

3.3. In Vitro Cytotoxicity Screening

The *in vitro* cytotoxic activity of the new compounds **3a-c–6a,b** was screened against HepG-2 and MCF-7 cancer cell lines using the MTT assay[33]. The cells used in the cytotoxicity assay were cultured in (RPMI 1640) medium supplemented with 10% fetal calf serum and placed in 10^4 cells/well for 24 h, then fresh medium which containing different concentration of the tested sample was added. Serial two-fold dilutions of the tested samples at concentrations (200, 100, 50, 25, 12.5, 6.25, 3.125, 1.56 and 0 μg L^{-1}) was used. The cytotoxicity was estimated as IC_{50} value (the concentration of the tested compound that inhibits 50% of the growth of cancer cells) in μM and the determined IC_{50} values are listed in Table 3.

4. Conclusion

A new series of thieno[2,3-*b*]pyridine-based compounds (**3a-c–6a,b**) was synthesized starting with 3- aminothienopyridine derivatives (**2a,b**). Then, all the new compounds were screened for their *in vitro* antimicrobial and anticancer activities. The target compounds were evaluated as antimicrobial agents against five bacterial and five fungal strains, while their anticancer activity were determined against HepG-2 and MCF-7 cell lines. The results obtained for the tested compounds in (Tables 1-3) revealed that the 4-(p-tolyl)-6-phenyl- derivatives acquire more potent antimicrobial and anticancer activity than their 4,6- dimethyl analogues. Moreover, the 3-(4-methoxyphenyl)thioureido)-6-phenyl-4-(p-tolyl) derivative **3c** showed the most potent antibacterial and antifungal activity compared with the reference drugs. Also, the 4-oxobut-2-enoic acid derivative **4b** showed significant wide spectrum antimicrobial activity. In addition, the cytotoxicity screening of the target compounds against HepG2 and MCF-7 cell lines showed that **4b** elicited the most potent cytotoxicity against the two cell line, while **3c** was slightly less than **4b** in the cytotoxic potency against both cell lines. The results gained from this study highlighted the importance of thieno[2,3-*b*]pyridine-based compounds, which could provide by further research and study more potent derivatives as antimicrobial and anticancer agents.

5. Conflicts of interest

"There are no conflicts to declare".

6. Acknowledgement

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7. References

[1] Brower J.L. The Threat and Response to Infectious Diseases (Revised). *Microbial ecology*, **76**(1), 19–36(2018). doi.org/10.1007/s00248-016-0806-9

[2] Sridhar S., Turbett S.E., Harris J.B., LaRocque R.C. Antimicrobial-resistant bacteria in international travelers. *Current Opinion in Infectious Diseases*, **34**(5), 423–31(2021). doi: 10.1097/QCO.0000000000000751

[3] Chokshi A., Sifri Z., Cennimo D., Horng H. Global Contributors to Antibiotic Resistance. *Journal of global infectious diseases*, **11**(1), 36–42(2019). doi: 10.4103/jgid.jgid_110_18

[4] Lomazzi M., Moore M., Johnson A., Balasegaram M., Borisch B. Antimicrobial resistance – moving forward?. *BMC Public Health* , **19**(1), 858(2019). https://doi.org/10.1186/s12889-019-7173-7

[5] de Kraker M.E., Stewardson A.J., Harbarth S. Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050?. *PLoS Medicine*, **13**(11), e1002184(2016). doi: 10.1371/journal.pmed.1002184.

[6] Mohi El-Deen E.M., Abd El-Meguid E.A., Karam E.A., Nossier E.S., Ahmed M.F. Synthesis and Biological Evaluation of New Pyridothienopyrimidine Derivatives as Antibacterial Agents and Escherichia coli Topoisomerase II Inhibitors. *Antibiotics*, **9**(10), 695(2020). https://doi.org/10.3390/antibiotics9100695

[7] Miethke M., Pieroni M., Weber T., et al. Towards the sustainable discovery and development of new antibiotics. *Nature Reviews Chemistry*, **5**, 726–749(2021). https://doi.org/10.1038/s41570-021-00313-1

[8] Sung H., Ferlay J., Siegel R.L., Laversanne M, Soerjomataram I., Jemal A.. Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *Ca-A Cancer Journal for Clinicians*, **71**(3), 209–249(2021). https://doi.org/10.3322/caac.21660

[9] Pelizzaro F., Ramadori G., Farinati F. Systemic therapies for hepatocellular carcinoma: an evolving landscape. *Hepatoma Research*, **7**, 36(2021). doi: 10.20517/2394-5079.2021.24

[10] Presti D., Quaquarini E. The PI3K/AKT/mTOR and CDK4/6 Pathways in Endocrine Resistant HR+/HER2- Metastatic Breast Cancer: Biological Mechanisms and New Treatments. *Cancers (Basel)*, **11**(9), 1242(2019). doi: 10.3390/cancers11091242

[11] Mansoori B., Mohammadi A., Davudian S., Shirjang S., Baradaran B. The Different Mechanisms of Cancer Drug Resistance: A Brief Review. *Advanced pharmaceutical bulletin*, **7**, 339–348(2017). https://doi.org/10.15171/apb.2017.041

[12] Sharma P., Kaur S., Chadha B.S., Kaur R., Kaur M., Kaur S. Anticancer and antimicrobial potential of enterocin 12a from Enterococcus faecium. *BMC microbiology*, **21**(1), 39(2021). https://doi.org/10.1186/s12866-021-02086-5

[13] Felício M.R., Silva O.N., Gonçalves S., Santos N.C., Franco O.L. Peptides with Dual Antimicrobial and Anticancer Activities. *Frontiers in Chemistry*, **5**, 5(2017). https://doi.org/10.3389/fchem.2017.00005

[14] Mohi El-Deen E.M., Anwar M.M., El-Gwaad A.A.A., Karam E.A., El-Ashrey M.K., Kassab R.R. Novel Pyridothienopyrimidine Derivatives: Design, Synthesis and Biological Evaluation as Antimicrobial and Anticancer Agents. *Molecules*, **27**(3), 803(2022). https://doi.org/10.3390/molecules27030803

[15] Abdelaziz M.E., El-Miligy M.M.M., Fahmy S.M., Mahran M.A., Hazzaa A.A. Design, synthesis and docking study of pyridine and thieno[2,3-*b*] pyridine derivatives as anticancer PIM-1 kinase inhibitors. *Bioorganic Chemistry*, **80**, 674–692(2018). https://doi.org/10.1016/j.bioorg.2018.07.024.

[16] Al-Trawneh S.A., Tarawneh A.H., Gadetskaya A.V., Seo E., Al-Ta'ani M.R., Al-Taweel S.A., El-Abadelah M.M. Synthesis and Cytotoxicity of Thieno[2,3-b]Pyridine Derivatives Toward Sensitive and Multidrug-Resistant Leukemia Cells. *Acta chimica slovenica*, **68**, 458–465(2021). https://doi.org/10.17344/acsi.2020.6609

[17] Mansour, H. Thiophenethieno[2,3-b]pyridine-chitosan nanorods; synthesis, characterization, BSA-Binding and kinetic interactions with BSA, antibacterial and in-vitro release studies. *Journal of molecular structure*, *1219*, 128611(2020). doi: 10.1016/j.molstruc.2020.128611

[18] Mohi El-Deen E.M., Abd El-Meguid E.A., Hasabelnaby S., Karam E.A., Nossier E.S. Synthesis, Docking Studies, and In Vitro Evaluation of Some Novel Thienopyridines and Fused Thienopyridine–Quinolines as Antibacterial Agents and DNA Gyrase Inhibitors. *Molecules*, **24**(20), 3650(2019). https://doi.org/10.3390/molecules24203650

[19] Liu H., Li Y., Wang X.Y., Wang B., He H.Y., Liu J.Y., Xiang M.L., He J., Wu X.H., Yang L. Synthesis, preliminary structure-activity relationships, and in vitro biological evaluation of 6-aryl-3-amino-thieno[2,3-b]pyridine derivatives as potential anti-inflammatory agents. *Bioorganic and Medicinal Chemistry Letters*, **23**(8), 2349–52(2013). doi: 10.1016/j.bmcl.2013.02.059.

[20] Amorim R., DeMeneses M.D.F., Borges J.C., Pinheiro L.C.S., Caldas L.A., Cirne-Santos C.C., DeMello M.V., De Souza A.M.T., Castro H.C., et al. Thieno[2,3-b]pyridine derivatives: a new class of antiviral drugs against Mayaro virus. *Archives of virology*, **162**, 1577–1587(2017).

[21] Rizk O.H., Teleb M., Abu-Serie M.M, Shaaban O.G. Dual VEGFR-2/PIM-1 kinase inhibition towards surmounting the resistance to antiangiogenic agents via hybrid pyridine and thienopyridine-based scaffolds: Design, synthesis and biological evaluation. *Bioorganic Chemistry*, **92**, 103189(2019). doi: 10.1016/j.bioorg.2019.103189.

[22] Mekky A.E.M., Sanad S.M.H., Said A.Y., Elneairy M.A.A. Synthesis, cytotoxicity, in-vitro antibacterial screening and in-silico study of novel thieno[2,3-b]pyridines as potential pim-1 inhibitors, *Synthetic Communications*, **50**(15), 2376–2389(2020). doi: 10.1080/00397911.2020.1778033

[23] Zaki R.M., Kamal El-Dean A.M., Radwan S.M., Ammar M.A. Synthesis, Reactions, and Antimicrobial Activity of Novel Heterocyclic Compounds Containing Cyclopenta[d]thieno[2,3-b]pyridine Moiety and Related Fused Heterocycles. *Russian Journal of Bioorganic Chemistry*, **46**, 85–96(2020). https://doi.org/10.1134/S1068162020010148

[24] Haverkate N.A., Leung E., Pilkington L.I., Barker D. Tethered Aryl Groups Increase the Activity of Anti-Proliferative Thieno[2,3-b]Pyridines by Targeting a Lipophilic Region in the Active Site of PI-PLC. *Pharmaceutics*, **13**(12), 2020(2021). https://doi.org/10.3390/pharmaceutics13122020

[25] Mohareb R.M., Ibrahim R.A. Design, cytotoxicity and toxicity of new thiophene and thieno [2,3-b] pyridine derivatives. *Medicinal Chemistry Research*, **26**, 587–602(2017). https://doi.org/10.1007/s00044-017-1780-6

[26] Ghorab M.M., Alsaid M.S., Al-Dosary M.S., Nissan Y.M., Attia S.M. Design, synthesis and anticancer activity of some novel thioureido-benzenesulfonamides incorporated biologically active moieties. *Chemistry central journal*, **10**, 19(2016). https://doi.org/10.1186/s13065-016-0161-4

[27] Arshad N., Bhatti M.H., Farooqi S.I., Saleem S., Mirza B. Synthesis, photochemical and electrochemical studies on triphenyltin(IV) derivative of (Z)-4-(4-cyanophenylamino)-4-oxobut-2-enoic acid for its binding with DNA: Biological interpretation. *Arabian journal of chemistry*, **9**(3), 451–462(2016). https://doi.org/10.1016/j.arabjc.2014.08.018

[28] Shukla S., Srivastava R.S., Shrivastava S.K., Sodhi A., Kumar P. Synthesis, characterization, in vitro anticancer activity, and docking of Schiff bases of 4-amino-1,2-naphthoquinone. *Medicinal Chemistry Research*, **22**, 1604–1617(2013). https://doi.org/10.1007/s00044-012-0150-7

[29] Mohi El-Deen E.M., Anwar M.M., Kotb E.R. Synthesis and Cytotoxic Evaluation of New 6,7,8,9-Tetrahydropyrido[3',2':4,5]thieno[3,2-b]quinolone Derivatives. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, **5**, 1535(2014).

[30] Youssefyeh R.D., Brown R.E., Wilson J., Shah U., Jones H., Loev B., Khandwala A., Leibowitz M.J. Sonnino-Goldman, P. Pyrido[3',2':4,5]thieno[3,2-d]-N-triazines: a new series of orally active antiallergic agents. *Journal of medicinal chemistry*, **27**(12), 1639–1643(1984). doi: 10.1021/jm00378a019

[31] Penna C.A., Marino, S.G.; Gutkind, G.O.; Clavin, M.; Ferraro, G.; Martino, V. Antimicrobial activity of Eupatorium species

growing in Argentina. *Journal of Herbs, Spices and Medicinal Plants*, **5**, 21–28(1988).

[32] Wiegand I., Hilpert K, Hancock R.E. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances. *Nature protocols*, **3**(2), 163–175(2008). doi:10.1038/nprot.2007.521

[33] van Meerloo J., Kaspers G.J., Cloos J. Cell sensitivity assays: the MTT assay. *Methods in molecular biology*, **731**, 237–245(2011). doi: 10.1007/978-1-617

ملخص البحث باللغة العربية

يشكل الخطر الناجم عن تطور مقاومة مضادات الميكروبات ، بالإضافة إلى الزيادة السنوية في معدلات الإصابة بالسرطان ، أكبر تهديد للصحة العالمية ، مما أدى إلى الحاجة الملحة لاكتشاف جزيئات جديدة لها خصائص قوية مضادة للميكروبات ومضادة للسرطان.
لذلك، تضمنت الدراسة الحالية تشييد بعض المركبات الجديدة القائمة على النظام الحلقي ثيينو [3،2-ب] بيريدين عن طريق تفاعل مركبات مشتقات 3- امينو ثيينو [3،2-ب] بيريدين-2-كربوكساميد البادئة مع اريل ايزوثيوسيانات و ماليك انهيدريد وسيكلوبنتانون لينتج مركبات ثيينو[3،2-ب] بيريدين محتوية على مستبدلات مختلفة في الموضع-3. اضافة الى ذلك تم تحضير مشتقات رباعي الحلقات سيكلوبنتا بيريدين-ثيينوبيريدين-9- امين بمفاعلة مشتقات سيكلوبنتيليدين امينو مع فوسفورس اكسي كلوريد. تم تقييم النشاط الخارجي للمركبات الجديدة كمضادات للميكروبات على خمس سلالات بكتيرية وخمس سلالات فطرية. وايضا تم اختبار نشاط السمية الخلوية للمركبات ضد نوعين من الخلايا السرطانية وهما سرطان الكبد وسرطان الثدي.
وقد اظهرت المركبات نشاط واعد كمضادات للميكروبات والسرطان. حيث اظهر المركب 3c النشاط الاقوي بين المركبات ضد السلالات البكتيرية والفطريات و كان له قيم اقل تركيز مثبط للميكروبات يتراوح من 4 الى 16 ميكروجرام لكل مليليتر.
في حين ان النشاط الاقوى السام لخلايا الكبد وخلايا الثدي السرطانية كان للمركب 4 ب الذي اعطي اقل قيم للتركيزات المثبطة ل 50% من خلايا سرطان الكبد وسرطان الثدي بقيم 3.12 و20.55 ميكرومول بالترتيب.