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A FACILE SYNTHESIS OF SOME NOVEL 1,3,4-THIADIAZOLES AND PYRIDINES LINKED TO BENZOFURAN AS ANTIMICROBIAL AGENTS.

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ABSTRACT

In the present study, a new series of benzofuran-integrated 1,3,4-thiadiazoles were prepared starting from pyrazol-4-carboxaldehyde derivatives **3a,b**. Thus, reaction of compounds **3a,b** with benzyl hydrazine carbodithioate afforded hydrazine carbodithioate derivatives **4a,b**. Treatment of compound **4a** with hydrazonoyl halides **5e,f** afforded 1,3,4-thiadiazoles **6a, b** ,also, the reaction of **4b** with hydrazonoyl halides **5a-d** yielded 1,3,4-thiadiazoles **7a-d**. on the other hand, new pyridine derivatives can be synthesized via the reaction from the reaction of chalcone **8** with different *C*-nucleophiles like ethyl acetoacetate, benzoyl acetonitrile and acetyl acetone afforded pyridines **9-11** derivatives were characterized by complete spectral data and elemental analysis. Some of the newly prepared compounds were investigated against different pathogenic microbes. The results of the antimicrobial activity revealed that all the tested compounds showed no activity except compound **6a** which showed weak activity against all tested microorganisms. Compound **6b** showed weak activity against *B. subtilis too* and compound **7c** revealed intermediate activity against *E. coli*.

Key words: 2-Acetyl benzofuran, Thiadiazoles, Pyridines, Hydrazonoyl halides, Antimicrobial activity.

INTRODUCTION

Benzofuran scaffold is present in many naturally occurring compounds and synthetic materials, recent studies demonstrated that benzofuran derivatives have significant pharmacological properties such as antimicrobial [1-3], antitubercular [4-6], anticonvulsant [7], anti-AChE [8], anti-inflammatory [9, 10], antagonistic [11], antioxidant [12, 13], anticancer [14, 15] and anti-TB [16] activities. In addition, they are used as anti-Alzheimer's disease [17-19], anti-parasitic [20] and antiviral [21] activities. Also, compounds bearing 1,3,4-thiadiazole moiety possess antimicrobial [22, 23], anticancer [24] and anti-inflammatory [25] activities. Moreover, pyridine is present in many natural products such as vitamins (vitamin B_6) and alkaloids (trigonelline). and antimicrobial [26] and anticancer [27] activities,

From the above, we try to synthesize some new benzofuran derivatives containing either thiadiazole or pyridine moiety and testing the antimicrobial activity for these derivatives.

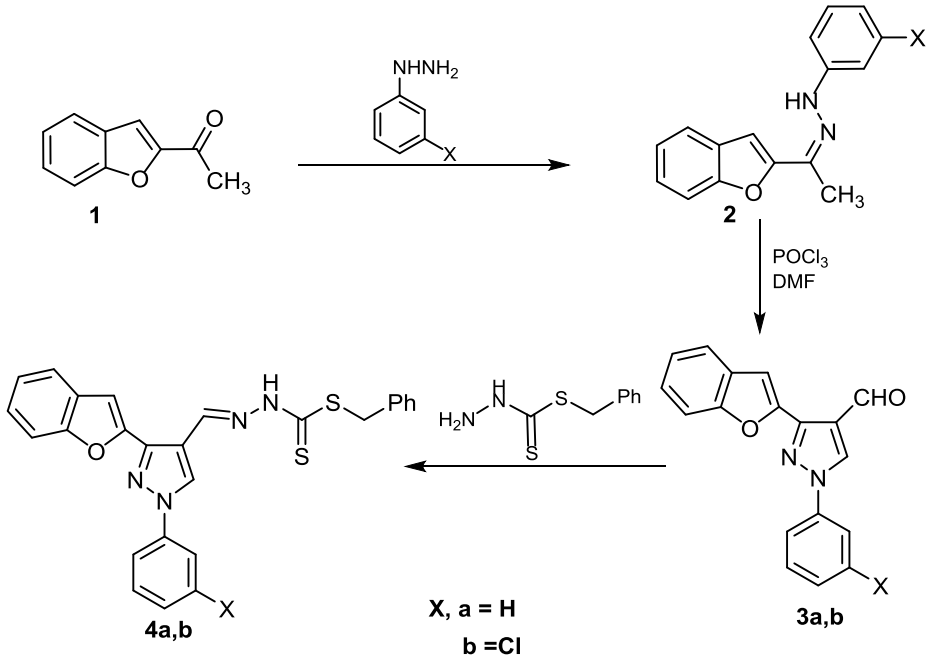
RESULTS AND DISCUSSION

The synthetic pathways for the formation of title compounds were illustrated in schemes 1-3. Thus, condensation of 2-acetyl benzofuran (**1**) with either phenyl hydrazine or 3-chloro phenyl hydrazine in ethanol catalyzed with acetic acid yielded 1-(1-(benzofuran-2-yl)ethylidene)-2-(substituted phenyl hydrazine **2a**,**b**. Vilsmeier- Haack reaction for **2a,b** furnished 3-(benzofuran-2-yl)-1-(substituted phenyl)-1*H*-pyrazole-4-carbaldehyde **3a,b**[28], respectively; (Scheme 1). The IR spectrum of **3b** displayed absorption peaks at 1681 cm^{-1} characteristic to formyl group. Whereas, the ^1H NMR spectrum recorded two singlet signals for CH-pyrazole and formyl group at δ 8.44 and 10.24 ppm , respectively.

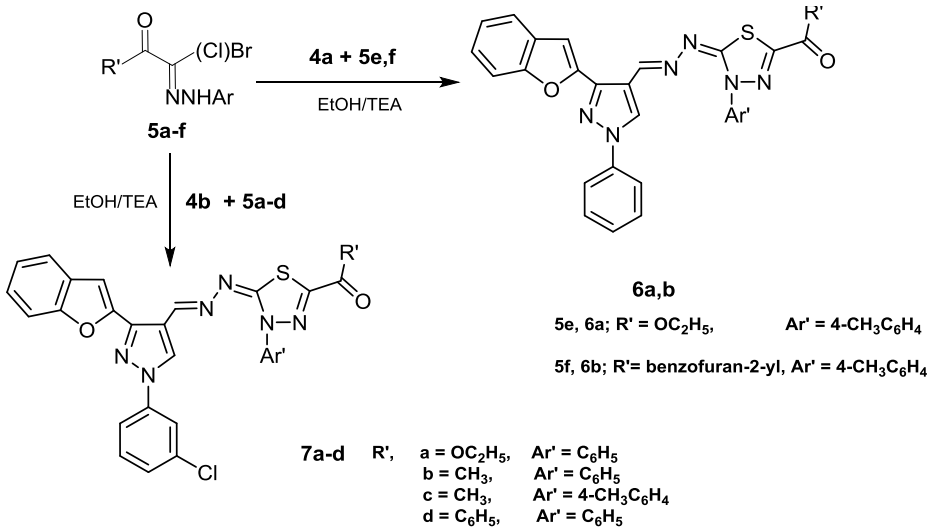
The formyl group in compound **3a,b** is condensed with benzyl hydrazinecarbodithioate [28] in isopropanol

under stirring yielded the condensation produce **4a[30], b**, respectively (Scheme 1). The IR spectrum of **4b** lakes aldehydic carbonyl group and revealed new peaks assigned to NH group at 3165 cm^{-1} and 1319 cm^{-1} (C=S). ^1H NMR spectrum of **4b** assigned four singlet signals at δ 4.51, 8.73, 9.06 and 13.38 ppm assigned to SCH_2, CH=N, CH-pyrazole and NH groups, respectively; Scheme 1.

Cyclocondensation of compound **4a** with hydrazonoyl halides **5e,f32-35]** in ethanol containing triethylamine as a catalyst furnished 1,3,4-thiadiazoles **6a,b**, respectively**;** (Scheme 2). The reaction proceeded via elimination of hydrogen halide and benzyl mercaptant molecule. The structure The structure of 1,3,4-thiadiazoles 6a,b was assigned through right elemental analysis and spectral data. The infrared spectrum of **6a,b** lakes the NH function and two showed band for C=O at 1734 and 1735 cm^{-1}. Additionally, ^1H NMR spectrum of **6a** recorded signals at δ 1.50 and 4.21 ppm, corresponds to CH_3 (triplet) and CH_2



Scheme1,Synthesis of some new hydrazones.

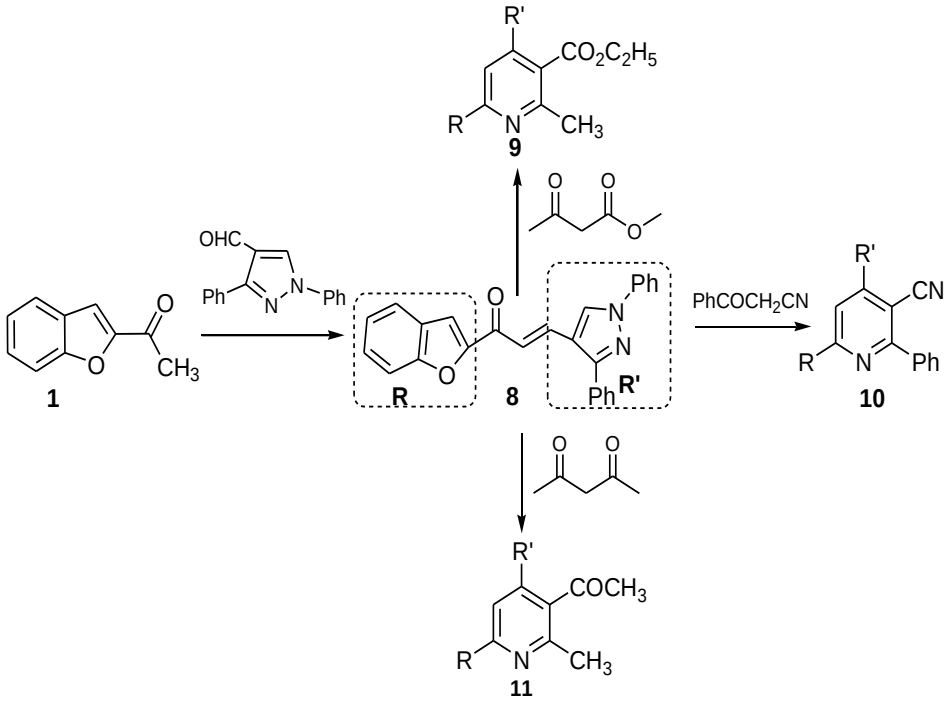


Scheme 2, Synthesis of 1,3,4 thiadiazoles.

(quartet) of ester group, beside a singlet signal at δ 3.27 ppm for methyl protons, two new singlet signals appeared at δ δ 8.62 & 9.25 ppm related to CH=N and CH-pyrazole, respectively. Similarly, 1,3,4-thiadiazoles **7a-d** were accomplished via the reaction of compound **4b** with hydrazonoyl halides **5a-d** [32-35] under similar conditions. Spectral data and elemental analysis of the prepared compounds approved their structures. For instance, IR spectra of **7a-d** revealed absorption peaks for carbonyl group in the range 1732-1651 cm^{-1}. The ^1H NMR spectrum of **7a** lakes a signal due to NH group and demonstrated the appearance of triplet and quartet signals for ester group at δ 1.31 & 4.35 ppm, besides the signals due to aromatic protons in region δ 7.30-8.14 ppm and two singlet signals at δ 8.67 and 9.14 ppm due to CH=N and CH-pyrazole, respectively.

The ^1H NMR spectrum of **(7b**;DMSO-d_6) recorded new singlet signal at δ 2.77 ppm for acetyl group, protons for aromatic at δ 7.27-7.82 ppm and at δ 8.46 ppm for CH=N. Whilst, the ^1H NMR spectrum of **(7c** ; DMSO-d_6) illustrated new singlet signals at 2.40 and 2.66 ppm related to methyl and acetyl proton, consequently, as well as aromatic protons at δ 7.26-8.08 ppm and singlet signals at δ 8.45 ppm related to CH=N.

Finally, treatment of chalcone **8** with different *C*-nucleophile such as ethyl acetoacetate, benzoyl acetonitrile or acetyl acetone in acetic acid in presence of ammonium acetate under reflux afforded pyridines **9-11**, respectively (Scheme 3). Spectroscopic data of the synthesized products elucidated their structure. Thus, the IR spectrum of **9** displayed absorption band at 1720 cm^{-1} corresponds to (C=O ester). Its ^1H NMR spectrum showed triplet signal at δ 1.06 ppm and quartet signal δ 4.21 ppm for ester group beside singlet signal at δ 2.24 ppm for CH_3 group, and at δ 7.26-7.82 ppm for aromatic protons. Furthermore the mass spectrum of **9** displayed a molecular ion peak at m/z 500 (M^+ +1, 1.2), 77 (100). Furthermore, in the IR spectrum of **10** absorption peaks at 2221 cm^{-1} was observed for cyano group. Its ^1H NMR spectrum recorded signals for aromatic protons at δ 7.27–8.50 ppm. The ^1H NMR spectrum **11** revealed singlet signals at δ 2.63 and 2.89 ppm corresponds to CH_3 and $COCH_3$ protons, respectively, aromatic protons appeared in region 7.26-8.03 ppm.



Biological Screening

Some of newly prepared compounds were investigated against two (G +ve) bacteria, two (G-ve) bacteria and two fungal species. The screening results revealed that all the tested compounds showed no activity except thiadiazole derivative **6a** which showed week activity against all tested microorganisms. Compound **6b** was week active against *B. subtilis* and compound **7c** was intermediate active against *E. coli*.

EXPERIMENTAL SECTION

The melting points of the prepared compounds were measured on an electrothermal apparatus and may be uncorrected. The infrared spectra were determined (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. Mass spectra were determined on Thermo Scientific ISQLT mass spectrometer at the Regional Center for Mycology and Biotechnology, Al-Azhar University. The ^{1}H NMR spectra were performed on a Bruker spectrometer at 400 MHz, TMS was the internal standard.

Compounds **3a** [29], **4a** [30], **8** [31] and hydrazonoyl halides **5a-f** [32-35] were previously prepared.

Synthesis of 3-(benzofuran-2-yl)-1-(3-chlorophenyl)-1*H*-pyrazole-4-carbaldehyde (3b).

To *N*, *N*-dimethyl formamide (15 mL), phosphorus oxychloride (2 mL) was added drop wise at 0–5 °C with stirring, hydrazone **2b** (2.50 g) was added very slowly and stirred for 3h, . The precipitate was filtered, dried and crystallized from DMF yielded compound **3b**. White; yield: 91 %; mp.: 190-92°C. FT-IR (KBr, ν cm^{-1}): 3120, 2916, 2877 (CH), 1681 (C=O), 1569 (C=N); ^{1}H NMR: δ 7.35–8.12 (m, 9H, Ar-H), 8.44 (s, 1H, pyrazole ring), 10.24 ppm (s, 1H, CHO). Anal. Calcd for $C_{18}H_{11}ClN_2O_2$ (322.75): C, 66.99; H, 3.44 ; N, 8.68. Found: C, 66.91; H, 3.54; N, 8.60.

Synthesis of benzyl-2-(3-(benzofuran-2-yl)-1-(3-chlorophenyl)-1*H*-pyrazol-4-yl-methylene)-hydrazine carbodithioate (4b)

Equimolar amounts of **3b** and benzyl hydrazine carbodithioate in isopropanol were stirred for 30 min. The solid formed was collected and crystallized from DMF to give **4b**. Paige; yield: 82%; mp.: 230-32°C; FT-IR (KBr, ν cm^{-1}): 3165 (NH), 3062, 2916 (CH), 1589 (C=N), 1319 (C=S); ^{1}H NMR: δ 4.51 (s, 2H, SCH_2), 7.25-7.47 (m, 10H), 7.53 (t, 1H),

Table1: Response of various microorganisms to some of synthesized compounds.

Compd. NO.	Mean* of zone diameter nearest whole mm.					
	Gram - positive bacteria		**Gram - negative bacteria**		**Yeasts and Fungi****	
	S .aureus	*B. subtilis*	*S. typhimurium*	*E. coli*	*C. albicans*	*A. fumigatus*
3b	-	-	-	-	-	-
4b	-	-	-	-	-	-
6a	10	10	11	13	-	11
6b	-	11	-	-	-	-
7a	-	-	-	-	-	-
7c	-	-	-	15	-	-
7d	-	-	-	-	-	-
11	-	-	-	-	-	-
Control #	**35**	**35**	**36**	**38**	**35**	**37**

* = Calculate from 3 values; ** = identified on the basis of routine cultural, morphological and microscopical characteristics, - = No effect, #: Chloroamphencol(Gram+ve),Cephalothin(Gram–ve),Cyclohexamide in case of fungi.

7.64 (d, 1H, *J* = 8Hz), 7.79 (d, 1H, *J* = 8Hz), 7.99 (d, 1H, *J* = 8Hz), 8.73 (s, 1H, CH=N), 9.06 (s, 1H, CH-pyrazole), 13.38 ppm (s,1H, NH). Anal. Calcd. For $C_{26}H_{19}ClN_4OS_2$(503.04): C, 62.08; H, 3.81; N, 11.14. Found: C, 62.15; H, 3.89; N, 11.20.

Synthesis of 1,3,4-thiadiazoles 6a,b and 7a-d.

To stirred solution of **4a or 4b** (5 mmol) in 20 mL ethanol having 0.01 mole trimethylamine as catalyst, hydrazonoyl halides **5a-f** (5 mmol) was added separately. The precipitate was filtered and crystallized from a proper solvent and gave thiadiazoles **6a,b** and **7a-d**, respectively.

2-(Ethoxycarbonyl)-5-(2-((3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4,5-dihydro-4-(4-methylphenyl)-1,3,4-thiadiazole (6a).

Yellow (DMF), yield: 80%; mp.: 210-11°C; FT-IR (KBr, *v* cm^{-1}): 3039, 2978 (CH), 1735 (C=O), 1597 (C=N); ^{1}H NMR: δ 1.50 (t, 3H, *J* = 7*Hz*, CH_3), 3.27 (s, 3H, CH_3), 4.21 (q, 2H, *J* = 7*Hz*, CH_2), 7.33-7.71 (m, 10H, Ar-H), 7.75 (d, 2H, J = 8Hz), 7.79 (d, 2H, J = 8Hz), 8.62 (s, 1H, CH=N), 9.25 ppm (s, 1H, CH-pyrazole). Anal Calcd. for $C_{30}H_{24}N_6O_3S$ (548.16): C, 65.68; H, 4.41; N, 15.32; . Found: C, 65.75; H, 4.50; N, 15.40.

2-(Benzofuran-2-yl-carbonyl)-5-(2-((3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4,5-dihydro-4-(4-methyl phenyl)-1,3,4-thiadiazole (6b)

Red (DMF), yield: 82%; mp.: 230-31°C; FT-IR (KBr, *v* cm^{-1}): 3101, 2978 (CH), 1734 (C=O), 1597 (C=N); ^{1}H NMR: δ 4.51 (s, 3H, CH_3), 7.23-8.02 (m, 19H, Ar-H), 8.73 (s, 1H, CH=N), 9.04 (s, 1H, CH-pyrazole). Anal Calcd. for $C_{36}H_{24}N_6O_3S$ (620.16): C, 69.66; H, 3.90; N, 13.54. Found: C, 69.74; H, 3.99; N, 13.45.

2-(Ethoxycarbonyl)-5-(2-((3-(benzofuran-2-yl)-1-(3-chlorophenyl)-1*H*-pyrazol-4-yl)methylene)hydrazono)-4,5-dihydro-4-phenyl-1,3,4-thiadiazole (7a).

Yellow (DMF), yield: 85%; mp 207-8°C; FT-IR (KBr, *v* cm^{-1}): 3059, 2932 (CH), 1732 (C=O), 1597 (C=N); ^{1}H NMR: δ 1.31 (t, 3H, *J* = 7*Hz*, CH_3), 4.35 (q, 2H, *J* = 7*Hz*, CH_2), 7.30-8.14 (m, 13H, ArH), 8.67 (s, 1H, CH=N), 9.14 ppm (s, 1H, CH-pyrazole). Anal Calcd. for $C_{29}H_{21}ClN_6O_3S$(569.03): C,61.21; H, 3.72; N, 14.77. Found: C, 61.11; H, 3.63; N, 14.70.

2-Acetyl-5-(2-((3-(benzofuran-2-yl)-1-(3-chlorophenyl)-1*H*-pyrazol-4-yl)methylene)hydrazono)-4,5-dihydro-4-phenyl-1,3,4-thiadiazole (7b)

Yellow (EtOH); yield: 83%; mp.: 110-12°C; FT-IR (KBr, *v* cm^{-1}): 3062, 2970 (CH), 1681 (C=O), 1597 (C=N); ^{1}H NMR: δ 2.77 (s 3H, $COCH_3$), 7.27-7.59 (m, 14H, ArH), 7.82 (d, 1H, *J* = 8 Hz), 8.46 ppm (s, 1H, CH=N). Anal Calcd. for $C_{28}H_{19}ClN_6O_2S$(539.01): C, 62.39; H, 3.55; N, 15.59. Found: C, 62.29; H, 3.65; N, 15.50.

2-Acetyl-5-(2-((3-(benzofuran-2-yl)-1-(3-chlorophenyl)-1*H*-pyrazol-4-yl)methylene)hydrazono)-4,5-dihydro-4-(4-methylphenyl)-1,3,4-thiadiazole (7c)

Red (DMF), yield: 83%; mp.: 265-67°C; FT-IR (KBr, *v* cm^{-1}): 3068, 2927 (CH), 1666 (C=O), 1593 (C=N); ^{1}H NMR: δ 2.40 (s, 3H, CH_3), 2.66 (s 3H, $COCH_3$), 7.26-7.34 (m, 3H, ArH), 7.61-7.78 (m, 7H, ArH), 7.92 (d, 2H, *J* = 8 Hz), 8.08 (d, 2H, *J* = 8 Hz), 8.45 ppm (s, 1H, CH=N). Anal Calcd. for $C_{29}H_{21}ClN_6O_2S$ (553.03): C, 62.98; H, 3.83; N, 15.20. Found: C, 62.88; H, 3.90; N, 15.27.

2-Benzoyl-5-(2-((3-(benzofuran-2-yl)-1-(3-chlorophenyl)-1*H*-pyrazol-4-yl)methylene)hydrazono)-4,5-dihydro-4-phenyl-1,3,4-thiadiazole (7d)

Red (DMF), yield: 84%; mp.:180-81°C; FT-IR (KBr, *v* cm^{-1}): 3050, 2935 (CH), 1651 (C=O), 1620 (C=N); ^{1}H NMR: δ 7.31-8.24 (m, 19H, ArH), 8.45 (s, 1H, CH=N), 9.16 ppm (s, 1H, CH-pyrazole). Anal Calcd. for $C_{33}H_{21}ClN_6O_2S$ (601.08): C, 65.94; H, 3.52; N, 13.98. Found: C, 65.86; H, 3.60; N, 13.90.

Synthesis of pyridine derivatives 9-11.

To a solution of **8** (5 mmol) in acetic acid (20ml) having ammonium acetate (10mmol), ethyl acetoacetate, benzoyl acetonitrile and acetyl acetone (5 mmol) was added separately.

The mixture were boiled for 3 h. then allowed to cool. The precipitate was collected and crystallized from a proper solvent to give **9-11**, respectively.

Ethyl 4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2-methyl-6-(benzofuran-2-yl) pyrid- ine-3-carboxylate (9).

White (EtOH); Yield: 85%; mp.: 159-60 °C. FT-IR (KBr, ν, cm^{-1}): 3058, 2962, 2873 (CH), 1720 (C=O), 1639 (C=N); ^{1}H NMR: δ 1.06 (t, 3H, *J* = 7.5 Hz, CH_3), 2.24 (s, 3H, CH_3), 4.21 (q, 2H, *J* = 7.5 Hz, CH_2), 7.26-7.44 (m, 12H, ArH's), 7.67 (d, 2H, *J* = 8 Hz), 7.75 (s, 1H), 7.82 ppm (d, 2H, *J* = 8 Hz); MS m/z (%): 500 (M^+ +1, 1.2), 77 (100). Anal. Calcd for $C_{32}H_{25}N_3O_3$ (499.56): C, 76.94; H, 5.04; N, 8.41. Found: C, 76.84; H, 5.14; N, 8.31.

6-(Benzofuran-2-yl)-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2-phenyl pyridine-3-carbonitrile (**10**).

Yellow (AcOH); yield: 80%; mp.: 210-11°C; FTIR (KBr, ν, cm^{-1}): 3055 (CH), 2221 (CN), 1596 (C═N);^{1}H NMR: δ 7.27–7.67 (m, 16H), 7.81 (s, 1H), 7.85 (d, 2H, *J* = 8 Hz), 7.97 (t, 2H, *J* = 7.6 Hz), 8.50 ppm (s, 1H). Anal. Calcd for $C_{35}H_{22}N_4O$ (514.58): C, 81.69; H, 4.31; N, 10.89. Found: C, 81.79; H, 4.41; N, 10.80.

1-(6-(Benzofuran-2-yl)-2-methyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridin-3-yl)ethanone (**11**).

Brown (AcOH); yield: 80%; mp: 220-21°C; FTIR (KBr, ν, cm^{-1}): 3055 (CH), 1680 (C=O), 1596 (C═N); ^{1}H NMR: δ 2.63 (s, 3H, CH_3), 2.89 (s, 3H, $COCH_3$), 7.26–7.42 (m, 13H), 7.46 (t, 1H, *J* = 7.6 Hz), 7.58 (d, 1H, *J* = 8 Hz), 7.68 (d, 1H, *J* = 8 Hz), 8.03 ppm (s, 1H). Anal. Calcd for $C_{31}H_{23}N_3O_2$ (469.53): C, 79.30; H, 4.94; N, 8.95. Found: , 79.20; H, 4.87; N, 8.86.

1. Biological Screening

Investigation of the antimicrobial activity of some prepared compounds were carried out using standardized disc – agar diffusion method [36].

Conflict of interest

There are no conflicts to declare

CONCLUSIONS

In this research, new series of thiadiazoles and pyridines **(6a,b)** , **(7a-e)** and **(9-11)** were investigated for their antimicrobial activity against different pathogenic microorganisms. The results revealed that all the tested compounds showed no activity except compound **6a** which showed week activity against all tested microorganisms. Compound **6b** showed week active against *B. subtilis* and compound **7c** showed intermediate active against *E. coli*.

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الملخص العربي

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في هذه الدراسة، تم تحضير سلسلة جديدة من مشتقات 1،3،4- ثياديازول ابتداءا من بيرازول -4- ألدهيد **3أ،ب**. وهكذا، فإن تفاعل المركب **3أ،ب** مع بنزيل هيدرازين كربوداثيوات أعطي مشتقات الهيدرازين كربوداثيوات **4أ،ب**. عند معالجة المركب **4**أ بهاليدات الهيدرازونويل **5هـ ،و** تكونت مشتقات الثياديازول **6أ،ب** بينما أدي تفاعل المركب **4ب** مع هاليدات الهيدرازونويل **5أـد** تكونت مشتقات الثياديازول **7أـد**. من ناحية أخري، أمكن تحضير مشتقات البيريدين الجديدة **9-11** من خلال تفاعل الشالكون **8** مع الكواشف النيوكليوفيلية المختلفة مثل الإيثيل أسيتو أسيتات والبنزويل أسيتو نيتريل والأسيتيل أسيتون. كما تم اثبات التركيب الكيميائي للمركبات التي تم تحضيرها حديثا بالتحاليل الطيفية ، و تم فحص نشاط بعض المركبات ضد بعض الميكروبات وأوضحت النتائج أن كل المركبات ليس لها نشاط ما عدا المركب 6أ والذي كان له نشاط ضعيف ضد الميكروبات المختبرة والمركب **6ب** كان له نشاط ضعيف ضد البكتيريا موجبة الجرام باسيلس سبتيلس والمركب **7جـ** والذي كان له نشاط ضعيف ضد البكتيريا سالبة الجرام ايشيريشيا كولاي.