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Synthesis, characterization, and cytotoxic activity of some imides from galloyl hydrazide

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A new series of amic acids **[III]**$_{a-e}$ and *N*-substituted-imides **[IV]**$_{a-e}$ containing a 1,2,4-triazole moiety were designed, synthesized, and evaluated for its antimicrobial activities and cytotoxic effects. The structural modifications at position 3 of the 4-amino-5-mercapto-4*H*-1,2,4-triazole ring (linked to a bioactive 3,4,5-trihydroxyphenyl moiety) were expected to give new 1,2,4-triazole derivatives with a wide spectrum of biological activities. FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopic analyses were used for structure elucidation of these compounds. Furthermore, all the new compounds were investigated for the potential antibacterial activities against two types of bacteria: *Staphylococcus aureus* and *Klebsiella pneumonia*. Some of these target compounds showed good activity comparable to ampicillin (used as the reference antibiotic). Finally, the cytotoxic effects of compounds **[III]**$_{d}$ and **[IV]**$_{d}$ were assessed by using two cell lines (MCF7 and MDA-MB231) with increasing concentrations by the MTT assay. The results against both cell lines indicated the resistance to compound **[III]**$_{d}$, however, the highest dose (40 µM) reduced the viability in both cell lines to nearly similar percentage (87.6% and 88.7%, respectively). The compound **[IV]**$_{d}$ was more effective than compound **[III]**$_{d}$ on both cell lines. In addition, MDA-MB231 was more sensitive than MCF7 to compound **[IV]**$_{d}$ (IC_{50} for MCF7 = 20 µM; IC_{50} for MDA-MB231 = 10 µM). The results of the biological evaluation of the antibacterial/cytotoxic activities of some Imides from galloyl hydrazide showed that compounds **[III]**$_{d}$ and **[IV]**$_{d}$ surprisingly exhibited very high and significant anticancer (mainly) and antibacterial activities, and they could be very promising lead and parent compounds for the design and synthesis of new drugs by further *in vivo* biological evaluations and structural modifications.

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KEYWORDS

Galloyl hydrazide; microwave-assisted method; antibacterial activity; cytotoxic assay; MCF-7; MDA-MB231; *Staphylococcus aureus*; *Klebsiella pneumonia*.

Introduction

Microwave (MW)-assisted synthesis has revolutionized in chemical synthesis. Small molecules can be built in a fraction of the corresponding time required by the conventional methods. Green chemistry holds the promise of reducing health and environmental damage. In this study, we have focused to design chemicals that are safer for

the environment and human. MW-assisted reactions in organic chemistry achieve the same by ensuring facilitation of faster reactions under bulk conditions as well as promoting reduction of reaction times [1-3].

Galloyl hydrazide is a very important and unique organic chemical intermediate with, mainly, anti-inflammatory, antibacterial, antifungal, antidiabetic, antioxidant, and anticancer biological activities [4–7]. In addition, the interest of the structure of galloyl hydrazide as a credited structural system in pharmaceutical organic and medicinal chemistry has encouraged the advances of the further therapeutic potentials of this antitumor compound [1,2]. Galloyl hydrazide synthesis in the previous literature is very challenging, confusing, not standardized, and without any consensus. Therefore, one of the main objectives of Rabie's research studies was to make a standard and fixed method of greener synthesis of galloyl hydrazide through designing and constructing a new one-pot solventless greener MW-assisted synthetic method [1,2]. On the other hand, the cyclic imides are an important class of substrates suitable for biological, pharmacological, and chemical applications. These compounds have also proved to have analgesic, anticonvulsant, anti-inflammatory, antitumor, cytostatic, orexigenic, and antispasmodic activities [8-11].

In view of all the above datum facts, we approached designing and synthesizing new compounds, whose molecules include the three moieties, galloyl hydrazide, 1,2,4-triazole ring, and cyclic imide together, since the combination of all these biologically active moieties in the same molecule may give the chance for producing more effective newly-developed drugs with a vast range of various biological activities, as an attempt to correlate the biological results with their structural characteristics.

Experimental

Materials and equipment

The chemicals were obtained from Aldrich, Merck, and GCC Chemicals Co. On a Shimadzu (8300 s), Fourier Transform Infrared Spectrometer (FT-IR), spectra were recorded; Bruker, Ultra Shield (500 MHz), Switzerland, was used to record both ^{1}H-NMR and ^{13}C-NMR spectra in DMSO-d_6 using $(CH_3)_4Si$ as an internal standard. Mass spectra were obtained with mass agilant high resolution instrument.

Specific and general synthetic procedures

*Synthesis of galloyl hydrazide **[I]***

This compound was prepared following the procedure described by A.M. Rabie *via* a new green solvent-free one-pot, MW-assisted method from gallic acid: off-white fine powdered solid, m.p. = 294-297 °C [1].

*Synthesis of 5-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)benzene-1,2,3-triol **[II]***

A mixture of KOH (0.01 mol, 0.14 g) and acid hydrazide **[I]** (0.01 mol, 1.84 g) was dissolved in absolute EtOH (15 mL). The solution was cooled in ice bath and CS_2 (0.015 mol) was added in small portions with constant stirring. The mixture was stirred for 18 hours. Dry ether (30 mL) was added to the solution with constant stirring for 1 hour, then $NH_2NH_2.H_2O$ (0.01 mol) was added under reflux until the evolution of H_2S (the color changed from yellow to green) [12]. The reaction mixture was cooled, acidified with 5% HCl. The light yellow residue produced was filtered, washed with cold water, dried, and recrystallized from methanol to afford the compound **[II]**. Yield: 74%; m.p. = 172-174 °C.

*Synthesis of amic acids **[III]**$_{a-e}$*

A solution of different cyclic anhydrides (0.01 mol) in acetone (15 mL) was added dropwise

for 4 hours to a solution of compound **[II]** (0.01 mol) in (15 mL) of acetone with stirring [13,14]. The precipitated solids were filtered out and recrystallized from diethyl ether to give the corresponding amic acids **[III]$_{a-e}$**.

*Synthesis of N-substituted-imides **[IV]$_{a-e}$***

A mixture of amic acid (0.01 mol) **[III]$_{a-e}$** in acetic anhydride (15 mL) and anhydrous sodium acetate (0.01 mol) was heating for 90 min. The mixture was cooled for about 1 hour at room temperature, then poured on ice-water (100 mL), filtered out, and recrystallized from acetone [14,15]. The physical properties of the compounds **[III]$_{a-e}$** and **[IV]$_{a-e}$** are listed in Table 1.

TABLE 1 The physical properties of compounds **[III]$_{a-e}$** and **[IV]$_{a-e}$**

Comp. No.	Molecular formula	M.P. (°C)	Yield (%)	Color	Comp. No.	Molecular formula	M.P. (°C)	Yield (%)	Color
[III]$_a$	$C_{12}H10N_4O_5S$	155-157	74	Light Yellow	**[IV]$_a$**	$C_{12}H_{12}N_4O_6S$	174-176	73	Dark Beige
[III]$_b$	$C_{12}H_8N_4O_5S$	153-155	80	Light Beige	**[IV]$_b$**	$C_{12}H_{10}N_4O_6S$	168-170	71	Dark Beige
[III]$_c$	$C_{16}H_{10}N_4O_5S$	228-230	77	White	**[IV]$_c$**	$C_{16}H_{12}N_4O_6S$	216-218	65	Gray
[III]$_d$	$C_{16}H_9N_5O_7S$	218-220	84	Light Gray	**[IV]$_d$**	$C_{16}H_{11}N_5O_8S$	184-186	68	Dark Gray
[III]$_e$	$C_{20}H_{12}N_4O_5S$	238-240	82	Light Yellow	**[IV]$_e$**	$C_{20}H_{14}N_4O_6S$	220-222	80	Dark Yellow

Biological evaluation

Antibacterial activity

All synthesized compounds have been screened for antibacterial activities against *Staphylococcus aureus (G+)* and *Klebsiella pneumonia (G-)* in Muller Hinton Agar medium using agar well diffusion method. All compounds were dissolved in DMSO at a concentration of 100 µg/mL. The plates were incubated at 28 °C for 72 hours and compared with the common antibiotic ampicillin. The inhibition zones formed were measured in millimeters [16].

Cytotoxicity assay

In this study, two human cells lines, MCF7 estrogen receptor harboring cells (ER+VE) and MDA-MB231 estrogen receptor lacking cells (ER-VE) were used for the cytotoxicity evaluation purpose. Both cell lines were derived from patients with breast cancer. MCF7 cells were purchased from LEANGENE Co. (Amman, Jordan). MDA-MB231 cells were obtained from Biotechnology department/Baghdad University. Cells were maintained in RPMI media (Capricorn, Germany) supplemented with 10% fetal bovine serum (BSA) (Capricorn, Germany) and 1% penicillin/streptomycin antibiotics (Gibco, USA). Cells were kept in a humidified chamber at 37 °C with 5% CO_2 [17].

Cells viability was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay after incubating cells with compounds [III]$_d$ and [IV]$_d$ for 24 hours. MTT working solution is prepared by dissolving MTT powder (Macklin, China) in PBS (5 mg/mL). The optimum number of cells were seeded per well (7*103 for MDA-MB231; 10*103 for MCF7) for 24 hours in 96-well plate for adherence. Then, escalating doses (1 µg/mL, 5 µg/mL, 10 µg/mL, 20 µg/mL, and 40 µg/mL) of compounds **[III]$_d$** and **[IV]$_d$** were added to the cells for 24 hours. Following that, wells were emptied and 20 µL of MTT

was added before returning the plate to the incubator for further 3 hours. To dissolve MTT formazan, 50 µL of DMSO was added and the plate was agitated gently in an orbital shaker for 15 min before reading by ELISA reader (Expert Plus reader, Austria) at 492 nm wavelength. The formula below was used to calculate the percentage of viability from triplicate wells [18].

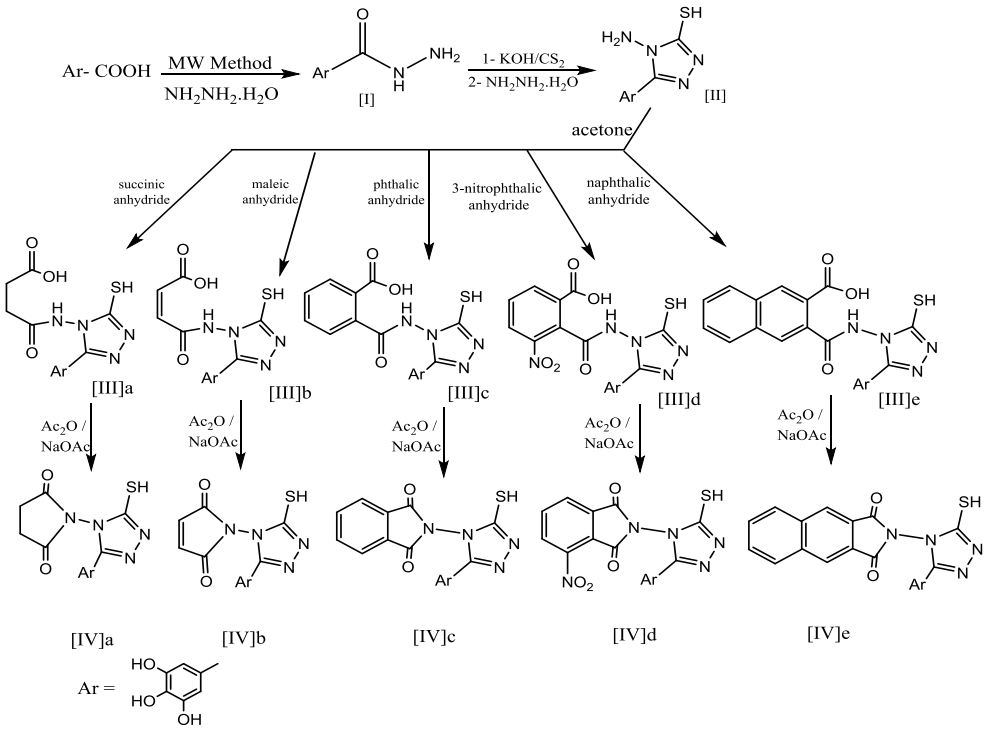
Viability % = (A test/ A control) x 100, in which "A" denotes absorbance. GraphPad prism software was then used to calculate the concentration that inhibits 50% of growth (IC_{50}).

Results and discussion

Chemistry

The work involves synthesis of a series of amic acids **[III]$_{a-e}$** and imides **[IV]$_{a-e}$** derivatives based on 1,2,4-triazole ring concerted to 3,4,5-trihydroxyphenyl moiety. The initial step employs designing of a newer and greener method for the synthesis of galloyl hydrazide **[I]** from gallic acid using the MW-assisted procedure as the main synthetic method without the use of nonrenewable resources and polluting solvents, with decreasing the reaction time, heating power, and the number of synthetic steps, and further with increasing the yield and selectivity, following the advantageous original synthetic protocol of A.M. Rabie [1]. Refluxing the acid hydrazide **[I]** with CS_2 in alcoholic alkaline solution was done in the second step to afford compound **[II]**, which is then used for the synthesis of new amic acids **[III]$_{a-e}$** by employing different acid anhydrides including succinic anhydride, maleic anhydride, phthalic anhydride, 3-nitrophthalic anhydride, or naphthalic anhydride [19]. The ring closure of amic acids **[III]$_{a-e}$** was performed to produce the imides **[IV]$_{a-e}$** *via* treatment with acetic anhydride and anhydrous sodium acetate, Scheme 1.

The newly-synthesized compounds were assigned and correlated with their designed/proposed chemical structures using the spectroscopic analyses [20]. The collective FT-IR spectral data obtained for elegant compounds are listed in Tables 2 & 3. While, ^{1}H-NMR and ^{13}C-NMR spectra are given in Tables 4 & 5, respectively.



SCHEME 1 Synthesis of the target *N*-substituted-imides **[IV]$_{a-e}$**

TABLE 2 FT-IR spectral data (cm^{-1}) of amic acids **[III]$_{a-e}$**

Comp. No.	FT-IR spectra data (cm^{-1})							
	υ (O-H) υ (N-H) amide	υ (C-H) arom.	υ (C-H) aliph.	υ (C=O) acidic	υ (C=O) amide	υ (C=N) triazole	υ (C=C) aromatic	υ (C-S)
[III]a	3445 3367	3059	2931,2850	1734	1693	1620	1539, 1465	721
[III]b	3495 3367	3070	2939,2854	1730	1693	1616	1539, 1466	721
[III]c	3495 3371	3066	2900,2862	1740	1685	1620	1546, 1480	733
[III]d	3495 3344	3070	2924,2870	1716	1654	1616	1570, 1539	732
[III]e	3495 3375	3060	2920,2866	1738	1660	1624	1581, 1512	775

TABLE 3 FT-IR spectral data (cm^{-1}) of cyclic imides **[IV]$_{a-e}$**

Comp. No.	υ (O-H)	υ (C-H) arom.	υ (C-H) aliph.	υ (C=O) imide	υ (C=N) triazole	υ (C=C) arom.	υ (N-H)	υ (C-O)	υ (C-S)
[IV]a	3430	3050	2930,2848	1775	1697	1600,1587	1370	1110	735
[IV]b	3394	3060	2910,2840	1770	1689	1581,1512	1303	1122	725
[IV]c	3429	3035	2920,2850	1782	1627	1600,1546	1369	1184	713
[IV]d	3433	3082	2924,2850	1778	1630	1597,1496	1373	1188	714
[IV]e	3485	3062	2901,2860	1772	1680	1580,1518	1310	1128	775

TABLE 4 ^{1}H-NMR spectral data (ppm) for selected compounds

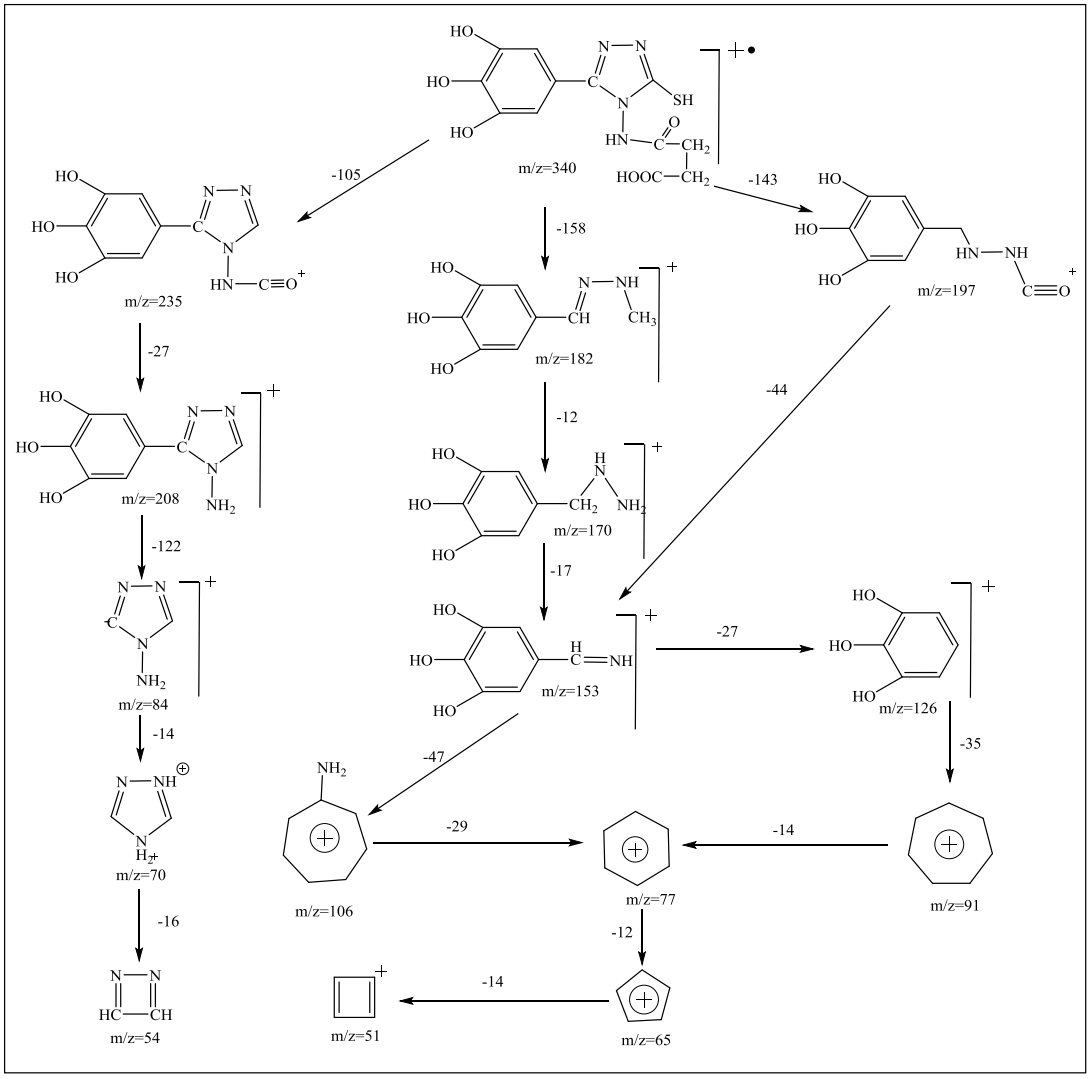
Comp. No.	Signals in ^{1}H-NMR spectra (δ, ppm) (in DMSO-d_6)
[III]$_a$	2.13-2.43 (m, 4H, CH_2-CH_2), 6.52-6.92 (s, 2H, Ar-H), 6.38 (s, 1H, NH), 8.86-9.19 (s, 4H, OH), 12.14 (s, 1H, SH).
[III]$_c$	6.92 (s, 2H, Ar-H), 7.56-7.66 (m, 4H, Ar-H), 7.61 (s, 1H, NH), 8.84-9.19 (s, 4H, OH), 12.61 (s, 1H, SH).
[III]$_e$	6.92 (s, 2H, Ar-H), 6.92-7.96(m, 4H, Ar-H), 7.77 (s, 1H, NH), 8.00-9.22 (s, 3H, OH), 9.84 (s, 1H, OH), 14.67 (s, 1H, SH).
[IV]$_b$	3.13-3.31 (m, 2H, CH=CH), 6.90 (s, 2H, Ar-H), 7.32 (s, 1H, NH), 8.81-9.20 (s, 3H, OH), 12.60 (s, 1H, SH).
[IV]$_e$	6.93 (s, 2H, Ar-$H_{gallic\ ring}$), 7.58-7.70 (m, 6H, Ar-$H_{naphthalic\ ring}$), 7.66 (s, 1H, NH), 8.87-9.21 (s, 3H, OH), 12.66 (broad, 1H, SH).

TABLE 5 ^{13}C-NMR spectral data (ppm) for selected compounds

Comp. No.	Signals in ^{13}C-NMR spectra (δ, ppm) (in DMSO-d_6)
[I]	(δ = 106.58-145.51) ppm to aromatic carbons, (δ = 166.53) ppm (C=O) to amide carbon
[III]$_a$	(δ = 28.56-28.93) ppm to (-CH_2- CH_2-) , (δ = 107.50-142.51) ppm aromatic carbons, (δ = 145.86) ppm (C=N) carbon in triazole ring, (δ = 148.56) ppm (HS-C=N) carbon triazole ring, (δ = 170.69) ppm (C=O) amide carbon, (δ = 191.36) ppm (C=O) carboxyl
[III]$_e$	(δ = 121.54-122.80) ppm to (-CH=CH-) , (δ = 106.83-140.82) ppm aromatic carbons, (δ = 167.21) ppm (C=N) carbon in triazole ring, (δ = 169.21) ppm (HS-C=N) carbon triazole ring, (δ = 179.51) ppm (C=O) amide carbon,(δ = 190.21) ppm (C=O) carboxyl
[IV]$_c$	(δ = 107.56-142.55) ppm aromatic carbons, (δ = 161.90) ppm (C=N) carbon in triazole ring, (δ = 167.12) ppm (HS-C=N) carbon triazole ring, (δ = 171.60) ppm, (C=O) amide carbon.

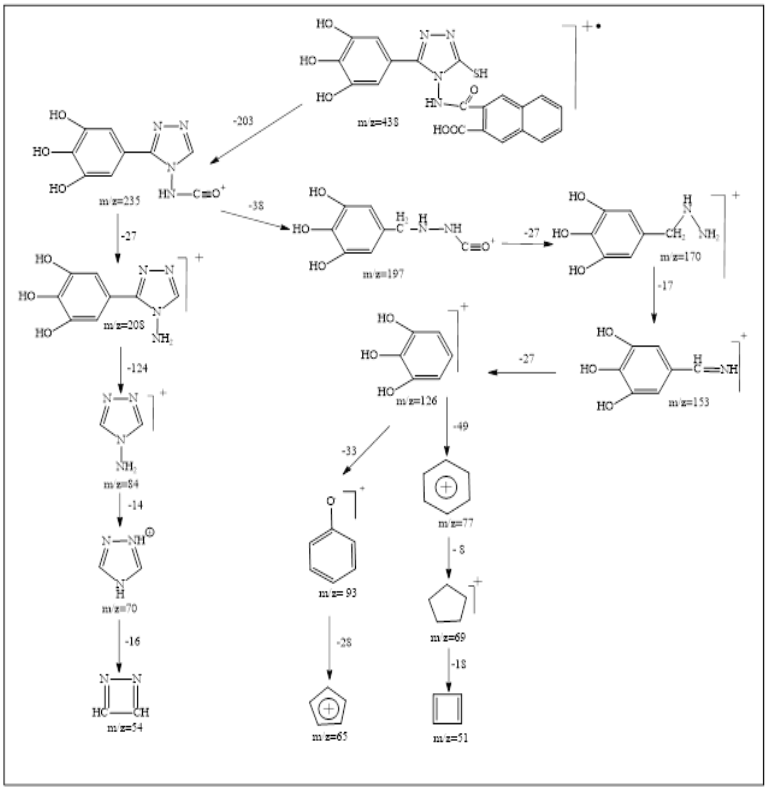
The mass spectrum of galloyl hydrazide **[I]**: $C_7H_8N_2O_4$ (M.Wt. = 184.15) showed base peak at ($m\backslash z$ = 185), further revealed several fragments at ($m\backslash z$ = 166.9, 152.9, 128, 126.8,

and 113.7) which corresponds to the molecular weight of structure suggested for this compound [1]. The mass spectrum of compound **[III]$_a$**: $C_{12}H_{12}N_4O_6S$ (M.Wt. = 340.31) indicated the interesting base peak at ($m\backslash z$ = 153), also showed several fragments at ($m\backslash z$ = 197, 126, 106, 91, 77, 65, and 51) refer to aromaticity at this compound [20]. The spectrum also demonstrated peaks refer to 1,2,4-triazole ring in this compound at ($m\backslash z$ = 208, 84, 70, and 54), this is a good evidence for the presence of benzene-1,2,3-triol and triazole ring in this compound .The other important fragments are proposed in Scheme 2.



SCHEME 2 Mass fragments of compound **[III]$_a$**

The mass spectrum of compound **[III]$_d$**: $C_{20}H_{14}N_4O_6S$ (M.Wt. = 438.41). Besides, it revealed base peak at ($m\backslash z$ = 153.9), and several fragments at ($m\backslash z$ = 197, 170, 126, 77, 69, and 51) refer to aromaticity at this compound, as well as a peaks at ($m\backslash z$ = 208, 84, 70, and 54) of the characteristic fragmentation of the triazole ring. The scheme (3) illustrated the most characteristic fragments of this compound [20].



SCHEME 3 Mass fragments of compound **[III]$_d$**

Biological activity

Antibacterial activity

The synthesized compounds revealed a good to moderate range of antibacterial activity against two types of bacteria *Staphylococcus aureus* (G+) and *Klebsiella pnumonia* (G-). The inhibition zones (mm) of antibacterial activities of the target compounds are as presented in Table 6.

The synthesized compounds **[III]$_d$**, **[IV]$_d$**, **[III]$_c$**, and **[IV]$_c$** showed the excellent level of activities against these bacteria compared to the common potent antibiotic ampicillin, this could be related to the presence of the 1,2,4-triazole ring with SH and NO_2 groups in its composition [21,22]. These moieties are well known for their boosting effects on the net antibacterial effectiveness (of the compounds containing them) against the tested bacteria *in vitro*.

TABLE 6 Antibacterial screening data (zone of inhibition in mm) for compounds **[III]$_{a-e}$–[IV]$_{a-e}$**

Comp. No.	*Staphylococcus aureus* (G+)	*Klebsiella pnumonia* (G-)	Comp. No.	*Staphylococcus aureus* (G+)	*Klebsiella pnumonia* (G-)
[III]$_a$	22	16	**[IV]$_a$**	24	19
[III]$_b$	24	22	**[IV]$_b$**	22	18
[III]$_c$	24	20	**[IV]$_c$**	26	22
[III]$_d$	27	25	**[IV]$_d$**	27	24
[III]$_e$	23	14	**[IV]$_e$**	20	18
Ampicillin	22	22			

Cytotoxicity assay

Cytotoxicity of the selected compounds was assessed on 2 cell lines (MCF7 and MDA-MB231) after 24 hours of exposure with increasing concentrations by MTT assay. Both cell lines were resistant to compound **[III]$_d$**,

however, the highest dose (40 µM) reduced the viability in both cell lines to nearly similar percentage (87.6% for MCF7 and 88.7% for MDA-MB231), as displayed in Figure 1. Interestingly, compound **[IV]$_d$** was more effective than compound **[III]$_d$** on both cell lines. In addition, MDA-MB231 was more sensitive than MCF7 to compound **[IV]$_d$** (IC_{50} for MCF7 = 20 µM; IC_{50} for MDA-MB = 10 µM) (Figure 1).

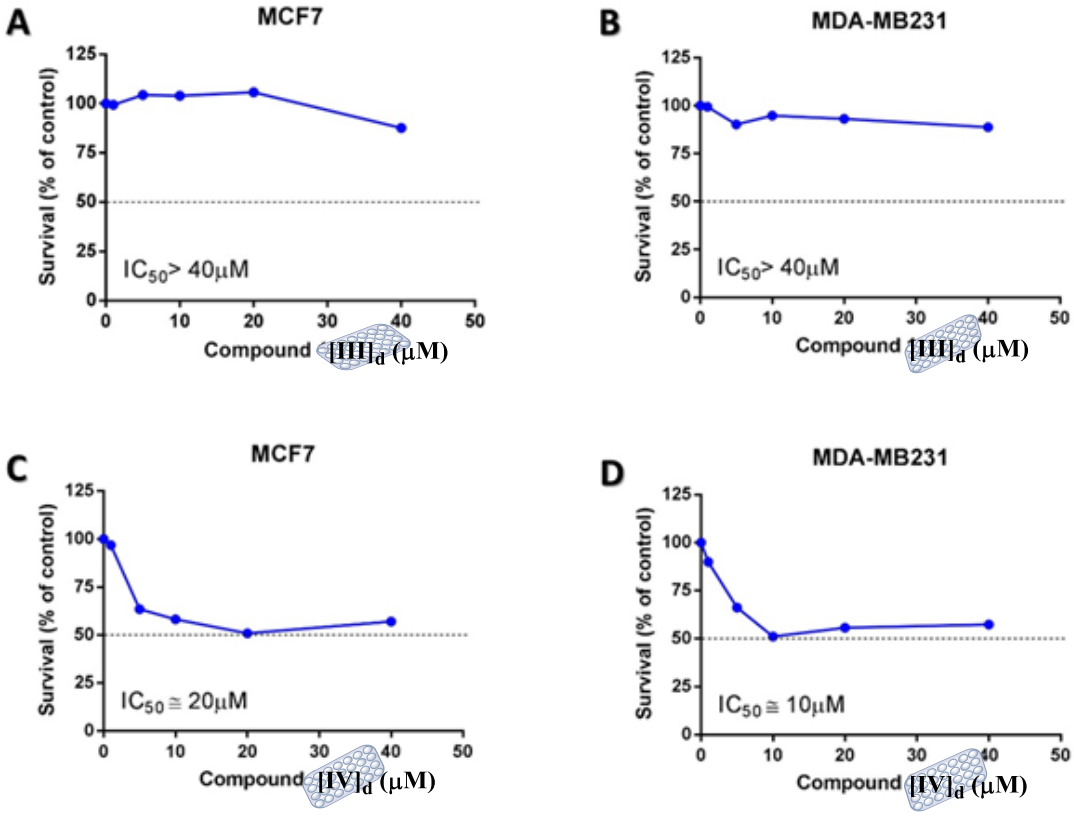


FIGURE 1 Cytotoxic effects of compounds **[III]$_d$** and **[IV]$_d$** on breast cancer cells *in vitro*. MCF7 cells (A & C) and MDA-MB231 cells (B & D) were incubated with escalating doses of compound **[III]$_d$** (top panel, A & B) and compound **[IV]$_d$** (bottom panel, C & D) for 24 hours. GraphPad prism software was used to plot the linear curves and detect the IC_{50} values. Curve points represent the mean of 3 replicate wells

Conclusion

Galloyl hydrazide was prepared following the advantageous original synthetic procedure in very good yield, *via* a new green solvent-free one-pot, MW-assisted method from gallic acid, with decreasing the reaction time, heating power, and number of synthetic steps (Rabie's Method). Then, we have designed and synthesized a new series of amic acid and imide compounds derived from gallic acid (which is a bioactive aromatic compound) directly linked with a 1,2,4-triazole moiety. The synthesized compounds revealed a wide range of antibacterial activities. Compounds **[III]$_d$** and **[IV]$_d$** interestingly exhibited very potent anticancer activity on breast cancer cells *in vitro* against MCF7 cells and MDA-MB231 cells, this could be related to the presence of the 1,2,4-triazole ring with the SH and NO_2 groups in its composition, so they are expected to be very promising lead and parent compounds for the design and synthesis of new pharmaceutical drugs by further biological evaluation and advanced studies.

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Authors' contributions

All authors equally contributed toward data analysis, drafting the manuscript, and revising the final paper considered as part of the student Fayyadh A. Nashaan's Ph.D. thesis, and they agreed to be responsible for all the aspects of this work.

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