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Original article

Antibacterial and antifungal activities of new pyrazolo[3,4-*d*]pyridazin derivatives

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Abstract

Several new pyrazolo[3,4-*d*]pyridazin derivatives were prepared by the reaction of two new 1*H*-pyrazole-3-carboxylic acids and various hydrazines. The compounds were tested for antimicrobial activities against Gram-negative, Gram-positive bacteria and fungi. The compounds named as **7e**, **f** had the highest antimicrobial activities against Gram-negative, Gram-positive bacteria and fungi with minimum inhibitory concentrations in the range of 0.31 to < 0.0024 mg ml^{-1} .

Keywords: Pyrazole; Antimicrobial activity; Pyrazolo-pyridazin

1. Introduction

In recent years, the number of life-threatening infectious caused by multi-drug resistant Gram-positive and Gram-negative pathogen bacteria have reached an alarming level in many countries around the world [1,2]. A number of clinic reports in the United States and worldwide have independently described the emergence of vancomycin-resistance in methicillin-resistance *Staphylococcus aureus* (MRSA) isolates and other human pathogen Gram-negative isolates [3]. Infections caused by these microorganisms pose a serious challenge to the medical community and the need for an effective therapy has led to a search for novel antibacterial agents. Besides, several researchers reported that pyrazole compounds posses numerous chemical, biological, medicinal and agricultural applications because of their versatile biological activities appearing as antimicrobial [4,5] and anti-inflammatory [6] agents. On the other hand, cyclic oxalyl compounds of type **1** have been used successfully as starting materials to synthesize various 1,4,5-trisubstituted pyrazol-3-carboxylic acids and their derivatives via the reactions with various hydrazines or hydrazones for about two decades [7–9]. Here, we report the chemical behavior of furandione **1** toward methylhydrazine and 2-hydrazinopyridine. As the results of these reactions were synthesized new pyrazole-3-carboxylic acids. The new acids were converted into various derivatives of the pyrazole-pyridazine with different hydrazines. The new compounds were tested against representative Gram-negative and Gram-positive bacteria, as well as fungi.

2. Results and discussion

2.1. Chemistry

In this study were studied the reactions of furandione **1** with 2-hydrazinopyridine and methylhydrazine. The preparation of 4-benzoyl-5-phenyl-1-pyridin-2-yl-1*H*-pyrazole-3-carboxylic acid **2** was carried out by refluxing equimolar amount of 4-benzoyl-5-phenylfuran-2,3-dione **1** and 2-hydrazinopyridine in dry benzene for about 30 minutes Additionally, 4-benzoyl-1-methyl-5-phenyl-1*H*-pyrazole-3-carboxylic acid **3** was synthesized with a equimolar mixture of furandione **1** and methylhydrazine at room temperature in dry benzene for approximately 60 minutes (Scheme 1). Structure of the compounds **2** and **3** was confirmed by analytical and spectral data (see Section 3 for details).

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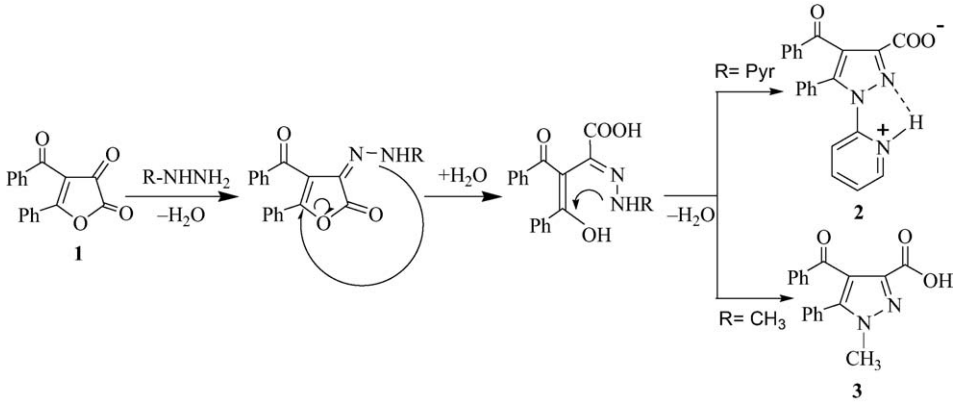
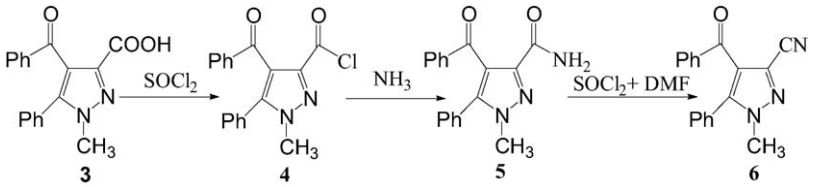
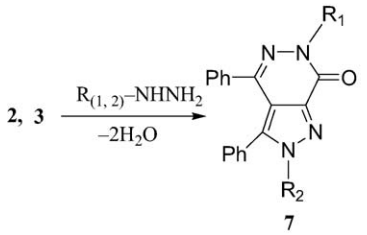


Scheme 1.



Scheme 2.



7	R_1	R_2
a	H	CH_3
b	Ph	CH_3
c	CH_3	CH_3
d	C_6H_4COOH (4)	CH_3
e	$C_6H_3Cl_2$ (2,5)	Pyr
f	$C_6H_2Cl_3$ (2,4,6)	CH_3

Scheme 3.

The compound **3** can easily be transformed into the corresponding acid chloride **4** and amide **5** derivatives by the usual chemical procedures.

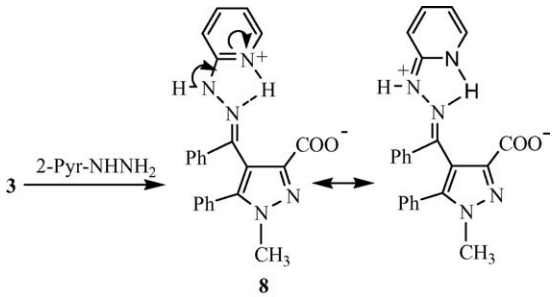
Furthermore, a cold solution of the acid amide **5** in a mixture of DMF and $SOCl_2$ was stirred at 0–5 °C for 2 hours to give nitrile **6** (Scheme 2) (see Section 3 for details).

Reactions of pyrazole derivatives having the dicarbonyl group in the suitable position with hydrazines were convenient methods to build the pyrazolo[3,4-*d*]pyridazine systems [8,10]. Thus, the pyrazole acids **2** and **3** were cyclized with various hydrazine compounds to the pyrazolo[3,4-*d*]pyridazinones **7a**–**f**, in approximately 55–75 % yields (Scheme 3).

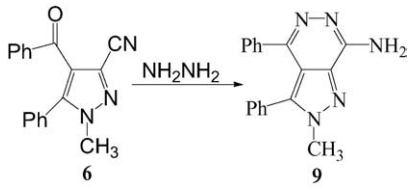
The structures of **7a**–**f** were assigned on the basis of their satisfactory analytical and spectral data (see Section 3 for details).

On the other hand, the reaction of the compound **3** with 2-hydrazinopyridine, instead of the corresponding pyrazolo[3,4-*d*]pyridazine derivative led to a new pyrazole acid **8** containing a hydrazone group. Hydrazono-pyrazole acid of this type from analogue pyrazole acids have been described previously [9] (Scheme 4).

In a similar way, the pyrazole-3-carbonitrile **6** with anhydrous hydrazine in boiling 1-butanol containing a catalytic amount of metallic sodium was also cyclized to the 7-amino pyrazolo[3,4-*d*]pyridazine derivative **9** in approximately 40 % yield (Scheme 5).



Scheme 4.



Scheme 5.

Structure elucidation of **9** is mainly based on IR and ^{13}C-NMR spectroscopy (see Section 3 for details).

2.2. Biological results

Antimicrobial activities of the prepared compounds were tested against bacteria, such as *Bacillus cereus* ATCC 7064, *S. aureus* ATCC 6538, *Escherichia coli* ATCC 4230, *Pseudomonas putida* ATCC 12633 and against human pathogenic fungi, such as *Candida albicans* ATCC 27541 using tube dilution method. Ampicillin trihydrate for bacteria and fluconazole for fungi were used as reference drugs. The minimal inhibitory concentrations (MICs, mg ml^{-1}) of tested compounds against bacteria and fungi are shown in Table 1.

In general, the compounds showed weak activity, whereas the compound **9** was inactive at the highest tested concentration against Gram-negative, Gram-positive bacteria and fungi. These results confirmed that slight differences between antimicrobial activities of the compounds tested against microorganisms, except **7e**, **f**. These compounds had the highest antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi with MICs in the range of 0.31 to <0.0024 mg ml^{-1} (Table 1). The reason for this higher antimicrobial activity might be related to the presence of the chloro group. The compounds **7e**, **f** exhibited selective and effective activity against two Gram-positive bacteria (*B. cereus* ATCC 7064, *S. aureus* ATCC 6538), one Gram-negative bacterium (*P. putida* ATCC 12633) and one yeast (*C. albicans* ATCC 27541), but poor activity of **7e**, **f** against *E. coli* ATCC 4230. *E. coli* ATCC 4230 strain is highly pathogenic to humans. Indeed, this bacterium showed lower microbial susceptibility compared to other tested microorganisms. In conclusion, our study revealed that some of the prepared pyrazolo[3,4-*d*]pyridazine derivatives, containing chloro group, displayed higher MIC values than the above mentioned standard drugs. Therefore, we suggested that the compounds **7e**, **f** might be a promising candidate of new antimicrobial agents.

Table 1
MICs[a] of the compounds **7a**, **7b**, **7c**, **7d**, **7e**, **7f**, **8** and **9** derivatives against Gram-positive, Gram-negative bacteria and fungi

Compounds	*B. cereus* ATCC 7064	*S. aureus* ATCC 6538	*E. coli* ATCC 4230	*P. putida* ATCC 12633	*C. albicans* ATCC 27541
7a	>0.62	>0.62	>0.62	0.31	>0.62
7b	>0.62	0.62	>0.62	>0.62	0.62
7c	>0.62	>0.62	0.62	0.15	0.31
7d	0.31	>0.62	>0.62	0.31	0.15
7e	<0.0024	0.0024	0.31	<0.0024	<0.0024
7f	0.0024	0.0098	0.31	<0.0024	<0.0024
8	>0.62	>0.62	>0.62	0.62	0.62
9	>0.62	>0.62	>0.62	>0.62	>0.62
Ampicilline	0.05	0.012	0.012	0.025	n.t.[b]
Fluconazole	n.t.	n.t.	n.t.	n.t.	0.05

[a] MICs values were determined as mg ml^{-1} active compounds in medium.
[b] n.t., not tested.

3. Experimental protocols

Solvents were dried by refluxing with the appropriate drying agents (metallic sodium for ether; $CaCl_2$ or Na_2SO_4 for benzene, toluene...) and distilled before use. Melting points were determined on an Electrothermal Gallenkamp apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer Model 1108. The IR spectra were obtained in as potassium bromide pellets using a Mattson 1000 FTIR spectrometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on Varian XL-200 (200 MHz) and Varian XL-200 (50 MHz) spectrometers, respectively, using TMS as an internal standard. All experiments were followed by TLC using DC Alufolien Kieselgel 60 F 254 Merck and Camag TLC lamp (254/366 nm).

3.1. Syntheses

3.1.1. 4-Benzoyl-5-phenyl-1-pyridin-2-yl-1H-pyrazole-3-carboxylic acid (*2*)

An equimolar mixture of furandione **1** (0.278 g, 1 mmol) and 2-hydrazinopyridine (0.109 g, 1 mmol) was refluxed in 30 ml of dry benzene for approximately 30 minutes After evaporation, the oily residue obtained was treated with dry ether. The crude product formed was recrystallized from a mixture of benzyl alcohol and *n*-butanol to give 0.258 g (70 %) of **2**, m.p. 208 °C; IR: 3130–3050 cm^{-1} (b, OH, COOH), 1676 cm^{-1} (C=O, benzoyl), 1635, 1580 cm^{-1} (C=O, COOH); ^{1}H-NMR (deuteriochloroform): δ = 8.6-7.2 ppm (m, 14H, H_{arom}); ^{13}C-NMR (deuteriochloroform): δ = 192.9 (C=O, benzoyl), 162.1 (C=O, COOH), 152.5, 151.9, 149.8, 141.5, 138.7, 138.1, 135.8, 132.5, 130.9, 130.7, 130.6, 130.4, 129.2, 125.9, 123.7, 119.4 ppm (C_4). Anal. $C_{22}H_{15}N_3O_3$.

3.1.2. 4-Benzoyl-1-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid (*3*)

An equimolar mixture of furandione **1** (0.278 g, 1 mmol) and methylhydrazine (3.1 ml, 1 mmol) was mixture in room temperature in 30 ml of dry benzene for approximately 60 minutes. After the precipitate was filtered off and treated with dry ether to give a crude solid that was recrystallized from methyl alcohol. The yield 0.137 g (45 %), m.p. 213 °C; IR: 3400–2500 cm^{-1} (b, OH, COOH), 1668 cm^{-1} (C=O, COOH), 1650 cm^{-1} (C=O, benzoyl); ^{1}H-NMR (deuteriochloroform): δ = 10.18-10.11 (b, 1H, H_{acid}), 7.67–7.13 (m, 10H, H_{arom}), 3.90 ppm (s, 3H, CH_3); ^{13}C-NMR (deuteriochloroform): δ = 195.5 (C=O, benzoyl), 164.5 (C=O, COOH), 149.1 (C_3), 144.3 (C_5), 139.2, 135.0, 131.9, 131.8, 131.3, 130.7, 130.0, 129.5 (C-Ph), 122.6 (C_4), 40.4 ppm (CH_3). Anal. $C_{18}H_{14}N_2O_3$.

3.1.3. 4-Benzoyl-1-methyl-5-phenyl-1H-pyrazole-3-carbonitrile (*6*)

The compound **3** (0.306 g, 1 mmol) and thionylchloride (1 ml, 13.8 mmol) were refluxed on a steam bath for 5 hours. After cooling, the crude precipitate was isolated by filtration

and recrystallized from carbon tetrachloride to give of **4**, yield 0.216 g (68 %), m.p. 160 °C; IR: 1750 (C=O, COOH), 1669 cm^{-1} (C=O, benzoyl); ^{1}H-NMR (deuteriochloroform): δ = 7.76–7.31 (m, 10H, H_{arom}), 3.96 ppm (s, 3H, CH_3); ^{13}C-NMR (deuteriochloroform): δ = 192.1 (C=O, benzoyl), 163.3 (C=O, COOH), 147.7 (C_3), 144.7 (C_5), 139.3, 135.6, 132.1, 131.6, 131.3, 131.0, 130.5, 128.9 (C-Ph), 125.0 (C_4), 40.7 ppm (CH_3). Anal. $C_{18}H_{13}N_2O_2Cl$.

A moderate stream of gaseous ammonia was allowed to bubble through a solution of pyrazole-3-carboxylic acid chloride **4** (0.324 g, 1 mmol) in 10 ml of carbon tetrachloride during 30 minutes with ice-cooling. Then the crude precipitate was filtered off and recrystallized from methanol to give of **5**, yield 0.201 g (65 %), m.p. 220 °C; IR: 3451–3320 cm^{-1} (NH), 1662 cm^{-1} (C=O, benzoyl), 1624 cm^{-1} (C=O, amide). ^{1}H-NMR (deuteriochloroform): δ = 7.69–7.20 (m, 10H, H_{arom}), 5.57–5.55 (bs, 2H, NH_2), 3.89 ppm (s, 3H, CH_3). ^{13}C-NMR (deuteriochloroform): δ = 194.4 (C=O, benzoyl), 164.5 (C=O, amide), 147.5 (C_3), 147.4 (C_5), 145.9, 140.2, 134.8, 132.1, 131.5, 131.4, 130.8, 129.9 (C-Ph), 122.7 (C_4), 40.0 ppm (CH_3). Anal. $C_{18}H_{15}N_3O_2$.

A cold solution of the acid amide **5** (0.287 g, 1 mmol) in a mixture of DMF (0.7 ml) and $SOCl_2$ (0.15 ml) was stirred at 0–5 °C for 2 hours. After heating to room temperature, stirring was continued for overnight, then the reaction mixture poured over crushed ice and the separated solid was filtered off, washed with water and recrystallized from methanol to give 0.186 g (65 %) of carbonitrile **6**, m.p. 169 °C; IR: 2237 cm^{-1} (CN), 1676 cm^{-1} (C=O, benzoyl).

*3.1.4. 3,4-Diphenyl-2-methyl-2,6-dihydro-pyrazolo[3,4-*d*]-pyridazin-7-one (**7a**)*

3.1.4.1. General procedure. A milliequimolar mixture of **3** (0.306 g, 1 mmol) and hydrazinhydrate (0.1 ml) were refluxed in xylene for 4 hours. The solvent was evaporated, then the oily residue was treated with ether and the formed crude product was crystallized from ethanol. Compound **7a** was obtained in yield 0.180 g (60 %), m.p. 344 °C; IR: 3350–2900 cm^{-1} (b, NH ⇌ OH), 1689 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ = 12.51 (b, 1H, OH), 7.36–7.00 (m, 10H, H_{arom}), 3.96 ppm (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ = 157.8 (C=O), 145.1 (C_3), 142.7 (C_{7a}), 141.5, 136.1 (C_4), 132.0, 131.0, 131.0, 130.0, 129.9, 129.5, 129.1, 117.8 (C_{3a}), 41.3 ppm (CH_3). Anal. $C_{18}H_{14}N_4O$.

*3.1.5. 3,4,6-Triphenyl-2-methyl-2,6-dihydro-pyrazolo[3,4-*d*]pyridazin-7-one (**7b**)*

Compound **7b** was prepared according to the general procedure above with a reflux time of 4 hours resulting in yield 0.24 g (65 %), m.p. 260 °C; IR: 1681 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ = 7.74–6.94 (m, 15H, H_{arom}), 4.04 ppm (s, 3H, CH_3); ^{13}C-NMR (deuteriochloroform): δ = 155.6 (C=O), 144.9 (C_3), 143.3 (C_{7a}), 142.9, 141.2 (C_4), 135.0, 131.2, 131.0, 130.4, 129.5, 129.4, 129.2, 128.7, 128.5, 128.3, 127.0, 117.1 (C_{3a}), 39.8 ppm (CH_3). Anal. $C_{24}H_{18}N_4O$.

*3.1.6. 3,4-Diphenyl-2,6-dimethyl-2,6-dihydro-pyrazolo[3,4-*d*]pyridazin-7-one (**7c**)*

Compound **7c** was prepared according to the general procedure above with a reflux time of 4 hours resulting in yield 0.189 g (60 %), m.p. 210 °C; IR: 3100–3000 cm^{-1} (Ar-H), 2950–2840 cm^{-1} (CH_3), 1672 cm^{-1} (C=O); ^{1}H-NMR (deuteriochloroform): δ = 7.32–6.95 (m, 10H, H_{arom}), 4.03 and 3.91 ppm (s, 6H, CH_3). Anal. $C_{19}H_{16}N_4O$.

*3.1.7. 6-(4-Carboxyphenyl)-3,4-diphenyl-2-methyl-2,6-dihydro-pyrazolo[3,4-*d*]pyridazin-7-one (**7d**)*

Compound **7d** was prepared according to the general procedure above with a reflux time of 4 hours resulting in yield 0.232 g (55 %), m.p. 236 °C; IR: 3400–2500 cm^{-1} (b, OH, COOH), 1692 and 1604 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ = 9.64 (1H, H_{acid}), 7.81–7.24 (m, 14H, H_{arom}), 3.90 ppm (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ = 169.1 (C=O, COOH), 164.1 (C=O), 150.7, 145.2, 142.3, 140.3, 139.9, 132.6, 131.0, 130.5, 130.4, 129.9, 129.5, 127.3, 122.4, 115.1, 113.9, 40.0 ppm (CH_3). Anal. $C_{25}H_{18}N_4O_3$.

*3.1.8. 6-(2,5-Dichlorophenyl)-3,4-diphenyl-2-(pyridine-2-yl)-2,6-dihydro-pyrazolo[3,4-*d*]pyridazin-7-one (**7e**)*

A milliequimolar mixture of **2** (0.369 g, 1 mmol) and 2,5-dichlorophenyl hydrazine (0.177 g, 1 mmol) were refluxed in 1-butanol for 6 hours. The solvent was evaporated, then the oily residue was treated with ether and the formed crude product was crystallized from ethanol. Compound **7e** was obtained in yield 0.305 g (60 %), m.p. 190 °C; IR: 1592 cm^{-1} (C=O); ^{13}C-NMR (DMSO-d_6): δ = 162.1 (C=O), 152.7, 151.3, 149.9, 142.6, 142.3, 141.7, 138.3, 137.6, 134.8, 132.6, 132.3, 130.9, 130.6, 130.4, 130.1, 128.2, 127.9, 125.7, 122.2, 118.9, 117.3, 115.3, 113.5 ppm. Anal. $C_{28}H_{17}N_5OCl_2$.

*3.1.9. 6-(2,4,6-Trichlorophenyl)-3,4-diphenyl-2-methyl-2,6-dihydro-pyrazolo[3,4-*d*] pyridazin-7-one (**7f**)*

Compound **7f** was prepared according to the general procedure above with a reflux time of 4 hours resulting in yield 0.260 g (55 %), m.p. 242 °C; IR: 1712 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ = 8.10–7.16 (m, 12H, H_{arom}), 3.96 ppm (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6): δ = 164.1 (C=O), 145.0 (C_{7a}), 142.8 (C_4), 142.1 (C_3), 139.5, 139.4, 131.1, 130.8, 130.5, 130.3, 129.9, 129.6, 129.1, 129.0, 127.2, 114.2 (C_{3a}), 40.9 ppm (CH_3). Anal. $C_{24}H_{15}Cl_3N_4O$.

*3.1.10. 1-Methyl-5-phenyl-4-[phenyl-(pyridine-2-yl-hydrazono)-methyl]-1H-pyrazole-3-carboxylic acid (**8**)*

A milliequimolar mixture of **3** (0.306 g, 1 mmol) and 2-hydrazinopyridine (0.109 g, 1 mmol) were refluxed in xylene on an oil-bath for 5 hours. The solvent was evaporated and the remaining oily residue was treated with ether to give a crude product which recrystallized from ethanol, yield 0.278 g (70 %), m.p. 260 °C; IR: 3233 cm^{-1} (NH), 1661.25 cm^{-1} (C=N), 1619, 1525 (COO^-); ^{1}H-NMR (DMSO-d_6): δ = 9.32 (b, 1H, H_{acid}), 8.09 (b, 1H, NH), 7.69–6.82 (m, 14H, H_{arom}) and 3.89 ppm (s, 3H, CH_3); ^{13}C-NMR (DMSO-

d_6): δ = 164.1 (COO^-), 158.4 ($C_{2'}$, Pyr), 149.3 (C=N), 145.2 (C_3), 141.9 ($C_{6'}$, pyr.), 140.2 (C_5), 139.9, 139.8, 131.1, 130.6, 130.1, 129.9, 129.9, 129.6, 127.3, 117.4, 114.7, 109.0(C_4), 40.9 ppm (CH_3). Anal. $C_{23}H_{19}N_5O_2$.

*3.1.11. 2-Methyl-3,4-diphenyl-2,6-dihydro-pyrazolo[3,4-*d*]-pyridazin-7-yl-amine (**9**)*

The compound **6** (0.287 g, 1 mmol) and anhydrous hydrazine (0.032 g, 1 mmol) were refluxed in 1-butanol containing catalytic amount of metallic sodium on an oil-bath for 6 hours. The precipitate formed in boiling 1-butanol was isolated by filtration and recrystallized from toluene, yield 0.135 g (45 %), m.p. 365 °C; IR: 3400–3000 cm^{-1} (NH), 1687 cm^{-1} (C=NH); ^{13}C-NMR (DMSO-d_6): δ = 156.6 (C=NH), 146.0, 145.8, 143.2, 141.1, 136.5, 132.0, 131.0, 130.0, 129.9, 129.5, 129.1, 127.9, 40.9 ppm (CH_3). Anal. $C_{18}H_{15}N_5$.

3.2. Biological assays

3.2.1. Compounds

Test compounds were dissolved in DMSO at an initial concentration of 2.5 mg ml^{-1} and then were serially diluted in culture medium.

3.2.2. Cells

Bacterial and fungal strains were supplied from American Type Culture Collection (ATCC).

3.2.3. Antimicrobial assays

The MICs of the chemical compounds assays were carried out as described by Clause [11] with minor modifications. Ampicillin trihydrate and fluconazole were used as reference antimicrobial drugs. Solutions of the test compounds and reference drugs were dissolved in DMSO at a concentration of 5 mg ml^{-1} . The twofold dilution of the compounds and reference drug were prepared (2.5, 1.25, 0.625, 0.312, 0.156 >0.078 mg ml^{-1}). Antibacterial activities of the bacteria were carried out in Muller–Hinton broth (Difco) medium, at pH 7.2, with an inoculum of (1–2) × 10^3 cells ml^{-1}. Also, antimycotic activity of the yeast were determined using Sabouraud dextrose broth (Difco) medium, at pH 5.7, with an inoculum of (1–2) × 10^3 CFU ml^{-1}. The chemical compounds-broth medium serial tube dilutions inoculated with each microorganism were incubated on a rotary shaker at 37 °C for 18 hours at 150 rpm. The MICs of the chemical compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no growth (i.e. no turbidity) of inoculated bacteria.

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