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Anticancer and antimicrobial activities of some synthesized pyrazole and triazole derivatives

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ABSTRACT

*5-[1-(Aryl)-5-phenyl-1H-pyrazol-3-yl]-4-phenyl-2,4-dihydro[1,2,4]triazole-3-thione derivatives **1a-c** were reacted with chloropropanol, chloroacetone, chlorodiethyl ether and epichlorohydrine to afford the corresponding acyclonucleosides **2a-c-5a-c**, respectively. Also, compound **1c** was reacted with formaldehyde and 4-chloroaniline or piperidine to give the corresponding Mannish products **6** and **7**, respectively. In addition, **1c** was reacted with acrylonitrile or benzoyl chloride to give N-triazole derivatives **8** and **9**, respectively. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, MS spectral data and elemental analysis. All the compounds were screened for their antibacterial and antifungal activities and they showed high activity compared with Ciprofloxacin and Fusidic acid as positive controls. The compounds **2b, 3b, 5b, 6** and **7** were screened for their anticancer activities against breast carcinoma (MCF7) and cervix carcinoma (HELA) human cell lines compared with **Doxorubicin** positive control. The detailed synthesis, spectroscopic data, antimicrobial and anticancer activities of some synthesized compounds were reported.*

Key words: Triazole thione derivatives; S-acyclonucleosides; N-alkylated derivatives; anticancer activity; antimicrobial activity.

INTRODUCTION

The chemistry of triazole thiones have been of increasing interest since many of these derivatives produces useful applications as chemotherapeutic agents. Our previous work showed the highest activity towards hepatitis A virus (HAV) and herpes simplex virus type 1 (HSV-1) [1]. Triazole thiones possess various biological activities including antimicrobial [2-10], antifungal [11-13], anticancer [14,15], anti-inflammatory [16,17], antidepressant [18], antiproliferative [19], antiulicer [20,21], antioxidant [21], antiviral [22,23], antagonistic [24], and hypoglycaemic activities [25]. Also, they are used as drug targets for the treatment of neuroinflammatory and neurodegenerative diseases [26] against severe pandemic H1N1 influenza A/Mexico[27] and in vitro inhibition of cyclooxygenase and lipoxygenase activities [28]. In addition, some of triazoles were used as pesticide agents [29]. On the other hand, pyrazol derivatives are important class of

compounds with wide range of biological and pharmacological activities such as antioxidant [30], antimicrobial [31], antimycotic [32] and anticancer agents [33,34]. In view of the aforementioned facts, it seemed most interesting to synthesize some triazolopyrazole derivatives with the aim to evaluate their antimicrobial and anticancer activities.

MATERIALS AND METHODS

Chemistry

Melting points were measured using Electrothermal IA 9100 apparatus, (Shimadzu, Tokyo, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). ^{1}H NMR was determined on a Jeol-Ex-300 NMR spectrometer (JEOL, Tokyo, Japan) and chemical shifts were expressed as part per million; ppm (δ values) against TMS as internal reference. Mass spectra were recorded on VG 2AM-3F mass spectrometer (Thermo electron corporation, USA) Microanalyses were operated using Mario El Mentar apparatus, Organic Microanalysis Unit, and the results were within the accepted range (± 0.20) of the calculated values. Follow up of the reactions and checking the purity of the compounds was made by TLC on silica gel-precoted aluminum sheets (Type 60 F254, Merck, Darmstadt, Germany).

3-{-5-[1-(Aryl)-5-phenyl-1*H*-pyrazol-3-yl]-4-phenyl-4*H*-[1,2,4] triazole- 3-ylthio} propan-1-ol (2a-c)

To a solutiom of potassium hydroxide (1 mmol) in absolute ethanol (20 ml), compounds **1a-c** (1 mmole) was added. The reaction mixture was stirred at room temperature for 1 h, then chloropropanol (3 mmol) was added and stirred at 70°C for 5 hrs. The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol to afford the corresponding triazole derivatives **2a-c,** respectively.

1-{-5-[1-(Aryl)-5-phenyl-1*H*-pyrazol-3-yl]-4-phenyl-4*H*-[1,2,4] triazole-3-ylthio} propan-2-one (3a-c)

To a solutiom of absolute ethanol (20 ml) containing potassium hydroxide (1 mmol), compound **1a-c** (1 mmole) was added and the reaction mixture was stirred at room temperature for 1h, then chloroacetone (3 mmol) was added. The mixture was stirred for 2 hrs., the solid precipitate was purified on silica gel column chromatography using a mixture of chloroform : pet. ether 60-80, 1: 9 as eluent.

3-(2-Ethoxyethylthio)-5-{1-(aryl)-5-phenyl-1*H*-pyrazol-3-yl}-4-phenyl-4*H*-[1,2,4] triazole (4a-c)

To a solution of sodium hydride (1 mmol) in dry acetonitrile (20 ml), compounds **1a-c** (1 mmole) was added. The reaction mixture was stirred at room temperature for 1 h, then, cooled to 0°C and chloroethyl ethyl ether (3 mmol) was added to the reaction mixture. The mixture was stirred at 60-70°C for 6 hrs, evaporated under reduced pressure. The residue was recrystallized from ethanol to afford products **4a-c,** respectively.

3-{[(Oxiran-2-yl)methylthio]-5-(1-(aryl))-5-phenyl-1*H*-pyrazol-3-yl}-4-phenyl-4*H*-[1,2,4]triazole (5a-c)

A mixture of compound **1a-c** (1 mmole) in dry acetonitrile (20 ml) containing sodium hydride (1 mmol) was stirred at room temperature for 1 h, then the reaction mixture was cooled to 0°C. To the cooled mixture, epichlorohydrine (3 mmol) was added and stirred for **6** hrs. The precipitated solid was purified on silica gel column chromatography using (ethyl acetate:pet. ether 60-80, 1:9)

2-{(4-Chlorophenylamino)methyl}-5-{1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazol-3-yl}-5-phenyl-1*H*-pyrazol-3-yl}-4-phenyl-2*H*-[1,2,4]-triazole-3(4*H*)-thione (6)

A mixture of **1c** (0.01 mol) and formaldehyde solution (1.5 ml, 37%) in anhydrous ethanol (25 ml) was stirred at room temperature for 1h., then 4-chloroaniline (0.01 mol) was added to the mixture. The reaction mixture was stirred at room temperature over night, the obtained solid was filtered off, dried and crystallized from ethanol to give compound **6**.

5-{1-(4-Chlorophenyl)-5-phenyl-1*H*-pyrazole-3-yl}-4-phenyl-2-{(piperidin-1-yl) methyl} -2*H*-[1,2,4] triazole-3(4*H*)-thione (7)

Formaldehyde (1.5 ml, 37%) was added to compound **1c** (0.01 mole) in absolute ethanol (15 ml), the reaction mixture was heated for 5 minutes, then piperidin (0.01 mole) was added to the cold solution and the mixture was stirred for 3 hrs at room temperature. The separated precipitate was filtered off, and crystallized from ethanol.

3-{3-[1-(4-Chlorophenyl)-5-pheynl-1*H*-pyrazole-3-yl]-4,5-dihydro-4-phenyl-5-thioxo[1,2,4]triazol-1-yl}propanenitrile (8)

A mixture of compound **1c** (0.01 mol), acrylonitrile (0.015 mol), few drops of triethylamine in absolute ethanol (30 ml), was refluxed for 6 hrs. The reaction mixture was evaporated under reduced pressure, the residue was washed with distilled water, filtered off, dried and crystallized from ethanol to give **8**.

{3-[1-(4-Chlorophenyl)-5-phenyl-1*H*-pyrazole-3-yl]-4,5-dihydro-4-phenyl-5-thioxo-[1,2,4]triazol-1-yl}(phenyl)methanone (9)

A mixture of compound **1c** (0.01 mol), benzoyl chloride (0.01 mol), few drops of triethyl amine, in dry acetonitrile (30 ml) was stirred for 8 hrs at room temperature and for additional the reaction mixture was left overnight. The reaction mixture was evaporated under reduced pressure The residue was washed with distilled water, filtered off, dried and recrystallized from ethanol.

Biological screening

Anticancer screening

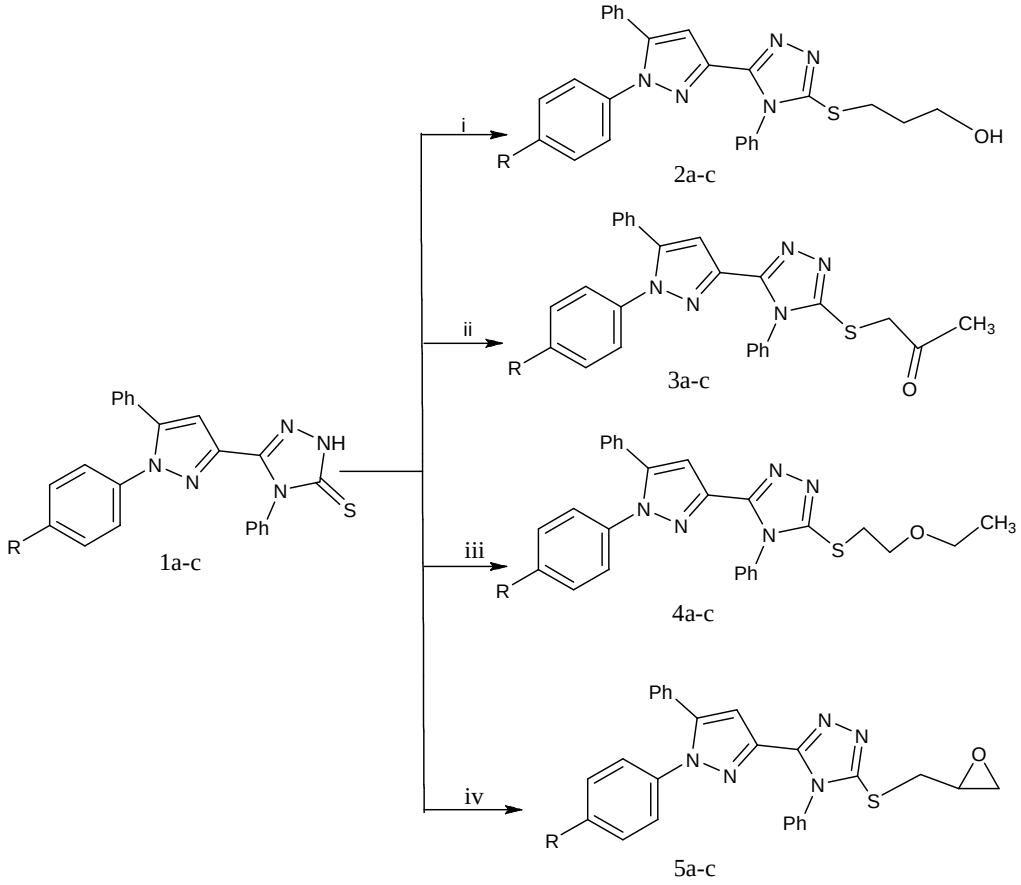
Preliminary experiments were done using the human breast carcinoma cell tumor line and cervix carcinoma cell line to identify the potential toxicity of five selected newly synthesized compounds **2b, 3b, 5b, 6** and **7** in comparison to the known anticancer drug Doxorubicin by Sulfo-Rhodamine-B (SRB) using the method Skehan et al.1990, [35] as follows: Cells were plated in 96-multiwell plates (104 cells/ well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentrations of the compounds under test (0.0, 1, 2.5, 5, and 10 g/ml) were added to the cell monolayer triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37◦C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained with Sulfo-Rhodamine-B (SRB) stain. Excess stain was washed with acetic acid and attached stain was recovered with tris EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentrations is plotted to get the survival curve of each tumor cell line after the specified compound

Antimicrobial assay

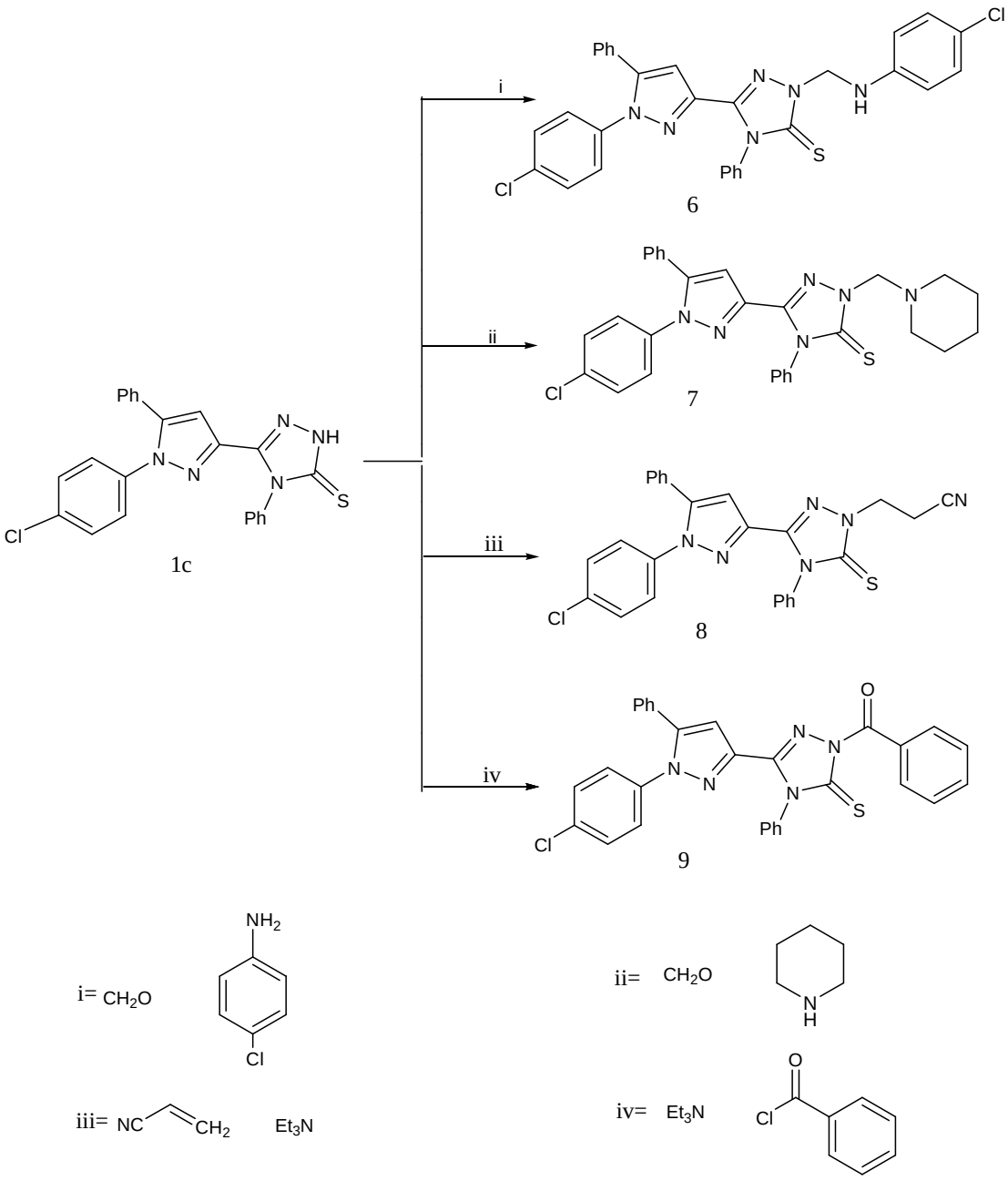
All compounds were screened *in vitro* for their antimicrobial activity against, by agar diffusion method [36]. A suspension of the organisms were added to sterile nutrient agar media at 45°C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 10 mm in diameter were made using a cork borer), an amount of 0.1 ml of the synthesized compounds was poured inside the holes. A hole filled with DMSO was also used as control. The plates were left for 1 h at room temperature as a period of pre-incubation diffusion to minimize the effects to

variation in time between the applications of the different solutions. The plates were then incubated at 37°C for 24 h and observed for antibacterial activity. The diameters of zone of inhibition were measured and compared with that of the standard, the values were tabulated. Ciprofloxacin (50 µg/ml) and Fusidic acid (50 µg/ml) were used as standard for antibacterial and antifungal activity respectively.

RESULTS AND DISCUSSION



(Scheme 1)



Scheme 2

Chemistry

The importance of the variations of acyclic oxygenated chain and its conformation in the interaction of such acyclic nucleosides, this led us to report the synthesis and preliminary pharmacological activity screening of several triazole thione derivatives as a key molecule for studying the synthesis of a number of S-acyclonucleosides analogues. Compounds **1a-c** have been reacted with different classes of acyclic oxygenated alkyl halides to give a series of [1,2,4]triazole acyclonucleoside analogues. Thus the alkylation of the triazole thiones **1a-c** with chloropropanol or chloroacetone in the presence of potassium hydroxide in absolute ethanol gave the corresponding pyrazolyl-[1,2,4]-triazole-3-ylthiopropane-1-ol **2a-c** or pyrazolyl-([1,2,4]triazole-3-ylthio)-propane-2-one **3a-c**, respectively. Compounds **1a-c** was reacted with chlorodiethyl ether or epichlorohydrine in dry acetonitrile to give the corresponding

ethoxyethylthio(pyrazolyl)[1,2,4]triazole **4a-c** or (oxiran-2-yl)methylthiopyrazolyl-[1,2,4]triazole **5a-c,** respectively. The IR spectrum of these compounds showed the absence of C=S group. The attachment of acyclic nucleosides to the sulfur atom rather than to nitrogen atom was supported by the value of chemical shift which showed at lower field due to the absence of deshielding effect of C=S. As example ^{1}H NMR spectrum of compound **4c** showed at δ, 2.85, 3.41 and 4.10 ppm. characteristic for CH_2 groups (Scheme 1).

Table 1. Physical and analytical properties of the new compounds

Comp. No.	Formula (M.wt.)	M.p. (^{0}C)	Yield (%)	Analysis (%) Calcd. /Found.			
				C%	H%	N%	S%
2a	$C_{26}H_{23}N_5OS$ 453.56	120-121	75	68.58 68.63	5.11 5.10	15.44 16.60	7.07 7.13
2b	$C_{27}H_{25}N_5OS$ 483.58	149-150	78	67.06 67.16	5.21 5.20	14.48 14.53	6.63 6.60
2c	$C_{26}H_{22}ClOS$ 488	106-107	80	63.99 63.85	4.54 4.53	14.35 14.4	6.57 6.50
3a	$C_{26}H_{21}N_5OS$ 451.54	94-95	70	69.16 69.26	4.69 4.72	15.5 15.65	7.10 7.18
3b	$C_{27}H_{23}N_5OS$ 481.57	131-132	80	67.34 67.45	4.81 4.80	14.54 14.42	6.66 6.55
3c	$C_{26}H_{20}ClOS$ 485.99	128-130	85	64.26 94.40	4.15 4.20	14.41 14.55	6.60 6.52
4a	$C_{27}H_{25}N_5OS$ 467.59	219-220	72	69.35 69.50	5.39 5.49	14.98 15.00	6.86 6.63
4b	$C_{28}H_{27}N_5OS$ 497.61	133-134	80	67.58 67.62	5.47 5.52	14.07 14.00	6.44 6.24
4c	$C_{27}H_{24}ClOS$ 502.03	142-143	85	64.60 64.63	4.81 4.90	13.95 14.02	6.39 6.45
5a	$C_{26}H_{21}N_5OS$ 451.54	139-140	72	69.16 69.46	4.69 4.65	15.51 15.62	7.10 7.30
5b	$C_{27}H_{23}N_5OS$ 481.57	108-110	82	67.34 67.45	4.81 4.80	14.54 14.32	6.66 6.52
5c	$C_{26}H_{20}ClOS$ 485.99	91-93	78	64.26 64.43	4.15 4.10	14.41 14.52	6.60 6.52
6	$C_{30}H_{22}ClOS$ 569.51	175-176	88	63.27 63.47	3.89 3.90	14.76 14.88	5.63 5.75
7	$C_{29}H_{27}ClNS$ 527.08	157-158	88	66.08 66.28	5.16 5.20	15.94 16.20	6.08 6.18
8	$C_{26}H_{19}ClNS$ 482.99	196-197	86	64.66 64.72	3.97 4.00	17.40 17.31	6.64 6.75
9	$C_{30}H_{20}ClOS$ 534.03	198-199	88	67.47 67.58	3.77 3.80	13.11 12.90	6.00 5.99

The reaction of the triazole thione **1c** with formaldehyde and 4-chloroaniline or piperidine in ethanol at room temperature gave the corresponding Mannish products, namely,2-{(4-chlorophenylamino)methyl}-5-{1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazol-3-yl}-4-phenyl-2*H*-[1,2,4]triazole-3(4)*H*-thione (**6**) and 5-{1-(4-chlorophenyl) -5-phenyl-1*H*-pyrazole-3-yl}-4-phenyl-2-{(piperidin-1-yl)methyl}-2*H*-[1,2,4]triazole-3(4*H*)-thione (**7**), respectively.

On the other hand, triazole thione **1c** was reacted with acrylonitrile via Michael addition reaction in ethanol containing of triethylamine as a base resulted in the formation of 3-{3-[1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-3-yl]-4,5-dihydro-4-phenyl-5-thioxo-[1,2,4]triazol-1-yl}propane-nitrile (**8**). Also, the reaction of triazole thione **1c** with benzoyl chloride in the presence triethylamine in dry acetonitrile afforded the corresponding {3-[1-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-3-yl]-4,5-dihydro-4-phenyl-5-thioxo-[1,2,4] tri-azolyl}(phenyl)methanone (**9**). The IR spectrum of **9** showed a characteristic absorption band at 1690 cm^{-1} corresponding to C=O and its Mass spectrum showed the molecular ion peak at m/z 533 as a base peak (Scheme 2). The structures of all prepared compounds were confirmed via elemental analysis and spectral data (**Tables 1, 2**).

Table 2. Spectral characterization of the new compounds

Comp. No.	IR (KBr, cm^{-1}), ^1H, ^{13}C NMR ($CDCl_3$, δ ppm) & MS [m/z (%)]
2a	3320-3335 (OH); 1.86 (m, 2H, CH_2), 2.0 (s, 1H, OH, exchangeable with D_2O), 2.92 (t, 2H, *J* = 8.6 Hz, CH_2), 3.52 (t, 2H, *J* = 8.4 Hz, CH_2), 6.7 (s, 1H, CH-pyrazole), 7.24-7.49 (m, 15H, Ar-H); 453.16[M^+, 17]
2b	3332-3336 (OH); 1.90 (m, 2H, CH_2), 2.1 (s, 1H, OH, exchangeable with D_2O), 2.93 (t, 2H, *J* = 8.4 Hz, CH_2), 3.53 (t, 2H, *J* = 8.2 Hz, CH_2), 3.75 (s, 3H, OCH_3), 6.75 (s, 1H, CH-pyrazole), 7.50-7.58 (m, 14H, Ar-H); 483.17[M^+, 22]
2c	3330-3336 (OH); 1.75 (m, 2H, CH_2), 2.2 (s, 1H, OH, exchangeable with D_2O), 2.94 (t, 2H, *J* = 8.4 Hz, CH_2), 3.55 (t, 2H, *J* = 8.44 Hz, CH_2), 6.65 (s, 1H, CH-pyrazole), 7.4-7.68 (m, 14H, Ar-H) 29.4, 32.4, 61.5 ($3CH_2$, aliphatic), 142.3, 143.3 (2C, triazole), 142, 143 (3C, pyrazole), 106 (CH, pyrazole).; 487[M^+, 19]
3a	1730 (C=O); 2.2 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 6.68 (s, 1H, CH-pyrazole), 7.20-7.52 (m, 15H, Ar-H); 451[M^+, 25]
3b	1730 (C=O); 2.35 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.25 (s, 2H, CH_2), 6.73 (s, 1H, CH-pyrazole), 7.16-7.53 (m, 14H, Ar-H); 481[M^+, 27]
3c	1730 (C=O); 2.21 (s, 3H, CH_3), 4.13 (s, 2H, CH_2), 6.72 (s, 1H, CH-pyrazole), 7.20-7.48 (m, 14H, Ar-H) 29.6 (CH_3), 48 (CH_2),143, 147.9 (2C, triazole), 106 (CH, pyrazole), 142, 143 (2C, pyrazole); 200 (C-carbonyl); 485[M^+, 29]
4a	Absence of C=S ; 1.14 (t, 3H, *J* = 6.4 Hz,CH_3), 3.43 (t, 4H, *J* = 6.8 Hz, $2CH_2$), 4.10 (t, 2H, *J* = 6.4 Hz, CH_2), 6.66 (s, 1H, CH-pyrazole), 7.20-7.49 (m, 15H, Ar-H); 467[M^+, 7]
4b	Absence of C=S; 1.13 (t,3H, *J* = 6.4 Hz, CH_3), 3.44 (m, 4H, *J* = 6.6 Hz, $2CH_2$), 4.12 (t, 2H, *J* = 6.4 Hz, CH_2), 3.8 (s, 3H, OCH_3), 6.7 (s, 1H, CH-pyrazole), 7.19-7.68 (m, 14H, Ar-H); 497[M^+, 8]
4c	absence of C=S; 1.14 (t, 3H, *J* = 6.2 Hz, CH_3), 3.41 (t, 4H, *J* = 6.4 Hz, $2CH_2$), 4.10 (t, 2H, *J* = 6.2 Hz, CH_2), 6.73 (s, 1H, CH-pyrazole), 7.22-7.56 (m, 14H, Ar-H); 15.6 (CH_3), 40, 66.6, 72 ($3CH_2$, aliphatic), 143, 147.6 (2C, triazole), 106 (CH, pyrazole), 142, 143 (2C, pyrazole); 501[M^+,12]
5a	Absence of C=S; 2.63 (d, 2H, *J* = 4.28 Hz, CH_2-oxirane), 2.82 (m, 1H, CH-oxirane) , 3.19 (d, 2H, *J* = 4.2 Hz, CH_2), 6.66 (s,1H, CH-pyrazole), 7.25-7.58 (m, 15H, Ar-H); 451[M^+,12]
5b	Absence of C=S; 2.78 (d, 2H, *J* = 4.6 Hz, CH_2-oxirane), 2.85 (m, 1H, CH-oxirane), 3.28 (d, 2H, *J* = 4.8 Hz, CH_2), 3.83 (s, 3H, OCH_3), 6.68 (s, 1H, CH-pyrazole), 7. 30-7.62 (m, 14H, Ar-H); 481[M^+, 10]
5c	Absence of C=S; 2.53 (d, 2H, *J* = 4.4Hz, CH_2.oxirane), 2.84 (m, 1H, CH-oxirane), 3.22 (d, 2H , *J* = 4.6 Hz, CH_2), 6.7 (s, 1H, CH-pyrazole), 7. 32-7.60 (m, 14 H, Ar-H); 40.6 (CH_2, aliphatic), 46.8 (CH_2, oxirane), 51.8 (CH, oxirane), 143, 147.6 (2C, triazole), 106 (CH, pyrazole), 142, 143 (2C, pyrazole); 487[M^+, 5]
6	3123 (NH), 1250 (C=S); 4.0 (s, 1H, NH, exchangeable with D_2O) 5.24 (s, 2H, CH_2) , 6.67 (s, 1H, CH, pyrazole), 6.6-7.68 (m, 18 H, Ar-H); 568[M^+, 33]
7	1252 (C=S); 1.5 (m, 6H, piperidine-H), 2.26 (t, 4H, *J* = 6.8 Hz, piperidine-H), 5.24 (s, 2H, CH_2), 6.67 (s, 1H, CH-pyrazole), 7.22-7.58 (m, 14H, Ar-H), 72.2 (CH_2, aliphatic), 52.6 ($2CH_2$, piperidine), 25.4 ($2CH_2$, piperidine), 25.8 (CH_2, piperidine), 143, 185.6 (2C, triazole), 106 (CH, pyrazole), 142,143 (2C, pyrazole); 526[M^+, 38]
8	2223 (CN), 1251 (C=S); 2.68 (t, 2H, *J* = 6.2 Hz, CH_2), 4.10 (t, 2H, *J* = 6.8Hz, CH_2), 6.7 (s, 1H, CH, pyrazole), 6.43-7.48 (m, 14H, Ar-H), 14.8, 51.5 ($2CH_2$, aliphatic), 112 (C, nitrile), 143, 185.6 (2C, triazole), 106 (CH, pyrazole), 142, 143 (2C, pyrazole); 482[M^+, 35]
9	1690 (C=O), 1253 (C=S); 6.7 (s, 1H, CH, pyrazole) 6.46-7.60 (m, 19H, Ar-H); 533[M^+, 39]

Biological evaluation

Anticancer activity

Chemotherapy is a major therapeutic approach for both localized and metastasized cancers. In the present work, five of the newly synthesized compounds **2b, 3b, 5b, 6** and **7** were selected to evaluate their in vitro growth inhibitory activities against two human cultured cell lines, which are breast carcinoma cell line (MCF7) and cervix carcinoma cell line (HELA) in comparison to the known anticancer drug, doxorubicin as a reference drug. It has been noticed from **Table 3** that all of the tested compounds showed significant potential antitumor activities and this might be explained that the presence of these nitrogen heterocyclic rings (triazole ring) which is responsible for these activities represented by **2b, 3b, 5b, 6** and **7** and the difference in activity between them is due to the difference of side chains. In comparison to doxorubicin lC50: 6.71 and 8.72 µg/ml against MCF7 and HELA, respectively. Best results were gained by compound **2b** and **5b** and this might be explained due to the presence of OH group in compound **2b** and free radical in **5b** which make more damage to the carcinoma cell. Fortunately, all of the tested derivatives showed good antitumor activity against both types of carcinoma cell lines (lC50: 2.72 - 5.85 µg/ml) than that obtained by doxorubicin lC50: 6.71 and 8.72 µg/ml against MCF7 and HELA, respectively.

Table 3. Effect of some selected triazole thion derivatives on MCF7 and HELA tumor cell lines.

Compound	IC50{µg/ml}	
	MCF7	HELA
Doxorubicin (Dox.)	6.71	8.72
2b	2.72	2.98
3b	4. 28	4.84
5b	3.63	3.92
6	5.26	5.85
7	3.89	4.20

The new compounds tested for anticancer activity in the Cairo University, National Cancer Institute, Cancer Biology Department, Cairo, Egypt.

Antimicrobial Activity

The antibacterial activity of the synthesized compounds was tested against *Bacillus subtilis, Staphylococcus aureus* (Gram-positive bacteria), *Escherichia coli*, *Pseudomonas sp.* (Gram-negative bacteria) using nutrient agar medium. The antifungal activity of the compounds was tested against *Candida albicans, Aspergillus Niger and Pencillium sp.* using Sabouraud dextrose agar medium.

Table 4: **Inhibition zone in mm as a criterion of antibacterial and antifungal activities of the newly synthesized compounds**

Compds.	***Microorganism inhibition zone diameter (mm)***						
	Gram +ve bacteria		***Gram -ve bacteria***		***Fungi***		
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeuroginosa*	*Candida albicans*	*Aspergillus niger*	*Penicillium sp.*
2a	*20*	*21*	*16*	*15*	*17*	*16*	*16*
2b	*23*	*20*	*22*	*23*	*17*	*16*	*18*
2c	*20*	*20*	*14*	*14*	*11*	*16*	*15*
3b	*6*	*2*	*4*	*4*	*12*	*3*	*6*
4a	*6.5*	*6*	*6.5*	*6.5*	*8*	*11*	*10*
4b	*12*	*9*	*9*	*8*	*7*	*7*	*5*
4c	*6*	*6*	*6*	*9*	*9*	*4*	*6*
5a	*6.5*	*6*	*7*	*9*	*9*	*4*	*6*
5b	*12*	*9*	*6*	*12*	*13*	*15*	*14*
5c	*12*	*9*	*9*	*8*	*9*	*9*	*8*
6	*7*	*6*	*6*	*7*	*6*	*1*	*2*
7	*6*	*6*	*6*	*7*	*6*	*1*	*2*
8	*15*	*12*	*13*	*12*	*16*	*13*	*14*
9	*7*	*6*	*7*	*6*	*6*	*1*	*2*

Highly active = (inhibition zone > 20 mm)
Moderately active = (inhibition zone 11 - 19 mm)
Slightly active = (inhibition zone 6 - 10 mm)
Inactive = (inhibition zone < 6 mm)

The results of the preliminary antimicrobial and the antifungal activities are shown in **Table 4**. The result revealed that compounds showed varying degrees of inhibition against the tested microorganisms. In general, the best antibacterial activity was displayed by compounds **2a**, **2b**, **2c** and **8**. Compound **2b** showed strong activity, while compounds **2a**, **2c** and **8** displayed good activity against Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeuroginosa* and compound **5c** showed good activity against *Pseudomonas aeuroginosa*. Also, compounds **2a**, and **2c** displayed strong activity, compound **8** showed good activities against Gram- positive bacteria *Bacillus subtilis, Staphylococcus aureus*, while compounds **4b, 5b** and **5c** displayed good activity against *Bacillus subtilis*. Compounds **2a**, **2b, 2c, 5b** and **8** exhibited good antifungal activity.

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